学位申請論文

Development of a Method for Producing Optically Active Secondary Alcohols Using the Kinetic Resolution of Racemic Compounds, and the Total Synthesis of Naturally Occurring Polyoxy-compounds, Violaceoids A and B

（速度論的光学分割法を用いる
光学活性第二級アルコールの製造法の開発ならびに
天然ポリオキシ化合物ビオールアセオイド A および B の全合成）

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平成 31 年 3 月

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Chapter 1 Introduction

Introduction

Organic chemistry can gives us a lot of choices to get medicines, chemicals, and functional materials. We can also get the new materials and compounds using our knowledge gained until now of organic chemistry. So the development of synthetic methods of the chiral compounds is needed by all the people.

Many medicinal compounds have stereogenic hydroxyl and ether groups. Some examples are shown in Figure 1.

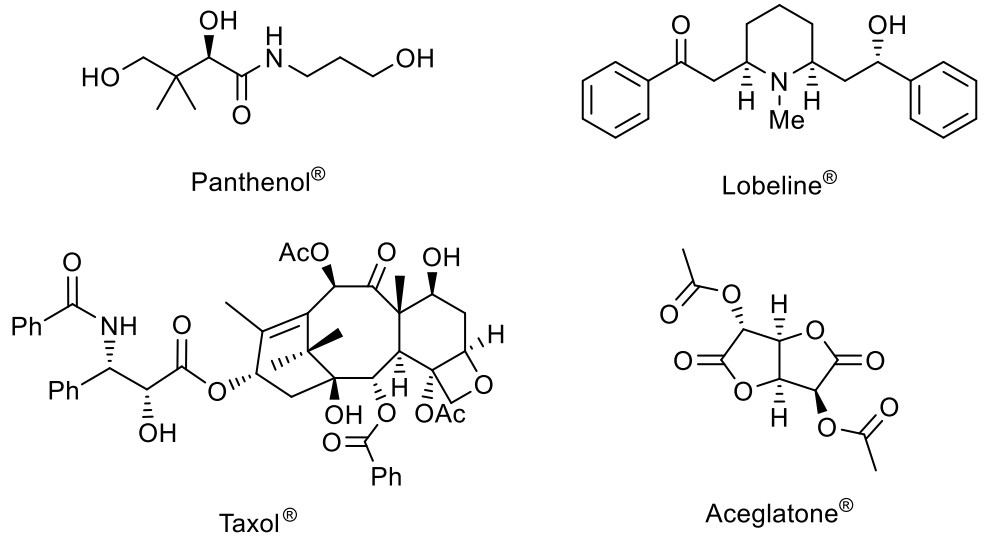


Figure 1. Example of Drugs Possessing Stereogenic Hydroxy Group.

Considering the above, we focused the methods to obtain the chiral alcohols.

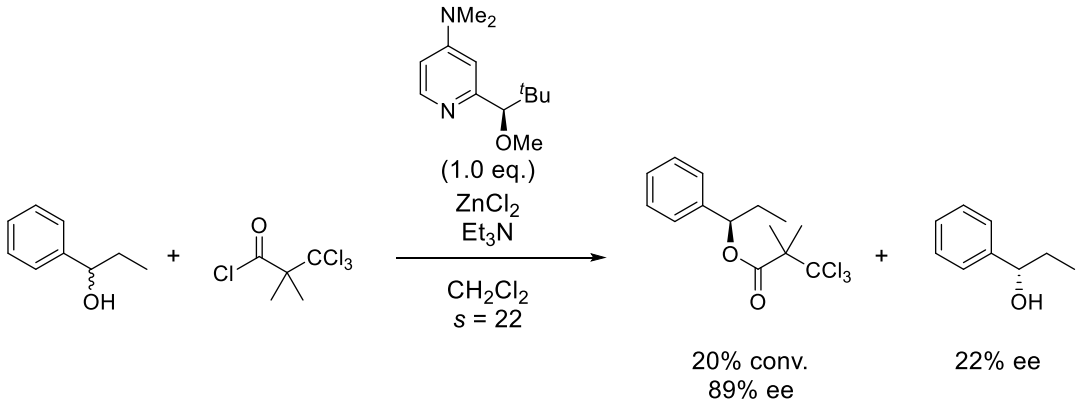
There are mainly four methods for getting chiral alcohols: (i) asymmetric synthesis, (ii) chiral pool method, (iii) optical resolution. Asymmetric synthesis is the method of making a new stereogenic center using chiral sources including the organometallic catalyst and organocatalysis. In recent decades, many researchers have developed the academic field. Especially, asymmetric aldol

reaction reported by Lerner, Barbas, List[1] and asymmetric Diels–Alder reaction reported by MacMillan[2] were the trigger. Organocatalyst is generally stable in air and moisture. This property assisted this flow and the development. Chiral pool method is the strategy that synthesize from chiral and natural substrate such as sugars and amino acids to the target compound. This method is superior in the point of reliability of chirality. Optical resolution is the method of resolution from racemic compounds to enantiopure ones and there are the two methods in optical resolution: (iii-A) the method of using chiral derivatizing agent, (iii-B) chromatograph. The method of using chiral derivatizing agent is the strategy to separate diastereomixture utilizing the difference of physical property by derivatizing the racemic compounds to the corresponding diastereomixture using easily available chiral resolving reagents. In the case of separating enantiomers using chromatograph, we usually use high performance liquid chromatography, so called HPLC. By using chiral supported stationary phase for column chromatography, we can get the chiral compound. However, this method depends on the diameter of column and ability of the HPLC machine.

In addition, the modified method of (iii-A), is kinetic resolution. In this method, one enantiomer only react with the chiral sources and the another remains without reaction. We can theoretically get the enantiopure compound in 50% yield and in 100% ee to the maximum. Even if the reaction doesn't ideally proceed, we can get the enