学位申請論文

# Synthesis and structure-activity relationship analysis of novel lincomycin (LCM) derivatives possessing significantly potent antibacterial activities against resistant *Streptococcus pneumoniae*

# （耐性肺炎球菌に強力な抗菌活性を有する新規リンコマイシン誘導体の合成と構造活性相関研究）

平成３０年３月

脇山　佳也

Contents

# 1. Introduction

Macrolide antibiotics possess broad-spectrum of antibacterial activity against Gram-positive bacteria (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, *etc*.), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Neisseria gonorrhoeae,* and also have a safety profile as oral drugs. Therefore, macrolide antibiotics have been used as chemotherapeutic agents in clinical sites over many years. Resistant bacteria, however, have markedly increased[1-4] and this phenomenon has caused serious problems in treatment of bacterial respiratory infections.

Macrolide antibiotics inhibit bacterial protein synthesis. Macrolide antibiotics have potent antibacterial activities through inhibiting elongation of an amino acid sequence by binding to 23S ribosomal RNA.[5-8] The mechanisms of action for bacteria to gain resistance are manifold, in general, these can be characterized as involving drug efflux, alterations in the drug target site, or drug inactivation. Resistant mechanisms in macrolides have diversified recently. Notably, there are major bacterial strains in clinical site with point mutation in the drug target site,[9,10] methylase production by *erm* gene,[11,12] and efflux pump produced by *mef* gene.[12-14]

The methylase of bacteria inhibits macrolide binding to 23S ribosomal RNA through either methylation or dimethylation at the N-6 position of the adenine residue (A2058Ec).[9,12,15] On the other hand, the efflux pump of bacteria is able to transport a variety of compounds, thus conferring resistance to a broad range of antibiotics.

Clarithromycin (CAM)(**1-1**)[16] and azithromycin (AZM)(**1-2**)[17-19] (Figure 1-1) are not effective enough against resistant bacteria (*S. pneumoniae* and *S. pyogenes*) with *erm* gene, and influenced by *S. pneumoniae* with *mef* gene. On the other hand, telithromycin (TEL) (**1-3**),[20,21] which was launched as the first ketolide antibiotic, is effective against resistant bacteria with *erm* gene and *mef* gene. The X-Ray crystallographic[8,22] and footprinting analysis[23-25] indicated that TEL is capable of binding not only to domain V (A2058Ec, A2059Ec) of 23S *r*RNA but also to domain II (A752). TEL, however, has possibly cause serious liver damage[26-28] and loss of consciousness,[28,29] and medication with TEL was discontinued in Japan. Furthermore, its production cost seems to be relatively high due to its complicated structure. Cethromycin(**1-4**)[30] (Figure 1-1), which is ketolide antibiotic such as TEL, was synthesized by Abbott laboratories, and it was not approved for the treatment of community-acquired pneumonia in 2009 by FDA. Development of Enanta's modithromycin, which was acquired by Shionogi & Co., Ltd., was discontinued in 2010 in Japan. Solithromycin (**1-5**),[31] which is ketolide antibiotic synthesized by Cempra, Inc., and its new drug application (NDA) was rejected by FDA, and FDA required additional information of nine thousands cases on safty profile to evaluate hepatotoxic risk. Novel azalides[32,33] reported by Miura *et al*. are also effective against the aforementioned resistant pathogens, but these analogs are still under research process. Development of an oral antibiotic possessing potent antibacterial activities against the resistant bacteria with *erm* gene and/or *mef* gene, and an acceptable safety profile is strongly desired in clinical sites for respiratory infections.

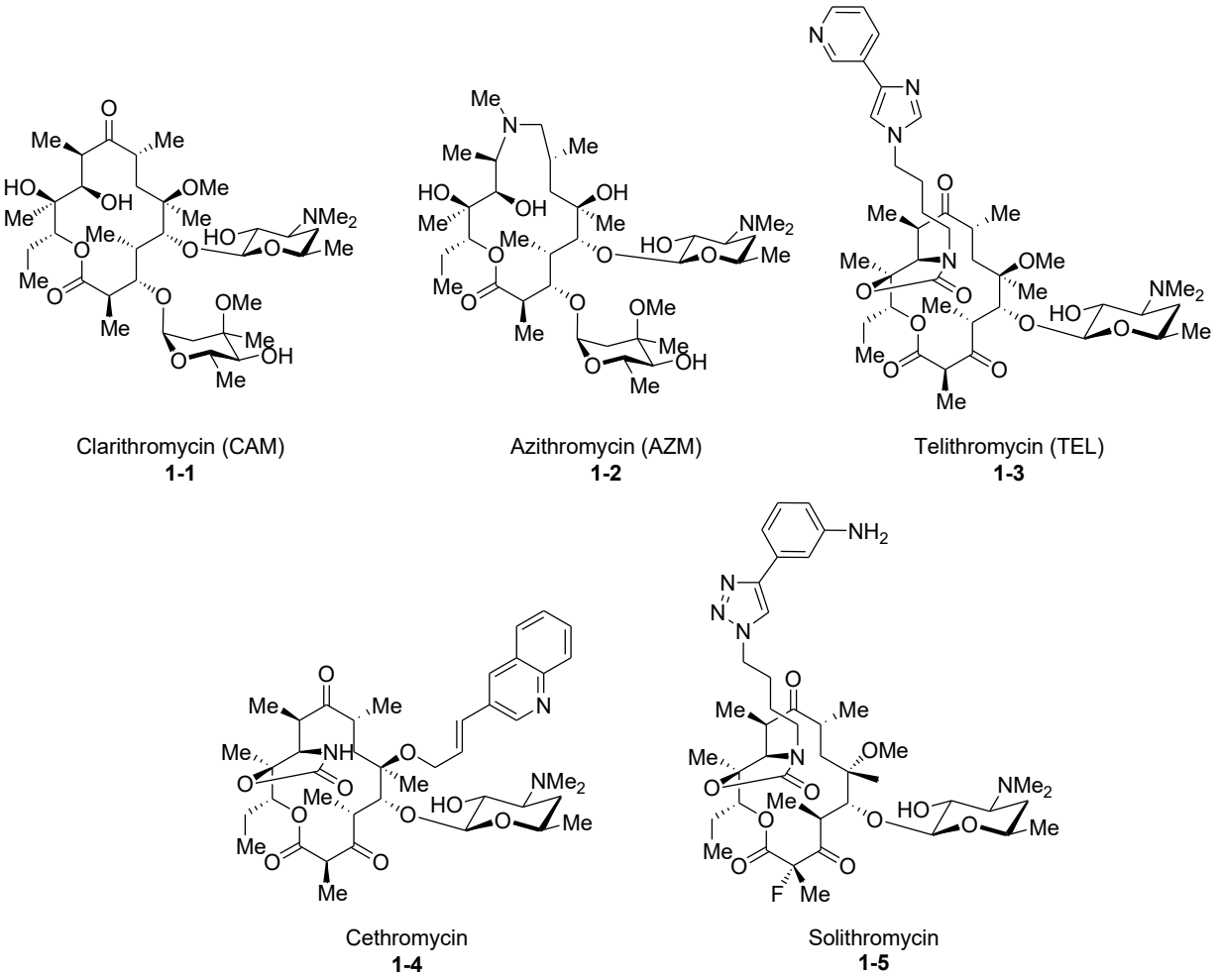
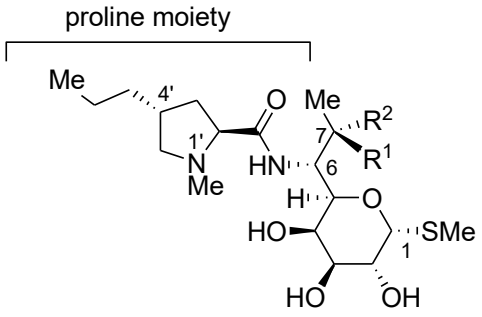



Figure 1-1. Chemical structures of Clarithromycin (CAM), Azithromycin (AZM), Telithromycin (TEL), Cethromycin and Solithromycin.

Lincomycin (LCM)(**1-6**)[34-37] was isolated as a secondary metabolite from the fermentation broth of *Streptomyces lincolnensis*. Clindamycin (CLDM)(**1-7**)[38] was synthesized by chemical modification of LCM (Figure 1-2). LCM and CLDM inhibited bacterial protein synthesis same as macrolide antibiotics. The structures of lincomycin analogs are different from those of macrolide antibiotics, but X-ray crystallographic analysis indicated that their binding sites to *r*RNA are closely located in a neighboring area.[5,7,9,10] According to the report,[5,7,9,10] there were several major interactions by hydrogen bonding between the peptidyl transferase cavities (A2058Ec, A2059Ec, and G2520Ec) and hydroxyl groups at the sugar portion of CLDM. These data suggest that it is difficult for us to improve antibacterial activity by chemical modification at the sugar moiety. In fact, 2-deoxylincomycin[39] has been reported to show only 1% activity compared with LCM.




**1-6** Lincomycin (LCM): $R^1$ = OH, $R^2$ = H
**1-7** Clindamycin (CLDM): $R^1$ = H, $R^2$ = Cl

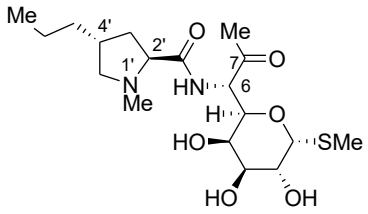
Figure 1-2. Chemical structures of Lincomycin (LCM) and Clindamycin (CLDM).

As an overview, CLDM exhibits the following positive characters: (1) availability in p.o. (per os) and i.v. (intravenous) administrations (switch therapy is possible), (2) good distributions to the tissue and cells, (3) possessing antibacterial activities against both susceptible strains and resistant strains with *mef* gene. But they are not effective against resistant bacteria (*S. pneumoniae* and *S. pyogenes*) with *erm* gene (4) suppression[40] of toxin production by Streptococcal strains, and (5) expected reasonable production cost of its analogs compared with that of ketolides with a complex chemical structure.

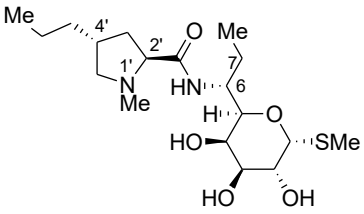
Chemical modifications at the C-7 positions of LCM (7-dehydrolincomycin (7-ketolincomycin) (**1-8**),[41] 7-deoxylincomycin (**1-9**),[42] lincomycin-7-acylate (**1-10**),[43] lincomycin-7-carbonate (**1-11**),[43] (7*R*)-7-azido-7-deoxylincomycin (**1-12**),[37] (7*R*)-7-amino-7-deoxylincomycin (**1-13**),[37] (7*R*)-7-cyano-7 -deoxylincomycin (**1-14**),[37] (7*R*)-7-deoxy-7-thiolincomycin (**1-15**)[44] (7*R*)-7-chloro-7-deoxylincomycin (**1-16**),[38] 7-deoxy-7-methyllincomycin (**1-17**),[45] (7*S*)-7-deoxy-7-thiolincomycin (**1-20**),[44] (7*S*)-7-bro mo-7-deoxylincomycin (**1-21**),[38] (7*S*)-7-deoxy-7-iodolincomycin (**1-22**),[38] and 7-epilincomycin ((7*S*)-l incomycin)(**1-23**),[38] and so on) have been investigated so far. (Figure 1-3) In these compounds, (7*S*)-7-bromo-7-deoxylincomycin (**1-21**) and (7*S*)-7-deoxy-7-iodolincomycin (**1-22**), exhibited enha nced antibacterial activities in the same order of magnitude as CLDM, and (7*R*)-7-azido-7-deoxyli ncomycin had the same antibacterial activities as LCM.

In the case of possessing a chlorine atom at the 7-position, CLDM ((7*S*)-Cl) had stronger antibacterial activities than 7-epiclindamycin ((7*R*)-Cl). 7-Epilincomycin ((7*S*)-lincomycin) had one-half of the potency of the LCM possessing (7*R*)-configuration ((7*S*)-OH < (7*R*)-OH).

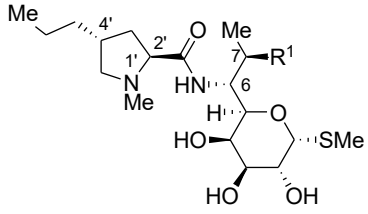
(7*R*)-7-*O*-Methyllincomycin (**1-18**), of which 7-hydroxyl group was protected, showed improved potency, whereas (7*S*)-7-*O*-methyllincomycin (**1-24**) had stronger activities of 3.5 times the response of LCM against *Sarcina lutea* ((7*S*)-OMe (**1-24**) > (7*R*)-OMe (**1-18**).[46,47] Unfortunately, both bulky alkoxy groups and substituted alkoxy groups resulted in weaker antibacterial activities than those of LCM.



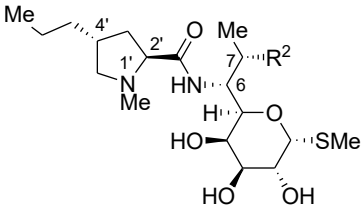
**1-8** 7-Dehydrolincomycin (7-Ketolincomycin)



**1-9** 7-Deoxylincomycin



**1-10** Lincomycin-7-acylate: $R^1$ = OCOR
**1-11** Lincomycin-7-carbonate: $R^1$ = OCOOR
**1-12** (7*R*)-7-Azido-7-deoxylincomycin: $R^1 = N_3$
**1-13** (7*R*)-7-Amino-7-deoxylincomycin: $R^1 = NH_2$
**1-14** (7*R*)-7-Cyano-7-deoxylincomycin: $R^1$ = CN
**1-15** (7*R*)-7-Deoxy-7-thiolincomycin: $R^1$ = SH
**1-16** (7*R*)-7-Chloro-7-deoxylincomycin: $R^1$ = Cl
**1-17** 7-Deoxy-7-methyllincomycin: $R^1$ = Me
**1-18** (7*R*)-7-*O*-Methyllincomycin: $R^1$ = OMe
**1-19** (7*R*)-7-Deoxy-7-imidazol-2-yl-thiolincomycin: $R^1$ = imidazol-2-yl-thio



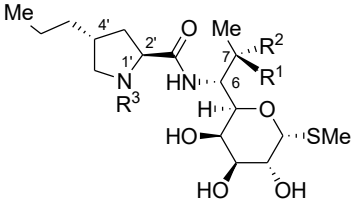
**1-20** (7*S*)-7-Deoxy-7-thiolincomycin: $R^2$ = SH
**1-21** (7*S*)-7-Bromo-7-deoxylincomycin: $R^2$ = Br
**1-22** (7*S*)-7-Deoxy-7-iodolincomycin: $R^2$ = I
**1-23** 7-Epilincomycin ((7*S*)-lincomycin): $R^2$ = OH
**1-24** (7*S*)-7-*O*-Methyllincomycin: $R^2$ = OMe
**1-25** (7S)-7-Deoxy-7-phenylthiolincomycin: $R^2$ = SPh

Figure 1-3. Chemical structures of a variety of reported analogs of lincomycin (1).

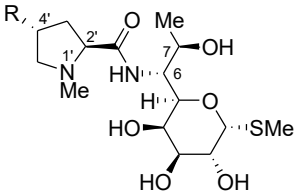
On the other hand, both (7*S*)-7-deoxy-7-thiolincomycin (**1-20)** and (7*R*)-7-deoxy-7-thiolincomycin (**1-15)** showed only 10% activity as compared with LCM. (7*S*)-7-Alkylthio-7-deoxylincomycin (e.g.: alkylthio = methylthio, ethylthio, *n*-propylthio and so on) and (7*S*)-7-substituted alkylthio-7-deoxylincomycin (e.g.: substituted alkylthio = 2-hydroxyethylthio)[48-52] were more active than LCM against Gram-positive or Gram-negative organisms, and (7*R*)-7-deoxy-7-imidazol-2-yl-thiolincomycin (**1-19)**, which had been reported by Sztaricskai and Ōmura *et al.*,[53] retained the same order of magnitude of antibacterial activities against tested organisms as those of LCM. Antibacterial activities were affected by both configuration and a structure of a substituent at the 7-position. (7*S*)-7-Deoxy-7-phenylthiolincomycin (**1-25)** was reported by Bannister *et al*., but no antibacterial activity of this compound was reported.[52] (Figure 1-3)

Chemical modification of a proline moiety at the C-6 position of LCM and CLDM was performed by several research groups, as shown in Figure 1-4.[37,45,54-58] This portion has the following features. (1) Regarding configuration between the 2'- and 4'-positions of a proline ring, an analog with *trans* configuration exhibited more potent antibacterial activity compared with one with *cis* configuration. (2) Althogh 4'-depropyl-3'-propyllincomycin has not been synthesized, 4'-depropyl-5'-propyllincomycin has already been synthesized, whose antibacterial activity is weaker than that of LCM. (3)

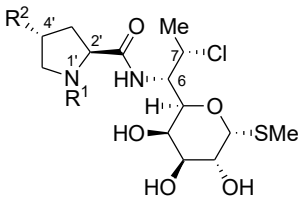
1’-Demethylclindamycin (Figure 1-4) was twice as active *in vitro* against *Sarcina lutea* as CLDM, but 1’-demethyllincomycin was about one twentieth as active as LCM (relative potency against *S. lutea*: 1’-demethylclindamycin (**1-27**) : CLDM (**1-7**) : LCM (**1-6**) : 1’-demethyllincomycin (**1-26**) = 8 : 4 : 1 : 0.05).[42,54-55] 1’-Demethyl-1’-*N*-ethyllincomycin possessed the same activity as LCM.



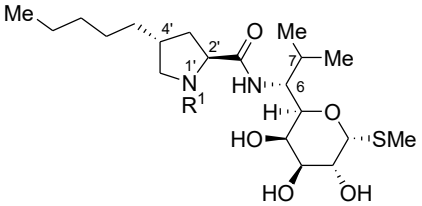
**1-26** 1'-Demethyllincomycin:
$R^1$ = OH, $R^2$ = H, $R^3$ = H
**1-27** 1'-Demethylclindamycin:
$R^1$ = H, $R^2$ = Cl, $R^3$ = H



**1-28** 4'-Substituted lincomycins: R = H, Me to $^n$octyl
**1-29** 4'-Depropyl-4'-ethoxylincomycin: R = ethoxy
**1-30** 4'-Depropyl-4'-ethoxycarbonylmethyllincomycin:
R = ethoxycarbonylmethyl
**1-31** 4'-Depropyl-4'-*p*-toluenesulfonyloxylincomycin:
R = *p*-toluensulfonyloxy



**1-32** 4'-Depropyl-4'-$^n$pentylclindamycin:
$R^1$ = Me, $R^2$ = $^n$pentyl
**1-33** 1'-Demethyl-4'-depropyl-4'-$^n$pentylclindamycin:
$R^1$ = H, $R^2$ = $^n$pentyl

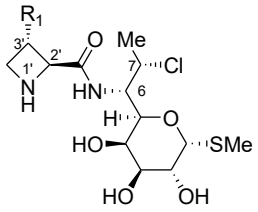


**1-34** VIC105403: $R^1$ = H
**1-35** VIC105404: $R^1$ = 2-hydroxyethyl
**1-36** VIC105405: $R^1$ = 2-(*R*)-hydroxypropyl
**1-37** VIC105446: $R^1$ = 2-(*S*)-hydroxypropyl

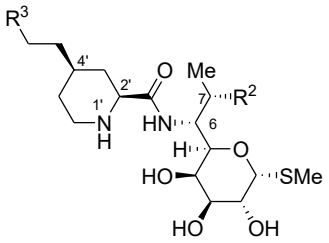
Figure 1-4. Chemical structures of a variety of reported analogs of lincomycin (2).

(4) Regarding SAR of a chain length (H, Me to *n*-octyl) at the 4’-position (**1-28**) of the proline moiety at the 6-position of LCM (Figure 1-4), the *in vitro* antibacterial activities were enhanced until reaching a maximum at the hexyl analog.[42] A similar *in vivo* activity was indicated, but maximum effect was exhibited by an *n*-pentyl group. Furthermore, alternative *in vitro* SAR were observed by changing a chain length for a 4’-alkyl-substituent of CLDM and a 4’-alkyl-substituent of 1’-demethylclindamycin (relative potency: 4’-depropyl-4’-*n*-pentylclindamycin (**1-32**) > CLDM (**1-7**), 1’-demethyl-4’-depropyl-4’-*n*-pentylclindamycin (**1-33**) > 1’-demethylclindamycin (**1-27**)).[42,56] However, antibacterial activities of those compounds against resistant pathogens with *erm* gene were not disclosed. (5) 4’-Depropyl-4’-ethoxylincomycin (**1-29**) had only about 2% antibacterial activities of LCM, and 4’-depropyl-4’-ethoxycarbonylmethyllincomycin (**1-30**) and 4’-depropyl-4’-*p*-toluenesulfonyloxylincomycin (**1-31**) were essentially inactive in antibacterial testing.[37,42,57] (Figure 1-4) On the other hand, Vicuron Co., which was consolidated by Pfizer Inc., reported the following compounds. VIC 105403 (**1-34**) (Figure 1-4),[45] possessing 1’-demethyl, 4’-*n*-pentyl and 7-methyl group, had potent activities compared with CLDM. VIC 105404 (**1-35**),[45] possessing

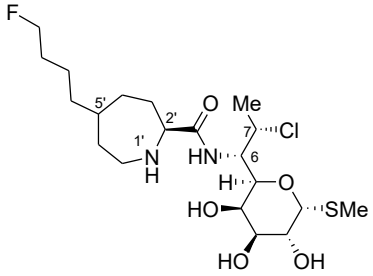
1'-*N*-(2-hydroxyethyl), 4'-*n*-pentyl and 7-methyl group, was already reported to have potent antibacterial activities as VIC 105403 (**1-34**). However, those did not show antibacterial activities against resistant pathogens with *erm* gene. Furthermore, VIC 105405 (**1-36**) and VIC 105446 (**1-37**),[45] having a branched side chain at the 1'-position, showed less antibacterial activities than CLDM. Other VIC compounds possessing a branched side chain, a 3-(pyridin-4-yl)propyl or an *n*-butylthio group at the 4'-position, were already synthesized but their antibacterial activities were not disclosed in their patent.[58] As another background information on chemical modifications at the C-6, azetidine,[58-61] piperidine[58,59,62-64] and azepane analogs[58,59] were synthesized accompanied with modifications at the C-7. Regarding azetidine analogs, 3'-*trans*-cyclobutylethyl azetidine analog (**1-38**) (Figure 1-5) showed significant antibacterial activities against sensitive *S. pneumoniae* compared with CLDM, but 3'-*trans*-cyclopropylmethyl (**1-39**), 3'-*trans*-*n*-propyl (**1-40**) and 3'-*trans*-*n*-butyl (**1-41**) azetidine analogs exhibited similar potency as CLDM. As a piperidine analog, 4'-*cis*-ethyl analog, pirlimycin (**1-42**), is used in mastitis therapy for cattle in the EU and US. On the other hand, VIC-105555 (**1-43**) was selected as a candidate, which exhibited preferable pharmacokinetics and characteristic *in vitro* antibacterial activities against MRSA and *Enterococcus faecalis*. Furthermore, azepane-type analogs were synthesized and 5'-(4-fluorobutyl) analog (**1-44**) was 32 times as active (MIC: 0.25 μg/mL) against *H. influenzae* as CLDM (MIC: 8 μg/mL).[58] (Figure 1-5) None of the C-6 modified compounds were disclosed to possess activities against Gram-positive resistant bacteria with *erm* gene. LCM analogs might be clinically more valuable than ketolide antibiotics, if they are effective against Gram-positive pathogens with *erm* gene.




**1-38** 3'-*trans*-Cyclobutylethyl azetidine analog: $R^1$ = 3'-cyclobutylethyl
**1-39** 3'-*trans*-Cyclopropylmethyl azetidine analog: $R^1$ = 3'-cyclopropylmethyl
**1-40** 3'-*trans*-$^n$Propyl azetidine analog: $R^1$ = 3'-$^n$propyl
**1-41** 3'-*trans*-$^n$Butyl azetidine analog: $R^1$ = 3'-$^n$butyl




**1-42** Pirlimycin: $R^2$ = Cl; $R^3$ = H
**1-43** VIC-105555: $R^2$ = $R^3$ = Me




**1-44** 5'-(4-Fluorobutyl)azepane analog

Figure 1-5. Derivatives of methyl α-thiolincosaminide, Pirlimycin and VIC-105555.

An outline of the author's research program and chemical modification is shown in Figure 1-6. The author focused (7*S*)-configuration and X-ray crystallographic analysis of CLDM. Especially, X-ray analysis indicated that there is a three-dimensional space around the C-7 position of CLDM. So, the author hypothesized that antibacterial activities against resistant pathogens could be enhanced by occupying its three-dimensional space with a hetero ring *via* sulfur atom at the C-7 position of LCM. First, the author prepared 2,3,4-tri-*O*-trimethylsilyllincomycin as key intermediate in the 2 steps from LCM and then, the author prepared novel LCM analogs possessing (7*S*)-configuration by Mitsunobu reaction from the key intermediate. Consequently, novel LCM analogs in the Chapter 2, having 6-aminobenzothiazol-2-yl (**2-17**), 4-(methoxycarbonyl)phenyl (**2-29**), 5-amino-1,3,4-thiadiazol-2-yl (**2-31**), 5-phenyl-1,3,4-thiadiazol-2-yl (**2-37**) and 5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-yl (**2-41**) at the C-7 position *via* sulfur atom, showed weak antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. For the purpose of improving antibacterial activities, the author synthesized novel LCM analogs possessing NH-CO-R or CO-$NR_2$ groups at the *p*-position on the phenyl group at C-7 position in Chapter 3. As a result, antibacterial activities of novel LCM analogs having a morpholinocarbonyl group at the *p*-position on the phenyl group (**3-18**) were improved against *S. pneumoniae* with *erm* gene and *H. influenzae*. On the other hand, LCM analogs having a (2*S*)-(methoxymethyl)pyrrolidine-1-carbonyl group (**3-21**) and a (2*S*)-(dimethylaminomethyl)pyrrolidine-1-carbonyl group (**3-22**) also exhibited potent antibacterial activities ageinst *S. pneumoniae* with *erm* gene. In order to investigate these results, the author performed docking simulation analysis using compound (**3-18**) with bacterial 23S rRNA of *Haloarcula marismortui*. Its analysis indicated that carbonyl oxygen has hydrogen bonding with U2620Hm, and ethylene of a morpholine has hydrophobic interaction by CH-π stacking with uracil of U2621Hm. Next, the author synthesized novel LCM analogs having basicity at the *p*-position on the phenyl group *via* sulfer atom at the C-7 position in Chapter 4 (Figure 1-6). Consequently, pyridine-3-yl analog (**4-17**), pyrimidin-5-yl analog (**4-31**) and 1-methyl-piperidin-3-yl analog (**4-38**) (diastereo mixture) showed potent antibacterial activities against resistant pathogens with *erm* gene, respectively. The author modified the 1'-portion in the C-6 moiety of (7*S*)-heteroarylthio-substituted LCM analogs in Chapter 5. As a result, it was difficult to enhance antibacterial activities by substitution at the 1'-position with a relatively larger group than a methyl group. Then, the author additionally modified the 4'-position in the C-6 moiety of (7*S*)-7-(5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl)thio-substituted LCM analogs. Consequently, compounds **5-53**~**5-56**) possessing an *n*-pentyl group instead of an *n*-propyl group significantly enhanced antibacterial activities against resistant bacteria with *erm* gene. The author fixed 4-(pyrimidin-5-yl)phenyl group as the substituent at the C-7 position with (7*S*)-configuration and performed chemical modification at the C-6 position of LCM in Chapter 6. Compound **6-46** and **6-75** possessing a (2'*S*, 4'*R*)-4'-cyclopropylmethylpiperidine-2'-carbonyl group at the C-6 position showed significant antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene and *H. influenzae*. *In vivo* efficacy of these two selected compounds, 6-46 (1'-*N*H) and 6-75 (1'-*N*Me), were investigated by pulmonary infection model

(subcutaneous administration) in mice. These compounds showed significantly potent *in vivo* efficacy reflecting *in vitro* potency and hence these compounds were selected as candidates for development.

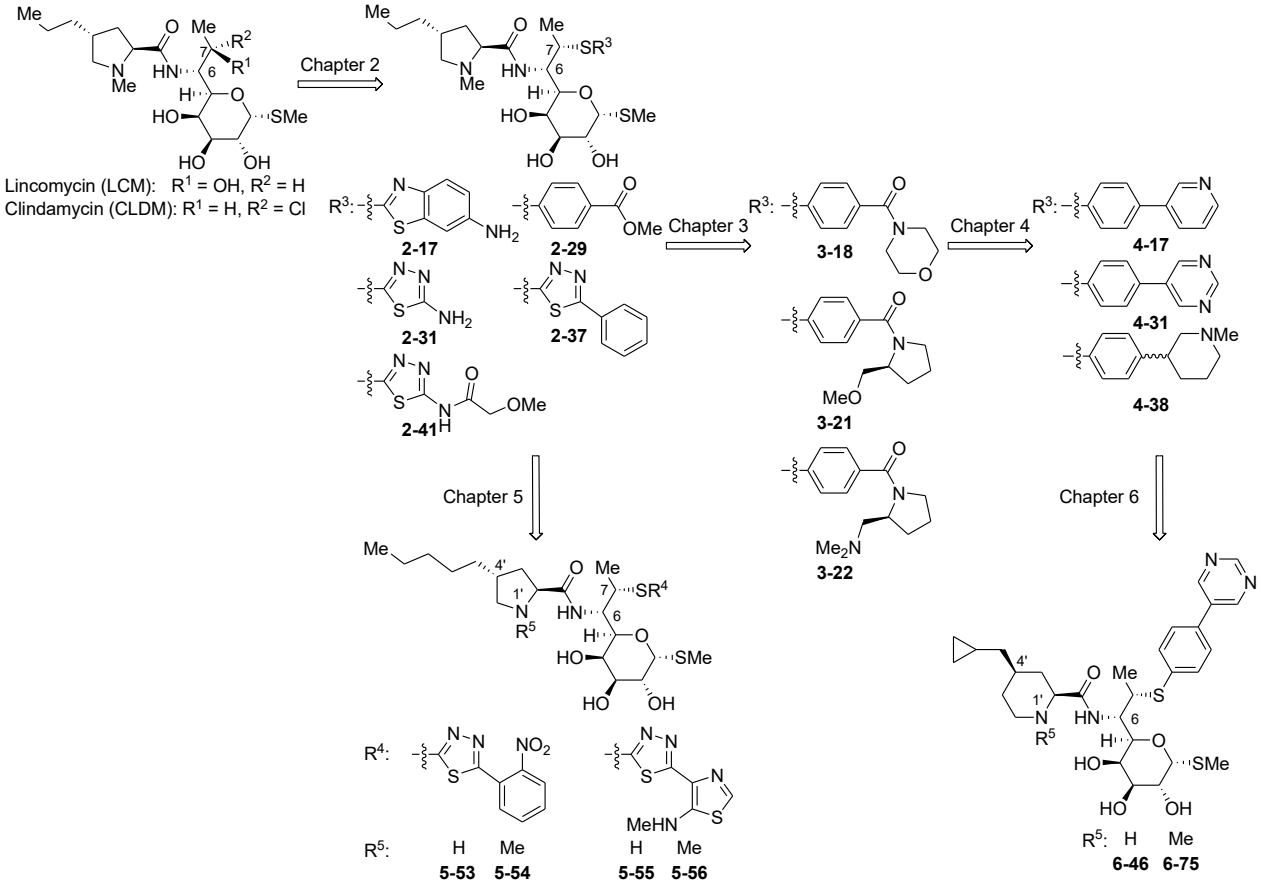



Figure 1-6. Outline of the author's research described in this manuscript.

# 2. Design, synthesis and structure-activity relationship analysis of novel (7*S*)-substituted-lincomycin (LCM) derivatives

## 2.1. Design, synthesis and structure-activity relationship analysis of novel LCM derivatives

### 2.1.1. Design and synthesis of novel (7*S*)-7-arylthio-7-deoxylincomycin derivatives

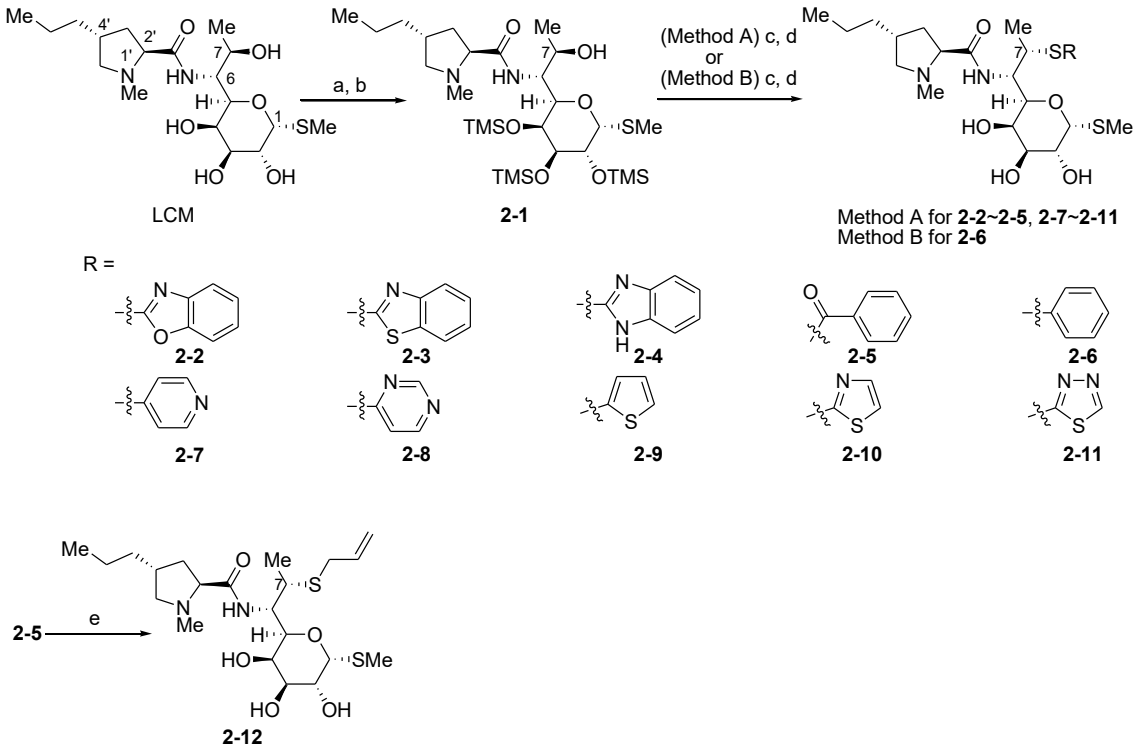
CLDM possessing a simple structure has antibacterial activity against both susceptible strains and resistant strains with *mef* gene, and exhibits acceptable oral absorption in human. However, CLDM is not effective enough against resistant bacteria of *S. pneumoniae* or *S. pyogenes* with *erm* gene. So, a novel oral lincomycin analog, which is effective against resistant bacteria with *erm* gene and/or *mef* gene and does not have any problems in safety, taste, or pharmacokinetics, is strongly desired for treatment of respiratory infections in clinical sites.

(7*R*)-7-azido-7-deoxylincomycin (**1-12**), CLDM (**1-7**), (7*S*)-7-bromo-7-deoxylincomycin (**1-21**) and (7*S*)-7-alkylthio-7-deoxylincomycin (e.g.: alkylthio = methylthio, ethylthio and *n*-propyl) had the same or stronger antibacterial activity compared with LCM. According to the relationships between configuration and a substituent ((7*S*)-Cl (**1-7**) > 7(*R*)-Cl (**1-16**) and (7*S*)-OMe (**1-24**) > 7(*R*)-OMe (**1-16**)), enhancement of activities in (7*S*)-configuration might require a hydrophobic substituent such as a chlorine atom or a methyl group, not as OH or SH ((7*S*)-OH < (7*R*)-OH (LCM), (7*S*)-SH ≈ (7*R*)-SH < LCM). Bulky alkoxy groups and substituted alkoxy groups with (7*S*)-configuration resulted in weaker antibacterial activities than those of LCM, while (7*S*)-7-alkylthio-7-deoxylincomycin was more active than LCM against Gram-positive organisms. As a result, a sulfur atom might be better than an oxygen atom at the 7-position for enhancing antibacterial activities. 7(*R*)-7-Deoxy-7-imidazol-2-yl-thiolincomycin (**1-19**) had the same antibacterial activity as LCM. Thus, the author was interested in derivatives with a heterocyclic ring introduced *via* sulfur atom at the C-7 position with (7*S*)-configuration.

The results of X-ray crystallographic analysis[5-7] have already been reported in application of CLDM. According to three dimensional information around the 7-position of CLDM, it was hypothesized that CLDM had enough 3D space around the 7-position and it might be able to generate unreported antibacterial activity against respiratory infection-related Gram-positive bacteria with *erm* gene by filling the space with an appropriate substituent. So, the author designed (7*S*)-LCM derivatives possessing a hydrophobic heterocyclic ring *via* sulfur atom and practically synthesized (7*S*)-7-arylthio-7-deoxylincomycin by Mitsunobu reaction.

Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives is outlined in Scheme 2-1. The author prepared a key intermediate **2-1**[65] derived from LCM in 2 steps, in order to construct the same configuration at the 7-position as CLDM in final target molecules. The author's synthesis began with silylation of all OH

groups of LCM, and the 7-*O*-TMS group was selectively deprotected by AcOH to give the key intermediate (**2-1**) with an excellent yield. LCM derivatives (**2-2**~**2-5** and **2-7**~**2-11**), which possess a heterocyclic ring at the C-7 position *via* sulfur atom, were synthesized from **2-1** with the corresponding thiol under the Mitsunobu reaction conditions (Method A).[66,67] Compound **2-6**[52] possessing a phenylthio group was synthesized by Method B in application of the corresponding disulfide. Furthermore, compound **2-12**[52] was prepared by allylation of **2-5** under the NaOMe condition to investigate SAR of an allyl group.




Scheme 2-1. Synthesis of (7S)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) TMSCl, HMDS, Py, r.t., 2 h, 90.7%; b) 80% AcOH, MeOH, r.t., 16 h, 90.7%; Method A: c) $PPh_3$, DEAD, the corresponding HSR, THF or toluene, 0°C to r.t., 16-24 h; d) 1-2 N HCl, MeOH, r.t., 30 min, 71.0% in 2 steps (**2-2**), 79.2% in 2 steps (**2-3**), 76.1% in 2 steps (**2-4**), 23.7% in 2 steps (**2-5**), 40.2% in 2 steps (**2-7**), 49.7% in 2 steps (**2-8**), 10.0% in 2 steps (**2-9**), 6.98% in 2 steps (**2-10**), 62.0% in 2 steps (**2-11**); Method B: c) $P^nBu_3$, DEAD, the corresponding Ar-S-S-Ar, THF, 0°C to r.t., 26 h; d) 2 N HCl, r.t., 30 min, 90.5% in 2 steps (**2-6**); e) NaOMe, allyl iodide, MeOH, r.t., 14 h, 30.0% (**2-12**).

Next, bacteria strains, their characteristics and their abbreviated notation are shown in Table 2-1. Evaluated bacteria strains include *Streptococcus pneumoniae* (*S. pneumoniae*), *Streptococcus pyogenes* (*S. pyogenes*) and *Haemophilus influenzae* (*H. influenzae*). *S. pneumoniae*-6 is constitutive resistant *S. pneumoniae* with both methylase produced by *erm* gene and efflux pump activated by *mef* gene. Constitutive resistant strains mean constitutive resistant strain always produces methylase by *erm* gene without contact of drugs such as erythromycin and these strains have high resistant abilities for drugs of macrolide–lincosamide-streptogramin B ($MLS_B$). *S. pneumoniae*-7 is inducible resistant *S. pneumoniae* and inducible resistant strains mean relatively weak resistant strains producing methylase by *erm* gene contacting

with drugs such as erythromycin. Structures of control drugs and their antibacterial activities (minimum inhibitory concentration (MIC), μg/mL) are shown in Figure 1-1 and 1-2 and Table 2-2, respectively.

Table 2-1. Test organisms, characteristics, and the abbreviated notation in Table of antibacterial activities.

| | | abbreviated notation in Table of antibacterial activities | |
|---|---|---|---|
| Test organism* | Characteristics | Test organism* | Characteristics |
| *Streptococcus pneumoniae* DP1 TypeI | susceptible | *S. pneumoniae* DP1 TypeI | s |
| *Streptococcus pneumoniae* -2 | susceptible | *S. pneumoniae* -2 | s |
| *Streptococcus pneumoniae* -3 | susceptible | *S. pneumoniae* -3 | s |
| *Streptococcus pneumoniae* -4 | *ermAM* methylase (constitutive resistant) | *S. pneumoniae* -4 | *ermAM* (c) |
| *Streptococcus pneumoniae* -5 | *ermAM* methylase (constitutive resistant) | *S. pneumoniae* -5 | *ermAM* (c) |
| *Streptococcus pneumoniae* -6 | *ermAM* methylase (constitutive resistant) + *mefE* | *S. pneumoniae* -6 | *ermAM* (c) + *mefE* |
| *Streptococcus pneumoniae* -7 | *ermAM* methylase (inducible resistant) | *S. pneumoniae* -7 | *ermAM* (i) |
| *Streptococcus pneumoniae* -8 | *ermAM* methylase (inducible resistant) | *S. pneumoniae* -8 | *ermAM* (i) |
| *Streptococcus pneumoniae* -9 | *mefE* efflux | *S. pneumoniae* -9 | *mefE* efflux |
| *Streptococcus pyogenes* Cook | susceptible | *S. pyogenes* Cook | s |
| *Streptococcus pyogenes* -2 | *ermAM* methylase (constitutive resistant) | *S. pyogenes* -2 | *ermAM* (c) |
| *Streptococcus pyogenes* -3 | *mefE* efflux | *S. pyogenes* -3 | *mefE* efflux |
| *Haemophilus influenzae* | susceptible | *H. influenzae* | s |
| *Haemophilus influenzae* -2 | susceptible | *H. influenzae* -2 | s |
| *Haemophilus influenzae* -3 | susceptible | *H. influenzae* -3 | s |
| *Haemophilus influenzae* -4 | ⊿acr | *H. influenzae* -4 | ⊿acr |

*All strains except standard organisms were clinically isolated.; Gray shading strains are target strains.

Table 2-2. Antibacterial activities (MIC, μg/mL) of CAM, AZM, TEL, LCM and CLDM.

| Test organism* | Characteristics** | CAM | AZM | TEL | LCM | CLDM |
|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.06 | ≦0.008 | 1 | 0.06 |
| *S. pneumoniae* -2 | s | 0.03 | 0.03 | ≦0.008 | 1 | 0.12 |
| *S. pneumoniae* -3 | s | 0.015 | 0.03 | ≦0.008 | 0.25 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | >128 | >128 | 0.5 | >128 | >128 |
| *S. pneumoniae* -5 | *ermAM* (c) | >128 | >128 | 2 | >128 | >128 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | >128 | >128 | 1 | >128 | >128 |
| *S. pneumoniae* -7 | *ermAM* (i) | >128 | >128 | 0.03 | 128 | 128 |
| *S. pneumoniae* -8 | *ermAM* (i) | >128 | >128 | 0.03 | 128 | 128 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.5 | 0.5 | 0.06 | 1 | 0.12 |
| *S. pyogenes* Cook | s | 0.015 | 0.06 | ≦0.008 | 0.12 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | >128 | >128 | 16 | >128 | 128 |
| *S. pyogenes* -3 | *mefE* efflux | 8 | 8 | 0.25 | 0.25 | 0.12 |
| *H. influenzae* | s | 2 | 0.25 | 0.5 | 8 | 16 |
| *H. influenzae* -2 | s | 4 | 1 | 2 | 16 | 8 |
| *H. influenzae* -3 | s | 8 | 2 | 1 | 16 | 16 |
| *H. influenzae* -4 | ⊿acr | 0.5 | 0.5 | 0.25 | 4 | 1 |

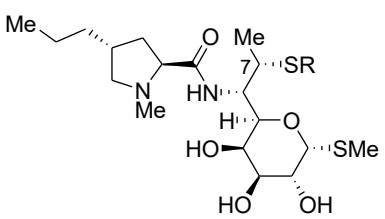
*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible; Gray shading strains are target strains.

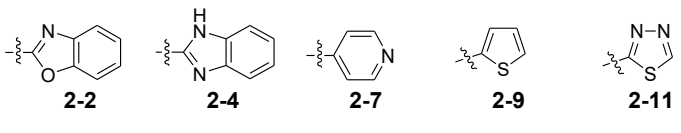
## 2.1.2. SAR analysis of LCM derivatives possessing a heterocycle at the C-7 position *via* sulfur atom

Antibacterial activity of LCM derivatives **2-2**~**2-4** and **2-6**~**2-12**, which possesses a heterocyclic ring, the benzene ring, or an allyl group at the C-7 position *via* sulfur atom, is shown in Table 2-3. Compound **2-2** was shown to be slightly more potent against *H. influenzae* than CLDM. Compound **2-3** had weak activity against *S. pyogenes* with *erm* gene, although CLDM did not have any activities against the pathogen. Derivatives possessing a phenyl, thienyl, or 1,3,4-thiadiazolyl group at the 7 position did not exhibit remarkable activity against *S. pyogenes* with *erm* gene.

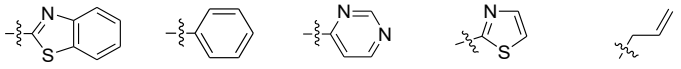
It was hypothesized that occupation of a space around the C-7 position might enhance antibacterial activities against resistant *S. pyogenes* with *erm* gene. Thus, the author selected **2-3** as a fundamental bicycle framework for further optimization. Additionally, **2-6** and **2-11** were selected as general examples of an isolated 6-membered ring and an isolated 5-membered ring, respectively. Next, the author tried to enhance antibacterial activities by introducing a substituent to the selected three frameworks and their synthesis and structure-activities relationship analysis are shown in Chapters 2.2, 2.3 and 2.4, respectively.

Table 2-3. Antibacterial activities (MIC, μg/mL) of (7*S*)-7-thio-substituted derivatives.




R = 

**2-2** **2-4** **2-7** **2-9** **2-11**



**2-3** **2-6** **2-8** **2-10** **2-12**

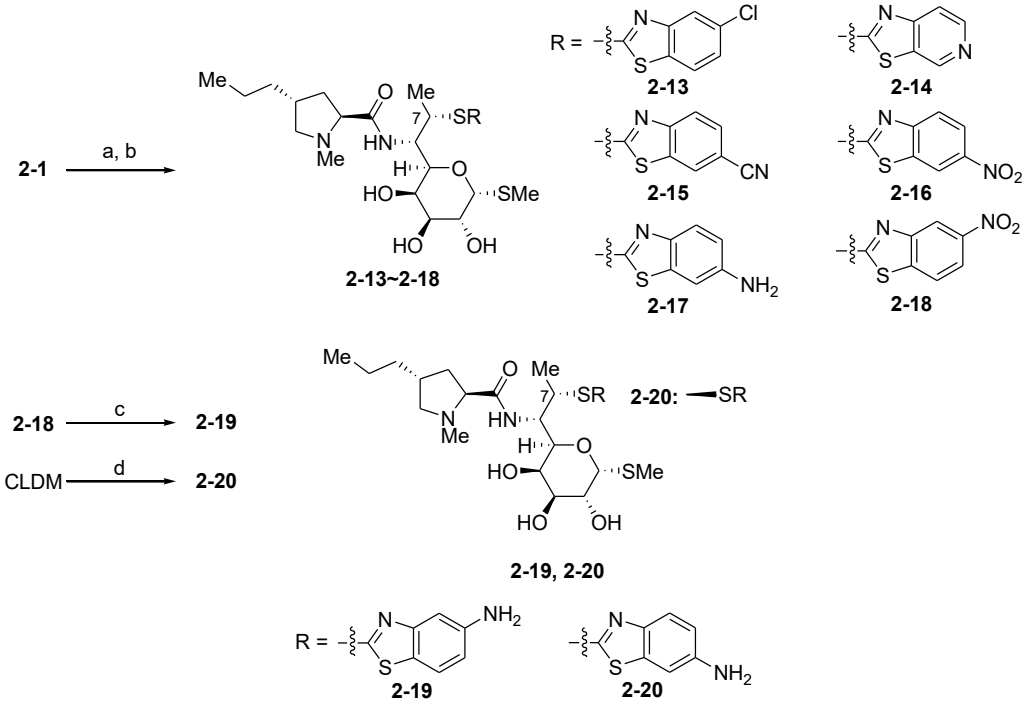
| Test organism* | Characteristics** | CLDM | **2-2** | **2-3** | **2-4** | **2-6** | **2-7** | **2-8** | **2-9** | **2-10** | **2-11** | **2-12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.06 | 0.06 | 0.25 | 0.06 | 0.25 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 |
| *S. pneumoniae* -2 | s | 0.12 | 0.06 | 0.25 | 0.12 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 |
| *S. pneumoniae* -3 | s | 0.06 | 0.06 | 0.25 | 0.03 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | >128 | 128 | 128 | >128 | 128 | >128 | >128 | 128 | >128 | 128 | >128 |
| *S. pneumoniae* -5 | *ermAM* (c) | >128 | >128 | 128 | >128 | 128 | >128 | >128 | 128 | 128 | 128 | >128 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | >128 | >128 | 128 | >128 | 128 | >128 | >128 | 128 | >128 | 128 | >128 |
| *S. pneumoniae* -7 | *ermAM* (i) | 128 | >128 | 128 | >128 | 128 | 128 | >128 | 128 | 64 | 128 | 128 |
| *S. pneumoniae* -8 | *ermAM* (i) | 128 | 64 | 128 | >128 | 128 | 128 | >128 | 128 | 64 | 128 | >128 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.12 | 0.06 | 0.25 | 0.03 | 0.12 | 0.06 | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 |
| *S. pyogenes* Cook | s | 0.06 | 0.03 | 0.12 | 0.03 | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 | 0.06 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | 128 | 64 | 16 | 64 | 128 | 64 | 64 | 64 | 128 | 128 | >128 |
| *S. pyogenes* -3 | *mefE* efflux | 0.12 | 0.06 | 0.25 | 0.12 | 0.12 | 0.25 | 0.25 | 0.25 | 0.12 | 0.25 | 0.12 |
| *H. influenzae* | s | 16 | 8 | 64 | 32 | 16 | 32 | 32 | 32 | 64 | 16 | 16 |
| *H. influenzae* -2 | s | 8 | 4 | 16 | 32 | 8 | 8 | 16 | 8 | 32 | 16 | 8 |
| *H. influenzae* -3 | s | 16 | 16 | 64 | 64 | 32 | 32 | 64 | 64 | 128 | 32 | 32 |
| *H. influenzae* -4 | ⊿acr | 1 | 0.5 | 2 | 1 | 0.5 | 1 | 2 | 0.5 | 1 | 1 | 1 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible; Gray shading strains are target strains.

## 2.2. Synthesis and SAR analysis of LCM derivatives possessing a substituted benzothiazolyl group at the C-7 position *via* sulfur atom

### 2.2.1. Synthesis of substituted benzothiazole derivatives

Synthesis of substituted benzothiazole derivatives are outlined in Scheme 2-2. Substituted benzothiazole derivatives (**2-13**~**2-18**) are prepared by the similar procedure as described for preparation of compound **2-2**. As a part of chemical modification of the benzothiazole group, **2-19** was also prepared by reduction of the nitro group of **2-18** using $SnCl_2 \cdot H_2O$-$NaBH_4$. Next, **2-20** was synthesized by $S_N2$ reaction of CLDM with the corresponding thiol under the basic condition to confirm the effect on antibacterial activity by configuration at the C-7 position.

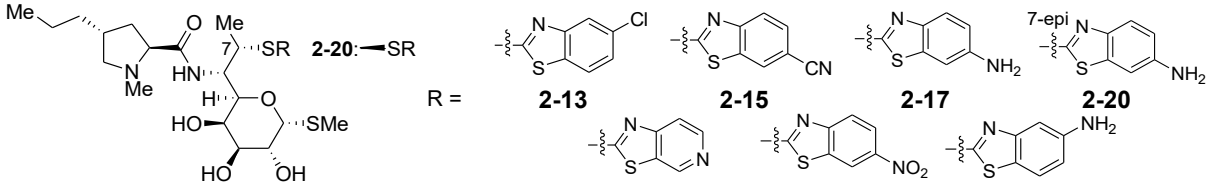



Scheme 2-2. Synthesis of (7*S*)-7-benzothiazolylthio-7-deoxylincomycin derivatives. Conditions: a) $PPh_3$, DEAD, the corresponding HS-Ar, THF or toluene, 0°C to r.t., 3-20 h; b) 1-2 N HCl, MeOH, r.t., 30 min, 73.2% in 2 steps (**2-13**), 72.0% in 2 steps (**2-14**), 65.9% in 2 steps (**2-15**), 66.1% in 2 steps (**2-16**), 67.1% in 2 steps (**2-17**), 45.1% in 2 steps (**2-18**); c) $SnCl_2 \cdot H_2O$, $NaBH_4$, EtOH, r.t., 3 h, 48.0%; d) 6-aminobenzo[*d*]thiazole-2-thiol, $K_2CO_3$, DMF, 100°C, 16 h, 40.9%.

## 2.2.2. SAR analysis of LCM derivatives possessing a benzothiazol-2-ylthio group at the 7-position

LCM derivatives having a benzothiazoyl or a thiazoropyridinyl group at the 7-position were synthesized and their antibacterial activities are shown in Table 2-4. Notably, conversion of **2-3** to **2-13**, **2-16**, or **2-17** at the 7-position improved antibacterial activity against *S. pneumoniae* with *erm* gene. Especially, antibacterial activity of **2-17** was significantly enhanced. An amino group might play a role to enhance antibacterial activity, and may interact with a certain binding site on 23S *r*RNA. Compound **2-19** possessing an amino group at the 5-position in the benzothiazole ring generally exhibited improved antibacterial activity against *S. pneumoniae* with *erm* gene compared with **2-3**. On the other hand, the author prepared **2-20** possessing the (*R*)-configuration at the 7-position to confirm its potency. Based on comparison of antibacterial activities of compound **2-20** to those of compound **2-17**, the author found that (*S*)-configuration at the 7-position was important for potent antibacterial activities.

Table 2-4. Antibacterial activities (MIC, μg/mL) of LCM derivatives possessing a substituted benzothiazol-2-ylthio group at the 7-position.



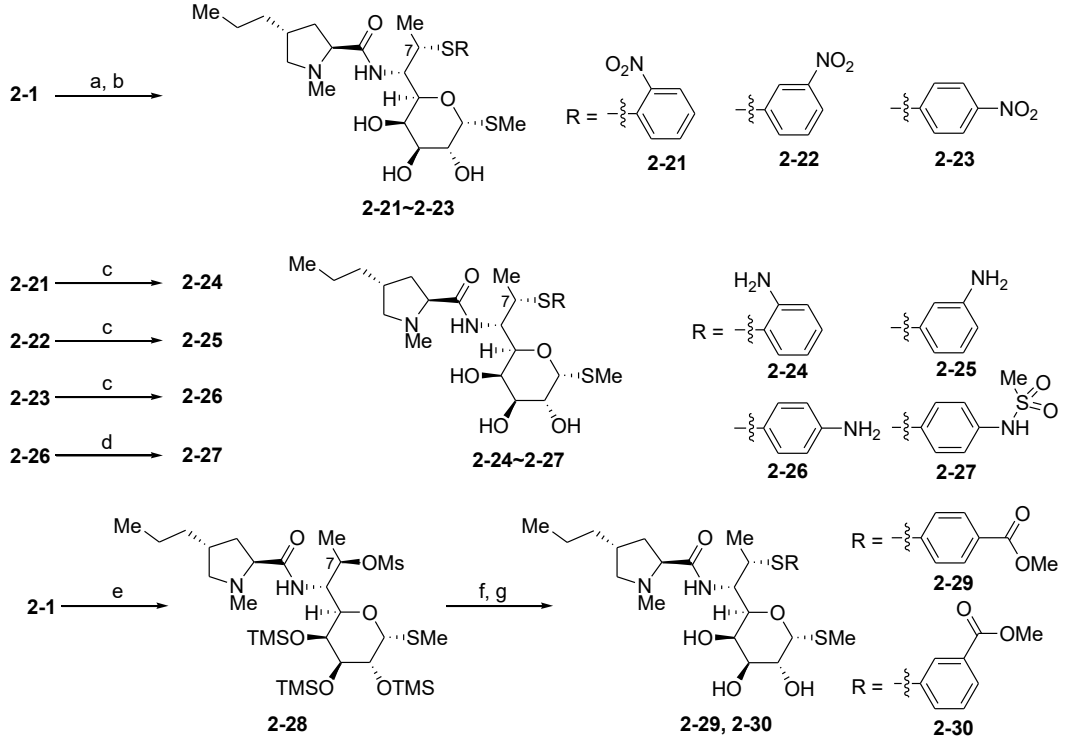

| Test organism* | Characteristics** | **2-13** | **2-14** | **2-15** | **2-16** | **2-17** | **2-19** | **2-20** |
|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.12 | 0.12 | 0.25 | 0.06 | 0.06 | 0.12 | 0.03 |
| *S. pneumoniae* -2 | s | 0.12 | 0.12 | 0.25 | 0.06 | 0.06 | 0.12 | 0.03 |
| *S. pneumoniae* -3 | s | 0.12 | 0.12 | 0.12 | 0.03 | 0.03 | 0.06 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 64 | 64 | 128 | 64 | 8 | 32 | 32 |
| *S. pneumoniae* -5 | *ermAM* (c) | 32 | >128 | 128 | 64 | 32 | 64 | 32 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 64 | >128 | 128 | 64 | 64 | 128 | 64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 64 | 128 | 64 | 32 | 16 | 32 | 32 |
| *S. pneumoniae* -8 | *ermAM* (i) | 32 | 128 | 64 | 32 | 8 | 64 | 32 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.12 | 0.12 | 0.12 | 0.06 | 0.03 | 0.06 | 0.03 |
| *S. pyogenes* Cook | s | 0.12 | 0.06 | 0.12 | 0.06 | 0.03 | 0.06 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | 16 | 32 | 16 | 16 | 4 | 32 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | 0.25 | 0.12 | 0.25 | 0.06 | 0.06 | 0.12 | 0.06 |
| *H. influenzae* | s | 32 | 32 | 64 | 32 | 8 | 32 | 16 |
| *H. influenzae* -2 | s | 32 | 16 | 16 | 16 | 4 | 8 | 16 |
| *H. influenzae* -3 | s | 64 | 64 | 64 | 64 | 32 | 32 | 32 |
| *H. influenzae* -4 | ⊿acr | 2 | 1 | 1 | 0.25 | 0.25 | 0.5 | 0.5 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 2.3. Synthesis and SAR analysis of LCM derivatives possessing a substituted phenyl group at the C-7 position *via* sulfur atom

### 2.3.1. Synthesis of substituted phenyl derivatives

Next, the author pursued modification of LCM derivatives possessing a substituted phenyl group at the C-7 position *via* sulfur atom. These syntheses are outlined in Scheme 2-3. The nitrophenyl derivatives (**2-21**~**2-23**), which were synthesized under the Mitsunobu condition, were reduced to give the corresponding aminophenyl derivatives (**2-24**~**2-26**). Because compound **2-26** was the most potent compared to **2-24** or **2-25**, **2-26** was converted to compound **2-27**. On the other hand, Mitsunobu conditions had still problems, and thus compounds **2-21**, **2-23**, and **2-29** were synthesized in only low yields. So, compounds **2-23**, **2-29**, and **2-30** were synthesized by $S_N2$ reactions with the corresponding thiol in good yields under the basic conditions in application of a methanesulfonate **2-28** synthesized from **2-1**.



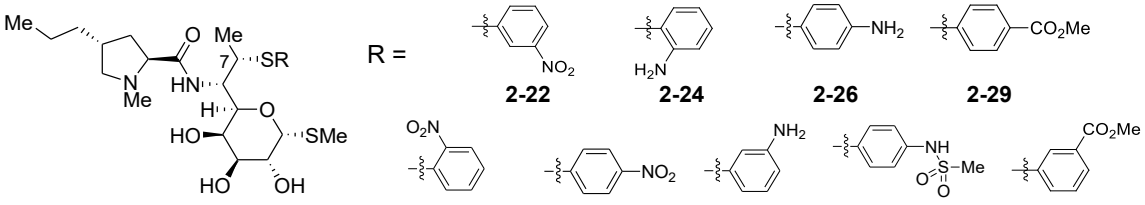

Scheme 2-3. Synthesis of (7*S*)-7-phenylthio-7-deoxylincomycin derivatives. Conditions: a) $PBu_3$, DEAD, the corresponding R-S-S-R, THF, 0°C to r.t., 10-25 h; b) 2 N HCl, r.t., 3.5 h, 22.7% in 2 steps (**2-21**), 41.7% in 2 steps (**2-22**), 16.8% in 2 steps (**2-23**); c) $SnCl_2{\cdot}H_2O$, $NaBH_4$, EtOH, r.t., 1-3 h, 28.9% (**2-24**), 16.2% (**2-25**), 34.7% (**2-26**); d) MsCl, TEA, DMF, r.t., 20 min, 29.0% (**2-27**); e) MsCl, TEA, $CHCl_3$, r.t., 3 h, 97.9% (**2-28**); f) the corresponding HS-Ar, $K_2CO_3$, DMF, 80°C, 3 h; g) 1 N HCl , MeOH, r.t., 2 h, 72.7% in 2 steps (**2-29**), 64.0% in 2 steps (**2-30**).

### 2.3.2. SAR analysis of LCM derivatives possessing a phenylthio group at the 7-position

Their antibacterial activities are shown in Table 2-5. The enhanced antibacterial activities by

introducing an amino (**2-17**) or a nitro group (**2-16**) as shown in Table 2-4 encouraged me to further explore SAR through introducing an amino or a nitro group at the *o*-, *m*-, and *p*-position on the phenyl ring. Unexpectedly, compounds **2-21**~**2-23**, **2-24**~**2-26** showed weaker antibacterial activities against resistant bacteria with *erm* gene than **2-16** or **2-17**. Among nitrophenyl and aminophenyl derivatives in Table 2-5, the *para*-amino derivative (**2-26**) exhibited relatively stronger activities against susceptible *S. pneumoniae and H. influenzae*. Conversion of the amino group to a methoxycarbonyl group (**2-26** to **2-29**) at the *p*-position on the phenyl ring improved antibacterial activities against bacteria with *erm* gene. Based on SAR analysis of compounds **2-21**~**2-23**, **2-24**~**2-26**, **2-29**, and **2-30**, *para*-substituted analogs exhibited relatively stronger antibacterial activities against resistant bacteria than *o*-substituted or *m*-substituted analogs. Furthermore, **2-27** possessing a methanesulfonyl group at the amino group of **2-26** exhibited the most potent antibacterial activity in the phenylthio derivatives, except some strains belonging to *S. pneumoniae* with *erm* gene. These results suggest that (i) it is important for a substituent to keep a specific size, length, and three dimensional direction for appropriate binding to *r*RNA, and (ii) there are several important hydrogen bondings with some functional moieties such as C=O, N=O, S=O or $NH_2$.

Table 2-5. Antibacterial activities (MIC, μg/mL) of LCM derivatives possessing a substituted phenylthio group at the 7-position.



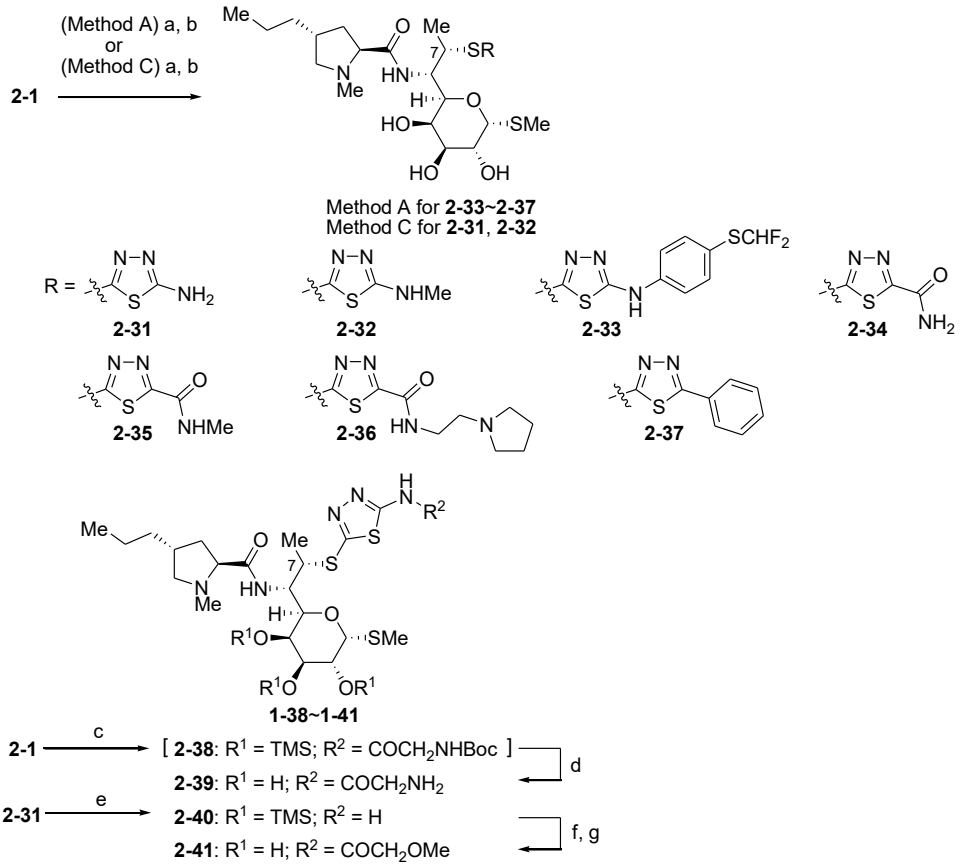

| Test organism* | Characteristics** | **2-21** | **2-22** | **2-23** | **2-24** | **2-25** | **2-26** | **2-27** | **2-29** | **2-30** |
|---|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 1 | 0.25 | 0.25 | 0.5 | 0.25 | 0.12 | 0.03 | 0.25 | 0.12 |
| *S. pneumoniae* -2 | s | 1 | 0.25 | 0.25 | 1 | 0.25 | 0.25 | 0.03 | 0.25 | 0.25 |
| *S. pneumoniae* -3 | s | 0.5 | 0.25 | 0.12 | 0.5 | 0.25 | 0.12 | 0.03 | 0.06 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | >128 | 128 | 128 | >128 | >128 | >128 | 64 | 32 | 128 |
| *S. pneumoniae* -5 | *ermAM* (c) | >128 | 128 | 128 | >128 | >128 | >128 | 128 | 64 | 128 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 128 | 128 | >128 | >128 | >128 | >128 | 128 | 128 | 128 |
| *S. pneumoniae* -7 | *ermAM* (i) | 128 | 128 | 128 | >128 | >128 | 128 | 16 | 32 | 128 |
| *S. pneumoniae* -8 | *ermAM* (i) | 128 | 128 | 128 | >128 | >128 | 128 | 16 | 32 | 128 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.5 | 0.25 | 0.12 | 0.25 | 0.25 | 0.06 | 0.03 | 0.06 | 0.06 |
| *S. pyogenes* Cook | s | 0.5 | 0.12 | 0.12 | 0.12 | 0.25 | 0.06 | 0.03 | 0.25 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | >128 | 128 | 128 | >128 | >128 | >128 | 8 | 32 | 32 |
| *S. pyogenes* -3 | *mefE* efflux | 1 | 0.25 | 0.25 | 0.25 | 0.25 | 0.12 | 0.03 | 0.25 | 0.25 |
| *H. influenzae* | s | >128 | 128 | 128 | 128 | 32 | 16 | 4 | 64 | 64 |
| *H. influenzae* -2 | s | 128 | 64 | 32 | 32 | 8 | 8 | 16 | 32 | 64 |
| *H. influenzae* -3 | s | >128 | 128 | >128 | >128 | 32 | 32 | 32 | 128 | 128 |
| *H. influenzae* -4 | ⊿acr | 64 | 1 | 1 | 2 | 1 | 0.5 | 0.25 | 1 | 1 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 2.4. Synthesis and SAR analysis of LCM derivatives possessing a substituted 1,3,4-thiadiazolyl group at the C-7 position *via* sulfur atom

### 2.4.1. Synthesis of substituted 1,3,4-thiadiazole derivatives

Synthesis of substituted 1,3,4-thiadiazole derivatives are outlined in Scheme 2-4. Substituted 1,3,4-thiadiazole derivatives (**2-31**~**2-37**) are prepared in application of the similar procedure (Method A) as described for preparation of compound **2-2** or Method C as the above. A Boc group and three TMS groups of **2-38** prepared by the Mitsunobu condition were simultaneously deprotected to give a desired compound **2-39**. TMS protection of **2-31** gave **2-40**, which was reacted with 2-methoxyacetyl chloride with TEA, and then deprotected to provide a methoxyacethyl derivative (**2-41**).

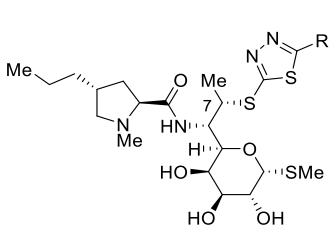



Scheme 2-4. Synthesis of (7*S*)-7-(1,3,4-thiadiazolyl)thio-7-deoxylincomycin derivatives. Conditions: Method A: a) $PPh_3$, DEAD, the corresponding HSR, THF or toluene, 0°C to 50°C, 17 h; b) 1-2 N HCl, MeOH, r.t., 30 min-1 h, 38.0% in 2 steps (**2-33**), 32.0% in 2 steps (**2-34**), 12.1% in 2 steps (**2-35**), 28.0% in 2 steps (**2-36**), 20.7% in 2 steps (**2-37**); Method C: a) $PPh_3$, DEAD, *tert*-butyl 5-mercapto-1,3,4-thiadiazol-2-ylcarbamate or *tert*-butyl 5-mercapto-1,3,4-thiadiazol-2-yl(methyl)carbamate, THF, 0°C to r.t., 17 h; b) TFA, r.t., 1 h, 55.4% in 2 steps (**2-31**), 71.3% in 2 steps (**2-32**); c) $PPh_3$, DEAD, *tert*-butyl 2-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-2-oxoethylcarbamate, THF, 0°C to r.t., 17 h, not isolated (**2-38**); d) TFA, r.t., 30 min, 24.2% (**2-39**); e) TMSCl, HMDS, Py, r.t., 2.5 h, 81.9% (**2-40**); f) 2-methoxyacetyl chloride, TEA, THF, 0°C, 2 h, 96.1%; g) 1 N HCl , MeOH, r.t., 2 h, 46.9% (**2-41**).

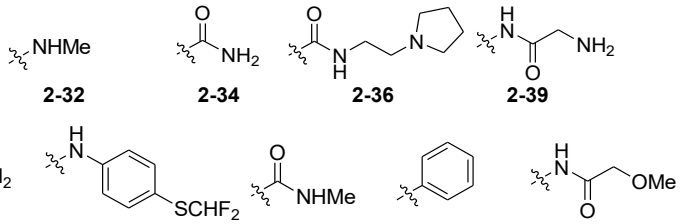
### 2.4.2. SAR analysis of LCM derivatives possessing a 1,3,4-thiadiazolylthio group at the 7-position

Next, the author pursued chemical modification of LCM derivatives possessing a substituted 1,3,4-thiadiazole at the C-7 position *via* sulfur atom and their antibacterial activities are shown in Table 2-6. The author could find several important functional moieties for improvement of activity so far. Then, the author firstly introduced an amino group on the 1,3,4-thiadiazole ring. Compound **2-31** exhibited improved activities against both resistant bacteria with *erm* gene and *H. influenzae* compared to **2-11**. The author synthesized several compounds **2-32**, **2-33**, **2-39** and **2-41**, which have an additional group introduced to the amino group of **2-31**. Compound **2-39** possessing a glycyl moiety as an aliphatic amine had weaker antibacterial activities than **2-31**. Conversion of the glycyl moiety to a methoxyacetyl moiety (**2-39** → **2-41**) improved antibacterial activities. Furthermore, derivatives **2-32** and **2-33** were synthesized and a difluoromethylthiophenyl analog (**2-33**) showed stronger activities against *S. pneumoniae* with *erm* gene than **2-31**. These results suggest that the phenyl moiety of **2-33** is an important group and it enhances antibacterial activities against resistant bacteria with *erm* gene. The author synthesized **2-37** in order to confirm this hypothesis. As expected, **2-37** showed relatively stronger antibacterial activities against bacteria with *erm* gene compared with **2-31**. Finally, the author was interested in conversion of a NH-CO bonding to a CO-NH bonding (**2-39** and **2-41** → **2-34**~**2-36**). Compound **2-36** also exhibited effective antibacterial activities against bacteria with *erm* gene. These results suggest that filling a space around the 7-position of LCM plays an important role to enhance antibacterial activities by hydrogen bonding, π-π stacking, or CH-π interaction to undefined binding site on 23S *r*RNA.

Table 2-6. Antibacterial activities (MIC, μg/mL) of LCM derivatives possessing a substituted 1,3,4-thiadiazolylthio group at the 7-position.



R =



| | | **2-31** | **2-32** | **2-33** | **2-34** | **2-35** | **2-36** | **2-37** | **2-39** | **2-41** |
|---|---|---|---|---|---|---|---|---|---|---|
| Test organism* | Characteristics** | **2-31** | **2-32** | **2-33** | **2-34** | **2-35** | **2-36** | **2-37** | **2-39** | **2-41** |
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.06 | 0.12 | 0.25 | 0.12 | 0.12 | 0.06 | 0.25 | 0.06 |
| *S. pneumoniae* -2 | s | 0.06 | 0.06 | 0.12 | 0.25 | 0.12 | 0.12 | 0.06 | 0.5 | 0.03 |
| *S. pneumoniae* -3 | s | 0.06 | 0.03 | 0.12 | 0.12 | 0.06 | 0.12 | 0.03 | 0.25 | 0.12 |
| *S. pneumoniae* -4 | *ermAM* (c) | 16 | 64 | 16 | 128 | 64 | 16 | 8 | 128 | 64 |
| *S. pneumoniae* -5 | *ermAM* (c) | 64 | 128 | 16 | >128 | 64 | 16 | 8 | >128 | 64 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 128 | N.D. | 32 | >128 | N.D. | 128 | 64 | >128 | 64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 16 | 32 | 8 | 128 | 32 | 8 | 8 | 128 | 8 |
| *S. pneumoniae* -8 | *ermAM* (i) | 16 | 16 | 2 | >128 | 32 | 16 | 8 | 128 | 8 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.03 | 0.03 | 0.12 | 0.25 | 0.12 | 0.12 | 0.06 | 0.25 | 0.06 |
| *S. pyogenes* Cook | s | 0.03 | 0.06 | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 | 0.25 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | 8 | 32 | 8 | 128 | 16 | 16 | 2 | 64 | 8 |
| *S. pyogenes* -3 | *mefE* efflux | 0.06 | 0.06 | 0.12 | 0.25 | 0.12 | 0.25 | 0.12 | 1 | 0.06 |
| *H. influenzae* | s | 8 | 8 | 16 | 64 | 8 | 32 | 16 | 64 | 32 |
| *H. influenzae* -2 | s | 4 | 8 | 8 | 64 | 8 | 64 | 8 | 64 | 16 |
| *H. influenzae* -3 | s | 8 | 16 | 32 | 64 | 32 | 128 | 32 | 128 | 32 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.5 | 0.25 | 2 | 0.5 | 2 | 0.5 | 4 | 0.5 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 2.5. Summary

With a purpose of generating new effective templates against bacteria, the author prepared the key intermediate **2-1**[65] derived from LCM with two steps to synthesize LCM analogs possessing the same configuration at the 7-position as CLDM in final target molecules. Our LCM derivatives were generally synthesized under Mitsunobu reaction conditions with the corresponding thiol from the key intermediate (**2-1**).

Compounds **2-17**, **2-31**, and **2-37** exhibited antibacterial activities against respiratory infection-related Gram-positive bacteria with *erm* gene, although CLDM did not have any activities against those pathogens. Furthermore, the author confirmed that (7*S*)-configuration was necessary for enhancing antibacterial activities on the basis of comparison results of configurations of **2-17** and **2-20**.[66-70] This work suggests that LCM derivatives may overcome resistant bacteria. SAR analysis, as indicated in this Chapter 2, would be useful for further medicinal chemistry in application of LCM derivatives.

# 3. Design, synthesis and structure-activity relationship analysis of novel (7*S*)-substituted-phenylthio-LCM

## 3.1. Design, synthesis and structure-activity relationship analysis of novel (7*S*)-7-deoxy-7-(substituted-phenylthio)lincomycin derivatives

### 3.1.1. Design of novel derivatives possessing a NH-CO or a CO-NH as substituent on phenyl group and accommodation of palladium-catalyzed cross-coupling reaction for novel lincomycin derivatives

The author had already reported synthesis and antibacterial activities of LCM derivatives possessing a hetero ring at the 7 position *via* sulfur atom with (7*S*)-configuration in Chapter 2. Among them, compounds **2-17**, **2-29**, **2-31** and **2-37** had potent activities against resistant bacteria of *S. pneumoniae* and *S. pyogenes* with *erm* gene when compared with LCM or CLDM. These results suggest that filling a space around the 7-position of CLDM plays an important role to enhance antibacterial activities by hydrogen bonding, π-π stacking, or CH-π interaction to undefined binding site on 23S *r*RNA.

In the author's medicinal chemistry, the author has already had SAR information, which suggested that a carbonyl group or an ester function was important to enhance antibacterial activities in the case of 7-phenylthio derivatives such as compound **2-29** (Figure 3-1). On the other hand, the author also had already reported compound **3-1** with co-workers.[71] Thus, the author first replaced the thiadiazolyl group in my selected compound **2-41** with a phenyl group. In this Chapter 3, the author will discuss SAR of these molecules focusing on substituted phenylthio groups at the 7-position of LCM with (7*S*)-configuration.

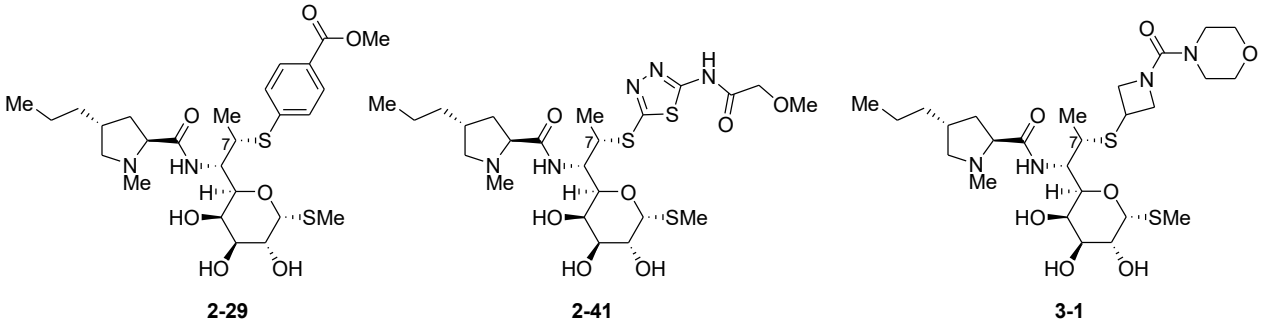
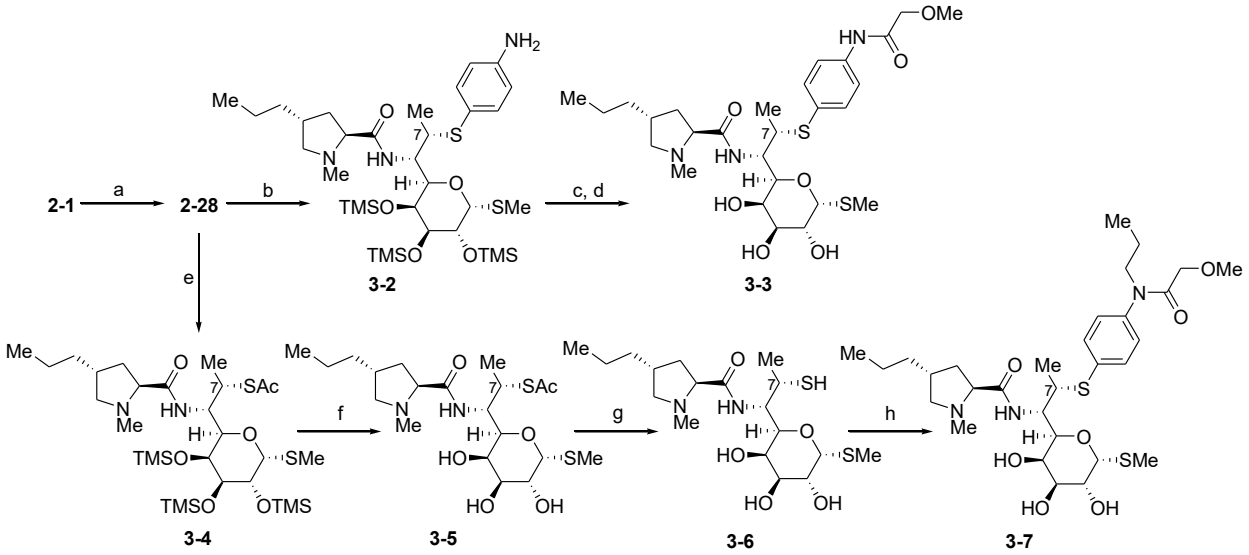



Figure 3-1. A key compound **2-29** and an alternative series of the author's novel LCM derivatives **2-41** and **3-1**.

Synthesis of (7*S*)-7-deoxy-7-(substituted-arylthio)lincomycin derivatives are shown in Scheme 3-1 and Scheme 3-2. The author had utilized compounds **2-1** and **2-28** as key intermediates in my drug discovery program, the author also applied these intermediates to synthesize a variety of derivatives in this Chapter 3, which had the same (7*S*)-configuration as CLDM. Protected (7*R*)-7-methanesulfonate (**2-28**) is a very useful

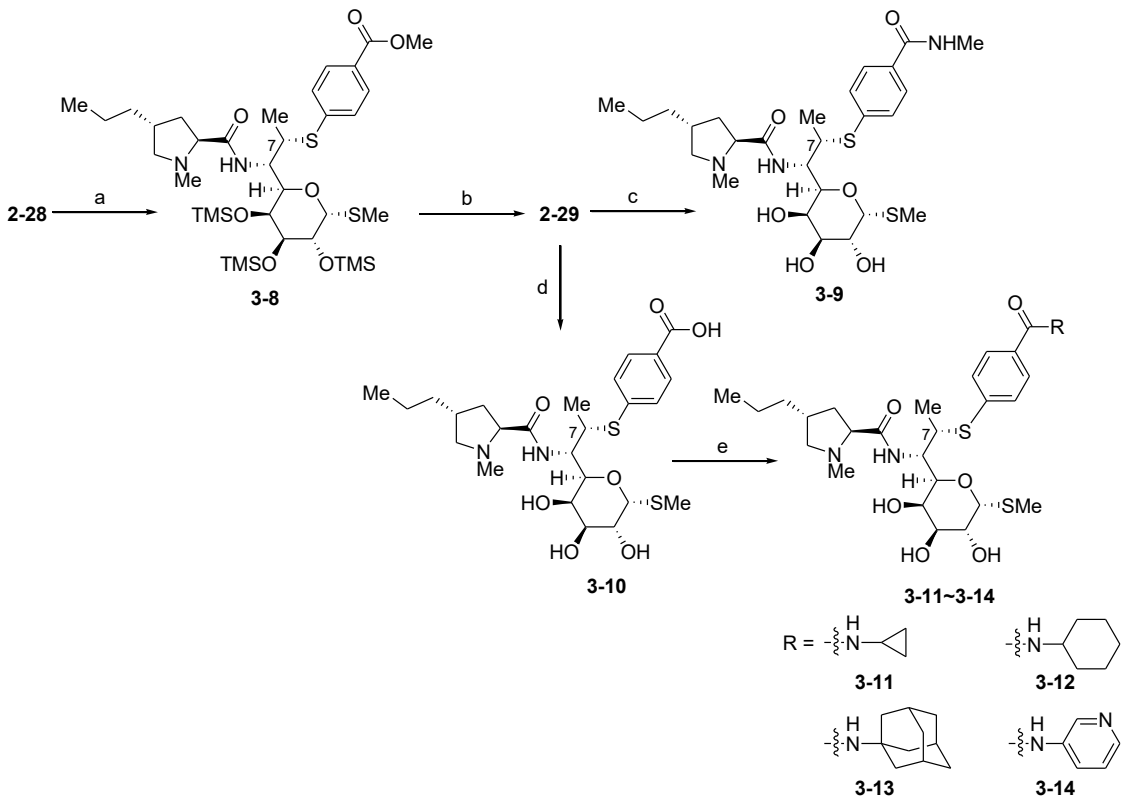
intermediate to synthesize LCM derivatives, and it was firstly synthesized from compound **2-1**. An $S_N2$ reaction of **2-28** under basic condition with the corresponding thiol gave desired molecule **3-2**. Compound **3-2** was treated with methoxymethylcarbonyl chloride and $Et_3N$, followed by deprotection of TMS groups under the 1N HCl condition provided **3-3** in 99% yield with two steps.

Compound **3-4** was prepared from the methanesulfonate (**2-28**) with KSAc under the heat (60°C) condition. Both TMS groups and an acetyl group were successively removed under the 1N HCl condition and then the sodium methoxide condition to give a key intermediate, compound **3-6**. Palladium-catalyzed cross-coupling reactions[72] of **3-6** with an aryl bromide or an aryl iodide, which are more powerful than Mitsunobu reactions of **2-1** or $S_N2$ reactions of **2-28** in my research, were used to synthesize further novel derivatives **3-7**.




Scheme 3-1. Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) methanesulfonyl chloride, $Et_3N$, $CHCl_3$, r.t., 3 h, quant; b) 1) 4-aminobenzenethiol, $K_2CO_3$, DMF, 100°C, 4.5 h, 2) 1 N HCl , MeOH, r.t., 45 min., 67.2%, 3) trimethylchlorosilane, hexamethyldisilazane, pyridine, r.t., 20 h, 97.3%, Because a part of TMS groups were removed during $S_N2$ reaction with aminobenzenethiol, total deprotection and total re-protection by TMS groups were performed.; c) 2-methoxyacetyl chloride, $Et_3N$, THF, 3 h; d) 1 N HCl, MeOH, r.t., 40 min., 99.7% in 2 steps; e) KSAc, DMF, 60°C, 4 h, 88%; f) 2 N HCl, MeOH, r.t., 10 min., 97.5%; g), sodium methoxide, MeOH, r.t., 20 min., 94.5%; h) *N*-(4-bromophenyl)-2-methoxy-*N*-propylacetamide, Xantphos, $Pd_2(dba)_3$, *N,N*-diisopropylethylamine, 1,4-dioxane, reflux, 6 h, 76.0%.

On the other hand, Compound **3-8** was prepared by $S_N2$ reaction of the corresponding thiol under the basic condition. TMS groups of an ester **3-8** were deprotected under the 1 N HCl condition to give the corresponding analogs **2-29** in a good yield. Carbamoylphenyl analog **3-9** were prepared from the ester (**2-29**) by aminolysis. Carboxylic acid **3-10** was prepared by hydrolysis of the ester (**2-29**) under the 1 N NaOH condition and then followed by condensation with a variety of amines to give the carbamoylphenyl analogs **3-11**~**3-14**.

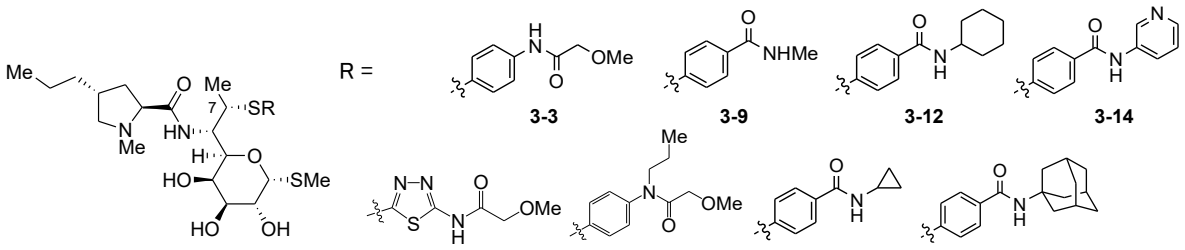



Scheme 3-2. Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) methyl 4-mercaptobenzoate, $K_2CO_3$, DMF, 80°C, 1 h, not isolated; b) 1 N HCl , MeOH, r.t., 1 h, 71% in 2 steps; c) $NH_2Me$, MeOH, reflux, 20 h, 17.6%; d) 1 N NaOH, MeOH, r.t., 19 h, quant; e) the corresponding amine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl, 1-hydroxybenzotriazole, DMF, r.t., 4-16 h, 44.8% (**3-11**), 25.2% (**3-12**), 55.0% (**3-13**), 29.2% (**3-14**).

### 3.1.2. SAR analysis of LCM derivatives possessing a substituted phenyl moiety at the C-7 position *via* sulfur atom with (7*S*)-configuration

Antibacterial activities of LCM derivatives possessing a substituted phenyl moiety at the C-7 position *via* sulfur atom are shown in Table 3-1. Thus, the author first replaced the thiadiazolyl group in my selected compound **2-41** with a phenyl group. As a result, **3-3** generally showed stronger antibacterial activities than **2-41**. Compound **3-7**, which possessed a propyl group at the methoxymethylcarbonylamino group of **3-3**, had the strongest activity against resistant *Streptococcus* species with *erm* gene, but exhibited comparable activity to **2-41** against *H. influenzae*. Next, the author was interested in changing direction of an amide bond, and the author constructed a CONH-type bond instead of a NHCO-type to provide **3-9**. This compound had the similar activities to **3-3**. In order to accumulate the SAR information around the C-7 position, the author substituted the methyl group in **3-9** with a larger group such as a cyclopropyl, cyclohexyl, adamantyl, and pyridin-3-yl group, respectively, and compounds **3-11**~**3-14** were prepared. Modification of the R moiety on (7*S*)-7-sulfur-Ph-CONHR derivatives could not improve antibacterial activities of **3-9**.

Table 3-1. Antibacterial activities (MIC, μg/mL) of (7*S*)-7-deoxy-7-(4-substituted-phenylthio)-LCM derivatives.



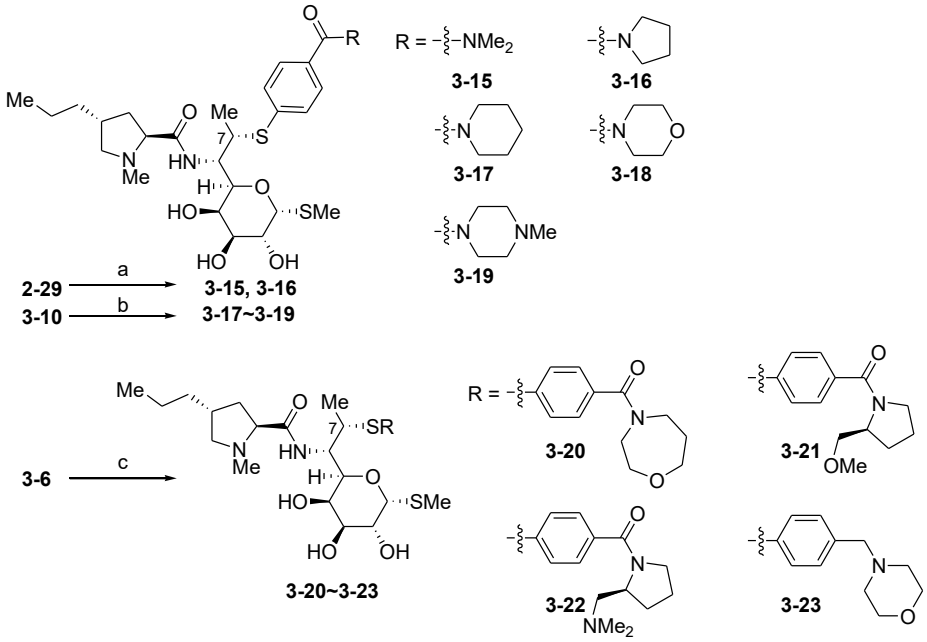

| Test organism* | Characteristics** | **2-41** | **3-3** | **3-7** | **3-9** | **3-11** | **3-12** | **3-13** | **3-14** |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.06 | 0.015 | 0.06 | 0.06 | 0.06 | 0.12 | 0.25 | 0.03 |
| *S. pneumoniae* -2 | s | 0.03 | 0.015 | 0.06 | 0.06 | 0.12 | 0.12 | 0.25 | 0.03 |
| *S. pneumoniae* -3 | s | 0.12 | 0.03 | 0.06 | 0.06 | 0.06 | 0.12 | 0.25 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 64 | 4 | 2 | 4 | 16 | 16 | 32 | 32 |
| *S. pneumoniae* -5 | *ermAM* (c) | 64 | 8 | 2 | 8 | 16 | 16 | 32 | 16 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 64 | 32 | 4 | 32 | 32 | 64 | 64 | 64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 8 | 4 | 0.5 | 4 | 4 | 8 | 32 | 8 |
| *S. pneumoniae* -8 | *ermAM* (i) | 8 | 2 | 0.5 | 4 | 8 | 8 | 16 | 8 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.06 | 0.015 | 0.03 | 0.03 | 0.06 | 0.12 | 0.25 | 0.03 |
| *S. pyogenes* Cook | s | 0.06 | 0.03 | 0.06 | 0.06 | 0.06 | 0.12 | 0.25 | 0.015 |
| *S. pyogenes* -2 | *ermAM* (c) | 8 | 4 | 1 | 8 | 8 | 8 | 32 | 8 |
| *S. pyogenes* -3 | *mefE* efflux | 0.06 | 0.03 | 0.06 | 0.12 | 0.06 | 0.12 | 0.25 | 0.03 |
| *H. influenzae* | s | 32 | 8 | 8 | 8 | 16 | 32 | 32 | 32 |
| *H. influenzae* -2 | s | 16 | 4 | 16 | 8 | 16 | 16 | 32 | 16 |
| *H. influenzae* -3 | s | 32 | 16 | 64 | 16 | 32 | 64 | ＞128 | 64 |
| *H. influenzae* -4 | ⊿acr | 0.5 | 0.12 | 0.25 | 0.25 | 0.5 | 0.5 | 2 | 0.25 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 3.2. Synthesis and SAR analysis of LCM derivatives possessing a 4-(*N*, *N*-disubstituted-carbamoyl)phenyl group at the C-7 position *via* sulfur atom with (7*S*)-configuration

### 3.2.1. Synthesis of novel LCM derivatives possessing a 4-(*N*, *N*-disubstituted-carbamoyl) phenyl group

Next, (7*S*)-7-sulfur-Ph-CONR$_2$ derivatives, which possessed a hetero ring attached to a carbonyl group, were synthesized to investigate further modifications at the *para* position of the phenyl group in Scheme 3-3. Disubstituted amido analogs **3-15** and **3-16** were prepared from the ester (**2-29**) by aminolysis, respectively. Carboxylic acid **3-10** was coupled with a variety of amines to give the corresponding disubstituted amido analogs (**3-17**~**3-19**). A variety of LCM analogs **3-20**~**3-23** were prepared by the similar palladium-catalyzed cross-coupling reactions[72] as described for the preparation of compound **3-7**.



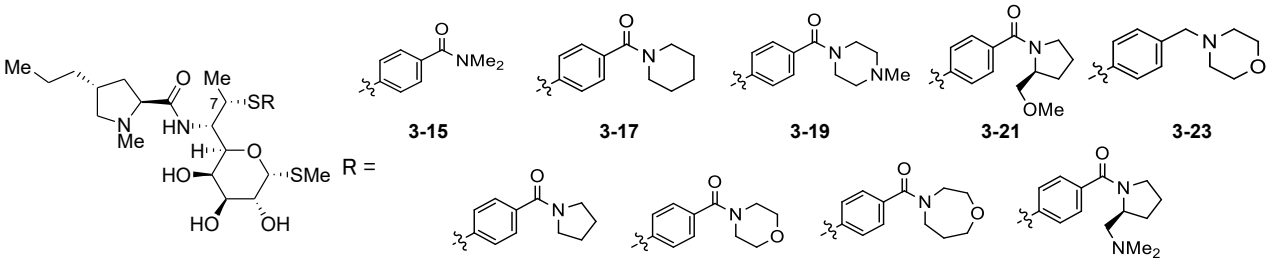

Scheme 3-3. Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) the corresponding amine, MeOH, 110°C in sealed tube or reflux, 3 or 72 h, 15.8% (**3-15**), 32.7% (**3-16**); b) the corresponding amine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl, 1-hydroxybenzotriazole, DMF, r.t., 24-28 h, 63.2% (**3-17**), 63.0% (**3-18**), 69.1% (**3-19**); c) Ar-Br or Ar-I, Xantphos, $Pd_2(dba)_3$, *N,N*-diisopropylethylamine, 1,4-dioxane, reflux, 3-22 h, 73.1% (**3-20**), 79.2% (**3-21**), 82.4% (**3-22**), 74.7% (**3-23**).

### 3.2.2. SAR analysis of LCM derivatives possessing a 4-(*N*, *N*-disubstituted-carbamoyl) phenyl group at the C-7 position *via* sulfur atom with (7*S*)-configuration

Conversions of the methylamino group of **3-9** to other dialkylamino groups were accomplished and antibacterial activities of the resulting compounds are shown in Table 3-2. Compound **3-15** also showed

almost the same antibacterial spectrum as that of **3-9**. A variety of substituted amino functional groups (pyrrolidinyl, piperidinyl, morpholinyl, 1-methylpiperazinyl, 1,4-oxazepanyl group) were constructed to improve antibacterial activities. Consequently, the morpholinyl derivative (**3-18**) had strong activities against major pathogens which caused respiratory infections, i.e., *S. pneumoniae*, *S. pyogenes,* and *H. influenzae*. Compounds **3-21** and **3-22** possessing a substituent in the pyrrolidine ring were prepared. Although compounds **3-21** and **3-22** exhibited potent activities against *S. pneumoniae and S. pyogenes* with *erm* gene and/or *mef* gene, they showed weaker activities against *H. influenzae* than **3-18**. On the other hand, the tertiary amino analog (**3-23**) generally showed comparable antibacterial activities to **3-18**.

Table 3-2. Antibacterial activities (MIC, μg/mL) of
(7*S*)-7-deoxy-7-(4-(*N,N*-disubstituted-carbamoyl)phenylthio)-LCM derivatives.



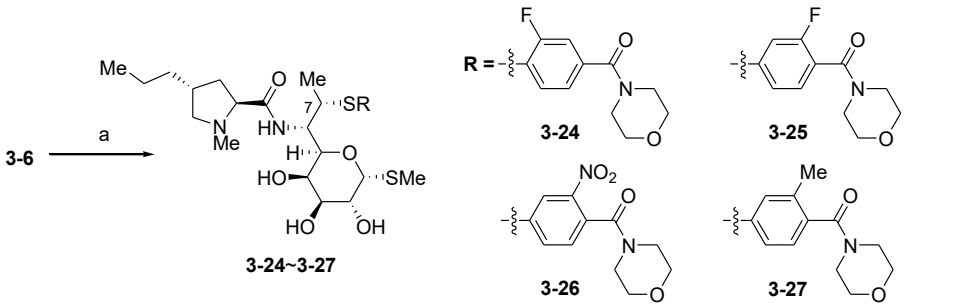

| Test organism* | Characteristics** | 3-15 | 3-16 | 3-17 | 3-18 | 3-19 | 3-20 | 3-21 | 3-22 | 3-23 |
|---|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.12 | 0.06 | 0.06 | 0.12 | 0.03 | 0.03 | 0.03 | 0.03 |
| *S. pneumoniae* -2 | s | 0.03 | 0.06 | 0.06 | 0.06 | 0.12 | 0.06 | 0.06 | 0.03 | 0.03 |
| *S. pneumoniae* -3 | s | 0.03 | 0.12 | 0.06 | 0.06 | 0.12 | 0.06 | 0.06 | 0.06 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 8 | 4 | 2 | 8 | 16 | 8 | 2 | 2 | 8 |
| *S. pneumoniae* -5 | *ermAM* (c) | 8 | 4 | 4 | 2 | 16 | 4 | 2 | 2 | 8 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 32 | 16 | 8 | 8 | 32 | 16 | 8 | 4 | 32 |
| *S. pneumoniae* -7 | *ermAM* (i) | 4 | 2 | 2 | 2 | 8 | 2 | 1 | 1 | 2 |
| *S. pneumoniae* -8 | *ermAM* (i) | 4 | 2 | ND | 1 | 8 | 2 | 1 | ND | 2 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.03 | 0.06 | 0.06 | 0.03 | 0.12 | 0.015 | 0.015 | 0.03 | 0.015 |
| *S. pyogenes* Cook | s | 0.03 | 0.12 | 0.06 | 0.06 | 0.12 | 0.03 | 0.06 | 0.03 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | 4 | 4 | 2 | 4 | 8 | 2 | 2 | 2 | 4 |
| *S. pyogenes* -3 | *mefE* efflux | 0.03 | 0.12 | 0.06 | 0.06 | 0.12 | 0.03 | 0.06 | 0.25 | 0.03 |
| *H. influenzae* | s | 8 | 8 | 8 | 4 | 8 | 8 | 8 | 8 | 8 |
| *H. influenzae* -2 | s | 8 | 8 | 8 | 4 | 8 | 8 | 8 | 16 | 8 |
| *H. influenzae* -3 | s | 32 | 32 | 16 | 16 | 64 | 32 | 32 | 64 | 32 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.5 | 0.25 | 0.25 | 1 | 0.12 | 0.12 | 0.25 | 0.25 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 3.3. Synthesis and SAR analysis of novel derivatives possessing a substituent on the phenyl group

### 3.3.1. Synthesis of novel (7*S*)-7-deoxy-7-(4-(morpholinylcarbonyl)phenylthio)lincomycin derivatives possessing a fluorine atom, a nitro or a methyl group as a substituent on the phenyl group

Next, the author introduced several kinds of substituents on the phenyl group of **3-18**. Thus, (7*S*)-7-mercapto intermediate **3-6** was coupled with aryl halide to synthesize novel LCM derivatives **3-24**~**3-27** as shown in Scheme 3-4.

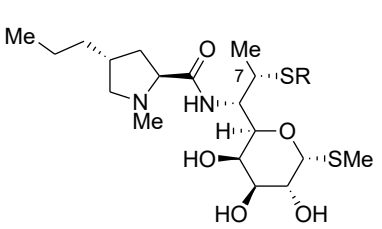



Scheme 3-4. Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) Ar-Br, Xantphos, $Pd_2(dba)_3$, *N,N*-diisopropylethylamine, 1,4-dioxane, reflux, 2.5-8.5 h, 81.6% (**3-24**), 81.4% (**3-25**), 80.0% (**3-26**), 78.1% (**3-27**).

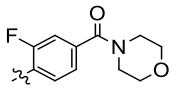
### 3.3.2. SAR analysis of LCM derivatives possessing a 4-(morpholinylcarbonyl)phenyl group at the C-7 position *via* sulfur atom with (7*S*)-configuration

Antibacterial activities of compounds **3-24**~**3-27**, which possess several kinds of substituents on the phenyl group of **3-18**, are shown in Table 3-3. Introducing a substituent on the phenyl group of **3-18** did not improve its antibacterial activities, even though it was an electron withdrawing group or an electron donating group.

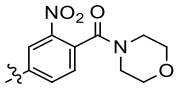
Table 3-3. Antibacterial activities (MIC, μg/mL) by substituent effects on the phenyl group of **3-18**.



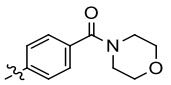

R =



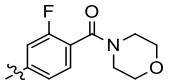
**3-24**



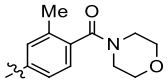
**3-26**



**3-18**



**3-25**



**3-27**

| Test organism* | Characteristics** | **3-18** | **3-24** | **3-25** | **3-26** | **3-27** |
|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 |
| *S. pneumoniae* -2 | s | 0.06 | 0.06 | 0.12 | 0.12 | 0.06 |
| *S. pneumoniae* -3 | s | 0.06 | 0.06 | 0.12 | 0.12 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | 8 | 8 | 16 | 32 | 8 |
| *S. pneumoniae* -5 | *ermAM* (c) | 2 | 16 | 16 | 32 | 8 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 8 | 128 | 128 | >128 | 64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 2 | 8 | 8 | 8 | 4 |
| *S. pneumoniae* -8 | *ermAM* (i) | 1 | 8 | 8 | 8 | 4 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.03 | 0.03 | 0.03 | 0.06 | 0.03 |
| *S. pyogenes* Cook | s | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | 4 | 8 | 8 | 8 | 4 |
| *S. pyogenes* -3 | *mefE* efflux | 0.06 | 0.06 | 0.12 | 0.12 | 0.06 |
| *H. influenzae* | s | 4 | 16 | 16 | 16 | 16 |
| *H. influenzae* -2 | s | 4 | 16 | 16 | 32 | 16 |
| *H. influenzae* -3 | s | 16 | 64 | 64 | 64 | 32 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.25 | 0.5 | 0.5 | 0.25 |

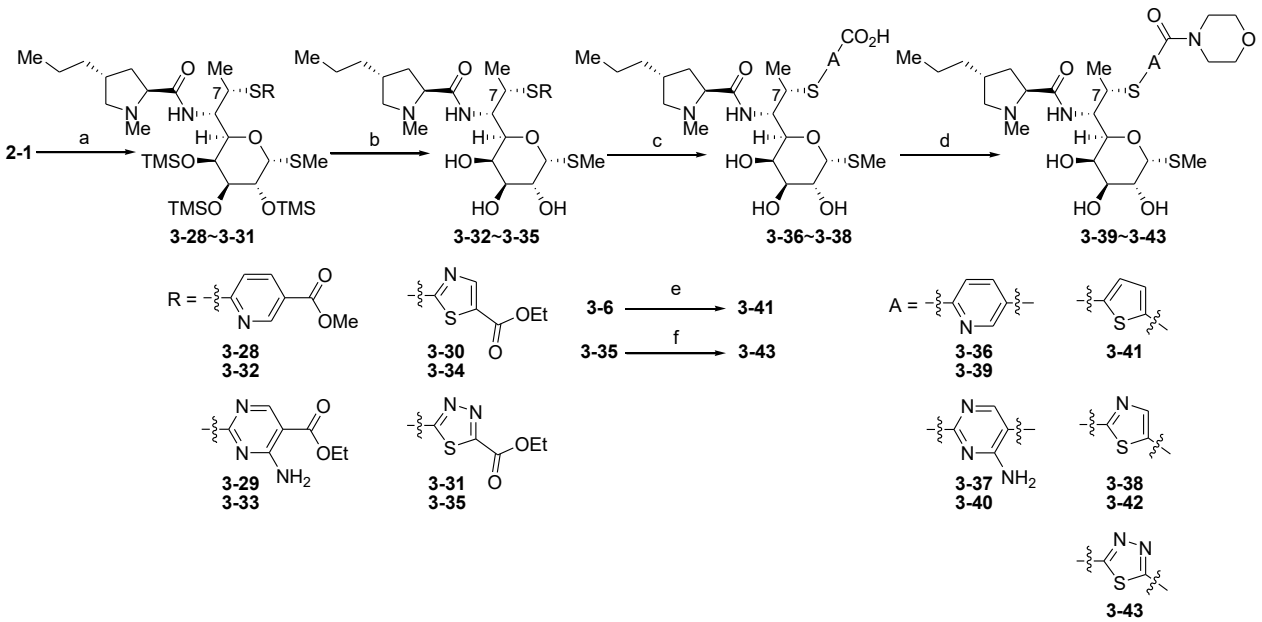
*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 3.4. Synthesis and SAR analysis of novel derivatives possessing a variety of hetero rings with a morpholin-1-yl-carbonyl moiety

### 3.4.1. Synthesis of novel derivatives possessing a variety of hetero rings with a morpholin-1-yl-carbonyl moiety

Next, the author investigated conversion of the benzene ring in the compound **3-18** to other hetero rings. These syntheses were showed in Scheme 3-5.

The desired intermediates **3-28**~**3-31** were directly synthesized from **2-1** by Mitsunobu reaction. All TMS groups of ester (**3-28**~**3-31**) were deprotected under the 1 N HCl condition to give the corresponding analogs (**3-32**~**3-35**) in middle to good yields. Carboxylic acids **3-36**~**3-38** were prepared by hydrolysis of the ester precursors (**3-32**~**3-34**) under the 1 N NaOH condition and then followed by coupling with a variety of amines to give the corresponding morpholinylcarbonyl analogs (**3-39**, **3-40** and **3-42**). A thiophene analog **3-41** was prepared by palladium-catalyzed cross-coupling reaction with 5-morpholinocarbonylthienyl-2-iodide from (7*S*)-7-SH intermediate **3-6**, while a thiadiazole analog **3-43** was prepared from the corresponding ester (**3-35**) by aminolysis.

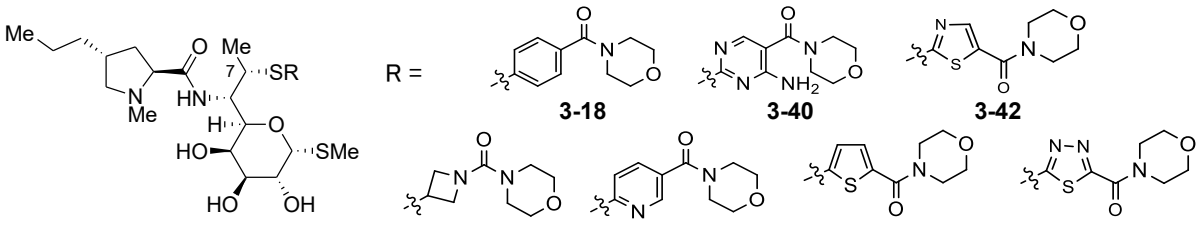



Scheme 3-5. Synthesis of (7*S*)-7-arylthio-7-deoxylincomycin derivatives. Conditions: a) triphenylphosphine, diethylazodicarboxylate or diisopropylazodicarboxylate, the corresponding HS-Ar, THF or toluene, 0°C to r.t., 7-16 h, not isolated (**3-28~3-31**); b) 1 N HCl , MeOH, r.t., 1 h, 76.3% in 2 steps (**3-32**), 73.7% in 2 steps (**3-33**), 66.0% in 2 steps (**3-34**), 45.4% in 2 steps (**3-35**); c) 1 N or 5 N NaOH, MeOH or EtOH, r.t., 1-18 h, 80.5% (**3-36**), not isolated (**3-37**), not isolated (**3-38**); d) the corresponding amine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl or *N,N'*-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, DMF, r.t. to 60°C, 16-48 h, $Et_3N$ (**3-37** and **3-38** only), 70.2% (**3-39**), 6.1% in 2 steps from **3-33** to **3-40**, 6.5% in 2 steps from **3-34** to **3-42**; e) 5-morpholinocarbonylthienyl-2-iodide, Xantphos, $Pd_2(dba)_3$, *N,N*-diisopropylethylamine, 1,4-dioxane, reflux, 6 h, 75.6% (**3-41**); f) morpholine, EtOH, reflux, 3 h, 64.4% (**3-43**).

### 3.4.2. SAR analysis of LCM derivatives possessing a morpholin-1-yl-carbonylaryl moiety at the C-7 position *via* sulfur atom with (7*S*)-configuration

Antibacterial activities of LCM derivatives possessing a morpholin-1-yl-carbonylaryl moiety are shown in Table 3-4. Conversion of the benzene ring to other hetero rings did not enhance antibacterial activities of **3-18**.

Table 3-4. Antibacterial activities (MIC, μg/mL) of (7*S*)-7-deoxy-7-((morpholin-1-yl-carbonyl)arylthio)-LCM derivatives.




| Test organism* | Characteristics** | 3-1 | 3-18 | 3-39 | 3-40 | 3-41 | 3-42 | 3-43 |
|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.12 | 0.06 | 0.06 | 0.5 | 0.03 | 0.03 | 0.03 |
| *S. pneumoniae* -2 | s | 0.12 | 0.06 | 0.12 | 1 | 0.06 | 0.03 | 0.06 |
| *S. pneumoniae* -3 | s | 0.12 | 0.06 | 0.06 | 0.5 | 0.06 | 0.03 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 16 | 8 | 32 | 16 | ＞128 | 16 | 32 |
| *S. pneumoniae* -5 | *ermAM* (c) | 16 | 2 | 8 | 16 | ＞128 | 16 | 64 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 32 | 8 | 32 | 64 | ＞128 | 32 | 128 |
| *S. pneumoniae* -7 | *ermAM* (i) | 8 | 2 | N.T. | 8 | 16 | 4 | 16 |
| *S. pneumoniae* -8 | *ermAM* (i) | ND | 1 | N.T. | 16 | 16 | 4 | 16 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.12 | 0.03 | ND | 0.5 | 0.06 | 0.03 | 0.03 |
| *S. pyogenes* Cook | s | 0.12 | 0.06 | 0.12 | 0.5 | 0.03 | 0.03 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | 4 | 4 | 4 | 8 | 8 | 8 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | 0.12 | 0.06 | 0.12 | 0.5 | 0.06 | ND | 0.06 |
| *H. influenzae* | s | 4 | 4 | 16 | 16 | 16 | 8 | 16 |
| *H. influenzae* -2 | s | 8 | 4 | 16 | 32 | 8 | 8 | 16 |
| *H. influenzae* -3 | s | 16 | 16 | 32 | 64 | 32 | 32 | 64 |
| *H. influenzae* -4 | ⊿acr | 1 | 0.25 | 0.5 | 1 | 0.25 | 0.25 | 0.5 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.;
**(c): constitutive; (i): inducible; Gray shading strains are target strains

### 3.5. Docking simulation of the key compound 3-18

Finally, the author investigated three dimensional analysis[5,7-8] of the complexation of **3-18** and peptidyl transferase was conducted as shown in Figure 3-2 (Docking simulation was calculated by data on bacteria, *Haloarcula marismortui* (Hm)). The analysis indicated that an oxygen atom of a carbonyl group in the C-7 side chain of **3-18** has a hydrogen bonding with U2620Hm (U2585Ec) (The numbers in parenthesis are expressed as the case of *Escherichia coli* (Ec)) on 23S rRNA (ribosomal RNA). Furthermore, an ethylene part of the morpholine ring in **3-18** was analyzed and determined to have a hydrophobic interaction of CH-π stacking with uracil (cytosine) ring of U2621Hm (C2586Ec) on 23S rRNA.

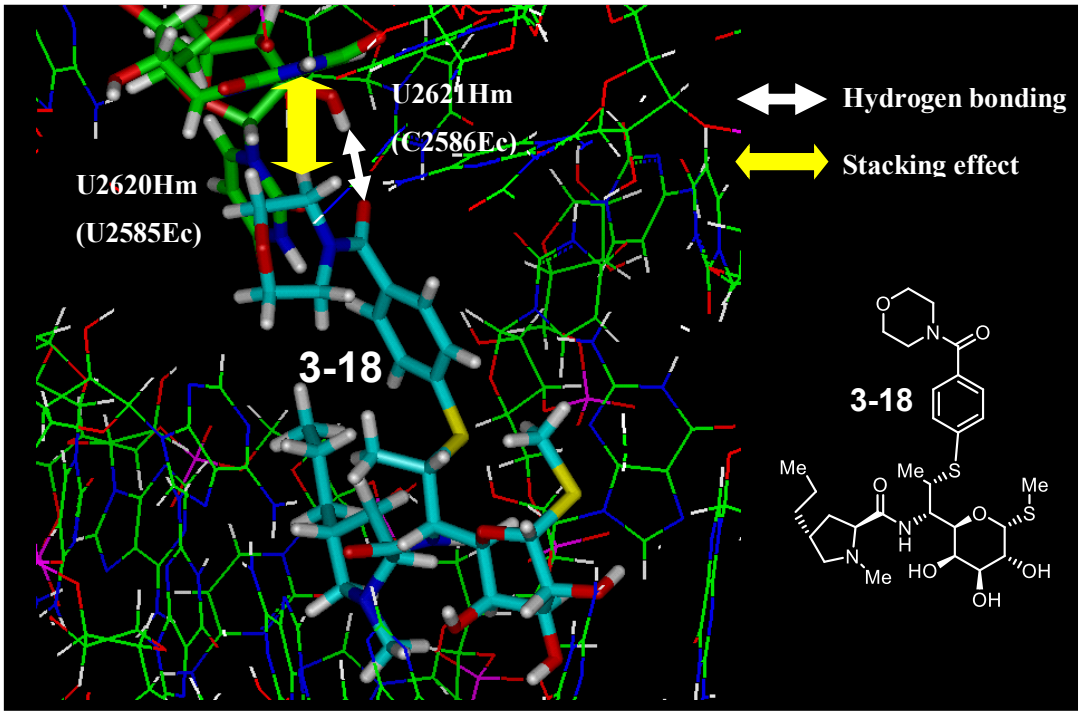



Figure 3-2. Three dimensional analysis of **3-18** and the peptidyl transferase.

## 3.6. Summary

At the beginning of my lincomycin analogs research program, the author was interested in lincomycin derivatives possessing a hetero ring at the C-7 position *via* sulfur atom with (7*S*)-configuration. The author synthesized them by two kinds of reactions; 1) Mitsunobu reaction of 2,3,4-tris-*O*-(trimethylsilyl)-LCM (**2-1**) with the corresponding thiol, and 2) $S_N2$ reaction of 7-*O*-methanesulfonyl-2,3,4-tris-*O*-(trimethylsilyl)-LCM (**2-28**) with the corresponding thiol. These synthetic procedures, however, had limitation (low yield and deproductivity) in preparation of various 7-(arylthio)lincomycin analogs in order to investigate their SAR. So, the author has developed a novel synthetic route for synthesis of a variety of 7-thio-modified lincomycin derivatives by application of palladium-catalyzed cross-coupling reaction[72] of 7-deoxy-7-epi-7-mercapto-LCM (**3-6**) with an aryl bromide or an aryl iodide. This methodology was very useful to synthesize a various 7-thio-modified lincomycin analogs.

The author first synthesized and biologically evaluated (7*S*)-7-deoxy-7-phenylthio analogs possessing either the NHCO-type or the CONH-type bond at the C-7 substituent. As a result, compound **3-18** possessing the morpholine ring had potent antibacterial activities against major pathogens that caused respiratory infections, compared with CLDM. A substitution introduced on the benzene ring of **3-18**, however, didn't enhance antibacterial activities. Furthermore, conversion of the phenyl group of **3-18**[73] to other hetero rings also decreased antibacterial activities. Consequently, compounds **3-21** and **3-22** (Table 3-2) showed the strongest antibacterial activities against *S. pneumoniae and S. pyogenes* with *erm* gene, but, antibacterial activities against *H. influenzae* of these analogs were not improved compared to those of CLDM.

# 4. Design, synthesis and structure-activity relationship analysis of novel (7*S*)-substituted-phenylthio-LCM derivatives possessing aliphatic amine or aromatic amine groups at *p*-position on the phenyl group

## 4.1. Design, synthesis and structure-activity relationship analysis of novel LCM derivatives possessing an aliphatic amine as a substituent on the phenyl group at the C-7 position

### 4.1.1. Design and synthesis of (7*S*)-7-deoxy-7-(substituted-phenylthio)lincomycin derivatives

In the previous Chapter, it was reported that **3-18** and **3-22** exhibited stronger antibacterial activities against resistant *S. pneumoniae* with *erm* and *mef* genes than those of CAM, AZM, LCM, and CLDM, as shown in Figure 4-1 and Table 4-1. These data prompted me to hypothesize that a benzene ring or a hetero ring with basicity are important to enhance antibacterial activities against resistant bacteria with *erm* and *mef* genes. In this Chapter 4, the author reports synthesis and biological evaluation of novel lincomycin analogs possessing a benzene ring and a hetero ring with basicity *via* sulfur atom with (7*S*)-configuration.

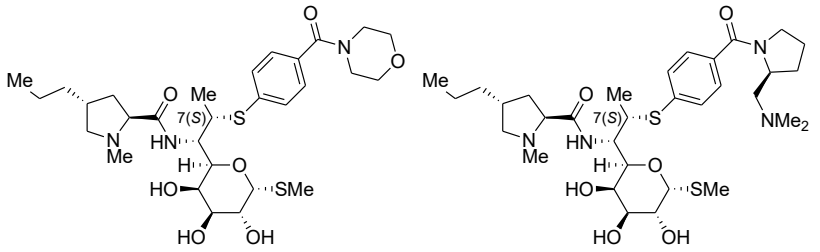


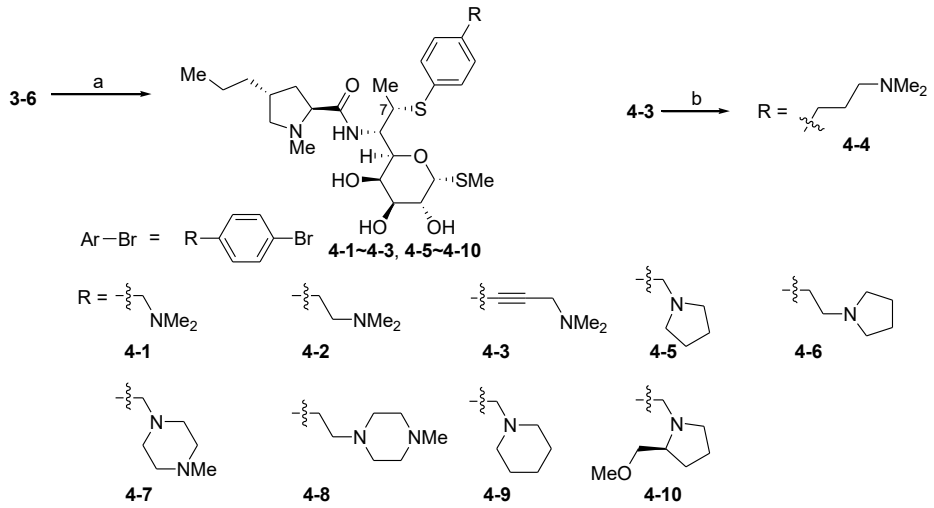

Figure 4-1. Previously reported lincomycin analogs modified at the C-7 position.

Table 4-1. Antibacterial activities (MIC, μg/mL) of the representative macrolides, lincomycin (LCM), clindamycin (CLDM), and previously reported lincomycin derivatives (**3-18** and **3-22**).

| Test organism* | Characteristics** | CAM | AZM | LCM | CLDM | **3-18** | **3-22** |
|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.06 | 1 | 0.06 | 0.06 | 0.03 |
| *S. pneumoniae* -2 | s | 0.03 | 0.03 | 1 | 0.12 | 0.06 | 0.03 |
| *S. pneumoniae* -3 | s | 0.015 | 0.03 | 0.25 | 0.06 | 0.06 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | >128 | >128 | >128 | >128 | 8 | 2 |
| *S. pneumoniae* -5 | *ermAM* (c) | >128 | >128 | >128 | >128 | 2 | 2 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | >128 | >128 | >128 | >128 | 8 | 4 |
| *S. pneumoniae* -7 | *ermAM* (i) | >128 | >128 | 128 | 128 | 2 | 1 |
| *S. pneumoniae* -8 | *ermAM* (i) | >128 | >128 | 128 | 128 | 1 | N.T. |
| *S. pneumoniae* -9 | *mefE* efflux | 0.5 | 0.5 | 1 | 0.12 | 0.03 | 0.03 |
| *S. pyogenes* Cook | s | 0.015 | 0.06 | 0.12 | 0.06 | 0.06 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | >128 | >128 | >128 | 128 | 4 | 2 |
| *S. pyogenes* -3 | *mefE* efflux | 8 | 8 | 0.25 | 0.12 | 0.06 | 0.25 |
| *H. influenzae* | s | 2 | 0.25 | 8 | 16 | 4 | 8 |
| *H. influenzae* -2 | s | 4 | 1 | 16 | 8 | 4 | 16 |
| *H. influenzae* -3 | s | 8 | 2 | 16 | 16 | 16 | 64 |
| *H. influenzae* -4 | ⊿acr | 0.5 | 0.5 | 4 | 1 | 0.25 | 0.25 |

Abbreviations: AZM, azithromycin; CAM, clarithromycin; N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible; Gray shading strains are target strains

Synthesis of (7*S*)-7-deoxy-7-(substituted-phenylthio)lincomycin derivatives is shown in Scheme 4-1. The author has already reported synthetic route of (7*S*)-7-mercapto intermediate (**3-6**) in the Chapter 3.[66,68,69,73] The author applied a different synthetic route for compound **3-6** from the previously reported route by Magerlein's group.[44] The author firstly prepared a key intermediate **3-6** derived from LCM in six steps in order to construct the same configuration at the C-7 position as CLDM in the final target molecules. A palladium-catalyzed cross-coupling reaction of **3-6** with various arylhalides is a widely applicable method to synthesize novel LCM derivatives in my research compared with Mitsunobu reaction or an $S_N2$ reaction in application of a methanesulfonyl intermadiate.[66,68,69,73] In this reaction, aryl halides such as aryl bromide and aryl iodide, and aryl triflate can be used.[72,73] Compounds **4-1**~**4-3**, **4-5**~**4-10** were synthesized by the cross-coupling reaction to investigate the antibacterial activities of aliphatic amine compounds having a benzene ring and a basic moiety *via* sulfur atom at the C-7 position of LCM. Compound **4-4** was synthesized by reduction of a triple bond in compound **4-3** to evaluate its antibacterial activity compared with that of compound **4-1** or **4-2** focusing on the distance between a phenyl group and a dimethylamino group.



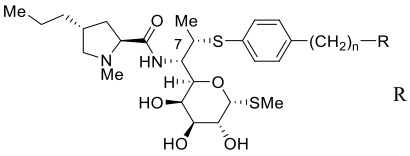

Scheme 4-1. Synthesis of (7*S*)-7-aminoalkylphenylthio-7-deoxylincomycin derivatives. Conditions: a) Ar-Br, Xantphos, $Pd_2(dba)_3$, *i*$Pr_2NEt$, dioxane, reflux, 2-14 h, 78.4% (**4-1**), 60.0% (**4-2**), 65.4% (**4-3**), 86.4% (**4-5**), 70.1% (**4-6**), 91.8% (**4-7**), 66.9% (**4-8**), 88.9% (**4-9**), 30 min, microwave irradiation, 58.8% (**4-10**); b) Pd/C, $H_2$, MeOH, r.t., 14 h, 63.6% (**4-4**).

## 4.1.2. SAR analysis of LCM derivatives possessing an aliphatic amine as a substituent on the phenyl group at the C-7 position

Antibacterial activities of LCM derivatives possessing an aliphatic amine as a substituent on the phenyl group at the C-7 position *via* sulfur atom are shown in Table 4-2. As described above, the author newly hypothesized that a benzene ring and a hetero ring with basicity were important to enhance antibacterial activities against resistant bacteria with *erm* gene. So, the author firstly evaluated the distance between the phenyl group and the dimethylamino group in the C-7 substituent. As a result, compounds **4-1** and **4-2**, which possessed one or two carbon atom(s) between the phenyl group and the dimethylamino group, exhibited relatively potent antibacterial activities against resistant *S. pneumoniae* with *erm* gene and *H. influenzae* compared with **4-4**. Next, the author fixed the number of carbon atom(s) between the phenyl group and the basic functionality as one or two, and the author replaced the dimethylamino group with a hetero ring such as pyrrolidine, mono-*N*-methylpiperazine and piperidine. Consequently, compounds **4-5**, **4-6**, and **4-9** had the similar antibacterial activities as compounds **4-1** and **4-2**. On the other hand, the author reported[73] that a 2-(methoxymethyl)pyrrolidine group was an important moiety to enhance antibacterial activities against resistant bacteria with *erm* gene. Then, the author introduced the 2-methoxymethyl group on the pyrrolidine ring of **4-5** to afford **4-10**. Consequently, the desired product **4-10** exhibited four times potent activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene compared with **4-5**. These results suggest that a phenyl group and a basic moiety (especially, a hetero ring with a substituent) are important to

enhance antibacterial activities against resistant bacteria with *erm* gene, and the number of carbon atoms between the phenyl group and the basic functionality might be optimized with one or two.

Table 4-2. Antibacterial activities (MIC, μg/mL) of dimethylamino derivatives and cyclicaminoalkyl derivatives.




R =


| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n = | 1 | 2 | 3 | 1 | 2 | 1 | 2 | 1 | 1 |
| Test organism* | Characteristics** | **4-1** | **4-2** | **4-4** | **4-5** | **4-6** | **4-7** | **4-8** | **4-9** | **4-10** |
| *S. pneumoniae* DP1 TypeI | s | 0.015 | ≦0.008 | 0.015 | 0.015 | 0.015 | 0.03 | 0.06 | 0.015 | 0.03 |
| *S. pneumoniae* -2 | s | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.03 | 0.06 | 0.015 | 0.03 |
| *S. pneumoniae* -3 | s | 0.03 | 0.015 | 0.015 | 0.03 | 0.03 | 0.03 | 0.06 | 0.03 | 0.06 |
| *S. pneumoniae* -4 | *ermAM* (c) | 8 | 4 | 64 | 4 | 8 | 64 | >128 | 4 | 1 |
| *S. pneumoniae* -5 | *ermAM* (c) | 8 | 4 | 64 | 4 | 8 | 32 | 128 | 2 | 1 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 16 | 8 | 64 | 8 | 32 | 64 | >128 | 8 | 2 |
| *S. pneumoniae* -7 | *ermAM* (i) | 1 | 1 | 4 | 0.5 | 2 | 4 | 0.5 | 0.25 | 0.12 |
| *S. pneumoniae* -9 | *mefE* efflux | ≦0.008 | ≦0.008 | ≦0.008 | ≦0.008 | 0.015 | 0.015 | 0.06 | ≦0.008 | 0.015 |
| *S. pyogenes* Cook | s | 0.03 | 0.015 | 0.03 | 0.03 | 0.06 | 0.06 | 0.12 | 0.03 | 0.06 |
| *S. pyogenes* -2 | *ermAM* (c) | 2 | N.T. | 16 | 2 | 4 | 8 | 32 | 4 | 0.5 |
| *S. pyogenes* -3 | *mefE* efflux | 0.03 | 0.015 | 0.015 | 0.03 | 0.03 | 0.06 | 0.12 | 0.03 | 0.06 |
| *H. influenzae* | s | 8 | 2 | 32 | 2 | 8 | 16 | 64 | 4 | 4 |
| *H. influenzae* -2 | s | 4 | 2 | 8 | 4 | 8 | 16 | 64 | 4 | 8 |
| *H. influenzae* -3 | s | 16 | 8 | 32 | 16 | 32 | 64 | >128 | 16 | 16 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.25 | 0.5 | 0.25 | 0.5 | 0.5 | 2 | 0.25 | 0.25 |

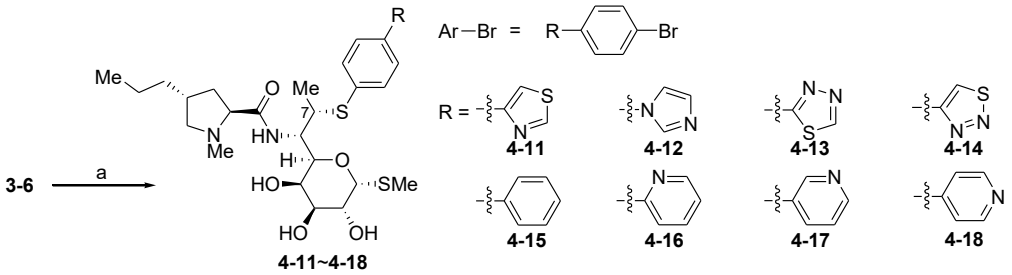
Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 4.2. Synthesis and SAR analysis of novel LCM derivatives possessing a hetero ring as a substituent on the phenyl group at the C-7 position

### 4.2.1. Synthesis of novel lincomycin derivatives having a hetero ring as a substituent on the phenyl group

Synthesis of novel lincomycin derivatives having a hetero ring as a substituent on the phenyl group is shown in Scheme 4-2.

Thus, Compound **4-11**~**4-18** possessing a benzene ring and an aromatic amine were synthesized by the cross-coupling reaction and their antibacterial activities were evaluated.

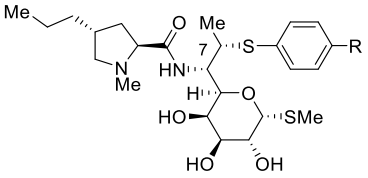


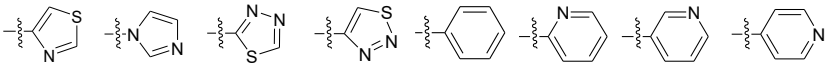

Scheme 4-2. Synthesis of (7*S*)-7-biphenylthio-7-deoxylincomycin and (7*S*)-7-deoxy-7-heteroarylphenylthiolincomycin derivatives. Conditions: a) Ar-Br, Xantphos, $Pd_2(dba)_3$, *i*$Pr_2$NEt, dioxane, reflux, 3-6.5 h, 68.0% (**4-11**), 42.3% (**4-12**), 64.0% (**4-13**), 52.0% (**4-14**), 91.5% (**4-15**), 91.4% (**4-16**), 88.2% (**4-17**), 86.1% (**4-18**),.

### 4.2.2. SAR analysis of LCM derivatives possessing a heteroaryl group as a substituent on the phenyl group at the C-7 position

Novel aromatic derivatives possessing a phenyl or a heteroaryl group as a substituent on the phenyl group at the C-7 position *via* sulfur atom were synthesized and their antibacterial activities are shown in Table 4-3. Consequently, the heterocyclic substituent on the phenyl group at the C-7 position also improved antibacterial activities against resistant pathogens. Especially, compounds **4-14** and **4-17** had potent activities against resistant Streptococcus strains with *erm* gene and *H. influenzae*. Moreover, antibacterial activities of **4-17**, when compared with those of **4-16** or **4-18** suggested that the location of the nitrogen atom was an important factor to enhance antibacterial activities.

Table 4-3. Antibacterial activities (MIC, μg/mL) of a variety of heteroaromatic derivatives and compound **4-15**.



R = 

| Test organism* | Characteristics** | **4-11** | **4-12** | **4-13** | **4-14** | **4-15** | **4-16** | **4-17** | **4-18** |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.015 | 0.015 | ≦0.008 | 0.25 | 0.03 | ≦0.008 | 0.03 |
| *S. pneumoniae* -2 | s | 0.03 | 0.015 | 0.015 | ≦0.008 | 0.25 | 0.06 | ≦0.008 | 0.03 |
| *S. pneumoniae* -3 | s | 0.03 | 0.015 | 0.015 | 0.015 | 0.25 | 0.03 | 0.015 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 4 | 4 | 2 | 1 | 32 | 8 | 0.5 | 8 |
| *S. pneumoniae* -5 | *ermAM* (c) | 8 | 4 | 8 | N.T. | >64 | 16 | 1 | 16 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 16 | 16 | 32 | 4 | >64 | >64 | 2 | >64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 4 | 1 | 1 | 0.5 | 16 | 4 | 0.25 | 4 |
| *S. pneumoniae* -8 | *ermAM* (i) | 1 | 2 | 2 | 0.12 | 16 | 4 | 0.25 | 4 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 | 0.25 | 0.03 | ≦0.008 | 0.03 |
| *S. pyogenes* Cook | s | 0.015 | 0.015 | 0.015 | ≦0.008 | 0.25 | 0.03 | 0.015 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | 4 | 1 | 4 | 0.5 | 16 | 8 | 0.5 | 8 |
| *S. pyogenes* -3 | *mefE* efflux | 0.03 | 0.015 | 0.03 | ≦0.008 | 0.25 | 0.03 | 0.015 | 0.06 |
| *H. influenzae* | s | 16 | 8 | 16 | 4 | >64 | 32 | 4 | 16 |
| *H. influenzae* -2 | s | 8 | 4 | 8 | 2 | 32 | 16 | 2 | 16 |
| *H. influenzae* -3 | s | >64 | 16 | 32 | 8 | >128 | >64 | 16 | >64 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.12 | 0.25 | 0.03 | 4 | 0.25 | 0.06 | 0.25 |

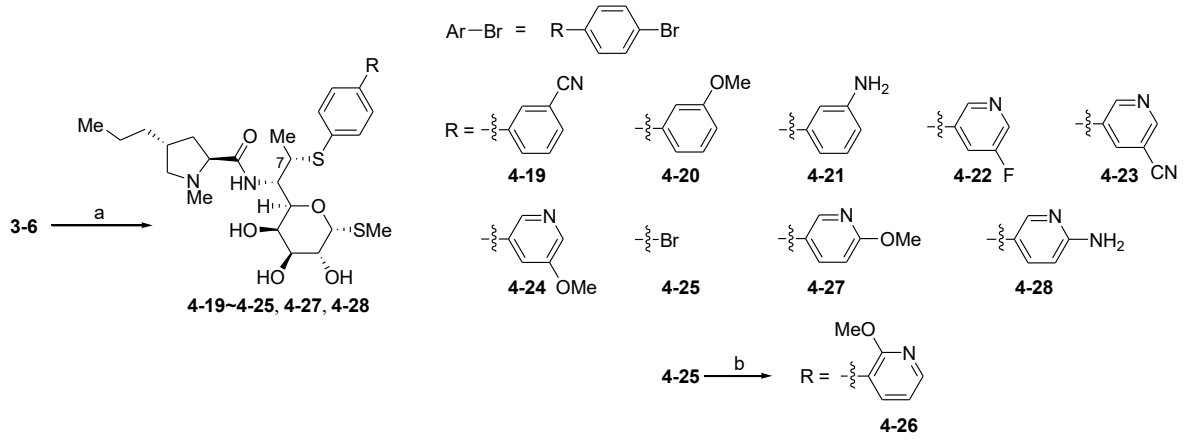
Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 4.3. Synthesis and SAR analysis of novel LCM derivatives possessing a substituted phenyl or pyridinyl group as a substituent on the phenyl group at the C-7 position

### 4.3.1. Synthesis of (7*S*)-7-deoxy-7-(substituted phenyl or pyridylphenylthio)lincomycin derivatives

Synthesis of (7*S*)-7-deoxy-7-(substituted phenyl or pyridinylphenylthio)lincomycin derivatives is shown in Scheme 4-3.

Compounds **4-19**~**4-25**, **4-27** and **4-28** were synthesized by the similar procedure as described for the preparation of compound **4-1**. Compound **4-26** was prepared in application of Suzuki-Miyaura cross-coupling reaction from **4-25**. This type of reaction, the palladium-catalyzed cross-coupling reaction of arylboronic acid with a lincomycin intermediate (**4-25**) possessing an aryl bromide moiety *via* sulfur at the C-7 position, was reported for the first time.[73]



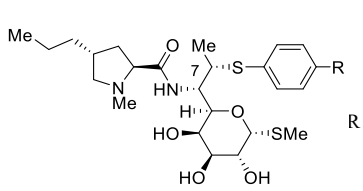

Scheme 4-3. Synthesis of (7*S*)-7-biphenylthio-7-deoxylincomycin and (7*S*)-7-deoxyl-7-pyridylphenylthiolincomycin derivatives. Conditions; a) Ar-Br, Xantphos, $Pd_2(dba)_3$, *i*$Pr_2NEt$, dioxane, reflux, 3-6 h, 40.9% (**4-19**), 85.9% (**4-20**), 51.0% (**4-21**), 73.2% (**4-22**), 58.6% (**4-23**), 77.5% (**4-24**), 73.3% (**4-25**), 90.6% (**4-27**),.12.9% (**4-28**); b) (2-methoxypyridin-3-yl)boronic acid, $Pd(PPh_3)_4$, $Na_2CO_3$, DMF, $H_2O$, 80°C, 10 h, 70.6% (**4-26**).

### 4.3.2. SAR analysis of LCM derivatives possessing a substituted phenyl or pyridinyl group as a substituent on the phenyl group at the C-7 position

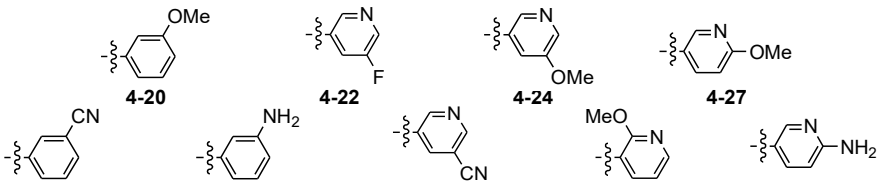
Antibacterial activities of alternative biaryl derivatives possessing a substituted phenyl or pyridinyl group as a substituent on the phenyl group at the C-7 position are shown in Table 4-4. As a result, the 5-methoxypyridin-3-yl derivative (**4-24**) exhibited dramatically stronger activities against resistant bacteria than the 3-methoxyphenyl derivative (**4-20**) or the 6-methoxypyridin-3-yl derivative (**4-27**). The pyridine

analog (**4-24**) was shown to be the most potent among substituted pyridine analogs. However, it was less potent when compared with non-substituted pyridine analog (**4-17**).

Table 4-4. Antibacterial activities (MIC, μg/mL) of substituted phenyl derivatives and substituted pyridinyl derivatives.




R =



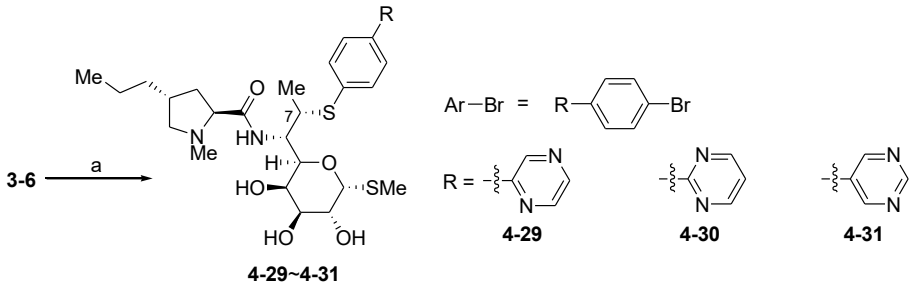

| | | **4-19** | **4-20** | **4-21** | **4-22** | **4-23** | **4-24** | **4-26** | **4-27** | **4-28** |
|---|---|---|---|---|---|---|---|---|---|---|
| Test organism* | Characteristics** | | | | | | | | | |
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.12 | 0.06 | 0.015 | 0.015 | 0.015 | 0.06 | 0.12 | 0.03 |
| *S. pneumoniae* -2 | s | 0.03 | 0.12 | 0.06 | 0.03 | 0.03 | 0.015 | 0.06 | 0.12 | 0.03 |
| *S. pneumoniae* -3 | s | 0.03 | 0.12 | 0.06 | 0.015 | 0.015 | 0.015 | 0.06 | 0.12 | 0.03 |
| *S. pneumoniae* -4 | *ermAM* (c) | 4 | 32 | 2 | 4 | 2 | 1 | 16 | >64 | >64 |
| *S. pneumoniae* -5 | *ermAM* (c) | 4 | 32 | 4 | 4 | 2 | 1 | 8 | >64 | 32 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 16 | 32 | 16 | 8 | 4 | 8 | 32 | >64 | >64 |
| *S. pneumoniae* -7 | *ermAM* (i) | 2 | 8 | 2 | 0.5 | 0.25 | 0.5 | 1 | 32 | N.T. |
| *S. pneumoniae* -8 | *ermAM* (i) | 1 | 8 | 1 | N.T. | N.T. | 0.5 | N.T. | N.T. | N.T. |
| *S. pneumoniae* -9 | *mefE* efflux | 0.015 | 0.03 | 0.03 | ≦0.008 | ≦0.008 | 0.015 | 0.03 | 0.03 | 0.015 |
| *S. pyogenes* Cook | s | 0.015 | 0.12 | 0.06 | 0.03 | 0.03 | 0.015 | 0.06 | 0.03 | 0.03 |
| *S. pyogenes* -2 | *ermAM* (c) | 2 | 16 | 1 | 1 | 1 | 1 | 4 | 32 | 2 |
| *S. pyogenes* -3 | *mefE* efflux | 0.06 | 0.25 | 0.06 | 0.03 | 0.03 | 0.015 | 0.06 | 0.12 | 0.03 |
| *H. influenzae* | s | 32 | >64 | 16 | 16 | 32 | 16 | 32 | 128 | 32 |
| *H. influenzae* -2 | s | 16 | 32 | 8 | 16 | 16 | 8 | 16 | 32 | 16 |
| *H. influenzae* -3 | s | >64 | >128 | 32 | 32 | 32 | 32 | >64 | >128 | >64 |
| *H. influenzae* -4 | ⊿acr | 0.5 | 2 | 0.25 | 0.25 | 0.25 | 0.12 | 0.5 | 2 | 0.25 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains.

## 4.4. Synthesis and SAR analysis of optimized (7*S*)-7-thiolincomycin analogs possessing a 4-(pyrimidin-5-yl)phenyl group at the C-7 position

### 4.4.1. Synthesis of novel LCM derivatives possessing pyrazine or pyrimidine as a substituent on the phenyl group at the C-7 position

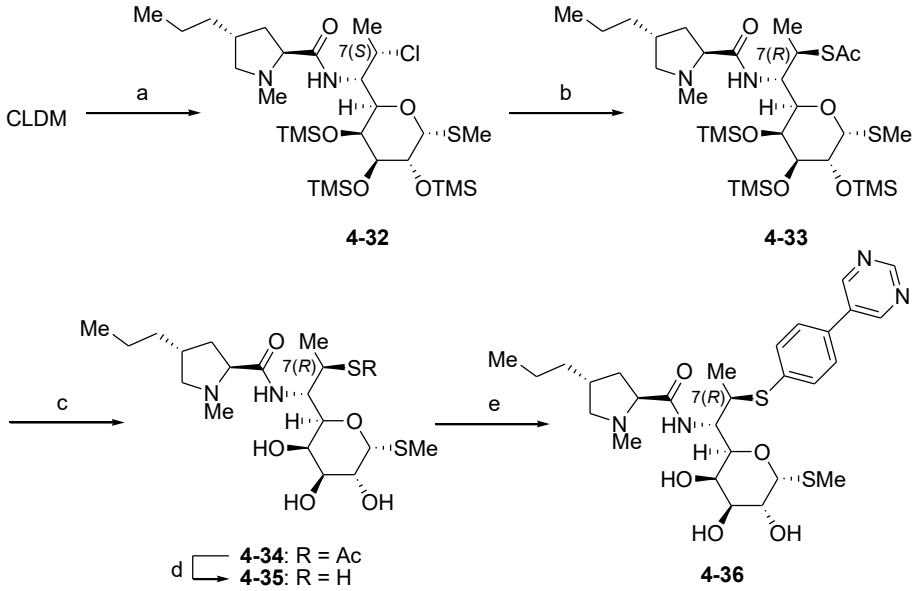
Synthesis of novel LCM derivatives possessing pyrazine or pyrimidine as a substituent on the phenyl group at the C-7 position is shown in Scheme 4-4. Compounds **4-29**~**4-31** possessing a benzene ring and an aromatic amine were also prepared by palladium-catalyzed cross-coupling reaction and their antibacterial activities were evaluated.




Scheme 4-4. Synthesis of (7*S*)-7-deoxy-7-pyrimidinylphenylthiolincomycin and (7*S*)-7-deoxy-7-pyrazinylphenylthiolincomycin derivatives.Conditions: a) Ar-Br, Xantphos, $Pd_2(dba)_3$, *i*$Pr_2NEt$, dioxane, reflux, 4-6 h, 47.6% (**4-29**), 92.6% (**4-30**), 78.8% (**4-31**).

### 4.4.2. Synthesis of (7*R*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin

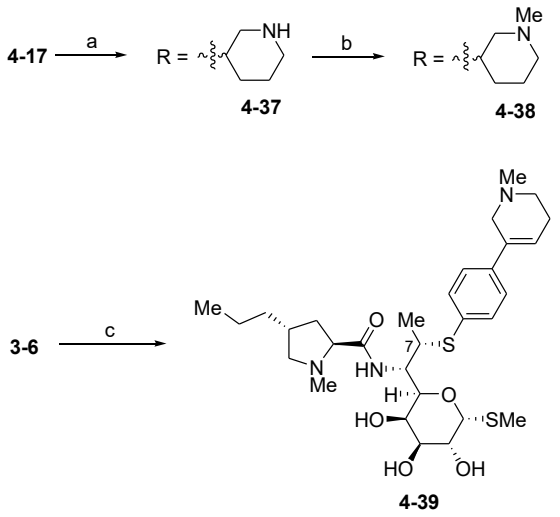
Synthesis of (7*R*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (**4-36**) is shown in Scheme 4-5. The author prepared compound **4-36** possessing a 4-(pyrimidin-5-yl)phenyl group with (7*R*)-configuration *via* sulfur atom at the C-7 position of LCM in order to evaluate its activity compared with that of compound **4-31** with the (7*S*)-configuration. Preparation of **4-36** began with protection of all hydroxyl groups of CLDM. The protected compound **4-32** was reacted with potassium thioacetate by an $S_N2$ reaction to give the corresponding thioacetate (**4-33**). Compound **4-34** was prepared by removal of all TMS groups of compound **4-33** under the acidic condition and followed by removal of the acetyl group to give a key intermediate **4-35**. The desired pyrimidinylphenylthio derivative (**4-36**) with (7*R*)-configuration was synthesized in application of 5-(4-bromophenyl)pyrimidine.




Scheme 4-5. Synthesis of (7*R*)-7-deoxy-7-thiolincomycin **4-35** and compound **4-36**. Conditions: a) TMSCl, HMDS, Py, r.t., 2 h, 97.3% (**4-32**); b) KSAc, DMF, 100°C, 18 h, not isolated (**4-33**); c) 1 N HCl, MeOH, r.t., 10 min, 17.6% in 2 steps (**4-34**); d) NaOMe, MeOH, r.t., 20 min, 20.9% (**4-35**); e) Xantphos, $Pd_2(dba)_3$, *i*$Pr_2$NEt, dioxane, reflux, 6.5 h, 44.9% (**4-36**).

### 4.4.3. Synthesis of novel LCM derivatives possessing a piperidin-3-yl, 1-methylpiperidin-3-yl or 1-methyl-1,2,5,6-tetrahydropyridin-3-yl group

Synthesis of novel LCM derivatives possessing a piperidin-3-yl, 1-methylpiperidin-3-yl or 1-methyl-1,2,5,6-tetrahydropyridin-3-yl group as a substituent on the phenyl group at the C-7 position is shown in Scheme 4-6. The pyridine ring of compound **4-17** was reduced to give the corresponding piperidin-3-yl derivative (**4-37**). Then, compound **4-37** was converted to the desired *N*-methyl derivative (**4-38**) by reductive aminoalkylation. Compounds **4-37** and **4-38** were isolated as a mixture of each diastereoisomer. Furthermore, compounds **4-39** were also prepared by palladium-catalyzed cross-coupling reaction.

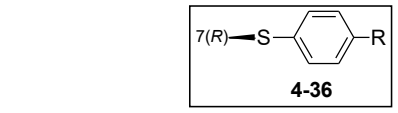



Scheme 4-6. Synthesis of (7*S*)-7-deoxyl-7-piperidinylphenylthiolincomycin derivatives. Conditions: a) Pt black, $H_2$, MeOH, 1 N HCl, r.t., 4 days, 33.5%; b) HCHO, AcOH, $NaBH(OAc)_3$, MeOH, r.t., 40 min, 75.8%; c) 3-(4-bromophenyl)-1-methyl-1,2,5,6-tetrahydropyridine, Xantphos, $Pd_2(dba)_3$, *i*$Pr_2$NEt, dioxane, reflux, 6 h, 76.8%.

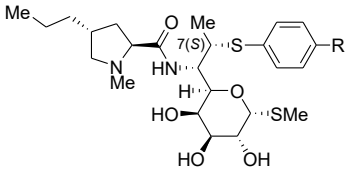
### 4.4.4. SAR analysis of optimized LCM derivatives possessing a six-membered hetero ring as a substituent on the phenyl group at the C-7 position

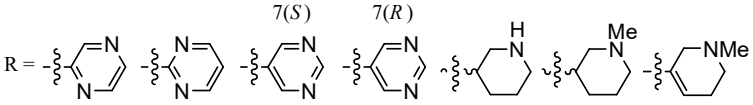
Antibacterial activities of optimized LCM derivatives possessing a six-membered hetero ring as a substituent on the phenyl group at the C-7 position are shown in Table 4-5. A pyrimidine analog (**4-31**) exhibited slightly improved antibacterial activities compared with the pyridin-3-yl analog (**4-17**) against *S. pneumoniae* and *H. influenzae*. Moreover, non-aromatic derivatives **4-37**~**4-39** also exhibited potent antibacterial activities against *S. pneumoniae* with *erm* gene and markedly improved activities against both *S. pyogenes* with *erm* gene and *H. influenzae*. The author has already reported the importance of (7*S*)-configuration to enhance antibacterial activities.[70] Then, the author also investigated the importance of (7*S*) stereochemistry in pyrimidinylphenyl analogs. As a result, the author could reconfirm that (7*S*)-configuration was important to improve antibacterial activities based on the comparison results of potency between compound **4-31** ((7*S*)-configuration) and compound **4-36** ((7*R*)-configuration). According to the previously reported docking simulation analysis[73] of (7*S*)-7-deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin, it was supposed that steric hindrance occurs between the 8-methyl group and a carbohydrate moiety in compound **4-36** and its three dimensional structure is not appropriate for antibacterial activity.

Table 4-5. Antibacterial activities (MIC, μg/mL) of optimized derivatives with a heterocycle and telithromycin (TEL).




**4-36**




R = 


| Test organism* | Characteristics** | **4-29** | **4-30** | **4-31** | **4-36** | **4-37** | **4-38** | **4-39** | TEL |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.015 | 0.015 | ≦0.008 | 0.06 | 0.015 | 0.015 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -2 | s | 0.015 | 0.015 | ≦0.008 | 0.06 | 0.015 | 0.015 | 0.015 | ≦0.008 |
| *S. pneumoniae* -3 | s | 0.015 | 0.015 | ≦0.008 | 0.06 | 0.03 | 0.03 | 0.015 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | 1 | 4 | 0.5 | >128 | 0.5 | 0.5 | 0.5 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | 1 | 8 | 1 | >128 | 1 | 0.5 | 0.5 | 0.03 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 4 | >64 | 2 | >128 | 2 | 1 | 1 | 1 |
| *S. pneumoniae* -7 | *ermAM* (i) | 0.5 | 1 | 0.25 | >64 | 0.25 | 0.25 | 0.5 | 0.03 |
| *S. pneumoniae* -8 | *ermAM* (i) | 0.25 | 2 | 0.25 | >64 | 0.25 | 0.25 | 0.25 | 0.03 |
| *S. pneumoniae* -9 | *mefE* efflux | ≦0.008 | ≦0.008 | ≦0.008 | 0.06 | ≦0.008 | ≦0.008 | 0.015 | 0.06 |
| *S. pyogenes* Cook | s | ≦0.008 | 0.015 | ≦0.008 | 0.03 | 0.015 | 0.015 | 0.015 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | 0.5 | 4 | 0.5 | 32 | 0.12 | 0.25 | 0.12 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | 0.015 | 0.03 | 0.015 | 0.03 | 0.03 | 0.03 | 0.015 | 0.25 |
| *H. influenzae* | s | 8 | 16 | 4 | >128 | 2 | 2 | 1 | 0.5 |
| *H. influenzae* -2 | s | 4 | 8 | 2 | 128 | 4 | 2 | 2 | 2 |
| *H. influenzae* -3 | s | 16 | >64 | 8 | >128 | 8 | 8 | 8 | 1 |
| *H. influenzae* -4 | ⊿acr | 0.12 | 0.25 | 0.06 | 2 | 0.12 | 0.06 | 0.12 | N.T. |

Abbreviations: N.T., Not tested; TEL, telithromycin; *All strains except standard organisms were clinically isolated.;
**(c): constitutive; (i): inducible; Gray shading strains are target strains.

## 4.5. Summary

The author was interested in lincomycin analogs possessing a phenyl ring and a hetero ring with basicity *via* sulfur atom at the C-7 position focusing on the (7*S*)-configuration. The author synthesized a variety of lincomycin analogs in application of the palladium-catalyzed cross-coupling reaction[66,68,69,73,74] of (7*S*)-7-deoxy-7-thiolincomycin (**3-6**) with an aryl bromide or an aryl iodide. This methodology was very useful to synthesize various (7*S*)-7-thio-modified lincomycin analogs. Antibacterial activities of lincomycin analogs with a linear moiety, which possessed one or two carbon atom(s) between the phenyl group and the dimethylamino group, were relatively effective against resistant bacteria. Furthermore, the author found that the location of the nitrogen atom was important to improve antibacterial activities based on the results of compounds **4-16**~**4-18**. Consequently, the author found that compounds **4-17**, **4-31** and **4-37**~**4-39**[74] had potent antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene and *H. influenzae*. On the other hand, the author confirmed that the (7*S*)-configuration was important to enhance antibacterial activities in the comparison results of potency between compound **4-31** ((7*S*)-configuration) and compound **4-36** ((7*R*)-configuration). Antibacterial activities against *S. pneumoniae* with *erm* gene of my novel derivatives reported in this Chapter were catching up with those of TEL, and the activities against *S. pyogenes* with *erm* gene and Streptococcus strains with *mef* gene of my selected derivative were stronger than those of TEL as shown in Table 4-5. The author selected the 4-(pyrimidin-5-yl)phenyl group in compound **4-31** as the C-7 substituent for further medicinal chemistry toward generation of candidates, because it exhibited physicochemical stability without additional stereochemistry.

# 5. Optimization of lincomycin analogs by chemical modification at the C-6 and C-7 positions (1)

## 5.1. Design, synthesis and SAR analysis of novel (7*S*)-7-(1,3,4-thiadiazoyl)thio-7-deoxylincomycin derivatives modified at the 1'- and/or 4'-position(s) at the proline moiety

### 5.1.1. Design of novel (7*S*)-substituted LCM derivatives modified at the 1'- and/or 4'-position(s) at the proline moiety

In the Chapter 2, the author reported (7*S*)-thiolincomycin analogs, such as compounds **2-17** and **2-31**, as the first generation derivatives (Figure 5-1). Those compounds possessed weak antibacterial activities against resistant *S. pneumoniae* with *erm* and *mef* genes but compound **5-1**[75] exhibited clearly improved activities compared with CAM, AZM, LCM, and CLDM as shown in Table 5-1 at page 49 (antibacterial activities of existing antibiotics are shown in Table 2-2)

Focusing on X-ray crystallographic analysis and in-house three dimensional simulation, the author could optimize a structure of the C-7 position such as a 4-(pyrimidin-5-yl)phenylthio group. Then, the author started chemical modification of a proline moiety at the 6-position without conversion of a pyrrolidine ring itself.

On the basis of the above hypothesis, the author designed and synthesized novel (7*S*)-substituted LCM derivatives modified at the 1'- and/or 4'-position(s) at the proline moiety. Antibacterial activities of these novel compounds are also disclosed in this Chapter 5.

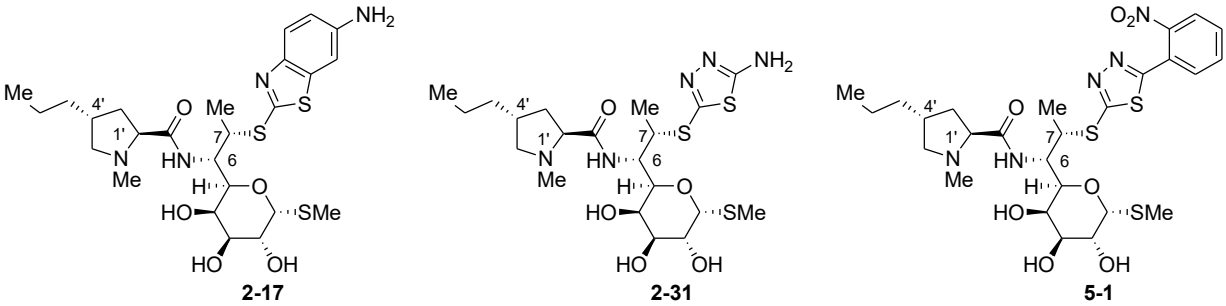
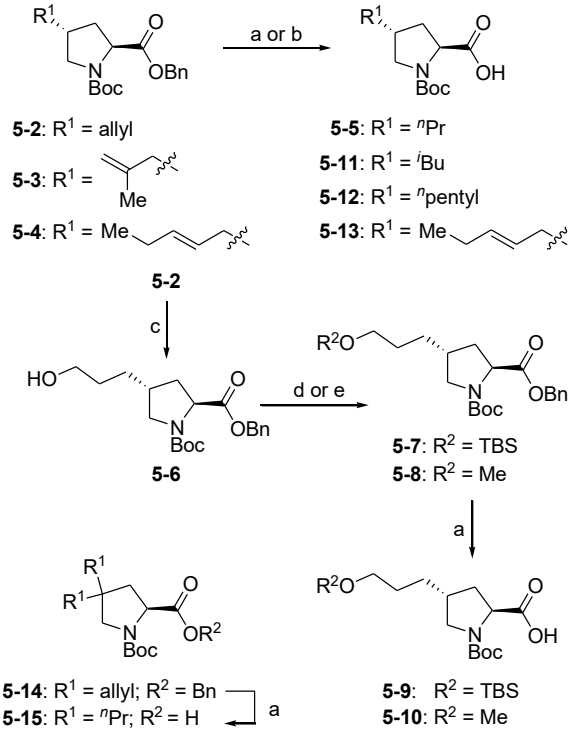



Figure 5-1. Chemical structures of lincomycin analogs **2-17**, **2-31** and **5-1**.

### 5.1.2. Synthesis of proline derivatives

Synthesis of proline derivatives is shown in Scheme 5-1. Synthetic route for modification of the proline

moiety at the 4'-position was already reported by several researchers.[76-79] The author firstly prepared starting materials (**5-2**~**5-4** and **5-14**), and compound **5-6** was synthesized by hydroboration of **5-2** followed by treatment with TBSCl or MeI under the basic condition to give compounds **5-7** and **5-8**. The compounds **5-2**~**5-4**, **5-7**, **5-8** and **5-14** were reduced with $H_2$ in the presence of Pd/C to give the corresponding carboxylic acids (**5-5**, **5-9**~**5-12** and **5-15**), respectively. Compound **5-13** was prepared by hydrolysis of **5-4**. $^1$H NMR spectra of compounds **5-5**, **5-6**, **5-8**, **5-11**~**5-13** and **5-15** were observed as two sets of signals because of a rotamer by the Boc group.

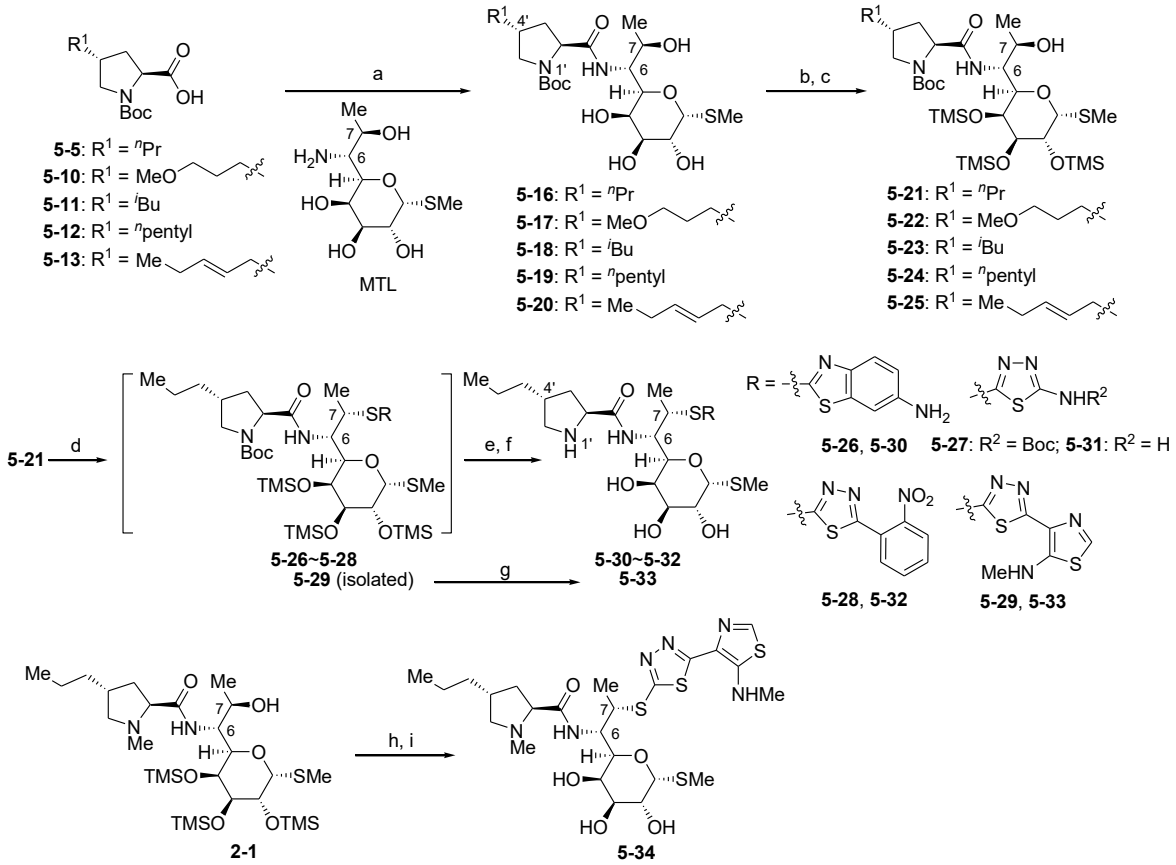



Scheme 5-1. Synthesis of proline derivatives. Conditions: a) $H_2$, Pd/C, MeOH, r.t., 0.5-4.5 h, quant (**5-5**), not isolated (**5-9**), not isolated (**5-10**), 95.7% (**5-11**), 89.5% (**5-12**), quant (**5-15**); b) 1 N NaOH, MeOH, r.t., 22 h, 94.5% (**5-13**); c) 1) 9-BBN,THF, 50°C, 1 h, 2) 1 N NaOH, 35% $H_2O_2$, 0°C, 2 h, 86.8% (**5-6**); d) TBSCl, imidazole, DMF, r.t., 0.5 h, not isolated (**5-7**); e) MeI, NaH, DMF, r.t., 1 h, 25.7% (**5-8**).

## 5.1.3. Synthesis of key intermediates 5-21 to 5-25 and transformation of 5-21 and 2-1

Synthesis of key intermediates **5-21**~**5-25** and transformations of **5-21** and **2-1** are shown in Scheme 5-2. Compounds **5-16**~**5-20** were synthesized by condensation of compounds **5-5** and **5-10**~**5-13** with methyl α-thiolincosaminide (MTL),[80] respectively. Tetra-*O*-trimethylsilylation of all hydroxyl groups and successive regioselective deprotection of the TMS group at the 7-position gave key intermediates (**5-21**~**5-25**). Furthermore, novel LCM derivatives **5-30**~**5-33** were synthesized *via* 2 or 3 steps from

compound **5-21** by the Mitsunobu reaction at the 7-position and deprotection of the TMS groups and the Boc group at the 1'-position. On the other hand, 1'-*N*-methyl analog **5-34** was prepared from **2-1** following the similar procedure as the above. $^1$H NMR spectra of compounds **5-16**~**5-18** and **5-21** were observed as two sets of signals because of a rotamer by the Boc group and compounds **5-23**~**5-25** showed broad peaks in $^1$H NMR spectra. Compounds **5-30**~**5-33** whose Boc groups were deprotected, however, showed a single set of signals and sharp peaks in $^1$H NMR spectra.



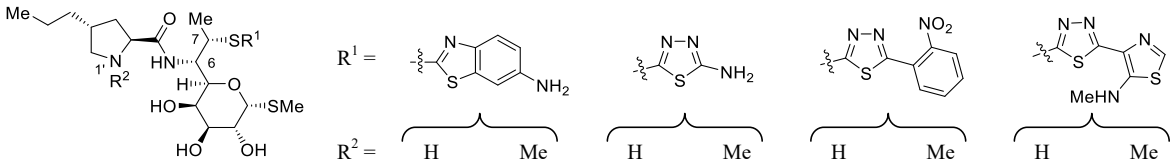

Scheme 5-2. Synthesis of key intermediates **5-21** to **5-25** and transformation of **5-21** and **5-34**. Conditions: a) DCC, HOBt, DMF, r.t., 3-23 h, not isolated (**5-16**), 88.5% (**5-17**), 92.7% (**5-18**), not isolated (**5-19**), not isolated (**5-20**); b) TMSCl, HMDS, Py, r.t., 30 min-1 h; c) 6 N AcOH, MeOH, r.t., 0.5-11 h, 70.6% in 3 steps (**5-21**), 68.7% in 2 steps (**5-22**), 79.8% in 2 steps (**5-23**), 74.0% in 3 steps (**5-24**), 81.8% in 3 steps (**5-25**); d) DEAD, $PPh_3$, HSR, THF, 0$^o$C to r.t., 3-18 h, not isolated (**5-26**, **5-27**, **5-28**), 34.2% (**5-29**); e) 1 N HCl, MeOH, r.t., 0.5-2.5 h; f) 4 N HCl-EtOAc, MeOH, r.t., 2-2.5 h, 61.4% in 3 steps (**5-30**), 17.8% in 3 steps (**5-31**), 19.4% in 3 steps (**5-32**); g) 4 N HCl-EtOAc, MeOH, 0$^o$C to r.t., 3.5 h 68.3% (**5-33**); h) DEAD, $PPh_3$, 5-(5-(methylamino)thiazol-4-yl)-1,3,4-thiadiazole-2-thiol, THF, r.t., 2 h; i) 1 N HCl, MeOH, r.t., 1 h, 37.0% in 2 steps (**5-34**).

## 5.1.4. SAR analysis of 7-*S*-substituted 1'-*N*H LCM derivatives (5-30~5-33) and 1'-*N*-Me analog 5-34

Antibacterial activity of LCM was reduced by 1'-*N*-demethylation, but that of CLDM was enhanced by

1'-*N*-demethylation. Thus, the author was interested in the potency of 1'-*N*-demethyl products of (7*S*)-7-substituted LCM derivatives (**2-17**, **2-31** and **5-1** shown in Table 5-1). So, the author synthesized 1'-demethyl analogs **5-30**~**5-32** and compounds **5-33** and **5-34** possessing an alternative 7-substituent. Antibacterial activities of those derivatives are shown in Table 5-1. Among them, 1'-*N*H derivatives **5-30**, **5-32** and **5-33** exhibited improved antibacterial activities against *S. pneumoniae* with *erm* gene compared with the corresponding 1'-*N*-methyl analogs (**2-17**, **5-1** and **5-34**), respectively. Because **5-32** and **5-33** especially showed enhanced antibacterial activities against the target pathogens, the author found that double modifications at the C-6 and C-7 positions were important to further improve antibacterial activities against *S. pneumoniae* with *erm* gene.

Table 5-1. Antibacterial activities (MIC, μg/mL) of 7-*S*-substituted 1'-*N*H LCM derivatives (**5-30**~**5-33**) and 1'-*N*-Me analog **5-34**.



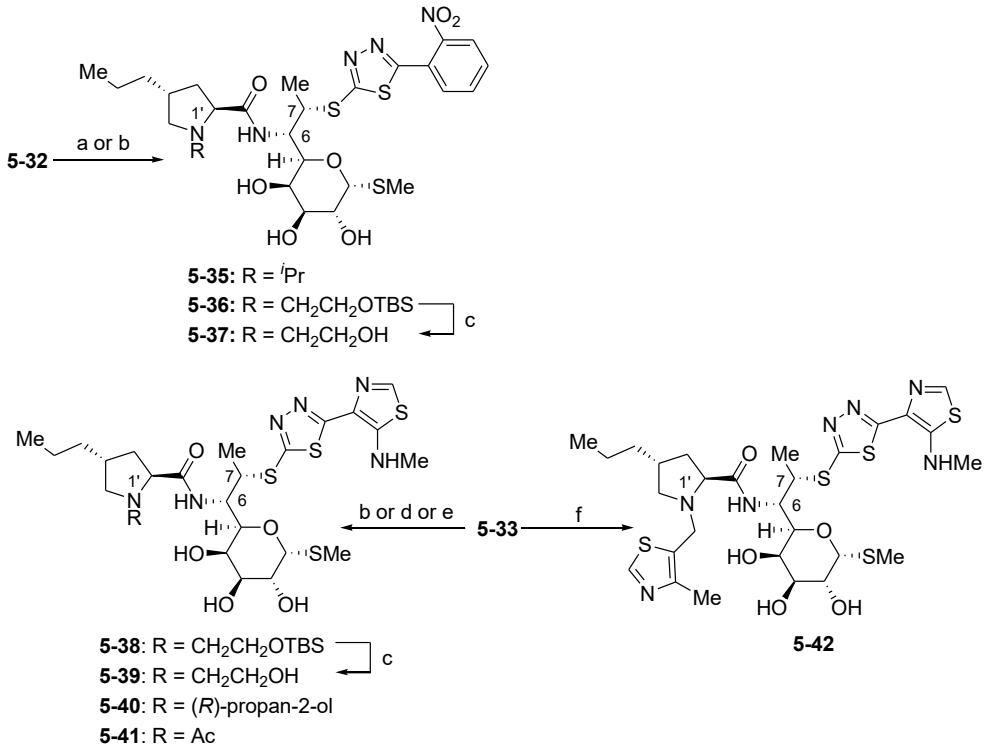

| Test organism* | Characteristics** | **5-30** | **2-17** | **5-31** | **2-31** | **5-32** | **5-1** | **5-33** | **5-34** |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.06 | 0.06 | 0.5 | 0.03 | 0.03 | 0.015 | 0.12 | 0.12 |
| *S. pneumoniae* -2 | s | 0.12 | 0.06 | 0.5 | 0.06 | 0.03 | 0.015 | 0.12 | 0.12 |
| *S. pneumoniae* -3 | s | 0.03 | 0.03 | 0.5 | 0.06 | 0.03 | 0.03 | 0.12 | 0.12 |
| *S. pneumoniae* -4 | *ermAM* (c) | 8 | 16 | 128 | 16 | 1 | 4 | 1 | 2 |
| *S. pneumoniae* -5 | *ermAM* (c) | 64 | 64 | >128 | 64 | 2 | 8 | 2 | 4 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 64 | 64 | >128 | 128 | 8 | 16 | 8 | 16 |
| *S. pneumoniae* -7 | *ermAM* (i) | 8 | 16 | 128 | 16 | 1 | 2 | 2 | 4 |
| *S. pneumoniae* -8 | *ermAM* (i) | 8 | 8 | 128 | 16 | 1 | 2 | 2 | 2 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.06 | 0.06 | 0.5 | 0.03 | 0.015 | 0.015 | 0.12 | 0.06 |
| *S. pyogenes* Cook | s | 0.03 | 0.03 | 0.5 | 0.03 | 0.03 | 0.03 | 0.12 | 0.12 |
| *S. pyogenes* -2 | *ermAM* (c) | 8 | 8 | 32 | 8 | 1 | 2 | 1 | 2 |
| *S. pyogenes* -3 | *mefE* efflux | 0.12 | 0.06 | 0.5 | 0.06 | 0.06 | 0.03 | 0.12 | 0.12 |
| *H. influenzae* | s | 32 | 8 | 64 | 8 | 16 | 16 | 8 | 4 |
| *H. influenzae* -2 | s | 32 | 4 | >128 | 4 | 8 | 8 | 8 | 4 |
| *H. influenzae* -3 | s | 32 | 32 | 128 | 8 | 16 | 16 | 16 | 16 |
| *H. influenzae* -4 | ⊿acr | 0.5 | 0.25 | 8 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible; Gray shading strains are target

## 5.1.5. Synthesis of 1'-*N*-modified novel LCM derivatives possessing a substituted 1,3,4-thiadiazol-2-ylthio group at the 7-position

Synthesis of 1'-*N*-modified novel LCM derivatives possessing a substituted 1,3,4-thiadiazol-2-ylthio group at the 7-position is shown in Scheme 5-3. Desired 1'-*N*-modified derivatives **5-35**, **5-36**, **5-38** and **5-42** were prepared from **5-32** or **5-33** by reductive aminoalkylation. Consequently, the TBS groups of **5-36**

and **5-38** were removed by TBAF to give compounds **5-37** and **5-39**, respectively. Compound **5-40** was synthesized in application of (*R*)-2-methyloxirane under the basic condition from **5-33**. Compound **5-41** was also prepared by acetic anhydride from **5-33**.



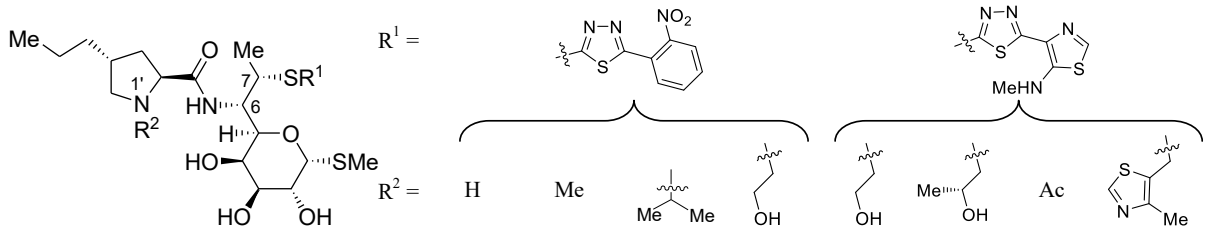

Scheme 5-3. Synthesis of 1'-*N*-modified novel LCM derivatives possessing a substituted 1,3,4-thiadiazol-2-ylthio group at the 7-position. Conditions: a) acetone, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, 0°C to r.t., 15 h, 61.7% (**5-35**); b) 2-(*tert*-butyldimethylsilyloxy)acetaldehyde, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, 0 °C to r.t., 15 h 44% (**5-36**), 58.5% (**5-38**); c) TBAF, THF, 0°C to r.t., 5-15 h 72.1% (**5-37**), 67.0% (**5-39**); d) (*R*)-2-methyloxirane, $^iPr_2NEt$, MeOH, 0°C, 16 h, 33.7% (**5-40**); e) $Ac_2O$, MeOH, 0°C, 1.5 h, 33.4% (**5-41**); f) 4-methylthiazole-5-carbaldehyde, $NaBH(OAc)_3$, AcOH, MeOH, r.t., 15 h, 22.5% (**5-42**).

## 5.1.6. SAR analysis of antibacterial activities of 7-*S*-substituted 1'-*N*-modified LCM derivatives

For the purpose of accumulating detail information of SAR at the 1'-position, the author synthesized novel LCM derivatives possessing various substituents at the 1'-position. At this point, the 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl group and the 5-(5-methylamino-thiazol-4-yl)-1,3,4-thiadiazol-2-yl group were selected as a 7-substituent because of their SAR analysis (Tables 5-1). Consequently, compounds **5-37** and **5-39**, possessing a 2-hydroxyethyl group at the 1'-position, showed antibacterial activities against target pathogens as shown in Table 5-2, but the author concluded that it was difficult to enhance antibacterial

activities against *S. pneumoniae* with *erm* gene by introducing an alternative substituent at the 1' position except a hydrogen atom or a methyl group. These results were closely related to SAR of 1'-*N*-alkyl-1'-demethyllincomycin.[37,42,45,54] Then, the author selected a hydrogen atom and a methyl group at the 1'-position for further modification of the proline moiety.

Table 5-2. Antibacterial activities (MIC, μg/mL) of 7-*S*-substituted 1'-*N*-modified LCM derivatives (**5-35**, **5-37**, **5-39**~**5-42**).



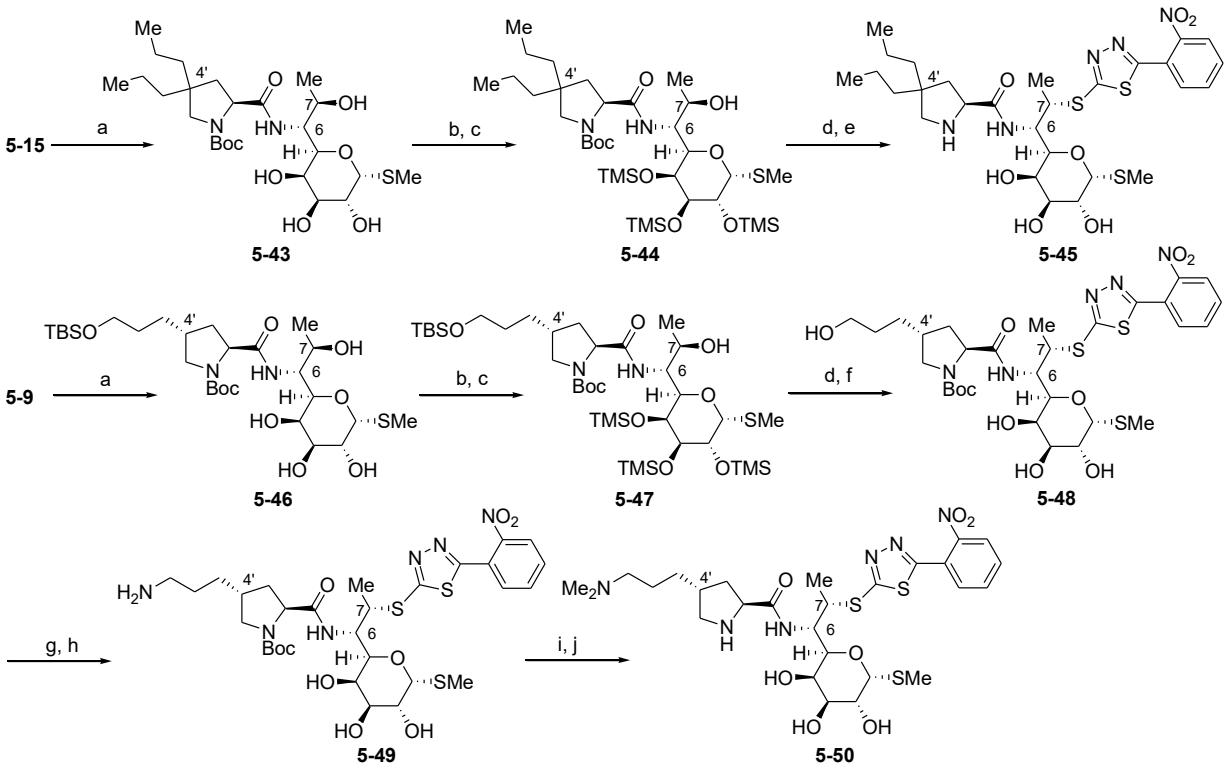

| Test organism* | Characteristics** | **5-32** | **5-1** | **5-35** | **5-37** | **5-39** | **5-40** | **5-41** | **5-42** |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.03 | 0.015 | 0.5 | 0.06 | 0.12 | 2 | 2 | 1 |
| *S. pneumoniae* -2 | s | 0.03 | 0.015 | 0.5 | 0.06 | 0.12 | 4 | 2 | 2 |
| *S. pneumoniae* -3 | s | 0.03 | 0.03 | 0.5 | 0.06 | 0.12 | 2 | 2 | 2 |
| *S. pneumoniae* -4 | *ermAM* (c) | 1 | 4 | 128 | 8 | 2 | >128 | 64 | 128 |
| *S. pneumoniae* -5 | *ermAM* (c) | 2 | 8 | 128 | 8 | 2 | >128 | 64 | 128 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 8 | 16 | >128 | 64 | 16 | >128 | 128 | >128 |
| *S. pneumoniae* -7 | *ermAM* (i) | 1 | 2 | 128 | 4 | 2 | >128 | 64 | 128 |
| *S. pneumoniae* -8 | *ermAM* (i) | 1 | 2 | 128 | 4 | 2 | >128 | 64 | 128 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.015 | 0.015 | 0.5 | 0.03 | 0.06 | 1 | 1 | 1 |
| *S. pyogenes* Cook | s | 0.03 | 0.03 | 0.5 | 0.03 | 0.12 | 2 | 2 | 2 |
| *S. pyogenes* -2 | *ermAM* (c) | 1 | 2 | 64 | 4 | 1 | >128 | 32 | 32 |
| *S. pyogenes* -3 | *mefE* efflux | 0.06 | 0.03 | 1 | 0.06 | 0.12 | 2 | 2 | 2 |
| *H. influenzae* | s | 16 | 16 | >128 | 16 | 4 | >128 | >128 | >128 |
| *H. influenzae* -2 | s | 8 | 8 | >128 | 8 | 4 | >128 | >128 | >128 |
| *H. influenzae* -3 | s | 16 | 16 | >128 | 32 | 16 | >128 | >128 | >128 |
| *H. influenzae* -4 | ⊿acr | 0.25 | 0.25 | 16 | 0.25 | 0.25 | 32 | 16 | 8 |

*All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains

## 5.1.7. Synthesis of novel LCM derivatives possessing a germinal bis-*n*-propyl moiety or a 3-(dimethylamino)propyl group at the 4'-position

Synthesis of novel LCM derivatives **5-45** and **5-50** is shown in scheme 5-4, which possess a geminal bis-*n*-propyl moiety and a 3-(dimethylamino)propyl group, respectively, at the 4'-position, and have 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio group at the 7-position. Key intermediates **5-44** and **5-47** were respectively synthesized in application of condensation, tetrakis-*O*-trimethylsilylation and selective deprotection with the similar procedure to compound **5-21**. And then, a 7-*S*-substituent was introduced to

**5-44** by the Mitsunobu reaction, and deprotection gave a desired derivative **5-45**. Compound **5-47** was transformed to **5-48** by the Mitsunobu reaction and desilylation. Then, compound **5-48** was reacted with sodium azide, and an azide group was reduced to an amino group with triphenylphosphine-water. The afforded amino group in **5-49** was applied with reductive aminoalkylation followed by deprotection of the Boc group under the acidic condition with TFA to give the desired novel derivative **5-50**. $^1$H NMR spectra of compounds **5-44** and **5-47** were also observed as broad peaks by the influence of a Boc group. Although the final product **5-50** could be purified as a single molecule, both intermediates **5-48** and **5-49** partially included impurity that was not removed by purification steps.

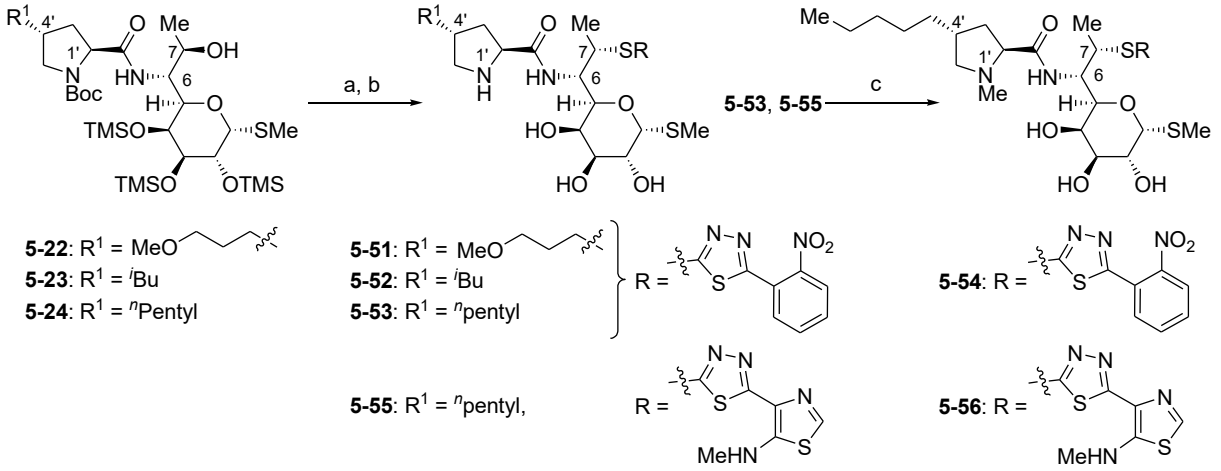



Scheme 5-4. Synthesis of 4'-*N*-modified novel LCM derivatives possessing the 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio group at the 7 position. Conditions: a) MTL, DCC, HOBt, DMF, r.t., 14 h, not isolated (**5-43**), 62.5% in 3 steps from **5-6** (**5-46**); b) TMSCl, HMDS, Py, r.t., 20 min-1 h; c) 6 N AcOH, MeOH, r.t., 1-1.5 h, 41.6% in 3 steps (**5-44**), 74.8% in 2 steps (**5-47**); d) 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol, DEAD, $PPh_3$, THF, 0°C to r.t., 6-10 h; e) TFA, 0°C to r.t., 30 min, 36.1% in 2 steps (**5-45**); f) TBAF, AcOH, THF, r.t., 5 h, 96.7% in 2 steps with unseparable impurity (**5-48**); g) $NaN_3$, $CBr_4$, $PPh_3$, DMF, r.t. to 50°C, 2 h; h) $PPh_3$, $H_2O$, THF, r.t. to 50°C, 2 h, 90.1% in 2 steps with unseparable impurity (**5-49**); i) HCHO, $NaBH(OAc)_3$, AcOH, MeOH, r.t., 20 min; j) TFA, 0°C to r.t., 30 min, 57.6% in 2 steps (**5-50**).

## 5.1.8. Synthesis of novel LCM derivatives with a variety of 4'-substituents possessing the substituted 1,3,4-thiadiazol-2-ylthio group at the 7-position

Synthesis of novel LCM derivatives is shown in Scheme 5-5, which have a 3-methoxypropyl, an *i*-butyl,

or an *n*-pentyl group at the 4'-position and the substituted 1,3,4-thiadiazol-2-yl-thio group at the 7-position. Compounds **5-51**~**5-53** and **5-55** were prepared from key intermediates **5-22**~**5-24** by the similar procedure to compound **5-45**. Reductive aminoalkylation of **5-53** and **5-55** afforded the desired compounds **5-54** and **5-56**, respectively.

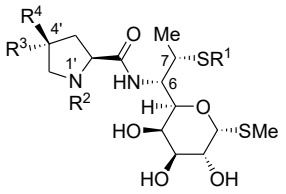


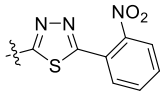

Scheme 5-5. Synthesis of novel LCM derivatives with a variety of 4'-substituents possessing the substituted 1,3,4-thiadiazol-2-yl-thio group at the 7-position. Conditions: a) DEAD, $PPh_3$, HSR, THF, 0°C to r.t., 15-24 h; b) TFA, 0°C to r.t., 15-30 min, 48.3% in 2 steps (**5-51**), 22.5% in 2 steps (**5-52**), 20.9% in 2 steps (**5-53**), 17.2% in 2 steps (**5-55**); c) HCHO, $NaBH(OAc)_3$, AcOH, MeOH, r.t., 1 h, 85.7% (**5-54**), 80.3% (**5-56**).

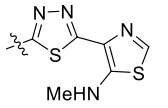
## 5.1.9. SAR analysis of 7-*S*-substituted 1'-*N*- and 4'-modified LCM derivatives and telithromycin (TEL)

In order to confirm whether 7-*S*-substituted LCM analogs with 1,3,4-thiadiazole analog show similar SAR to those previously reported by other groups,[37,42,56,57] the author synthesized 1'-demethyllincomycin derivatives possessing various substituents at the 4'-position. Structures of 7-*S*-substituents are same as those in Table 5-2. As shown in Table 5-3, compounds **5-53** and **5-54**, possessing an *n*-pentyl group instead of an *n*-propyl group at the 4'-position, exhibited unexpectedly strong antibacterial activities against resistant bacteria with *erm* gene. Although antibacterial activities of telithromycin (TEL) against *S. pneumoniae* with *erm* gene were stronger than those of **5-53**, antibacterial activities of **5-53** against *S. pyogenes* with *erm* gene and resistant bacteria with *mef* gene were remarkably stronger than those of TEL.

Table 5-3. Antibacterial activities (MIC, mg/mL) of 7-*S*-substituted 1'-*N*- and 4'-modified LCM derivatives (**5-45**, **5-50**~**5-56**) and telithromycin (TEL).







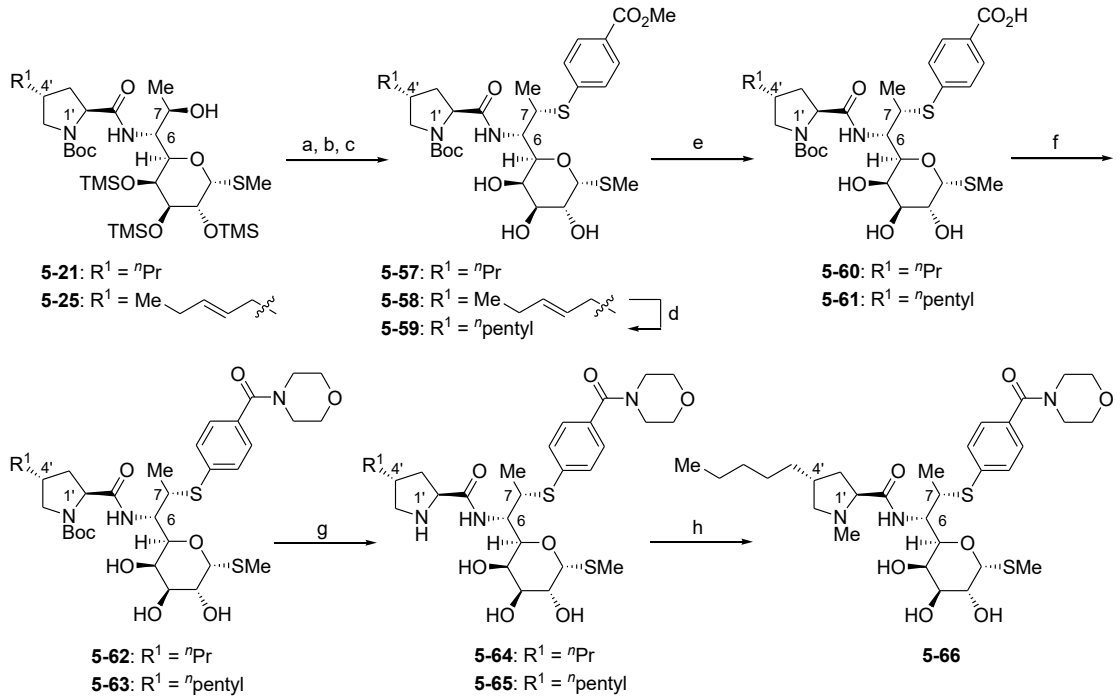
| | | $R^1$ = | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^2$ = | H | H | H | H | H | Me | H | Me | |
| | | $R^3$ = | $^n$Pr | 3-$NMe_2$-Pr | 3-MeO-Pr | $^i$Bu | $^n$pentyl | $^n$pentyl | $^n$pentyl | $^n$pentyl | |
| | | $R^4$ = | $^n$Pr | H | H | H | H | H | H | H | |
| Test organism* | Characteristics** | | **5-45** | **5-50** | **5-51** | **5-52** | **5-53** | **5-54** | **5-55** | **5-56** | TEL |
| *S. pneumoniae* DP1 TypeI | s | | 16 | 128 | 0.06 | 0.06 | ≦0.008 | ≦0.008 | 0.03 | 0.03 | ≦0.008 |
| *S. pneumoniae* -2 | s | | 16 | 128 | 0.06 | 0.06 | ≦0.008 | 0.015 | 0.06 | 0.06 | ≦0.008 |
| *S. pneumoniae* -3 | s | | 16 | 32 | 0.06 | 0.03 | ≦0.008 | ≦0.008 | N.T. | 0.015 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | | 64 | >128 | 32 | 32 | 0.5 | 1 | 1 | 2 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | | 64 | >128 | 16 | 32 | 0.5 | 1 | 2 | 4 | 2 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | | 64 | >128 | 64 | 128 | 2 | 4 | 4 | 8 | 1 |
| *S. pneumoniae* -7 | *ermAM* (i) | | 64 | >128 | 8 | 8 | N.T. | N.T. | N.T. | N.T. | 0.03 |
| *S. pneumoniae* -8 | *ermAM* (i) | | 64 | >128 | 8 | 8 | 0.5 | 0.5 | 1 | 2 | 0.03 |
| *S. pneumoniae* -9 | *mefE* efflux | | 16 | 64 | 0.06 | 0.03 | ≦0.008 | ≦0.008 | 0.06 | 0.015 | 0.06 |
| *S. pyogenes* Cook | s | | 2 | 8 | 0.06 | 0.03 | 0.015 | 0.015 | 0.12 | 0.06 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | | 64 | >128 | 8 | 8 | 0.5 | 0.5 | 0.5 | 0.5 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | | 8 | 8 | 0.12 | 0.06 | 0.015 | 0.03 | 0.06 | 0.06 | 0.25 |
| *H. influenzae* | s | | >128 | >128 | 128 | 64 | 8 | 8 | 16 | 8 | 0.5 |
| *H. influenzae* -2 | s | | 128 | >128 | 128 | 32 | 8 | 4 | 8 | 4 | 2 |
| *H. influenzae* -3 | s | | >128 | >128 | >128 | 128 | 16 | 8 | 16 | 8 | 1 |
| *H. influenzae* -4 | ⊿acr | | 32 | >128 | 2 | 2 | 0.25 | 0.06 | 0.25 | 0.12 | 0.25 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains

## 5.2. Synthesis and SAR analysis of novel (7*S*)-7-deoxy-7-phenylthiolincomycin derivatives modified at the 1'- and/or 4'-position(s) at the proline moiety

### 5.2.1. Synthesis of proline-modified novel LCM derivatives possessing a 4-(morpholinocarbonyl)phenylthio group at the 7-position

Synthesis of proline-modified novel LCM derivatives possessing a 4-(morpholinocarbonyl)phenylthio group at the 7-position is shown in Scheme 5-6. Because LCM derivatives possessing a 4-(morpholinocarbonyl)phenylthio group at the 7-position exhibited improved antibacterial activities, the author designed compounds **5-64**~**5-66**. The author already reported the Ms (methane sulfonyl) route[70,73] to introduce a phenyl group *via* sulfur atom at the 7-position. The Ms route was applied to compounds **5-21** and **5-25** to give intermediates **5-57** and **5-58**, respectively. $^1$H NMR spectra of compounds **5-57**~**5-59** were observed as two sets of signals because of a rotamer by the Boc group.



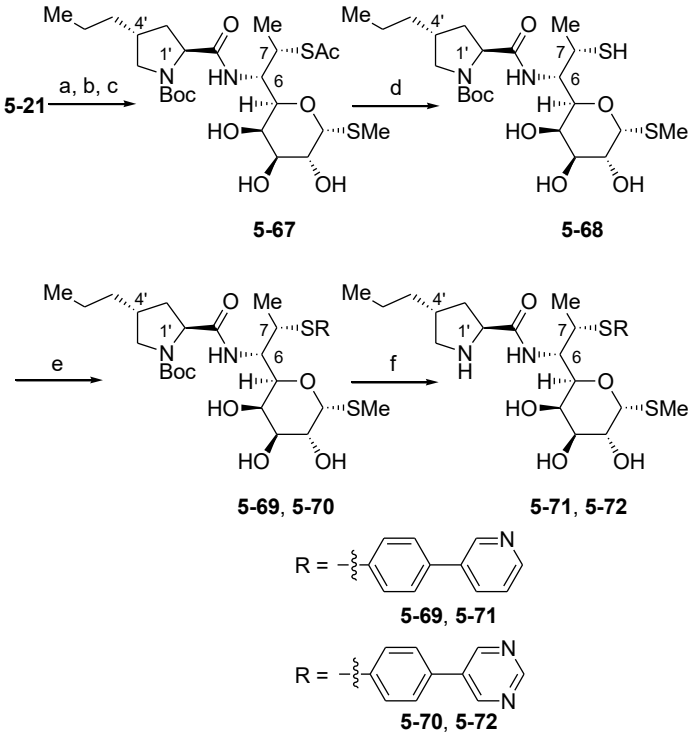

Scheme 5-6. Synthesis of proline-modified novel LCM derivatives possessing a 4-(morpholinocarbonyl)phenylthio group at the 7-position. Conditions: a) MsCl, $NEt_3$, $CHCl_3$, r.t., 30 min; b) methyl 4-mercaptobenzoate, $K_2CO_3$, DMF, 80-100°C, 1-6 h; c) 1 N HCl, MeOH, r.t., 20 min, 27.6% in 3 steps (**5-57**), 92.2% in 3 steps (**5-58**); d) $H_2$, Pd/C, MeOH, r.t.,15 h, 92.1%; e) 1 N NaOH, MeOH, r.t., 1-7 days, 94.7% (**5-60**), 96.1% (**5-61**); f) morpholine, WSC, HOBt, DMF, r.t. 22-62 h, 96.8% (**5-62**), 81.3% (**5-63**); g) TFA, -15°C to 0°C, 40 min, 56.5% (**5-64**), 80.6% (**5-65**); h) HCHO, AcOH, $NaBH(OAc)_3$, MeOH, 30 min, 97.8%.

The desired analogs **5-64** and **5-65** were prepared from **5-57** and **5-59**, respectively, by (i) hydrolysis under the basic condition, (ii) condensation with morpholine, and (iii) deprotection of the Boc group with

TFA. Compound **5-66** was synthesized from **5-65** by reductive aminoalkylation with HCHO and $NaBH(OAc)_3$ in an acidic condition by AcOH.

## 5.2.2. Synthesis of 1'-*N*H analogs possessing a biaryl substituent *via* sulfur atom at the 7-position

Synthesis of novel LCM derivatives **5-71** and **5-72** is shown in Scheme 5-7. The author has already reported a palladium-catalyzed cross-coupling route to introduce an aryl group at the 7-position of (7*S*)-7-deoxy-7-mercaptolincomycin.[73,74] A key intermediate **5-68** was prepared *via* 4 steps from **5-21**, and precursors **5-69** and **5-70** were synthesized by palladium-catalyzed cross-coupling reaction of **5-68**[72-74] with the corresponding bromides. Deprotection of the Boc group afforded the desired analogs **5-71** and **5-72**. $^1$H NMR spectra of compounds **5-69** and **5-70** were observed as two sets of signals because of a rotamer by the Boc group, but both of the final compounds **5-71** and **5-72** showed a single set and sharp peaks in NMR spectra.

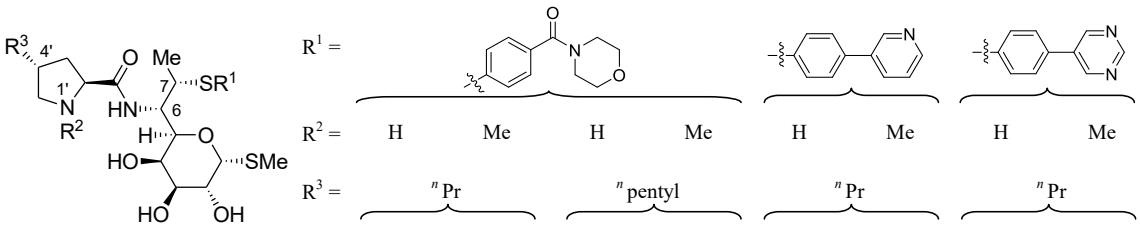



Scheme 5-7 Synthesis of 1'-*N*H analogs possessing a biaryl substituent *via* sulfer atom at the 7-position. Conditions: a) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C,1 h; b) AcSK, DMF, 60°C, 10 h, 40.2% in 2 steps; c) 1 N HCl, MeOH, r.t., 1 h, 87.6%; d) NaOMe, MeOH, r.t., 1.5 h, 95.1%; e) 3-(4-bromophenyl)pyridine or 5-(4-bromophenyl)pyrimidine, $Pd_2(DBA)_3$, Xantphos, *i*-$Pr_2NEt$, dioxane, reflux, 5-6 h, 80.4% (**5-69**), 77.7% (**5-70**); f) TFA, $CH_2Cl_2$, -20°C to r.t., 3-5.5 h, 92.7% (**5-71**), 82.1% (**5-72**).

## 5.2.3. SAR analysis of 1'-*N*- and 4'-modified LCM derivatives with a 4-(substituted) phenylthio group at the 7-position

The author have reported significant potent antibacterial activities of LCM derivatives possessing a substituted phenyl group at the C-7 position so far.[74] Here, the author transformed the proline moiety (the 1'- and 4'-position) of 7-*S*-substituted phenyl derivatives and afforded (7*S*)-7-{4-(morphorinocarbonyl)phenylthio}lincomycin (**3-18**), (7*S*)-7-{4-(pyridin-3-yl)phenylthio}lincomycin (**4-17**), and (7*S*)-7-{4-(pyrimidin-5-yl)phenylthio}lincomycin (**4-31**). Their partial structures are shown in Table 5-4. The *n*-pentyl analogs **5-65** and **5-66** could not exhibit improved antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene compared with the corresponding substituted 1,3,4-thiadiazolyl derivatives **5-53** and **5-54** (Table 5-3). On the other hand, 1'-*N*H LCM derivatives **5-71** and **5-72** with a 4-(pyridin-3-yl)phenyl group and a 4-(pyrimidin-5-yl)phenyl group, respectively, exhibited markedly potent antibacterial activities against *S. pneumoniae* with *erm* gene. The author confirmed that combination modification at the C-6 position (the proline moiety) and the C-7 position was important to enhance antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene.

Table 5-4. Antibacterial activities (MIC, μg/mL) of 1'-*N*- and 4'-modified LCM derivatives with a 4-(substituted)phenylthio group at the 7-position.




| Test organism* | Characteristics** | **5-64** | **3-18** | **5-65** | **5-66** | **5-71** | **4-17** | **5-72** | **4-31** |
|---|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.25 | 0.06 | N.T. | N.T. | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -2 | s | 0.25 | 0.06 | 0.12 | 0.06 | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -3 | s | 0.25 | 0.06 | 0.25 | 0.12 | 0.03 | 0.015 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | 16 | 8 | 4 | 4 | 1 | 0.5 | 0.5 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | 16 | 2 | 8 | 4 | 2 | 1 | N.T. | 1 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 64 | 8 | 16 | 16 | 4 | 2 | 2 | 2 |
| *S. pneumoniae* -7 | *ermAM* (i) | 4 | 2 | 2 | 1 | 0.5 | 0.25 | 0.25 | 0.25 |
| *S. pneumoniae* -8 | *ermAM* (i) | 8 | 1 | 0.5 | 0.5 | 0.5 | 0.25 | 0.25 | 0.25 |
| *S. pneumoniae* -9 | *mefE* efflux | 0.25 | 0.03 | 0.06 | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pyogenes* Cook | s | 0.12 | 0.06 | 0.12 | 0.12 | 0.03 | 0.015 | ≦0.008 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | 4 | 4 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| *S. pyogenes* -3 | *mefE* efflux | 0.25 | 0.06 | 0.12 | 0.06 | 0.03 | 0.015 | ≦0.008 | 0.015 |
| *H. influenzae* | s | 32 | 4 | 32 | 8 | 8 | 4 | 8 | 4 |
| *H. influenzae* -2 | s | 64 | 4 | 32 | 8 | 8 | 2 | 4 | 2 |
| *H. influenzae* -3 | s | 128 | 16 | 32 | 16 | 16 | 16 | 8 | 8 |
| *H. influenzae* -4 | ⊿acr | 2 | 0.25 | 1 | 0.12 | 0.25 | 0.06 | 0.12 | 0.06 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible;
Gray shading strains are target strains

## 5.3. Summary

In order to modify both the C-6 position (the proline moiety) and the C-7 position of LCM, The author firstly prepared various substituted proline intermediates. The intermediates were coupled with MTL to give a wide variety of 1'-*N*-Boc-1'-demethyllincomycin derivatives. The 7-*S*-substituents were introduced as follows. Key intermediates **2-1**, **5-21**~**5-24**, **5-44** and **5-47** were reacted with the corresponding thiols by the Mitsunobu reaction.[70,73] On the Other hand, intermediates **5-21** and **5-25** were transformed to 7-*S*-benzoate by an $S_N2$ reaction[70,73] of the corresponding methansulfnates. A methylbenzoate was finally converted to a 4-(morpholinocarbonyl)phenyl moiety (Scheme 5-6). (7*S*)-7-Deoxy-7-thiolincomycin (**5-68**) was coupled with biaryl bromide under the palladium-catalyzed cross-coupling reaction (Scheme 5-7).[72-74] Compounds **5-35**, **5-37**, **5-39**~**5-42** were also prepared from **5-32** or **5-33**. Those methodologies were found to be very practical to synthesize various lincomycin analogs modified at the C-6 and -7 positions.

By SAR analysis of combination modification at the 1'- and 7-position, the author concluded that it was difficult to enhance antibacterial activities against *S. pneumoniae* with *erm* gene by introducing relatively larger substituent at the 1'-position except a hydrogen atom or a methyl group. Then, the author selected a hydrogen atom and a methyl group at the 1'-position for further modification of the proline moiety. The author next modified the 4'-position (in the proline moiety) of LCM derivatives possessing a 5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl group or a 5-(5-methylamino-thiazol-4-yl)-1,3,4-thiadiazol-2-yl group at the C-7 position (Schemes 5-4 and 5-5). Compounds **5-53** and **5-54**, possessing an *n*-pentyl group instead of an *n*-propyl group at the 4'-position, exhibited strong antibacterial activities against resistant bacteria with *erm* gene (Table 5-3).[81,82] Although antibacterial activities of telithromycin (TEL) against *S. pneumoniae* with *erm* gene were stronger than those of **5-53**, antibacterial activities of **5-53** against *S. pyogenes* with *erm* gene and resistant bacteria with *mef* gene were remarkably stronger than those of TEL. The author found that combination modification at the C-6 position (the proline moiety) and the C-7 position was quite important to enhance antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. The above SAR might be partially related to the polarity or water solubility of a molecule, but SAR required so far were still limited and insufficient. Further combination modification at the C-6 and C-7 positions of lincomycin analogs is discussed in the Chapter 6.

# 6. Optimization of lincomycin analogs by chemical modification at the C-6 and C-7 positions (2)

## 6.1. Design, synthesis and SAR analysis of novel (7*S*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin derivatives modified at the C-6 position

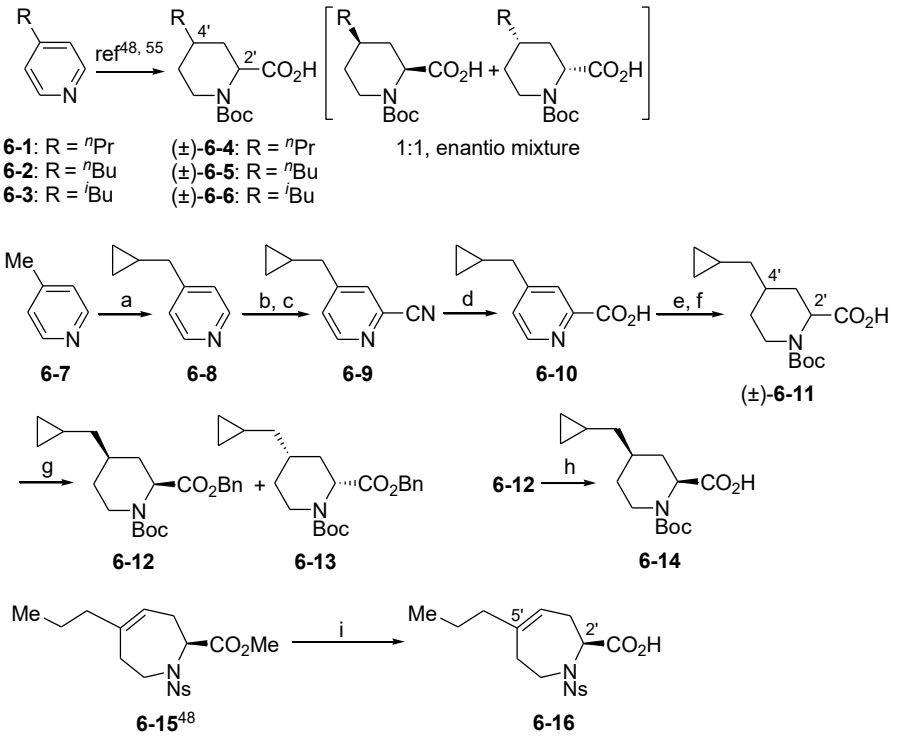
### 6.1.1. Design of novel (7*S*)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin derivatives modified at the C-6 position

In the Chapter 5, the author reported that novel (7*S*)-substituted analogs[81] modified at the N-1' and C-4' positions in a proline moiety had potent activities against Gram-positive resistant bacteria with *erm* gene. The author further pursued modifications of LCM with a combination manner at the C-6 and C-7 positions in order to generate novel LCM derivatives exhibiting as strong antibacterial activities as TEL. Then, the author synthesized novel (7*S*)-substituted analogs attached with piperidine or azepane instead of pyrrolidine (a part of proline) at the C-6 position. The author has found three representative molecules so far and the author chose a "pyrimidin-5-yl"-phenyl derivative (**4-31**) (Scheme 4-4) as a C-7 side chain for optimization of a C-6 moiety, because a "1-methylpiperidin-3-yl" moiety has a chiral center (anxiety for relatively complex production) and a "1-methyl-1,2,5,6-tetrahydropyridin-3-yl" moiety has an isolated double bond (anxiety for potential instability) (Scheme 4-6).

### 6.1.2. Synthesis of the substituted piperidines and 2,3,6,7-tetrahydro-1*H*-azepine

Synthesis of substituted piperidines and 2,3,6,7-tetrahydro-1*H*-azepine is shown in Scheme 6-1. Substituted piperidines (±)-**6-4**~**6-6** and 2,3,6,7-tetrahydro-1*H*-azepine **6-15** were synthesized by methods reported by Shuman *et al*.[83] and Lewis *et al*.[58] Compound (±)-**6-11** was prepared from 4-methylpyridine (**6-7**) in improved reaction conditions based on reported methods[58,83] shown in Scheme 6-1. It was reported that hydrogenation of disubstituted pyridine in the presence of $PtO_2$ resulted a racemate of isomeric *cis*-products as major products by Lewis *et al*.[58] At the beginning of this research, the author used (±)-*cis*-carboxylic acids **6-4**~**6-6** and **6-11**, but later on the author could separate (±)-**6-11** into each *cis*-enantiomer for efficient synthetic study. Carboxylic acid (±)-**6-11** was protected by a benzyl group for the purpose of optical resolution by HPLC, and both enantiomers were purified by chiral column chromatography to obtain a desired compound **6-12**. Stereochemistry of compounds **6-12** and **6-13**[84] was assigned as following. Pirlimycin and VIC-105555 are reported as representative lincomycin derivatives possessing a substituted piperidine moiety (Figure 1-5). Absolute stereochemistry of pirlimycin was clarified

by X-ray crystallographic studies.[59] Absolute stereochemistry of VIC-105555 was reported by Vicuron at 44th Interscience Conference on Antimicrobial Agents and Chemotherapy[64] Both compounds have 2'-β-4'-β-configuration and they showed remarkable polarity and stronger potency compared with the corresponding 2'-α-4'-α-diastereoisomer, respectively.[85] When the author coupled a substituted pipecolic acid with MTL, the author assigned 2'-β-4'-β-configuration for a polar product. The benzyl group in **6-12** was removed by hydrogenolysis to give a key intermediate **6-14**. A seven-membered intermediate (**6-16**) was prepared by basic hydrolysis of **6-15**.

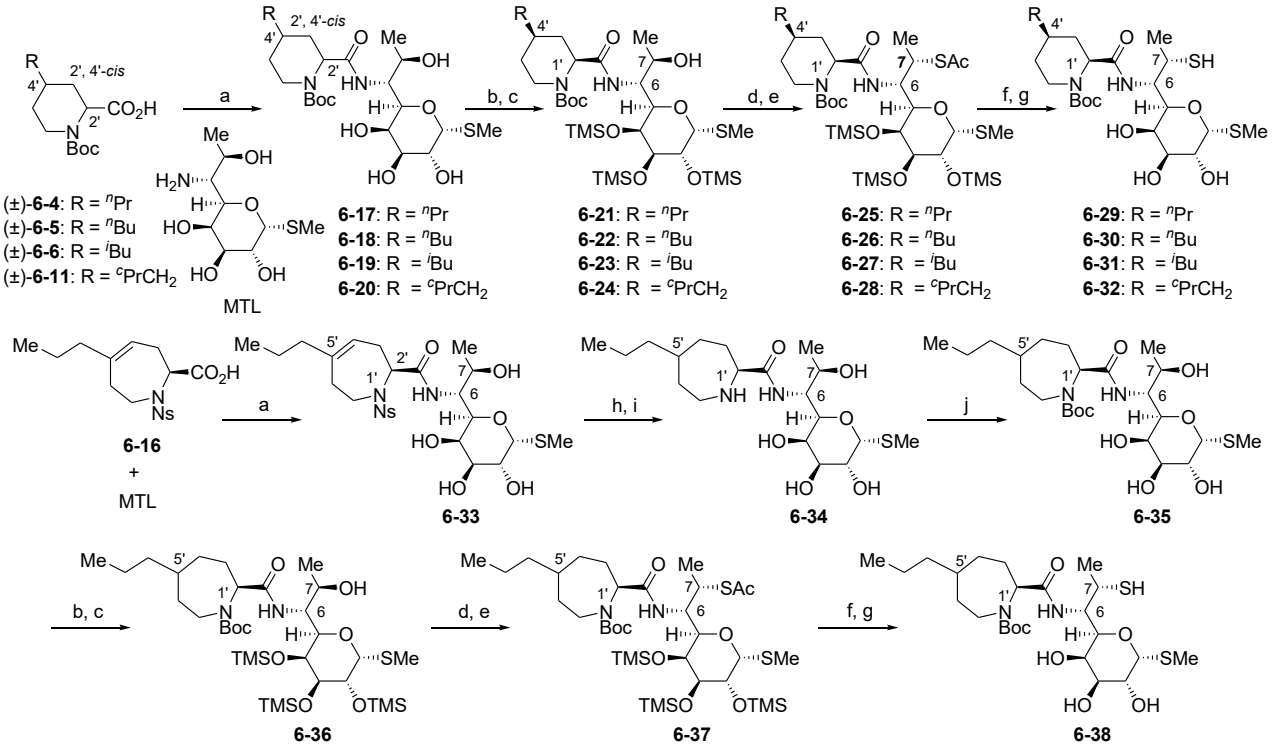



Scheme 6-1. Synthesis of substituted piperidines and 2,3,6,7-tetrahydro-1*H*-azepine. Conditions: a) bromocyclopropane, lithium diisopropylamide, THF, -78°C, 1 h, 50.9%; b) *m*-CPBA, $CH_2Cl_2$, 0°C to r.t., 1 h; c) TMSCN, $Me_2NCOCl$, $CH_2Cl_2$, 20°C 40 min, then r.t.,17 h, 84.2% in 2 steps; d) 5 N NaOH, MeOH, 50°C, 8 h, 96.5%; e) $H_2$, $PtO_2$, AcOH, r.t., 24 h; f) $Boc_2O$, 2 N NaOH, dioxane, r.t., 15 h, 95.5% in 2 steps; g) BnBr, $^iPr_2NEt$, $CH_3CN$, r.t., 48 h, 31.0% (**6-12**), 30.7% **(6-13**); h) $H_2$, Pd/C, MeOH, r.t., 1 h, quant; i) $LiOH{\cdot}H_2O$, dioxane:$H_2O$ = 4:1, r.t. 5 h, not purified.

## 6.1.3. Synthesis of key intermediates 6-29~6-32 and 6-38

Synthesis of key intermediates **6-29**~**6-32** and **6-38** are shown in Scheme 6-2. Diastereomeric mixtures **6-17**~**6-20** and compound **6-33** were synthesized by coupling of compounds (±)-**6-4**~**6-6**, (±)-**6-11** and **6-16** with methyl α-thiolincosaminide (MTL),[80] respectively. MTL was prepared by a reported method.[80] Although each isomer was almost one to one mixture except **6-16** when the coupling reactions were

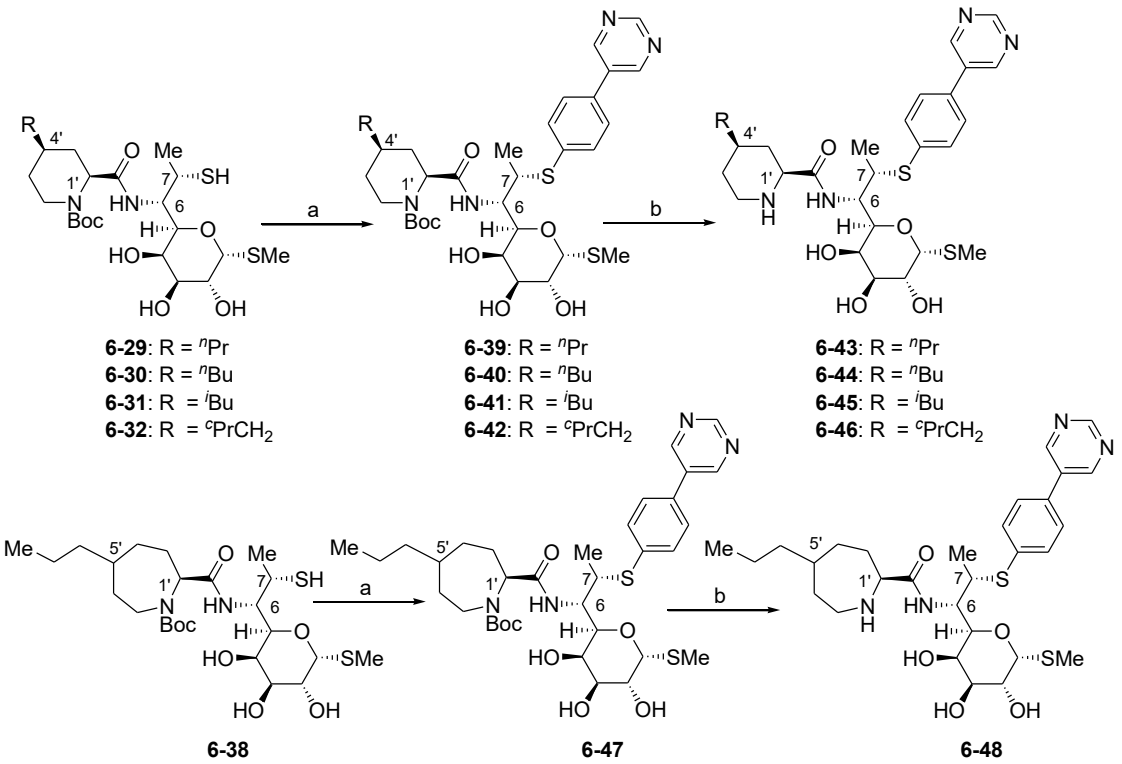
completed, precipitation process gave 2'-β-4'-β-rich *cis*-isomers. As experimental reported, ratio of diastereoisomeric mixture was difference for each compound. Tetra-*O*-trimethylsilylation of mixtures **6-17**~**6-20** and regioselective deprotection[65] of the 7-*O*-TMS group followed by silica gel column chromatography finally gave single compounds **6-21**~**6-24**[58] as 2'-β-4'-β-pure *cis*-isomers. Methanesulfonylation of the 7-OH group and then $S_N2$ reaction by potassium thioacetate gave compounds **6-25**~**6-28**. Key intermediates **6-29**~**6-32**[68,69,84] were prepared by deprotections of all TMS groups and an acetyl group. On the other hand, the Ns group of compound **6-33** was deprotected by 4-bromobenzenethiol under the basic condition, and then the olefin group was reduced by hydrogenation to give an azepane intermediate **6-34** (stereochemistry at the C-5' position is not assigned). An amino group of **6-34** was protected by a Boc group to give **6-35**, and a key intermediate **6-38** was synthesized from **6-35** by the similar procedures as described for the preparation of **6-29**.




Scheme 6-2. Synthesis of key intermediates **6-29~6-32** and **6-38**. Conditions: a) DCC or EDC·HCl, HOBt, DMF, r.t., 6-20 h, 84.9% (**6-17**), 87% (**6-18**), quant (**6-19**), 92.7% (**6-20**), 83.6% (**6-33**); b) TMSCl, HMDS, pyridine, r.t., 20 min-1 h; c) 6 N AcOH or 2 N AcOH, MeOH, r.t., 40 min-6 h, 48.2% in 2 steps (**6-21**), 70.7% in 2 steps (**6-22**), 89.8% in 2 steps (**6-23**), 61.7% in 2 steps (**6-24**); d) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C to r.t.,1 h; e) AcSK, DMF, 80°C, 1.5-3 h, 66.1% in 2 steps (**6-25**), 51.9% in 2 steps (**6-26**), 55.0% in 2 steps (**6-27**), 53.9% in 2 steps (**6-28**), 56.3% in 4 steps (**6-37**); f) 1 N HCl, MeOH, r.t. or 0°C, 5-100 min; g) NaOMe, MeOH, r.t., 15 min-3 h, 96.0% in 2 steps (**6-29**), 91.8% in 2 steps (**6-30**), 88.0% in 2 steps (**6-31**), 99.0% in 2 steps (**6-32**), 32.8% in 2 steps (**6-38**); h) 4-bromobenzenethiol, $Cs_2CO_3$, DMF, r.t., 2 h, 81.4%; i) $H_2$ (0.95 MPa), Pd/C, MeOH, 40°C, 70 h, 85.9%; j) $Boc_2O$, $LiOH·H_2O$, dioxane:$H_2O$ = 1:1, r.t. 3 h, 69.5%.

### 6.1.4. Synthesis of novel (7S)-7-(4-(pyrimidin-5-yl)phenylthio)-LCM derivatives possessing piperidine or azepane as the C-6 side chain

Synthesis of novel (7S)-7-(4-(pyrimidin-5-yl)phenylthio)-LCM derivatives possessing piperidine or azepane as the C-6 side chain are shown in Scheme 6-3. Compounds **6-39**~**6-42** and **6-47** were synthesized from key intermediates **6-29**~**6-32** and **6-38** by palladium-catalyzed cross-coupling reaction with 5-(4-bromophenyl)pyrimidine, respectively.[66,68,69,72-74,81,84] The Boc group of **6-39**~**6-42** and **6-47** was finally removed with TFA to give desired compounds **6-43**~**6-46** and **6-48**.



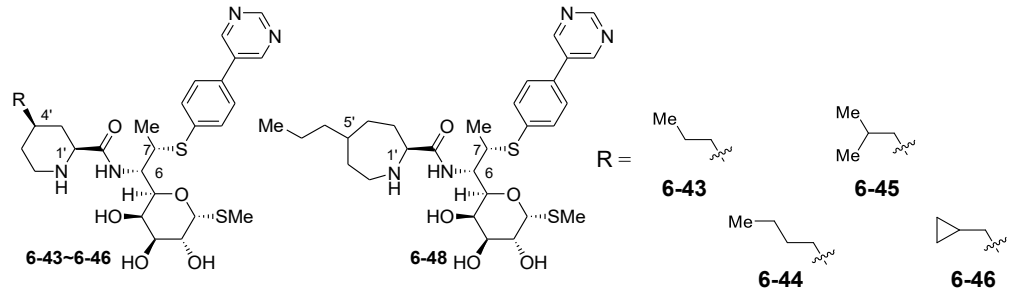

Scheme 6-3. Synthesis of novel (7*S*)-7-(4-(pyrimidin-5-yl)phenylthio)-LCM derivatives possessing piperidine or azepane as the C-6 side chain. Conditions: a) 5-(4-bromophenyl)pyrimidine, $Pd_2(dba)_3$, Xantphos, $^iPr_2NEt$, dioxane, reflux, 2-6 h, 82.8% (**6-39**), 78.1% (**6-40**), 81.6% (**6-41**), 93.4% (**6-42**), 88.1% (**6-47**); b) TFA, $CH_2Cl_2$, -20°C to r.t., 1.5-6 h, 88.4% (**6-43**), 79.6% (**6-44**), 64.3% (**6-45**), 80.9% (**6-46**), 78.1% (**6-48**).

### 6.1.5. SAR analysis of C-6 modified and (7*S*)-7-(4-(pyrimidin-5-yl)phenylthio)-substituted LCM derivatives 6-43~6-46 and 6-48

The author reported potent antibacterial activities of **4-31** possessing the (7S)-(4-(pyrimidin-5-yl)phenyl)thio group at the C-7 position. For the purpose of generating novel

compounds possessing more potent antibacterial activities against resistant Gram-positive pathogens with *erm* gene, the author performed an SAR analysis of C-6 modified and (7S)-7-(4-(pyrimidin-5-yl)phenyl)thio-substituted LCM derivatives **6-43**~**6-46** and **6-48** (Table 6-1). According to SAR studies reported by the author, (7*S*) stereochemistry was selected among all novel derivatives.[70,74] Compound **6-43**, which possesses *n*-propyl-piperidine instead of *n*-propyl-pyrrolidine as the C-6 side chain, showed stronger activities against resistant *S. pneumoniae* with *erm* gene than **4-31**. However, its antibacterial activity against resistant *S. pneumoniae* with both *erm* and *mef* genes (*S. pneumoniae*-6) was not sufficient (MIC: 1 μg/mL). Because there were a couple of reports[42,56,81] stating that elongation of a side chain in a piperidine ring enhanced antibacterial activity, the author synthesized alternative derivatives with a longer carbon chain or a branched side chain. However, antibacterial activities of compounds **6-44** and **6-45** were not improved. On the other hand, both compounds **6-46** and **6-48** possessing a 4'-*cis*-(cyclopropylmethyl)piperidine-2-carbonyl and 5'-*n*-propylazepane-2-carbonyl group at the N-6 position exhibited potent antibacterial activities against resistant *S. pneumoniae* with *erm* gene. Because the cyclopropylmethyl analog (**6-46**) especially exhibited stronger activities against Gram-positive pathogens with *erm* gene even compared with TEL, the author chose a 4'-*cis*-cyclopropylmethyl moiety as the C-6 side chain for further medicinal chemistry.

Table 6-1. Antibacterial activities (MIC, μg/mL) of novel lincomycin derivatives modified at the C-6 position.



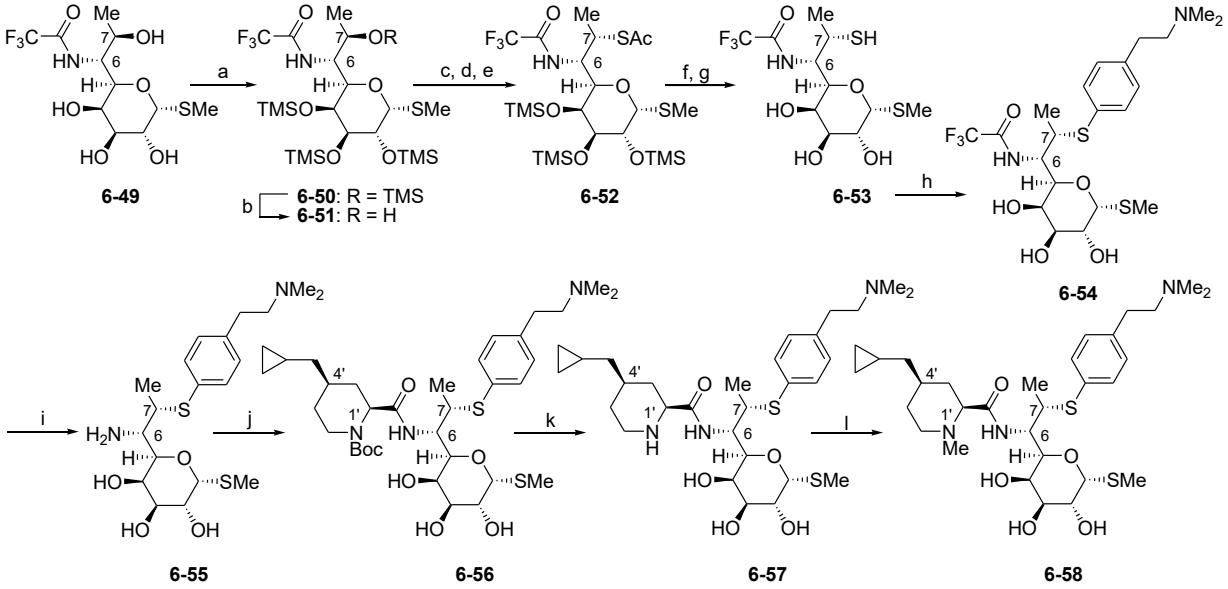

| Test organism* | Characteristics** | **6-43** | **6-44** | **6-45** | **6-46** | **6-48** | TEL |
|---|---|---|---|---|---|---|---|
| *S. pneumoniae* DP1 TypeI | s | 0.015 | 0.015 | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -2 | s | 0.015 | 0.015 | 0.03 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -3 | s | 0.015 | 0.03 | 0.015 | 0.015 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | 0.5 | 1 | 2 | 0.03 | 0.12 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | 0.25 | 1 | 2 | 0.03 | 0.12 | 2 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | 1 | 2 | 2 | 0.06 | 0.25 | 1 |
| *S. pneumoniae* -7 | *ermAM* (i) | 0.06 | 0.25 | N.T. | 0.015 | ≦0.008 | 0.03 |
| *S. pneumoniae* -8 | *ermAM* (i) | 0.03 | 0.12 | N.T. | 0.015 | N.T. | 0.03 |
| *S. pneumoniae* -9 | *mefE* efflux | ≦0.008 | ≦0.008 | N.T. | ≦0.008 | ≦0.008 | 0.06 |
| *S. pyogenes* Cook | s | 0.015 | ≦0.008 | 0.015 | 0.015 | ≦0.008 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | 0.25 | 0.5 | 0.06 | 0.03 | 0.03 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | 0.015 | 0.03 | 0.015 | 0.015 | ≦0.008 | 0.25 |
| *H. influenzae* | s | 2 | 4 | 16 | 1 | 2 | 0.5 |
| *H. influenzae* -2 | s | 2 | 4 | 16 | 1 | 2 | 2 |
| *H. influenzae* -3 | s | 8 | 16 | >64 | 2 | 4 | 1 |
| *H. influenzae* -4 | ⊿acr | 0.06 | 0.12 | 0.5 | 0.03 | 0.03 | 0.25 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.;
**(c): constitutive; (i): inducible; Gray shading strains are target strains

## 6.2. Synthesis and antibacterial activities of novel LCM derivatives possessing an aliphatic or aromatic amine at the *para*-position of phenylthio group at the C-7 position

### 6.2.1. Synthesis of a divergent intermediate **6-53** and novel LCM derivatives possessing a 4-(2-(dimethylamino)ethyl)phenylthio group at the C-7 position

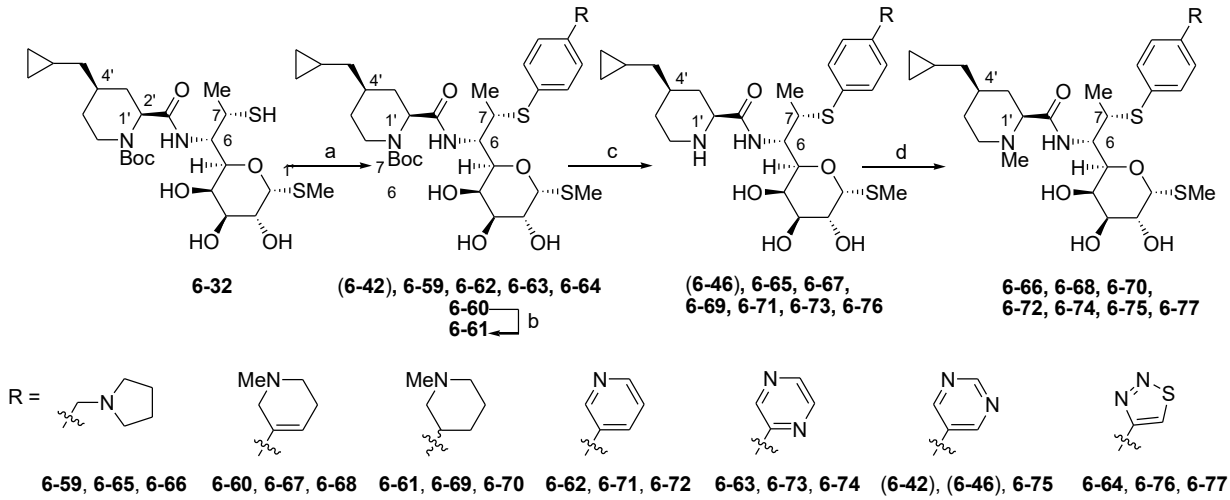
Because the author had to develop a more divergent synthetic route than those exemplified in Schemes 6-2 and 6-3, the author decided to apply the next key intermediate **6-53**. Synthesis of divergent intermediate **6-53** and novel LCM derivatives possessing a 4-(2-(dimethylamino)ethyl)phenylthio group at the C-7 position are shown in Scheme 6-4. Compound **6-49**[86] was synthesized by trifluoroacetylation of an amino group of MTL, and tetra-*O*-trimethylsilylation of all OH groups of **6-49** gave compound **6-50**. Divergent intermediate **6-53** was synthesized from **6-50** by the similar procedures as described for preparation of **6-29**. Palladium-catalyzed cross-coupling reaction of **6-53** with 2-(4-bromophenyl)-*N*,*N*-dimethylethanamine gave **6-54**, which was hydrolyzed in the presence of phase transfer catalyst under the basic condition to give diamine **6-55**. A coupling reaction of **6-55** with enantio-pure **6-14** provided desired **6-56** with all carbon's framework. Deprotection of the Boc group finally gave **6-57** and its reductive *N*-methylation provided compound **6-58**.




Scheme 6-4. Synthesis of a divergent intermediate **6-53** and novel LCM derivatives possessing a 4-(2-(dimethylamino)ethyl)phenylthio group at the C-7 position. Conditions: a) TMSCl, HMDS, pyridine, r.t., 1 h; b) 6 N AcOH, MeOH, r.t., 15 min, 91.0% in 2 steps; c) MsCl, $NEt_3$, $CHCl_3$, r.t., 1 h; d) AcSK, DMF, 80°C, 1.5 h; e) TMSCl, HMDS, pyridine, r.t., 3 h, 24.8% in 3 steps; f) 1 N HCl, MeOH, r.t., 10 min; g) NaOMe, MeOH, r.t., 15 min, 99.0% in 2 steps; h) 2-(4-bromophenyl)-*N*, *N*-dimethylethanamine, $Pd_2(dba)_3$, Xantphos, $^iPr_2NEt$, dioxane, reflux, 17 h, 79.8%; i) 20% aq. KOH, *N*-benzyl-*N*, *N*, *N*-triethylammonium bromide, r.t., 4 h, 94.0%; j) **6-14**, EDC·HCl, HOBt, DMF, r.t., 5.5 h, 72.6%; k) TFA, $CH_2Cl_2$, 0°C, 3.5 h, 98.9%; l) HCHO, $NaBH(OAc)_3$, AcOH, MeOH, r.t., 1 h, 90.9%.

## 6.2.2. Synthesis of novel 4'-*cis*-(cyclopropylmethyl)piperidine LCM derivatives possessing a 4-substituted phenylthio group at the C-7 position

Synthesis of novel 4'-*cis*-(cyclopropylmethyl)piperidine LCM derivatives possessing a 4-substituted phenylthio group at the C-7 position are shown in Scheme 6-5. Compounds **6-59, 6-60** and **6-62**~**6-64** were synthesized from the key intermediate **6-32** by palladium-catalyzed cross-coupling reaction with the corresponding 4-substituted phenyl bromides. Reduction of **6-60** afforded saturated *N*-methylpiperidine **6-61** as a mixture of diastereoisomers at an *N*-methylpiperidine ring. The first half of desired compounds **6-65, 6-67**, **6-69**, **6-71**, **6-73** and **6-76** were prepared by deprotection of a Boc group and their free secondary amine was methylated by reductive alkylation to give the second half of desired compounds **6-66**, **6-68**, **6-70**, **6-72**, **6-74** and **6-77**, respectively. Compound **6-75** was also synthesized from **6-46** with the similar procedure. The author confirmed that compound **6-75** derived from compound **6-32** had 4'-*cis*-stereochemistry by ROESY experiments. As the above, 4'-*cis*-stereochemistry of compound **6-11** was assigned.

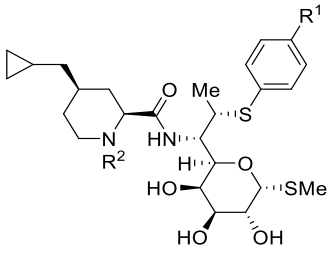



Scheme 6-5. Synthesis of novel 4'-*cis*-(cyclopropylmethyl)piperidine LCM derivatives possessing an aliphatic- or aromatic-phenylthio group at the C-7 position. Conditions: a) the corresponding 4-substituted phenylbromides, $Pd_2(dba)_3$, Xantphos, $^iPr_2NEt$, dioxane, reflux, 4-5 h, 80.7% (**6-59**), 85.8% (**6-60**), not isolated (**6-62**), not isolated (**6-63**), not isolated (**6-64**); b) 4-methylbenzenesulfonohydrazide, toluene, reflux, 5.5 h, 13.7%; c) TFA, $CH_2Cl_2$, -20 $^oC$ to r.t., 30 min-5 h, 81.3% (**6-65**), 94.2% (**6-67**), 76.0% (**6-69**), 52.0% in 2steps (**6-71**), 47.5% in 2steps (**6-73**), 50.6% in 2steps (**6-76**); d) 36% HCHO, $NaBH(OAc)_3$, AcOH, MeOH, r.t., 30 min-2 h, 87.6% (**6-66**), 91.6% (**6-68**), 97.8% (**6-70**), 97.6% (**6-72**), 94.0% (**6-74**), quant (**6-75**), 90.0% (**6-77**).

### 6.2.3. Antibacterial activities of novel LCM derivatives **6-57**, **6-58** and **6-65**~**6-70** possessing an aliphatic amine at the *para*-position of a phenylthio group at the C-7 position

For the purpose of accumulating detail information of SAR on (7*S*)-7-(4-substituted-phenylthio) LCM derivatives with a 4'-*cis*-(cyclopropylmethyl)piperidine moiety, the author synthesized novel derivatives possessing various substituents at the C-7 position with a set of $R^2$ = both "*N*-H" and *N*-Me" analogs (Table 6-2). Consequently, compounds **6-57**, **6-65** and **6-67**~**6-70** showed potent antibacterial activities against target pathogens with *erm* gene, and their activities were relatively stronger even when compared with those of TEL. Additionally, antibacterial activity of all compounds against *S. pyogenes* with *erm* gene was significantly potent than that of TEL. The author confirmed that combination of chemical modifications with the 4'-*cis*-(cyclopropylmethyl)piperidine group at the C-6 position and an aliphatic amine to the *para*-position of a phenylthio group at the C-7 position was important to enhance antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene.

Table 6-2. Antibacterial activities (MIC, μg/mL) of novel lincomycin derivatives modified at the C-7 position with an aliphatic amine.



| | | $R^1$ = | $-NMe_2$ | |  | |  | |  | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^2$ = | H | Me | H | Me | H | Me | H | Me | |
| Test organism* | Characteristics** | | **6-57** | **6-58** | **6-65** | **6-66** | **6-67** | **6-68** | **6-69** | **6-70** | TEL |
| *S. pneumoniae* DP1 TypeI | s | | 0.03 | ≦0.008 | 0.03 | 0.015 | 0.015 | 0.06 | 0.06 | 0.015 | ≦0.008 |
| *S. pneumoniae* -2 | s | | 0.03 | ≦0.008 | 0.03 | 0.03 | 0.015 | 0.06 | 0.06 | 0.03 | ≦0.008 |
| *S. pneumoniae* -3 | s | | 0.06 | 0.03 | 0.06 | 0.06 | 0.015 | 0.06 | 0.06 | 0.03 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | | 0.5 | 1 | 0.25 | 0.5 | 0.06 | 0.25 | 0.25 | 0.25 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | | 0.5 | 0.5 | 0.25 | 0.5 | 0.06 | 0.25 | 0.25 | 0.25 | 2 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | | 0.5 | 2 | 0.25 | 1 | 0.06 | 0.5 | 0.12 | 0.5 | 1 |
| *S. pneumoniae* -7 | *ermAM* (i) | | 0.03 | 0.015 | 0.03 | 0.06 | 0.03 | 0.06 | 0.06 | 0.06 | 0.03 |
| *S. pneumoniae* -8 | *ermAM* (i) | | N.T. | N.T. | N.T. | N.T. | 0.03 | 0.06 | 0.06 | 0.06 | 0.03 |
| *S. pneumoniae* -9 | *mefE* efflux | | 0.015 | ≦0.008 | 0.015 | ≦0.008 | 0.015 | 0.03 | 0.03 | 0.015 | 0.06 |
| *S. pyogenes* Cook | s | | 0.015 | 0.015 | 0.06 | 0.06 | 0.015 | 0.03 | 0.03 | 0.03 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | | 0.12 | 0.5 | 0.12 | 0.5 | 0.03 | 0.12 | 0.06 | 0.12 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | | 0.03 | 0.015 | 0.06 | 0.12 | 0.015 | 0.03 | 0.03 | 0.03 | 0.25 |
| *H. influenzae* | s | | 2 | 2 | 1 | 4 | 0.5 | 2 | 1 | 2 | 0.5 |
| *H. influenzae* -2 | s | | 4 | 1 | 4 | 2 | 1 | 2 | 4 | 4 | 2 |
| *H. influenzae* -3 | s | | 4 | 4 | 4 | 8 | 2 | 4 | 4 | 8 | 1 |
| *H. influenzae* -4 | ⊿acr | | 0.12 | 0.12 | 0.12 | 0.12 | 0.06 | 0.12 | 0.12 | 0.12 | 0.25 |

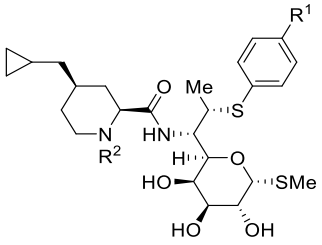
Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.; **(c): constitutive; (i): inducible; Gray shading strains are target strains

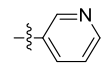
## 6.2.4. Antibacterial activities of novel LCM derivatives **6-46** and **6-71**~**6-77** possessing an aromatic amine at the *para*-position of a phenylthio group at the C-7 position

In order to expand possibilities of the combined modification at both the C-6 and C-7 positions, the author synthesized novel derivatives possessing various aromatic amines as a substituent on the phenyl group with a set of both "*N*-H" and "*N*-Me" analogs (Table 6-3). All their antibacterial activities against target Gram-positive pathogens with *erm* gene were also relatively stronger than those of TEL. To be more precise, compounds **6-46** and **6-71** showed potent activities in "*N*-H" analogs, and compound **6-75** exhibited the strongest activities among all "*N*-Me" analogs in this article. Because pharmacokinetic property must be different between "*N*-H" and "*N*-Me" analogs, it is important to select these two types of analogs for further development. Furthermore, antimicrobial activity of compounds **6-71**, **6-46** and **6-76** against *H. influenzae* was relatively strong among all LCM derivatives the author reported, and their potency was stronger than that of CAM and catching up with that of TEL. The author also investigated antibacterial activity against

*Mycoplasma pneumoniae* (Table 6-3), because resistant *M. pneumoniae* is causing problems for respiratory infections in clinical sites.[87,88] All evaluated compounds including **6-46** and **6-75** had significant antibacterial activity against resistant *M. pneumoniae*, which TEL was not effective against. The author could generate several novel LCM derivatives exhibiting very strong antibacterial activities against resistant Gram-positive pathogens with *erm* and/or *mef* genes by combined modification at the C-6 position (the proline moiety) and the C-7 position. These derivatives were also effective against resistant *M. pneumoniae*.

Table 6-3. Antibacterial activities (MIC, μg/mL) of optimized novel lincomycin derivatives modified at the C-7 position with an aromatic amine.




| | | $R^1$ = |  | |  | |  | |  | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^2$ = | H | Me | H | Me | H | Me | H | Me | |
| Test organism* | Characteristics** | | **6-71** | **6-72** | **6-73** | **6-74** | **6-46** | **6-75** | **6-76** | **6-77** | TEL |
| *S. pneumoniae* DP1 TypeI | s | | 0.015 | 0.03 | ≦0.008 | 0.03 | ≦0.008 | ≦0.008 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pneumoniae* -2 | s | | 0.015 | 0.03 | ≦0.008 | 0.03 | ≦0.008 | ≦0.008 | ≦0.008 | 0.015 | ≦0.008 |
| *S. pneumoniae* -3 | s | | 0.015 | 0.06 | 0.015 | 0.06 | 0.015 | 0.03 | 0.015 | 0.015 | ≦0.008 |
| *S. pneumoniae* -4 | *ermAM* (c) | | 0.03 | 0.5 | 0.06 | 0.5 | 0.03 | 0.25 | 0.06 | 0.5 | 0.5 |
| *S. pneumoniae* -5 | *ermAM* (c) | | 0.06 | 0.25 | 0.06 | 0.5 | 0.03 | 0.12 | 0.12 | 0.5 | 2 |
| *S. pneumoniae* -6 | *ermAM* (c) + *mefE* | | 0.06 | 0.5 | 0.12 | 1 | 0.06 | 0.5 | 0.25 | 0.5 | 1 |
| *S. pneumoniae* -7 | *ermAM* (i) | | 0.015 | 0.06 | 0.03 | 0.25 | 0.015 | 0.015 | 0.03 | 0.25 | 0.03 |
| *S. pneumoniae* -8 | *ermAM* (i) | | N.T. | N.T. | 0.03 | 0.25 | 0.015 | 0.03 | 0.03 | 0.25 | 0.03 |
| *S. pneumoniae* -9 | *mefE* efflux | | ≦0.008 | 0.015 | ≦0.008 | 0.03 | ≦0.008 | ≦0.008 | ≦0.008 | ≦0.008 | 0.06 |
| *S. pyogenes* Cook | s | | ≦0.008 | 0.015 | ≦0.008 | 0.015 | 0.015 | 0.015 | ≦0.008 | ≦0.008 | ≦0.008 |
| *S. pyogenes* -2 | *ermAM* (c) | | 0.06 | 0.25 | 0.03 | 0.25 | 0.03 | 0.12 | 0.03 | 0.12 | 16 |
| *S. pyogenes* -3 | *mefE* efflux | | 0.015 | 0.03 | 0.015 | 0.03 | 0.015 | ≦0.008 | 0.015 | 0.015 | 0.25 |
| *H. influenzae* | s | | 1 | 4 | 2 | 4 | 1 | 4 | 1 | 4 | 0.5 |
| *H. influenzae* -2 | s | | 2 | 4 | 2 | 4 | 1 | 2 | 1 | 2 | 2 |
| *H. influenzae* -3 | s | | 2 | 8 | 4 | 8 | 2 | 4 | 2 | 4 | 1 |
| *H. influenzae* -4 | ⊿acr | | 0.03 | 0.12 | 0.03 | 0.12 | 0.03 | 0.06 | 0.03 | 0.03 | 0.25 |
| *Mycoplasma pneumoniae* -1 | susceptible | | N.T. | N.T. | ≦0.004 | N.T. | ≦0.004 | ≦0.004 | ≦0.004 | N.T. | ≦0.004 |
| *M. pneumoniae* -2 | A2063G | | N.T. | N.T. | ≦0.03 | N.T. | ≦0.03 | ≦0.03 | ≦0.03 | N.T. | 64 |

Abbreviations: N.T., Not tested; *All strains except standard organisms were clinically isolated.;
**(c): constitutive; (i): inducible; Gray shading strains are target strains

## 6.3. *In vitro* antibacterial activity (sensitivity distribution analysis) of selected compounds against sixty clinical isolates of *S. pneumoniae*

The author evaluated the antibacterial activity of compounds **6-46**, **6-67**, **6-71**, **6-75**, **6-76** and TEL against sixty clinical isolates of *S. pneumoniae* including susceptible strains and resistant strains with *erm* and/or *mef* genes for sensitivity distribution analysis (Figure 6-1). $MIC_{90}$ values of five novel LCM derivatives (0.06-0.125 μg/mL) were relatively smaller than that of TEL (0.25 μg/mL). Notably, **6-46** and **6-71** were significantly potent among tested compounds. These results reflect MIC values in Table 6-3 and it was suggested that these derivatives would also be effective against *S. pneumoniae* in clinical sites.

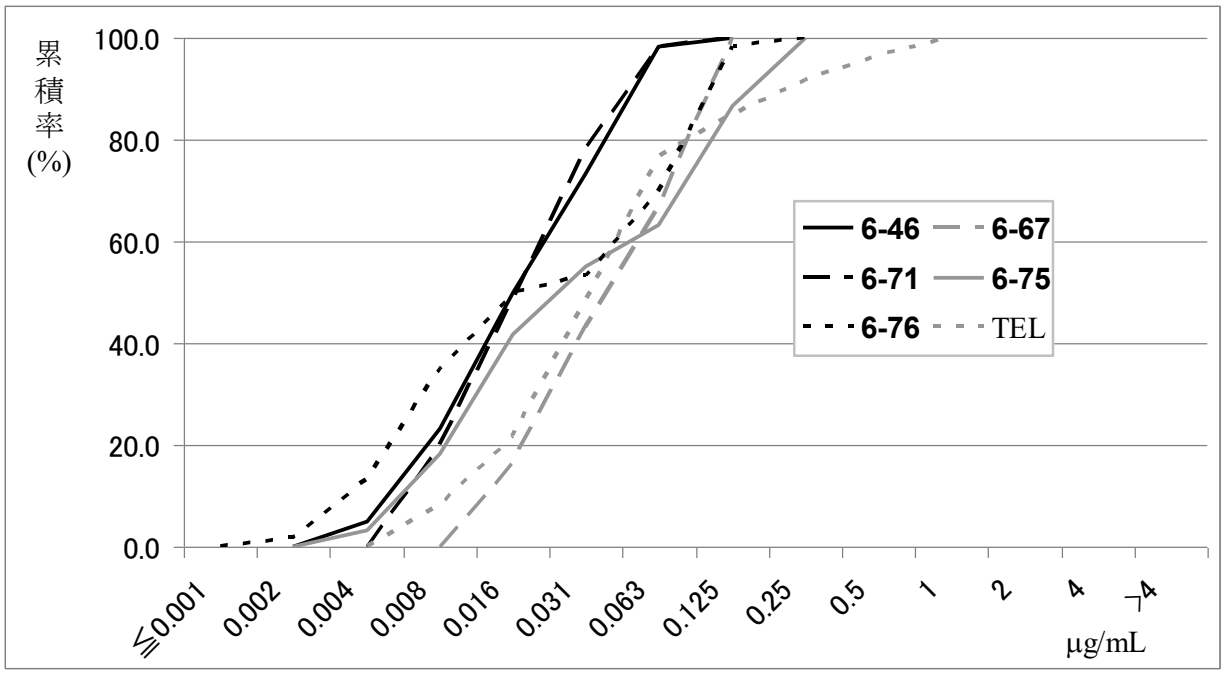



Figure 6-1. *In vitro* antibacterial activity (sensitivity distribution) of compounds **6-46**, **6-67**, **6-71**, **6-75**, **6-76** and TEL against sixty clinical isolates of *S. pneumoniae*.

## 6.4. *In vivo* efficacy of **6-46** and **6-75** (subcutaneous administration) in rat pulmonary infection model with resistant *S. pneumoniae* with *erm* + *mef* genes and *mef* gene

The author finally investigated the *in vivo* efficacy of selected compounds in rat pulmonary infection model with resistant *S. pneumoniae* with *erm* + *mef* genes. Among derivatives reported in this article, *in vitro* activities of compounds **6-46** and **6-71** are rather strong (Figure 6-1). On the other hand, the author had to clarify *in vivo* efficacy in the set of "*N*-H" and "*N*-Me" in the piperidine moiety (to evaluate "**6-71** and **6-72**" or "**6-46** and **6-75**"). Because *in vitro* activities of **6-72** were slightly weaker than those of **6-75**, the author decided to select the set of compounds **6-46** and **6-75** for *in vivo* evaluation. Compound **6-71** had weak hemolytic activity, and thus compound **6-71** might not be appropriate for further evaluation. Compounds **6-46**, **6-75** and TEL were subcutaneously administered (10 mg/kg) to rats at 2 h after bacterial infection, and *in vivo* efficacies are shown in Figure 6-2a. Compound **6-46** exhibited strong *in vivo* efficacy (3 log reduction or more) against resistant *S. pneumoniae* with *erm* + *mef* genes and its efficacy was constant (small s.d. value) compared with that of TEL (less than 2 log reduction). For the author's references, the author also evaluated *in vivo* efficacy of those by subcutaneous administration (3 mg/kg) to rats at 2 h after bacterial infection with *S. pneumoniae* with *mef* gene, because resistant strains with *mef* gene have increased in the US.[89] As a result shown in Figure 6-2b, **6-46** and **6-75** had significantly strong *in vivo* efficacy as expected on the basis of *in vitro* evaluation. *In vivo* efficacy of **6-75** (5 log reduction) was very constant (zero s.d. value) compared with that of TEL. Clinical efficacy of these novel LCM derivatives is very positively expected from the above fundamental experimental data.

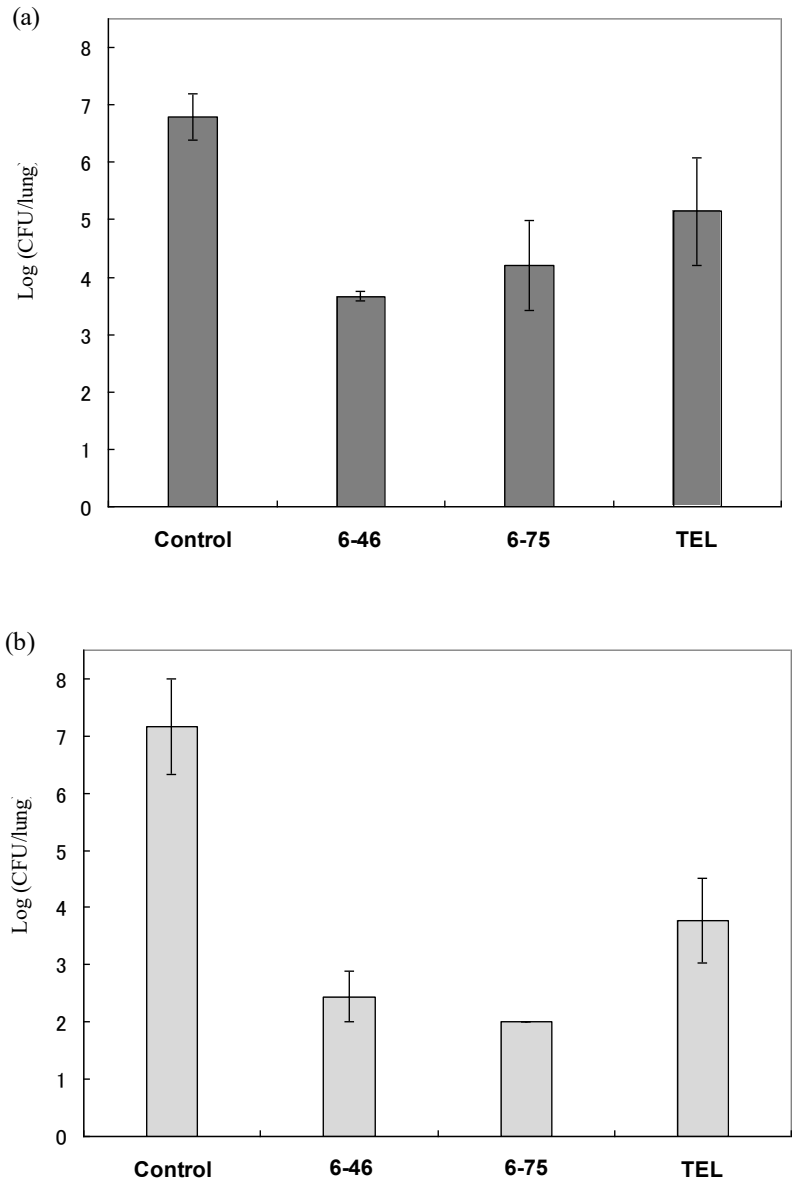



Figure 6-2. Comparison of the efficacy of novel lincomycin derivatives **6-46** and **6-75** in a rat pulmonary neutropenic infection model with *S. pneumoniae* MSC06856 (*erm* + *mef*) (a) and *S. pneumonia*e MSC06729 (*mef*) (b). Three rats per group were rendered neutropenic, and $10^6$ CFU per rat of *S. pneumoniae* MSC06856 or *S. pneumonia*e MSC06729 was injected into the lung, followed by s.c. administration of the test compounds at 2 h after infection. The mean $\log_{10}$ CFU per lung recovered from the infected lung after 24 h is shown. Error bars represent the s.d.

## 6.5. Summary

As the result of SAR studies at the 6-position of **6-43**~**6-46** and **6-48**, compound **6-46** possessing 4'-*cis*-(cyclopropylmethyl)piperidine showed significantly strong antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene. On the basis of SAR, The author synthesized novel analogs possessing 4'-*cis*-(cyclopropylmethyl)piperidine by transformation of a C-7 substituent. Consequently, compounds **6-46**, **6-67**, **6-71**, **6-75** and **6-76** (Figure 6-3) exhibited significantly strong activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene even when compared with those of TEL. Then, the *in vitro* antibacterial activities of compounds **6-46**, **6-67**, **6-71**, **6-75**, **6-76** and TEL were evaluated (sensitivity distribution analysis) against sixty clinical isolates of *S. pneumoniae* containing sensitive bacteria and resistant bacteria with *erm* and/or *mef* genes. As a result, compounds **6-46** and **6-71** showed relatively strong activities than TEL. Finally, the *in vivo* efficacy of compound **6-46** and its 1'-*N*-Me-derivative **6-75** was evaluated in the rat pulmonary infection model (subcutaneous administration) with resistant *S. pneumoniae* with *erm* + *mef* gene. Compound **6-46** exhibited strong and constant *in vivo* efficacy. Moreover, compounds **6-46** and **6-75**[84] showed strong *in vivo* efficacy against resistant *S. pneumoniae* with *mef* gene. These two compounds are under consideration toward next developing stage.

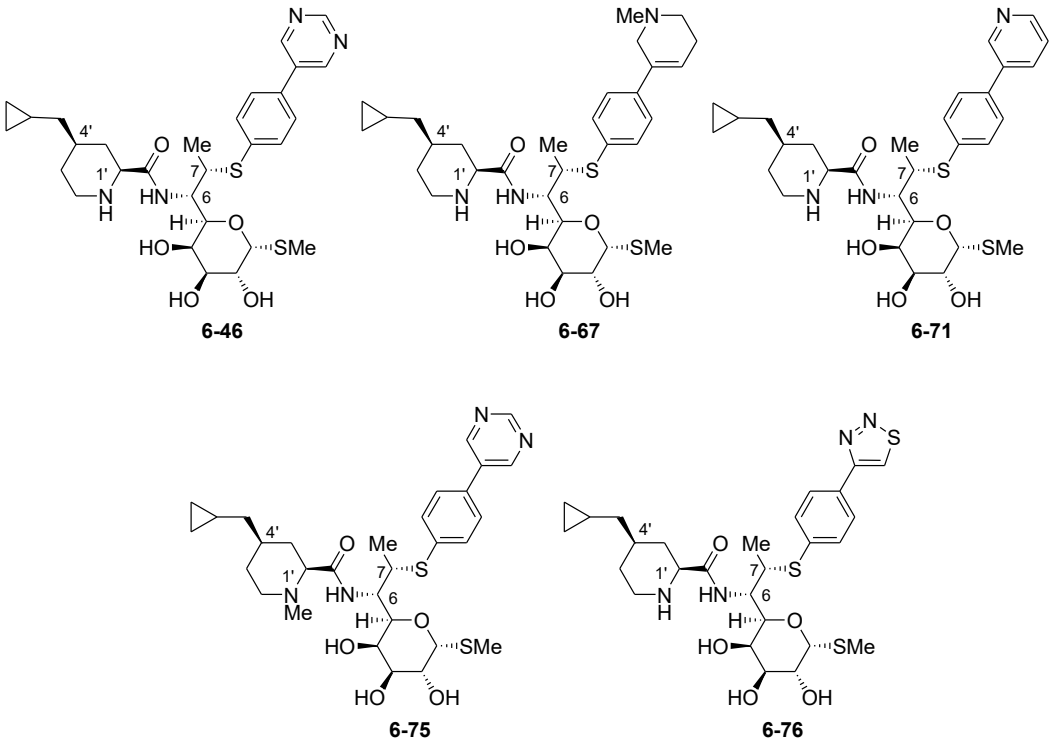



Figure 6-3. Structures of novel lincomycin derivatives possessing strong *in vitro* antibacterial activity.

# 7. Conclusion

As a result of X-ray crystallographic analysis, CLDM was found to have a three-dimensional space around the C-7 position. The author hypothesized that filling the 3D-space in the (7*S*)-configuration by groups such as hetero cycles might be able to enhance antibacterial activities against resistant pathogens with *erm* gene. An outline of author's chemical modifications and their results were shown in Figure 7-1.

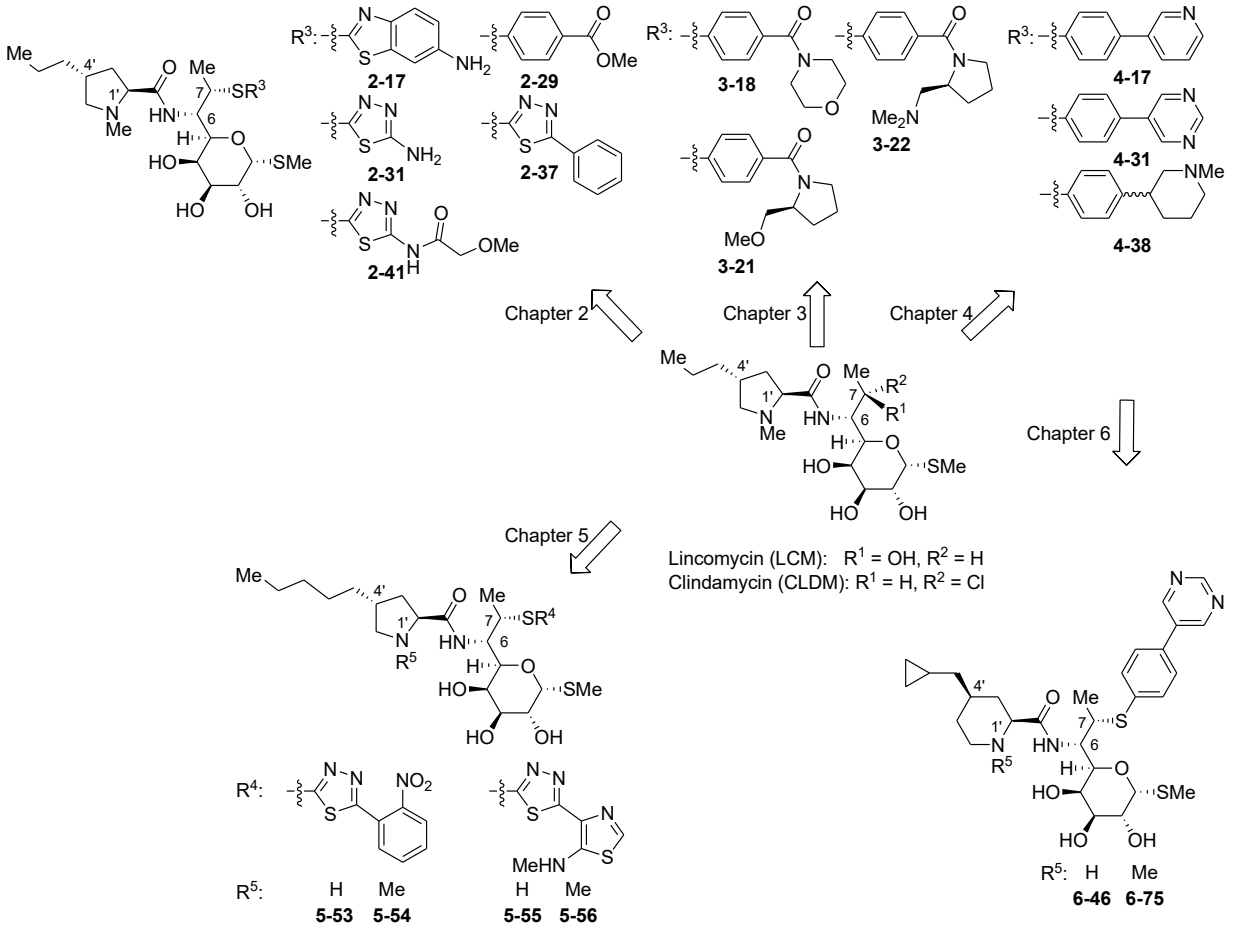



Figure 7-1. Outline of author's research and its chemical modification.

The desired (7*S*)-products, **2-17**, **2-29**, **2-31**, **2-37** and **2-41**, showed weak antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene, respectively (Chapter 2). These results suggest that filling the space around the 7-position of LCM with an appropriate moiety such as carbonyl, amino and/or aryl groups plays an important role to enhance antibacterial activities by hydrogen bonding, π-π stacking, or CH-π interaction to undefined binding site on 23S *r*RNA. The author investigated SAR of (7*S*)-lincomycin analogs possessing an NH-COR or a CO-$NR_2$ group, which is possible to have hydrogen bonding with 23S *r*RNA. The novel lincomycin analog **3-18** improved antibacterial activities against not only resistant *S.*

*pneumoniae* but also *H. influenzae* (Chapter 3). In order to clarify of this result, the author performed docking simulation analysis using **3-18** with bacterial 23S *r*RNA of *Haloarcula marismortui*. Its result indicated that carbonyl oxygen had hydrogen bonding with U2620Hm, and ethylene of morpholine had hydrophobic interaction by CH-π stacking with uracil of U2621Hm. On the other hand, LCM derivatives **3-21** and **3-22** also had potent antibacterial activities against *S. pneumoniae* with *erm* gene. On the base of the Chapters 2 and 3, the author newly hypothesized that a benzene ring and a hetero ring with basicity are important to enhance antibacterial activities against resistant bacteria with *erm* and *mef* genes (Chapter 4). Novel lincomycin analogs **4-17**, **4-31** or **4-38** showed potent antibacterial activities against resistant pathogens with *erm* gene, respectively. The result indicated that basicity as a substituent on the phenyl group was important to improve antibacterial activities. The author modified LCM at the C-6 and C-7 positions in the Chapter 5. Consequently, it was difficult for the author to enhance antibacterial activities except hydrogen or a methyl group as a substituent at the 1'-position of (7*S*)-7-substituted-LCM. Furthermore, replacing an *n*-propyl with an *n*-pentyl group at the 4'-position of (7*S*)-7-substituted-LCM significantly enhanced antibacterial activities against resistant bacteria with *erm* gene. Finally, the author optimized structure by chemical modifications at the C-6 and C-7 positions of LCM analogs in the Chapter 6. Compound **6-46** (Figure 7-2) showed significant antibacterial activities against *S. pneumoniae* and *S. pyogenes* with *erm* gene and resistant *M. pneumoniae*. Consequently, this compound has potent antibacterial activities against *S. pneumoniae* of sixty strains including of susceptible strains and strains with *erm* and/or *mef* gene isolated in clinical site even when compared with TEL. Furthermore, its 1'-Me-analog **6-75** exhibited the most potent antibacterial activity among 1'-*N*-methyl analogs. Two compounds showed potent *in vivo* efficacy reflecting *in vitro* antibacterial activities against resistant bacteria with *erm*+*mef* or *mef* gene, respectively.

The author found that the novel (7*S*)-lincomycin analogs possessing potent antibacterial activities against resistant bacteria with *erm* gene were not influenced by resistant bacteria with *mef* gene. With regard to *in vitro* antibacterial activities and *in vivo* efficacy, these two compounds **6-46** and **6-75** were indicated as candidates for further development.

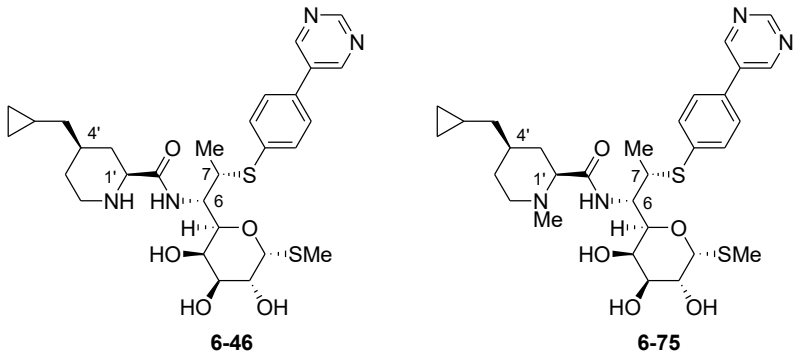



Figure 7-2. Candidates for further development.

# Experimental section

## General methods

$^1$H NMR spectra were measured with a BRUKER Ascend$^{TM}$ 400 NMR spectrometer for 400 MHz, JEOL JNM-GSX 400 NMR spectrometer for 400 MHz or a Varian Gemini 300 NMR spectrometer for 300 MHz in $CDCl_3$ or $CD_3OD$. TMS (0 ppm) in $CDCl_3$ or $CD_3OD$ was used as internal reference standard. Mass spectra (MS) were obtained on a JEOL JMS-700 mass spectrometer or Agilent Technologies 6530-Q-TOF LC/MS mass spectrometer. The optical rotations were recorded with Jasco P-2300 digital polarimeter. Column chromatography was performed with silica gel (Wakogel C200). Preparative thin layer chromatography (preparative TLC) was performed with silica gel (Merck: TLC plates Silica gel 60 F254). All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

## Docking simulation of the key compound **3-18**

Docking simulation was performed with Insight II (Accelrys, Inc.) using CHARMm force fields. The crystal structure of azithromycin bound to the 50S ribosomal subunit from *Haloarcula marismortui* (PDB entry 1M1K)[7] was used for the docking template. In preparation for docking simulation, the azithromycin and the ribonucleic acid residues other than around the ligand binding site were removed from the template. In docking simulation, **3-18** was manually placed in the ligand binding site refer to crystal structure of clindamycin bound to the 50S ribosomal subunit from *Haloarcula marismortui* (PDB entry 1YJN),[6] and minimized in the template.

## *In vitro* antibacterial activity

Minimum inhibitory concentration (MIC, μg/mL) was determined by the agar dilution method, which was described in Clinical and Laboratory Standards Institute (M07-07 in 2006). Test strains of *S. pneumoniae* and *S. pyogenes* were subjected to seed culture using brain heart infusion agar (BHIA; Becton Dickinson and Company, Tokyo, Japan) and 5% defibrinated horse blood. Test strains of *H. influenzae* were subjected to seed culture using sensitivity disk agar-N "Nissui" (SDA; Nissui, Tokyo, Japan), 5% defibrinated horse blood, 5 μg/mL Hemin and 15 μg/mL nicotinamide adenine dinucleotide (NAD). A 5 μl portion of cell suspension of the test strains having about $10^6$ CFU per mL was inoculated into SDA supplemented with 5% defibrinated horse blood, 5 μg/mL Hemin and 15 μg/mL NAD, and incubated at 37°C for 18-22 h. Then, minimum inhibitory concentration was measured.

## *In vitro* antibacterial activity (Sensitivity distribution against *S. pneumoniae* of sixty strains)

The MIC for *Streptococcus pneumoniae* was determined by the two-fold microdilution broth method

using cation-adjusted Mueller-Hinton broth (CAMHB ; Difco Laboratories, Detroit,USA) supplemented with 2% lysed horse blood recommended by the Clinical and Laboratory Standards Institute (CLSI)[90]. The inoculum was prepared by making a direct colony Suspension, equivalent to a 0.5 McFarland standard, with isolated colonies selected from Mueller-Hinton agar（MHA ; Difco Laboratories, Detroit）supplemented with 5% defibrinated sheep blood. Fifty μL of the adjusted inoculum was added to each well already containing 50 μL of antimicrobial agent in the dilution series. The final test concentration of bacteria was approximately $5\times10^4$ CFU/well. The MIC was determined as the lowest concentration that prevented visible growth of bacteria after incubation at 35℃ for 20 h.

## Neutropenic rat lung infection model

The study and its protocol were complied with Guidelines on the Management of Animal Experiments established by the Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd. and approved by the Animal Experiment Management Committee of it. Rats used in this study are six-week-old, specific-pathogen-free, male SD rats (Charles River Laboratories Japan, Inc., Kanagawa, Japan) weighing 160–180 g. These rats were bred under controlled conditions (temperature, 21–25°C; humidity, 50%–70%; lighting h, 07:00 to 19:00) and feed (CRF-1; Oriental Yeast Co., Ltd., Tokyo, Japan) and water were available ad libitum. The rats were allowed to acclimatize for 1 week before the study. The rats were rendered neutropenic by intraperitoneal administration of cyclophosphamide (Sigma-Aldrich) 4 days and the day before infection (80 mg/kg of body weight). The rats were infected with *S. pneumoniae* by the injection of $10^6$ CFU into lung through trachea under anesthesia with mixture of ketamine hydrochloride and xylazine hydrochloride (5:1) by injection intramuscularly. The rats were treated by subcutaneous administration of the test compound at 2 h after infection and were euthanized 24 h after infection by injection of excessive amounts of pentobarbital. The lung was removed and homogenized. Each homogenate was diluted 10-fold serially with physiological saline, and an aliquot of each initial homogenate and dilution series was smeared onto a plate of Brain Heart Infusion Agar (BHIA) with 5% horse blood. After was incubation at 35°C for 24 h, the number of colonies grown on the plate was counted. The detection limit was set at $< 2.0$ $\log_{10}$ CFU/lung; if no colonies were detected in the initial homogenate, the value of 2.0 $\log_{10}$ CFU/lung was adopted. The data were expressed as the mean ± SD $\log_{10}$ CFU/lung.

## 2,3,4-Tris-*O*-(trimethylsilyl)lincomycin (2-1)

To a solution of lincomycin (50.0 g, 123 mmol) in pyridine (200 ml) were added trimethylchlorosilane (90.0 ml, 704 mmol) and hexamethyldisilazane (65.0 ml, 310 mmol). A reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was diluted with water, then extracted with hexane, washed with water and concentrated under reduced pressure. To a solution of the resulting residue in methanol (150 ml) was added 80% aqueous acetic acid (22.5 ml) stirred at room temperature for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (30.0 ml) and concentrated

under reduced pressure. The residue was diluted with water and hexane, then extracted with hexane, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained as a colorless solid (69.5 g, 90.7%). ESI-MS *m/z* 623 $(M+H)^+$ as $C_{27}H_{58}N_2O_6SSi_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.14 (s, 18 H), 0.18 (s, 9 H), 0.85-0.93 (m, 3 H), 1.14 (d, *J* = 6.4 Hz, 3 H), 1.22-1.35 (m, 4 H), 1.79-1.90 (m, 1 H), 1.92-2.07 (m, 3 H), 2.09 (s, 3 H), 2.38 (s, 3 H), 3.00 (dd, *J* = 10.9, 3.9 Hz, 1 H), 3.07 (br d, *J* = 1.6 Hz, 1 H), 3.12-3.21 (m, 1 H), 3.59 (dd, *J* = 9.5, 2.5 Hz, 1 H), 3.80 (br d, *J* = 2.5 Hz, 1 H), 4.00 (d, *J* = 9.5 Hz, 1 H), 4.04-4.13 (m, 1 H), 4.15 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.27-4.33 (m, 1 H), 5.21 (d, *J* = 5.6 Hz, 1 H), 7.42 (d, *J* = 9.8 Hz, 1 H).

## (7*S*)-7-(Benzo[*d*]oxazol-2-ylthio)-7-deoxylincomycin (2-2)

To a solution of compound **2-1** (240 mg, 0.39 mmol) in tetrahydrofuran (5 ml) at 0˚C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.10 ml, 0.55 mmol), benzo[*d*]oxazole-2-thiol (85.0 mg, 0.56 ml) and stirred at 0˚C for 1 h. The mixture was stirred at r.t. for 16 h, diluted with 2*N* HCl (1 ml)-MeOH (1 ml), stirred at r.t. for 30 min and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound as a colorless solid (147.6 mg, 71.0%). $[\alpha]_D^{26}$ +77.6° (c 0.77, MeOH); ESI-MS *m/z* 540 $(M+H)^+$ as $C_{25}H_{37}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_6S_2$: 540.2202, found: 540.2204; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.97 (m, 3 H), 1.26-1.40 (m, 4 H), 1.61 (d, *J* = 6.8 Hz, 3 H), 1.77-1.85 (m, 1 H), 1.87 (s, 3 H), 1.97-2.09 (m, 2 H), 2.12-2.28 (m, 1 H), 2.35 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.21 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.83 (br d, *J* = 3.2 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.43 (br d, *J* = 9.8 Hz, 1 H), 4.45 (dq, *J* = 6.8, 3.2 Hz, 1 H), 4.64 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.27-7.36 (m, 2 H), 7.49-7.60 (m, 2 H).

## (7*S*)-7-(Benzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-3)

Compound **2-1** (320 mg, 0.51 mmol) and benzo[*d*]thiazole-2-thiol (250 mg, 1.49 mmol) were treated at 0 °C for 1h and then treated at room temperature for 2 h according to the similar procedure as described for the preparation of **2-2** to afford **2-3** (226 mg, 79.2%) as a colorless solid. $[\alpha]_D^{26}$ 74.1° (c 1.05, MeOH); ESI-MS *m/z* 556 $(M+H)^+$ as $C_{25}H_{37}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_5S_3$: 556.1974, found: 556.1975; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.98 (m, 3 H), 1.24-1.40 (m, 4 H), 1.59 (d, *J* = 6.8 Hz, 3 H), 1.78-1.90 (m, 1 H), 1.83 (s, 3 H), 1.98-2.10 (m, 2 H), 2.12-2.27 (m, 1 H), 2.34 (s, 3 H), 3.01 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.19 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.58 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.82 (br dd, *J* = 3.3, 0.6 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.52 (dq, *J* = 6.8, 3.1 Hz, 1 H), 4.62 (dd, *J* = 9.7, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.35 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H), 7.81-7.89 (m, 2 H).

### (7*S*)-7-(1*H*-Benzo[*d*]imidazol-2-ylthio)-7-deoxylincomycin (**2-4**)

Compound **2-1** (240 mg, 0.39 mmol) and 1*H*-benzo[*d*]imidazole-2-thiol (87.9 mg, 0.59 mmol) were treated at 0 °C for 1h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-4** (158 mg, 76.1%) as a colorless solid. $[\alpha]_D^{27}$ +91.9° (c 1.06, MeOH); ESI-MS *m/z* 539 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_2$: 539.2362, found: 539.2361; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.25-1.38 (m, 4 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 1.72-1.83 (m, 1 H), 1.90-2.05 (m, 2 H), 1.93 (s, 3 H), 2.14-2.28 (m, 1 H), 2.24 (s, 3 H), 3.01 (dd, *J* = 10.3, 5.4 Hz, 1 H), 3.13 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.60 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.84 (br d, *J* = 3.4 Hz, 1 H), 4.12 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.16 (dq, *J* = 7.1, 3.2 Hz, 1 H), 4.43-4.49 (m, 1 H), 4.51 (dd, *J* = 9.5, 3.2 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.19-7.26 (m, 2 H), 7.50 (br s, 2 H).

### (7*S*)-*S*-(7-Deoxylincomycin-7-yl)benzothioate (**2-5**)

To a solution of compound **2-1** (500 mg, 0.8 mmol) in toluene (5 ml) at 0˚C were added triphenylphosphine (316 mg, 1.20 mmol), diethylazodicarboxylate (0.22 ml, 1.20 mmol) and benzothioic S-acid (172 mg, 1.24 mmol). A reaction mixture was stirred at room temperature for 3 h, diluted with 2*N* HCl (2 ml) and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 9/1/0.1) to obtain the title compound as a colorless solid (100 mg, 23.7%). ESI-MS *m/z* 527 $(M+H)^+$ as $C_{25}H_{38}N_2O_6S_2$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.98 (m, 3 H), 1.23-1.39 (m, 4 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.83-1.92 (m, 1 H), 1.88 (s, 3 H), 1.98-2.07 (m, 1 H), 2.07-2.15 (m,1 H), 2.15-2.28 (m, 1 H), 2.43 (s, 3 H), 3.07 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.27 (dd, *J* = 8.3, 5.8 Hz, 1 H), 3.55 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.78-3.85 (m, 1 H), 4.11 (dd, *J* = 10.2, 5.7 Hz, 1 H), 4.23-4.32 (m, 2 H), 4.58 (dd, *J* = 9.7, 3.2 Hz, 1 H), 5.25 (d, *J* = 5.7 Hz, 1 H), 7.42-7.55 (m, 2 H), 7.59-7.68 (m, 1 H), 7.91-8.00 (m, 2 H).

### (7*S*)-7-Deoxy-7-phenylthiolincomycin (**2-6**)

To a solution of compound **2-1** (1.00 g, 1.60 mmol) in THF (15 ml) at 0˚C were added tributylphosphine (971 mg, 4.80 mmol), diethylazodicarboxylate (0.59 ml, 3.24 mmol) and 1,2-diphenyldisulfide (530 mg, 2.43 mmol). A reaction mixture was stirred at room temperature for 24 h, diluted with 2*N* HCl (1 ml) and stirred at r.t. for 30 min and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1 → 9/1/0.1) to obtain the title compound as a colorless solid (724.0 mg, 90.5%). $[\alpha]_D^{26}$ +111.1° (*c* 0.63, MeOH); ESI-MS *m/z* 499 $(M+H)^+$ as $C_{24}H_{38}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for

$C_{24}H_{38}N_2O_5S_2$: 499.2300, found: 499.2304; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.29 (d, $J$ = 6.9 Hz, 3 H), 1.31-1.41 (m, 4 H), 1.80-1.90 (m, 1 H), 1.95-2.04 (m, 1 H), 2.00 (s, 3 H), 2.05-2.25 (m, 2 H), 2.39 (s, 3 H), 2.98 (dd, $J$ = 10.7, 4.6 Hz, 1 H), 3.24 (dd, $J$ = 8.3, 5.9 Hz, 1 H), 3.58 (dd, $J$ = 10.2, 3.3 Hz, 1 H), 3.74 (br d, $J$ = 3.3 Hz, 1 H), 3.86 (qd, $J$ = 6.9, 2.6 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.35 (dd, $J$ = 9.7, 0.6 Hz, 1 H), 4.41 (dd, $J$ = 9.7, 2.6 Hz, 1 H), 5.26 (d, $J$ = 5.6 Hz, 1 H), 7.22-7.28 (m, 1 H), 7.29-7.36 (m, 2 H), 7.40-7.46 (m, 2 H).

### (7*S*)-7-Deoxy-7-(pyridin-4-ylthio)lincomycin (2-7)

Compound **2-1** (100 mg, 0.16 mmol) and pyridine-4-thiol (27.6 mg, 0.25 mmol) were treated at room temperature for 24 h according to the similar procedure as described for the preparation of **2-2** to afford **2-7** (46.2 mg, 40.2%) as a colorless solid. $[\alpha]_D^{26}$ +88.3° (*c* 0.94, MeOH); ESI-MS *m/z* 500 $(M+H)^+$ as $C_{23}H_{37}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{37}N_3O_5S_2$: 500.2253, found: 500.2259; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.28-1.40 (m, 4 H), 1.46 (d, $J$ = 7.0 Hz, 3 H), 1.78 (s, 3 H), 1.79-1.89 (m, 1 H), 1.96-2.11 (m, 2 H), 2.13-2.25 (m, 1 H), 2.39 (s, 3 H), 2.98 (dd, $J$ = 10.5, 4.9 Hz, 1 H), 3.24 (dd, $J$ = 8.4, 5.9 Hz, 1 H), 3.57 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.80 (br dd, $J$ = 3.2, 0.8 Hz, 1 H), 4.09 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.11 (dq, $J$ = 7.0, 2.9 Hz, 1 H), 4.37 (br dd, $J$ = 9.6, 0.8 Hz, 1 H), 4.59 (dd, $J$ = 9.6, 2.9 Hz, 1 H), 5.23 (d, $J$ = 5.6 Hz, 1 H), 7.33-7.39 (m, 2 H), 8.29-8.35 (m, 2 H).

### (7*S*)-7-Deoxy-7-(pyrimidin-4-ylthio)lincomycin (2-8)

Compound **2-1** (100 mg, 0.16 mmol) and pyrimidine-4-thiol (27.9 mg, 0.25 mmol) were treated at room temperature for 24 h according to the similar procedure as described for the preparation of **2-2** to afford **2-8** (57.2 mg, 49.7%) as a colorless solid. $[\alpha]_D^{27}$ +85.0° (*c* 1.53, MeOH); ESI-MS *m/z* 501 $(M+H)^+$ as $C_{22}H_{36}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{36}N_4O_5S_2$: 501.2205, found: 501.2208; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.26-1.41 (m, 4 H), 1.48 (d, $J$ = 6.7 Hz, 3 H), 1.79 (s, 3 H), 1.79-1.90 (m, 1 H), 1.97-2.12 (m, 2 H), 2.13-2.26 (m, 1 H), 2.37 (s, 3 H), 3.01 (dd, $J$ = 10.5, 5.1 Hz, 1 H), 3.24 (dd, $J$ = 8.4, 6.0 Hz, 1 H), 3.55 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.80 (br dd, $J$ = 3.2, 0.7 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.34 (br dd, $J$ = 9.5 Hz, 0.7, 1 H), 4.49-4.60(m, 2 H), 5.23 (d, $J$ = 5.6 Hz, 1 H), 7.40 (dd, $J$ = 5.6, 1.5 Hz, 1 H), 8.36 (br dd, $J$ = 5.6, 0.4 Hz, 1 H), 8.87 (br dd, $J$ = 1.5, 0.4 Hz, 1 H).

### (7*S*)-7-Deoxyl-7-(thiophen-2-ylthio)lincomycin (2-9)

Compound **2-1** (240 mg, 0.39 mmol) and thiophene-2-thiol (100 mg, 0.86 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-9** (19.4 mg, 10.0%) as a colorless solid. $[\alpha]_D^{26}$ +140.7° (*c* 0.47, MeOH); ESI-MS *m/z* 505 $(M+H)^+$ as $C_{22}H_{36}N_2O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{36}N_2O_5S_3$: 505.1865, found: 505.1863; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.27 (d, $J$ = 7.1 Hz, 3H), 1.30-1.41 (m, 4 H), 1.78-1.89 (m, 1 H), 1.92-2.00 (m, 1 H), 2.01-2.08 (m, 1 H), 2.08-2.19 (m, 1 H), 2.21 (s, 3 H), 2.33 (s, 3

H), 2.96 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.20 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.54-3.65 (m, 2 H), 3.73 (br d, *J* = 2.8 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.34 (dd, *J* = 9.8, 2.9 Hz, 1 H), 4.37-4.43 (m, 1 H), 5.29 (d, *J* = 5.6 Hz, 1 H), 7.06 (dd, *J* = 5.4, 3.5 Hz, 1H), 7.22 (dd, *J* = 3.5, 1.2 Hz, 1 H), 7.55 (dd, *J* = 5.4, 1.2 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(thiazol-2-ylthio)lincomycin (2-10)

Compound **2-1** (240 mg, 0.39 mmol) and thiazole-2-thiol (43.0 mg, 0.37 mmol) were treated at 0 ºC for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-10** (13.6 mg, 6.98%) as a colorless solid. $[\alpha]_D^{26}$ +109.5° (*c* 0.67, MeOH); ESI-MS *m/z* 506 $(M+H)^+$ as $C_{21}H_{35}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_3O_5S_3$: 506.1817, found: 506.1802; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.27-1.40 (m, 4 H), 1.61 (d, *J* = 7.0 Hz, 3 H), 1.79-1.92 (m, 1H), 1.95-2.14 (m, 2H), 2.01 (s, 3H), 2.15-2.29 (m, 1 H), 2.35 (s, 3 H), 3.01 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.26 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.78 (br d, *J* = 3.3 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.13 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.39 (br d, *J* = 9.8 Hz, 1 H), 4.51 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.54 (d, *J* = 3.5 Hz, 1 H), 7.73 (d, *J* = 3.5 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(1,3,4-thiadiazol-2-ylthio)lincomycin (2-11)

Compound **2-1** (240 mg, 0.39 mmol) and 1,3,4-thiadiazole-2-thiol (80.0 mg, 0.68 mmol) were treated at 0 ºC for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-11** (121.0 mg, 62.0%) as a colorless solid. $[\alpha]_D^{27}$ +100.2° (*c* 2.03, MeOH); ESI-MS *m/z* 507 $(M+H)^+$ as $C_{20}H_{34}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{20}H_{34}N_4O_5S_3$: 507.1770, found: 507.1773; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.26-1.42 (m, 4 H), 1.53 (d, *J* = 6.8 Hz, 3 H), 1.80-1.90 (m, 1 H), 1.93 (s, 3 H), 1.97-2.12 (m, 2 H), 2.15-2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.27 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37-4.46 (m, 2 H), 4.60 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 9.37 (s, 1H).

### (7*S*)-7-Allylthio-7-deoxylincomycin (2-12)

To a solution of compound **2-5** (83.2 mg, 0.16 mmol) in methanol (1 ml) were added allyl iodide (26.5 mg, 0.16 mmol) and 28% sodium methoxide in methanol (0.56 ml). A reaction mixture was stirred at room temperature for 14 h, diluted with 1*N* HCl (1 ml) and concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound as a colorless solid (22.0 mg, 30.0%). $[\alpha]_D^{25}$ +115.3° (*c* 0.34, MeOH); ESI-MS *m/z* 463 $(M+H)^+$ as $C_{21}H_{38}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{38}N_2O_5S_2$: 463.2300, found: 463.2295; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.27-1.40 (m, 4 H), 1.31 (d, *J* = 7.0 Hz, 3 H), 1.82-1.92

(m, 1 H), 2.00 (ddd, *J* = 12.5, 7.6, 4.7 Hz, 1 H), 2.08-2.27 (m, 2 H), 2.19 (s, 3 H), 2.44 (s, 3 H), 3.05 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.23-3.39 (m, 4 H), 3.56 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.67-3.74 (m, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.21 (br d, *J* = 9.8 Hz,1 H), 4.27 (dd, *J* = 9.8, 2.4 Hz, 1 H), 5.04-5.11 (m, 1 H), 5.19 (dq, *J* = 17.0, 1.4 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 5.85 (ddt, *J* = 17.0, 10.7, 1.0 Hz, 1 H).

### (7*S*)-7-(5-Chlorobenzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-13)

Compound **2-1** (160 mg, 0.26 mmol) and 5-chlorobenzo[*d*]thiazole-2-thiol (160 mg, 0.79 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-13** (111 mg, 73.2%) as a colorless solid. $[\alpha]_D^{26}$ +52.8° (*c* 0.25, MeOH); ESI-MS *m/z* 590 $(M+H)^+$ as $C_{25}H_{36}ClN_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}ClN_3O_5S_3$: 590.1584, found: 590.1581; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.27-1.39 (m, 4 H), 1.59 (d, *J* = 7.0 Hz, 3 H), 1.78-1.88 (m, 1 H), 1.86 (s, 3 H), 1.97-2.08 (m, 2 H), 2.13-2.27 (m, 1 H), 2.32 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.20 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.7, 0.9 Hz, 1 H), 4.53 (dq, *J* = 7.0, 3.3 Hz, 1 H), 4.61 (dd, *J* = 9.7, 3.3 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.81-7.87 (m, 2 H).

### (7*S*)-7-Deoxyl-7-(thiazolo[5,4-*c*]pyridin-2-ylthio)lincomycin (2-14)

Compound **2-1** (320 mg, 0.51 mmol) and thiazolo[5,4-*c*]pyridine-2-thiol (250 mg, 1.49 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 2 h according to the similar procedure as described for the preparation of **2-2** to afford **2-14** (206 mg, 72.0%) as a colorless solid. $[\alpha]_D^{26}$ +67.1° (*c* 0.50, MeOH); ESI-MS *m/z* 505 $(M+H)^+$ as $C_{24}H_{36}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{36}N_4O_5S_3$: 557.1926, found: 557.1924; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.27-1.41 (m, 4 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.82 (s, 3 H), 1.80-1.91 (m, 1 H), 1.98-2.13 (m, 2 H), 2.15-2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.24 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.73 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.5, 0.73 Hz, 1 H), 4.63-4.72 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.82 (dd, *J* = 5.6, 0.9 Hz, 1 H), 8.51 (d, *J* = 5.6 Hz, 1 H), 9.06 (d, *J* = 0.9 Hz, 1 H).

### (7*S*)-7-(6-Cyanobenzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-15)

Compound **2-1** (160 mg, 0.26 mmol) and 6-cyanobenzo[*d*]thiazole-2-thiol (55 mg, 0.29 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-15** (98.4 mg, 65.9%) as a colorless solid. $[\alpha]_D^{26}$ +73.0° (*c* 1.10, MeOH); ESI-MS *m/z* 581 $(M+H)^+$ as $C_{26}H_{36}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{36}N_4O_5S_3$: 581.1926, found: 581.1926; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.25-1.41 (m, 4 H), 1.61 (d, *J* = 6.6 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.82 (s, 3 H), 1.98-2.09 (m, 2 H), 2.14-2.26 (m, 1 H),

2.35 (s, 3 H), 2.98 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.21 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.7 Hz, 1 H), 4.42 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.60-4.70 (m, 2 H), 5.24 (d, *J* = 5.7 Hz, 1 H), 7.76 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.94 (br dd, *J* = 8.5, 0.6 Hz, 1 H), 8.32 (br dd, *J* = 1.7, 0.6 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(6-nitrobenzo[*d*]thiazol-2-ylthio)lincomycin (2-16)

Compound **2-1** (240 mg, 0.39 mmol), and 6-nitrobenzo[*d*]thiazole-2-thiol (180 mg, 0.85 mmol) were treated in toluene (5 ml) at 0 °C for 10 min and then treated at room temperature for 20 h according to the similar procedure as described for the preparation of **2-2** to afford **2-16** (153 mg, 66.1%) as a colorless solid. $[\alpha]_D^{29}$ +67.6° (*c* 0.60, MeOH); ESI-MS *m/z* 601 $(M+H)^+$ as $C_{25}H_{36}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}N_4O_7S_3$: 601.1824, found: 601.1827; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.28-1.40 (m, 4 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.77-1.89 (m, 1 H), 1.83 (s, 3 H), 1.98-2.09 (m, 2 H), 2.14-2.27 (m, 1 H), 2.36 (s, 3 H), 2.99 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.22 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.62-4.71 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.95 (d, *J* = 9.0, 1 H), 8.32 (dd, *J* = 9.0, 2.3, Hz, 1 H), 8.85 (d, *J* = 2.3 Hz, 1 H).

### (7*S*)-7-(6-Aminobenzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-17)

Compound **2-1** (630 mg, 1.01 mmol) and 6-aminobenzo[*d*]thiazole-2-thiol (300 mg, 1.65 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-17** (387 mg, 67.1%) as a colorless solid. $[\alpha]_D^{26}$ +89.0° (*c* 1.11, MeOH); ESI-MS *m/z* 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2075; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.26-1.38 (m, 4 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.75-1.89 (m, 1 H), 1.94 (s, 3 H), 1.95-2.11 (m, 2 H), 2.12-2.25 (m, 1 H), 2.32 (s, 3 H), 3.03 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.17 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.27 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.43 (br dd, *J* = 9.8, 0.7 Hz, 1 H), 4.55 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.5 Hz, 1 H), 6.85 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.08 (dd, *J* = 2.3, 0.25 Hz, 1 H), 7.59 (dd, *J* = 8.7, 0.25 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(5-nitrobenzo[*d*]thiazol-2-ylthio)lincomycin (2-18)

Compound **2-1** (320 mg, 0.51 mmol) and 5-nitrobenzo[*d*]thiazole-2-thiol (120 mg, 0.57 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-18** (139 mg, 45.1%) as a colorless solid. $[\alpha]_D^{26}$ +58.2° (*c* 0.81, MeOH); ESI-MS *m/z* 601 $(M+H)^+$ as $C_{25}H_{36}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{36}N_4O_7S_3$: 601.1824, found: 601.1826; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.30-1.40 (m, 4 H), 1.62 (d, *J* = 6.8 Hz, 3 H), 1.80-1.90 (m, 1 H), 1.85 (s, 3 H), 1.99-2.10 (m, 2 H), 2.16-2.30 (m, 1 H),

2.36 (s, 3 H), 3.01 (dd, *J* = 10.3, 5.3 Hz, 1 H), 3.25 (dd, *J* = 8.7, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.84 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.11 (dd, *J* = 10.3, 5.7 Hz, 1 H), 4.42 (br dd, *J* = 9.6, 0.8 Hz, 1 H), 4.61 (dd, *J* = 6.8, 3.3 Hz, 1 H), 4.65 (dd, *J* = 9.6, 3.3 Hz, 1 H), 5.25 (d, *J* = 5.7 Hz, 1 H), 8.08 (d, *J* = 8.8, 1 H), 8.21 (dd, *J* = 8.8, 2.2, Hz, 1 H), 8.64 (br dd, *J* = 2.2, 0.24 Hz, 1 H).

### (7*S*)-7-(5-Aminobenzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-19)

To a solution of compound **2-18** (75.0 mg, 0.12 mmol) in ethanol (3.0 ml) were added $SnCl_2 \cdot H_2O$ (140 mg, 0.62 mmol) and $NaBH_4$ (6.50 mg, 0.17 mmol). A reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. The resulting residue was dissolved by ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound as a colorless solid (34.2 mg, 48.0%). $[\alpha]_D^{25}$ +59.4° (*c* 0.58, MeOH); ESI-MS *m/z* 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2090; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.25-1.39 (m, 4 H), 1.55 (d, *J* = 7.0 Hz, 3 H), 1.76-1.86 (m, 1 H), 1.88 (s, 3 H), 1.96-2.08 (m, 2 H), 2.12-2.24 (m, 1 H), 2.32 (s, 3 H), 2.99 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.18 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.81 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.39 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.42 (br dd, *J* = 9.7, 0.7 Hz, 1 H), 4.58 (dd, *J* = 9.7, 3.1 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 6.81 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.16-7.18 (m, 1 H), 7.52 (dd, *J* = 8.6, 0.2 Hz, 1 H).

### 7(*R*)-7-(6-Aminobenzo[*d*]thiazol-2-ylthio)-7-deoxylincomycin (2-20)

To a solution of clindamycin hydrochloride (460 mg, 1.00 mmol) in DMF (5 ml) were added $K_2CO_3$ (152 mg, 1.10 mmol) and 6-aminobenzo[*d*]thiazole-2-thiol (200 mg, 1.10 mmol). A reaction mixture was stirred at 100˚C for 16 h and then concentrated under reduced pressure. The residue was diluted with water, then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound as a colorless solid (233 mg, 40.9%). $[\alpha]_D^{27}$ +129.5° (*c* 0.45, MeOH); ESI-MS *m/z* 571 $(M+H)^+$ as $C_{25}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_4O_5S_3$: 571.2083, found: 571.2079; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.27-1.39 (m, 4 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 1.75-1.87 (m, 1 H), 1.95-2.01 (m, 1 H), 2.05 (dd, *J* = 10.2, 8.9 Hz, 1 H), 2.17 (s, 3 H), 2.13-2.26 (m, 1 H), 2.39 (s, 3 H), 2.98 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.21 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.54 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.80-3.84 (m, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.28 (br dd, *J* = 9.2, 0.6 Hz, 1 H), 4.30 (dq, *J* = 7.1, 3.9 Hz, 1 H), 4.65 (dd, *J* = 9.2, 3.9 Hz, 1 H), 5.29 (d, *J* = 5.6 Hz, 1 H), 6.84 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.08 (dd, *J* = 2.3, 0.4 Hz, 1 H), 7.57 (dd, *J* = 8.7, 0.4 Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 18.9 ml/min, 50 mM $AcONH_4$/$CH_3CN$ = 35/65) to obtain the highly purified title compound as a colorless solid.

### (7*S*)-7-Deoxy-7-(2-nitrophenylthio)lincomycin (2-21)

Compound **2-1** (200 mg, 0.32 mmol) and 1,2-bis(2-nitrophenyl)disulfide (149 mg, 0.48 mmol) were treated at room temperature for 10 h according to the similar procedure as described for the preparation of **2-6** to afford **2-21** (39.6 mg, 22.7%) as a colorless solid. $[\alpha]_D^{27}$ +69.9° (*c* 0.91, MeOH); ESI-MS *m/z* 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2157; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.99 (m, 3 H), 1.29-1.38 (m, 4 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.79 (s, 3 H), 1.81-1.92 (m, 1 H), 1.98-2.14 (m, 2 H), 2.14-2.26 (m, 1 H), 2.42 (s, 3 H), 3.01 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.28 (dd, *J* = 8.7, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.79 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.06 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.08 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.37 (br dd, *J* = 9.8, 0.8 Hz, 1 H), 4.57 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.21 (d, *J* = 5.6 Hz, 1 H), 7.38 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1 H), 7.64 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1 H), 7.70 (br dd, *J* = 8.2, 1.2 Hz, 1 H), 8.05 (dd, *J* = 8.3, 1.4 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(3-nitrophenylthio)lincomycin (2-22)

Compound **2-1** (1.00 g, 1.61 mmol) and 1,2-bis(3-nitrophenyl)disulfide (742 mg, 2.41 mmol) were treated at room temperature for 25 h according to the similar procedure as described for the preparation of **2-6** to afford **2-22** (364 mg, 41.7%) as a colorless solid. $[\alpha]_D^{29}$ +75.2° (*c* 0.48, MeOH); ESI-MS *m/z* 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2148; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.30-1.37 (m, 4 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.93 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.24 (m, 1 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.24 (dd, *J* = 8.3, 5.9 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.79 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 3.99 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.5, 0.8 Hz, 1 H), 4.52 (dd, *J* = 9.5, 2.8 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.55-7.61 (m, 1 H), 7.81 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1 H), 8.09 (br ddd, *J* = 8.2, 2.2, 0.9 Hz, 1 H), 8.21-8.23 (m, 1 H).

### (7*S*)-7-Deoxy-7-(4-nitrophenylthio)lincomycin (2-23)

Compound **2-1** (200 mg, 0.32 mmol) and 1,2-bis(4-nitrophenyl)disulfide (149 mg, 0.48 mmol) were treated at room temperature for 20 h according to the similar procedure as described for the preparation of **2-6** to afford **2-23** (29.3 mg, 16.8%) as a colorless solid. $[\alpha]_D^{26}$ +67.1° (*c* 0.29, MeOH); ESI-MS *m/z* 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2151; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.30-1.39 (m, 4 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.81 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.26 (m, 1 H), 2.40 (s, 3 H), 3.00 (dd, *J* = 10.6, 5.0 Hz, 1 H), 3.25 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.03-4.16 (m, 1 H), 4.37 (br dd, *J* = 9.7, 0.8 Hz, 1 H), 4.58 (dd, *J* = 9.7, 2.9 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.51-7.57 (m, 2 H), 8.13-8.19 (m, 2 H).

### (7*S*)-7-(2-Aminophenylthio)-7-deoxylincomycin (**2-24**)

To a solution of compound **2-21** (39.6 mg, 0.07 mmol) in ethanol (2 ml) at were added $SnCl_2 \cdot H_2O$ (82.1 mg, 0.36 mmol) and $NaBH_4$ (13.7 mg, 4.97 mmol). A reaction mixture was stirred at room temperature for 3 h, added aq $NaHCO_3$, then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 9/1/0.1) to obtain the title compound as a colorless solid (10.8 mg, 28.9%). $[\alpha]_D^{28}$ +74.5° (*c* 0.33, MeOH); ESI-MS *m/z* 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2412; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.17 (d, *J* = 7.1 Hz, 3 H), 1.28-1.40 (m, 4 H), 1.75-1.85 (m, 1 H), 1.89-1.98 (m, 1 H), 2.04-2.12 (m, 1 H), 2.14-2.23 (m, 1 H), 2.19 (s, 3 H), 2.32 (s, 3 H), 3.01 (dd, *J* = 10.6, 5.0 Hz, 1 H), 3.25 (dd, *J* = 8.3, 5.9 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.67 (dq, *J* = 7.1, 2.8 Hz, 1 H), 3.74 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.31 (dd, *J* = 9.8, 2.8 Hz, 1 H), 4.38 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 6.61-6.67 (m, 1 H), 6.81 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.13 (ddd, *J* = 8.8, 7.2, 1.5 Hz, 1 H), 7.34 (dd, *J* = 7.7, 1.5 Hz, 1 H).

### (7*S*)-7-(3-Aminophenylthio)-7-deoxylincomycin (**2-25**)

Compound **2-22** (238 mg, 0.44 mmol), $SnCl_2 \cdot H_2O$ (494 mg, 2.19 mmol) and $NaBH_4$ (82.9 mg, 2.19 mmol) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **2-24** to afford **2-25** (36.5 mg, 16.2%) as a colorless solid. $[\alpha]_D^{29}$ +91.0° (*c* 0.60, MeOH); ESI-MS *m/z* 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2408; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.31 (d, *J* = 7.0 Hz, 3 H), 1.30-1.40 (m, 4 H), 1.79-1.92 (m, 1 H), 1.93-2.10 (m, 2 H), 2.02 (s, 3 H), 2.11-2.23 (m, 1 H), 2.38 (s, 3 H), 2.97 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.72 (br d, *J* = 3.3 Hz, 1 H), 3.75-3.83 (m, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.33-4.40 (m, 2 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 6.59 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1 H), 6.71 (ddd, J = 7.7, 1.7, 0.9 Hz, 1 H), 6.78-6.82 (m, 1 H), 6.99-7.06 (m, 1 H).

### (7*S*)-7-(4-Aminophenylthio)-7-deoxylincomycin (**2-26**)

Compound **2-23** (29.3 mg, 0.054 mmol), $SnCl_2 \cdot H_2O$ (60.8 mg, 0.27 mmol) and $NaBH_4$ (10.0 mg, 0.26 mmol) were treated at room temperature for 3 h according to the similar procedure as described for the preparation of **2-24** to afford **2-26** (9.6 mg, 34.7%) as a colorless solid. $[\alpha]_D^{28}$ +142.0° (*c* 0.51, MeOH); ESI-MS *m/z* 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2411; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.20 (d, *J* = 7.1 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.80-1.90 (m, 1 H), 1.92-2.00 (m, 1 H), 2.04-2.21 (m, 2 H), 2.17 (s, 3 H), 2.34 (s, 3 H), 2.98 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.53 (dq, *J* = 7.1, 2.8 Hz, 1 H), 3.60 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.68-3.72 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.25 (dd, *J* = 9.9, 2.8 Hz, 1 H), 4.38 (br d, *J* = 9.9 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 6.62-6.68 (m, 2 H), 7.20-7.26 (m, 2 H).

### (7*S*)-7-(4-Methanesulfonamidophenylthio)-7-deoxylincomycin (**2-27**)

To a solution of compound **2-26** (83.8 mg, 0.16 mmol) in DMF (1 ml) were added triethylamine (0.027 ml, 0.20 mmol) and methanesulfonyl chloride (0.015 ml, 0.20 mmol). A reaction mixture was stirred at room temperature for 20 min., added saturated aqueous $NaHCO_3$ (10 ml), then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (28.0 mg, 29.0%). $[\alpha]_D^{26}$ +94.2° (*c* 1.01, MeOH); ESI-MS *m/z* 592 $(M+H)^+$ as $C_{25}H_{41}N_3O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{41}N_3O_7S_3$: 592.2185, found: 592.2180; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.28 (d, *J* = 7.0 Hz, 3 H), 1.31-1.41 (m, 4 H), 1.78-1.92 (m, 1 H), 1.99 (ddd, *J* = 12.9, 7.9, 5.0 Hz, 1 H), 2.04 (s, 3 H), 2.05-2.11 (m, 1 H), 2.11-2.23 (m, 1 H), 2.38 (s, 3 H), 2.94-3.03 (m, 1 H), 2.97 (s, 3 H), 3.25 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.74 (br d, *J* = 3.2 Hz, 1 H), 3.78 (dq, *J* = 7.0, 2.5 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.31-4.36 (m, 1 H), 4.38 (dd, *J* = 9.7, 2.5 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.18-7.25 (m, 2 H), 7.40-7.48 (m, 2 H).

### 7-*O*-Methanesulfonyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**2-28**)

To a solution of compound **2-1** (5.0 g, 8.0 mmol) in chloroform (25 ml) were added triethylamine (2.79 ml, 20.1 mmol) and methanesulfonyl chloride (1.24 ml, 16.1 mmol). A reaction mixture was stirred at room temperature for 3 h, dissolved by chloroform (60 ml), washed with saturated aqueous $NaHCO_3$ (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to obtain the title compound as a colorless solid (5.51 g, 97.9%). ESI-MS *m/z* 701 $(M+H)^+$ as $C_{28}H_{60}N_2O_8S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.17 (s, 9 H), 0.89 (br t, *J* = 6.9 Hz, 3 H), 1.21-1.36 (m, 4 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.79-1.89 (m, 1 H), 1.92-2.09 (m, 3 H), 2.11 (s, 3 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.7, 3.7 Hz, 1 H), 3.09 (s, 3 H), 3.14-3.21 (m, 1 H), 3.52 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.75 (br d, *J* = 2.4 Hz, 1 H), 3.90 (d, *J* = 9.7 Hz, 1 H), 4.15 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.70-4.78 (m, 1 H), 5.09-5.15 (m, 1 H), 5.16 (d, *J* = 5.6 Hz, 1 H), 7.61 (d, *J* = 10.7 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-methoxycarbonylphenylthio)lincomycin (**2-29**)

To a solution of compound **2-28** (100 mg, 0.14 mmol) in DMF (1.0 ml) were added $K_2CO_3$ (59.8 mg, 0.43 mmol) and methyl 4-mercaptobenzoate (48.9 mg, 0.29 mmol). A reaction mixture was stirred at 80˚C for 3 h, cooled down to r.t., diluted with 1*N* HCl (2 ml)-MeOH (1 ml), stirred at r.t. for 2 h and concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. To the mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 5/1/0.1) to obtain the title compound as a colorless solid (58.0 mg, 72.7%). $[\alpha]_D^{24}$ +84.6° (*c* 0.97, MeOH); ESI-MS *m/z* 557 $(M+H)^+$ as $C_{26}H_{40}N_2O_7S_2$; TOF-ESI-HRMS

$(M+H)^+$ calcd for $C_{26}H_{40}N_2O_7S_2$: 557.2355, found: 557.2359; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.29-1.37 (m, 4 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.79-1.91 (m, 1 H), 1.84 (s, 3 H), 1.96-2.05 (m, 1 H), 2.05-2.12 (m, 1 H), 2.12-2.25 (m, 1 H), 2.40 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.78 (br dd, *J* = 3.2, 0.7 Hz,1 H), 3.89 (s, 3 H), 4.03 (dq, *J* = 6.8, 2.8 Hz,1 H), 4.10 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.37 (br dd, *J* = 9.7, 0.7 Hz, 1 H), 4.52 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.42-7.49 (m, 2 H), 7.90-7.97 (m, 2 H).

### (7*S*)-7-Deoxy-7-(3-methoxycarbonylphenylthio)lincomycin (2-30)

Compound **2-28** (200 mg, 0.29 mmol) and methyl 3-mercaptobenzoate (95.9 mg, 0.57 mmol) were treated at room temperature for 3 h according to the similar procedure as described for the preparation of **2-29** to afford **2-30** (101.6 mg, 64.0%) as a colorless solid. $[\alpha]_D^{29}$ +93.6° (*c* 2.37, MeOH); ESI-MS *m/z* 557 $(M+H)^+$ as $C_{25}H_{37}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{37}N_3O_6S_2$: 557.2355, found: 557.2355; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.29-1.40 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.78-1.91 (m, 1 H), 1.95-2.04 (m, 1 H), 1.97 (s, 3 H), 2.04-2.11 (m, 1 H), 2.11-2.23 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.23 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74-3.79 (m, 1 H), 3.87-3.96 (m, 1 H), 3.91 (s, 3 H), 4.11 (dd, *J*=10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.48 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.42-7.49 (m, 1 H), 7.67 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1 H), 7.87-7.92 (m, 1 H), 8.02-8.06 (m, 1 H).

### (7*S*)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (2-31)

To a solution of compound **2-1** (240 mg, 0.39 mmol) in tetrahydrofuran (5 ml) at 0˚C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.1 ml, 0.55 mmol) and *t*-butyl (5-mercapto-1,3,4-thiadiazol-2-yl)carbamate (130 mg, 0.56 mmol). A reaction mixture was stirred at room temperature for 17 h, concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ (10 ml), extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (Hexane/ethyl acetate) to obtain (7*S*)-7-(5-amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin as a colorless solid (271 mg, 84.0%).

(7*S*)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (271.3 mg, 0.32 mmol) in 90% aqueous trifluoroacetic acid (5 ml) was kept at room temperature for 1 h. The mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ (10 ml), then extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 5/1/0.1) to obtain the title compound as a colorless solid (111.4 mg, 66%). $[\alpha]_D^{26}$ +139.8° (*c* 0.28, MeOH); ESI-MS *m/z* 520 $(M+H)^+$ as $C_{20}H_{35}N_5O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{20}H_{35}N_5O_5S_3$: 522.1879, found: 522.1877; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.27-1.38 (m, 4 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.76-1.90

(m, 1 H), 1.92-2.07 (m, 2 H), 2.11 (s, 3 H), 2.14-2.26 (m, 1 H), 2.33 (s, 3 H), 2.97 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.26 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.74-3.78 (m, 1 H), 3.94 (dq, *J* = 7.0, 2.9 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.39 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.45 (dd, *J* = 9.8, 2.9 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 18.9 ml/min, 50 mM $AcONH_4/CH_3CN$ = 70/30) and precipitated (MeOH/ethyl acetate) to obtain the highly purified title compound as a colorless solid.

### (7*S*)-7-Deoxy-7-(5-methylamino-1,3,4-thiadiazol-2-ylthio)lincomycin (2-32)

Compound **2-1** (240 mg, 0.39 mmol) and *t*-butyl (5-mercapto-1,3,4-thiadiazol-2-yl)(methyl)carbamate (100 mg, 0.40 mmol) were treated at 0 ºC for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-31** to afford **2-32** (147 mg, 71.3% (2 steps)) as a colorless solid. $[\alpha]_D^{26}$ +118.4° (*c* 0.27, MeOH); ESI-MS *m/z* 534 $(M+H)^+$ as $C_{21}H_{37}N_5O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{37}N_5O_5S_3$: 536.2035, found: 536.2039; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.27-1.38 (m, 4 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.77-1.88 (m, 1 H), 1.93-2.01 (m, 1 H), 2.04 (dd, *J* = 10.1, 8.7 Hz, 1 H), 2.12 (s, 3 H), 2.14-2.26 (m, 1 H), 2.33 (s, 3H), 2.93-3.01 (m, 1 H), 2.97 (s, 3 H), 3.25 (dd, *J* = 8.4, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.78 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 3.94 (dq, *J* = 7.0, 2.9 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.38 (br dd, *J* = 9.8, 0.7 Hz, 1 H), 4.46 (dd, *J* = 9.8, 2.9 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(5-(4-(difluoromethylthio)phenylamino)-1,3,4-thiadiazol-2-ylthio)lincomycin (2-33)

Compound **2-1** (240 mg, 0.39 mmol) and 5-(4-(difluoromethylthio)phenylamino)-1,3,4-thiadiazole-2-thiol (120 mg, 0.41 mmol) were treated at 0 ºC for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-33** (99.5 mg, 38.0%) as a colorless solid. $[\alpha]_D^{24}$ +96.7° (*c* 0.78, MeOH); ESI-MS *m/z* 680 $(M+H)^+$ as $C_{27}H_{39}F_2N_5O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{39}F_2N_5O_5S_4$: 680.1880, found: 680.1876; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.95 (m, 3 H), 1.26-1.39 (m, 4 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.78-1.88 (m, 1 H), 1.93-2.06 (m, 2 H), 2.12 (s, 3 H), 2.14-2.28 (m, 1 H), 2.33 (s, 3 H), 2.95-3.02 (m, 1 H), 3.26 (dd, *J* = 8.4, 6.2 Hz, 1 H), 3.59 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.79 (br d, *J* = 3.3 Hz, 1 H), 4.02-4.10 (m, 1 H), 4.12 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.41 (br d, *J* = 9.8 Hz, 1 H), 4.49 (dd, *J* = 9.8, 3.6 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.00 (t, *J* = 56.8 Hz, 1 H), 7.52-7.58 (m, 2 H), 7.64-7.70 (m, 2 H).

### (7*S*)-7-(5-Carbamoyl-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (2-34)

Compound **2-1** (240 mg, 0.39 mmol), and 5-mercapto-1,3,4-thiadiazole-2-carboxamide (95.0 mg, 0.59 mmol) were treated at 50˚C for 16 h according to the similar procedure as described for the preparation of

**2-2** to afford **2-34** (67.8 mg, 32.0%) as a colorless solid. $[\alpha]_D^{26}$ +83.6° (*c* 0.69, MeOH); ESI-MS *m/z* 550 $(M+H)^+$ as $C_{21}H_{35}N_5O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_5O_6S_3$: 550.1828, found: 550.1829; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.30-1.41 (m, 4 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.94 (s, 3 H), 1.97-2.09 (m, 2 H), 2.13-2.26 (m, 1 H), 2.37 (s, 3 H), 2.99 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.24 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.7, 0.8 Hz, 1 H), 4.49 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.61 (dd, *J* = 9.7, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 18.9 ml/min, 50 mM $AcONH_4/CH_3CN$ = 50/50) to obtain the highly purified title compound as a colorless solid.

## (7*S*)-7-Deoxy-7-(5-methylcarbamoyl-1,3,4-thiadiazol-2-ylthio)lincomycin (2-35)

Compound **2-1** (240 mg, 0.39 mmol) and 5-mercapto-*N*-methyl-1,3,4-thiadiazole-2-carboxamide (100 mg, 0.57 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-35** (26.1 mg, 12.1%) as a colorless solid. $[\alpha]_D^{26}$ +81.8° (*c* 1.29, MeOH); ESI-MS *m/z* 564 $(M+H)^+$ as $C_{22}H_{37}N_5O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{37}N_5O_6S_3$: 564.1984, found: 564.1977; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.98 (m, 3 H), 1.26-1.42 (m, 4 H), 1.56 (d, *J* = 6.8 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.94 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.27 (m, 1 H), 2.38 (s, 3 H), 2.94 (s, 3 H), 3.00 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.25 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.79-3.84 (m, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br d, *J* = 9.8 Hz, 1 H), 4.48 (dq, *J* = 6.8, 3.1 Hz, 1 H), 4.62 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H). For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 11.3 ml/min, 0.1% aq. TFA/$CH_3CN$ = 60/40) to obtain the highly purified title compound as a colorless solid.

## (7*S*)-7-Deoxy-7-(5-(2-(pyrrolidin-1-yl)ethylcarbamoyl)-1,3,4-thiadiazol-2-ylthio)lincomycin (2-36)

Compound **2-1** (240 mg, 0.39 mmol) and 5-(2-(pyrrolidin-1-yl)ethylcarbamoyl)-1,3,4-thiadiazole-2-thiol (130 mg, 0.50 mmol) were treated at 0 °C for 1 h and then treated at room temperature for 16 h according to the similar procedure as described for the preparation of **2-2** to afford **2-36** (69.8 mg, 28.0%) as a colorless solid. $[\alpha]_D^{27}$ +78.0° (*c* 0.54, MeOH); ESI-MS *m/z* 647 $(M+H)^+$ as $C_{27}H_{46}N_6O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{46}N_6O_6S_3$: 647.2719, found: 647.2716; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.28-1.39 (m, 4 H), 1.56 (d, *J* = 7.0 Hz, 3 H), 1.77-1.90 (m, 5 H), 1.94 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.26 (m, 1 H), 2.37 (s, 3 H), 2.57-2.67 (m, 4 H), 2.73 (t, *J* = 6.7 Hz, 2 H), 2.98 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.24 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.51-3.60 (m, 3 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.7, 0.8 Hz, 1 H), 4.48 (dq, *J* = 7.0, 3.1 Hz, 1 H), 4.62 (dd, *J* = 9.7, 3.1 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(5-phenyl-1,3,4-thiadiazol-2-ylthio)lincomycin (2-37)

Compound **2-1** (240 mg, 0.39 mmol) and 5-phenyl-1,3,4-thiadiazole-2-thiol (100 mg, 0.51 mmol) in toluene (5 ml) were treated according to the similar procedure as described for the preparation of **2-2** to afford **2-37** (46.5 mg, 20.7%) as a colorless solid. $[\alpha]_D^{27}$ +157.2° (*c* 1.47, $CHCl_3$); ESI-MS *m/z* 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2086; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.26-1.38 (m, 4 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.79-1.91 (m, 1 H), 1.96-2.11 (m, 2 H), 2.03 (s, 3 H), 2.15-2.28 (m, 1 H), 2.38 (s, 3 H), 3.03 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.27 (dd, *J* = 8.5, 6.1 Hz, 1 H), 3.58 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 4.12 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.36-4.46 (m, 2 H), 4.60 (dd, *J* = 9.7, 3.2 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.49-7.58 (m, 3 H), 7.89-7.95 (m, 2 H).

### (7*S*)-7-(5-(2-Aminoacetamido)-1,3,4-thiadiazol-2-ylthio)-7-deoxylincomycin (2-39)

To a solution of compound **2-1** (240 mg, 0.39 mmol) in tetrahydrofuran (5 ml) at 0˚C were added triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (0.10 ml, 0.55 mmol) and *t*-butyl (2-((5-mercapto-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)carbamate (150 mg, 0.52 mmol). A reaction mixture was stirred room temperature for 17 h and then concentrated under reduced pressure. The resulting residue (compound **2-38**) in 90% aqueous trifluoroacetic acid (5 ml) was stirred at room temperature for 30 min. and then concentrated under reduced pressure. The resulting residue was purified by preparative reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 18.9 ml/min, 0.1% aq TFA/$CH_3CN$ = 85/15). This trifluoroacetate was desalted by preparative reverse-phase column chromatography (YMC triart C18, 20*250 mm, r.t., 18.9 ml/min, $H_2O$/MeOH = 100/0 (15 min) → 0/100 (15-40 min)) to obtain the highly purified title compound as a colorless solid (54.0 mg, 24.2%). $[\alpha]_D^{25}$ +100.4° (*c* 0.29, MeOH); ESI-MS *m/z* 578 $(M+H)^+$ as $C_{22}H_{38}N_6O_6S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{22}H_{38}N_6O_6S_3$: 579.2093, found: 579.2095; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.29-1.39 (m, 4 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.77-1.87 (m, 1 H), 1.93-2.09 (m, 2 H), 2.06 (s, 3 H), 2.13-2.25 (m, 1 H), 2.32 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.26 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.54-3.62 (m, 2 H), 3.78 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 4.08 (dq, *J* = 7.0, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.47 (dd, *J* = 9.8, 2.8 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

### (7*S*)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (2-40)

To a solution of compound **2-31** (403 mg, 0.77 mmol) in pyridine (8 ml) were added trimethylchlorosilane (0.61 ml, 4.8 mmol) and hexamethyldisilazane (1.05 ml, 5.0 mmol). A reaction mixture was stirred at room temperature for 2.5 h and then concentrated under reduced pressure. The residue was diluted with saturated aqueous $NH_4Cl$ and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound as a colorless solid (467 mg, 81.9%). ESI-MS *m/z* 738 $(M+H)^+$ as $C_{29}H_{59}N_5O_5S_3Si_3$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.13 (s, 18H), 0.17 (s, 9 H), 0.79-0.97 (m, 3 H), 1.15-1.37 (m, 4 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.71-1.90 (m, 2 H), 1.91-2.06 (m, 2 H), 2.08 (s, 3 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.7, 3.6 Hz, 1 H), 3.12-3.23 (m, 1 H), 3.61 (dd, *J* = 9.6, 2.5 Hz, 1 H), 3.74 (br d, *J* = 2.2 Hz, 1 H), 4.04-4.24 (m, 3 H), 4.60-4.70 (m, 1 H), 5.23 (d, *J* = 5.5 Hz, 1 H), 5.50 (s, 2 H), 7.59 (d, *J* = 10.7 Hz, 1 H).

## (7*S*)-7-Deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)lincomycin (2-41)

To a solution of compound **2-40** (104 mg, 0.14 mmol) in tetrahydrofuran (3 ml) were added triethylamine (0.06 ml, 0.43 mmol) and 2-methoxyacetyl chloride (0.02 ml, 0.22 mmol). A reaction mixture was stirred at 0˚C for 2 h, diluted with saturated aqueous $NH_4Cl$, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$ = 19/1) to obtain (7*S*)-7-deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)-2,3,4-tris-*O*-(trimethylsilyl)lincomycin as a colorless solid (109.8 mg, 96.1%).

(7*S*)-7-Deoxy-7-(5-(2-methoxyacetamido)-1,3,4-thiadiazol-2-ylthio)-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (109.8 mg, 0.14 mmol) in 1*N* HCl (1 ml)-MeOH (1 ml) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The resulting residue was dissolved by water, washed with diethyl ether. The mixture was added $NaHCO_3$ (150 mg), then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3/CH_3OH$/28% aq $NH_4OH$ = 5/1/0.1) to obtain the title compound as a colorless solid (37.8 mg, 46.9%). $[\alpha]_D^{26}$ +98.3° (*c* 0.65, MeOH); ESI-MS *m/z* 594 $(M+H)^+$ as $C_{23}H_{39}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{39}N_5O_7S_3$: 594.2090, found: 594.2095; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.30-1.41 (m, 4 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.82-1.92 (m, 1 H), 1.97-2.08 (m, 1 H), 2.04 (s, 3 H), 2.08-2.15 (m, 1 H), 2.15-2.27 (m, 1 H), 2.39 (s, 3 H), 3.08 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.25-3.34 (m, 1 H), 3.48 (s, 3 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.77-3.81 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.16-4.24 (m, 1 H), 4.21 (s, 2 H), 4.39 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.53 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

## (7*S*)-7-(4-Aminophenylthio)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (3-2)

To a solution of compound **2-28** (5.62 g, 8.02 mmol) in DMF (50 ml) were added $K_2CO_3$ (3.33 g, 24.1 mmol) and 4-aminobenzenethiol (2.01 g, 16.1 mmol). A reaction mixture was stirred at 100˚C for 4.5 h, diluted with 1N HCl (100 ml)-MeOH (50 ml), reacted at room temperature for 45 min and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with $Et_2O$. The mixture was added the saturated aqueous $NaHCO_3$, then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 20/1/0.1) to obtain the (7*S*)-7-(4-aminophenylthio)-7-deoxylincomycin as a colorless solid (2.77 g, 67.2%). $[\alpha]_D^{28}$ +142.0° (*c* 0.51, MeOH); ESI-MS *m/z* 514 $(M+H)^+$ as $C_{24}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_5S_2$: 514.2409, found: 514.2411; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.20 (d, *J* = 7.1 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.80-1.90 (m, 1 H), 1.92-2.00 (m, 1 H), 2.04-2.21 (m, 2 H), 2.17 (s, 3 H), 2.34 (s, 3 H), 2.98 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.53 (dq, *J* = 7.1, 2.8 Hz, 1 H), 3.60 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.68-3.72 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.25 (dd, *J* = 9.9, 2.8 Hz, 1 H), 4.38 (br d, *J* = 9.9 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 6.62-6.68 (m, 2 H), 7.20-7.26 (m, 2 H).

To a solution of (7*S*)-7-(4-aminophenylthio)-7-deoxylincomycin (2.00 g, 3.89 mmol) in pyridine (20 ml) were added trimethylchlorosilane (2.00 ml, 15.7 mmol) and hexamethyldisilazane (2.1 ml, 16.0 mmol). A reaction mixture was stirred at room temperature for 20 h and then concentrated under reduced pressure. The residue was diluted with water, then extracted with EtOAc, washed with water and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the title compound as a colorless solid (2.77 g, 97.3%). $[\alpha]_D^{28}$ +106.6° (*c* 1.15, $CHCl_3$); ESI-MS *m/z* 730 $(M+H)^+$ as $C_{33}H_{63}N_3O_5S_2Si_3$; TOF-ESI-HRMS (M+H)+ calcd for $C_{33}H_{63}N_3O_5S_2Si_3$: 730.3595, found: 730.3583; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.19 (m, 9 H), 0.84-0.95 (m, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.20-1.39 (m, 4 H), 1.78-1.89 (m, 1 H), 1.91-2.11 (m, 3 H), 2.21 (s, 3 H), 2.44 (s, 3 H), 2.98 (dd, *J* = 10.8, 4.0 Hz, 1 H), 3.15-3.25 (m, 1 H), 3.59-3.79 (m, 5 H), 4.12-4.22 (m, 2 H), 4.55-4.65 (m, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 6.55-6.63 (m, 2 H), 7.12-7.22 (m, 2 H), 7.63 (d, *J* = 10.6 Hz, 1 H).

## (7*S*)-7-Deoxy-7-(4-methoxyacetamidophenylthio)lincomycin (3-3)

To a solution of compound **3-2** (100 mg, 0.14 mmol) in THF (1 ml) were added $Et_3N$ (57.2 µl, 0.42 mmol) and 2-methoxyacetyl chloride (18.7 µl, 0.21 mmol). A reaction mixture was stirred at room temperature for 3 h, diluted with 1N HCl (2.6 ml)-MeOH (1.3 ml), reacted at room temperature for 40 min and then concentrated under reduced pressure. The resulting residue was dissolved by water, washed with $Et_2O$. The mixture was added $NaHCO_3$ (70 mg), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (80.0 mg, 99.7%). $[\alpha]_D^{28}$ +109.3° (*c* 2.16, MeOH); ESI-MS *m/z* 586 $(M+H)^+$ as $C_{27}H_{43}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_7S_2$: 586.2621, found: 586.2621; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.27 (d, *J* = 7.0 Hz, 3 H), 1.29-1.40 (m, 4 H), 1.79-1.89 (m, 1 H), 1.92-2.02 (m, 1 H), 2.02-2.09 (m, 1 H), 2.06 (s, 3 H), 2.10-2.21 (m, 1 H), 2.36 (s, 3 H), 2.97 (dd, *J* = 10.6, 4.5 Hz, 1 H), 3.22 (dd, *J* = 7.9, 6.0 Hz, 1 H), 3.48 (s, 3 H), 3.59 (dd, *J* = 10.3, 3.5 Hz, 1 H), 3.70-3.82 (m, 2 H), 4.03 (s, 2 H), 4.11 (dd, *J* = 10.3, 5.5 Hz, 1 H), 4.30-4.43 (m, 2 H), 5.28 (d, *J* = 5.5 Hz, 1 H), 7.39-7.46 (m, 2 H), 7.58-7.66 (m, 2 H).

### (7*S*)-7-Acetylthio-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (3-4)

To a solution of compound **2-28** (200 mg, 0.29 mmol) in DMF (0.65 ml) was added potassium ethanethioate (163 mg, 1.43 mmol) at 60˚C for 4 h. The mixture was diluted with EtOAc and washed with 10% aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to obtain the title compound as a colorless solid (170 mg, 87.5%). ESI-MS *m/z* 681 $(M+H)^+$ as $C_{29}H_{60}N_2O_6S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.09-0.20 (m, 27 H), 0.84-0.93 (m, 3 H), 1.20-1.47 (m, 7 H), 1.76-1.87 (m, 1 H), 1.90-2.09 (m, 6 H), 2.31 (s, 3 H), 2.40 (s, 3 H), 2.93-3.02 (m, 1H), 3.12-3.20 (m, 1H), 3.56 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.72 (d, *J* = 2.4 Hz, 1 H), 3.94 (d, *J* = 10.0 Hz, 1 H), 4.07 (dt, *J* = 7.1, 2.2 Hz, 1 H), 4.15 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.55 (ddd, *J* = 10.7, 10.0, 2.2 Hz, 1 H), 5.18 (d, *J* = 5.6 Hz, 1 H), 7.34 (d, *J* = 10.7 Hz, 1 H).

### (7*S*)-7-Acetylthio-7-deoxylincomycin (3-5)

To a solution of compound **3-4** (10.6 g, 15.6 mmol) in MeOH (50 ml) was added 2N HCl (39 ml). A reaction mixture was stirred at room temperature for 10 min, diluted with 10% aqueous $NaHCO_3$ (30 ml) and concentrated under reduced pressure. The resulting residue was diluted with EtOAc and washed with 10% aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/methanol = 19/1) to obtain the title compound as a colorless solid (7.05 g, 97.5%). ESI-MS *m/z* 465 $(M+H)^+$ as $C_{20}H_{36}N_2O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{20}H_{36}N_2O_6S_2$: 465.2093, found: 465.2092; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.88-0.95 (m, 3 H), 1.22-1.42 (m, 7 H), 1.82-2.13 (m, 7 H), 2.35-2.44 (m, 7 H), 2.72 (d, *J* = 10.0 Hz, 1 H), 3.05 (dd, *J* = 10.5, 4.6 Hz, 1 H), 3.19-3.28 (m, 1 H), 3.46-3.56 (m, 1 H), 3.61 (br s, 1H), 3.94 (d, *J* = 10.2 Hz, 1 H), 4.11 (dd, *J* = 10.5, 4.6 Hz, 1 H), 4.17 (dq, *J* = 7.1, 2.4 Hz, 1 H), 4.25 (ddd, *J* = 10.2, 9.5, 2.4 Hz, 1 H), 5.07 (d, *J* = 2.9 Hz, 1 H), 5.31 (d, *J* = 5.6 Hz, 1 H), 7.79 (d, *J* = 9.5 Hz, 1 H).

### (7*S*)-7-Deoxy-7-mercaptolincomycin (3-6)

To a solution of compound **3-5** (7.05 g, 15.2 mmol) in MeOH (50 ml) was added sodium methoxide (2.46 g, 45.5 mmol). A reaction mixture was stirred at room temperature for 20 min, diluted with saturated aqueous $NH_4Cl$ and concentrated under reduced pressure. The resulting residue was diluted with EtOAc and washed with 10% aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 95/5/0.1) to obtain the title compound as a colorless solid (6.06 g, 94.5%). $[\alpha]_D^{26}$ +152.6° (*c* 0.98, MeOH); ESI-MS *m/z* 423 $(M+H)^+$ as $C_{18}H_{34}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{18}H_{34}N_2O_5S_2$: 423.1987, found: 423.1987; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.28 (d, *J* = 7.1 Hz, 3 H), 1.28-1.41 (m, 4 H), 1.81-1.93 (m, 1 H), 1.96-2.05 (m, 1 H), 2.06-2.23 (m, 2 H), 2.17 (s, 3 H), 2.43 (s, 3 H), 3.02 (dd, *J* = 10.8, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.3, 5.6 Hz, 1 H), 3.54 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.58 (dq, *J* = 7.1, 2.0 Hz, 1 H), 3.70 (br dd, *J* = 3.3, 0.6 Hz, 1 H), 4.04 (br dd, *J* = 10.0, 0.6 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.7 Hz, 1 H),

4.26 (dd, *J* = 10.0, 2.0 Hz, 1 H), 5.25 (d, *J* = 5.7 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(methoxy-*N*-propylacetamido)phenylthio)lincomycin (3-7)

To a solution of compound **3-6** (70.0 mg, 0.17 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (9.70 mg, 16.7 μmol) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (7.60 mg, 8.35 μmol) in 1,4-dioxane (1 ml) were added *N*-(4-bromophenyl)-2-methoxy-*N*-propylacetamide (94.7 mg, 0.33 mmol) and *N,N*-diisopropylethylamine (57.7 μl, 0.33 mmol). A reaction mixture was refluxed for 6 h, diluted with saturated aqueous $NaHCO_3$ (15 ml), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (79.0 mg, 76.0%). $[\alpha]_D^{30}$ +83.2° (*c* 2.21, MeOH); ESI-MS *m/z* 628 $(M+H)^+$ as $C_{30}H_{49}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_7S_2$: 628.3090, found: 628.3086; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90 (t, *J* = 7.5 Hz, 3 H), 0.88-0.97 (m, 3 H), 1.32-1.42 (m, 4 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.52 (sxt, *J* = 7.4 Hz, 2 H), 1.82-1.97 (m, 1 H), 1.93 (s, 3 H), 2.03 (ddd, *J* = 12.7, 7.6, 5.0 Hz, 1 H), 2.08-2.26 (m, 2 H), 2.45 (s, 3 H), 3.06 (dd, *J* = 10.5, 4.8 Hz, 1 H), 3.23-3.30 (m, 4 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.61-3.68 (m, 2 H), 3.72-3.80 (m, 3 H), 3.94 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.35 (br d, *J* = 9.7, 0.5 Hz, 1 H), 4.49 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.20-7.27 (m, 2 H), 7.46-7.52 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-methylcarbamoylphenylthio)lincomycin (3-9)

To a solution of compound **2-29** (100 mg, 0.18 mmol) in 30% methylamine methanol solution (1.2 ml) was refluxed 20 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (18.0 mg, 17.6%). $[\alpha]_D^{33}$ +80.5° (*c* 0.65, MeOH); ESI-MS *m/z* 556 $(M+H)^+$ as $C_{26}H_{41}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{41}N_3O_6S_2$: 556.2515, found: 556.2515; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.30-1.41 (m, 4 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.80-1.95 (m, 1 H), 1.87 (s, 3 H), 1.97-2.06 (m, 1 H), 2.08-2.25 (m, 2 H), 2.43 (s, 3 H), 2.90 (s, 3 H), 3.06 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.27 (dd, *J* = 7.9, 5.4 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.75-3.80 (m, 1 H), 3.98 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.37 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.51 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.25 (d, *J* = 5.5 Hz, 1 H), 7.42-7.48 (m, 2 H), 7.72-7.78 (m, 2 H).

### (7*S*)-7-(4-Carboxylphenylthio)-7-deoxylincomycin (3-10)

To a solution of compound **2-29** (1.84 g, 3.31 mmol) in MeOH (20 ml) was added 1N NaOH (5 ml). A reaction mixture was stirred at room temperature for 19 h, diluted with 1N HCl (5 ml) and concentrated under reduced pressure. The resulting residue was purified by Diaion HP-20 (Mitsubishi Chemical) column chromatography to obtain the title compound as a colorless solid (1.78 g, quant). $[\alpha]_D^{28}$ +161.2° (*c* 0.34, DMF); ESI-MS *m/z* 543 $(M+H)^+$ as $C_{25}H_{38}N_2O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_2O_7S_2$:

543.2199, found: 543.2194; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.29-1.45 (m, 4 H), 1.38 (d, $J$ = 6.8 Hz, 3 H), 1.87 (s, 3 H), 1.92-2.03 (m, 1 H), 2.03-2.13 (m, 1 H), 2.17-2.29 (m, 1 H), 2.30-2.38 (m, 1 H), 2.57 (s, 3 H), 3.36 (dd, $J$ = 10.3, 5.2 Hz, 1 H), 3.41 (dd, $J$ = 9.0, 6.1 Hz, 1 H), 3.58 (dd, $J$ = 10.2, 3.3 Hz, 1 H), 3.80 (br dd, $J$ = 3.3, 0.8 Hz, 1 H), 3.98 (dq, $J$ = 6.8, 2.7 Hz, 1 H), 4.09 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, $J$ = 9.8, 0.8 Hz, 1 H), 4.55 (dd, $J$ = 9.8, 2.7 Hz, 1 H), 5.25 (d, $J$ = 5.6 Hz, 1 H), 7.38-7.44 (m, 2 H), 7.88-7.95 (m, 2 H).

For the qualified analytical purpose, the above colorless solid was further purified by reverse-phase column chromatography (Biotage SNAP Ultra C18, 25 um, room temperature, 12.0 ml/min, $H_2O$/MeOH = 100/0-0/100) to obtain the highly purified title compound as a colorless solid.

## (7*S*)-7-(4-Cyclopropylcarbamoylphenylthio)-7-deoxylincomycin (3-11)

To a solution of compound **3-10** (100 mg, 0.18 mmol) in DMF (1 ml) were added 1-hydroxybenzotriazole (37.3 mg, 0.28 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (53.0 mg, 0.28 mmol) and cyclopropylamine (19.0 µl, 0.28 mmol). A reaction mixture was stirred at room temperature for 4 h, diluted with saturated aqueous $NaHCO_3$ (10 ml), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (48.0 mg, 44.8%). $[\alpha]_D^{29}$ +84.0° (*c* 1.77, MeOH); ESI-MS *m/z* 582 $(M+H)^+$ as $C_{28}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{43}N_3O_6S_2$: 582.2672, found: 582.2669; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.59-0.66 (m, 2 H), 0.75-0.84 (m, 2 H), 0.89-0.98 (m, 3 H), 1.29-1.42 (m, 4 H), 1.37 (d, $J$ = 6.8 Hz, 3 H), 1.80-1.92 (m, 1 H), 1.87 (s, 3 H), 1.96-2.05 (m, 1 H), 2.06-2.25 (m, 2 H), 2.41 (s, 3 H), 2.83 (tt, $J$ = 7.4, 3.8 Hz, 1 H), 3.03 (dd, $J$ = 10.5, 4.8 Hz, 1 H), 3.26 (dd, $J$ = 8.1, 5.6 Hz, 1 H), 3.58 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.77 (br dd, $J$ = 3.2, 0.6 Hz, 1 H), 3.98 (dq, $J$ = 6.8, 2.8 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.37 (br dd, $J$ = 9.7, 0.6 Hz, 1 H), 4.50 (dd, $J$ = 9.7, 2.8 Hz, 1 H), 5.25 (d, $J$ = 5.6 Hz, 1 H), 7.40-7.47 (m, 2 H), 7.70-7.78 (m, 2 H).

## (7*S*)-7-(4-Cyclohexylcarbamoylphenylthio)-7-deoxylincomycin (3-12)

Compound **3-10** (100 mg, 0.18 mmol) and cyclohexylamine (31.5 µl, 0.28 mmol) were treated at room temperature for 4 h according to the similar procedure as described for the preparation of **3-11** to afford **3-12** (29.0 mg, 25.2%) as a colorless solid. $[\alpha]_D^{30}$ +105.0° (*c* 1.91, $CHCl_3$); ESI-MS *m/z* 624 $(M+H)^+$ as $C_{31}H_{49}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_6S_2$: 624.3141, found: 624.3149; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.16-1.47 (m, 9 H), 1.37 (d, $J$ = 6.9 Hz, 3 H), 1.64-1.73 (m, 1 H), 1.77-1.97 (m, 5 H), 1.89 (s, 3 H), 1.97-2.06 (m, 1 H), 2.07-2.26 (m, 2 H), 2.41 (s, 3 H), 3.02 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.26 (dd, $J$ = 8.2, 5.6 Hz, 1 H), 3.58 (dd, $J$ = 10.2, 3.3 Hz, 1 H), 3.77 (br dd, $J$ = 3.3, 0.6 Hz, 1 H), 3.79-3.90 (m, 1 H), 3.98 (dq, $J$ = 6.9, 2.7 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.37 (br dd, $J$ = 9.7, 0.6 Hz, 1 H), 4.50 (dd, $J$ = 9.7, 2.7 Hz, 1 H), 5.25 (d, $J$ = 5.6 Hz, 1 H), 7.41-7.47 (m, 2 H), 7.72-7.78 (m, 2 H).

### (7*S*)-7-(4-(Adamant-1-yl)carbamoylphenylthio)-7-deoxylincomycin (3-13)

Compound **3-10** (100 mg, 0.18 mmol) and 1-adamantylamine (41.1 μl, 0.28 mmol) were treated at room temperature for 16 h according to the similar procedure as described for the preparation of **3-11** to afford **3-13** (68.6 mg, 55.0%) as a colorless solid. $[\alpha]_D^{31}$ +74.5° (*c* 1.95, MeOH); ESI-MS *m/z* 676 $(M+H)^+$ as $C_{35}H_{53}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{35}H_{53}N_3O_6S_2$: 676.3454, found: 676.3453; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.29-1.42 (m, 4 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.68-1.80 (m, 6 H), 1.81-1.95 (m, 1 H), 1.90 (s, 3 H), 1.96-2.05 (m, 1 H), 2.06-2.24 (m, 11 H), 2.42 (s, 3 H), 3.04 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.27 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.76-3.79 (m, 1 H), 3.97 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.50 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.39-7.45 (m, 2 H), 7.66-7.72 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(pyridin-3-yl)carbamoylphenylthio)lincomycin (3-14)

Compound **3-10** (40.5 mg, 74.6 μmol) and 3-aminopyridine (10.5 mg, 0.11 mmol) were treated at room temperature for 8 h according to the similar procedure as described for the preparation of **3-11** to afford **3-14** (13.5 mg, 29.2%) as a colorless solid. $[\alpha]_D^{30}$ +31.1° (*c* 0.10, MeOH); ESI-MS *m/z* 619 $(M+H)^+$ as $C_{30}H_{42}N_4O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{42}N_4O_6S_2$: 619.2624, found: 619.2623; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.93 (br t, *J* = 6.9 Hz, 3 H), 1.26-1.45 (m, 4 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.85-1.98 (m, 1 H), 1.88 (s, 3 H), 2.01-2.11 (m, 1 H), 2.15-2.28 (m, 2 H), 2.50 (s, 3 H), 3.14-3.24 (m, 1 H), 3.30-3.38 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80 (br d, *J* = 3.2 Hz,1 H), 4.04 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br d, *J* = 9.8 Hz, 1 H), 4.57 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.45 (br ddd, *J* = 8.3, 4.8, 0.7 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.88-7.96 (m, 2 H), 8.25 (ddd, *J* = 8.3, 2.4, 1.4 Hz, 1 H), 8.31 (br dd, *J* = 4.8, 1.4 Hz, 1 H), 8.86-8.91 (m, 1 H).

### (7*S*)-7-Deoxy-7-(4-dimethylcarbamoylphenylthio)lincomycin (3-15)

Compound **2-29** (300 mg, 0.54 mmol) and 2M dimethylamine methanol solution (20 ml) were treated at 110°C in sealed tube for 3 h according to the similar procedure as described for the preparation of **3-9** to afford **3-15** (48.6 mg, 15.8%) as a colorless solid. $[\alpha]_D^{31}$ +90.9° (*c* 1.12, MeOH); ESI-MS *m/z* 570 $(M+H)^+$ as $C_{27}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_6S_2$: 570.2672, found: 570.2681; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.29-1.42 (m, 4 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.82-1.90 (m, 1 H), 1.92 (s, 3 H), 1.97-2.07 (m, 1 H), 2.08-2.26 (m, 2 H), 2.44 (s, 3 H), 3.00 (s, 3 H), 3.05 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.08 (s, 3 H), 3.28 (dd, *J* = 8.1, 5.5 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.75-3.80 (m, 1 H), 3.97 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.35 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.49 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 7.36-7.42 (m, 2 H), 7.44-7.50 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-pyrrolidinocarbonylphenylthio)lincomycin (3-16)

A solution of compound **2-29** (100 mg, 0.18 mmol) and pyrrolidine (0.95 ml) were treated at reflux for

72 h according to the similar procedure as described for the preparation of **3-9** to afford **3-16** (35.0 mg, 32.7%) as a colorless solid. $[\alpha]_D^{30}$ +64.2° (*c* 0.24, MeOH); ESI-MS *m/z* 596 $(M+H)^+$ as $C_{29}H_{45}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{45}N_3O_6S_2$: 596.2828, found: 596.2825; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90-0.97 (m, 3 H), 1.30-1.43 (m, 4 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.85-2.02 (m, 5 H), 1.91 (s, 3 H), 2.03-2.12 (m, 1 H), 2.17-2.32 (m, 2 H), 2.54 (s, 3 H), 3.22-3.30 (m, 1 H), 3.35-3.42 (m, 1 H), 3.47 (t, *J* = 6.6 Hz, 2 H), 3.55-3.61 (m, 3 H), 3.79 (br dd, *J* = 3.1, 0.5 Hz, 1 H), 3.96 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.38 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.53 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.43-7.51 (m, 4 H).

### (7*S*)-7-Deoxy-7-(4-piperidinocarbonylphenylthio)lincomycin (3-17)

Compound **3-10** (100 mg, 0.18 mmol) and piperidine (27.3 µl, 0.28 mmol) were treated at room temperature for 24 h according to the similar procedure as described for the preparation of **3-11** to afford **3-17** (71.0 mg, 63.2%) as a colorless solid. $[\alpha]_D^{32}$ +65.4° (*c* 0.18, MeOH); ESI-MS *m/z* 610 $(M+H)^+$ as $C_{30}H_{47}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_6S_2$: 610.2985, found: 610.2981; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.30-1.42 (m, 4 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.48-1.77 (m, 7 H), 1.85-1.97 (m, 1 H), 1.92 (s, 3 H), 1.99-2.10 (m, 1 H), 2.14-2.27 (m, 2 H), 2.47 (s, 3 H), 3.08-3.17 (m, 1 H), 3.32-3.45 (m, 2 H), 3.57 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.61-3.74 (m, 2 H), 3.77 (br d, *J* = 3.2 Hz, 1 H), 3.95 (dq, *J* = 6.8, 2.5 Hz, 1 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.36 (br d, *J* = 9.8 Hz, 1 H), 4.50 (br dd, *J* = 9.8, 2.5 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.32-7.37 (m, 2 H), 7.44-7.49 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin (3-18)

Compound **3-10** (200 mg, 0.37 mmol) and morpholine (48.2 µl, 0.55 mmol) were treated at room temperature for 28 h according to the similar procedure as described for the preparation of **3-11** to afford **3-18** (142 mg, 63.0%) as a colorless solid. $[\alpha]_D^{31}$ +78.7° (*c* 2.08, MeOH); ESI-MS *m/z* 612 $(M+H)^+$ as $C_{29}H_{45}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{45}N_3O_7S_2$: 612.2777, found: 612.2772; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.28-1.42 (m, 4 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.81-1.91 (m, 1 H), 1.91 (s, 3 H), 1.97-2.06 (m, 1 H), 2.07-2.14 (m, 1 H), 2.14-2.25 (m, 1 H), 2.43 (s, 3 H), 3.03 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.27 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.33-3.57 (m, 2 H), 3.57 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.57-3.85 (m, 6 H), 3.77 (br dd, *J* = 3.3, 0.6 Hz, 1 H), 3.97 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.35 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.49 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.36-7.42 (m, 2 H), 7.45-7.52 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(4-methylpiperazin-1-yl)carbonylphenylthio)lincomycin (3-19)

Compound **3-10** (67.8 mg, 0.12 mmol) and 1-methylpiperazine (20.5 µl, 0.19 mmol) were treated at room temperature for 24 h according to the similar procedure as described for the preparation of **3-11** to afford **3-19** (54.0 mg, 69.1%) as a colorless solid. $[\alpha]_D^{31}$ +77.0° (*c* 1.31, MeOH); ESI-MS *m/z* 625 $(M+H)^+$

as $C_{30}H_{48}N_4O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{48}N_4O_6S_2$: 625.3094, found: 625.3091; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.98 (m, 3 H), 1.27-1.42 (m, 4 H), 1.36 (d, $J$ = 6.8 Hz, 3 H), 1.81-1.95 (m, 1 H), 1.91 (s, 3 H), 1.97-2.07 (m, 1 H), 2.08-2.25 (m, 2 H), 2.33 (s, 3 H), 2.36-2.58 (m, 4 H), 2.43 (s, 3 H), 3.05 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.28 (dd, $J$ = 8.1, 5.5 Hz, 1 H), 3.38-3.61 (m, 2 H), 3.57 (dd, $J$ = 10.1, 3.2 Hz, 1 H), 3.61-3.88 (m, 3 H), 3.97 (dq, $J$ = 6.8, 2.7 Hz, 1 H), 4.10 (dd, $J$ = 10.1, 5.5 Hz, 1 H), 4.35 (br dd, $J$ = 9.7, 0.5 Hz, 1 H), 4.49 (dd, $J$ = 9.7, 2.7 Hz, 1 H), 5.25 (d, $J$ = 5.5 Hz, 1 H), 7.35-7.40 (m, 2 H), 7.45-7.51 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(1,4-oxazepane-4-carbonyl)phenylthio)lincomycin (3-20)

Compound **3-6** (72.9 mg, 0.17 mmol) and (4-bromophenyl)(1,4-oxazepan-4-yl)methanone (49.0 mg, 0.17 mmol) were treated at reflux for 3 h according to the similar procedure as described for the preparation of **3-7** to afford **3-20** (79.0 mg, 73.1%) as a colorless solid. $[\alpha]_D^{31}$ +74.3° (*c* 3.26, MeOH); ESI-MS *m/z* 626 $(M+H)^+$ as $C_{30}H_{47}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_7S_2$: 626.2934, found: 626.2934; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.28-1.41 (m, 4 H), 1.35 (d, $J$ = 6.8 Hz, 3 H), 1.75-1.91 (m, 2 H), 1.92 (s, 3 H), 1.94-2.06 (m, 2 H), 2.07-2.26 (m, 2 H), 2.43 (s, 3 H), 3.04 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.28 (dd, $J$ = 5.6, 2.4 Hz, 1 H), 3.49-3.57 (m, 2 H), 3.58 (dd, $J$ = 10.1, 2.3 Hz, 1 H), 3.67 (br t, $J$ = 4.9 Hz, 1 H), 3.73-3.88 (m, 6 H), 3.96 (dq, $J$ = 6.8, 2.5 Hz, 1 H), 4.10 (dd, $J$ = 10.1, 5.6 Hz, 1 H), 4.35 (br d, $J$ = 9.7 Hz, 1 H), 4.49 (dd, $J$ = 9.7, 2.5 Hz, 1 H), 5.26 (d, $J$ = 5.6 Hz, 1 H), 7.34-7.42 (m, 2 H), 7.43-7.52 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-((*S*)-2-methoxymethylpyrrolidinocarbonyl)phenylthio)lincomycin (3-21)

Compound **3-6** (70 mg, 0.17 mmol) and (*S*)-(4-bromophenyl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (98.7 mg, 0.33 mmol) were treated at reflux for 3.5 h according to the similar procedure as described for the preparation of **3-7** to afford **3-21** (84.0 mg, 79.2%) as a colorless solid. $[\alpha]_D^{31}$ +46.2° (*c* 1.85, MeOH); ESI-MS *m/z* 640 $(M+H)^+$ as $C_{31}H_{49}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_7S_2$: 640.3090, found: 640.3092; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.29-1.40 (m, 4 H), 1.36 (d, $J$ = 6.8 Hz, 3 H), 1.69-1.81 (m, 1 H), 1.81-1.90 (m, 1 H), 1.91 (s, 3 H), 1.90-2.27 (m, 7 H), 2.42 (s, 3 H), 3.02 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.04-3.14 (m, 1 H), 3.27 (dd, $J$ = 8.1, 5.7 Hz, 1 H), 3.39 (s, 3 H), 3.46-3.67 (m, 4 H), 3.78 (br dd, $J$ = 3.2, 0.6 Hz, 1 H), 3.97 (dq, $J$ = 6.8, 2.6 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.36 (br d, $J$ = 9.7 Hz, 1 H), 4.49 (dd, $J$ = 9.7, 2.6 Hz, 1 H), 5.26 (d, $J$ = 5.6 Hz, 1 H), 7.41-7.50 (m, 4 H).

### (7*S*)-7-Deoxy-7-(4-((*S*)-2-dimethylaminomethylpyrrolidinocarbonyl)phenylthio)lincomycin (3-22)

Compound **3-6** (70 mg, 0.17 mmol) and (*S*)-(4-bromophenyl)(2-((dimethylamino)methyl)pyrrolidin-1-yl)methanone (103.7 mg, 0.33 mmol) were

treated at reflux for 4 h according to the similar procedure as described for the preparation of **3-7** to afford **3-22** (90.0 mg, 82.4%) as a colorless solid. $[\alpha]_D^{31}$ +33.2° (*c* 2.39, MeOH); ESI-MS *m/z* 653 $(M+H)^+$ as $C_{32}H_{52}N_4O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{32}H_{52}N_4O_6S_2$: 653.3407, found: 653.3399; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.25-1.42 (m, 7 H), 1.75-2.25 (m, 13 H), 2.38 (s, 6 H), 2.41 (s 3 H), 2.76 (br dd, *J* = 11.7, 3.2 Hz, 1 H), 3.00 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.26 (dd, *J* = 8.2, 5.9 Hz, 1 H), 3.35-3.46 (m, 1 H), 3.48-3.68 (m, 2 H), 3.75-3.80 (m, 1 H), 3.92-4.20 (m, 1 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.35 (d, *J* = 9.7 Hz, 1 H), 4.49 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.40-7.53 (m, 4 H).

### (7*S*)-7-Deoxy-7-(4-morpholinomethylphenylthio)lincomycin (3-23)

Compound **3-6** (70.0 mg, 0.17 mmol) and 4-(4-bromobenzyl)morpholine (84.8 mg, 0.33 mmol) were treated at reflux for 22 h according to the similar procedure as described for the preparation of **3-7** to afford **3-23** (74.0 mg, 74.7%) as a colorless solid. $[\alpha]_D^{28}$ +98.2° (*c* 2.63, MeOH); ESI-MS *m/z* 598 $(M+H)^+$ as $C_{29}H_{47}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{47}N_3O_6S_2$: 598.2985, found: 598.2983; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 1.29-1.41 (m, 4 H), 1.80-1.91 (m, 1 H), 1.95-2.04 (m, 1 H), 1.98 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.35-2.50 (m, 4 H), 2.40 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.49 (s, 2 H), 3.57 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.63-3.71 (m, 4 H), 3.74 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 3.85 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.5 Hz, 1 H), 4.32 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.41 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 7.28-7.34 (m, 2 H), 7.36-7.43 (m, 2 H).

### (7*S*)-7-Deoxy-7-(2-fluoro-4-morpholinocarbonylphenylthio)lincomycin (3-24)

Compound **3-6** (190.7 mg, 0.45 mmol) and (4-bromo-3-fluorophenyl)(morpholino)methanone (260 mg, 0.90 mmol) were treated at reflux for 7 h according to the similar procedure as described for the preparation of **3-7** to afford **3-24** (232 mg, 81.6%) as a colorless solid. $[\alpha]_D^{31}$ +82.4° (*c* 8.43, MeOH); ESI-MS *m/z* 630 $(M+H)^+$ as $C_{29}H_{44}FN_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{44}FN_3O_7S_2$: 630.2683, found: 630.2673; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 1.28-1.92 (m, 4 H), 1.79-1.92 (m, 1 H), 1.98 (s, 3 H), 1.98-2.05 (m, 1 H), 2.06-2.13 (m, 1 H), 2.13-2.26 (m, 1 H), 2.42 (s, 3 H), 3.01 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.27 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.35-3.82 (m, 10 H), 4.01 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.32 (br dd, *J* = 9.7, 0.4 Hz, 1 H), 4.49 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 7.22-7.28 (m, 2 H), 7.55-7.62 (m, 1 H).

### (7*S*)-7-Deoxy-7-(3-fluoro-4-morpholinocarbonylphenylthio)lincomycin (3-25)

Compound **3-6** (187 mg, 0.44 mmol) and (4-bromo-2-fluorophenyl)(morpholino)methanone (255 mg, 0.89 mmol) were treated at reflux for 2.5 h according to the similar procedure as described for the preparation of **3-7** to afford **3-25** (227 mg, 81.4%) as a colorless solid. $[\alpha]_D^{31}$ +73.4° (*c* 5.35, MeOH); ESI-MS *m/z* 630 $(M+H)^+$ as $C_{29}H_{44}FN_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{44}FN_3O_7S_2$: 630.2683,

found: 630.2685; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.27-1.38 (m, 4 H), 1.39 (d, $J$ = 6.8 Hz, 3 H), 1.79-1.89 (m, 1 H), 1.92 (s, 3 H), 1.96-2.12 (m, 2 H), 2.12-2.26 (m, 1 H), 2.40 (s, 3 H), 2.99 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.25 (dd, $J$ = 8.4, 5.9 Hz, 1 H), 3.31-3.40 (m, 2 H), 3.57 (dd, $J$ = 10.1, 3.2 Hz, 1 H), 3.59-3.66 (m, 2 H), 3.70-3.81 (m, 5 H), 3.99 (dq, $J$ = 6.8, 2.8 Hz, 1 H), 4.11 (dd, $J$ = 10.1, 5.6 Hz, 1 H), 4.33 (br dd, $J$ = 9.6, 0.4 Hz, 1 H), 4.52 (dd, $J$ = 9.6, 2.8 Hz, 1 H), 5.27 (d, $J$ = 5.6 Hz, 1 H), 7.24 (dd, $J$ = 10.2, 1.5 Hz, 1 H), 7.27-7.32 (m, 1 H), 7.33-7.39 (m, 1 H).

### (7*S*)-7-Deoxy-7-(4-morpholinocarbonyl-3-nitrophenylthio)lincomycin (3-26)

Compound **3-6** (70 mg, 0.17 mmol) and (4-bromo-2-nitrophenyl)(morpholino)methanone (104 mg, 0.33 mmol) were treated at reflux for 8.5 h according to the similar procedure as described for the preparation of **3-7** to afford **3-26** (87.0 mg, 80.0%) as a colorless solid. $[\alpha]_D^{31}$ +60.4° (*c* 2.62, MeOH); ESI-MS *m/z* 657 $(M+H)^+$ as $C_{29}H_{44}N_4O_9S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{44}N_4O_9S_2$: 657.2628, found: 657.2632; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.28-1.39 (m, 4 H), 1.41 (d, $J$ = 6.9 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.93 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.26 (m, 1 H), 2.41 (s, 3 H), 3.00 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.20-3.34 (m, 3 H), 3.57 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.62 (t, $J$ = 4.8 Hz, 2 H), 3.67-3.88 (m, 5 H), 4.04 (dq, $J$ = 6.9, 2.9 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.35 (br dd, $J$ = 9.5, 0.7 Hz, 1 H), 4.55 (dd, $J$ = 9.5, 2.9 Hz, 1 H), 5.26 (d, $J$ = 5.6 Hz, 1 H), 7.45 (d, $J$ = 8.0 Hz, 1 H), 7.81 (dd, $J$ = 8.0, 1.8 Hz, 1 H), 8.16 (d, $J$ = 1.8 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(3-methyl-4-morpholinocarbonylphenylthio)lincomycin (3-27)

Compound **3-6** (70 mg, 0.17 mmol) and (4-bromo-2-methylphenyl)(morpholino)methanone (94.1 mg, 0.33 mmol) were treated at reflux for 5 h according to the similar procedure as described for the preparation of **3-7** to afford **3-27** (81.0 mg, 78.1%) as a colorless solid. $[\alpha]_D^{29}$ +81.7° (*c* 2.65, MeOH); ESI-MS *m/z* 626 $(M+H)^+$ as $C_{30}H_{47}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_7S_2$: 626.2934, found: 626.2925; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.26-1.42 (m, 4 H), 1.33 (d, $J$ = 6.8 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.95 (s, 3 H), 2.01 (ddd, $J$ = 12.8, 7.9, 4.7 Hz, 1 H), 2.06-2.13 (m, 1 H), 2.13-2.24 (m, 1 H), 2.28 (s, 3 H), 2.42 (s, 3 H), 3.00 (dd, $J$ = 10.6, 4.6 Hz, 1 H), 3.21-3.29 (m, 3 H), 3.53-3.64 (m, 3 H), 3.68-3.82 (m, 5 H), 3.93 (dq, $J$ = 6.8, 2.7 Hz, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.32 (br dd, $J$ = 9.7, 0.5 Hz, 1 H), 4.46 (dd, $J$ = 9.7, 2.7 Hz, 1 H), 5.26 (d, $J$ = 5.6 Hz, 1 H), 7.16 (d, $J$ = 7.8 Hz, 1 H), 7.27-7.34 (m, 2 H).

### (7*S*)-7-Deoxy-7-(5-methoxycarbonylpyridin-2-ylthio)lincomycin (3-32)

To a solution of compound **2-1** (200 mg, 0.32 mmol) in THF (3 ml) at 0˚C were added triphenylphosphine (84.2 mg, 0.32 mmol), diisopropylazodicarboxylate (65.4 µl, 0.32 mmol), methyl 6-mercaptonicotinate (36.2 mg, 0.21 mmol). A reaction mixture was stirred at room temperature for 7 h and then concentrated under reduced pressure. The resulting residue (compound **3-28**) in MeOH (3 ml) was added 1N HCl (3 ml), stirred at room temperature for 40 min. and concentrated under reduced pressure. The

resulting residue was dissolved by water, washed with $Et_2O$. The mixture was added $NaHCO_3$ (150 mg), then extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (91.0 mg, 76.3%). $[\alpha]_D^{28}$ +71.2° (*c* 0.25, MeOH); ESI-MS *m/z* 558 $(M+H)^+$ as $C_{25}H_{39}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{39}N_3O_7S_2$: 558.2308, found: 558.2301; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.99 (m, 3 H), 1.29-1.40 (m, 4 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 1.79 (s, 3 H), 1.80-1.90 (m, 1 H), 1.97-2.11 (m, 2 H), 2.12-2.26 (m, 1 H), 2.36 (s, 3 H), 2.99 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.25 (dd, *J* = 8.4, 6.0 Hz, 1 H), 3.55 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.77 (br dd, *J* = 3.2, 0.6 Hz, 1 H), 3.91 (s, 3 H), 4.09 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.33 (br dd, *J* = 9.7, 0.6 Hz, 1 H), 4.45 (dq, *J* = 6.8, 3.2 Hz,1 H), 4.52 (dd, *J* = 9.7, 3.2 Hz, 1 H), 5.22 (d, *J* = 5.6 Hz, 1 H), 7.39 (dd, *J* = 8.4, 0.8 Hz, 1 H), 8.10 (dd, *J* = 8.4, 2.2 Hz, 1 H), 8.96 (dd, *J* = 2.2, 0.8 Hz, 1 H).

### (7*S*)-7-(4-Amino-5-ethoxycarbonylpyrimidin-2-ylthio)-7-deoxylincomycin (3-33)

Compound **2-1** (1.87 g, 3.00 mmol), triphenylphosphine (1.18 g, 6.86 mmol), diethylazodicarboxylate (0.71 ml, 390 mmol), ethyl 4-amino-2-mercaptopyrimidine-5-carboxylate (894 mg, 4.49 mmol) and toluene (24 ml) were treated at 0°C for 1 h and then at room temperature for 16 h according to the similar procedure as described for the preparation of **3-32** to afford **3-33** (1.30 g, 73.7%) as a colorless solid. $[\alpha]_D^{29}$ +43.3° (*c* 6.21, MeOH); ESI-MS *m/z* 588 $(M+H)^+$ as $C_{25}H_{41}N_5O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{41}N_5O_7S_2$: 588.2526, found: 588.2519; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.26-1.38 (m, 4 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 1.77-1.87 (m, 1 H), 1.87 (s, 3 H), 1.95-2.10 (m, 2 H), 2.10-2.26 (m, 1 H), 2.36 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.22 (dd, *J* = 8.5, 6.1 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.4 Hz, 1 H), 3.77-3.82 (m, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.29-4.40 (m, 4 H), 4.51 (dd, *J* = 9.7, 3.2 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 8.58 (s, 1 H).

### (7*S*)-7-Deoxy-7-(5-ethoxycarbonylthiazol-2-ylthio)lincomycin (3-34)

Compound **2-1** (930 mg, 1.49 mmol), triphenylphosphine (600 mg, 2.29 mmol), diethylazodicarboxylate (0.40 ml, 2.20 mmol), ethyl 2-mercaptothiazole-5-carboxylate (350 mg, 1.85 mmol) and toluene (15 ml) were treated at 0°C for 1 h and then at room temperature for 16 h according to the similar procedure as described for the preparation of **3-32** to afford **3-34** (569.2 mg, 66.0%) as a colorless solid. $[\alpha]_D^{28}$ +85.7° (*c* 0.32, MeOH); ESI-MS *m/z* 578 $(M+H)^+$ as $C_{24}H_{39}N_3O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{39}N_3O_7S_3$: 578.2028, found: 578.2023; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.29-1.39 (m, 4 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.52 (d, *J* = 6.8 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.94 (s, 3 H), 1.96-2.10 (m, 2 H), 2.13-2.27 (m, 1 H), 2.36 (s, 3 H), 2.98 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.24 (dd, *J* = 8.5, 6.1 Hz, 1 H), 3.55 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.77-3.81 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.29-4.40 (m, 4 H), 4.58 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 8.21 (s, 1 H).

## (7*S*)-7-Deoxy-7-(5-ethoxycarbonyl-1,3,4-thiadiazol-2-ylthio)lincomycin (3-35)

Compound **2-1** (950 mg, 1.52 mmol), triphenylphosphine (550 mg, 2.10 mmol), diethylazodicarboxylate (0.50 ml, 2.74 mmol), ethyl 5-mercapto-1,3,4-thiadiazole-2-carboxylate (141 mg, 0.75 mmol) and toluene (20 ml) were treated at 0°C for 1 h and then at room temperature for 16 h according to the similar procedure as described for the preparation of **3-32** to afford **3-35** (345.3 mg, 45.4%) as a colorless solid. $[\alpha]_D^{29}$ +90.7° (*c* 0.63, EtOH); ESI-MS *m/z* 579 $(M+H)^+$ as $C_{23}H_{38}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{38}N_4O_7S_3$: 579.1981, found: 579.1976; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.28-1.38 (m, 4 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.78-1.90 (m, 1 H), 1.94 (s, 3 H), 1.97-2.12 (m, 2 H), 2.13-2.28 (m, 1 H), 2.38 (s, 3 H), 3.01 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.26 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.55 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.8, 0.8 Hz, 1 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 4.53 (dq, *J* = 7.0, 3.2 Hz, 1 H), 4.62 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H).

## (7*S*)-7-(5-Carboxylpyridin-2-ylthio)-7-deoxylincomycin (3-36)

Compound **3-32** (622 mg, 1.12 mmol), 1N NaOH (6.2 ml) and MeOH (6.2 ml) were treated at room temperature for 18 h according to the similar procedure as described for the preparation of **3-10** to afford **3-36** (488 mg, 80.5%) as a colorless solid. $[\alpha]_D^{29}$ +90.4° (*c* 0.30, DMF); ESI-MS *m/z* 544 $(M+H)^+$ as $C_{24}H_{37}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{37}N_3O_7S_2$: 544.2151, found: 544.2151; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.98 (t, *J* = 7.1 Hz, 3 H), 1.25-1.50 (m, 4 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.83 (s, 3 H), 1.96-2.16 (m, 2 H), 2.20-2.33 (m, 1 H), 2.38-2.47 (m, 1 H), 2.62 (s, 3 H), 3.45-3.55 (m, 2 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80-3.83 (m, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.32-4.42 (m, 2 H), 4.53 (dd, *J* = 9.7, 3.2 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 7.30-7.35 (m, 1 H), 8.09 (dd, *J* = 8.4, 2.1 Hz, 1 H), 8.92-8.97 (m, 1 H).

## (7*S*)-7-Deoxy-7-(5-molpholinocarbonylpyridin-2-ylthio)lincomycin (3-39)

Compound **3-36** (96.9 mg, 0.18 mmol) and morpholine (24.0 μl, 0.28 mmol) were treated at room temperature for 16.5 h according to the similar procedure as described for the preparation of **3-11** to afford **3-39** (76.7 mg, 70.2%) as a colorless solid. $[\alpha]_D^{29}$ +55.4° (*c* 2.46, MeOH); ESI-MS *m/z* 613 $(M+H)^+$ as $C_{28}H_{44}N_4O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{44}N_4O_7S_2$: 613.2730, found: 613.2735; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.27-1.41 (m, 4 H), 1.47 (d, *J* = 6.9 Hz, 3 H), 1.79 (s, 3 H), 1.82-1.92 (m, 1 H), 2.02 (ddd, *J* = 13.0, 7.9, 5.1 Hz, 1 H), 2.07-2.14 (m, 1 H), 2.14-2.27 (m, 1 H), 2.39 (s, 3 H), 3.03 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.26 (dd, *J* = 8.4, 5.9 Hz, 1 H), 3.40-3.83 (m, 8 H), 3.55 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.75-3.80 (m, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.34 (br dd, *J* = 9.8, 0.4 Hz, 1 H), 4.43 (dq, *J* = 6.9, 3.1 Hz, 1 H), 4.52 (dd, *J* = 9.8, 3.1 Hz, 1 H), 5.23 (d, *J* = 5.6 Hz, 1 H), 7.38 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.67 (dd, *J* = 8.3, 2.3 Hz, 1 H), 8.49 (dd, *J* = 2.3, 0.9 Hz, 1 H).

### (7*S*)-7-(4-Amino-5-molpholinocarbonylpyrimidin-2-ylthio)-7-deoxylincomycin (3-40)

To a solution of compound **3-33** (117.2 mg, 0.2 mmol) in MeOH (1 ml) was added 1N NaOH (0.3 ml). A reaction mixture was stirred at room temperature for 10 h, diluted with 1N HCl (0.3 ml) and concentrated under reduced pressure. The resulting residue (crude compound **3-37**), morpholine (8.00 µl, 92.0 µmol), *N,N*'-dicyclohexylcarbodiimide (30.7 mg, 0.15 mmol), 1-hydroxybenzotriazole (20.3 mg, 0.15 mmol) and $Et_3N$ (12.0 µl, 86.0 µmol) treated at room temperature for 16 h according to the similar procedure as described for the preparation of **3-11** to afford **3-40** (7.7 mg, 2 steps 6.1%) as a colorless solid. $[\alpha]_D^{31}$ +22.4° (*c* 0.11, MeOH); ESI-MS *m/z* 629 $(M+H)^+$ as $C_{27}H_{44}N_6O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{44}N_6O_7S_2$: 629.2791, found: 629.2792; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.84-0.97 (m, 3 H), 1.24-1.39 (m, 4 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.78-1.91 (m, 1 H), 1.86 (s, 3 H), 1.94-2.10 (m, 2 H), 2.12-2.26 (m, 1 H), 2.37 (s, 3 H), 2.98 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.22 (dd, *J* = 8.4, 6.2 Hz, 1 H), 3.50-3.74 (m, 9 H), 3.75-3.80 (m, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.29-4.38 (m, 2 H), 4.49 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.22 (d, *J* = 5.6 Hz, 1 H), 7.96 (s, 1 H).

### (7*S*)-7-Deoxy-7-(5-morpholinocarbonylthiophen-2-ylthio)lincomycin (3-41)

Compound **3-6** (90.4 mg, 0.21 mmol) and (5-iodothiophen-2-yl)(morpholino)methanone (69.0 mg, 0.21 mmol) were treated at reflux for 6 h according to the similar procedure as described for the preparation of **3-7** to afford **3-41** (100 mg, 75.6%) as a colorless solid. $[\alpha]_D^{29}$ +102.9° (*c* 2.49, MeOH); ESI-MS *m/z* 618 $(M+H)^+$ as $C_{27}H_{43}N_3O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{43}N_3O_7S_3$: 618.2341, found: 618.2347; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.25-1.40 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.99 (ddd, *J* = 12.8, 7.9, 4.7 Hz, 1 H), 2.02-2.09 (m, 1 H), 2.11-2.23 (m, 1 H), 2.17 (s, 3 H), 2.37 (s, 3 H), 2.98 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.22 (dd, *J* = 8.4, 5.9 Hz, 1 H), 3.58 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.66-3.79 (m, 10 H), 4.11 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.34 (br dd, *J* = 9.6, 0.6 Hz, 1 H), 4.42 (dd, *J* = 9.6, 3.0 Hz, 1 H), 5.29 (d, *J* = 5.6 Hz, 1 H), 7.18 (d, *J* = 3.8 Hz, 1 H), 7.32 (d, *J* = 3.8 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(5-molpholinocarbonylthiazol-2-ylthio)lincomycin (3-42)

To a solution of compound **3-34** (430 mg, 0.74 mmol) in EtOH (8 ml) was added 5N NaOH (0.3 ml) and stirred at room temperature for 1 h. The mixture was diluted with 5N HCl (0.3 ml) and concentrated under reduced pressure. The resulting residue (crude compound **3-38**), morpholine (0.32 ml, 3.70 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (213 mg, 1.11 mmol), 1-hydroxybenzotriazole (150 mg, 1.11 mmol) and $Et_3N$ (1.03 ml, 7.40 mmol) treated at 60˚C for 2 days according to the similar procedure as described for the preparation of **3-11** to afford **3-42** (29.9 mg, 6.5%) as a colorless solid. $[\alpha]_D^{27}$ +84.5° (*c* 3.39, MeOH); ESI-MS *m/z* 619 $(M+H)^+$ as $C_{26}H_{42}N_4O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{42}N_4O_7S_3$: 619.2294, found: 619.2288; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.26-1.41 (m, 4 H), 1.51 (d, *J* = 7.0 Hz, 3 H), 1.77-1.89 (m, 1 H), 1.96 (s, 3 H), 1.96-2.11 (m, 2 H), 2.11-2.27 (m, 1 H), 2.37 (s, 3 H), 2.99 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.24 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H),

3.66-3.77 (m, 8 H), 3.77-3.82 (m, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30 (dq, *J* = 7.0, 3.2 Hz, 1 H), 4.36 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.57 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.93 (s, 1 H).

### (7*S*)-7-Deoxy-7-(5-morpholinocarbonyl-1,3,4-thidiazol-2-ylthio)lincomycin (3-43)

To a solution of compound **3-35** (50 mg, 86.4 μmol) in EtOH (1 ml) was added morpholine (0.10 ml) and refluxed for 3 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound as a colorless solid (34.5 mg, 64.4%). $[\alpha]_D^{31}$ +73.4° (*c* 0.92, MeOH); ESI-MS *m/z* 620 $(M+H)^+$ as $C_{25}H_{41}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{41}N_5O_7S_3$: 620.2246, found: 620.2239; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.27-1.40 (m, 4 H), 1.57 (d, *J* = 6.8 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.96 (s, 3 H), 1.97-2.11 (m, 2 H), 2.14-2.27 (m, 1 H), 2.38 (s, 3 H), 3.00 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.25 (dd, *J* = 8.5, 6.1 Hz, 1 H), 3.55 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.72-3.83 (m, 7 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.24 (br t, *J* = 4.7 Hz, 2 H), 4.39 (dd, *J* = 9.8, 0.7 Hz, 1 H), 4.47 (dq, *J* = 6.8, 3.2 Hz, 1 H), 4.61 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-((dimethylamino)methyl)phenylthio)lincomycin (4-1)

To a solution of 1-(4-bromophenyl)-*N*, *N*-dimethylmethanamine (23.2 mg, 0.11 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (10.4 mg, 18.0 μmol) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (8.3 mg, 9.10 μmol) in 1,4-dioxane (1 ml) were added compound **3-6** (38.2 mg, 90.4 μmol) and *N,N*-diisopropylethylamine (31.4 μl, 0.18 mmol). A reaction mixture was refluxed for 3 h and then filtrated by either Chromatodisc (0.45 μm) (KURABO INDUSTRIES Ltd., Osaka, Japan) or celite. The filtered solid were washed with MeOH three times and then the assembled solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound as an off white solid (39.4 mg, 78.4%). $[\alpha]_D^{24}$ +98.0° (*c* 1.94, MeOH); ESI-MS *m/z* 556 $(M+H)^+$ as $C_{27}H_{45}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{45}N_3O_5S_2$: 556.2879, found: 556.2883; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.31-1.41 (m, 4 H), 1.95-2.05 (m, 1 H), 1.97 (s, 3 H), 2.06-2.13 (m, 1 H), 2.13-2.22 (m, 1 H), 2.26 (s, 6 H), 2.41 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.49 (s, 2 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.72-3.78 (m, 1 H), 3.87 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.34 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.42 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.26-7.32 (m, 2 H), 7.37-7.43 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(2-(dimethylamino)ethyl)phenylthio)lincomycin (4-2)

Compound **3-6** (106 mg, 0.25 mmol), 2-(4-bromophenyl)-*N*, *N*-dimethylethan-1-amine (125 mg, 0.55 mmol), Xantphos (15.8 mg, 27.3 μmol), $Pd_2(dba)_3$ (12.9 mg, 14.1 μmol), and *N,N*-diisopropylethylamine (64.0 μl, 0.37 mmol) in 1,4-dioxane (3 ml) were treated for 14 h according to the similar procedure as

described for the preparation of **4-1** to afford **4-2** (85.7 mg, 60.0%) as a colorless solid. $[\alpha]_D^{24}$ +102° (*c* 0.64, MeOH); ESI-MS *m/z* 570 $(M+H)^+$ as $C_{28}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{47}N_3O_5S_2$: 570.3035, found: 570.3034; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.98 (m, 3 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.30-1.42 (m, 4 H), 1.79-1.91 (m, 1 H), 1.95-2.04 (m, 1 H), 2.01 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.31 (s, 6 H), 2.39 (s, 3 H), 2.52-2.60 (m, 2 H), 2.74-2.82 (m, 2 H), 2.98 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.0, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74 (m, 1 H), 3.81 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.33 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.39 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.5 Hz, 1 H), 7.17-7.24 (m, 2 H), 7.34-7.41 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(3-(dimethylamino)prop-1-yn-1-yl)phenylthio)lincomycin (4-3)

Compound **3-6** (66.2 mg, 0.16 mmol), 3-(4-bromophenyl)-*N*, *N*-dimethylprop-2-yn-1-amine (42.3 mg, 0.18 mmol), Xantphos (9.8 mg, 16.9 μmol), $Pd_2(dba)_3$ (6.5 mg, 7.10 μmol), and *N,N*-diisopropylethylamine (38.9 μl, 0.22 mmol) in 1,4-dioxane (0.75 ml) were treated for 14 h according to the similar procedure as described for the preparation of **4-1** to afford **4-3** (59.4 mg, 65.4%) as a colorless solid. FAB-MS *m/z* 580 $(M+H)^+$ as $C_{29}H_{45}N_3O_5S_2$; FAB-HRMS $(M+H)^+$ calcd for $C_{29}H_{45}N_3O_5S_2$: 580.2879, found: 580.2878; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-1.00 (m, 3 H), 1.26-1.42 (m, 4 H), 1.34 (d, *J* = 6.9 Hz, 3 H), 1.78-1.90 (m, 1 H), 1.92-2.03 (m, 1 H), 1.94 (s, 3 H), 2.03-2.11 (m, 1 H), 2.11-2.22 (m, 1 H), 2.37 (s, 6 H), 2.38 (s, 3 H), 2.97 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.7 Hz, 1 H), 3.48 (s, 2 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.75 (br dd, *J* = 3.2, 0.6 Hz, 1 H), 3.89 (dq, *J* = 6.9, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.45 (dd, *J* = 9.8, 2.8 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.35-7.42 (m, 4 H).

### (7*S*)-7-Deoxy-7-(4-(3-(dimethylamino)propyl)phenylthio)lincomycin (4-4)

To a solution of compound **4-3** (21.4 mg, 36.9 μmol) in MeOH (2 ml) was added Pd/C (10.4 mg). A reaction mixture was vigorously stirred in hydrogen atmosphere at room temperature for 14 h and filtrated with celite. The filtered solid were washed with MeOH three times and then the assembled solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (**4-4**) (13.7 mg, 63.6%) as a colorless solid. $[\alpha]_D^{23}$ +87.1° (*c* 0.22, MeOH); ESI-MS *m/z* 584 $(M+H)^+$ as $C_{29}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{49}N_3O_5S_2$: 584.3192, found: 584.3192; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90-0.97 (m, 3 H), 1.26 (d, *J* = 7.0 Hz, 3 H), 1.31-1.41 (m, 4 H), 1.76 -1.91 (m, 3 H), 1.95-2.04 (m, 1 H), 2.01 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.28 (s, 6 H), 2.39 (s, 3 H), 2.37-2.44 (m, 2 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 2.98 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.5 Hz, 1 H), 3.57 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.73 (m, 1 H), 3.80 (dq, *J* = 7.0, 2.4 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.33 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.38 (dd, *J* = 9.8, 2.4 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.15-7.21 (m, 2 H), 7.34-7.39 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(pyrrolidin-1-ylmethyl)phenylthio)lincomycin (4-5)

Compound **3-6** (97.5 mg, 0.23 mmol), 1-(4-bromobenzyl)pyrrolidine (90.1 mg, 0.38 mmol), Xantphos (14.6 mg, 25.2 μmol), $Pd_2(dba)_3$ (11.1 mg, 12.1 μmol), and *N,N*-diisopropylethylamine (120 μl, 0.69 mmol) in 1,4-dioxane (2 ml) were treated for 3 h according to the similar procedure as described for the preparation of **4-1** to afford **4-5** (116 mg, 86.4%) as an off white solid. $[\alpha]_D^{23}$ +102° (*c* 3.96, MeOH); ESI-MS *m/z* 582 $(M+H)^+$ as $C_{29}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{47}N_3O_5S_2$: 582.3035, found: 582.3027; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.75 -1.83 (m, 4 H), 1.83-1.91 (m, 1 H), 1.98 (s, 3 H), 1.94-2.04 (m, 1 H), 2.05-2.11 (m, 1 H), 2.12-2.23 (m, 1 H), 2.40 (s, 3 H), 2.48-2.58 (m, 4 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.61 (s, 2 H), 3.72-3.76 (m, 1 H), 3.86 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30-4.36 (m, 1 H), 4.42 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.28-7.34 (m, 2 H), 7.36 -7.42 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(2-(pyrrolidin-1-yl)ethyl)phenylthio)lincomycin (4-6)

Compound **3-6** (83.0 mg, 0.20 mmol), 1-(4-bromophenethyl)pyrrolidine (50.0 mg, 0.20 mmol), Xantphos (11.0 mg, 19.0 μmol), $Pd_2(dba)_3$ (9.0 mg, 9.80 μmol), and *N,N*-diisopropylethylamine (173 μl, 0.99 mmol) in 1,4-dioxane (3 ml) were treated for 3 h according to the similar procedure as described for the preparation of **4-1** to afford **4-6** (82.0 mg, 70.1%) as a colorless solid. $[\alpha]_D^{25}$ +68.0° (*c* 0.25, MeOH); ESI-MS *m/z* 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3171; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.31-1.42 (m, 4 H), 1.82 -1.92 (m, 5 H), 1.95-2.04 (m, 1 H), 2.01 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.25 (m, 1 H), 2.39 (s, 3 H), 2.66-2.75 (m, 4 H), 2.75-2.89 (m, 4 H), 2.98 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.0, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.71-3.76 (m, 1 H), 3.81 (dq, *J* = 6.9, 2.5 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.33 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.39 (dd, *J* = 9.8, 2.5 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.18-7.24 (m, 2 H), 7.34-7.41 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-((4-methylpiperazin-1-yl)methyl)phenylthio)lincomycin (4-7)

Compound **3-6** (100 mg, 0.24 mmol), 1-(4-bromobenzyl)-4-methylpiperazine (144 mg, 0.54 mmol), Xantphos (14.6 mg, 25.2 μmol), $Pd_2(dba)_3$ (11.0 mg, 12.0 μmol), and *N,N*-diisopropylethylamine (120 μl, 0.69 mmol) in 1,4-dioxane (2 ml) were treated for 4 h according to the similar procedure as described for the preparation of **4-1** to afford **4-7** (133 mg, 91.8%) as a colorless solid. $[\alpha]_D^{25}$ +93.2° (*c* 2.52, MeOH); ESI-MS *m/z* 611 $(M+H)^+$ as $C_{30}H_{50}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{50}N_4O_5S_2$: 611.3301, found: 611.3285; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.28 (d, *J* = 6.8 Hz, 3 H), 1.28-1.41 (m, 4 H), 1.80-1.91 (m, 1 H), 1.95-2.04 (m, 1 H), 1.98 (s, 3 H), 2.04-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.27 (s, 3 H), 2.30-2.92 (m, 8 H), 2.40 (s, 3H), 2.99 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.25 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.51 (s, 2 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.71-3.77 (m, 1 H), 3.85 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2,

5.6 Hz, 1 H), 4.29-4.35 (m, 1 H), 4.41 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.26-7.33 (m, 2 H), 7.36-7.43 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(2-(4-methylpiperazin-1-yl)ethyl)phenylthio)lincomycin (4-8)

Compound **3-6** (90.0 mg, 0.21 mmol), 1-(4-bromophenethyl)-4-methylpiperazine (60.0 mg, 0.21 mmol), Xantphos (12.0 mg, 20.7 μmol), $Pd_2(dba)_3$ (9.7 mg, 10.6 μmol), and *N,N*-diisopropylethylamine (185 μl, 1.06 mmol) in 1,4-dioxane (3 ml) were treated for 2 h according to the similar procedure as described for the preparation of **4-1** to afford **4-8** (89.0 mg, 66.9%) as an off white solid. $[\alpha]_D^{23}$ +90.7° (*c* 2.05, MeOH); ESI-MS *m/z* 625 $(M+H)^+$ as $C_{31}H_{52}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{52}N_4O_5S_2$: 625.3457, found: 625.3461; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.98 (m, 3 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 1.30-1.40 (m, 4 H), 1.79-1.92 (m, 1 H), 1.94-2.04 (m, 1 H), 2.00 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.31 (s, 3 H), 2.39 (s, 3 H), 2.41-2.88 (m, 8 H), 2.58-2.64 (m, 2 H), 2.75-2.84 (m, 2 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.0, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.71-3.76 (m, 1 H), 3.80 (dq, *J* = 6.9, 2.4 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.31-4.35 (m, 1 H), 4.38 (dd, *J* = 9.8, 2.4 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.17-7.23 (m, 2 H), 7.34-7.40 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(piperidin-1-ylmethyl)phenylthio)lincomycin (4-9)

Compound **3-6** (98.1 mg, 0.23 mmol), 1-(4-bromobenzyl)piperidine (95.3 mg, 0.38 mmol), Xantphos (14.7 mg, 25.4 μmol), $Pd_2(dba)_3$ (10.8 mg, 11.8 μmol), and *N,N*-diisopropylethylamine (120 μl, 0.69 mmol) in 1,4-dioxane (2 ml) were treated for 3.5 h according to the similar procedure as described for the preparation of **4-1** to afford **4-9** (123 mg, 88.9%) as an off white solid. $[\alpha]_D^{23}$ +97.7° (*c* 4.26, MeOH); ESI-MS *m/z* 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3184; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.31-1.40 (m, 4 H), 1.40 -1.50 (m, 2 H), 1.52-1.64 (m, 4 H), 1.79-1.91 (m, 1 H), 1.93-2.04 (m, 1 H), 1.98 (s, 3 H), 2.04-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.30-2.48 (m, 4 H), 2.39 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.46 (s, 2 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.72-3.77 (m, 1 H), 3.86 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30-4.36 (m, 1 H), 4.41 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.25-7.32 (m, 2 H), 7.35 -7.41 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-((2(*S*)-(methoxymethyl)pyrrolidin-1-yl)methyl)phenylthio)lincomycin (4-10)

Compound **3-6** (70.0 mg, 0.17 mmol), (*S*)-1-(4-bromobenzyl)-2-(methoxymethyl)pyrrolidine (96.5 mg, 0.34 mmol), Xantphos (9.7 mg, 16.8 μmol), $Pd_2(dba)_3$ (7.6 mg, 8.30 μmol), and *N,N*-diisopropylethylamine (87.6 μl, 0.50 mmol) in 1,4-dioxane (2 ml) were treated under microwave irradiation for 30 min according to the similar procedure as described for the preparation of **4-1** to afford **4-10** (61.0 mg, 58.8%) as a colorless solid. $[\alpha]_D^{23}$ +72.0° (*c* 1.52, MeOH); ESI-MS *m/z* 626 $(M+H)^+$ as $C_{31}H_{51}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$

calcd for $C_{31}H_{51}N_3O_6S_2$: 626.3298, found: 626.3297; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.98 (m, 3 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 1.31-1.40 (m, 4 H), 1.54 -1.63 (m, 1 H), 1.64-1.75 (m, 2 H), 1.80-2.05 (m, 3 H), 2.00 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.22 (m, 1 H), 2.22-2.31 (m, 1 H), 2.40 (s, 3 H), 2.69-2.79 (m, 1 H), 2.84-2.91 (m, 1 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.32-3.36 (m, 1 H), 3.33 (s, 3 H), 3.37-3.46 (m, 2 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.72-3.76 (m, 1 H), 3.85 (dq, *J* = 6.9, 2.5 Hz, 1 H), 4.04-4.14 (m, 2 H), 4.31-4.37 (m, 1 H), 4.40 (dd, *J* = 9.8, 2.5 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.28-7.34 (m, 2 H), 7.36 -7.41 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(thiazol-4-yl)phenylthio)lincomycin (4-11)

Compound **3-6** (100 mg, 0.24 mmol), 4-(4-bromophenyl)thiazole (100 mg, 0.42 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (82.6 μl, 0.47 mmol) in 1,4-dioxane (2 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-11** (93.6 mg, 68.0%) as a colorless solid. $[\alpha]_D^{19}$ +98.1° (*c* 0.62, MeOH); ESI-MS *m/z* 582 $(M+H)^+$ as $C_{27}H_{39}N_3O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{39}N_3O_5S_3$: 582.2130, found: 582.2131; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.27-1.36 (m, 4 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.81-1.91 (m, 1 H), 1.95-2.04 (m, 1 H), 2.00 (s, 3 H), 2.05-2.13 (m, 1 H), 2.13-2.24 (m, 1 H), 2.40 (s, 3 H), 3.02 (dd, *J* = 10.5, 4.8 Hz, 1 H), 3.23 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.60 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74-3.79 (m, 1 H), 3.90 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37-4.42 (m, 1 H), 4.45 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.48-7.54 (m, 2 H), 7.88-7.95 (m, 3 H), 9.05 (d, *J* = 2.0 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(1*H*-imidazol-1-yl)phenylthio)lincomycin (4-12)

Compound **3-6** (100 mg, 0.24 mmol), 1-(4-bromophenyl)-1*H*-imidazole (70.0 mg, 0.31 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (82.6 μl, 0.47 mmol) in 1,4-dioxane (5 ml) were treated for 4 h according to the similar procedure as described for the preparation of **4-1** to afford **4-12** (56.5 mg, 42.3%) as a colorless solid. $[\alpha]_D^{25}$ +97.8° (*c* 1.40, MeOH); ESI-MS *m/z* 565 $(M+H)^+$ as $C_{27}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{40}N_4O_5S_2$: 565.2518, found: 565.2522; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.26-1.41 (m, 4 H), 1.34 (d, *J* = 6.9 Hz, 3 H), 1.81-1.92 (m, 1 H), 1.96-2.06 (m, 1 H), 2.01 (s, 3 H), 2.06-2.14 (m, 1 H), 2.14-2.25 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.25 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.78 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 3.91 (dq, *J* = 6.9, 2.8 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.37 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.48 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.27 (d, *J* = 5.5 Hz, 1 H), 7.14-7.17 (m, 1 H), 7.53-7.60 (m, 5 H), 8.13-8.17 (m, 1 H).

### (7*S*)-7-Deoxy-7-(4-(1,3,4-thiadiazol-2-yl)phenylthio)lincomycin (4-13)

Compound **3-6** (100 mg, 0.24 mmol), 2-(4-bromophenyl)-1,3,4-thiadiazole (100 mg, 0.42 mmol), Xantphos (20.0 mg, 34.6 μmol), $Pd_2(dba)_3$ (20.0 mg, 21.8 μmol), and *N,N*-diisopropylethylamine (82.6 μl,

0.47 mmol) in 1,4-dioxane (2 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-13** (88.3 mg, 64.0%) as a colorless solid. $[\alpha]_D^{20}$ +71.9° (*c* 0.40, MeOH); ESI-MS *m/z* 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2089; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90-0.96 (m, 3 H), 1.28-1.41 (m, 4 H), 1.41 (d, *J* = 6.9 Hz, 3 H), 1.82-1.94 (m, 1 H), 1.91 (s, 3 H), 1.98-2.08 (m, 1 H), 2.09-2.25 (m, 2 H), 2.45 (s, 3 H), 3.09 (dd, *J* = 10.3, 4.7 Hz, 1 H), 3.29 (dd, *J* = 7.9, 5.4 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.79 (br dd, *J* = 3.2, 0.5 Hz, 1 H), 4.03 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.39 (br dd, *J* = 9.7, 0.5 Hz, 1 H), 4.54 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.52-7.57 (m, 2 H), 7.93-7.99 (m, 2 H), 9.43 (s, 1 H).

### (7*S*)-7-Deoxy-7-(4-(1,2,3-thiadiazol-4-yl)phenylthio)lincomycin (4-14)

Compound **3-6** (100 mg, 0.24 mmol), 4-(4-bromophenyl)-1,2,3-thiadiazole (100 mg, 0.42 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (82.6 μl, 0.47 mmol) in 1,4-dioxane (3 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-14** (71.7 mg, 52.0%) as a colorless solid. $[\alpha]_D^{20}$ +71.8° (*c* 0.35, MeOH); ESI-MS *m/z* 583 $(M+H)^+$ as $C_{26}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{38}N_4O_5S_3$: 583.2083, found: 583.2085; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.26-1.38 (m, 4 H), 1.39 (d, *J* = 6.9 Hz, 3 H), 1.82-1.93 (m, 1 H), 1.96-2.06 (m, 1 H), 1.98 (s, 3 H), 2.07-2.24 (m, 2 H), 2.44 (s, 3 H), 3.06 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.26 (dd, *J* = 8.3, 5.6 Hz, 1 H), 3.60 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.78 (br dd, *J* = 3.2, 0.6 Hz, 1 H), 3.96 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.49 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.55-7.60 (m, 2 H), 8.05-8.09 (m, 2 H), 9.25 (s, 1 H).

### (7*S*)-7-([1,1'-Biphenyl]-4-ylthio)-7-deoxylincomycin (4-15)

Compound **3-6** (72.3 mg, 0.17 mmol), 4-bromo-1,1'-biphenyl (84.7 mg, 0.36 mmol), Xantphos (10.8 mg, 18.7 μmol), $Pd_2(dba)_3$ (8.1 mg, 8.87 μmol), and *N,N*-diisopropylethylamine (60.0 μl, 0.34 mmol) in 1,4-dioxane (1 ml) were treated for 4 h according to the similar procedure as described for the preparation of **4-1** to afford **4-15** (90.0 mg, 91.5%) as a colorless solid. $[\alpha]_D^{26}$ +101° (*c* 1.16, MeOH); ESI-MS *m/z* 575 $(M+H)^+$ as $C_{30}H_{42}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{42}N_2O_5S_2$: 575.2613, found: 575.2608; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.95 (m, 3 H), 1.25-1.40 (m, 4 H), 1.34 (d, *J* = 6.9 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.95-2.03 (m, 1 H), 2.02 (s, 3 H), 2.03-2.09 (m, 1 H), 2.10-2.21 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.21 (dd, *J* = 8.3, 5.8 Hz, 1 H), 3.60 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.73-3.80 (m, 1 H), 3.88 (dq, *J* = 6.9, 2.5 Hz, 1 H), 4.12 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.36-4.41 (m, 1 H), 4.42 (dd, *J* = 9.7, 2.5 Hz, 1 H), 5.28 (d, *J* = 5.5 Hz, 1 H), 7.31-7.36 (m, 1 H), 7.39-7.46 (m, 2 H), 7.48-7.54 (m, 2 H), 7.56-7.64 (m, 4 H).

### (7*S*)-7-Deoxy-7-(4-(pyridin-2-yl)phenylthio)lincomycin (4-16)

Compound **3-6** (70.6 mg, 0.17 mmol), 2-(4-bromophenyl)pyridine (77.8 mg, 0.33 mmol), Xantphos (11.4 mg, 0.020 mmol), $Pd_2(dba)_3$ (7.85 mg, 8.57 μmol), and *N,N*-diisopropylethylamine (58.0 μl, 0.33 mmol) in 1,4-dioxane (1 ml) were treated for 3 h according to the similar procedure as described for the preparation of **4-1** to afford **4-16** (87.9 mg, 91.4%) as a colorless solid. $[\alpha]_D^{25}$ +86.7° (*c* 2.58, MeOH); ESI-MS *m/z* 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2558; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.95 (m, 3 H), 1.28-1.37 (m, 4 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.95-2.04 (m, 1 H), 1.95-2.05 (m, 1 H), 1.97 (s, 3 H), 2.05-2.11 (m, 1 H), 2.11-2.22 (m, 1 H), 2.41 (s, 3 H), 3.02 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.23 (dd, *J* = 8.3, 5.6 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.76-3.82 (m, 1 H), 3.95 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.13 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.37-4.43 (m, 1 H), 4.49 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.29 (d, *J* = 5.5 Hz, 1 H), 7.34 (ddd, *J* = 6.9, 5.0, 1.7 Hz, 1 H), 7.49-7.56 (m, 2 H), 7.81-7.91 (m, 2 H), 7.91-7.96 (m, 2 H), 8.61 (ddd, *J* = 4.9, 1.6, 1.0 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(pyridin-3-yl)phenylthio)lincomycin (4-17)

Compound **3-6** (109 mg, 0.26 mmol), 3-(4-bromophenyl)pyridine (89.7 mg, 0.38 mmol), Xantphos (15.2 mg, 26.3 μmol), $Pd_2(dba)_3$ (12.5 mg, 13.7 μmol), and *N,N*-diisopropylethylamine (88.9 μl, 0.51 mmol) in 1,4-dioxane (1.8 ml) were treated for 5.5 h according to the similar procedure as described for the preparation of **4-1** to afford **4-17** (131 mg, 88.2%) as a colorless solid. $[\alpha]_D^{24}$ +83.9° (*c* 0.37, MeOH); ESI-MS *m/z* 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2573; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.26-1.41 (m, 4 H), 1.36 (d, *J* = 6.9 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.96-2.05 (m, 1 H), 1.98 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.41 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.76-3.80 (m, 1 H), 3.94 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.38 (br dd, *J* = 9.7, 0.4 Hz, 1 H), 4.47 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.51 (ddd, *J* = 8.0, 4.9, 0.7 Hz, 1 H), 7.54-7.58 (m, 2 H), 7.62-7.68 (m,2 H), 8.09 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1 H), 8.52 (dd, *J* = 4.9, 1.6 Hz, 1 H), 8.77-8.82 (m, 1 H).

### (7*S*)-7-Deoxy-7-(4-(pyridin-4-yl)phenylthio)lincomycin (4-18)

Compound **3-6** (61.9 mg, 0.15 mmol), 4-(4-bromophenyl)pyridine (67.5 mg, 0.29 mmol), Xantphos (8.81 mg, 15.2 μmol), $Pd_2(dba)_3$ (6.88 mg, 7.51 μmol), and *N,N*-diisopropylethylamine (50.0 μl, 0.29 mmol) in 1,4-dioxane (1 ml) were treated for 6.5 h according to the similar procedure as described for the preparation of **4-1** to afford **4-18** (72.6 mg, 86.1%) as an off white solid. $[\alpha]_D^{25}$ +87.3° (*c* 2.15, MeOH); ESI-MS *m/z* 576 $(M+H)^+$ as $C_{29}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{41}N_3O_5S_2$: 576.2566, found: 576.2562; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.97 (m, 3 H), 1.26-1.40 (m, 4 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.80-1.92 (m, 1 H), 1.95 (s, 3 H), 1.97-2.07 (m, 1 H), 2.07-2.14 (m, 1 H), 2.14-2.24 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.25 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.2 Hz, 1 H),

3.77-3.82 (m, 1 H), 3.97 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.13 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.35-4.43 (m, 1 H), 4.51 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.51-7.58 (m, 2 H), 7.68-7.78 (m, 4 H), 8.54-8.60 (m, 2 H).

### (7*S*)-7-(3'-Cyano-[1,1'-biphenyl]-4-ylthio)-7-deoxylincomycin (4-19)

Compound **3-6** (85.2 mg, 0.20 mmol), 4'-bromo-[1,1'-biphenyl]-3-carbonitrile (104 mg, 0.40 mmol), Xantphos (12.7 mg, 21.9 μmol), $Pd_2(dba)_3$ (10.4 mg, 11.4 μmol), and *N,N*-diisopropylethylamine (69.9 μl, 0.40 mmol) in 1,4-dioxane (1 ml) were treated for 4 h according to the similar procedure as described for the preparation of **4-1** to afford **4-19** (49.4 mg, 40.9%) as a colorless solid. $[\alpha]_D^{24}$ +91.6° (*c* 1.97, MeOH); ESI-MS *m/z* 600 $(M+H)^+$ as $C_{31}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{41}N_3O_5S_2$: 600.2566, found: 600.2559; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.27-1.39 (m, 4 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.95-2.05 (m, 1 H), 1.98 (s, 3 H), 2.06-2.21 (m, 1 H), 2.13-2.24 (m, 1 H), 2.42 (s, 3 H), 3.02 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.24 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.76-3.81 (m, 1 H), 3.93 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.12 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.48 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.50-7.55 (m, 2 H), 7.60-7.66 (m, 3 H), 7.67-7.71 (m, 1 H), 7.90-7.96 (m, 1 H), 7.96-8.00 (m, 1 H).

### (7*S*)-7-Deoxy-7-(3'-methoxy-[1,1'-biphenyl]-4-ylthio)lincomycin (4-20)

Compound **3-6** (56.1 mg, 1.33 mmol), 4'-bromo-3-methoxy-1,1'-biphenyl (45.6 mg, 0.17 mmol), Xantphos (8.10 mg, 14.0 μmol), $Pd_2(dba)_3$ (6.26 mg, 6.84 μmol), and *N,N*-diisopropylethylamine (46.0 μl, 0.26 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-20** (69.0 mg, 85.9%) as a colorless solid. $[\alpha]_D^{24}$ +100° (*c* 2.76, MeOH); ESI-MS *m/z* 605 $(M+H)^+$ as $C_{31}H_{44}N_2O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{44}N_2O_6S_2$: 605.2719, found: 605.2712; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.95 (m, 3 H), 1.24-1.37 (m, 4 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.79-1.89 (m, 1 H), 2.01 (s, 3 H), 1.95-2.09 (m, 2 H), 2.09-2.20 (m, 1 H), 2.38 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.20 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74-3.79 (m, 1 H), 3.83 (s, 3 H), 3.88 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.13 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.44 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.29 (d, *J* = 5.5 Hz, 1 H), 6.91 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.11-7.14 (m, 1 H), 7.14-7.19 (m, 1 H), 7.30-7.37 (m, 1 H), 7.46-7.51 (m, 2 H), 7.54-7.59 (m, 2 H).

### (7*S*)-7-(3'-Amino-[1,1'-biphenyl]-4-ylthio)-7-deoxylincomycin (4-21)

Compound **3-6** (66.9 mg, 0.16 mmol), 4'-bromo-[1,1'-biphenyl]-3-amine (75.9 mg, 0.31 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (7.26 mg, 7.93 μmol), and *N,N*-diisopropylethylamine (53.5 μl, 0.31 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-21** (47.6 mg, 51.0%) as a colorless solid. $[\alpha]_D^{28}$ +142° (*c* 0.51, MeOH); ESI-MS *m/z* 590 $(M+H)^+$ as $C_{30}H_{43}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{43}N_3O_5S_2$: 590.2722,

found: 590.2713; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.95 (m, 3 H), 1.25-1.40 (m, 4 H), 1.33 (d, $J$ = 6.9 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.95-2.05 (m, 1 H), 2.01 (s, 3 H), 2.05-2.21 (m, 2 H), 2.40 (s, 3 H), 3.02 (dd, $J$ = 10.5, 4.6 Hz, 1 H), 3.23 (dd, $J$ = 8.1, 5.6 Hz, 1 H), 3.60 (dd, $J$ = 10.2, 3.3 Hz, 1 H), 3.74-3.79 (m, 1 H), 3.86 (dq, $J$ = 6.9, 2.3 Hz, 1 H), 4.11 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.36-4.41 (m, 1 H), 4.43 (dd, $J$ = 9.7, 2.3 Hz, 1 H), 5.27 (d, $J$ = 5.6 Hz, 1 H), 6.71 (ddd, $J$ = 7.9, 2.2, 0.9 Hz, 1 H), 6.92 (ddd, $J$ = 7.7, 1.7, 1.0 Hz, 1 H), 6.96-7.00 (m, 1 H), 7.13-7.19 (m, 1 H), 7.45-7.50 (m, 2 H), 7.52-7.57 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(5-fluoropyridin-3-yl)phenylthio)lincomycin (4-22)

Compound **3-6** (66.0 mg, 0.16 mmol), 3-(4-bromophenyl)-5-fluoropyridine (50.0 mg, 0.20 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (13.5 μl, 77.4 μmol) in 1,4-dioxane (1.5 ml) were treated for 3 h according to the similar procedure as described for the preparation of **4-1** to afford **4-22** (72.0 mg, 73.2%) as a colorless solid. $[\alpha]_D^{25}$ +88.5° (*c* 1.78, MeOH); ESI-MS *m/z* 594 $(M+H)^+$ as $C_{29}H_{40}FN_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{40}FN_3O_5S_2$: 594.2472, found: 594.2473; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.26-1.40 (m, 4 H), 1.36 (d, $J$ = 7.0 Hz, 3 H), 1.79-1.92 (m, 1 H), 1.93-2.06 (m, 1 H), 1.97 (s, 3 H), 2.07-2.14 (m, 1 H), 2.14-2.24 (m, 1 H), 2.43 (s, 3 H), 3.04 (dd, $J$ = 10.5, 4.6 Hz, 1 H), 3.22-3.29 (m, 1 H), 3.60 (dd, $J$ = 10.1, 2.8 Hz, 1 H), 3.76-3.82 (m, 1 H), 3.93-4.01 (m, 1 H), 4.12 (dd, $J$ = 10.1, 5.5 Hz, 1 H), 4.36-4.41 (m, 1 H), 4.47-4.53 (m, 1 H), 5.28 (d, $J$ = 5.5 Hz, 1 H), 7.51-7.58 (m, 2 H), 7.64-7.71 (m, 2 H), 7.87-7.94 (m, 1 H), 8.41-8.47 (m, 1 H), 8.69 (s, 1 H).

### (7*S*)-7-(4-(5-Cyanopyridin-3-yl)phenylthio)-7-deoxylincomycin (4-23)

Compound **3-6** (66.0 mg, 0.156 mmol), 5-(4-bromophenyl)nicotinonitrile (50.0 mg, 0.19 mmol), Xantphos (20.0 mg, 34.6 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (60.0 μl, 0.34 mmol) in 1,4-dioxane (1.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-23** (55.0 mg, 58.6%) as a colorless solid. $[\alpha]_D^{25}$ +87.4° (*c* 0.81, MeOH); ESI-MS *m/z* 601 $(M+H)^+$ as $C_{30}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{40}N_4O_5S_2$: 601.2518, found: 601.2512; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.29-1.41 (m, 4 H), 1.37 (d, $J$ = 6.8 Hz, 3 H), 1.83-1.92 (m, 1 H), 1.95 (s, 3 H), 1.98-2.08 (m, 1 H), 2.08-2.25 (m, 2 H), 2.44 (s, 3 H), 3.05 (dd, $J$ = 10.6, 4.8 Hz, 1 H), 3.27 (dd, $J$ = 8.1, 5.6 Hz, 1 H), 3.59 (dd, $J$ = 10.1, 3.2 Hz, 1 H), 3.79 (br dd, $J$ = 3.2, 0.6 Hz, 1 H), 3.98 (dq, $J$ = 6.8, 2.7 Hz, 1 H), 4.11 (dd, $J$ = 10.1, 5.6 Hz, 1 H), 4.39 (br dd, $J$ = 9.7, 0.6 Hz, 1 H), 4.50 (dd, $J$ = 9.7, 2.7 Hz, 1 H), 5.27 (d, $J$ = 5.6 Hz, 1 H), 7.53-7.60 (m, 2 H), 7.68-7.73 (m, 2 H), 8.45-8.49 (m, 1 H), 8.87 (d, $J$ = 1.8 Hz, 1 H), 9.08 (d, $J$ = 2.2 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(5-methoxypyridin-3-yl)phenylthio)lincomycin (4-24)

Compound **3-6** (70.2 mg, 0.17 mmol), 3-(4-bromophenyl)-5-methoxypyridine (70.1 mg, 0.27 mmol), Xantphos (10.2 mg, 17.6 μmol), $Pd_2(dba)_3$ (8.1 mg, 8.82 μmol), and *N,N*-diisopropylethylamine (57.5 μl, 0.33 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the

preparation of **4-1** to afford **4-24** (78.0 mg, 77.5%) as a colorless solid. $[\alpha]_D^{26}$ +86.8° (*c* 2.82, MeOH); ESI-MS *m/z* 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2660; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.83-0.99 (m, 3 H), 1.27-1.39 (m, 4 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.95-2.05 (m, 1 H), 1.99 (s, 3 H), 2.06-2.13 (m, 1 H), 2.13-2.24 (m, 1 H), 2.42 (s, 3 H), 3.03 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.24 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.61 (dd, *J* = 10.1, 3.3 Hz, 1 H), 3.77-3.82 (m, 1 H), 3.90-3.98 (m, 1 H), 3.94 (s, 3 H), 4.13 (dd, *J* = 10.1, 5.5 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.49 (dd, *J* = 9.8, 2.7 Hz, 1 H), 5.29 (d, *J* = 5.5 Hz, 1 H), 7.50-7.56 (m, 2 H), 7.59 (br dd, *J* = 2.7, 1.7 Hz, 1 H), 7.61-7.67 (m, 2 H), 8.21 (d, *J* = 2.7 Hz, 1 H), 8.39 (d, *J* = 1.7 Hz, 1 H).

## (7*S*)-7-(4-Bromophenylthio)-7-deoxylincomycin (4-25)

Compound **3-6** (100 mg, 0.24 mmol), 1-bromo-4-iodobenzene (134 mg, 0.47 mmol), Xantphos (27.4 mg, 47.4 μmol), $Pd_2(dba)_3$ (21.7 mg, 23.7 μmol), and *N,N*-diisopropylethylamine (82.6 μl, 0.47 mmol) in 1,4-dioxane (1 ml) were treated for 3 h according to the similar procedure as described for the preparation of **4-1** to afford **4-25** (100 mg, 73.3%) as a colorless solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.27-1.40 (m, 4 H), 1.31 (d, *J* = 6.9 Hz, 3 H), 1.76-1.90 (m, 1 H), 1.93-2.03 (m, 1 H), 1.98 (s, 3 H), 2.06 (dd, *J* = 10.1, 8.6 Hz, 1 H), 2.10-2.22 (m, 1 H), 2.37 (s, 3 H), 2.98 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.22 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.60 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.72-3.79 (m, 1 H), 3.85 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.12 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.31-4.37 (m, 1 H), 4.42 (dd, *J* = 9.7, 2.7 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.31-7.37 (m, 2 H), 7.44-7.50 (m, 2 H).

## (7*S*)-7-Deoxy-7-(4-(2-methoxypyridin-3-yl)phenylthio)lincomycin (4-26)

To a solution of compound **4-25** (100 mg, 0.17 mmol) in DMF (1 ml) and water (0.25 ml) were added $Pd(PPh_3)_4$ (12.5 mg, 10.8 μmol), 2-methoxypyridine-3-boronic acid (62.6 mg, 0.41 mmol) and $Na_2CO_3$ (37.6 mg, 0.36 mmol). A reaction mixture was stirred at 80°C for 10 h, diluted with ethyl acetate-water and then filtrated with celite. The filtered solid was washed with ethyl acetate three times. The assembled solution was extracted with ethyl acetate and then the organic layer was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound as an off white solid (74.1 mg, 70.6%). $[\alpha]_D^{24}$ +97.8° (*c* 3.63, MeOH); ESI-MS *m/z* 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2670; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.27-1.39 (m, 4 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.96-2.04 (m, 1 H), 1.99 (s, 3 H), 2.06 (dd, *J* = 10.2, 8.5 Hz, 1 H), 2.11-2.24 (m, 1 H), 2.39 (s, 3 H), 2.99 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.23 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.60 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.74-3.79 (m, 1 H), 3.89 (dq, *J* = 6.9, 2.5 Hz, 1 H), 3.93 (s, 3 H), 4.12 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.35-4.40 (m, 1 H), 4.42 (dd, *J* = 9.7, 2.5 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.03 (dd, *J* = 7.3, 5.0 Hz, 1 H), 7.44-7.55 (m, 4 H), 7.69 (dd, *J* = 7.3, 1.8 Hz, 1 H), 8.11 (dd, *J* = 5.0, 1.8 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(6-methoxypyridin-3-yl)phenylthio)lincomycin (4-27)

Compound **3-6** (41.1 mg, 97.3 μmol), 5-(4-bromophenyl)-2-methoxypyridine (38.6 mg, 0.15 mmol), Xantphos (11.3 mg, 19.5 μmol), $Pd_2(dba)_3$ (8.90 mg, 9.72 μmol), and *N,N*-diisopropylethylamine (33.9 μl, 0.20 mmol) in 1,4-dioxane (0.82 ml) treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-27** (53.4 mg, 90.6%) as a colorless solid. $[\alpha]_D^{29}$ +96.1° (*c* 2.60, MeOH); ESI-MS *m/z* 606 $(M+H)^+$ as $C_{30}H_{43}N_3O_6S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{43}N_3O_6S_2$: 606.2672, found: 606.2664; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.27-1.37 (m, 4 H), 1.33 (d, *J* = 6.8 Hz, 3 H), 1.79-1.91 (m, 1 H), 1.96-2.04 (m, 1 H), 2.01 (s, 3 H), 2.04-2.10 (m, 1 H), 2.11-2.22 (m, 1 H), 2.40 (s, 3 H), 3.01 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.22 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.75-3.80 (m, 1 H), 3.89 (dq, *J* = 6.8, 2.6 Hz, 1 H), 3.93 (s, 3 H), 4.13 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36-4.40 (m, 1 H), 4.45 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.29 (d, *J* = 5.6 Hz, 1 H), 6.86 (dd, *J* = 8.6, 0.6 Hz, 1 H), 7.46-7.58 (m, 4 H), 7.92 (dd, *J* = 8.6, 2.6 Hz, 1 H), 8.37 (br dd, *J* = 2.6, 0.6 Hz, 1 H).

### (7*S*)-7-(4-(6-Aminopyridin-3-yl)phenylthio)-7-deoxylincomycin (4-28)

Compound **3-6** (100 mg, 0.24 mmol), 5-(4-bromophenyl)pyridin-2-amine (100 mg, 0.40 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (10.0 μl, 57.3 μmol) in 1,4-dioxane (5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-28** (18.0 mg, 12.9%) as a colorless solid. $[\alpha]_D^{25}$ +101° (*c* 0.33, MeOH); ESI-MS *m/z* 591 $(M+H)^+$ as $C_{29}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{42}N_4O_5S_2$: 591.2675, found: 591.2678; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.96 (m, 3 H), 1.25-1.40 (m, 4 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.80-1.91 (m, 1 H), 1.95-2.05 (m, 1 H), 2.03 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.21 (m, 1 H), 2.40 (s, 3 H), 3.01 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.23 (dd, *J* = 8.1, 5.4 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.73-3.78 (m, 1 H), 3.85 (dq, *J* = 6.9, 2.4 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36-4.40 (m, 1 H), 4.43 (dd, *J* = 9.8, 2.4 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 6.66 (dd, *J* = 8.7, 0.7 Hz, 1 H), 7.46-7.55 (m, 4 H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1 H), 8.17 (br dd, *J* = 2.4, 0.7 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(pyrazin-2-yl)phenylthio)lincomycin (4-29)

Compound **3-6** (100 mg, 0.24 mmol), 2-(4-bromophenyl)pyrazine (70.0 mg, 0.30 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (82.6 μl, 0.47 mmol) in 1,4-dioxane (2 ml) were treated for 4 h according to the similar procedure as described for the preparation of **4-1** to afford **4-29** (65.0 mg, 47.6%) as a colorless solid. $[\alpha]_D^{19}$ +85.2° (*c* 1.01, MeOH); ESI-MS *m/z* 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2515; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.27-1.38 (m, 4 H), 1.39 (d, *J* = 6.9 Hz, 3 H), 1.82-1.92 (m, 1 H), 1.95 (s, 3 H), 1.97 -2.07 (m, 1 H), 2.07-2.14 (m, 1 H), 2.14-2.24 (m, 1 H), 2.43 (s, 3 H), 3.05 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.26 (dd, *J* = 8.1, 5.6 Hz, 1 H), 3.60 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.76-3.81 (m, 1 H), 3.99 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.12 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.51 (dd, *J*

= 9.8, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.53-7.58 (m, 2 H), 8.04-8.08 (m, 2 H), 8.52 (d, *J* = 2.5 Hz, 1 H), 8.66 (dd, *J* = 2.5, 1.5 Hz, 1 H), 9.10 (d, *J* = 1.5 Hz, 1 H).

### (7*S*)-7-Deoxy-7-(4-(pyrimidin-2-yl)phenylthio)lincomycin (4-30)

Compound **3-6** (106 mg, 0.25 mmol), 2-(4-bromophenyl)pyrimidine (116 mg, 0.49 mmol), Xantphos (15.0 mg, 25.9 μmol), $Pd_2(dba)_3$ (11.6 mg, 12.7 μmol), and *N,N*-diisopropylethylamine (86.0 μl, 0.49 mmol) in 1,4-dioxane (1.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-30** (134 mg, 92.6%) as a colorless solid. $[\alpha]_D^{26}$ +83.6° (*c* 4.97, MeOH); ESI-MS *m/z* 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2512; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.95 (m, 3 H), 1.22-1.37 (m, 4 H), 1.39 (d, *J* = 6.8 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.93-2.07 (m, 2 H), 1.94 (s, 3 H), 2.07-2.23 (m, 1 H), 2.39 (s, 3 H), 3.00 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.20 (dd, *J* = 8.3, 5.9 Hz, 1 H), 3.63 (dd, *J* = 10.2, 3.4 Hz, 1 H), 3.75-3.82 (m, 1 H), 3.99 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.14 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.38-4.43 (m, 1 H), 4.51 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.30 (d, *J* = 5.5 Hz, 1 H), 7.33 (t, *J* = 4.9 Hz, 1 H), 7.47-7.54 (m, 2 H), 8.31-8.39 (m, 2 H), 8.82 (d, *J* = 4.9 Hz, 2 H).

### (7*S*)-7-Deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (4-31)

Compound **3-6** (69.5 mg, 0.16 mmol), 5-(4-bromophenyl)pyrimidine (74.6 mg, 0.32 mmol), Xantphos (10.1 mg, 17.5 μmol), $Pd_2(dba)_3$ (7.79 mg, 8.51 μmol), and *N,N*-diisopropylethylamine (55.0 μl, 0.32 mmol) in 1,4-dioxane (1 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-31** (74.7 mg, 78.8%) as an off white solid. $[\alpha]_D^{28}$ +142° (*c* 0.51, MeOH); ESI-MS *m/z* 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2508; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.27-1.42 (m, 4 H), 1.37 (d, *J* = 6.9 Hz, 3 H), 1.81-1.91 (m, 1 H), 1.96 (s, 3 H), 1.97-2.06 (m, 1 H), 2.06-2.13 (m, 1 H), 2.12-2.24 (m, 1 H), 2.43 (s, 3 H), 3.02 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.25 (dd, *J* = 8.3, 5.7 Hz, 1 H), 3.60 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.77-3.82 (m, 1 H), 3.98 (dq, *J* = 6.9, 2.8 Hz, 1 H), 4.12 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.35-4.42 (m, 1 H), 4.50 (dd, *J* = 9.7, 2.8 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.54-7.60 (m, 2 H), 7.68-7.73 (m, 2 H), 9.07 (s, 2 H), 9.13 (s, 1 H).

### (7*S*)-7-Chloro-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (4-32)

To a solution of clindamycin (1.0 g, 2.35 mmol) in pyridine (5 ml) were added trimethylchlorosilane (1.19 ml, 9.39 mmol) and hexamethyldisilazane (1.97 ml, 9.42 mmol). A reaction mixture was stirred at room temperature for 2 h and then added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with hexane and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound (1.47 g, 97.3%) as a colorless solid. ESI-MS *m/z* 641 $(M+H)^+$ as $C_{27}H_{57}ClN_2O_5SSi_3$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.13 (s, 9 H), 0.14 (s, 9 H), 0.18 (s, 9 H), 0.84-0.94 (m, 3 H), 1.22-1.35 (m, 4 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.78-1.91 (m, 1 H), 1.92-2.10 (m, 3 H), 2.16 (s, 3 H),

2.41 (s, 3 H), 3.00 (dd, *J* = 10.8, 3.7 Hz, 1 H), 3.18 (dd, *J* = 7.3, 5.4 Hz, 1 H), 3.62 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.74 (d, *J* = 2.4 Hz, 1 H), 4.02 (d, *J* = 9.9 Hz, 1 H), 4.16 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.46-4.54 (m, 1 H), 4.56-4.64 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.67 (d, *J* = 10.5 Hz, 1 H).

### (7*R*)-7-Acetylthio-7-deoxylincomycin (4-34)

To a solution of compound **4-32** (1.47 g, 2.29 mmol) in DMF (10 ml) was added potassium thioacetatate (1.31 g, 11.4 mmol). A reaction mixture was stirred at 100°C for 18 h to give (7*R*)-7-acetylthio-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (**4-33**). Compound **4-33** was dissolved with 1*N* HCl and MeOH, and it was stirred at room temperature for 10 min. After the reaction mixture was washed with diethyl ether, ethyl acetate and the saturated aqueous $NaHCO_3$ were added to the aqueous layer. The desired compound was extracted with ethyl acetate and then the organic layer was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ = 50/1 → 10/1) to obtain the title compound (187 mg, 17.6%) as a colorless solid. ESI-MS *m/z* 465 $(M+H)^+$ as $C_{20}H_{36}N_2O_6S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.99 (m, 3 H), 1.26-1.42 (m, 4 H), 1.32 (d, *J* = 7.1 Hz, 3 H), 1.75-1.88 (m, 1 H), 1.92-2.25 (m, 3 H), 2.16 (s, 3 H), 2.29 (s, 3 H), 2.38 (s, 3 H), 2.94 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.21 (dd, *J* = 8.6, 6.1 Hz, 1 H), 3.51 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.72-3.77 (m, 1 H), 4.04 (dq, *J* = 7.1, 3.7 Hz, 1 H), 4.08-4.13 (m, 1 H), 4.14-4.19 (m, 1 H), 4.44 (dd, *J* = 9.4, 3.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H).

### (7*R*)-7-Deoxy-7-mercaptolincomycin (4-35)

To a solution of compound **4-34** (187 mg, 0.40 mmol) in MeOH (2 ml) was added 4.1M sodium methoxide in MeOH solution (0.30 ml, 1.21 mmol). A reaction mixture was stirred at room temperature for 20 min, diluted with saturated aqueous $NH_4Cl$ and concentrated under reduced pressure. The resulting residue was diluted with ethyl acetate and 10% aqueous $NaHCO_3$. Then, the desired compound was extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$ = 50/1 → 10/1) to obtain the title compound (35.6 mg, 20.9%) as a colorless solid. ESI-MS *m/z* 423 $(M+H)^+$ as $C_{18}H_{34}N_2O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{18}H_{34}N_2O_5S_2$: 423.1987, found: 423.1982; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.25-1.40 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.77-1.88 (m, 1 H), 1.95-2.09 (m, 2 H), 2.11 (s, 3 H), 2.16-2.27 (m, 1 H), 2.41 (s, 3 H), 2.97 (dd, *J* = 10.5, 4.8 Hz, 1 H), 3.21 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.33-3.41 (m, 1 H), 3.55 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.80-3.85 (m, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.20-4.30 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

### (7*R*)-7-Deoxy-7-(4-(pyrimidin-5-yl)phenylthio)lincomycin (4-36)

Compound **4-35** (35.6 mg, 84.2 μmol), 5-(4-bromophenyl)pyrimidine (23.8 mg, 0.10 mmol), Xantphos (9.70 mg, 16.8 μmol), $Pd_2(dba)_3$ (7.70 mg, 8.41 μmol), and *N,N*-diisopropylethylamine (29.4 μl, 0.17 mmol)

in 1,4-dioxane (1 ml) were treated for 6.5 h according to the similar procedure as described for the preparation of **4-1** to afford **4-36** (21.8 mg, 44.9%) as a colorless solid. $[\alpha]_D^{24}$ +142° (*c* 1.05, MeOH); ESI-MS *m/z* 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2510; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.27-1.37 (m, 4 H), 1.38 (d, *J* = 7.1 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.95-2.05 (m, 1 H), 2.08 (dd, *J* = 10.1, 8.7 Hz, 1 H), 2.14 (s, 3 H), 2.16-2.27 (m, 1 H), 2.46 (s, 3 H), 3.01 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.24 (dd, *J* = 8.4, 6.1 Hz, 1 H), 3.53 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74-3.78 (m, 1 H), 3.84 (dq, *J* = 7.1, 3.8 Hz, 1 H), 4.08 (dd, *J* = 10.2, 5.7 Hz, 1 H), 4.22 (d, *J* = 9.4 Hz, 1 H), 4.45 (dd, *J* = 9.4, 3.8 Hz, 1 H), 5.26 (d, *J* = 5.7 Hz, 1 H), 7.54-7.61 (m, 2 H), 7.65-7.72 (m, 2 H), 9.06 (s, 2 H), 9.12 (s, 1 H).

## (7*S*)-7-Deoxy-7-(4-(piperidin-3-yl)phenylthio)lincomycin (4-37)

To a solution of compound **4-17** (12.4 mg, 21.5 μmol) in MeOH (1 ml) were added 1*N* HCl (0.1 ml) and Pt black (12.8 mg). A reaction mixture was stirred at room temperature for 22 h under the hydrogen gas atmosphere. Then, Pt black (12.4 mg) was added to the solution and stirred at room temperature for 3 days under the hydrogen gas atmosphere. The mixture was filtrated with celite and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 4/1/0.1) to obtain the title compound (4.20 mg, 33.5%) as a colorless solid. $[\alpha]_D^{29}$ +97.9° (*c* 0.74, MeOH); ESI-MS *m/z* 582 $(M+H)^+$ as $C_{29}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{47}N_3O_5S_2$: 582.3035, found: 582.3028; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.99 (m, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.61-1.70 (m, 2 H), 1.77-1.90 (m, 2 H), 1.92-2.04 (m, 2 H), 1.98 (s, 3 H), 2.05-2.12 (m, 1 H), 2.12-2.23 (m, 1 H), 2.38 (s, 3 H), 2.59-2.78 (m, 3 H), 2.98 (dd, *J* = 10.6, 4.7 Hz, 1 H), 3.40-3.12 (m, 2 H), 3.24 (dd, *J* = 8.2, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.74 (br dd, *J* = 3.3, 0.5 Hz, 1 H), 3.81 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.29-4.35 (m, 1 H), 4.38 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.18-7.24 (m, 2 H), 7.35-7.41 (m, 2 H).

## (7*S*)-7-Deoxy-7-(4-(1-methylpiperidin-3-yl)phenylthio)lincomycin (4-38)

To a solution of compound **4-37** (17.9 mg, 30.8 μmol) in MeOH (1 ml) were added acetic acid (17.5 μl, 0.31 mmol), 37% aqueous formaldehyde (23.0 μl, 0.31 mmol) and sodium triacetoxyborohydride (68.2 mg, 0.31 mmol). A reaction mixture was stirred at room temperature for 40 min. and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (13.9 mg, 75.8%) as a colorless solid. $[\alpha]_D^{18}$ +91.0° (*c* 0.64, MeOH); ESI-MS *m/z* 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3177; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.31-1.39 (m, 4 H), 1.44-1.56 (m, 1 H), 1.69-1.82 (m, 1 H), 1.82-1.94 (m, 3 H), 1.95-2.05 (m, 1 H), 1.98 (s, 3 H), 2.06-2.13 (m, 1 H), 2.13-2.25 (m, 3 H), 2.39 (s, 6 H), 2.83 (tt, *J* = 11.9, 3.4 Hz, 1 H), 2.95-3.06 (m, 3 H), 3.25 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.71-3.76 (m, 1 H), 3.82 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10

(dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30-4.35 (m, 1 H), 4.39 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.20-7.25 (m, 2 H), 7.35-7.42 (m, 2 H).

### (7*S*)-7-Deoxy-7-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)phenylthio)lincomycin (4-39)

Compound **3-6** (163 mg, 0.39 mmol), 5-(4-bromophenyl)-1-methyl-1,2,3,6-tetrahydropyridine (115 mg, 0.46 mmol), Xantphos (22.8 mg, 39.4 μmol), $Pd_2(dba)_3$ (17.7 mg, 19.3 μmol), and *N,N*-diisopropylethylamine (130 μl, 0.75 mmol) in 1,4-dioxane (2.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **4-1** to afford **4-39** (176 mg, 76.8%) as a colorless solid. $[\alpha]_D^{17}$ +89.1° (*c* 1.63, MeOH); ESI-MS *m/z* 594 $(M+H)^+$ as $C_{30}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_5S_2$: 594.3035, found: 594.3039; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-0.97 (m, 3 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.80-1.91 (m, 1 H), 1.94-2.03 (m, 1 H), 1.98 (s, 3 H), 2.04-2.10 (m, 1 H), 2.11-2.22 (m, 1 H), 2.37 (s, 3 H), 2.41 (dt, *J* = 6.1, 3.0 Hz, 2 H), 2.48 (s, 3 H), 2.62-2.69 (m, 2 H), 2.98 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.22 (dd, *J* = 8.1, 5.7 Hz, 1 H), 3.33-3.38 (m, 2 H), 3.58 (dd, *J* = 10.2, 2.6 Hz, 1 H), 3.72-3.76 (m, 1 H), 3.84 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.32-4.37 (m, 1 H), 4.41 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 6.20-6.25 (m, 1 H), 7.33-7.37 (m, 2 H), 7.38-7.42 (m, 2 H).

### (2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-*n*-propylpyrrolidine-2-carboxylic acid (5-5)

To a solution of compound **5-2** (1.00 g, 2.89 mmol) in MeOH (10 ml) was added Pd/C (100 mg). A reaction mixture was vigorously stirred in hydrogen atmosphere at room temperature for 2 h, filtrated with celite and then concentrated under reduced pressure. The resulting residue was filtrated with Chromatodisc (0.45 μm) (KURABO INDUSTRIES Ltd., Osaka, Japan). The filtrated solution was concentrated under reduced pressure to obtain the title compound (745 mg, quant) as a colorless solid. FAB-MS *m/z* 258 $(M+H)^+$ as $C_{13}H_{23}NO_4$; $^1$H NMR (400 MHz, $CD_3OD$) ) $\delta$ 0.70-0.93 (m, 3 H), 1.10-1.41 (m, 13 H), 1.65-1.87 (m, 1 H), 1.93-2.06 (m, 1 H), 2.10-2.27 (m, 1 H), 2.73-2.89 (m, 1 H), 3.43-3.63 (m, 1 H), 4.00-4.25 (m, 1 H).

### (2*S*,4*R*)-2-Benzyl 1-*tert*-butyl 4-(3-hydroxypropyl)pyrrolidine-1,2-dicarboxylate (5-6)

To a solution of compound **5-2** (1.03 g, 2.98 mmol) in THF (3 ml) was added 0.5 M 9-BBN in THF solution (8.95 ml, 4.47 mmol). A reaction mixture was stirred at 50°C for 1 h. Then, 1*N* NaOH (4 ml) and 35% $H_2O_2$ (4 ml) were add to the mixture and stirred at 0°C for 2 h. The solution was added to the saturated aqueous NaCl. The desired compound was extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/2) to obtain the title compound (937 mg, 86.8%) as a colorless solid. EI-MS *m/z* 363 $(M)^+$ as $C_{20}H_{29}NO_5$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31-1.48 (m, 11 H), 1.49-1.60 (m, 2 H), 1.75-1.92 (m, 1 H), 2.05-2.14 (m, 1 H), 2.19-2.39 (m, 1 H), 2.88-3.05 (m, 1 H), 3.57-3.83 (m, 3 H), 4.25-4.50 (m, 1 H), 4.96-5.32 (m, 2 H), 7.27-7.47 (m, 5 H).

**(2*S*,4*R*)-2-Benzyl 1-*tert*-butyl 4-(3-(*tert*-butyldimethylsilyloxy)propyl)pyrrolidine-1,2-dicarboxylate (5-7)**

To a solution of compound **5-6** (2.80 g, 7.70 mmol) in DMF (15 ml) were added imidazole (1.05 g, 15.4 mmol) and TBSCl (1.74 g, 11.56 mmol). A reaction mixture was stirred at room temperature for 30 min., extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was pumped up to obtain the title compound (3.50 g, crude). The total amount of this compound was used without purification to synthesize **5-9**.

**(2*S*,4*R*)-2-Benzyl 1-*tert*-butyl 4-(3-methoxypropyl)pyrrolidine-1,2-dicarboxylate (5-8)**

To a solution of compound **5-6** (900 mg, 2.48 mmol) in DMF (9 ml) was added 55% NaH in oil (99.2 mg, 3.72 mmol). A reaction mixture was stirred at room temperature for 30 min. To the mixture was added MeI (924 μl, 14.9 mmol) and then stirred at room temperature for 1 h. The solution was added to the saturated aqueous NaCl. The desired compound was extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1 to 4/1) to obtain the title compound (240 mg, 25.7%) as a colorless oil. ESI-MS *m/z* 378 $(M+H)^+$ as $C_{21}H_{31}NO_5$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33, 1.45 (s x 2, 9 H), 1.35-1.50 (m, 2 H), 1.50-1.57 (m, 2 H), 1.75-1.91 (m, 1 H), 2.03-2.13 (m, 1 H), 2.18-2.33 (m, 1 H), 2.90-3.04 (m, 1 H), 3.31 (s, 3 H), 3.25-3.40 (m, 2 H), 3.59-3.80 (m, 1 H), 4.25-4.47 (m, 1 H), 5.03-5.29 (m, 2 H), 7.29-7.42 (m, 5 H).

**(2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-(3-(*tert*-butyldimethylsilyloxy)propyl)pyrrolidine-2-carboxylic acid (5-9)**

Compound **5-7** (3.50 g, crude) in MeOH (50 ml) were treated for 30 min according to the similar procedure as described for the preparation of **5-5** to afford **5-9** (3.02g, crude). The total amount of this compound was used to synthesize **5-46**.

**(2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-(3-methoxypropyl)pyrrolidine-2-carboxylic acid (5-10)**

Compound **5-8** (200 mg, 0.53 mmol) in MeOH (2 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-5** to afford **5-10** (152 mg, crude). The total amount of this compound was used without purification to synthesize **5-17**.

**(2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-*i*-butylpyrrolidine-2-carboxylic acid (5-11)**

Compound **5-3** (195 mg, 0.54 mmol) in MeOH (2 ml) were treated for 30 min according to the similar procedure as described for the preparation of **5-5** to afford **5-11** (141 mg, 95.7%) as an off white solid. ESI-MS *m/z* 272 $(M+H)^+$ as $C_{14}H_{25}NO_4$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90 (d, $J$ = 6.7 Hz, 3 H), 0.92 (d, $J$

= 6.7 Hz, 3 H), 1.23-1.35 (m, 2 H), 1.41, 1.45 (s x 2, 9 H), 1.51-1.64 (m, 1 H), 1.76-1.95 (m, 1 H), 2.07-2.15 (m, 1 H), 2.28-2.44 (m, 1 H), 2.85-3.00 (m, 1 H), 3.57-3.74 (m, 1 H), 4.18-4.32 (m, 1 H).

### (2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-*n*-pentylpyrrolidine-2-carboxylic acid (5-12)

Compound **5-4** (1.69 g, 4.53 mmol) in MeOH (20 ml) were treated for 2 h according to the similar procedure as described for the preparation of **5-5** to afford **5-12** (1.16 g, 89.5%) as a colorless solid. FAB-MS *m/z* 286 $(M+H)^+$ as $C_{15}H_{27}NO_4$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.80-0.98 (m, 3 H), 1.20-1.51 (m, 8 H), 1.42, 1.46 (s x 2, 9 H), 1.78-1.98 (m, 1 H), 2.10 (ddd, $J$ = 12.7, 6.2, 2.1 Hz, 1 H), 2.19-2.36 (m, 1 H), 2.85-3.01 (m, 1 H), 3.57-3.75 (m, 1 H), 4.17-4.33 (m, 1 H).

### (2*S*,4*R*)-1-*N*-(*tert*-Butoxycarbonyl)-4-((*E*)-pent-2-enyl)pyrrolidine-2-carboxylic acid (5-13)

To a solution of compound **5-4** (2.00 g, 5.79 mmol) in MeOH (20 ml) was added 1M aqueous NaOH (20 ml). A reaction mixture was stirred at room temperature for 22 h, diluted with $H_2O$-$Et_2O$ and washed by $Et_2O$. Aqueous layer was added to the saturated aqueous citric acid, extracted with ethyl acetate, and then the organic phase was washed with $H_2O$, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound (1.55 g, 94.5%) as a colorless solid. FAB-MS *m/z* 284 $(M+H)^+$ as $C_{15}H_{25}NO_4$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.89-1.05 (m, 3 H), 1.41 (s, 6 H), 1.45 (s, 3 H), 1.85-2.15 (m, 6 H), 2.23-2.39 (m, 1 H), 2.92-3.09 (m, 1 H), 3.52-3.68 (m, 1 H), 4.18-4.31 (m, 1 H), 5.30-5.44 (m, 1 H), 5.46-5.60 (m, 1 H).

### 2(*S*)-1-*N*-(*tert*-Butoxycarbonyl)-4,4-di-*n*-propylpyrrolidine-2-carboxylic acid (5-15)

Compound **5-14** (2.00 g, 5.19 mmol) in MeOH (23 ml) were treated for 4.5 h according to the similar procedure as described for the preparation of **5-5** to afford **5-15** (1.55 g, quant) as an off white oil. ESI-MS *m/z* 300 $(M+H)^+$ as $C_{16}H_{29}NO_4$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.91 (t, $J$ = 6.9 Hz, 3 H), 0.93 (t, $J$ = 6.9 Hz, 3 H), 1.17-1.48 (m, 8 H), 1.42, 1.45 (s x 2, 9 H), 1.64-1.75 (m, 1 H), 2.11-2.24 (m, 1 H), 3.10 (d, $J$ = 10.6 Hz, 1 H), 3.35-3.42 (m, 1 H), 4.01-4.25 (m, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyllincomycin (5-16)

To a solution of compound **5-5** (745 mg, 2.90 mmol) in DMF (27 ml) were added 1-hydroxybenzotriazole (469 mg, 3.47 mmol), *N,N*'-dicyclohexylcarbodiimide (717 mg, 3.47 mmol) and MTL (1.10 g, 4.34 mmol). A reaction mixture was stirred at room temperature for 15 h, added to $H_2O$ and ethyl acetate. The desired compound was extracted with ethyl acetate, and then the organic phase was washed with $H_2O$, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound. The total amount of this compound was used without purification to synthesize **5-21**. For the qualified analytical purpose, the above crude compound **5-16** was purified by column chromatography (ethyl acetate only) to obtain the title compound as a colorless solid. FAB-MS *m/z* 493 $(M+H)^+$ as $C_{22}H_{40}N_2O_8S$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.78-0.93 (m, 3 H), 1.05-1.45 (m, 7 H), 1.35, 1.38 (s x 2, 9 H), 1.59-1.81 (m, 1

H), 1.88-2.09 (m, 1 H), 1.97 (s, 3 H), 2.23-2.43 (m, 1 H), 2.83 (br t, *J* = 10.1 Hz, 1 H), 3.43-3.63 (m, 2 H), 3.64-3.82 (m, 1 H), 3.84-4.09 (m, 3 H), 4.10-4.19 (m, 1 H), 4.21-4.39 (m, 1 H), 5.14 (br d, *J* = 5.4 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-(3-methoxypropyl)lincomycin (5-17)

To a solution of compound **5-10** (152 mg, 0.53 mmol) in DMF (1.5 ml) were added 1-hydroxybenzotriazole (93.0 mg, 0.69 mmol), *N*,*N*'-dicyclohexylcarbodiimide (142 mg, 0.69 mmol) and MTL (174 mg, 0.69 mmol). A reaction mixture was stirred at room temperature for 4.5 h, added to $H_2O$ and ethyl acetate. The desired compound was extracted with ethyl acetate, and then the organic phase was washed with $H_2O$, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane / ethyl acetate = 1/1 to ethyl acetate only to ethyl acetate/MeOH = 24/1) to obtain the title compound (245 mg, 88.5% in 2 steps from **5-8**) as a colorless solid. ESI-MS *m/z* 523 $(M+H)^+$ as $C_{23}H_{42}N_2O_9S$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 1.15-1.29 (m, 3 H), 1.44, 1.46 (s x 2, 9 H), 1.36-1.66 (m, 4 H), 1.73-1.88 (m, 1 H), 2.06, 2.07 (s x 2, 3 H), 2.09-2.17 (m, 1 H), 2.33-2.50 (m, 1 H), 2.93 (br t, *J* = 9.9 Hz, 1 H), 3.32 (s, 3 H), 3.40 (t, *J* = 6.3 Hz, 2 H), 3.53-3.96 (m, 3 H), 3.98-4.18 (m, 3 H), 4.20-4.26 (m, 1 H), 4.28-4.48 (m, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-*i*-butyllincomycin (5-18)

To a solution of compound **5-11** (57.9 mg, 0.21 mmol) in DMF (1.0 ml) were added 1-hydroxybenzotriazole (43.2 mg, 0.32 mmol), *N,N*'-dicyclohexylcarbodiimide (61.4 g, 0.32 mmol) and MTL (81.1 mg, 0.32 mmol). A reaction mixture was stirred at room temperature for 1 h and then added to the saturated aqueous $NaHCO_3$ and ethyl acetate. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform/MeOH = 10/1) to obtain the title compound (100 mg, 92.7%) as a colorless solid. FAB-MS *m/z* 507 $(M+H)^+$ as $C_{23}H_{42}N_2O_8S$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 6 H), 1.16-1.32 (m, 6 H), 1.44, 1.47 (s x 2, 9 H), 1.51-1.66 (m, 1 H), 1.70-1.86 (m, 1 H), 2.05, 2.06 (s x 2, 3 H), 2.07-2.15 (m, 1 H), 2.39-2.57 (m, 1 H), 2.90 (t, *J* = 10.1 Hz, 1 H), 3.55-3.71 (m, 1 H), 3.72-3.88 (m, 1 H), 3.98-4.19 (m, 2 H), 4.23 (d, *J* = 8.8 Hz, 1 H), 4.32-4.51 (m, 1 H), 5.23 (d, *J* = 5.4 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-*n*-pentyllincomycin (5-19)

Compound **5-12** (1.16 g, 4.05 mmol), 1-hydroxybenzotriazole (820 mg, 6.07 mmol), *N,N*'-dicyclohexylcarbodiimide (1.25 g, 6.07 mmol) and MTL ( 1.54 g, 6.07 mmol) in DMF (15.0 ml) were treated for 23 h according to the similar procedure as described for the preparation of **5-16** to afford **5-19**. The total amount of this compound was used without purification to synthesize **5-24**.

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-{(*E*)-pent-2-enyl}lincomycin (5-20)

Compound **5-13** (1.55 g, 5.47 mmol), 1-hydroxybenzotriazole (1.11 g, 8.21 mmol), *N*,*N*'-dicyclohexylcarbodiimide (1.69 g, 8.21 mmol) and MTL (2.08 mg, 8.21 mmol) in DMF (23 ml) were treated for 3 h according to the similar procedure as described for the preparation of **5-16** to afford **5-20**. The total amount of this compound was used without purification to synthesize **5-25**.

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-21)

To a solution of compound **5-16** (crude) in pyridine (15 ml) were added trimethylchlorosilane (1.85 ml, 14.5 mmol) and hexamethyldisilazane (3.03 ml, 14.5 mmol). A reaction mixture was stirred at room temperature for 30 min and added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, washed with $H_2O$ and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. To the resulting residue were added methanol (16.4 ml) and 6 *N* acetic acid (0.87 ml), and stirred at room temperature for 11 h. The mixture was added to the saturated aqueous $NaHCO_3$ and concentrated under reduced pressure to remove MeOH. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/2) to obtain the title compound (1.45 g, 70.6% in 3 steps from **5-5**) as a colorless solid. ESI-MS *m/z* 709 $(M+H)^+$ as $C_{31}H_{64}N_2O_8SSi_3$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.12-0.26 (m, 27 H), 0.85-1.00 (m, 3 H), 1.07-1.25 (m, 3 H), 1.26-1.41 (m, 4 H), 1.44, 1.46 (s x 2, 9 H), 1.66-1.93 (m, 1 H), 2.03, 2.05 (s x 2, 3 H), 1.98-2.42 (m, 2 H), 2.88-3.02 (m, 1 H), 3.54-4.40 (m, 8 H), 5.18 (d, $J$ = 5.4 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-(3-methoxypropyl)-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-22)

Compound **5-17** (290 mg, 0.56 mmol), trimethylchlorosilane (355 μl, 2.77 mmol) and hexamethyldisilazane (581 μl, 2.77 mmol) in pyridine (1.0 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (167 μl) in methanol (3.1 ml) were treated for 30 min according to the similar procedure as described for the preparation of **5-21** to afford **5-22** (282 mg, 68.7% in 2 steps from **5-17**) as a colorless solid. ESI-MS *m/z* 739 $(M+H)^+$ as $C_{32}H_{66}N_2O_9SSi_3$

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-*i*-butyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-23)

Compound **5-18** (652 mg, 1.63 mmol), trimethylchlorosilane (1.02 ml, 8.02 mmol) and hexamethyldisilazane (1.68 ml, 8.02 mmol) in pyridine (3.5 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (480 μl) in methanol (9 ml) were treated for 30 min according to the similar procedure as described for the

preparation of **5-21** to afford **5-23** (946 mg, 79.8% in 2 steps from **5-18**) as a colorless solid. FAB-MS *m/z* 723 $(M+H)^+$ as $C_{32}H_{66}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.11-0.21 (m, 27 H), 0.90 (d, *J* = 6.6 Hz, 6 H), 1.05-1.33 (m, 5 H), 1.49 (s, 9 H), 1.50-1.61 (m, 2 H), 2.07 (s, 3 H), 2.13-2.57 (m, 1 H), 2.72-3.13 (m, 1 H), 3.40-3.82 (m, 3 H), 3.94-4.19 (m, 3 H), 4.22-4.40 (m, 2 H), 5.19 (d, *J* = 5.6 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-*n*-pentyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-24)

Compound **5-19** (crude), trimethylchlorosilane (2.60 ml, 20.3 mmol) and hexamethyldisilazane (4.24 ml, 20.3 mmol) in pyridine (10.0 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (1.21 ml) in methanol (23 ml) were treated for 2 h according to the similar procedure as described for the preparation of **5-21** to afford **5-24** (2.21 g, 74.0% in 3 steps from **5-12**) as a colorless solid. FAB-MS *m/z* 737 $(M+H)^+$ as $C_{33}H_{68}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.07-0.25 (m, 27 H), 0.78-0.97 (m, 3 H), 1.05-1.42 (m, 11 H), 1.48 (s, 9 H), 2.07 (s, 3 H), 2.10-3.20 (m, 4 H), 3.40-3.90 (m, 3 H), 3.92-4.20 (m, 3 H), 4.23-4.47 (m, 2 H), 5.19 (br d, *J* = 5.4 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-{(*E*)-pent-2-enyl}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-25)

Compound **5-20** (crude), trimethylchlorosilane (3.50 ml, 27.4 mmol) and hexamethyldisilazane (5.70 ml, 27.4 mmol) in pyridine (10 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (1.64 ml) in methanol (31 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** to afford **5-25** (3.29 g, 81.8% in 3 steps from **5-13**) as a colorless solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.02-0.28 (m, 27 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 1.08-1.25 (m, 3 H), 1.48 (s, 9 H), 1.89-2.51 (m, 6 H), 2.02 (s, 3 H), 2.66-3.26 (m, 2 H), 3.40-3.64 (m, 2 H), 3.68-4.19 (m, 4 H), 4.22-4.50 (m, 2 H), 5.19 (br d, *J* = 5.1 Hz, 1 H), 5.26-5.39 (m, 1 H), 5.43-5.59 (m, 1 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-29)

To a solution of compound **5-21** (200 mg, 0.28 mmol) in THF (2 ml) at 0˚C were added triphenylphosphine (111 mg, 0.42 mmol), diethylazodicarboxylate (77 μl, 0.42 mmol), 5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazole-2-thiol (101 mg, 0.44 mmol). A reaction mixture was stirred at room temperature for 18 h and then purified by preparative TLC (hexane/ethyl acetate = 2/1) to obtain the title compound as an off white solid (88.8 mg, 34.2%). FAB-MS *m/z* 921 $(M+H)^+$ as $C_{37}H_{68}N_6O_7S_4Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.00-0.25 (m, 27 H), 0.80-1.00 (m, 3 H), 1.08-1.67 (m, 16 H), 1.74-2.99 (m, 7 H), 3.02-3.22 (m, 3 H), 3.43-3.90 (m, 3 H), 3.98-4.50 (m, 4 H), 4.60-4.94 (m, 1 H), 5.20

(br d, *J* = 5.4 Hz, 1 H), 7.85-8.00 (br s, 1 H).

### (7*S*)-7-(6-Aminobenzothiazol-2-ylthio)-7-deoxy-1'-demethyllincomycin (5-30)

To a solution of compound **5-21** (200 mg, 0.28 mmol) in THF (2 ml) at 0˚C were added triphenylphosphine (111 mg, 0.42 mmol), diethylazodicarboxylate (77 μl, 0.42 mmol), 6-aminobenzothiazole-2-thiol (79.7 mg, 0.44 mmol). A reaction mixture was stirred at room temperature for 4 h. To the solution was added 1*N* HCl (1 ml)-MeOH (1 ml), stirred at room temperature for 30 min. The solution was added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain (7*S*)-7-(6-aminobenzothiazol-2-yl)thio-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-2,3,4-tris-*O*-(trimet hylsilyl)lincomycin (197 mg, crude).

To the solution of this intermediate in MeOH (2 ml) was added 4*N* HCl-ethyl acetate (2.5 ml). A reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (96.4 mg, 61.4% in 3 steps from **5-21**) as an off white solid. $[\alpha]_D^{26}$ +92.1° (*c* 2.49, MeOH); ESI-MS *m/z* 557 $(M+H)^+$ as $C_{24}H_{36}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{36}N_4O_5S_3$: 557.1926, found: 557.1920; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.96 (m, 3 H), 1.25-1.40 (m, 4 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 1.69-1.82 (m, 1 H), 1.93 (s, 3 H), 1.96-2.13 (m, 2 H), 2.52 (dd, *J* = 10.4, 8.1 Hz, 1 H), 3.20 (dd, *J* = 10.4, 6.9 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80-3.87 (m, 2 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.27 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.39 (br dd, *J* = 10.0, 0.9 Hz, 1 H), 4.57 (dd, *J* = 10.0, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.08 (d, *J* = 2.1 Hz, 1 H), 7.59 (d, *J* = 8.7 Hz, 1 H).

### (7*S*)-7-(5-Amino-1,3,4-thiadiazol-2-ylthio)-7-deoxy-1'-demethyllincomycin (5-31)

To a solution of compound **5-21** (200 mg, 0.28 mmol) in THF (2 ml) at 0˚C were added triphenylphosphine (138 mg, 0.53 mmol), diethylazodicarboxylate (96 μl, 0.53 mmol), 5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazole-2-thiol (127 mg, 0.54 mmol). A reaction mixture was stirred at room temperature for 3 h. To the solution was added 1*N* HCl (1 ml)-MeOH (1 ml), stirred at room temperature for 50 min. The solution was added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain (7*S*)-7-[5-{(*tert*-butoxycarbonyl)amino}-1,3,4-thiadiazol-2-ylthio]-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7 -deoxylincomycin as a colorless solid (147 mg, 73.4%). $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.98 (m, 3 H), 1.25-1.60 (m, 25 H), 1.80-1.97 (m, 1 H), 1.98-2.17 (m, 1 H), 2.06, 2.10 (s x 2, 3 H), 2.22-2.40 (m, 1 H),

2.89-3.05 (m, 1 H), 3.50-3.60 (m, 1 H), 3.69-3.82 (m, 1 H), 3.84-4.00 (m, 1 H), 4.02-4.20 (m, 2 H), 4.26-4.42 (m, 2 H), 4.45-4.60 (m, 1 H), 5.27 (br d, $J$ = 5.4 Hz, 1 H).

To the solution of this intermediate (146.6 mg, 0.21 mmol) in MeOH (1.4 ml) was added 4*N* HCl-ethyl acetate (1.7 ml), stirred at room temperature for 2 h. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (25.4 mg, 24.2%) as a colorless solid. $[\alpha]_D^{25}$ +101° (*c* 0.33, MeOH); ESI-MS *m/z* 508 $(M+H)^+$ as $C_{19}H_{33}N_5O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{19}H_{33}N_5O_5S_3$: 508.1722, found: 508.1719; $^1$H NMR (400 MHz,$CD_3OD$) $\delta$ 0.89-0.98 (m, 3 H), 1.33-1.45 (m, 4 H), 1.37 (d, $J$ = 7.0 Hz, 3 H), 1.84-1.95 (m, 1 H), 2.03-2.18 (m, 2 H), 2.11 (s, 3 H), 2.66 (dd, $J$ = 10.6, 8.3 Hz, 1 H), 3.30-3.36 (m, 1 H), 3.56 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.81 (br dd, $J$ = 3.2, 0.7 Hz, 1 H), 3.96 (dq, $J$ = 7.0, 2.6 Hz, 1 H), 4.00 (dd, $J$ = 9.3, 4.0 Hz, 1 H), 4.09 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.37 (br dd, $J$ = 10.0, 0.7 Hz, 1 H), 4.52 (dd, $J$ = 10.0, 2.6 Hz, 1 H), 5.27 (d, $J$ = 5.6 Hz, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-32)

To a solution of compound **5-21** (200 mg, 0.28 mmol) in THF (2 ml) at 0˚C were added triphenylphosphine (111 mg, 0.42 mmol), diethylazodicarboxylate (77 µl, 0.42 mmol), 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (105 mg, 0.44 mmol). A reaction mixture was stirred at room temperature for 7 h and added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. To the resulting residue was added MeOH (4 ml)-1*N* HCl (1 ml) and stirred at room temperature for 2.5 h. The solution was added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (165 mg as crude). To the solution of this crude compound (63.9 mg) in MeOH (0.6 ml) was added 4*N* HCl-ethyl acetate (0.75 ml). A reaction mixture was stirred at room temperature for 2.5 h and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (13.0 mg, 19.4% in 3 steps from **5-21**) as a colorless solid. $[\alpha]_D^{26}$ +37.1° (*c* 0.21, MeOH); ESI-MS *m/z* 614 $(M+H)^+$ as $C_{25}H_{35}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{35}N_5O_7S_3$: 614.1777, found: 614.1778; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.83-0.99 (m, 3 H), 1.30-1.45 (m, 4 H), 1.56 (d, $J$ = 7.0 Hz, 3 H), 1.88-1.98 (m, 1 H), 1.99 (s, 3 H), 2.07-2.25 (m, 2 H), 2.69 (br dd, $J$ = 10.6, 8.4 Hz, 1 H), 3.32-3.42 (m, 1 H), 3.56 (dd, $J$ = 10.2, 3.2 Hz, 1 H), 3.82-3.88 (m, 1 H), 4.00-4.10 (m, 1 H), 4.10 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.36-4.46 (m, 1 H), 4.47 (dq, $J$ = 7.0, 2.5 Hz, 1 H), 4.66 (dd, $J$ = 10.0, 2.5 Hz, 1 H), 5.28 (d, $J$ = 5.6 Hz, 1 H), 7.74-7.87 (m, 3 H), 8.05-8.15 (m, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (5-33)

To the solution of compound **5-29** (88.8 mg 96.4 μmol) in MeOH (0.5 ml) was added 4*N* HCl-ethyl acetate (0.79 ml). A reaction mixture was stirred at 0°C for 1 h and then stirred at room temperature for 3.5 h. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (39.8 mg, 68.3%) as an off white solid. $[\alpha]_D^{26}$ +69.5° (*c* 0.60, MeOH); ESI-MS *m/z* 605 $(M+H)^+$ as $C_{23}H_{36}N_6O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{23}H_{36}N_6O_5S_4$: 605.1708, found: 605.1706; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.95 (m, 3 H), 1.29-1.41 (m, 4 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 1.78-1.87 (m, 1 H), 1.98 -2.14 (m, 2 H), 2.01 (s, 3 H), 2.56 (dd, *J* = 10.5, 8.1 Hz, 1 H), 3.11 (s, 3 H), 3.25 (dd, *J* = 10.5, 7.0 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 3.86 (dd, *J* = 9.2, 3.9 Hz, 1 H), 4.09 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.27 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.39 (br dd, *J* = 10.0, 0.9 Hz, 1 H), 4.59 (dd, *J* = 10.0, 2.7 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 8.12 (s, 1 H).

## (7*S*)-7-Deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (5-34)

Compound **2-1** (240 mg, 0.39 mmol), triphenylphosphine (150 mg, 0.57 mmol), diethylazodicarboxylate (100 μl, 0.64 mmol) and 5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazole-2-thiol (150 mg, 0.65 mmol) in THF (5 ml) were treated for 2 h, and then, to the solution was added 1*N* HCl (0.5 ml)-MeOH (5 ml), stirred at room temperature for 1 h. To the solution was added to the saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound **5-34** (88.2 mg, 37.0% in 2 steps) as an off white solid. $[\alpha]_D^{26}$ +125° (*c* 0.89, MeOH); ESI-MS *m/z* 619 $(M+H)^+$ as $C_{24}H_{38}N_6O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{38}N_6O_5S_4$: 619.1865, found: 619.1860; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.82-0.98 (m, 3 H), 1.21-1.39 (m, 4 H), 1.53 (d, *J* = 6.9 Hz, 3 H), 1.78-1.89 (m, 1 H), 1.92-2.08 (m, 2 H), 2.02 (s, 3 H), 2.09-2.25 (m, 1 H), 2.35 (s, 3 H), 3.00 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.13 (s, 3 H), 3.19 (dd, *J* = 8.5, 6.2 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.77-3.85 (m, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.27 (dq, *J* = 6.9, 3.0 Hz, 1 H), 4.44 (br dd, *J* = 9.8, 0.5 Hz, 1 H), 4.57 (dd, *J* = 9.8, 3.0 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 8.13 (s, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl}thio-1'-*N*-*i*-propyllincomycin (5-35)

To a solution of compound **5-32** (30.5 mg, 49.8 μmol) in 1,2-dichloroethane (1 ml) at 0°C were added acetone (40 μl, 0.54 mmol), AcOH (one drop) and $NaBH(OAc)_3$ (21.7 mg, 0.10 mmol). A reaction mixture was stirred at room temperature for15 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) and then LH-20 ($CHCl_3$/MeOH =

1/1) to obtain the title compound (20.1 mg, 61.7%) as a colorless solid. $[\alpha]_D^{26}$ +76.8° (*c* 0.59, MeOH); ESI-MS *m/z* 656 $(M+H)^+$ as $C_{28}H_{41}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_5O_7S_3$: 656.2246, found: 656.2243; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.98 (m, 3 H), 1.06-1.16 (m, 6 H), 1.28-1.42 (m, 4 H), 1.58 (d, *J* = 6.9 Hz, 3 H), 1.69-1.81 (m, 1 H), 1.99 (s, 3 H), 1.97-2.07 (m, 1 H), 2.07-2.20 (m, 1 H), 2.20-2.31 (m, 1 H), 2.76-2.90 (m, 1 H), 3.26-3.34 (m, 1 H), 3.39-3.52 (m, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.3, 0.8 Hz, 1 H), 4.51 (dq, *J* = 6.9, 3.4 Hz, 1 H), 4.59 (dd, *J* = 9.3, 3.4 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.74-7.86 (m, 3 H), 8.06-8.12 (m, 1 H).

### (7*S*)-1'-*N*-{2-(*tert*-Butyldimethylsilyloxy)ethyl}-1'-demethyl-7-deoxy-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-36)

Compound **5-32** (49.2 mg, 80.2 μmol), 2-(*tert*-butyldimethylsilyloxy)acetaldehyde (23 μl, 0.12 mmol), AcOH (one drop) and $NaBH(OAc)_3$ (34.2 mg, 0.16 mmol) in 1,2-dichloroethane (1 ml) were treated at 0°C for 15 h according to the similar procedure as described for the preparation of **5-35** to afford **5-36** (26.9 mg, 44.0%) as a colorless solid. FAB-MS *m/z* 772 $(M+H)^+$ as $C_{33}H_{53}N_5O_8S_3Si$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.82-0.98 (m, 12 H), 1.25-1.42 (m, 4 H), 1.59 (d, *J* = 6.8 Hz, 1 H), 1.68-1.87 (m, 1 H), 1.94-2.05 (m, 1 H), 1.97 (s, 3 H), 2.07-2.21 (m, 2 H), 2.54-2.92 (m, 2 H), 3.37-3.44 (m, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.71-3.92 (m, 4 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.35-4.44 (m, 1 H), 4.47-4.56 (m, 1 H), 4.58-4.65 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.74-7.86 (m, 3 H), 8.06-8.13 (m, 1 H).

### (7*S*)-1'-Demethyl-7-deoxy-1'-*N*-(2-hydroxyethyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-37)

To a solution of compound **5-36** (26.9 mg, 34.8 μmol) in THF (0.5 ml) at 0°C was added 1 M THF solution of *tetra*-*n*-butyl ammonium fluoride (100 μl, 0.10 mmol). A reaction mixture was stirred at room temperature for 15 h and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (16.5 mg, 72.1%) as a colorless solid. $[\alpha]_D^{25}$ +70.5° (*c* 0.22, MeOH); ESI-MS *m/z* 658 $(M+H)^+$ as $C_{27}H_{39}N_5O_8S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{39}N_5O_8S_3$: 658.2039, found: 658.2044; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.29-1.43 (m, 4 H), 1.60 (d, *J* = 6.9 Hz, 3 H), 1.79-1.93 (m, 1 H), 1.99 (s, 3 H), 2.02-2.10 (m, 1 H), 2.10-2.23 (m, 2 H), 2.64-2.75 (m, 1 H), 2.83-2.96 (m, 1 H), 3.31-3.40 (m, 1 H), 3.40-3.50 (m, 1 H), 3.56 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.63-3.77 (m, 2 H), 3.83 (dd, *J* = 3.2, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.45 (br dd, *J* = 9.9, 0.8 Hz, 1 H), 4.51 (dq, *J* = 6.9, 2.9 Hz, 1 H), 4.63 (dd, *J* = 9.9, 2.9 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.74-7.86 (m, 3 H), 8.06-8.12 (m, 1 H).

## (7*S*)-1'-*N*-{2-(*tert*-Butyldimethylsilyloxy)ethyl}-1'-demethyl-7-deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (**5-38**)

Compound **5-33** (74.3 mg, 0.12 mmol), 2-(*tert*-butyldimethylsilyloxy)acetaldehyde (34 μl, 0.18 mmol), AcOH (one drop) and $NaBH(OAc)_3$ (51.0 mg, 0.24 mmol) in 1,2-dichloroethane (1 ml) were treated at room temperature for 15 h according to the similar procedure as described for the preparation of **5-36** to afford **5-38** (54.8 mg, 58.5%) as a colorless solid. FAB-MS *m/z* 763 $(M+H)^+$ as $C_{31}H_{54}N_6O_6S_4Si$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.78-1.00 (m, 12 H), 1.23-1.42 (m, 4 H), 1.54 (d, *J* = 7.1 Hz, 3 H), 1.72-1.86 (m, 1 H), 1.92-2.05 (m, 1 H), 1.99 (s, 3 H), 2.08-2.22 (m, 2 H), 2.50-2.87 (m, 2 H), 3.12 (s, 3 H), 3.25-3.30 (m, 1 H), 3.36-3.44 (m, 1 H), 3.52-3.60 (m, 1 H), 3.68-3.88 (m, 3 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30-4.44 (m, 2 H), 4.54-4.62 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 8.13 (s, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-1'-*N*-(2-hydroxylethyl)-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (**5-39**)

Compound **5-38** (54.8 mg, 71.9 μmol) and 1 M THF solution of *tetra-n*-butyl ammonium fluoride (200 μl, 0.20 mmol) in THF (1 ml) were treated at 0°C for 1 h and then treated at room temperature for 5 h according to the similar procedure as described for the preparation of **5-37** to afford **5-39** (31.3 mg, 67.0%) as a colorless solid. $[\alpha]_D^{25}$ +51.1° (*c* 0.27, MeOH); ESI-MS *m/z* 649 $(M+H)^+$ as $C_{25}H_{40}N_6O_6S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{40}N_6O_6S_4$: 649.1970, found: 649.1973; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.96 (m, 3 H), 1.30-1.40 (m, 4 H), 1.54 (d, *J* = 6.9 Hz, 3 H), 1.79-1.90 (m, 1 H), 1.97-2.08 (m, 1 H), 2.00 (s, 3 H), 2.09-2.21 (m, 2 H), 2.62-2.72 (m, 1 H), 2.83-2.93 (m, 1 H), 3.11 (s, 3 H), 3.30-3.37 (m, 1 H), 3.39-3.45 (m, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.65-3.74 (m, 2 H), 3.81 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.33 (dq, *J* = 6.9, 2.8 Hz, 1 H), 4.43 (br dd, *J* = 9.8, 0.8 Hz, 1 H), 4.59 (dd, *J* = 9.8, 2.8 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 8.11 (s, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-1'-*N*-{2(*R*)-hydroxypropyl}-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (**5-40**)

To a solution of compound **5-33** (28.7 mg, 47.5 μmol) and *N,N*-diisopropylethylamine (10.0 μl, 57.4 μmol) in MeOH (1 ml) at 0°C was added (*R*)-2-methyloxirane (0.30 ml, 4.29 mmol). A reaction mixture was stirred at 0°C for 96 h and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (10.6 mg, 33.7%) as a colorless solid. $[\alpha]_D^{26}$ +29.2° (*c* 0.15, MeOH); ESI-MS *m/z* 663 $(M+H)^+$ as $C_{26}H_{42}N_6O_6S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{42}N_6O_6S_4$: 663.2127, found: 663.2127; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.96 (m, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.27-1.42 (m, 4 H), 1.55 (d, *J* = 6.9 Hz, 1 H), 1.78-1.87 (m, 1 H), 1.98-2.27 (m, 3 H), 1.99 (s, 3 H), 2.43-2.55 (m, 1 H), 2.56-2.66 (m, 1 H), 3.11 (s, 3 H), 3.39-3.46 (m, 1 H), 3.55 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 3.86-3.97 (m, 1 H), 4.10 (dd, *J* = 10.3, 5.7 Hz, 1 H), 4.33 (dq, *J* = 6.9, 2.9 Hz, 1 H), 4.42-4.48 (m, 1 H), 4.52-4.59 (m, 1 H), 4.61

(dd, *J* = 9.9, 2.9 Hz, 1 H), 5.25 (d, *J* = 5.7 Hz, 1 H), 8.11 (s, 1 H).

### (7*S*)-1'-*N*-Acetyl-1'-demethyl-7-deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]lincomycin (5-41)

To a solution of compound **5-33** (30.2 mg, 50.0 μmol) in MeOH (0.5 ml) at 0°C was added acetic anhydride (7.0 μl, 74.1 μmol). A reaction mixture was stirred at 0°C for 1.5 h and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (10.8 mg, 33.4%) as an off white solid. $[\alpha]_D^{25}$ +56.5° (*c* 1.25, MeOH); ESI-MS *m/z* 647 $(M+H)^+$ as $C_{25}H_{38}N_6O_6S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{38}N_6O_6S_4$: 647.1814, found: 647.1807; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.98 (m, 3 H), 1.25-1.42 (m, 4 H), 1.49 (d, *J* = 7.0 Hz, 3 H), 1.82-1.95 (m, 1 H), 1.98 (s, 3 H), 2.01-2.08 (m, 1 H), 2.09 (s, 3 H), 2.35-2.50 (m, 1 H), 3.12 (s, 3 H), 3.14-3.20 (m, 1 H), 3.56 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.79-3.87 (m, 1 H), 3.99 (br dd, *J* = 3.3, 1.0 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.27 (dq, *J* = 7.0, 2.4 Hz, 1 H), 4.36-4.43 (m, 1 H), 4.48 (dd, *J* = 8.8, 2.7 Hz, 1 H), 4.61 (dd, *J* = 10.0, 2.4 Hz, 1 H), 8.12 (s, 1 H).

### (7*S*)-1'-Demethyl-7-deoxy-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]-1'-*N*-(4-methylthiazol-5-ylmethyl)lincomycin (5-42)

Compound **5-33** (24.0 mg, 39.7 μmol), 4-methylthiazole-5-carbaldehyde (16.2 mg, 0.13 mmol), AcOH (one drop) and $NaBH(OAc)_3$ (25.5 mg, 0.12 mmol) in MeOH (0.5 ml) were treated at room temperature for 15 h according to the similar procedure as described for the preparation of **5-35** to afford **5-42** (6.4 mg, 22.5%) as a colorless solid. $[\alpha]_D^{26}$ +26° (*c* 0.05, MeOH); ESI-MS *m/z* 716 $(M+H)^+$ as $C_{28}H_{41}N_7O_5S_5$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_7O_5S_5$: 716.1851, found: 716.1854; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.75-0.86 (m, 3 H), 1.15-1.26 (m, 4 H), 1.42 (d, *J* = 6.8 Hz, 3 H), 1.68-1.78 (m, 1 H), 1.89-2.15 (m, 3 H), 1.94 (s, 3 H), 2.27 (s, 3 H), 3.00 (s, 3 H), 3.09 (dd, *J* = 8.2, 6.2 Hz, 1 H), 3.24-3.31 (m, 1 H), 3.50 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.72 (d, *J* = 14.3 Hz, 1 H), 3.79 (br dd, *J* = 3.2, 1.0 Hz, 1 H), 3.85 (d, *J* = 14.3 Hz, 1 H), 4.01 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.13-4.21 (m, 1 H), 4.28-4.34 (m, 1 H), 4.44 (dd, *J* = 8.8, 4.6 Hz, 1 H), 5.16 (d, *J* = 5.5 Hz, 1 H), 8.03 (s, 1 H), 8.69 (s, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-propyllincomycin (5-43)

Compound **5-15** (1.55 g, 5.19 mmol), 1-hydroxybenzotriazole (1.05 g, 7.78 mmol), *N*,*N*'-dicyclohexylcarbodiimide (1.61 g, 7.78 mmol) and MTL ( 1.97 g, 7.78 mmol) in DMF (15 ml) were treated for 14 h according to the similar procedure as described for the preparation of **5-16** to afford **5-43**. The total amount of this compound was used without purification to synthesize **5-44**. For the qualified analytical purpose, the above crude **5-43** was purified by column chromatography (ethyl acetate only) to obtain the title compound as a colorless solid. ESI-MS *m/z* 535 $(M+H)^+$ as $C_{25}H_{46}N_2O_8S$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.76-0.90 (m, 6 H), 1.04-1.32 (m, 11 H), 1.35, 1.36 (s x 2, 9 H), 1.57-1.72 (m, 1 H), 1.97,

1.99 (s x 2, 3 H), 2.00-2.15 (m, 1 H), 3.03 (br t, *J* = 10.4 Hz, 1 H), 3.29-3.56 (m, 2 H), 3.67-3.90 (m, 1 H), 3.91-4.36 (m, 5 H), 5.15 (br d, *J* = 5.4 Hz, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-propyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-44)

Compound **5-43** (crude), trimethylchlorosilane (3.32 ml, 25.9 mmol) and hexamethyldisilazane (5.44 ml, 25.9 mmol) in pyridine (5.0 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (1.55 ml) in methanol (29.4 ml) were treated for 1 h according to the similar procedure as described for the preparation of **5-21** to afford **5-44** (1.66 g, 41.6% in 3 steps from **5-15**) as a colorless solid. ESI-MS *m/z* 751 $(M+H)^+$ as $C_{34}H_{70}N_2O_8SSi_3$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.14 (s, 18 H), 0.18 (s, 9 H), 0.82-0.98 (m, 6 H), 1.08-1.35 (m, 11 H), 1.46 (s, 9 H), 1.80-2.35 (m, 1 H), 2.06 (s, 3 H), 2.66-3.30 (m, 2 H), 3.36-4.41 (m, 8 H), 5.13-5.24 (m, 1 H).

### (7*S*)-1'-Demethyl-7-deoxy-4'-*n*-propyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-45)

To a solution of compound **5-44** (400 mg, 0.53 mmol) in THF (4 ml) at 0˚C were added triphenylphosphine (210 mg, 0.80 mmol), diethylazodicarboxylate (0.15 ml, 0.80 mmol), 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (297 mg, 1.24 mmol). A reaction mixture was stirred at room temperature for 6 h and then purified by preparative TLC (hexane/ethyl acetate = 2/1) to obtain (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-*n*-propyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl thio}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (235 mg with inseparable impurity). To this crude compound (235 mg, 0.24 mmol) was added 2,2,2-trifluoroacetic acid (1 ml) at 0ºC, stirred at room temperature for 30 min. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (57.3 mg, 36.1% in 2 steps from **5-44**) as a colorless solid. $[\alpha]_D^{26}$ +91.0° (*c* 0.40, MeOH); ESI-MS *m/z* 656 $(M+H)^+$ as $C_{28}H_{41}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_5O_7S_3$: 656.2246, found: 656.2239; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 6 H), 1.22-1.42 (m, 8 H), 1.56 (d, *J* = 6.8 Hz, 3 H), 1.63 (dd, *J* = 13.0, 8.2 Hz, 1 H), 2.00 (s, 3 H), 2.11-2.19 (m, 1 H), 2.79-2.88 (m, 2 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.80-3.86 (m, 1 H), 3.93 (t, *J* = 8.4 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.38-4.43 (m, 1 H), 4.45 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.64 (dd, *J* = 10.0, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.75-7.86 (m, 3 H), 8.07-8.13 (m, 1 H).

### 1'-*N*-(*tert*-Butoxycarbonyl)-4'-{3-(*tert*-butyldimethylsilyloxy)propyl}-1'-demethyl-4'-deprop yllincomycin (5-46)

Compound **5-9** (3.02, crude), 1-hydroxybenzotriazole (1.35 g, 10.0 mmol), *N*,*N*'-dicyclohexylcarbodiimide (2.07 g, 10.0 mmol) and MTL (2.54 g, 10.0 mmol) in DMF (15.0 ml) were

treated for 13 h according to the similar procedure as described for the preparation of **5-17** to afford **5-46** (3.0 g, 62.5% in 3 steps from **5-6**) as a colorless solid. ESI-MS *m/z* 623 $(M+H)^+$ as $C_{28}H_{54}N_2O_9SSi$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.15-1.27 (m, 3 H), 1.37-1.64 (m, 4 H), 1.44, 1.47 (s x 2, 9 H), 1.74-1.91 (m, 1 H), 2.06, 2.07 (s x 2, 3 H), 2.09-2.18 (m, 1 H), 2.30-2.45 (m, 1 H), 2.94 (br t, *J* = 10.0 Hz, 1 H), 3.53-3.72 (m, 4 H), 3.74-3.93 (m, 1 H), 3.98-4.17 (m, 3 H), 4.24 (br dd, *J* = 8.9, 1.3 Hz, 1 H), 4.27-4.46 (m, 1 H), 5.24 (d, *J* = 5.4 Hz, 1 H).

## 1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-4'-depropyl-4'-{3-(*tert*-butyldimethylsilyloxy)propyl}- 2,3,4-tris-*O*-(trimethylsilyl)lincomycin (5-47)

Compound **5-46** (3.00 g, 4.82 mmol), trimethylchlorosilane (3.08 ml, 24.1 mmol) and hexamethyldisilazane (5.05 ml, 24.1 mmol) in pyridine (10 ml) were treated for 20 min according to the similar procedure as described for the preparation of **5-21** and then, the crude compound and 6 *N* acetic acid (1.45 ml) in methanol (27 ml) were treated for 80 min according to the similar procedure as described for the preparation of **5-21** to afford **5-47** (3.02 g, 74.8% in 2 steps from **5-46**) as a colorless solid. ESI-MS *m/z* 839 $(M+H)^+$ as $C_{37}H_{78}N_2O_9SSi_4$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.04 (s, 6 H), 0.07-0.20 (m, 27 H), 0.89 (s, 9 H), 1.05-1.22 (m, 3 H), 1.35-1.90 (m, 5 H), 1.48 (s, 9 H), 2.07 (s, 3 H), 2.11-3.25 (m, 3 H), 3.44-3.66 (m, 4 H), 3.70-3.89 (m, 1 H), 3.91-4.18 (m, 3 H), 4.19-4.42 (m, 2 H), 5.19 (br d, *J* = 5.6 Hz, 1 H).

## (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-4'-(3-hydroxypropyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-48)

To a solution of compound **5-47** (2.87 g, 3.41 mmol) in THF (15 ml) at 0˚C were added triphenylphosphine (1.34 g, 5.12 mmol), diethylazodicarboxylate (932 µl, 5.12 mmol) and 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (1.26 g, 5.29 mmol). A reaction mixture was stirred at room temperature for 10 h, substituted by toluene and then purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 4/1) to obtain 1'-*N*-(*tert*-butoxycarbonyl)-4'-{3-(*tert*-butyldimethylsilyloxy)propyl}-1'-demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (2.62 g, crude). To this crude compound (2.62 g) was added 1 M THF solution of *tetra*-*n*-butyl ammonium fluoride (14.8 ml, 14.8 mmol) and acetic acid (0.848 ml, 14.8 mmol), stirred at room temperature for 5 h. The mixture was diluted with brine and ethyl acetate, extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1 to ethyl acetate only to ethyl acetate/MeOH = 10/1) to obtain the title compound (1.74 g with inseparable impurity (96.7% in 2 steps a)). FAB-MS *m/z* 752 $(M+Na)^+$ as $C_{30}H_{43}N_5O_{10}S_3$

## (7*S*)-4'-(3-Aminopropyl)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (**5-49**)

To a solution of compound **5-48** (500 mg, 0.69 mmol), sodium azide (223 mg, 3.43 mmol) and triphenylphosphine (359 mg, 1.37 mmol) in DMF (7 ml) was added tetrabromomethane (454 mg, 1.37 mmol). A reaction mixture was stirred at 50°C for 2 h, diluted with brine and ethyl acetate, extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform/MeOH = 10/1) to obtain (7*S*)-4'-(3-azidopropyl)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (468 mg with inseparable impurity (91% as reference yield)). To a solution of this crude compound (239 mg, 0.32 mmol) in THF (3 ml) was added triphenylphosphine (249 mg, 0.95 mmol). A reaction mixture was stirred at room temperature for 1 h, and then added $H_2O$, stirred at 50°C for 2 h. The mixture was diluted with brine, ethyl acetate and 1*N* HCl (400 µl), washed with ethyl acetate, and then the aqueous phase was added to the saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound (229 mg with inseparable impurity (99% )).

## (7*S*)-1'-Demethyl-7-deoxy-4'-depropyl-4'-(3-dimethylaminopropyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (**5-50**)

Compound **5-49** (69.0 mg, 92.6 µmol), 36% aqueous formaldehyde (23.1 µl, 0.28 mmol), AcOH (79.5 µl, 1.39 mmol) and $NaBH(OAc)_3$ (294 mg, 1.39 mmol) in MeOH (1 ml) were treated at room temperature for 20 min according to the similar procedure as described for the preparation of **5-35** to afford (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-4'-(3-dimethylaminopropyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (75.0 mg, crude). To this crude compound (75.0 mg) was added 2,2,2-trifluoroacetic acid (1 ml) at 0°C. A reaction mixture was stirred at room temperature for 30 min., and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/4/0.4) to obtain the title compound (35.0 mg, 57.6% in 2 steps from **5-49**) as a colorless solid. $[\alpha]_D^{25}$ +83.7° (*c* 0.45, MeOH); ESI-MS *m/z* 657 $(M+H)^+$ as $C_{27}H_{40}N_6O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{40}N_6O_7S_3$: 657.2199, found: 657.2193; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 1.34-1.44 (m, 2 H), 1.48-1.64 (m, 2 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.76-1.88 (m, 1 H), 2.01 (s, 3 H), 2.04-2.13 (m, 2 H), 2.34 (s, 6 H), 2.46 (t, *J* = 7.8 Hz, 2 H), 2.56 (dd, *J* = 10.3, 7.8 Hz, 1 H), 3.24 (dd, *J* = 10.3, 6.8 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.81 (dd, *J* = 9.3, 3.9 Hz, 1 H), 3.83 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.9, 0.8 Hz, 1 H), 4.46 (dq, *J* = 7.0, 2.8 Hz, 1 H), 4.62 (dd, *J* = 9.9, 2.8 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.75-7.87 (m, 3 H), 8.06-8.15 (m, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-4'-depropyl-4'-(3-methoxypropyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}lincomycin (5-51)

Compound **5-22** (266 mg, 0.36 mmol), triphenylphosphine (142 mg, 0.54 mmol), diethylazodicarboxylate (98.0 µl, 0.54 mmol) and 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (132 mg, 0.56 mmol) in THF (2 ml) were treated for 18 h according to the similar procedure as described for the preparation of **5-29** to afford (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-4'-(3-methoxypropyl)-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (325 mg as crude). To this crude compound (325 mg) was added 2,2,2-trifluoroacetic acid (1 ml) at 0°C, stirred at room temperature for 15 min. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (112 mg, 48.3% in 2 steps from **5-22**) as a colorless solid. $[\alpha]_D^{24}$ +82.6° (*c* 0.45, MeOH); ESI-MS *m/z* 644 $(M+H)^+$ as $C_{26}H_{37}N_5O_8S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{37}N_5O_8S_3$: 644.1883, found: 644.1880; $^1H$ NMR (400 MHz,$CD_3OD$) $\delta$ 1.40-1.52 (m, 2 H), 1.54-1.65 (m, 2 H), 1.57 (d, *J* = 6.9 Hz, 3 H), 1.89-1.97 (m, 1 H), 2.01 (s, 3 H), 2.09-2.23 (m, 2 H), 2.68 (dd, *J* = 10.7, 8.0 Hz, 1 H), 3.30 (s, 3 H), 3.32-3.36 (m, 1 H), 3.39 (t, *J* = 6.2, 2 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.85 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 4.02 (dd, *J* = 9.1, 4.1 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.42 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.47 (dq, *J* = 6.9, 2.7 Hz, 1 H), 4.66 (dd, *J* = 10.0, 2.7 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.76-7.87 (m, 3 H), 8.06-8.14 (m, 1 H).

## (7*S*)-4'-*i*-Butyl-1'-demethyl-7-deoxy-4'-depropyl-7-(5-(2-nitrophenyl)-1,3,4-thiadiazol-2-yl)thiolincomycin (5-52)

Compound **5-23** (204 mg, 0.28 mmol), triphenylphosphine (109 mg, 0.42 mmol), diethylazodicarboxylate (75.8 µl, 0.42 mmol) and 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (103 mg, 0.43 mmol) in THF (2 ml) were treated for 14.5 h according to the similar procedure as described for the preparation of **5-29** to afford (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-*i*-butyl-1'-demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (170 mg as crude). To this crude compound (170 mg) was added 2,2,2-trifluoroacetic acid (1 ml) at 0°C, stirred at room temperature for 30 min. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (39.0 mg, 22.5% in 2 steps from **5-23**) as a colorless solid. $[\alpha]_D^{24}$ +85.8° (*c* 0.54, MeOH); ESI-MS *m/z* 628 $(M+H)^+$ as $C_{26}H_{37}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{37}N_5O_7S_3$: 628.1933, found: 628.1936; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.90 (d, *J* = 5.3 Hz, 3 H), 0.91 (d, *J* = 5.4 Hz, 3 H), 1.23-1.34 (m, 2 H), 1.53-1.64 (m, 1 H), 1.57 (d, *J* = 6.8 Hz, 3 H), 1.81-1.92 (m, 1 H), 2.00 (s, 3 H), 2.04-2.15 (m, 1 H), 2.15-2.27 (m, 1 H), 2.58 (dd, *J* = 10.4, 8.7 Hz, 1 H), 3.26-3.30 (m, 1 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.84 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 3.92 (dd, *J* = 9.2, 4.3 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.47 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.65 (dd, *J* = 10.0, 2.8 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.76-7.87 (m, 3 H), 8.08-8.13 (m, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-4'-*n*-pentyllincomycin (5-53)

Compound **5-24** (400 mg, 0.54 mmol), triphenylphosphine (214 mg, 0.81 mmol), diethylazodicarboxylate (150 µl, 0.81 mmol) and 5-(2-nitrophenyl)-1,3,4-thiadiazole-2-thiol (201 mg, 0.84 mmol) in THF (4 ml) were treated for 24 h according to the similar procedure as described for the preparation of **5-29** to afford (7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-4'-*n*-pentyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (374 mg as crude). To this crude compound (374 mg) was added 2,2,2-trifluoroacetic acid (1 ml) at 0°C, stirred at room temperature for 30 min. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (72.6 mg, 20.9% in 2 steps from **5-24**) as a colorless solid. $[\alpha]_D^{25}$ +34.3° (*c* 0.10, MeOH); ESI-MS *m/z* 642 $(M+H)^+$ as $C_{27}H_{39}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{39}N_5O_7S_3$: 642.2090, found: 642.2083; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.80-0.95 (m, 3 H), 1.21-1.43 (m, 8 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.81-1.95 (m, 1 H), 2.02-2.14 (m, 2 H), 2.09 (s, 3 H), 2.62 (dd, *J* = 10.4, 7.9 Hz, 1 H), 3.27 (dd, *J* = 10.5, 6.8 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.83 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 3.91 (dd, *J* = 9.1, 4.2 Hz, 1 H), 4.14 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.34-4.40 (m, 1 H), 4.42 (dq, *J* = 7.0, 2.9 Hz, 1 H), 4.57 (dd, *J* = 10.0, 2.9 Hz, 1 H), 5.31 (d, *J* = 5.6 Hz, 1 H), 7.71-7.87 (m, 3 H), 8.07-8.14 (m, 1 H).

## (7*S*)-7-Deoxy-4'-depropyl-7-{5-(2-nitrophenyl)-1,3,4-thiadiazol-2-ylthio}-4'-*n*-pentyllincomycin (5-54)

Compound **5-53** (56.1 mg, 87.4 µmol), 36% aqueous formaldehyde (22.0 µl, 0.26 mmol), AcOH (30.0 µl, 0.52 mmol) and $NaBH(OAc)_3$ (55.5 mg, 0.26 mmol) in MeOH (0.6 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **5-35** to afford **5-54** (49.1 mg, 85.7%) as a colorless solid. $[\alpha]_D^{25}$ +91.6° (*c* 1.16, MeOH); ESI-MS *m/z* 656 $(M+H)^+$ as $C_{28}H_{41}N_5O_7S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_5O_7S_3$: 656.2246, found: 656.2238; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.83-0.92 (m, 3 H), 1.21-1.42 (m, 8 H), 1.57 (d, *J* = 7.0 Hz, 3 H), 1.78-1.91 (m, 1 H), 1.96-2.10 (m, 2 H), 2.01 (s, 3 H), 2.12-2.27 (m, 1 H), 2.39 (s, 3 H), 3.02 (dd, *J* = 10.5, 5.1 Hz, 1 H), 3.23-3.29 (m, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.81 (dd, *J* = 3.2, 0.7 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.39-4.49 (m, 1 H), 4.60 (dd, *J* = 9.8, 3.2 Hz, 1 H), 5.27 (d, *J* = 5.6, 1 H), 7.75-7.85 (m, 3 H), 8.06-8.11 (m, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-4'-depropyl-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]-4'-*n*-pentyllincomycin (5-55)

Compound **5-24** (400 mg, 0.54 mmol), triphenylphosphine (213.5 mg, 0.81 mmol), diethylazodicarboxylate (150 µl, 0.81 mmol) and 5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazole-2-thiol (193.9 mg, 0.84 mmol) in THF (4 ml) were treated for 24 h according to the similar procedure as described for the preparation of **5-29** to afford

(7*S*)-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]-4'-*n*-pentyl-2,3,4-tris-*O*-(trimethylsilyl)lincomycin (110 mg, 21.3%). To the compound (110 mg, 0.12 mmol) was added 2,2,2-trifluoroacetic acid (1 ml) at 0°C, stirred at room temperature for 30 min. The solution was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (59.0 mg, 80.6%) as a colorless solid. $[\alpha]_D^{25}$ +48.5° (*c* 0.22, MeOH); ESI-MS *m/z* 633 $(M+H)^+$ as $C_{25}H_{40}N_6O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{25}H_{40}N_6O_5S_4$: 633.2021, found: 633.2021; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.83-0.94 (m, 3 H), 1.21-1.43 (m, 8 H), 1.50 (d, *J* = 6.8 Hz, 3 H), 1.80-1.91 (m, 1 H), 2.02 (s, 3 H), 2.02-2.13 (m, 2 H), 2.59 (dd, *J* = 10.5, 8.0 Hz, 1 H), 3.12 (s, 3 H), 3.24-3.30 (m, 1 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.85 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 3.93 (dd, *J* = 9.1, 4.0 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.29 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.37-4.44 (m, 1 H), 4.61 (dd, *J* = 10.0, 2.7 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 8.13 (s, 1 H).

## (7*S*)-7-Deoxy-4'-depropyl-7-[5-{5-(methylamino)thiazol-4-yl}-1,3,4-thiadiazol-2-ylthio]-4'-*n*-pentyllincomycin (5-56)

Compound **5-55** (35.8 mg, 56.6 μmol), 36% aqueous formaldehyde (14.0 μl, 0.17 mmol), AcOH (20.0 μl, 0.34 mmol) and $NaBH(OAc)_3$ (36.0 mg, 0.17 mmol) in MeOH (0.5 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **5-35** to afford **5-56** (29.4 mg, 80.3%) as an off white solid. $[\alpha]_D^{25}$ +64.5° (*c* 0.30, MeOH); ESI-MS *m/z* 647 $(M+H)^+$ as $C_{26}H_{42}N_6O_5S_4$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{26}H_{42}N_6O_5S_4$: 647.2178, found: 647.2176; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.84-0.93 (m, 3 H), 1.19-1.39 (m, 8 H), 1.54 (d, *J* = 6.9 Hz, 3 H), 1.80-1.92 (m, 1 H), 2.02 (s, 3 H), 1.96-2.21 (m, 3 H), 2.40 (s, 3 H), 3.06-3.14 (m, 1 H), 3.12 (s, 3 H), 3.21 (dd, *J* = 7.9, 5.5 Hz, 1 H), 3.61 (dd, *J* = 10.2, 3.1 Hz, 1 H), 3.84 (dd, *J* = 3.1, 0.6 Hz, 1 H), 4.12 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.28 (dq, *J* = 6.9, 2.9 Hz, 1 H), 4.43-4.44 (m, 1 H), 4.59 (dd, *J* = 10.0, 2.9 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 8.14 (s, 1 H).

## (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-{4-(methoxycarbonyl)phenylthio}lincomycin (5-57)

To a solution of compound **5-21** (5.00 g, 7.05 mmol) in $CHCl_3$ (22 ml) were added $Et_3N$ (2.45 ml, 17.6 mmol) and methanesulfonyl chloride (1.10 ml, 14.1 mmol). A reaction mixture was stirred at room temperature for 30 min., added to saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, dried over $Na_2SO_4$ and then concentrated under reduced pressure. To a solution of crude compound in DMF (50 ml) were added $K_2CO_3$ (2.92 g, 21.2 mmol) and methyl 4-mercaptobenzoate (2.37 g, 14.1 mmol), stirred at 100°C for 6 h and concentrated under reduced pressure. The resulting residue in MeOH (50 ml) was added to 1*N* HCl (100 ml), stirred at room temperature for 20 min. The mixture was added to the saturated aqueous $NaHCO_3$, then extracted with ethyl acetate, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ =

20/1/0.1) to obtain the title compound as a colorless solid (1.25 g, 27.6% in 3 steps from **5-21**). ESI-MS *m/z* 643 $(M+H)^+$ as $C_{30}H_{46}N_2O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-1.00 (m, 3 H), 1.25-1.65 (m, 16 H), 1.45, 1.48 (s x 2, 9 H), 1.73-1.99 (m, 1 H), 1.79, 1.85 (s x 2, 3 H), 2.07-2.20 (m, 1 H), 2.22-2.42 (m, 1 H), 2.92-3.01 (m, 1 H), 3.53-3.61 (m, 1 H), 3.63-3.74 (m, 1 H), 3.88 (s, 3 H), 3.90-4.15 (m, 3 H), 4.28-4.50 (m, 2 H), 4.54-4.68 (m, 1 H), 5.24 (d, *J* = 5.4 Hz, 1 H), 7.39-7.46 (m, 2 H), 7.89-7.96 (m, 2 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-(4-(methoxycarbonyl) phenyl)thio -4'-{(*E*)-pent-2-enyl}lincomycin (5-58)

Compound **5-25** (1.45 g, 1.97 mmol), $Et_3N$ (0.69 ml, 4.93 mmol) and methanesulfonyl chloride (0.31 ml, 3.93 mmol) in $CHCl_3$ (6.1 ml) were treated at room temperature for 30 min according to the similar procedure as described for the preparation of **5-57** to afford 1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-4'-depropyl-7-*O*-methanesulfonyl-4'-{(*E*)-pent-2-enyl}-2,3,4-tris-*O*-(trimethylsilyl)lincomycin. To a solution of crude compound were added, $K_2CO_3$ (1.23 g, 8.87 mmol) and methyl 4-mercaptobenzoate (0.99 g, 5.91 mmol) in DMF (13.8 ml), and treated at 80˚C for 1 h. The resulting residue and 1*N* HCl (14 ml) in MeOH (14 ml) were treated at room temperature for 20 min according to the similar procedure as described for the preparation of **5-57** to afford **5-58** (1.21g, 92.2% in 3 steps from **5-25**) as a colorless solid. EI-MS *m/z* 668 $(M)^+$ as $C_{32}H_{48}N_2O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.95 (t, *J* = 7.4 Hz, 3 H), 1.33-1.44 (m, 3 H), 1.45, 1.48 (s x 2, 9 H), 1.80, 1.85 (s x 2, 3 H), 1.87-2.17 (m, 6 H), 2.26-2.40 (m, 1 H), 3.01-3.09 (m, 1 H), 3.51-3.67 (m, 2 H), 3.88 (s, 3 H), 3.91-4.12 (m, 3 H), 4.27-4.46 (m, 2 H), 4.53-4.64 (m, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H), 5.31-5.45 (m, 1 H), 5.47-5.59 (m, 1 H), 7.36-7.44 (m, 2 H), 7.86-7.95 (m, 2 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-{4-(methoxycarbonyl )phenylthio}-4'-*n*-pentyllincomycin (5-59)

Compound **5-58** (105 mg, 0.16 mmol) and Pd/C (100 mg) in MeOH (2 ml) were treated for 15 h according to the similar procedure as described for the preparation of **5-5** to afford **5-59** (97.0 mg, 92.1%) as a colorless solid. ESI-MS *m/z* 671 $(M+H)^+$ as $C_{32}H_{50}N_2O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.18-0.92 (m, 3 H), 1.15-1.52 (m, 11 H), 1.44, 1.47 (s x 2, 9 H), 1.71-1.93 (m, 1 H), 1.78, 1.83 (s x 2, 3 H), 2.05-2.18 (m, 1 H), 2.20-2.36 (m, 1 H), 2.95 (br t, *J* = 10.0 Hz, 1 H), 3.52-3.61 (m, 1 H), 3.61-3.73 (m, 1 H), 3.87 (s, 3 H), 3.91-4.03 (m, 2 H), 4.03-4.15 (m, 1 H), 4.28-4.47 (m, 2 H), 4.53-4.65 (m, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.35-7.47 (m, 2 H), 7.85-7.95 (m, 2 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-7-{4-(carboxyl)phenylthio}-1'-demethyl-7-deoxylincomycin (5-60)

To a solution of compound **5-57** (761 mg, 1.18 mmol) in MeOH (20 ml) was added 1*N* NaOH (1.78 ml, 1.78 mmol). A reaction mixture was stirred at room temperature for 7 days. The mixture was added 1*N* HCl

(pH = 3), extracted with $CHCl_3$, dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain the title compound (705 mg, 94.7%) as an off white solid. ESI-MS *m/z* 629 $(M+H)^+$ as $C_{29}H_{44}N_2O_9S_2$

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-7-{4-(carboxyl)phenylthio}-1'-demethyl-7-deoxy-4'-depropyl-4'-*n*-pentyllincomycin (5-61)

Compound **5-59** (97.0 mg, 0.15 mmol) and 1*N* NaOH (0.55 ml) in MeOH (1.1 ml) were treated for 18 h according to the similar procedure as described for the preparation of **5-60** to afford **5-61** (91.3 mg, 96.1%) as a colorless solid. FAB-MS *m/z* 695 $(M+K)^+$ as $C_{31}H_{48}N_2O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.82-0.92 (m, 3 H), 1.20-1.45 (m, 11 H), 1.46, 1.48 (s x 2, 9 H), 1.75-1.95 (m, 1 H), 1.81, 1.86 (s x 2, 3 H), 2.09-2.19 (m, 1 H), 2.21-2.37 (m, 1 H), 2.90-3.02 (m, 1 H), 3.54-3.62 (m, 1 H), 3.63-3.75 (m, 1 H), 3.90-4.05 (m, 2 H), 4.05-4.15 (m, 1 H), 4.30-4.49 (m, 2 H), 4.53-4.67 (m, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.37-7.45 (m, 2 H), 7.89-7.97 (m, 2 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-{4-(morpholinocarbonyl)phenylthio}lincomycin (5-62)

To a solution of compound **5-60** (200 mg, 0.32 mmol), 1-hydroxybenzotriazole (64.5 mg, 0.48 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl salt (91.5 mg, 0.48 mmol) in DMF (2 ml) was added morpholine (42.0 µl, 0.48 mmol). A reaction mixture was stirred at room temperature for 22 h, added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (215 mg, 96.8%) as a colorless solid. ESI-MS *m/z* 698 $(M+H)^+$ as $C_{33}H_{51}N_3O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.25-1.45 (m, 7 H), 1.46, 1.48 (s x 2, 9 H), 1.78-1.95 (m, 1 H), 1.88, 1.91 (s x 2, 3 H), 2.06-2.18 (m, 1 H), 2.24-2.40 (m, 1 H), 2.92-2.99 (m, 1 H), 3.37-3.85 (m, 10 H), 3.88-3.99 (m, 2 H), 4.05-4.14 (m, 1 H), 4.30-4.45 (m, 2 H), 4.52-4.63 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.35-7.42 (m, 2 H), 7.43-7.48 (m, 2 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-4'-depropyl-7-{4-(morpholinocarbonyl)phenylthio}-4'-*n*-pentyllincomycin (5-63)

Compound **5-61** (91.3 mg, 0.14 mmol), 1-hydroxybenzotriazole (28.1 mg, 0.21 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl salt (40.0 mg, 0.21 mmol) and morpholine (18.0 µl, 0.21 mmol) in DMF (1 ml) were treated for 62 h according to the similar procedure as described for the preparation of **5-62** to afford **5-63** (82.0 mg, 81.3%) as a colorless solid. FAB-MS *m/z* 726 $(M+H)^+$ as $C_{35}H_{55}N_3O_9S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.82-0.94 (m, 3 H), 1.21-1.42 (m, 11 H), 1.46, 1.48 (s x 2, 9 H), 1.77-1.95 (m, 1 H), 1.87, 1.91 (s x 2, 3 H), 2.08-2.18 (m, 1 H), 2.20-2.38 (m, 1 H), 2.90-3.01 (m, 1 H), 3.38-3.84 (m, 10 H), 3.87-4.01 (m, 2 H), 4.05-4.14 (m, 1 H), 4.29-4.46 (m, 2 H), 4.52-4.63 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.35-7.42 (m, 2 H), 7.42-7.48 (m, 2 H).

### (7*S*)-1'-Demethyl-7-deoxy-7-{4-(morpholinocarbonyl)phenylthio}lincomycin (5-64)

To the compound **5-62** (215 mg, 0.32 mmol) was added 2,2,2-trifluoroacetic acid (2 ml) at 0°C. A reaction mixture was stirred for 40 min. and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (104 mg, 56.5%) as a colorless solid. $[\alpha]_D^{25}$ +70.5° (*c* 0.42, MeOH); ESI-MS *m/z* 598 $(M+H)^+$ as $C_{28}H_{43}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{43}N_3O_7S_2$: 598.2621, found: 598.2623; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88-0.97 (m, 3 H), 1.30-1.44 (m, 4 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.80-1.93 (m, 1 H), 1.90 (s, 3 H), 2.05-2.18 (m, 2 H), 2.65 (dd, *J* = 10.4, 8.2 Hz, 1 H), 3.26-3.32 (m, 1 H), 3.35-3.56 (m, 2 H), 3.56 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.52-3.85 (m, 6 H), 3.79 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 3.90-3.98 (m, 2 H), 4.08 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37 (br dd, *J* = 9.9, 0.8 Hz, 1 H), 4.54 (dd, *J* = 9.9, 2.7 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.35-7.41 (m, 2 H), 7.43-7.49 (m, 2 H).

### (7*S*)-1'-Demethyl-7-deoxy-4'-depropyl-7-{4-(morpholinocarbonyl)phenylthio}-4'-*n*-pentyl lincomycin (5-65)

Compound **5-63** (82.0 mg, 0.11 mmol) and 2,2,2-trifluoroacetic acid (1 ml) were treated at -15°C to 0°C for 40 min according to the similar procedure as described for the preparation of **5-64** to afford **5-65** (57.0 mg, 80.6%) as a colorless solid. $[\alpha]_D^{26}$ +74.0° (*c* 0.51, MeOH); ESI-MS *m/z* 626 $(M+H)^+$ as $C_{30}H_{47}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_7S_2$: 626.2934, found: 626.2924; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.83-0.93 (m, 3 H), 1.23-1.44 (m, 8 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.77-1.88 (m, 1 H), 1.90 (s, 3 H), 1.99-2.15 (m, 2 H), 2.61 (dd, *J* = 10.4, 8.2 Hz, 1 H), 3.24 (dd, *J* = 10.4, 7.0 Hz, 1 H), 3.36-3.57 (m, 2 H), 3.56 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.57-3.84 (m, 6 H), 3.78 (br dd, *J* = 3.2, 0.7 Hz, 1 H), 3.88 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.95 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.08 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36 (br dd, *J* = 9.9, 0.7 Hz, 1 H), 4.53 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.34-7.41 (m, 2 H), 7.42-7.50 (m, 2 H).

### (7*S*)-7-Deoxy-4'-depropyl-7-{4-(morpholinocarbonyl)phenylthio}-4'-*n*-pentyllincomycin (5-66)

Compound **5-65** (31.0 mg, 49.5 μmol), 36% aqueous formaldehyde (12.0 μl, 0.15 mmol), AcOH (17.0 μl, 0.30 mmol) and $NaBH(OAc)_3$ (31.6 mg, 0.15 mmol) in MeOH (0.5 ml) were treated at room temperature for 30 min according to the similar procedure as described for the preparation of **5-35** to afford **5-66** (31.0 mg, 97.8%) as a colorless solid. $[\alpha]_D^{26}$ +68° (*c* 0.12, MeOH); ESI-MS *m/z* 640 $(M+H)^+$ as $C_{31}H_{49}N_3O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_7S_2$: 640.3090, found: 640.3080; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.94 (m, 3 H), 1.23-1.43 (m, 8 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.81-1.92 (m, 1 H), 1.91 (s, 3 H), 2.03 (ddd, *J* = 13.0, 7.8, 5.0 Hz, 1 H), 2.08-2.25 (m, 2 H), 2.44 (s, 3 H), 3.06 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.25-3.30 (m, 1 H), 3.38-3.84 (m, 9 H), 3.58 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.97 (dq, *J* = 6.8, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.33-4.39 (m, 1 H), 4.51 (dd, *J* = 9.7, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.37-7.42 (m, 2 H), 7.45-7.50 (m, 2 H).

### (7*S*)-7-Acetylthio-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxylincomycin (5-67)

To a solution of compound **5-21** (500 mg, 0.71 mmol) in $CH_2Cl_2$ (10 ml) were added $Et_3N$ (0.25 ml, 1.77 mmol) and methanesulfonyl chloride (0.11 ml, 1.39 mmol). A reaction mixture was stirred at 0°C for 1 h, added to saturated aqueous $NH_4Cl$, extracted with ethyl acetate, washed with 25% brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. To a solution of this crude compound in DMF (8 ml) was added AcSK (502 mg, 4.39 mmol), stirred at 60˚C for 10 h. The mixture was added to the saturated aqueous $NaHCO_3$, then extracted with ethyl acetate, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 2/1) to obtain (7*S*)-7-acetylthio-1'-*N*-(*tert*-butoxycarbonyl)-1'-demethyl-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)lincomycin as a colorless solid (218 mg, 40.2% in 2 steps from **5-21**). To a solution of this intermediate in MeOH (2.2 ml) was added 1*N* HCl (2.2 ml). A reaction mixture was stirred at room temperature for 1 h, added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform/MeOH = 40/1) to obtain the title compound (137 mg, 87.6%) as a colorless solid. ESI-MS *m/z* 551 $(M+H)^+$ as $C_{24}H_{42}N_2O_8S_2$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.98 (m, 3 H), 1.26-1.41 (m, 7 H), 1.46 (s, 9 H), 1.76-1.96 (m, 1 H), 2.01, 2.03 (s, 3 H), 1.95-2.17 (m, 1 H), 2.20-2.38 (m, 1 H), 2.32 (s, 3 H), 2.95 (t, *J* = 9.8 Hz, 1 H), 3.51 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.66 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.81-4.01 (m, 2 H), 4.01-4.12 (m, 1 H), 4.13-4.37 (m, 2 H), 4.41-4.50 (m, 1 H), 5.21 (d, *J* = 5.5 Hz, 1 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-mercaptolincomycin (5-68)

To a solution of compound **5-67** (137 mg, 0.25 mmol) in MeOH (1.5 ml) was added sodium methoxide (43.2 mg, 0.76 mmol)。 A reaction mixture was stirred at room temperature for 1.5 h, diluted with 8% aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/$CH_3OH$ = 40/1 to 10/1) to obtain the title compound (120 mg, 95.1%) as a colorless solid. FAB-MS *m/z* 509 $(M+H)^+$ as $C_{22}H_{40}N_2O_7S_2$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.99 (m, 3 H), 1.23-1.42 (m, 7 H), 1.47 (s, 9 H), 1.80-1.98 (m, 1 H), 2.05-2.15 (m, 1 H), 2.15 (s, 3 H), 2.20-2.39 (m, 1 H), 2.97 (br t, *J* = 9.6 Hz, 1 H), 3.39-3.58 (m, 1 H), 3.54 (dd, *J* = 10.2, 3.0 Hz, 1 H), 3.66 (dd, *J* = 10.2, 7.4 Hz, 1 H), 3.80-3.90 (m, 1 H), 4.02-4.18 (m, 2 H), 4.26-4.46 (m, 2 H), 5.25 (d, *J* = 5.5 Hz, 1 H).

### (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-{(4-(pyridin-3-yl)phenylthio}lincomycin (5-69)

To a solution of 3-(4-bromophenyl)pyridine (75.4 mg, 0.32 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (13.4 mg, 23.6 μmol) and

tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (12.3 mg, 13.4 μmol) in 1,4-dioxane (1 ml) were added compound **5-68** (120 mg, 0.24 mmol) and *N,N*-diisopropylethylamine (82.0 μl, 0.47 mmol). A reaction mixture was refluxed for 5 h, filtrated by either Chromatodisc (0.45 μm) (KURABO INDUSTRIES Ltd., Osaka, Japan) or celite and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound as an off white solid (126 mg, 80.4%). FAB-MS *m/z* 662 $(M+H)^+$ as $C_{33}H_{47}N_3O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-1.00 (m, 3 H), 1.21-1.43 (m, 7 H), 1.48 (s, 9 H), 1.77-1.95 (m, 1 H), 1.94, 1.97 (s x 2, 3 H), 2.05-2.21 (m, 1 H), 2.22-2.44 (m, 1 H), 2.97 (t, *J* = 9.6 Hz, 1 H), 3.59 (dd, *J* = 10.0, 3.2 Hz, 1 H), 3.68 (br dd, *J* = 9.8, 8.1 Hz, 1 H), 3.85-4.01 (m, 2 H), 4.05-4.16 (m, 1 H), 4.28-4.41 (m, 1 H), 4.41-4.50 (m, 1 H), 4.51-4.64 (m, 1 H), 5.27 (d, *J* = 5.5 Hz, 1 H), 7.47-7.57 (m, 3 H), 7.59-7.69 (m, 2 H), 8.05-8.14 (m, 1 H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.78-8.83 (m, 1 H).

## (7*S*)-1'-*N*-(*tert*-Butoxycarbonyl)-1'-demethyl-7-deoxy-7-{4-(pyrimidin-5-yl)phenylthio}lincomycin (5-70)

Compound **5-68** (116 mg, 0.23 mmol), 5-(4-bromophenyl)pyrimidine (107 mg, 0.46 mmol), Xantphos (14.2 mg, 24.5 μmol), $Pd_2(dba)_3$ (11.8 mg, 12.9 μmol), and *N,N*-diisopropylethylamine (79.5 μl, 0.46 mmol) in 1,4-dioxane (1.5 ml) were treated for 6 h according to the similar procedure as described for the preparation of **5-69** to afford **5-70** (118 mg, 77.7%) as a colorless solid. FAB-MS *m/z* 663 $(M+H)^+$ as $C_{32}H_{46}N_4O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-1.00 (m, 3 H), 1.25-1.43 (m, 7 H), 1.48, 1.47 (s x 2, 9 H), 1.80-1.95 (m, 1 H), 1.92, 1.95 (s x 2, 3 H), 2.04-2.20 (m, 1 H), 2.21-2.44 (m, 1 H), 2.97 (t, *J* = 9.6 Hz, 1 H), 3.56-3.75 (m, 2 H), 3.88-4.03 (m, 2 H), 4.06-4.19 (m, 1 H), 4.29-4.42 (m, 1 H), 4.46 (d, *J* = 9.6 Hz, 1 H), 4.54-4.67 (m, 1 H), 5.28 (d, *J* = 5.5 Hz, 1 H), 7.50-7.59 (m, 2 H), 7.65-7.73 (m, 2 H), 9.07 (s, 2 H), 9.13 (s, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-7-{(4-(pyridin-3-yl)phenylthio}lincomycin (5-71)

Compound **5-69** (126 mg, 0.19 mmol) and 2,2,2-trifluoroacetic acid (0.29 ml) in $CH_2Cl_2$ (2.5 ml) were treated at -20°C for 10 min, and then treated 0°C for 3 h according to the similar procedure as described for the preparation of **5-64** to afford **5-71** (99.1 mg, 92.7%) as a colorless solid. $[\alpha]_D^{25}$ +91.4° (*c* 0.74, MeOH); ESI-MS *m/z* 562 $(M+H)^+$ as $C_{28}H_{39}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{39}N_3O_5S_2$: 562.2409, found: 562.2407; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.86-0.97 (m, 3 H), 1.30-1.42 (m, 4 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.77-1.87 (m, 1 H), 1.97 (s, 3 H), 2.02 -2.13 (m, 2 H), 2.59 (dd, *J* = 10.3, 8.0 Hz, 1 H), 3.22 (dd, *J* = 10.3, 7.0 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.79 (br dd, *J* = 3.3, 0.9 Hz, 1 H), 3.86 (dd, *J* = 9.3, 3.7 Hz, 1 H), 3.93 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.51 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.51 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1 H), 7.51-7.58 (m, 2 H), 7.60-7.68 (m, 2 H), 8.07 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1 H), 8.51 (dd, *J* = 4.9, 1.6 Hz, 1 H), 8.79 (dd, *J* = 2.4, 0.9 Hz, 1 H).

## (7*S*)-1'-Demethyl-7-deoxy-7-{4-(pyrimidin-5-yl)phenylthio}lincomycin (5-72)

Compound **5-70** (118 mg, 0.18 mmol) and 2,2,2-trifluoroacetic acid (0.27 ml) in $CH_2Cl_2$ (2.5 ml) were treated at -20 °C for 20 min, and then treated room temperature for 5 h according to the similar procedure as described for the preparation of **5-71** to afford **5-72** (82.2 mg, 82.1%) as a colorless solid. $[\alpha]_D^{25}$ +91.7° (*c* 0.33, MeOH); ESI-MS *m/z* 563 $(M+H)^+$ as $C_{27}H_{38}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{38}N_4O_5S_2$: 563.2362, found: 563.2356; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.78-0.88 (m, 3 H), 1.20-1.32 (m, 4 H), 1.25 (d, *J* = 6.9 Hz, 3 H), 1.68-1.78 (m, 1 H), 1.86 (s, 3 H), 1.92 -2.05 (m, 2 H), 2.55 (dd, *J* = 10.2, 8.0 Hz, 1 H), 3.12 (dd, *J* = 10.2, 6.7 Hz, 1 H), 3.48 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.69 (br dd, *J* = 3.3, 0.7 Hz, 1 H), 3.75 (dd, *J* = 9.1, 3.4 Hz, 1 H), 3.87 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.01 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.27-4.32 (m, 1 H), 4.43 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.18 (d, *J* = 5.5 Hz, 1 H), 7.43-7.50 (m, 2 H), 7.55-7.65 (m, 2 H), 8.97 (s, 2 H), 9.03 (s, 1 H).

## 4-(Cyclopropylmethyl)pyridine (6-8)

To a solution of **6-7** (19.0 g, 204 mmol) in THF (136 ml) at -78°C was added 2.0 M lithium diisopropylamide (LDA) in THF solution (204 ml, 408 mmol). A reaction mixture was stirred in argon atmosphere at -40°C for 20 min. The mixture was cooled to -78°C. Then, bromocyclopropane (16.3 ml, 204 mmol) was added with dropwise to the solution. After stirring for 1 h, the solution was poured into saturated aqueous $NH_4Cl$. The desired compound was extracted with ethyl acetate, was washed with brine and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by distillation under reduced pressure (84°C/8 mmHg) to obtain the title compound (13.8 g, 50.9%) as colorless oil. FAB-MS *m/z* 134 $(M+H)^+$ as $C_9H_{11}N$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.18-0.26 (m, 2 H), 0.54-0.62 (m, 2 H), 0.93-1.05 (m, 1 H), 2.54 (d, *J* = 7.1 Hz, 2 H), 7.17-7.23 (m, 2 H), 8.47-8.53 (m, 2 H).

## 4-(Cyclopropylmethyl)picolinonitrile (6-9)

To a solution of **6-8** (25.5 g, 191 mmol) in $CH_2Cl_2$ (300 ml) at 0°C was added *m*-chloroperoxybenzoic acid (*m*CPBA ) (50.8 g, 191 mmol). A reaction mixture was stirred at room temperature for 1 h. To the mixture was added $Na_2S_2O_3$ solution (75.0 g in 150 ml of $H_2O$). The solution was added to mixture of saturated aqueous $NaHCO_3$ (500 ml), saturated aqueous $K_2CO_3$ (40 ml) and $CHCl_3$ (500 ml). The organic phase was separated and then further extracted twice with $CHCl_3$ (500 ml)-isopropanol (100 ml), the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain 4-(cyclopropylmethyl)pyridine *N*-oxide (30.7 g as crude). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.15-0.26 (m, 2 H), 0.54-0.66 (m, 2 H), 0.90-1.02 (m, 1 H), 2.54 (d, *J* = 7.1 Hz, 2 H), 7.11-7.24 (m, 2 H), 8.08-8.18 (m, 2 H).

To a solution of 4-(cyclopropylmethyl)pyridine *N*-oxide (30.7 g) in $CH_2Cl_2$ (350 ml) were added trimethylsilanecarbonitrile (30.6 ml, 0.23 mmol) and dimethylcarbamic chloride (7.03 ml, 76.3 mmol) at room temperature. Then, dimethylcarbamic chloride (7.03 ml, 76.3 mmol) was added in two portions after 20

min interval to the mixture at 20°C. The mixture was stirred at room temperature for 17 h. The solution was added to 10% aqueous $K_2CO_3$. The desired compound was extracted with $CH_2Cl_2$ and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 17/3) to obtain the title compound (25.5 g, 84.2% in 2 steps) as a colorless oil. EI-MS *m/z* 158 $(M)^+$ as $C_{10}H_{10}N_2$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.22-0.28 (m, 2 H), 0.60-0.70 (m, 2 H), 0.92-1.06 (m, 1 H), 2.61 (d, *J* = 7.1 Hz, 2 H), 7.41-7.46 (m, 1 H), 7.64 (br dd, *J* = 1.7, 0.7 Hz, 1 H), 8.55-8.64 (m, 1 H).

## 4-(Cyclopropylmethyl)picolinic acid (**6-10**)

To a solution of **6-9** (25.5 g, 161 mmol) in MeOH (300 ml) was added 5 N aqueous NaOH (250 ml). A reaction mixture was stirred at 50°C for 8 h, cooled down to 0°C, added to 5 N aqueous HCl (250 ml) at 0°C and then concentrated under reduced pressure to remove MeOH. The solution was adjusted at pH 3 by 1 N aqueous HCl, extracted with $CHCl_3$ (500 ml)-isopropanol (150 ml), and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound (27.6 g, 96.5%) as a colorless solid. FAB-MS *m/z* 178 $(M+H)^+$ as $C_{10}H_{11}NO_2$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.22-0.30 (m, 2 H), 0.60-0.67 (m, 2 H), 0.95-1.11 (m, 1 H), 2.68 (d, *J* = 7.1 Hz, 2 H), 7.48-7.54 (m, 1 H), 8.15-8.20 (m, 1 H), 8.58 (d, *J* = 5.1 Hz, 1 H).

## *N*-(*tert*-Butoxycarbonyl)-4-(cyclopropylmethyl)piperidine-2-carboxylic acid ((±)-**6-11**)

To a solution of **6-10** (6.90 g, 38.9 mmol) in AcOH (62 ml) was added $PtO_2$ (442 mg). A reaction mixture was vigorously stirred in hydrogen atmosphere at room temperature for 24 h, filtrated with celite and concentrated under reduced pressure to obtain 4-(cyclopropylmethyl)piperidine-2-carboxylic acid (5.30 g as crude). For the qualified analytical purpose, the above crude compound was purified by reverse-phase column chromatography (0.1% aqueous TFA/$CH_3CN$ = 90/10 to 10/90) to obtain the highly purified 4-(cyclopropylmethyl)piperidine-2-carboxylic acid TFA salt as a colorless solid. ESI-MS *m/z* 184 $(M+H)^+$ as $C_{10}H_{17}NO_2$; $^1$H NMR (400 MHz, $D_2O$) $\delta$ -0.08-0.02 (m, 2 H), 0.31-0.41 (m, 2 H), 0.58-0.72 (m, 1 H), 1.10-1.43 (m, 4 H), 1.71-1.85 (m, 1 H), 1.92-2.03 (m, 1 H), 2.35-2.45 (m, 1 H), 2.91-3.03 (m, 1 H), 3.39-3.48 (m, 1 H), 3.85-3.94 (m, 1 H).

To a solution of the above disubstituted piperidine (5.30 g) in 1,4-dioxane (100 ml) were added 2 N aqueous NaOH (74.0 ml, 148 mmol) and di-*tert*-butyl dicarbonate (14.3 ml, 62.2 mmol). A reaction mixture was stirred at room temperature for 15 h and then concentrated under reduced pressure to remove 1,4-dioxane. The solution was adjusted at pH 8 by1 N aqueous NaOH. Then, to the aqueous phase was added $H_2O$, washed with $Et_2O$, adjusted at pH 4 by 1 N aqueous HCl, extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to obtain the title compound (10.5 g, 95.5% in 2 steps) as a racemate of *cis*-isomers as a colorless solid. It was reported that hydrogenation of disubstituted pyridine in the presence of $PtO_2$ resulted in an approximately 1:1 mixture of

two isomeric *cis*-products by Birkenmeyer *et al*.[49] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ -0.04-0.08 (m, 2 H), 0.36-0.50 (m, 2 H), 0.60-0.73 (m, 1 H), 1.12-1.32 (m, 2 H), 1.35-1.55 (m, 1 H), 1.45 (s, 9 H), 1.66-1.89 (m, 3 H), 2.02-2.15 (m, 1 H), 3.55-3.60 (m, 2 H), 4.22-4.35 (m, 1 H).

### 2-Benzyl (2*S*, 4*R*)-*N*-(*tert*-butyl)-4-(cyclopropylmethyl)piperidine-1,2-dicarboxylate (6-12) 2-Benzyl (2*R*, 4*S*)-*N*-(*tert*-butyl)-4-(cyclopropylmethyl)piperidine-1,2-dicarboxylate (6-13)

To a solution of (±)-**6-11** (113 mg, 0.40 mmol) in $CH_3CN$ (1 ml) were added diisopropylethylamine (0.10 ml, 0.60 mmol) and benzylbromide (0.65 ml, 0.44 mmol). A reaction mixture was stirred at room temperature for 48 h and added to saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane/ethyl acetate = 5/1) to obtain 2-benzyl *N*-(*tert*-butyl) 4-(cyclopropylmethyl)piperidine-1,2-dicarboxylate (133 mg, 89.3%) as a colorless oil. The above colorless oil (32.0 g) was further purified by column chromatography (Chiralpak AD-H, n-hexane/IPA = 98/2) to obtain **6-12** (11.1 g, 34.7%) and **6-13** (11.0 g, 34.4%) as a colorless solid both. These enantiomers could be independently analyzed by the following condition: Chiralpak AD-H, 0.46 cm I.D. x 25 cm, *n*-hexane/IPA = 98/2, 1.0 ml/min, 40ºC, 208 nm. 5-12: $[\alpha]D_{27}$ -24.8° (c 0.65, $CHCl_3$); ESI-MS *m/z* 374 (M+H)+ as C22H31NO4; 1H NMR (400 MHz, $CDCl_3$) $\delta$ -0.12--0.02 (m, 2 H), 0.32-0.44 (m, 2 H), 0.52-0.66 (m, 1 H), 0.99-1.18 (m, 2 H), 1.30-1.50 (m, 1 H), 1.41 (s, 9 H), 1.69-1.88 (m, 3 H), 2.04 (ddd, *J* = 13.5, 6.5, 4.6 Hz, 1 H), 3.08-3.70 (m, 2 H), 4.38 (t, *J* = 6.3 Hz, 1 H), 5.08-5.23 (m, 2 H), 7.27-7.42 (m, 5 H). **6-13**: $[\alpha]_D^{26}$ +24.2° (*c* 1.03, $CHCl_3$); ESI-MS *m/z* 374 $(M+H)^+$ as $C_{22}H_{31}NO_4$. Compound **6-13** showed the exactly same $^1$H NMR spectrum with that of **6-12**.

### (2*S*, 4*R*)- *N*-(*tert*-Butoxycarbonyl)-4-(cyclopropylmethyl)piperidine-2-carboxylic acid (6-14)

To a solution of **6-12** (1.51 g, 4.04 mmol) in MeOH (45 ml) was added Pd/C (0.17 g). A reaction mixture was vigorously stirred in hydrogen atmosphere at room temperature for 1 h, filtrated with celite and concentrated under reduced pressure to obtain the title compound (1.15 g, quant) as a colorless solid. $[\alpha]_D^{27}$ -16.3° (*c* 0.40, MeOH); ESI-MS *m/z* 284 $(M+H)^+$ as $C_{15}H_{25}NO_4$; TOF-ESI-HRMS $(M-H)^-$ calcd for $C_{15}H_{25}NO_4$: 282.1705, found: 282.1718 ; Compound 5-14 showed the exactly same $^1$H NMR spectrum with that of (±)-5-11.

### (2*S*, *Z*)-1-(2-Nitrophenylsulfonyl)-5-*n*-propyl-2, 3, 6, 7-tetrahydro-1*H*-azepine-2-carboxylic acid (6-16)

To a solution of **6-15** (72.0 mg, 0.19 mmol) in 1,4-dioxane (0.8 ml)-$H_2O$ (0.2 ml) was added $LiOH{\cdot}H_2O$ (23.7 mg, 0.56 mmol). A reaction mixture was stirred at room temperature for 5 h, diluted with $H_2O$ and washed with $Et_2O$. The aqueous phase was adjusted at pH 3 by citric acid. The desired compound was extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated

under reduced pressure to obtain the title compound (70.0 mg as crude). This crude compound including a trace amount of citric acid could not be purified. ESI-MS *m/z* 369 $(M+H)^+$ as $C_{16}H_{20}N_2O_6S$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.73 (t, *J* = 7.4 Hz, 3 H), 1.16-1.31 (m, 2 H), 1.73-1.82 (m, 2 H), 2.15-2.26 (m, 2 H), 2.41-2.51 (m, 1 H), 2.62-2.70 (m, 1 H), 3.42 (ddd, *J* = 14.5, 7.8, 5.2 Hz, 1 H), 3.72 (dt, *J* = 14.6, 4.7 Hz, 1 H), 4.71 (dd, *J* = 7.1, 3.7 Hz, 1 H), 5.37 (t, *J* = 6.5 Hz, 1 H), 7.56-7.71 (m, 3 H), 7.95-8.03 (m, 1 H).

## Mixture **6-17** of methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-α-thiolincosaminide and methyl 6-*N*-((2'*R*, 4'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-α-thiolincosaminide

To a solution of (±)-**6-4** (11.7 g, 43.1 mmol) in DMF (100 ml) were added 1-hydroxybenzotriazole (7.55 g, 55.8 mmol), *N,N*'-dicyclohexylcarbodiimide (DCC) (10.7 g, 51.9 mmol) and methyl α-thiolincosaminide (MTL) (14.2 g, 56.1 mmol). A reaction mixture was stirred at room temperature for 12 h. To the mixture was added $H_2O$ and then the solution was filtrated, and ethyl acetate and saturated aqueous $NaHCO_3$ were added to the filtrate. The desired compound was extracted with ethyl acetate, extracted with $CHCl_3$, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 50/50 to ethyl acetate, then ethyl acetate to ethyl acetate/ MeOH = 90/10) to obtain 6-*N*-(*N*'-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-α-thiolincosaminide (18.5 g, 84.9%, (2'*S*, 4'*R*) isomer : (2'*R*, 4'*S*) isomer = ca 50:50) as a colorless solid. To this colorless solid was added ethyl acetate, and insoluble matter was filtrated off and ethyl acetate solution was concentrated under reduced pressure to obtain the mixture **6-17** (13.5 g, 20% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 60:40)) as a colorless solid.

## Mixture **6-18** of methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)- α-thiolincosaminide and methyl 6-*N*-((2'*R*, 4'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-α-thiolincosaminide

Compound (±)-**6-5** (12.6 g, 44.2 mmol), 1-hydroxybenzotriazole (7.77 g, 57.5 mmol), DCC (11.0 g, 53.3 mmol) and MTL (14.6 g, 57.5 mmol) in DMF (120 ml) were treated for 20 h according to the similar procedure as described for the preparation of mixture **6-17** to afford 6-*N*-(1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)- α-thiolincosaminide (20.0 g, 87.0%, (2'*S*, 4'*R*) isomer : (2'*R*, 4'*S*) isomer = ca 50:50) as a colorless solid. To this colorless solid (14.53 g) was added ethyl acetate, and insoluble matter was filtrated off and ethyl acetate solution was concentrated under reduced pressure to obtain the mixture **6-18** (8.15 g, 80% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 90:10)) as a colorless solid.

**Mixture 6-19 of methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)- α-thiolincosaminide and methyl 6-*N*-((2'*R*, 4'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-α-thiolincosaminide**

To a solution of (±)-**6-6** (6.00 g, 21.0 mmol) in DMF (57 ml) were added 1-hydroxybenzotriazole (2.84 g, 21.0 mmol), DCC (5.20 g, 25.2 mmol) and MTL (5.40 g, 21.3 mmol). A reaction mixture was stirred at room temperature for 6 h and concentrated under reduced pressure. To the resulting residue added ethyl acetate, and then the mixture was filtrated. The desired compound was washed with saturated aqueous $KHCO_3$, and then the organic phase was dried over $MgSO_4$, filtrated and concentrated under reduced pressure (10.9g, quant, (2'*S*, 4'*R*) isomer : (2'*R*, 4'*S*) isomer = ca 50:50). To the resulting residue was added ethyl acetate, and insoluble matter was filtrated off and ethyl acetate solution was concentrated under reduced pressure. To the resulting residue was added toluene, and insoluble matter was filtrated off and toluene solution was concentrated under reduced pressure to obtain the mixture **6-19** (5.70 g, 90% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 95:5)) as a colorless solid.

**Mixture 6-20 of methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-α-thiolincosaminide and methyl 6-*N*-((2'*R*, 4'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-α-thiolincosaminide**

Compound (±)-**6-11** (44.2 g, 156 mmol), 1-hydroxybenzotriazole monohydrate (28.6 g, 187 mmol), DCC (35.8 g, 174 mmol) and MTL (47.4 g, 187 mmol) in DMF (300 ml) were treated for 13 h. To the mixture were added ethyl acetate and acetone, and then the solution was filtrated, and concentrated under reduced pressure. To the resulting residue were added ethyl acetate, and the organic layer was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over $Na_2SO_4$, filtrated and then concentrated under reduced pressure (75g, 92.7%, (2'*S*, 4'*R*) isomer : (2'*R*, 4'*S*) isomer = ca 50:50). To the resulting residue was added ethyl acetate, and insoluble matter was filtrated off and ethyl acetate solution was concentrated under reduced pressure. To the resulting residue was added toluene, and insoluble matter was filtrated off and toluene solution was concentrated under reduced pressure to obtain the mixture **6-20** (36.0 g, 80% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 90:10)) as a colorless solid. FAB-MS *m/z* 519 $(M+H)^+$ as $C_{24}H_{42}N_2O_8S$.

**Methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-21)**

To a solution of mixture **6-17** (13.5 g, 26.6 mmol, 20% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 60:40)) in pyridine (50 ml) were added trimethylchlorosilane (17.0 ml, 133 mmol) and hexamethyldisilazane (27.9 ml, 133 mmol). A reaction mixture was stirred at room temperature for 40 min and added to saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, washed with saturated aqueous NaCl and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. To the resulting residue were added methanol (138 ml) and 6 N acetic acid (5.80 ml), and stirred at room

temperature for 2.5 h. The mixture was added to saturated aqueous $NaHCO_3$ and concentrated under reduced pressure to remove MeOH. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 19/1 to 3/1) to obtain the title compound (9.28 g, 48.2% (80.3% based on (2'*S*, 4'*R*) isomer) in 2 steps from mixture **6-17**) as a colorless solid. ESI-MS *m/z* 723 $(M+H)^+$ as $C_{32}H_{66}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.14 (s, 9 H), 0.16 (s, 9 H), 0.20 (s, 9 H), 0.90 (t, *J* = 7.0 Hz, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.22-1.39 (m, 4 H), 1.40-1.49 (m, 1 H), 1.46 (s, 9 H), 1.52-1.74 (m, 2 H), 1.75-1.87 (m, 1 H), 1.90-2.01 (m, 1 H), 2.04 (s, 3 H), 3.41-3.61 (m, 2 H), 3.75 (dd, *J* = 9.6, 2.5 Hz, 1 H), 3.78-3.87 (m, 1 H), 4.07-4.20 (m, 3 H), 4.23-4.32 (m, 2 H), 5.17 (d, *J* = 5.4 Hz, 1 H).

### Methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-22)

Mixture **6-18** (8.15g, 15.7 mmol, 80% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 90:10), trimethylchlorosilane (100 ml, 78.3 mmol) and hexamethyldisilazane (16.4 ml, 78.3 mmol) in pyridine (30 ml) were treated for 20 min according to the similar procedure as described for the preparation of **6-21** and then, the crude compound and 6 N acetic acid (3.4 ml) in MeOH (88 ml) were treated for 40 min according to the similar procedure as described for the preparation of **6-21** to afford **6-22** (8.20 g, 70.7% (78.8% based on (2'*S*, 4'*R*) isomer) in 2 steps from mixture **6-18**) as a colorless solid. ESI-MS *m/z* 737 $(M+H)^+$ as $C_{33}H_{68}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.14 (s, 18 H), 0.19 (s, 9 H), 0.82-0.93 (m, 3 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.18-1.36 (m, 7 H), 1.38-1.55 (m, 2 H), 1.46 (s, 9 H), 1.77-1.89 (m, 1 H), 2.00-2.10 (m, 1 H), 2.06 (s, 3 H), 2.90-3.03 (m, 1 H), 3.30-3.54 (m, 2 H), 3.60 (dd, *J* = 9.6, 2.6 Hz, 1 H), 3.85-3.92 (m, 1 H), 3.94-4.07 (m, 2 H), 4.07-4.17 (m, 1 H), 4.26-4.40 (m, 1 H), 5.17 (d, *J* = 5.4 Hz, 1 H), 6.32 (br d, *J* = 9.0 Hz, 1 H).

### Methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-23)

Mixture **6-19** (5.70 g, 10.9 mmol, 90% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 95:5), trimethylchlorosilane (13.2 ml, 104 mmol) and hexamethyldisilazane (21.7 ml, 104 mmol) in pyridine (21 ml) were treated for 1 h according to the similar procedure as described for the preparation of **6-21** and then, the crude compound and 6 N acetic acid (2.4 ml) in MeOH (61 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6-21** to afford **6-23** (7.25 g, 89.8% (94.5% based on (2'*S*, 4'*R*) isomer) in 2 steps from mixture **6-19**) as a colorless solid. ESI-MS *m/z* 737 $(M+H)^+$ as $C_{33}H_{68}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.14 (s, 9 H), 0.16 (s, 9 H), 0.20 (s, 9 H), 0.88 (d, *J* = 6.5 Hz, 6 H), 1.08-1.33 (m, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 1.46 (s, 9 H), 1.53-1.73 (m, 3 H), 1.77-1.88 (m, 1 H), 1.92-2.01 (m, 1 H), 2.05 (s, 3 H), 3.44-3.58 (m, 2 H), 3.74 (dd, *J* = 9.6, 2.6 Hz, 1 H), 3.78-3.88 (m, 1 H), 4.05-4.17 (m, 3 H), 4.23-4.32 (m, 2 H), 5.17 (d, *J* = 5.4 Hz, 1 H).

**Methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-24)**

Mixture **6-20** (35.0 g, 67.5 mmol, 80% de ((2'*S*, 4'*R*) : (2'*R*, 4'*S*) = 90:10), trimethylchlorosilane (43.1 ml, 337 mmol) and hexamethyldisilazane (70.6 ml, 337 mmol) in pyridine (130 ml) were treated for 1 h according to the similar procedure as described for the preparation of **6-21** and then, the crude compound and 6 N acetic acid (16.9 ml) in MeOH (350 ml) were treated for 140 min according to the similar procedure as described for the preparation of **6-21** to afford **6-24** (30.6 g, 61.7% (68.5% based on (2'*S*, 4'*R*) isomer) in 2 steps from mixture **6-20**) as a colorless solid. FAB-MS *m/z* 735 $(M+H)^+$ as $C_{33}H_{66}N_2O_8SSi_3$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ -0.04-0.04 (m, 2 H), 0.13 (s, 9 H), 0.16 (s, 9 H), 0.20 (s, 9 H), 0.40-0.49 (m, 2 H), 0.65-0.78 (m, 1 H), 1.17 (d, *J* = 6.2 Hz, 3 H), 1.17-1.35 (m, 2 H), 1.34-1.47 (m, 1 H), 1.47 (s, 9 H), 1.64-1.91 (m, 3 H), 1.98-2.10 (m, 1 H), 2.05 (s, 3 H), 3.40-3.66 (m, 2 H), 3.75 (dd, *J* = 9.7, 2.6 Hz, 1 H), 3.76-3.85 (m, 1 H), 4.12 (dd, *J* = 9.7, 5.4 Hz, 1 H), 4.13-4.19 (m, 1 H), 4.20-4.35 (m, 3 H), 5.18 (d, *J* = 5.4 Hz, 1 H).

**Methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-25)**

To a solution of **6-21** (500 mg, 0.69 mmol) in $CH_2Cl_2$ (2 ml) at 0°C were added $Et_3N$ (291 μl, 2.08 mmol) and methanesulfonyl chloride (107 μl, 1.38 mmol). A reaction mixture was stirred at room temperature for 1 h, added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain methyl 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-*O*-methanesulfonyl-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide as a crude compound (530 mg). To a solution of this crude compound (530 mg) in DMF (3.0 ml) was added AcSK (396 mg, 3.47 mmol). A reaction mixture was stirred at 80°C for 2 h, added to saturated aqueous $NaHCO_3$, then extracted with ethyl acetate, washed with 10% aqueous NaCl, dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 85/15) to obtain the title compound (357 mg, 66.1% in 2 steps from **6-21**) as a colorless solid. FAB-MS *m/z* 781 $(M+H)^+$ as $C_{34}H_{68}N_2O_8S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.126 (s, 9 H), 0.13 (s, 9 H), 0.18 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 1.10-1.21 (m, 1 H), 1.23-1.38 (m, 4 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.42-1.60 (m, 2 H), 1.49 (s, 9 H), 1.80-1.94 (m, 1 H), 1.95-2.08 (m, 1 H), 1.99 (s, 3 H), 2.29 (s, 3 H), 3.00-3.18 (m, 1 H), 3.57 (dd, *J* = 9.5, 2.2 Hz, 1 H), 3.63-3.83 (m, 2 H), 3.87-4.04 (m, 2 H), 4.13 (dd, *J* = 9.5, 5.6 Hz, 1 H), 4.22-4.33 (m, 1 H), 4.50-4.62 (m, 1 H), 5.15 (d, *J* = 5.6 Hz, 1 H), 6.04-6.37 (m, 1 H).

**Methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-26)**

Compound **6-22** (1.01g, 1.37 mmol), $Et_3N$ (490 μl, 3.48 mmol) and methanesulfonyl chloride (220 μl, 2.79 mmol) in $CH_2Cl_2$ (20 ml) at 0°C were treated for 1 h according to the similar procedure as described for

the preparation of **6-25** and then, a crude mesylate (1.17 g) and AcSK (992 mg, 8.68 mmol) in DMF (13 ml) at 80 ˚C were treated for 3 h according to the similar procedure as described for the preparation of **6-25** to afford **6-26** (565 mg, 51.9% in 2 steps from **6-22**) as a colorless solid. FAB-MS *m/z* 795 $(M+H)^+$ as $C_{35}H_{70}N_2O_8S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.11 (s, 9 H), 0.12 (s, 9 H), 0.17 (s, 9 H), 0.78-0.95 (m, 3 H), 1.07-1.32 (m, 7 H), 1.34 (d, *J* = 6.9 Hz, 3 H), 1.38-1.60 (m, 2 H), 1.48 (s, 9 H), 1.78-1.95 (m, 1 H), 1.95-2.11 (m, 1 H), 1.97 (s, 3 H), 2.27 (s, 3 H), 3.00-3.18 (m, 1 H), 3.54 (dd, *J* = 9.6, 2.2 Hz, 1 H), 3.62-3.85 (m, 2 H), 3.85-4.05 (m, 2 H), 4.06-4.16 (m, 1 H), 4.21-4.31 (m, 1 H), 4.50-4.62 (m, 1 H), 5.14 (d, *J* = 5.5 Hz, 1 H), 6.05-6.48 (m, 1 H).

### Methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-27)

Compound **6-23** (1.01g, 1.37 mmol), $Et_3N$ (930 μl, 6.85 mmol) and methanesulfonyl chloride (210 μl, 2.74 mmol) in $CH_2Cl_2$ (20 ml) at 0°C were treated for 1 h according to the similar procedure as described for the preparation of **6-25** and then, the crude mesylate (1.17 g) and AcSK (470 mg, 4.11 mmol) in DMF (6 ml) at 80˚C were treated for 3 h according to the similar procedure as described for the preparation of **6-25** to afford **6-27** (598 mg, 55.0% in 2 steps from **6-23**) as a colorless solid.

### Methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-28)

Compound **6-24** (7.40 g, 10.1 mmol), $Et_3N$ (4.24 ml, 30.3 mmol) and methanesulfonyl chloride (1.56 ml, 20.2 mmol) in $CHCl_3$ (70 ml) at 0°C were treated and then the solution was stirred at room temperature for 1 h according to the similar procedure as described for the preparation of **6-25** and then, the crude mesylate and AcSK (5.76 g, 50.5 mmol) in DMF (75 ml) at 80°C were treated for 1.5 h according to the similar procedure as described for the preparation of **6-25** to afford **6-28** (4.30 g, 53.9% in 2 steps from **6-24**) as a colorless solid. ESI-MS *m/z* 793 $(M+H)^+$ as $C_{35}H_{68}N_2O_8S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ -0.05-0.03 (m, 2 H), 0.125 (s, 9 H), 0.131 (s, 9 H), 0.18 (s, 9 H), 0.38-0.45 (m, 2 H), 0.60-0.73 (m, 1 H), 1.17-1.29 (m, 3 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.50 (s, 9 H), 1.59-1.72 (m, 2 H), 1.86-1.97 (m, 1 H), 2.00 (s, 3 H), 2.06-2.14 (m, 1 H), 2.29 (s, 3 H), 3.03-3.18 (m, 1 H), 3.58 (dd, *J* = 9.6, 2.3 Hz, 1 H), 3.67-3.84 (m, 2 H), 3.88-4.02 (m, 2 H), 4.12 (dd, *J* = 9.5, 5.4 Hz, 1 H), 4.30-4.38 (m, 1 H), 4.52-4.60 (m, 1 H), 5.16 (d, *J* = 5.4 Hz, 1 H), 6.10-6.45 (m, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-deoxy-7-mercapto-α-thiolincosaminide (6-29)

To a solution of **6-25** (341 mg, 0.44 mmol) in MeOH (4 ml) was added 1 N HCl (2.5 ml). A reaction mixture was stirred at room temperature for 5 min, was added to saturated aqueous $NaHCO_3$, concentrated under reduced pressure to remove MeOH until half volume, extracted with ethyl acetate, dried over $Na_2SO_4$

and concentrated under reduced pressure to obtain methyl (7*S*)-7-acetylthio- 6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-deoxy-α-thiolincosaminide (247 mg, quant) as a colorless solid. To a solution of this intermediate (244 mg, 0.43 mmol) in MeOH (2.5 ml) was added 28% NaOMe/MeOH solution (251 μl, 1.30 mmol), stirred at room temperature for 20 min. The mixture was added to a saturated aqueous $NH_4Cl$, extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 96/4) to obtain the title compound (234 mg, 96.0%) as a colorless solid. ESI-MS *m/z* 523 $(M+H)^+$ as $C_{23}H_{42}N_2O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.92 (t, *J* = 7.0 Hz, 3 H), 1.24-1.41 (m, 5 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.52-1.64 (m, 2 H), 1.77-1.90 (m, 1 H), 1.94-2.06 (m, 1 H), 2.15 (s, 3 H), 3.40-3.64 (m, 2 H), 3.46 (dq, *J* = 7.0, 2.4 Hz, 1 H), 3.54 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.94-4.01 (m, 1 H), 4.06 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.18-4.26 (m, 2 H), 4.32 (dd, *J* = 9.8, 2.4 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-mercapto-α-thiolincosaminide (6-30)

To a solution of **6-26** (565 mg, 0.71 mmol) in MeOH (5.6 ml) was added 1 N HCl (5.6 ml), stirred at room temperature for 100 min. The mixture was added to 8% aqueous $NaHCO_3$, extracted with ethyl acetate, washed with 25% aqueous NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30/1) to obtain methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-7-deoxy-α-thiolincosaminide (378 mg, 91.8%) as a colorless solid.

To a solution of this intermediate (378 mg, 0.65 mmol) in MeOH (4 ml) was added NaOMe (115 mg, 2.02 mmol), stirred at room temperature for 3 h. The mixture was added to 8% aqueous $NaHCO_3$, extracted with ethyl acetate, washed with 25% aqueous NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 40/1) to obtain the title compound (373 mg, quant) as a colorless solid. ESI-MS *m/z* 537$(M+H)^+$ as $C_{24}H_{44}N_2O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.87-0.95 (m, 3 H), 1.23-1.40 (m, 7 H), 1.30 (br d, *J* = 7.2 Hz, 3 H), 1.46 (s, 9 H), 1.50-1.65 (m, 2 H), 1.77-1.89 (m, 1 H), 1.96-2.06 (m, 1 H), 2.15 (s, 3 H), 3.42-3.60 (m, 2 H), 3.45 (dq, *J* = 7.1, 2.3 Hz, 1 H), 3.54 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.94-4.00 (m, 1 H), 4.06 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.10-4.26 (m, 2 H), 4.32 (dd, *J* = 9.8, 2.3 Hz, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-mercapto-α-thiolincosaminide (6-31)

To a solution of **6-27** (565 mg, 0.71 mmol) in MeOH (5.6 ml) was added 5 N HCl (0.3 ml). A reaction mixture was stirred at room temperature for 30 min, added to 8% aqueous $NaHCO_3$, extracted

with ethyl acetate, washed with 25% aqueous NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-7-deoxy-α-thiolincosaminide (410 mg) as a crude compound. Then, the crude compound (410 mg) in MeOH (13 ml) was added and 5 N NaOMe (430 μl, 2.15 mmol) in MeOH at room temperature were treated for 1 h according to the similar procedure as described for the preparation of **6-30** to afford **6-31** (362 mg, 88.0% in 2 steps from **6-27**) as a colorless solid. ESI-MS *m/z* 537 $(M+H)^+$ as $C_{24}H_{44}N_2O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.89 (d, $J$ = 2.8 Hz, 3 H), 0.90 (d, $J$ = 2.9 Hz, 3 H), 1.12-1.27 (m, 3 H), 1.30 (d, $J$ = 7.1 Hz, 3 H), 1.46 (s, 9 H), 1.49-1.60 (m, 1 H), 1.60-1.74 (m, 2 H), 1.75-1.88 (m, 1 H), 1.95-2.04 (m, 1 H), 2.15 (s, 3 H), 3.40-3.59 (m, 2 H), 3.45 (dq, $J$ = 7.1, 2.3 Hz, 1 H), 3.54 (dd, $J$ = 10.2, 3.4 Hz, 1 H), 3.93-4.02 (m, 1 H), 4.06 (dd, $J$ = 10.2, 5.6 Hz, 1 H), 4.11-4.26 (m, 2 H), 4.32 (dd, $J$ = 9.8, 2.3 Hz, 1 H), 5.25 (d, $J$ = 5.6 Hz, 1 H).

## Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-mercapto-α-thiolincosaminide (6-32)

To a solution of **6-28** (5.20 g, 6.55 mmol) in MeOH (70 ml) was added 1 N HCl (26.2 ml). A reaction mixture was stirred at room temperature for 5 min, added to 10% aqueous $NaHCO_3$, concentrated under reduced pressure until half volume to remove MeOH, extracted with ethyl acetate, washed with 25% aqueous NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-α-thiolincosaminide (4.70 g) as a crude compound. Then, the crude compound (4.70 g) and 28% NaOMe/MeOH solution (3.79 ml, 1.06 mmol) in MeOH (38 ml) at room temperature were treated for 15 min according to the similar procedure as described for the preparation of **6-29** to afford **6-32** (3.45 g, 99.0% in 2 steps from **6-28**) as a colorless solid. FAB-MS *m/z* 535 $(M+H)^+$ as $C_{24}H_{42}N_2O_7S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.01-0.06 (m, 2 H), 0.39-0.49 (m, 2 H), 0.63-0.78 (m, 1 H), 1.16-1.28 (m, 2 H), 1.30 (d, $J$ = 7.1 Hz, 3 H), 1.34-1.43 (m, 1 H), 1.47 (s, 9 H), 1.55-1.76 (m, 2 H), 1.82-1.93 (m, 1 H), 2.05-2.14 (m, 1 H), 2.15 (s, 3 H), 3.40-3.66 (m, 2 H), 3.45 (dq, $J$ = 7.1, 2.4 Hz, 1 H), 3.54 (dd, $J$ = 10.3, 3.4 Hz, 1 H), 3.94-4.01 (m, 1 H), 4.06 (dd, $J$ = 10.3, 5.6 Hz, 1 H), 4.13-4.25 (m, 2 H), 4.32 (dd, $J$ = 9.7, 2.4 Hz, 1 H), 5.25 (d, $J$ = 5.6 Hz, 1 H).

## Methyl 6-*N*-((2'*S*, *Z*)-1'-*N*-(2''-nitrophenylsulfonyl)-5'-*n*-propyl-2',3',6',7'-tetrahydro-1*H*-azepine-2'-carbonyl)-α-thiolincosaminide (6-33)

To a solution of **6-16** (482 mg, 1.31 mmol) in DMF (5 ml) were added 1-hydroxybenzotriazole (265 mg, 1.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (376 mg, 1.96 mmol) and MTL (497 mg, 1.96 mmol). A reaction mixture was stirred at room temperature for 14 h. To the mixture were added ethyl acetate and saturated aqueous $NaHCO_3$. The desired compound was extracted with ethyl acetate, washed with $H_2O$, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column

chromatography ($CHCl_3$/MeOH = 50/1 to 30/1) to obtain the title compound (660 mg, 83.6%) as a colorless solid. FAB-MS *m/z* 604 $(M+H)^+$ as $C_{25}H_{37}N_3O_{10}S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.83 (t, *J* = 7.3 Hz, 3 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 1.25-1.37 (m, 2 H), 1.08 (br t, *J* = 7.4 Hz, 2 H), 2.05 (s, 3 H), 2.23-2.56 (m, 3 H), 2.68-2.80 (m, 1 H), 3.58 (dd, *J* = 10.2, 3.4 Hz, 1 H), 3.73-3.88 (m, 3 H), 4.02-4.12 (m, 3 H), 4.36-4.41 (m, 1 H), 4.74 (dd, *J* = 8.0, 3.7 Hz, 1 H), 5.22 (d, *J* = 5.6 Hz, 1 H), 5.39 (br t, *J* = 6.3 Hz, 1 H), 7.74-7.86 (m, 3 H), 8.09-8.17 (m, 1 H).

**Methyl 6-*N*-((2'*S*)-5'-*n*-propylazepane-2-carbonyl)-α-thiolincosaminide (6-34)** (stereochemistry at the C-5' position is not assigned)

To a solution of **6-33** (1.15 g, 1.90 mmol) in DMF (10 ml) at 0°C were added 4-bromobenzenethiol (721 mg, 3.81 mmol) and cesium carbonate (1.25 g, 3.84 mmol). A reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 50/50, then $CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain methyl 6-*N*-((2'*S*, *Z*)-5'-*n*-propyl-2',3',6',7'-tetrahydro-1*H*-azepine-2-carbonyl)- α-thiolincosaminide (649 mg, 81.4%) as a colorless solid. To this intermediate (649 mg, 1.55 mmol) in MeOH (30 ml) was added Pd/C (324 mg) and then vigorously stirred in hydrogen atmosphere of 0.95 MPa at 40°C for 3.5 h. The mixture was filtrated off with celite and the mother liquor was concentrated under reduced pressure. To the resulting residue were added Pd/C (324 mg) and MeOH (30 ml), and then the mixture was vigorously stirred in hydrogen atmosphere of 0.95 MPa at 40°C for 65 h. The mixture was filtrated with celite and concentrated under reduced pressure to obtain the title compound (560 mg, 85.9%) as a colorless solid. FAB-MS *m/z* 421 $(M+H)^+$ as $C_{19}H_{36}N_2O_6S$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{19}H_{36}N_2O_6S$: 421.2372, found: 421.2370; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.90 (t, *J* = 7.2 Hz, 3 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 1.20-1.48 (m, 7 H), 1.59-1.71 (m, 1 H), 1.77-1.88 (m, 1 H), 1.93-2.04 (m, 2 H), 2.08 (s, 3 H), 2.73-2.84 (m, 1 H), 3.03 (ddd, *J* = 13.8, 5.5, 2.1 Hz, 1 H), 3.53-3.62 (m, 2 H), 3.94-4.05 (m, 2 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.15-4.20 (m, 1 H), 4.22-4.26 (m, 1 H), 5.24 (d, *J* = 5.4 Hz, 1 H).

**Methyl 6-*N*-((2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-α-thiolincosaminide (6-35)** (stereochemistry at the C-5' position is not assigned)

To a solution of **6-34** (560 mg, 1.34 mmol) in 1,4-dioxane (10 ml)-$H_2O$ (10 ml) were added $LiOH{\cdot}H_2O$ (84.0 mg, 2.00 mmol) and di-*tert*-butyl dicarbonate (0.37 ml, 1.6 mmol). A reaction mixture was stirred at room temperature for 3 h, added to saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. Then, the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/$CH_3OH$/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound (483.3 mg, 69.5%) as a colorless solid. ESI-MS *m/z* 521 $(M+H)^+$ as $C_{24}H_{44}N_2O_8S$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.96 (m, 3 H), 1.12-1.38 (m, 7 H), 1.47 (s, 9 H), 1.50-1.65 (m, 4 H), 1.66-1.80 (m, 1 H), 1.84-2.14 (m, 2 H), 2.07 (s, 3 H), 3.43-3.55 (m, 2 H), 3.59 (dd, *J* = 10.1, 3.3 Hz, 1 H),

3.75-3.90 (m, 1 H), 3.98-4.18 (m, 3 H), 4.26-4.45 (m, 2 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

**Methyl 6-*N*-((2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-36)** (stereochemistry at the C-5' position is not assigned)

Compound **6-35** (894 mg, 1.72 mmol), trimethylchlorosilane (1.09 ml, 8.59 mmol) and hexamethyldisilazane (1.80 ml, 8.59 mmol) in pyridine (10 ml) were treated for 30 min according to the similar procedure as described for the preparation of **6-21** and then, the crude fully protected intermediate and 2 N acetic acid (2.23 ml) in MeOH (36 ml) were stirred at room temperature for 1 h. The mixture was added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure to afford **6-36** as a crude compound.

**Methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-7-deoxy-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-37)** (stereochemistry at the C-5' position is not assigned)

Crude **6-36**, $Et_3N$ (1.20 ml, 8.58 mmol) and methanesulfonyl chloride (0.53 ml, 6.9 mmol) in $CHCl_3$ (20 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **6-25** and then, the crude mesylate and AcSK (1.19 g, 10.4 mmol) in DMF (9.8 ml) at 80°C were treated for 2 h according to the similar procedure as described for the preparation of **6-25** to afford **6-37** (769 mg, 56.3% in 4 steps from **6-35**) as a colorless solid. FAB-MS *m/z* 795 $(M+H)^+$ as $C_{35}H_{70}N_2O_8S_2Si_3$.

**Methyl 6-*N*-((2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-(7*S*)-7-mercapto-α-thiolincosaminide (6-38)** (stereochemistry at the C-5' position is not assigned)

To a solution of **6-37** (769 mg, 0.97mmol) in MeOH (16 ml) at 0°C was added 1 N HCl (1.6 ml), and then the mixture was stirred at 0°C for 30 min. The mixture was concentrated under reduced pressure to obtain methyl (7*S*)-7-acetylthio-6-*N*-((2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-7-deoxy-α-thiolincosaminide as a crude compound and then, the crude intermediate and 28% NaOMe/MeOH solution (0.24 ml, 0.97 mmol) in MeOH (16 ml) at room temperature were treated for 30 min according to the similar procedure as described for the preparation of **6-29** to afford **6-38** (170 mg, 32.8% in 2 steps from **6-37**) as a colorless solid. ESI-MS *m/z* 537 $(M+H)^+$ as $C_{24}H_{44}N_2O_7S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{24}H_{44}N_2O_7S_2$: 537.2668, found: 537.2668; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.92 (br t, *J* = 6.6 Hz, 3 H), 1.20-1.80 (m, 12 H), 1.48 (s, 9 H), 1.88-2.07 (m, 2 H), 2.15 (s, 3 H), 3.38-3.74 (m, 4 H), 3.76-3.94 (m, 1 H), 4.00-4.12 (m, 2 H), 4.23-4.34 (m, 1 H), 4.36-4.56 (m, 1 H), 5.24 (d, *J* = 5.6 Hz, 1 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-39)**

To a solution of 5-(4-bromophenyl)pyrimidine (103 mg, 0.44 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (18.8 mg, 31.5 μmol) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (13.4 mg, 14.6 μmol) in 1,4-dioxane (2.0 ml) were added compound **6-29** (152 mg, 0.29 mmol) and *N,N*-diisopropylethylamine (0.10 ml, 0.58 mmol). A reaction mixture was refluxed for 6 h, filtrated by either Chromatodisc (0.45 μm) (KURABO INDUSTRIES Ltd., Osaka, Japan) or celite and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (163 mg, 82.8%) as an off white solid. FAB-MS *m/z* 677 $(M+H)^+$ as $C_{33}H_{48}N_4O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*n*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-40)**

Compound **6-30** (150 mg, 0.28 mmol), 5-(4-bromophenyl)pyrimidine (99.3 mg, 0.42 mmol), Xantphos (17.3 mg, 29.0 μmol), $Pd_2(dba)_3$ (13.4 mg, 14.6 μmol), and *N,N*-diisopropylethylamine (97.0 μl, 0.56 mmol) in 1,4-dioxane (2.0 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6-39** to afford **6-40** (150.8 mg, 78.1%) as a colorless solid.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(*i*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-41)**

Compound **6-31** (100 mg, 0.19 mmol), 5-(4-bromophenyl)pyrimidine (50.0 mg, 0.21 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (60.0 μl, 0.35 mmol) in 1,4-dioxane (1.3 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6-39** to afford **6-41** (105 mg, 81.6%) as a colorless solid.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-42)**

Compound **6-32** (1.35 g, 2.52 mmol), 5-(4-bromophenyl)pyrimidine (771 mg, 3.28 mmol), Xantphos (151 mg, 0.25 mmol), $Pd_2(dba)_3$ (117 mg, 0.13 mmol), and *N,N*-diisopropylethylamine (0.88 ml, 5.04 mmol) in 1,4-dioxane (20 ml) were treated for 6 h according to the similar procedure as described for the preparation of **6-39** to afford **6-42** (1.63 g, 93.4%) as an off white solid. ESI-MS *m/z* 689 $(M+H)^+$ as $C_{34}H_{48}N_4O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(*n*-propyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-43)**

To a solution of **6-39** (163 mg, 0.24 mmol) in $CH_2Cl_2$ (3.3 ml) at -20°C was added 2,2,2-trifluoroacetic

acid (0.36 ml). A reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 9/2/0.2) to obtain the title compound (123 mg, 88.4%) as a colorless solid. $[\alpha]_D^{22}$ +85.2° (*c* 1.02, MeOH); ESI-MS *m/z* 577 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_2$; TOF-ESI-HRMS (M+H)+ calcd for $C_{28}H_{40}N_4O_5S_2$: 577.2518, found: 577.2516; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90 (t, *J* = 7.3 Hz, 3 H), 1.02-1.15 (m, 2 H), 1.20-1.29 (m, 2 H), 1.31-1.42 (m, 2 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.49-1.63 (m, 1 H), 1.68-1.77 (m, 1 H), 1.93 (s, 3 H), 1.96-2.05 (m, 1 H), 3.19 (dt, *J* = 10.9, 2.0 Hz, 1 H), 3.15-3.23 (m, 1 H), 3.40 (dd, *J* = 11.9, 2.8 Hz, 1 H), 3.58 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.88 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 3.93 (dq, *J* = 6.8, 2.4 Hz, 1 H), 4.09 (dd, *J* = 10.3, 5.5 Hz, 1 H), 4.44 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.61 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.27 (d, *J* = 5.5 Hz, 1 H), 7.52-7.58 (m, 2 H), 7.66-7.71 (m, 2 H), 9.06 (s, 2 H), 9.11 (s, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(*n*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-44)

Compound **6-40** (151 mg, 0.22 mmol) and 2,2,2-trifluoroacetic acid (0.33 ml) in $CH_2Cl_2$ (3.0 ml) were treated at -20 ºC for 10 min, and then treated room temperature for 2.5 h according to the similar procedure as described for the preparation of **6-43** to afford **6-44** (103 mg, 79.6%) as a colorless solid. $[\alpha]_D^{23}$ +81.2° (*c* 0.78, MeOH); ESI-MS *m/z* 591 $(M+H)^+$ as $C_{29}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{42}N_4O_5S_2$: 591.2675, found: 591.2669; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.85-0.96 (m, 3 H), 1.09-1.22 (m, 2 H), 1.23-1.41 (m, 6 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.51-1.66 (m, 1 H), 1.74-1.84 (m, 1 H), 1.93 (s, 3 H), 2.04-2.12 (m, 1 H), 2.78 (dt, *J* = 12.9, 2.8 Hz, 1 H), 3.21-3.29 (m, 1 H), 3.52 (dd, *J* = 12.1, 2.9 Hz, 1 H), 3.58 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.89 (br dd, *J* = 3.3, 0.8 Hz, 1 H), 3.93 (dq, *J* = 6.8, 2.5 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.45 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.63 (dd, *J* = 10.0, 2.5 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.51-7.58 (m, 2 H), 7.65-7.72 (m, 2 H), 9.06 (s, 2 H), 9.11 (s, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(*i*-butyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-45)

Compound **6-41** (100 mg, 0.15 mmol) and 2,2,2-trifluoroacetic acid (0.50 ml) were treated at 0°C for 1 h according to the similar procedure as described for the preparation of **6-43** to afford **6-45** (55.0 mg, 64.3%) as a colorless solid. $[\alpha]_D^{24}$ +93.9° (*c* 0.83, MeOH); ESI-MS *m/z* 591 $(M+H)^+$ as $C_{29}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{42}N_4O_5S_2$: 591.2675, found: 591.2674; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.91 (d, *J* = 5.7 Hz, 3 H), 0.90 (d, *J* = 5.7 Hz, 3 H), 1.08-1.20 (m, 3 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.64-1.82 (m, 4 H), 1.93 (s, 3 H), 2.03-2.12 (m, 1 H), 2.76-2.86 (m, 1 H), 3.21-3.28 (m, 1 H), 3.51-3.61 (m, 2 H), 3.89 (br dd, *J* = 3.2, 0.8 Hz, 1 H), 3.93 (dq, *J* = 7.0, 2.4 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.45 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.63 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.52-7.57 (m, 2 H), 7.66-7.71 (m, 2 H), 9.06 (s, 2 H), 9.11 (s, 1 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-46)**

Compound **6-42** (1.63 g, 2.36 mmol) and 2,2,2-trifluoroacetic acid (3.5 ml) in $CH_2Cl_2$ (32 ml) were treated at -20 °C for 20 min, and then treated room temperature for 5.5 h according to the similar procedure as described for the preparation of **6-43** to afford **6-46** (1.12 g, 80.9%) as a colorless solid. $[\alpha]_D^{24}$ +86.1° (*c* 0.25, MeOH); ESI-MS *m/z* 589 $(M+H)^+$ as $C_{29}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{40}N_4O_5S_2$: 589.2518, found: 589.2517; IR (KBr) $cm^{-1}$ 1046, 1078, 1415, 1508, 1602, 1653, 1671, 1698, 2338, 2360, 3001, 3347 and 3690 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ -0.01-0.08 (m, 2 H), 0.43-0.52 (m, 2 H), 0.67-0.78 (m, 1 H), 1.14-1.23 (m, 1 H), 1.24-1.40 (m, 3 H), 1.36 (d, *J* = 6.8 Hz, 3 H), 1.75-1.89 (m, 1 H), 1.90-2.00 (m, 1 H), 1.93 (s, 3 H), 2.28-2.37 (m, 1 H), 2.96 (dt, *J* = 13.1, 3.0 Hz, 1 H), 3.33-3.40 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.1 Hz, 1 H), 3.75 (dd, *J* = 12.4, 3.0 Hz, 1 H), 3.90 (br dd, *J* = 3.1, 0.8 Hz, 1 H), 3.93 (dq, *J* = 6.8, 2.5 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.46 (br dd, *J* = 10.0, 0.8 Hz, 1 H), 4.65 (dd, *J* = 10.0, 2.5 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.51-7.57 (m, 2 H), 7.65-7.73 (m, 2 H), 9.06 (s, 2 H), 9.11 (s, 1 H); $^{13}C$ NMR (100 MHz, $CD_3OD$) δ 5.1, 9.2, 13.8, 20.7, 33.8, 38.2, 38.8, 43.5, 44.8, 46.4, 53.8, 61.1, 69.6, 69.9, 71.0, 72.1, 90.2,128.6, 131.7, 133.0, 135.3, 138.6, 155.9, 157.9 and 176.5.

**Methyl (7*S*)-6-*N*-(2'*S*)-1'-*N*-(*tert*-butoxycarbonyl)-5'-*n*-propylazepane-2-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-47)** (stereochemistry at the C-5' position is not assigned)

Compound **6-38** (15.0 mg, 27.9 μmol), 5-(4-bromophenyl)pyrimidine (13.1 mg, 0.056 mmol), Xantphos (3.2 mg, 5.58 μmol), $Pd_2(dba)_3$ (5.1 mg, 5.6 μmol), and *N,N*-diisopropylethylamine (10.0 μl, 55.8 μmol) in 1,4-dioxane (0.2 ml) were treated for 2 h according to the similar procedure as described for the preparation of **6-39** to afford **6-47** (17.0 mg, 88.1%) as a colorless solid. ESI-MS *m/z* 691 $(M+H)^+$ as $C_{34}H_{50}N_4O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*)-5'-*n*-propylazepane-2-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenyl thio)-α-thiolincosaminide (6-48)** (stereochemistry at the C-5' position is not assigned)

Compound **6-47** (15.0 mg, 21.7 μmol) and 2,2,2-trifluoroacetic acid (0.3 ml) were treated at 0 °C for 20 min, and then treated room temperature for 1 h according to the similar procedure as described for the preparation of **6-43** to afford **6-48** (10.0 mg, 78.1%) as a colorless solid. $[\alpha]_D^{24}$ +82.9° (*c* 0.84, MeOH); ESI-MS *m/z* 591 $(M+H)^+$ as $C_{29}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{42}N_4O_5S_2$: 591.2675, found: 591.2667; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 0.91 (t, *J* = 7.1 Hz, 3 H), 1.21-1.45 (m, 5 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.45-1.55 (m, 1 H), 1.55-1.68 (m, 1 H), 1.80-1.91 (m, 1 H), 1.92-2.01 (m, 1 H), 1.94 (s, 3 H), 2.07-2.22 (m, 2 H), 2.98-3.08 (m, 1 H), 3.32-3.39 (m, 1 H), 3.60 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.90 (dd, *J* = 3.3, 0.8 Hz, 1 H), 3.95 (dq, *J* = 6.8, 2.4 Hz, 1 H), 3.98 (dd, *J* = 6.4, 5.1 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.46 (dd, *J* = 10.0, 0.8 Hz, 1 H), 4.64 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.29 (d, *J* = 5.6 Hz, 1 H), 7.52-7.59 (m, 2

H), 7.65-7.74 (m, 2 H), 9.07 (s, 2 H), 9.12 (s, 1 H).

### Methyl 6-*N*-(2,2,2-trifluoroacetyl)-2,3,4,7-tetrakis-*O*-(trimethylsilyl)-α-thiolincosaminide (6-50)

Compound **6-49** (6.88 g, 19.7 mmol), trimethylchlorosilane (12.6 ml, 98.5 mmol) and hexamethyldisilazane (20.6 ml, 98.5 mmol) in pyridine (40 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **6-21** to afford **6-50** (8.87 g, 71.0%) as a colorless solid. FAB-MS *m/z* 638 $(M+H)^+$ as $C_{23}H_{50}F_3NO_6SSi_4$.

### Methyl 6-*N*-(2,2,2-trifluoroacetyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-51)

To a solution of compound **6-50** (8.87 g, 13.9 mmol) in MeOH (65 ml) was added 6 N acetic acid (4.17 ml). A reaction mixture was stirred at room temperature for 15 min, added to saturated aqueous $NaHCO_3$ and concentrated under reduced pressure to remove MeOH. The desired compound was extracted with ethyl acetate, and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 95/5 to 80/20) to obtain the title compound (7.21 g, 91.0% in 2 steps) as a colorless solid. ESI-MS *m/z* 566 $(M+H)^+$ as $C_{20}H_{42}F_3NO_6SSi_3$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.133 (s, 9 H), 0.134 (s, 9 H), 0.14 (s, 9 H), 1.13 (d, $J$ = 6.5 Hz, 3 H), 2.06 (s, 3 H), 3.66 (dd, $J$ = 9.6, 2.4 Hz, 1 H), 3.92 (d, $J$ = 2.4 Hz, 1 H), 4.04 (dq, $J$ = 6.5, 4.5 Hz, 1 H), 4.14 (dd, $J$ = 9.6, 5.5 Hz, 1 H), 4.19 (d, $J$ = 9.6 Hz, 1 H), 4.40 (dd, $J$ = 9.6, 4.5 Hz, 1 H), 5.21 (d, $J$ = 5.5 Hz, 1 H).

### Methyl (7*S*)-7-acetylthio-7-deoxy-6-*N*-(2,2,2-trifluoroacetyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (6-52)

Compound **6-51** (4.42 g, 7.82 mmol), $Et_3N$ (21.8 ml, 15.6 mmol) and methanesulfonyl chloride (1.21 ml, 15.6 mmol) in $CHCl_3$ (20 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **6-25** to afford methyl 7-*O*-methaneslufonyl-6-*N*-(2,2,2-trifluoroacetyl)-2,3,4-tris-*O*-(trimethylsilyl)-α-thiolincosaminide (5.46 g, quant) as a colorless solid. To a solution of this mesylate (5.46 g, 7.82 mmol) in DMF (40 ml) was added AcSK (2.68 g, 23.4 mmol). A reaction mixture was stirred at 80°C for 1.5 h. The mixture was concentrated under reduced pressure, diluted with ethyl acetate and saturated aqueous $NaHCO_3$, extracted with ethyl acetate. The organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. To the resulting residue were added pyridine (16 ml), trimethylchlorosilane (6.35 ml, 50.0 mmol) and hexamethyldisilazane (10.5 ml, 50.0 mmol) and stirred at room temperature for 3 h. The mixture was added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate and then the organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane to hexane/ethyl acetate = 10/1) to obtain the title compound (2.88 g) as a crude compound. The crude compound (306 mg) was suspended in hexane, and then the solid was filtered,

washed with hexane to obtain the title compound (129 mg, 24.8% in 3 steps) as a colorless solid. Because compound **6-52** is partially soluble in hexane, a yield of the third step was low. ESI-MS *m/z* 624 $(M+H)^+$ as $C_{22}H_{44}F_3NO_6S_2Si_3$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.15 (s, 9 H), 0.16 (s, 9 H), 0.22 (s, 9 H), 1.41 (d, *J* = 7.1 Hz, 3 H), 2.01 (s, 3 H), 2.33 (s, 3 H), 3.65 (dd, *J* = 9.5, 2.7 Hz, 1 H), 3.76-3.86 (m, 1 H), 3.97-4.04 (m, 1 H), 4.10 (dd, *J* = 9.5, 5.4 Hz, 1 H), 4.14-4.21 (m, 1 H), 4.34-4.44 (m, 1 H), 5.18 (d, *J* = 5.4 Hz, 1 H), 7.20 (br dd, *J* = 9.5 Hz, 1 H).

### Methyl (7*S*)-7-deoxy-7-mercapto-6-*N*-(2,2,2-trifluoroacetyl)-α-thiolincosaminide (6-53)

Compound **6-52** (2.83 g, 4.54 mmol) and 1 N HCl (18.1 ml) in MeOH (30 ml) were treated at room temperature for 10 min according to the similar procedure as described for the preparation of **6-29** and then, the crude intermediate and 28% NaOMe/MeOH solution (2.63 ml, 8.68 mmol) in MeOH (25 ml) at room temperature were treated for 15 min according to the similar procedure as described for the preparation of **6-29** to afford **6-53** (1.65 g, 99.0% in 2 steps from **6-52**) as a colorless solid. ESI-MS *m/z* 366 $(M+H)^+$ as $C_{11}H_{18}F_3NO_5S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 1.29 (d, *J* = 7.0 Hz, 3 H), 2.16 (s, 3 H), 3.45 (dq, *J* = 7.0, 2.2 Hz, 1 H), 3.54 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.82 (dd, *J* = 3.2, 1.0 Hz, 1 H), 4.08 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.39 (dd, *J* = 9.9, 1.0 Hz, 1 H), 4.55 (dd, *J* = 9.9, 2.2 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H).

### Methyl (7*S*)-7-deoxy-7-((4-(2-dimethylaminoethyl)phenyl)thio-6-*N*-(2,2,2-trifluoroacetyl)-α-thiolincosaminide (6-54)

Compound **6-53** (3.44 g, 9.42 mmol), 2-(4-bromophenyl)-*N*,*N*-dimethylethanamine (3.22 g, 14.1 mmol), Xantphos (545 mg, 0.94 mmol), $Pd_2(dba)_3$ (431 mg, 0.47 mmol), and *N,N*-diisopropylethylamine (3.28 ml, 18.8 mmol) in 1,4-dioxane (37 ml) were treated for 17 h according to the similar procedure as described for the preparation of **6-39** to afford **6-54** (3.85 g, 79.8%) as a colorless solid. FAB-MS *m/z* 513 $(M+H)^+$ as $C_{21}H_{31}F_3N_2O_5S_2$; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 1.27 (d, *J* = 6.9 Hz, 3 H), 2.01 (s, 3 H), 2.36 (s, 6 H), 2.58-2.68 (m, 2 H), 2.74-2.84 (m, 2 H), 3.59 (dd, *J* = 10.3, 3.2 Hz, 1 H), 3.76 (dq, *J* = 6.9, 2.8 Hz, 1 H), 3.87-3.92 (m, 1 H), 4.09 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.59 (dd, *J* = 9.4, 0.7 Hz, 1 H), 4.64 (dd, *J* = 9.4, 2.8 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.16-7.22 (m, 2 H), 7.33-7.39 (m, 2 H).

### Methyl (7*S*)-7-deoxy-7-((4-(2-dimethylaminoethyl)phenyl)thio-α-thiolincosaminide (6-55)

To a solution of **6-54** (3.85 g, 7.51 mmol) in $CH_2Cl_2$ (73 ml) were added *N*-benzyl-*N*, *N, N*-triethylammonium bromide (171 mg, 0.75 mmol) and 20% aqueous potassium hydroxide (5.1 ml). A reaction mixture was stirred at room temperature for 4 h. To a solution of mixture was added 1 N HCl to adjust at pH 7 and then the solution was concentrated under reduced pressure. The resulting residue was diluted with MeOH, filtrated, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 20/1/0.1 to 10/1/0.1) to obtain the title compound (2.94 g, 94.0%) as off white solid. $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ 1.41 (d, *J* = 7.1 Hz, 3 H), 1.92

(s, 3 H), 2.30 (s, 6 H), 2.51-2.59 (m, 2 H), 2.73-2.81 (m, 2 H), 3.20 (dd, *J* = 8.8, 2.7 Hz, 1 H), 3.59 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.63 (dq, *J* = 7.1, 2.7 Hz, 1 H), 4.04-4.13 (m, 2 H), 4.23 (dd, *J* = 8.8, 1.2 Hz, 1 H), 5.22 (d, *J* = 5.8 Hz, 1 H), 7.14-7.20 (m, 2 H), 7.31-7.37 (m, 2 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-((4-(2-dimethylaminoethyl)phenyl)thio-α-thiolincosaminide (6-56)

Compound **6-14** (1.15 g, 4.04 mmol), **6-55** (2.02 g, 4.85 mmol), 1-hydroxybenzotriazole (0.82 g, 6.06 mmol) and EDC·HCl (1.16 g, 6.06 mmol) in DMF (20 ml) were treated for 5.5 h according to the similar procedure as described for the preparation of **6-33** to afford the title compound (2.00 g, 72.6%) as a colorless solid. ESI-MS *m/z* 682 $(M+H)^+$ as $C_{34}H_{55}N_3O_7S_2$.

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-((4-(2-dimethylaminoethyl)phenyl)thio-α-thiolincosaminide (6-57)

Compound **6-56** (2.00 g, 2.93 mmol) and 2,2,2-trifluoroacetic acid (3.25 ml) in $CH_2Cl_2$ (5.0ml) were treated at 0°C for 3.5 h according to the similar procedure as described for the preparation of **6-43** to afford **6-57** (1.69 g, 98.9%) as a colorless solid. $[\alpha]_D^{23}$ +101.3° (*c* 0.65, MeOH); ESI-MS *m/z* 582 $(M+H)^+$ as $C_{29}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{47}N_3O_5S_2$: 582.3035, found: 582.3032; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.02-0.06 (m, 2 H), 0.40-0.50 (m, 2 H), 0.67-0.78 (m, 1 H), 1.02-1.25 (m, 4 H), 1.25 (d, *J* = 7.0 Hz, 3 H), 1.60-1.74 (m, 1 H), 1.75-1.84 (m, 1 H), 1.97 (s, 3 H), 2.04-2.12 (m, 1 H), 2.31 (s, 6 H), 2.52-2.61 (m, 2 H), 2.62-2.72 (m, 1 H), 2.73-2.81 (m, 2 H), 3.13-3.21 (m, 1 H), 3.34 (dd, *J* = 11.8, 2.9 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.76 (dq, *J* = 7.0, 2.4 Hz, 1 H), 3.85 (dd, *J* = 3.3, 0.8 Hz, 1 H), 4.08 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.40 (dd, *J* = 9.9, 0.8 Hz, 1 H), 4.52 (dd, *J* = 9.9, 2.4 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 7.15-7.19 (m, 2 H), 7.29-7.41 (m, 2 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-((4-(2-dimethylaminoethyl)phenyl)thio-α-thiolincosaminide (6-58)

To a solution of **6-57** (1.19 g, 2.04 mmol) in MeOH (21 ml) were added 36% aqueous HCHO (0.51 ml, 6.12 mmol), AcOH (0.35 ml, 6.12 mmol) and $NaBH(OAc)_3$ (2.59 g, 12.2 mmol). A reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate and saturated aqueous $NaHCO_3$, extracted with ethyl acetate/MeOH = 5/1. The organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 20/1/0.1) to obtain the title compound (1.10 g, 90.9%) as a colorless solid. $[\alpha]_D^{22}$ +88.4° (*c* 1.58, MeOH); ESI-MS *m/z* 596 $(M+H)^+$ as $C_{30}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{49}N_3O_5S_2$: 596.3192, found: 596.3188; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.05-0.06 (m, 2 H), 0.38-0.49 (m, 2 H), 0.63-0.76 (m, 1 H), 1.13-1.38 (m, 4 H), 1.27 (d, *J* = 7.0 Hz, 3 H), 1.40-1.57 (m, 1 H), 1.75-1.84 (m, 1 H), 1.92-2.10 (m, 1 H), 1.99 (s, 3 H), 2.10-2.21 (m, 1 H), 2.26

(s, 3 H), 2.41 (s, 6 H), 2.60-2.73 (m, 3 H), 2.77-2.86 (m, 2 H), 2.92-3.02 (m, 1 H), 3.58 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.75-3.85 (m, 2 H), 4.10 (dd, *J* = 10.1, 5.6 Hz, 1 H), 4.41 (br dd, *J* = 9.8, 0.6 Hz, 1 H), 4.54 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.33-7.39 (m, 2 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrrolidin-1-ylmethyl)phenylthio)-α-thiolincosaminide (6-59)**

Compound **6-32** (40.2 mg, 73.9 μmol), 1-(4-bromobenzyl)pyrrolidine (64.6 mg, 0.27 mmol), Xantphos (4.6 mg, 7.70 μmol), $Pd_2(dba)_3$ (4.0 mg, 4.30 μmol), and *N,N*-diisopropylethylamine (38.5 μl, 0.22 mmol) in 1,4-dioxane (1 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6-39** to afford **6-59** (41.4 mg, 80.7%) as a colorless solid. FAB-MS *m/z* 694 $(M+H)^+$ as $C_{35}H_{55}N_3O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)phenylthio)-α-thiolincosaminide (6-60)**

Compound **6-32** (222 mg, 0.42mmol), 3-(4-bromophenyl)-1-methyl-1,2,5,6-tetrahydropyridine (126 mg, 0.50 mmol), Xantphos (25.8 mg, 43.0 μmol), $Pd_2(dba)_3$ (19.4 mg, 21.0 μmol), and *N,N*-diisopropylethylamine (144 μl, 0.83 mmol) in 1,4-dioxane (3.5 ml) were treated for 5 h according to the similar procedure as described for the preparation of **6-39** to afford **6-60** (251.9 mg, 85.8%) as a colorless solid. ESI-MS *m/z* 706 $(M+H)^+$ as $C_{36}H_{55}N_3O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methylpiperidin-3-yl)phenylthio)-α-thiolincosaminide (6-61)**
(a diastereo mixture at an *N*-methylpiperidine ring)

To a solution of **6-60** (202 mg, 0.29 mmol) in toluene (10 ml) was added 4-methylbenzenesulfonohydrazide (1.10 g, 5.72 mmol) at room temperature. A reaction mixture was refluxed for 3 h. To the mixture was further added 4-methylbenzenesulfonohydrazide (1.09 g, 5.70 mmol), and then stirred for 2.5 h under the reflux condition. The solution was added to 1 N NaOH, extracted with ethyl acetate. The organic phase was dried over $Na_2SO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($CHCl_3$/MeOH/28% aq $NH_4OH$ = 10/1/0.1) to obtain the title compound (27.7 mg, 13.7%) as a colorless solid. ESI-MS *m/z* 708 $(M+H)^+$ as $C_{36}H_{57}N_3O_7S_2$.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyridin-3-yl)phenylthio)-α-thiolincosaminide (6-62)**

Compound **6-32** (30.0 mg, 56.1 μmol), 3-(4-iodophenyl)pyridine (18.9 mg, 67.3 μmol), Xantphos (7.8 mg, 13.5 μmol), $Pd_2(dba)_3$ (5.1 mg, 5.6 μmol), and *N,N*-diisopropylethylamine (19.5 μl, 0.11 mmol) in 1,4-dioxane (0.5 ml) were treated for 5 h according to the similar procedure as described for the preparation

of **6-39** to afford **6-62** (39.3 mg as crude).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrazin-2-yl)phenylthio)-α-thiolincosaminide (6-63)

Compound **6-32** (80.0 mg, 0.15 mmol), 2-(4-bromophenyl)pyrazine (50.0 mg, 0.21 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (60.0 μl, 0.35 mmol) in 1,4-dioxane (1.5 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6-39** to afford **6-63** as a crude compound

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-1'-*N*-(*tert*-butoxycarbonyl)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1,2,3-thiadiazol-4-yl)phenylthio)-α-thiolincosaminide (6-64)

Compound **6-32** (80.0 mg, 0.15 mmol), 4-(4-bromophenyl)-1,2,3-thiadiazole (50.0 mg, 0.21 mmol), Xantphos (10.0 mg, 17.3 μmol), $Pd_2(dba)_3$ (10.0 mg, 10.9 μmol), and *N,N*-diisopropylethylamine (60.0 μl, 0.35 mmol) in 1,4-dioxane (1.5 ml) were treated for 4 h according to the similar procedure as described for the preparation of **6-39** to afford **6-64** as a crude compound. ESI-MS *m/z* 695 $(M+H)^+$ as $C_{32}H_{46}N_4O_7S_3$.

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrrolidin-1-ylmethyl)phenylthio)-α-thiolincosaminide (6-65)

Compound **6-59** (41.4 mg, 59.7 μmol) and 2,2,2-trifluoroacetic acid (0.09 ml) in $CH_2Cl_2$ (0.9 ml) were treated at -20°C for 5 min, and then treated room temperature for 5 h according to the similar procedure as described for the preparation of **6-43** to afford **6-65** (28.8 mg, 81.3%) as a colorless solid. $[\alpha]_D^{23}$ +68.9° (*c* 0.20, MeOH); ESI-MS *m/z* 594 $(M+H)^+$ as $C_{30}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{47}N_3O_5S_2$: 594.3035, found: 594.3031; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.01-0.06 (m, 2 H), 0.39-0.50 (m, 2 H), 0.66-0.79 (m, 1 H), 1.02-1.26 (m, 4 H), 1.28 (d, *J* = 6.8 Hz, 3 H), 1.60-1.74 (m, 1 H), 1.74-1.87 (m, 5 H), 1.93 (s, 3 H), 2.05-2.17 (m, 1 H), 2.49-2.60 (m, 4 H), 2.62-2.74 (m, 1 H), 3.12-3.24 (m, 1 H), 3.37 (dd, *J* = 11.8, 2.8 Hz, 1 H), 3.57 (dd, *J* = 10.2, 3.3Hz, 1 H), 3.63 (s, 2 H), 3.81 (dq, *J* = 6.8, 2.3 Hz, 1 H), 3.86 (br dd, *J* = 3.3, 0.7 Hz, 1 H), 4.08 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.38-4.46 (m, 1 H), 4.55 (dd, *J* = 10.1, 2.3 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.26-7.32 (m, 2 H), 7.34-7.39 (m, 2 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrrolidin-1-ylmethyl)phenylthio)-α-thiolincosaminide (6-66)

Compound **6-65** (16.4 mg, 27.6 μmol), 36% aqueous formaldehyde (21 μl, 0.28 mmol), AcOH (16 μl, 0.28 mmol) and $NaBH(OAc)_3$ (61.4 mg, 0.28 mmol) in MeOH (1.0 ml) were treated at room temperature for 2 h according to the similar procedure as described for the preparation of **6-58** to afford **6-66** (14.7 mg, 87.6%) as a colorless solid. $[\alpha]_D^{22}$ +65.9° (*c* 0.11, MeOH); ESI-MS *m/z* 608 $(M+H)^+$ as $C_{31}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)_+$ calcd for $C_{31}H_{49}N_3O_5S_2$: 608.3192, found: 608.3187; $^1$H NMR (400 MHz,

$CD_3OD$) $\delta$ -0.05-0.07 (m, 2 H), 0.37-0.51 (m, 2 H), 0.64-0.78 (m, 1 H), 1.10-1.22 (m, 2 H), 1.23-1.39 (m, 2 H), 1.30 (d, *J* = 6.8 Hz, 3 H), 1.41-1.58 (m, 1 H), 1.73-1.88 (m, 5 H), 1.91-2.01 (m, 1 H), 1.95 (s, 3 H), 2.07-2.19 (m, 1 H), 2.56 (s, 3 H), 2.53-2.66 (m, 5 H), 2.92-3.01 (m, 1 H), 3.57 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.65 (s, 2 H), 3.79-3.89 (m, 2 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37-4.44 (m, 1 H), 4.56 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 7.26-7.33 (m, 2 H), 7.35-7.43 (m, 2 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)phenylthio)-α-thiolincosaminide (6-67)**

Compound **6-60** (26.6 mg, 0.37 mmol) and 2,2,2-trifluoroacetic acid (60 µl) in $CH_2Cl_2$ (0.6 ml) were treated at -20°C for 20 min, and then treated room temperature for 4 h according to the similar procedure as described for the preparation of **6-43** to afford **6-67** (21.5 mg, 94.2%) as a colorless solid. $[\alpha]_D^{22}$ +91.4° (*c* 1.82, MeOH); ESI-MS *m/z* 606 $(M+H)^+$ as $C_{31}H_{47}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{47}N_3O_5S_2$: 606.3035, found: 606.3012; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.07-0.03 (m, 2 H), 0.38-0.48 (m, 2 H), 0.62-0.75 (m, 1 H), 1.07-1.25 (m, 4 H), 1.25 (d, *J* = 6.8 Hz, 3 H), 1.63-1.78 (m, 1 H), 1.78-1.87 (m, 1 H), 1.90 (s, 3 H), 2.10-2.19 (m, 1 H), 2.33-2.41 (m, 2 H), 2.44 (s, 3 H), 2.66 (t, *J* = 5.9 Hz, 2 H), 2.80 (dt, *J* = 12.9, 2.7 Hz, 1 H), 3.21-3.39 (m, 1 H), 3.32-3.38 (m, 2 H), 3.53-3.62 (m, 2 H), 3.80 (dq, *J* = 6.8, 2.4 Hz, 1 H), 3.89 (dd, *J* = 3.2, 0.7 Hz, 1 H), 4.09 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.43 (dd, *J* = 10.0, 0.7 Hz, 1 H), 4.57 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 6.17-6.23 (m, 1 H), 7.29-7.40 (m, 4 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)phenylthio)-α-thiolincosaminide (6-68)**

Compound **6-67** (38.4 mg, 0.063 mmol), 36% aqueous formaldehyde (48.0 µl, 0.65mmol), AcOH (36.5 µl, 0.64 mmol) and $NaBH(OAc)_3$ (141 mg, 0.63 mmol) in MeOH (2.2 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **6-58** to afford **6-68** (36.0 mg, 91.6%) as an off white solid. $[\alpha]_D^{23}$ +67.4° (*c* 2.48, MeOH); ESI-MS *m/z* 620 $(M+H)^+$ as $C_{32}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{32}H_{49}N_3O_5S_2$: 620.3192, found: 620.3187; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.05-0.06 (m, 2 H), 0.38-0.49 (m, 2 H), 0.63-0.76 (m, 1 H), 1.10-1.23 (m, 2 H), 1.24-1.43 (m, 2 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.52-1.67 (m, 1 H), 1.81-1.90 (m, 1 H), 1.94 (s, 3 H), 2.00-2.09 (m, 1 H), 2.31-2.46 (m, 1 H), 2.41 (s, 3 H), 2.46-2.56 (m, 2 H), 2.69 (s, 3 H), 2.90-3.00 (m, 3 H), 3.06-3.15 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.62-3.69 (m, 2 H), 3.78-3.87 (m, 2 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.43 (dd, *J* = 9.9, 0.6 Hz, 1 H), 4.59 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 6.23-6.29 (m, 1 H), 7.32-7.42 (m, 4 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methylpiperidin-3-yl)phenylthio)-α-thiolincosaminide (6-69)** (a diastero mixture at an *N*-methylpiperidine ring)

Compound **6-61** (6.90 mg, 9.75 μmol) and 2,2,2-trifluoroacetic acid (20 μl) in $CH_2Cl_2$ (0.2 ml) were treated at -20°C for 20 min, and then treated room temperature for 4 h according to the similar procedure as described for the preparation of **6-43** to afford **6-69** (4.5 mg, 76.0%) as a colorless solid. $[\alpha]_D^{23}$ +81.6° (*c* 0.65, MeOH); ESI-MS *m/z* 608 $(M+H)^+$ as $C_{31}H_{49}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{49}N_3O_5S_2$: 608.3192, found: 608.3175; $^1$H NMR (400 MHz,$CD_3OD$) $\delta$ -0.06-0.04 (m, 2 H), 0.37-0.47 (m, 2 H), 0.60-0.75 (m, 1 H), 1.08-1.28 (m, 4 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.38-1.52 (m, 1 H), 1.63-1.78 (m, 2 H), 1.78-1.89 (m, 3 H), 1.90 (s, 3 H), 2.12-2.24 (m, 3 H), 2.37 (s, 3 H), 2.72-2.83 (m, 2 H), 2.94-3.04 (m, 2 H), 3.18-3.26 (m, 1 H), 3.46-3.56 (m, 2 H), 3.73 (dq, *J* = 6.9, 2.3 Hz, 1 H), 3.79-3.85 (m, 1 H), 4.03 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.37 (m, 1 H), 4.50 (dd, *J* = 9.9, 2.3 Hz, 1 H), 5.21 (d, *J* = 5.6 Hz, 1 H), 7.12-7.19 (m, 2 H), 7.28-7.34 (m, 2 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(1-methylpiperidin-3-yl)phenylthio)-α-thiolincosaminide (6-70)** (a diastero mixture at an *N*-methylpiperidine ring)

Compound **6-69** (9.40 mg, 15.4 μmol), 36% aqueous formaldehyde (12.0 μl, 0.16 mmol), AcOH (9.0 μl, 0.16 mmol) and $NaBH(OAc)_3$ (37.1 mg, 0.17 mmol) in MeOH (0.6 ml) were treated at room temperature for 1.5 h according to the similar procedure as described for the preparation of **6-58** to afford **6-70** (9.4 mg, 97.8%) as a colorless solid. $[\alpha]_D^{22}$ +70.1° (*c* 0.15, MeOH); ESI-MS *m/z* 622 $(M+H)^+$ as $C_{32}H_{51}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{32}H_{51}N_3O_5S_2$: 622.3348, found: 622.3342; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.28 to -0.16 (m, 2 H), 0.29-0.39 (m, 2 H), 0.55-0.67 (m, 1 H), 1.04-1.14 (m, 2 H), 1.15-1.31 (m, 2 H), 1.19 (d, *J* = 6.8 Hz, 3 H), 1.38-1.57 (m, 2 H), 1.65-1.78 (m, 2 H), 1.79-1.89 (m, 2 H), 1.86 (s, 3 H), 1.89-1.97 (m, 1 H), 2.09-2.20 (m, 1 H), 2.23 (s, 3 H), 2.32-2.45 (m, 2 H), 2.47 (s, 3 H), 2.65 (br dd, *J* = 11.5, 2.4 Hz, 1 H), 2.73-2.84 (m, 1 H), 2.90-2.97 (m, 1 H), 3.05-3.15 (m, 2 H), 3.48 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.64-3.76 (m, 2 H), 4.00 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.30 (d, *J* = 9.8 Hz, 1 H), 4.46 (dd, *J* = 9.8, 2.6 Hz, 1 H), 5.16 (d, *J* = 5.6 Hz, 1 H), 7.09-7.16 (m, 2 H), 7.25-7.34 (m, 2 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyridin-3-yl)phenylthio)-α-thiolincosaminide (6-71)**

Compound **6-62** (39.3 mg, 57.1 μmol) and 2,2,2-trifluoroacetic acid (0.5 ml) in $CH_2Cl_2$ (0.1 ml) were treated at 0°C for 1 h according to the similar procedure as described for the preparation of **6-43** to afford **6-71** (17.2 mg, 52.0% in 2 steps from **6-32**) as a colorless solid. $[\alpha]_D^{23}$ +92.4° (*c* 1.12, MeOH); ESI-MS *m/z* 588 $(M+H)^+$ as $C_{30}H_{41}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{41}N_3O_5S_2$: 588.2566, found: 588.2560; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.04-0.05 (m, 2 H), 0.39-0.49 (m, 2 H), 0.65-0.76 (m, 1 H),

1.09-1.25 (m, 4 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.65-1.79 (m, 1 H), 1.79-1.88 (m, 1 H), 1.95 (s, 3 H), 2.10-2.20 (m, 1 H), 3.23 (dt, *J* = 10.9, 1.9 Hz, 1 H), 3.18-3.27 (m, 1 H), 3.49 (dd, *J* = 12.0, 2.9 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.4 Hz, 1 H), 3.86-3.95 (m, 2 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.45 (br dd, *J* = 9.9, 0.7 Hz, 1 H), 4.61 (dd, *J* = 9.9, 2.4 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.46-7.55 (m, 3 H), 7.58-7.66 (m, 2 H), 8.07 (ddd, *J* = 7.9, 2.3, 1.5 Hz, 1 H), 8.50 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.79 (dd, *J* = 2.3, 0.8 Hz, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(pyridin-3-yl)phenylthio)-α-thiolincosaminide (6-72)

Compound **6-71** (20.0 mg, 34.0 μmol), 36% aqueous formaldehyde (25.0 μl, 0.34 mmol), AcOH (19.0 μl, 0.30 mmol) and $NaBH(OAc)_3$ (18.0 mg, 84.9 μmol) in MeOH (2.2 ml) were treated at 0 °C for 1 h according to the similar procedure as described for the preparation of **6-58** to afford **6-72** (20.0 mg, 97.6%) as a colorless solid. $[\alpha]_D^{24}$ +57.4° (*c* 0.28, MeOH); ESI-MS *m/z* 602 $(M+H)^+$ as $C_{31}H_{43}N_3O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{31}H_{43}N_3O_5S_2$: 602.2722, found: 602.2714; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.05-0.05 (m, 2 H), 0.38-0.48 (m, 2 H), 0.62-0.74 (m, 1 H), 1.07-1.43 (m, 4 H), 1.37 (d, *J* = 7.0 Hz, 3 H), 1.54-1.69 (m, 1 H), 1.83-1.92 (m, 1 H), 1.96 (s, 3 H), 2.03-2.11 (m, 1 H), 2.40-2.55 (m, 1 H), 2.47 (s, 3 H), 2.98-3.08 (m, 1 H), 3.10-3.20 (m, 1 H), 3.59 (dd, *J* = 10.3, 3.3 Hz, 1 H), 3.85 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 3.91 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.46 (br dd, *J* = 9.9, 0.7 Hz, 1 H), 4.64 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.5 Hz, 1 H), 7.50-7.56 (m, 2 H), 7.51 (ddd, *J* = 8.0, 4.9, 0.8 Hz, 1 H), 7.60-7.67 (m, 2 H), 8.08 (ddd, *J* = 8.0, 2.3, 1.5 Hz, 1 H), 8.51 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.79 (br dd, *J* = 2.3, 0.8 Hz, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrazin-2-yl)phenylthio)-α-thiolincosaminide (6-73)

Compound **6-63** (crude) and 2,2,2-trifluoroacetic acid (0.5 ml) were treated at 0°C for 30 min according to the similar procedure as described for the preparation of **6-43** to afford **6-73** (41.1 mg, 47.5% in 2 steps from **6-32**) as a colorless solid. $[\alpha]_D^{22}$ +78.5° (*c* 1.20, MeOH); ESI-MS *m/z* 589 $(M+H)^+$ as $C_{29}H_{40}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{29}H_{40}N_4O_5S_2$: 589.2518, found: 589.2514; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.03-0.04 (m, 2 H), 0.40-0.48 (m, 2 H), 0.64-0.75 (m, 1 H), 1.09-1.27 (m, 4 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.65-1.78 (m, 1 H), 1.79-1.87 (m, 1 H), 1.91 (s, 3 H), 2.10-2.18 (m, 1 H), 2.70-2.81 (m, 1 H), 3.19-3.26 (m, 1 H), 3.49 (dd, *J* = 12.0, 2.9 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.89 (dd, *J* = 3.2, 0.8 Hz, 1 H), 3.94 (dq, *J* = 6.9, 2.4 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.45 (dd, *J* = 10.0, 0.8 Hz, 1 H), 4.63 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.99-8.06 (m, 2 H), 8.50 (d, *J* = 2.6 Hz, 1 H), 8.64 (dd, *J* = 2.6, 1.5 Hz, 1 H), 9.08 (d, *J* = 1.5 Hz, 1 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrazin-2-yl)phenylthio)-α-thiolincosaminide (6-74)**

Compound **6-73** (31.0 mg, 52.7 μmol), 36% aqueous formaldehyde (12.0 μl, 0.15 mmol), AcOH (17.0 μl, 0.30 mmol) and $NaBH(OAc)_3$ (31.6 mg, 0.15 mmol) in MeOH (0.5 ml) were treated at room temperature for 30 min according to the similar procedure as described for the preparation of **6-58** to afford **6-74** (28.4 mg, 94.0%) as a colorless solid. $[\alpha]_D^{25}$ +72.4° (*c* 0.64, MeOH); ESI-MS *m/z* 603 $(M+H)^+$ as $C_{30}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{42}N_4O_5S_2$: 603.2675, found: 603.2672; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.06-0.04 (m, 2 H), 0.37-0.47 (m, 2 H), 0.60-0.74 (m, 1 H), 1.08-1.22 (m, 2 H), 1.25-1.38 (m, 2 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.46-1.60 (m, 1 H), 1.78-1.85 (m, 1 H), 1.92 (s, 3 H), 1.95-2.02 (m, 1 H), 2.20-2.30 (m, 1 H), 2.34 (s, 3 H), 2.77 (br dd, *J* = 11.4, 2.1 Hz, 1 H), 2.99-3.07 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.85 (dd, *J* = 3.2, 0.6 Hz, 1 H), 3.96 (dq, *J* = 6.9, 2.6 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.45 (br dd, *J* = 9.9, 0.6 Hz, 1 H), 4.64 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.50-7.56 (m, 2 H), 8.01-8.07 (m, 2 H), 8.50 (d, *J* = 2.5 Hz, 1 H), 8.65 (dd, *J* = 2.5, 1.5 Hz, 1 H), 9.09 (d, *J* = 1.5 Hz, 1 H).

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(pyrimidin-5-yl)phenylthio)-α-thiolincosaminide (6-75)**

Compound **6-46** (894 mg, 1.52 mmol), 36% aqueous formaldehyde (1.10 ml, 14.8 mmol), AcOH (0.85 ml, 14.8 mmol) and $NaBH(OAc)_3$ (3.31 g, 14.8 mmol) in MeOH (44 ml) were treated at room temperature for 1 h according to the similar procedure as described for the preparation of **6-58** to afford **6-75** (916 mg, quant) as a colorless solid. $[\alpha]_D^{22}$ +75.4° (*c* 0.96, MeOH); ESI-MS *m/z* 603 $(M+H)^+$ as $C_{30}H_{42}N_4O_5S_2$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{30}H_{42}N_4O_5S_2$: 603.2675, found: 603.2672; IR (KBr) $cm^{-1}$ 1077, 1415, 1508, 1653, 2361, 3020 and 3690; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ -0.06-0.04 (m, 2 H), 0.37-0.46 (m, 2 H), 0.63-0.73 (m, 1 H), 1.12-1.19 (m, 2 H), 1.25-1.38 (m, 2 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.44-1.58 (m, 1 H), 1.75-1.84 (m, 1 H), 1.92-2.02 (m, 1 H), 1.94 (s, 3 H), 2.18 (dt, *J* = 12.1, 2.3 Hz, 1 H), 2.30 (s, 3 H), 2.69 (dd, *J* = 11.6, 2.7 Hz, 1 H), 2.95-3.03 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.1 Hz, 1 H), 3.85 (br dd, *J* = 3.1, 0.7 Hz, 1 H), 3.95 (dq, *J* = 6.8, 2.7 Hz, 1 H), 4.11 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.43 (br dd, *J* = 9.9, 0.7 Hz, 1 H), 4.64 (dd, *J* = 9.9, 2.7 Hz, 1 H), 5.27 (d, *J* = 5.6 Hz, 1 H), 7.52-7.58 (m, 2 H), 7.65-7.72 (m, 2 H), 9.06 (s, 2 H), 9.11 (s, 1 H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 5.1, 9.3, 13.9, 20.8, 30.8, 32.8, 37.3, 38.5, 42.6, 44.6, 44.8, 53.8, 56.8, 69.5, 70.2, 70.8, 70.9, 72.2, 90.3, 128.6, 131.9, 133.0, 135.2, 138.4, 155.9, 157.9 and 176.3.

**Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)piperidine-2'-carbonyl)-7-deoxy-7-(4-(1,2,3-thiadiazol-4-yl)phenylthio)-α-thiolincosaminide (6-76)**

Compound **6-64** (crude) and 2,2,2-trifluoroacetic acid (0.50 ml) were treated at 0°C for 30 min according to the similar procedure as described for the preparation of **6-43** to afford **6-76** (44.3 mg, 50.6% in 2 steps from **6-32**) as a colorless solid. $[\alpha]_D^{27}$ +80.4° (*c* 0.36, MeOH); ESI-MS *m/z* 595 $(M+H)^+$ as $C_{27}H_{38}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{27}H_{38}N_4O_5S_3$: 595.2083, found: 595.2073; $^1$H NMR (400

MHz, $CD_3OD$) $\delta$ 0.01-0.09 (m, 2 H), 0.43-0.54 (m, 2 H), 0.66-0.78 (m, 1 H), 1.15-1.22 (m, 1 H), 1.25-1.45 (m, 3 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.77-1.91 (m, 1 H), 1.94 (s, 3 H), 1.96-2.04 (m, 1 H), 2.32-2.41 (m, 1 H), 3.02 (dt, *J* = 13.1, 3.1 Hz, 1 H), 3.37-3.45 (m, 1 H), 3.59 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.38 (dd, *J* = 12.6, 3.1 Hz, 1 H), 3.89 (dd, *J* = 3.2, 0.9 Hz, 1 H), 3.94 (dq, *J* = 6.9, 2.5 Hz, 1 H), 4.10 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.47 (dd, *J* = 9.9, 0.9 Hz, 1 H), 4.66 (dd, *J* = 9.9, 2.5 Hz, 1 H), 5.28 (d, *J* = 5.6 Hz, 1 H), 7.49-7.56 (m, 2 H), 8.01-8.09 (m, 2 H), 9.22 (s, 1 H).

### Methyl (7*S*)-6-*N*-((2'*S*, 4'*R*)-4'-(cyclopropylmethyl)-1'-*N*-methylpiperidine-2'-carbonyl)-7-deoxy-7-(4-(1,2,3-thiadiazol-4-yl)phenylthio)-α-thiolincosaminide (6-77)

Compound **6-76** (29.7 mg, 49.9 μmol), 36% aqueous formaldehyde (12 μl, 0.15 mmol), AcOH (17 μl, 0.30 mmol) and $NaBH(OAc)_3$ (31.6 mg, 0.15 mmol) in MeOH (0.5 ml) were treated at room temperature for 30 min according to the similar procedure as described for the preparation of **6-58** to afford **6-77** (27.3 mg, 90.0%) as a colorless solid. $[\alpha]_D^{23}$ +48.9° (*c* 0.28, MeOH); ESI-MS *m/z* 609 $(M+H)^+$ as $C_{28}H_{40}N_4O_5S_3$; TOF-ESI-HRMS $(M+H)^+$ calcd for $C_{28}H_{40}N_4O_5S_3$: 609.2239, found: 609.2231; $^1H$ NMR (400 MHz, $CD_3OD$) $\delta$ -0.14-0.04 (m, 2 H), 0.30-0.40 (m, 2 H), 0.52-0.65 (m, 1 H), 1.00-1.18 (m, 2 H), 1.25-1.38 (m, 2 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.50-1.67 (m, 1 H), 1.78-1.88 (m, 1 H), 1.86 (s, 3 H), 1.97-2.06 (m, 1 H), 2.49 (s, 3 H), 2.50-2.64 (m, 1 H), 3.10-3.19 (m, 2 H), 3.51 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.77 (br dd, *J* = 3.2, 0.9 Hz, 1 H), 3.84 (dq, *J* = 7.0, 2.6 Hz, 1 H), 4.01 (dd, *J* = 10.2, 5.6 Hz, 1 H), 4.40 (br dd, *J* = 9.9, 0.9 Hz, 1 H), 4.57 (dd, *J* = 9.9, 2.6 Hz, 1 H), 5.18 (d, *J* = 5.6 Hz, 1 H), 7.42-7.49 (m, 2 H), 7.93-7.99 (m, 2 H), 9.14 (s, 1 H).

# References


1. Reinert, R. R., van der Linden, M. & Al-Lahham, A. Molecular characterization of the first telithromycin-resistant *Streptococcus pneumoniae* isolate in Germany. *Antimicrob. Agents Chemother*. **49**, 3520-3522 (2005).
2. Kim, S. H. Song, J., Chung, D. R., Thamlikitkul, V., Yang, Y., Wang, H., Lu, M., So, T. M., Hsueh, P., Yasin, R. M., Carlos, C. C., Pham, H. V., Lalitha, M. K., Shimono, N., Perera, J., Shibl, A. M., Baek, J. Y., Kang, C., Ko, K. S. & Peck, K. R. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob. Agents Chemother*. **56**, 1418-1426 (2012).
3. Ajito, K., Miura, T., Furuuchi, T. & Tamura, A. Sixteen-membered macrolides: Chemical modifications and future applications. *Heterocycles* **89**, 281-352 (2014).
4. Yamamoto, Y. Macrolide resistance-Molecular mechanisms of resistance to ketolide in Streptococcus pneumoniae. *Antibiotics & Chemotherapy* **30**, 44-54 (2014).
5. Schlünzen, F., Zarivach, R., Harms, J., Bashan, A., Tocilj, A., Albrecht, R., Yonath, A. & Franceschi, F. Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. *Nature* **413**, 814-821 (2001).
6. Poehlsgaard, J. & Douthwaite, S. The macrolide binding site on the bacterial ribosome. *Current Drug Targets-Infectious Disorders* **2**, 67-78 (2002).
7. Tu, D., Blaha, G., Moore, P. B. & Steitz, T. A. Structures of $MLS_BK$ antibiotics bound to mutated large ribosomal subunits provide a structural explanation for resistance. *Cell* **121**, 257-270 (2005).
8. Hansen, J. L., Ippolito, J. A., Ban, N., Nissen, P., Moore, P. B. & Steitz, T. A. The structures of four macrolide antibiotics bound to the large ribosomal subunit. *Mol. Cell*. **10**, 117-128 (2002).
9. Welsblum, B. Erythromycin resisrance by ribosome modification. *Antimicrob. Agents Chemother.* **39**, 577-585 (1995).
10. Vester, B. & Douthwaite, S. Macrolide resisrance conferred by base substitutions in 23S rRNA. *Antimicrob. Agents Chemother.* **45**, 1-12 (2001).
11. Liu, M., & Douthwaite, S. Activity of the ketolide telithromycin is refractory to erm monomethylation of bacterial rRNA. *Antimicrob. Agents Chemother.* **46**, 1629-1633 (2002).
12. Syrogiannopoulos, G. A., Grivea, I. N., Ednie, L. M., Bozdogan, B., Katopodis, G. D., Beratis, N. G., Davies, T. A. & Appelbaum, P. C. Antimicrobial susceptibility and macrolide resistance inducibility of *Streptococcus pneumoniae* carrying *erm*(A), *erm*(B), or *mef*(A). *Antimicrob. Agents Chemother.* **47**, 2699-2702 (2003).
13. Okubo, T., Iyobe, S., Fujika, U., & Sagai, H. Antimicrobial activities of macrolides against recent clinical isolates, and analysis of resistant mechanisms. *Jpn. J. antibiot.* **56**, 163-170 (2003).
14. Chancey, S. T., Zhou, X., Zähner, D. & Stephens, D. S. Induction of Efflux-Mediated Macrolide

Resistance in *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* **55**, 3413-3422 (2011).

15. O'hara, K. Up-to-date report on the resistance of macrolide antibiotics and future macrolides. *Japanese Journal of Chemotherapy* **48**, 169-190 (2000).
16. Morimoto, S., Takahashi, Y., Watanabe, Y. & Omura, S. Chemical modification of erythromycins. I. Synthesis and antibacterial activity of 6-*O*-methylerythromycins A. *J. Antibiot.* **37**, 187-189 (1984).
17. Djokić, S. Kobrehel, G., Lazaravski, G., Lopotar, N., Tamburašev, Z., Kamenar, B., Nagl, A. & Vicković, I. Erythromycin series. Part 11. Ring expansion of erythromycin A oxime by the Beckmann rearrangement. *J. Chem. Soc. Perkin Trans.* I 1881-1890 (1986).
18. Retsema, J., Girard, A., Schelkly, W., Manousos, M., Anderson, M., Bright, G., Borovoy, R., Brennan, L. & Mason, R. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against Gram-Negative Organisms. *Antimicrob. Agents Chemother*. 1939–1947 (1987).
19. Djokić, S. Kobrehel, G., Lopotar, N., Kamenar, B., Nagl, A. & Mrvoš, D. Erythromycin series. Part 13. Synthesis and structure elucidation of 10-dihydro-10-deoxo-11-methyl-11-azaerythromycin A. *J. Chem. Res. Synop.* 152–153 (1988).
20. Agouridas, C., Denis, A., Auger, J., Benedetti, Y., Bonnefoy, A., Bretin, F., Chantot, J., Dussarat, A., Fromentin, C., D'Ambrières, S. G., Lachaud, S., Laurin, P., Martret, O. L., Loyau, V. & Tessot, N. Synthesis and antibacterial activity of ketolides (6-*O*-methyl-3-oxoerythromycin derivatives): A new class of antibacterials highly potent against macrolide-resistant and -susceptible respiratory pathogens. *J. Med. Chem.* **41**, 4080-4100 (1998).
21. Denis, A., Agouridas, C., Auger, J., Benedetti, Y., Bonnefoy, A., Bretin, F., Chantot, J., Dussarat, A., Fromentin, C., D'Ambrières, S. G., Lachaud, S., Laurin, P., Martret, O. L., Loyau, V., Tessot, N., Pejac, J. & Perron, S. Synthesis and antibacterial activity of HMR 3647 a new ketolide highly potent against erythromycin-resistant and susceptible pathogens. *Bioorg. Med. Chem. Lett.* **9**, 3075-3080 (1999).
22. Berisio, R., Harms, J., Schluenzen, F., Zarivach, R., Hansen, H. A. S., Fucini, P. & Yonath, A. Structural insight into the antibiotic action of telithromycin against resistant mutants. *J. Bcteriol.* **185**, 4276-4279 (2003).
23. Douthwaite, S., Hansen, L. H. & Mauvais, P. Macrolide-ketolide inhibition of MLS-resistant ribosomes is improved by alternative drug interaction with domain II of 23S rRNA. *Mol. Microbiol*. **36**, 183-193 (2000).
24. Hansen, L. H., Mauvais, P. & Douthwaite, S. The macrolide–ketolide antibiotic binding site is formed by structures in domains II and V of 23S ribosomal RNA, *Mol. Microbiol.* **31**, 623–631 (1999).
25. Xiong, L., Shah, S., Mauvais, P. & Mankin, A. S. A ketolide resistance mutation in domain II of 23S rRNA reveals the proximity of hairpin 35 to the peptidyl transferase centre, *Mol. Microbiol.* **31**, 633–639 (1999).

26. Clay, K. D., Hanson, J. S., Pope, S. D., Rissmiller, R. W., Purdum III, P. P. & Banks, P. M. Severe hepatotoxicity of telithromycin: Three case reports and literature review. *Ann. Intern. Med.* **144**, 415-420 (2006).
27. Ross, D. B. The FDA and the case of ketek. *N. Engl. J. Med.* **356**, 1601–1604 (2007).
28. Department of Health and Human Services. Telithromycin (marketed as ketek) information available at http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm107824.htm., Accessed April 26, 2007.
29. Gleason, P. P., Walters, C., Heaton, A. H. & Schafer, J. A. Telithromycin: the perils of hasty adoption and persistence of off-label prescribing. *J. Manag. Care Pharm.* **13**, 420–425 (2007).
30. Georgopapadakou, N. H. The wobbly status of ketolides: where do we stand? *Expert Opin. Investig. Drugs*, **23**, 1313-1319 (2014).
31. Press release in December 29, 2016 by Cempra, Inc.: http://investor.cempra.com/releasedetail.cfm?ReleaseID=1005708
32. Miura, T., Natsume, S., Kanemoto, K., Atsumi, K., Fushimi, H., Sasai, H., Arai, T., Yoshida, T. & Ajito, K. Novel azalides derived from sixteen-membered macrolides. I. Isolation of the mobile dialdehyde and its one-pot macrocyclization with an amine. *J. Antibiot.*, **60**, 407-435 (2007).
33. Miura T., Natsume S, Kanemoto K, Shitara S, Fushimi H, Yoshida T. & Ajito, k. Novel azalides derived from 16-membered macrolides. III. Azalides modified at the C-15 and 4" positions: Improved antibacterial activities. *Bioorg. & Med. Chem.*, **18**, 2735-2747, (2010).
34. Mason, D. J., Dietz, A. & Deboer, C. Lincomycin, a new antibiotic I. Discovery and biological properties. *Antimicrob. Agents Chemother.* 554–559 (1962).
35. Magerlein, B. J. Lincomycin. X. The chemical synthesis of lincomycin. *Tetrahedron Lett.* **1**, 33–36 (1970).
36. Howarth, G. B., Szarek, W. A. & Jones, J. K. N. The synthesis of lincomycin. *J. Chem. Soc. (c)* **16**, 2218–2224 (1970).
37. Perlman, D. Structure-activity relationships among the semisynthetic antibiotics, (Academic Press, New York, San Francisco, London, A Subsidiary of Harcourt Brace Jovanovich, Publishers, 600–651, 1977).
38. Birkenmeyer, R. D. & Kagan, F. Lincomycin. XI. Synthesis and structure of clindamycin. A potent antibacterial agent. *J. Med. Chem.* **13**, 616–619 (1970).
39. Bannister, B. Modifications of lincomycin involving the carbohydrate portion. Part I. The 2-*O*-methyl and 2-deoxy-analogues. *J. Chem. Soc., Parkin Trans.* I. 3025-3030 (1972).
40. Shah, P. J., Vakil, N. & Kabakov, A. Role of intravenous immune globulin in streptococcal toxic shock syndrome and *Clostridium difficile* infection. *Am J Health-Syst Pharm* **72**, 1013-1019 (2015).
41. Hoeksema, H. Octoses from antibiotics. The Upjohn Company, Kalamazoo, Mich., Abstr. Pap.

Division of Carbohydrate Chemistry, 149th Meet. Am. Chem. Soc. Detroit, Mich., p. 9C (1965).

42. Magerlein, B. J., Birkenmeyer, R. D. & Kagan, F. Chemical modification of lincomycin. *Antimicrob. Agents Chemother* **6**, 727–736 (1966).
43. Sinkula, A. A., Morozowich, W., Lewis, C. & Mackellar, F. A. Synthesis and bioactivity of lincomycin-7-monoesters. *J. Pharm. Sci.* **58**, 1389–1392 (1969).
44. Magerlein, B. J. & Kagan, F. Lincomycin. IX. 7-Thiol and thioamido analogs of lincomycin. *J. Med. Chem.* **12**, 974–977 (1969).
45. Lewis, J. G., Atuegbu, A. E., Chen, T., Kumar, S. A., Patel, D. V., Hackbarth, C. J., Asano, R., Wu, C., Wang, W., Yuan, Z., Trias, J., White, R. J. & Gordeev, M. F. Novel antimicrobial 7-methyl Lincosamides: Prolamide Analogs. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-1388. (Washington, DC, USA, 2004).
46. Bannister, B. Modifications of lincomycin involving the carbohydrate portion. Part III. The 7-*O*-methyl and 6-de-(1-hydroxyethyl) analogues. *J. Chem. Soc. Perkin Trans*. *I*, 1676–1682 (1973).
47. Bannister, B. Modifications of lincomycin involving the carbohydrate portion. Part IV. (7*S*)-7-alkoxy-7-deoxy-analogues. *J. Chem. Soc. Perkin Trans. I* **3**, 360–369 (1974).
48. Bannister, B. & Mydlow, P. K. The *S*-alkylation of sulphides by an activated carbohydrate epimine under acidic catalysis: The formation of α-acetamido-sulphides. Part 5. The introduction of functionality into the sulphide substituent. *J. Chem. Res. (S)* 90–91 (1989).
49. Bannister, B. The *S*-alkylation of sulphides by an activated carbohydrate epimine under acidic catalysis: The formation of α-acetamido-sulphides. Part 4. Reaction with dithioacetals and monothioacetals. *J. Chem. Soc., Perkin. Trans. I* 540–552 (1980).
50. Bannister, B. (7*S*)-7-deoxy-7-substituted-alkylthio-lincomycins. *S*-Alkylation of sulphides by an activated epimine under acidic catalysis: formation of α-acetamido-sulphides. *Tetrahedron* **40**, 1633–1660 (1984).
51. Bannister, B. (The Upjohn company). Derivatives of lincomycin and its analogs and process. US Patent US3915954 A, (1973).
52. Bannister, B. (The Upjohn company). Derivatives of lincomycin and its analogs and process. Canadian Patent CA-971956 A1 (1972).
53. Sztaricskai, F., Dinya, Z., Puskaás, M. M., Batta, G., Masuma, R. & Ōmura, S. Semisynthetic modification of antibiotic lincomycin. *J. Antibiot.* **49**, 941–943 (1996).
54. Argoudelis, A. D., Coats, J. H., Mason, D. J. & Sebek, O. K. Microbial transformation of antibiotics. III. Conversion of clindamycin to 1'-demethylclindamycin and clindamycin sulfoxide by *Streptomyces* species. *J. Antibiot.* **22**, 309-314 (1969).
55. Magerlein, B. J., Birkenmeyer, R. D. & Kagan, F. Lincomycin. VI. 4'-alkyl analogs of lincomycin. Relationship between structure and antibacterial activity. *J. Med. Chem.*, **10**, 355–359 (1967).
56. Magerlein, B. J. Lincomycin. 14. An improved synthesis and resolution of the antimalarial agent,

1’-demethyl-4’-depropyl-4’(*R*)- and -(*S*)-pentylclindamycin hydrochloride (U-24,729A). *J. Med. Chem.*, **15**, 1255–1259 (1972).

57. Magerlein, B. J. Lincomycin. VII. 4’-Depropyl-4’-ethoxylincomycins. *J. Med. Chem.*, **10**, 1161–1163 (1967).
58. Lewis, J. G., Anandan, S. K., O’dowd, H., Gordeev, M. & Li, L. Novel lincomycin derivatives possessing antimicrobial activity. WO/2006/055070 A2, May 26 (2006).
59. Birkenmeyer, R. D., Kroll, S. J., Lewis, C., Stern, K. F. & Zurenko, G. E. Synthesis and antimicrobial activity of clindamycin analogues: pirlimycin, a potent antibacterial agent. *J. Med. Chem.*, **27**, 216-223, (1984).
60. O’Dowd, H., Lewis, J. G., Trias, J., Asano, R., Blais, J., Lopez, S. L., Park, C. K., Wu, C., Wang, W. & Gordeev, M. F. Novel antibacterial azetidine lincosamides. *Bioorg. Med. Chem. Lett.*, **18**, 2645-2648 (2008).
61. O’Dowd, H., Lewis, J. G., Trias, J., Asano, R., Blais, J., Lopez, S. L., Park, C. K., Wu, C., Wang, W. & Gordeev, M. F. Novel antibacterial azetidine lincosamides. 44rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-2037. (Washington, DC, USA, 2004).
62. Lewis, J. G., Gu, S., Kumar, S. A., Chen, T., O’Dowd, H., Patel, D. V., Hackbarth, C. J., Asano, R., Park, C., Blais, J., Wu, C., Wang, W., Yuan, Z., Trias, J., White, R. J. & Gordeev, M. F. Novel antimicrobial 7-methyl lincosamides: Pipecolamide analogs. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-1389. (Washington, DC, USA, 2004).
63. Chen, T., Gu, S., Lewis, J. G., Trias, J., Asano, R., Blais, J., Lopez, S. L., Park, C. K., Wu, C. & Gordeev, M. F. Novel 4’-cycloalkyl pipecolamide lincosamide analogs. 44rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-2036. (Washington, DC, USA, 2005).
64. Lopez, S.L., Blais, J., Kubo, A., Lewis, J. G., Gordeev, M. F., Yuan, Z., Trias, J. & White, R. J. Characterization of the spectrum of in vitro activity of VIC-105555, a new lincosamide. 44rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Poster F-2038. (Washington, DC, USA, 2005).
65. Houtman, R. L. & Mich, P. (The Upjohn company). Trimethylsilyl ethers of lincomycin and its compounds. US Patent US3418414 (1966).
66. Umemura, E., Wakiyama, Y., Ueda, K., Kumura, K., Natsume, S., Watanabe, T., Yamamoto, M., Kaji, C. & Ajito, K. Lincomycin derivative and antibacterial agent containing the same as active ingredient. Japanese patent: WO/2007/066805 A1, June 14 (2007).
67. Umemura, E., Wakiyama, Y., Kumura, K., Ueda, K., Masaki, S., Watanabe, T., Yamamoto, M., Hirai, Y., Fushimi, H., Yoshida, T. & Ajito, K. Synthesis of novel lincomycin derivatives and their *in vitro* antibacterial activities. *J. Antibiot*. **66**, 195–198 (2013).
68. Wakiyama, Y., Natsume, S., Kumura, K., Ueda, K., Sato, Y., Umemura, E., Hirai, Y. & kondo, H. Lincomycin derivatives and antibacterial agents containing the same as the active ingredient. Japanese

patent: WO/2008/146917 A1, December 4 (2008).

69. Umemura, E., Kumura, K., Masaki, S., Ueda, K., Wakiyama, Y., Sato, Y., Yamamoto, M., Ajito, K., Watanabe, T. & Kaji, C. Lincosamide derivative, and antibacterial agent comprising the same as active WO/2008/146919 A1, December 4 (2008).
70. Wakiyama, Y., Kumura, K., Umemura, E., Ueda, K., Masaki, S., Kumura, M., Fushimi, H. & Ajito, K. Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 1. Newly generated antibacterial activities against Gram-positive bacteria with *erm* gene by C-7 modification. *J. Antibiot.* **69**, 368–380 (2016).
71. Kumura, K., Wakiyama, Y., Ueda, K., Umemura, E., Watanabe, T., Shitara, E., Fushimi, H., Yoshida, T. & Ajito, K. Synthesis and antibacterial activity of novel lincomycin derivatives. I. Enhancement of antibacterial activities by introduction of substituted azetidines. *J. Antibiot.* **69**, 440–445 (2016).
72. Itoh, T. & Mase, T. A general palladium-catalyzed coupling of aryl bromides/triflates and thiols. *Org. Lett.* **6**, 4587-4590 (2004).
73. Wakiyama, Y., Kumura, K., Umemura, E., Masaki, S., Ueda, K., Watanabe, T., Yamamoto, M., Hirai, Y. & Ajito, K. Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 2. Synthesis of (7*S*)-7-deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin and its 3-dimensional analysis with rRNA. *J. Antibiot.* **69**, 428–439 (2016).
74. Wakiyama, Y., Kumura, K., Umemura, E., Masaki, S., Ueda, K., Sato, Y., Watanabe, T., Hirai, Y. & Ajito, K. Synthesis and structure–activity relationships of novel lincomycin derivatives Part 3: discovery of the 4-(pyrimidin-5-yl)phenyl group in synthesis of 7(*S*)-thiolincomycin analogs. *J. Antibiot.* **70**, 52–64 (2017).
75. Kumura, K., Wakiyama, Y., Ueda, K., Umemura, E., Watanabe, T., Kumura, M., Yoshida, T. & Ajito, K. Synthesis and antibacterial activity of novel lincomycin derivatives. II. Exploring (7*S*)-7-(5-aryl-1,3,4-thiadiazol-2-yl-thio)-7-deoxylincomycin derivatives. *J. Antibiot*. **70**, 655-663 (2017).
76. Pedregal, C., Ezquerra, J., Escribano, A., Carreńo, M. C. & Ruano, J. L. G. Highly chemoselective reduction of N-Boc protected lactams. *Tetrahedron Lett.*, **35**, 2053-2056 (1994).
77. Llinàs-Brunet, M., Bailey, M., Fazal, G., Ghiro, E., Gorys, V., Goulet, S., Halmos, T., Maurice, R., Poirier, M., Poupart, M., Rancourt, J., Thibeault, D., Wernic, D. & Lamarre, D. Highly potent and selective peptide-based inhibitors of the hepatitis C virus serine protease: towards smaller inhibitors. *Bioorg. Med. Chem. Lett.,* **10**, 2267-2270 (2000).
78. Bracci, A., Manzoni, L. & Scolastico. C. Stereoselective synthesis of a functionalized 2-oxo-1-azabicyclo[5.3.0]alkane as a potential scaffold for targeted chemotherapy strategies. *Synthesis*, **15**, 2363-2367 (2003).
79. Ezquerra, J., Pedregal, C., Rubio, A., Yruretagoyena, B., Escribano, A. & Sánchez-Ferrando, F. Stereoselective reactions of lithium enolates derived from N-Boc protected pyroglutamic esters.

*Tetrahedron,* **49**, 8665-8678 (1993).

80. Schroeder, W., Bannister, B. & Hoeksema, H. Lincomycin. III. The structure and stereochemistry of the carbohydrate moiety. *J. Am. Chem. Soc.*, **89**, 2448-2453 (1967).
81. Wakiyama, Y., Kumura, K., Umemura, E., Ueda, K., Watanabe, T., Yamada, K., Okutomi, T. & Ajito, K. Synthesis and structure-activity relationships of novel lincomycin derivatives. Part 4: Synthesis of novel lincomycin analogs modified at the 6- and 7-positions and their potent antibacterial activities. *J. Antibiot*.**70**, 888-906 (2017).
82. Kumura, K., Wakiyama, Y., Ueda, K., Umemura, E., Watanabe, T., Yamamoto, M., Yoshida, T. & Ajito, K. Synthesis and antibacterial activity of novel lincomycin derivatives. III. Optimization of a phenyl thiadiazole moiety. *J. Antibiot.* **71**, 104–112 (2018).
83. Shuman, R. T., Ornstein, P. L., Paschal, J. W. & Gesellchen, P. D., An improved synthesis of homoproline and derivatives. *J. Org. Chem*., **55**, 738-741 (1990).
84. Wakiyama, Y., Kumura, K., Umemura, E., Masaki, S., Ueda, K., Sato, Y., Hirai, Y., Hayashi, Y. & Ajito, K. Synthesis and SARs of novel lincomycin derivatives Part 5: optimization of lincomycin analogs exhibiting potent antibacterial activities by chemical modification at the 6- and 7-positions. *J. Antibiot*. **71**, 298-317 (2018)
85. Kumura, K., Wakiyama, Y., Ueda, K., Umemura, E., Hirai, Y., Yamada, K. & Ajito, K. Synthesis and antibacterial activity of novel lincomycin derivatives. IV. Optimization of an N-6 substituent. *J. Antibiot.* **70**, 1112–1121 (2017).
86. Magerlein, B. J. & Kagan, F., Lincomycin. VIII. 4'-Alkyl-1'-demethyl-4'-depropylclindamycins, potent antibacterial and antimalarial agents., *J. Med. Chem*., **12,** 780 (1969).
87. Kawai, Y. Nationwide surveillance and therapeutic efficacy of antimicrobial agents against macrolide-resistant *Mycoplasma pneumoniae* infection in pediatric patients. *Jpn. J. Chemother.*, **62**, 110-117 (2014).
88. Narita, M. Current status and future aspects of drug-resistant *Mycoplasma pneumoniae. modern media*, **53**, 297-306 (2007).
89. Farrell, D. J., Morrissey, I., Bakker, S. & Felmingham, D. Molecular characterization of macrolide resistance mechanisms among *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolated from the PROTEKT 1999-2000 study. *J. Antimicrob. Chemother*., **50** (suppl_2) 39-47 (2002).
90. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; sixteenth informational supplement. CLSI document M100-S16. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.

# Main articles and reference articles for a doctoral degree

## Main articles

1. Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 1. Newly generated antibacterial activities against Gram-positive bacteria with *erm* gene by C-7 modification
   Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Kazutaka Ueda, Satomi Masaki, Megumi Kumura, Hideki Fushimi and Keiichi Ajito
   The Journal of Antibiotics, **69**, 368-380 (2016)

2. Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 2. Synthesis of 7(*S*)-7-deoxy-7-(4-morpholinocarbonylphenylthio)lincomycin and its 3-dimensional analysis with rRNA
   Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Satomi Masaki, Kazutaka Ueda, Takashi Watanabe, Mikio Yamamoto, Yoko Hirai and Keiichi Ajito
   The Journal of Antibiotics, **69**, 428-439 (2016)

3. Synthesis and structure–activity relationships of novel lincomycin derivatives part 3: discovery of the 4-(pyrimidin-5-yl)phenyl group in synthesis of 7(*S*)-thiolincomycin analogs
   Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Satomi Masaki, Kazutaka Ueda, Yasuo Sato, Takashi Watanabe, Yoko Hirai and Keiichi Ajito
   The Journal of Antibiotics, **70**, 52-64 (2017)

4. Synthesis and structure–activity relationships of novel lincomycin derivatives. Part 4: synthesis of novel lincomycin analogs modified at the 6- and 7-positions and their potent antibacterial activities
   Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Kazutaka Ueda, Takashi Watanabe, Keiko Yamada, Takafumi Okutomi and Keiichi Ajito
   The Journal of Antibiotics, **70**, 888-906 (2017)

5. Synthesis and SARs of novel lincomycin derivatives Part 5: optimization of lincomycin analogs exhibiting potent antibacterial activities by chemical modification at the 6- and 7-positions
   Yoshinari Wakiyama, Ko Kumura, Eijiro Umemura, Satomi Masaki, Kazutaka Ueda, Yasuo Sato, Yoko Hirai, Yoshio Hayashi and Keiichi Ajito
   The Journal of Antibiotics, **71**, 298-317 (2018)

## Reference articles


1. Synthesis of novel lincomycin derivatives and their *in vitro* antibacterial activities
   Eijiro Umemura, Yoshinari Wakiyama, Ko Kumura, Kazutaka Ueda, Satomi Masaki, Takashi Watanabe, Mikio Yamamoto, Yoko Hirai, Hideki Fushimi, Takuji Yoshida, and Keiichi Ajito
   The Journal of Antibiotics, **66**, 195-198 (2013)

2. Synthesis and antibacterial activity of novel lincomycin derivatives. I. Enhancement of antibacterial activities by introduction of substituted azetidines
   Ko Kumura, Yoshinari Wakiyama, Kazutaka Ueda, Eijiro Umemura, Takashi Watanabe, Eiki Shitara, Hideki Fushimi, Takuji Yoshida, and Keiichi Ajito
   The Journal of Antibiotics, **69**, 440-445 (2016)

3. Synthesis and antibacterial activity of novel lincomycin derivatives. II. Exploring (7*S*)-7-(5-aryl-1,3,4-thiadiazol-2-yl-thio)-7-deoxylincomycin derivatives
   Ko Kumura, Yoshinari Wakiyama, Kazutaka Ueda, Eijiro Umemura, Takashi Watanabe, Megumi Kumura, Takuji Yoshida, and Keiichi Ajito
   The Journal of Antibiotics, **70**, 655-663 (2017)

4. Synthesis and antibacterial activity of novel lincomycin derivatives. III. Optimization of a phenyl thiadiazole moiety
   Ko Kumura, Yoshinari Wakiyama, Kazutaka Ueda, Eijiro Umemura, Takashi Watanabe, Mikio Yamamoto, Takuji Yoshida, and Keiichi Ajito
   The Journal of Antibiotics, **71**, 104–112 (2018)

5. Synthesis and antibacterial activity of novel lincomycin derivatives. IV. Optimization of an *N*-6 substituent
   Ko Kumura, Yoshinari Wakiyama, Kazutaka Ueda, Eijiro Umemura, Yoko Hirai, Keiko Yamada and Keiichi Ajito
   The Journal of Antibiotics, **70**, 1112–1121 (2017)

## Acknowledgements

First of all, I wish to express my special gratitude Professor Shin Aoki (Faculty of Pharmaceutical Sciences in Tokyo University of Science) for excellent supervision, valuable discussions and productive advice for this doctoral dissertation. Furthermore, I also wish to gratefully thank following professors in Tokyo University of Science for careful review and fruitful discussions during examination of this doctoral dissertation: Professors Hiromi Uchiro, Yoichi Hayakawa, Noriyasu Hada (Faculty of Pharmaceutical Sciences) and Professor Takashi Kamakura (Faculty of Science and Technology).

I am also deeply grateful to following researchers in Meiji Seika Pharma Co., Ltd. for providing me with an occasion of a doctoral degree. Their excellent supervision, valuable discussions for medical sciences in the lincomycin antibiotic field, introduction of professor Shin Aoki to me and warm encouragement are greatly appreciated: Dr. Keiichi Ajito (General Manager, Project Planning & Management Department), Dr. Eijiro Umemura (Pharmaceutical Research Center), Dr. Minoru Yonezawa (Associate General Manager, Pharmaceutical Research Center) and Dr. Takeru Yamakawa (Pharmaceutical Research Center).

I am also deeply grateful to following researchers in Meiji Seika Pharma Co., Ltd. for providing me with an occasion of a doctoral degree. Furthermore, I wish to express my sincere thanks for fruitful discussions in this studies and warm encouragement extended to me: Dr. Toshihiro kikkoji (Exective Officer), Dr. Toru Kurosawa (General Manager, Pharmaceutical Research Center), Dr. Katsuyoshi Iwamatsu (General Manager, Former Chemistry Laboratory), Dr. Toshiaki Kudo (Director, Former Chemistry Laboratory, (Current Affiliation; Scohia Pharma, Inc.)), Dr. Kunio Atsumi (Reserch Fellow, Former Chemistry Laboratory, (Current Affiliation; Fujiamide Chemical Co., Ltd.)), Dr. Yasuo Sato (Director, Former Medicinal Chemistry Laboratory, (Current Affiliation; Yokohama University Pharmacy)), Dr. Sojiro Shiokawa (Associate General Manager, Pharmaceutical Research Center), Dr. Takeshi Furuuchi (Manager, Medicinal Chemistry Laboratory), Dr. Satoshi Yoshida (Director, Medicinal Chemistry Laboratory), Dr. Hiroyuki Yamaguchi (General Manager, Chemistry, Manufacturing & Control Research Laboratory), Dr. Masaki Tsushima (Associate General Manager, Chemistry, Manufacturing & Control Research Laboratory), Dr. Hitoshi Yamaguchi (Manager, Process Chemistry Laboratory), Dr. Toshiro Sasaki (Process Chemistry Laboratory), Dr. Masayuki Okue (Process Chemistry Laboratory), Dr. Makoto Ohyama (Research Fellow, Intellectual Property Department), Dr. Tomoaki Miura (Director, Intellectual Property Department), Dr. Kokichi Suzuki (Research Fellow, Research Planning Department) and Dr. Eiki Shitara (Research Planning Department).

I also wish to express my gratitude to Professor Emeritus Dr. Masatoshi Konno (Teikyo University) and Professor Yoshio Hayashi (Tokyo University of Pharmacy and Life Sciences) for supervision and valuable discussions through my in-house drug discovery program in lincomycin field.

I would also like to gratefully thank to following researchers in Meiji Seika Pharma Co., Ltd. for design and synthesis of the large number of novel compounds, valuable discussions and warm encouragement: Ms. Satomi Masaki (Former Medicinal Chemistry Laboratory, (Current Affiliation; Tokyo Chemical Industry Co., Ltd.)), Dr. Kazutaka Ueda (PT. Meiji Indonesian Pharmaceutical Industries), Mr. Ko Kumura and Ms. Yuko Kano (Medicinal Chemistry Laboratory), Dr. Chika Kikuchi (Manager , Research Planning Department).

I owe a deep sense of gratitude to the following researchers in Meiji Seika Pharma Co., Ltd. for contribution toward computational chemistry and by analyzing the large number of samples such as LCMS, HRMS or NMR studies: Mr. Takashi Watanabe (Medicinal Chemistry Laboratory), Ms. Sigeko Miki (Former Medicinal Chemistry Laboratory), Ms. Takako Miyara, Ms. Kaori Kaneda, Mr. Takashi Murata, Ms. Fumi Nango and Ms. Rie Hiruta (Pharmacokinetics and Analysis Laboratory).

I would also like to gratefully thank to following researchers in Meiji Seika Pharma Co., Ltd. for contribution to biological studies, fruitful discussions that helped to shape this project and warm encouragement: Dr. Takashi Ida (Manager, Pharmacology Research Laboratory), Ms. Keiko Yamada, Ms. Chizuko Kazi and Mr. Takashi Matsuhira (Pharmacology Research Laboratory), Dr. Takafumi Okutomi (Intellectual Property Department), Dr. Hideki Fushimi (Clinical Research Planning Department), Ms. Yoko Hirai (Partnering Strategy and Business Development Department), Mr. Yoshihiro Takayama (Former Pharmacology Research Laboratory), Mr. Mikio Yamamoto (Former Pharmacology Research Laboratory, (Current Affiliation; Nanahoshi Pharmacy)), Ms. Megumi Kumura (Clinical Research Operation Department), Dr. Takuji Yoshida (Audit Department), Dr. Atsushi Tamura (HR & General Affairs Dept., Meiji Holding Co., Ltd.), Dr. Kazunori Maebashi (Research Fellow, Project Planning & Management Department), Dr. Hisashi Suzuki (Clinical Research Planning Department), Mr. Hiroshi Kondo (Research Planning Department).

I wish to express my personal appreciation for the following researchers in Meiji Seika Pharma Co., Ltd. for their guidance in intellectual properties, English manuscript and office procedure: Ms. Miyuki Ishii (Director, Intellectual Property Department), Ms. Mariko Takagi (Toxicology Laboratory), Ms. Mie Ito and Ms. Yoshie Saito (R&D Administration Department), Ms.Noriko Misaka (Pharmaceutical Research Center).

I would also like to gratefully thank to members of Pharmaceutical Research Center and Process Chemistry Laboratory for warm support and cooperation.

Finally, I am grateful thank to my wife, Masumi, and my family for their constant encouragement and warm support through getting my doctoral degree.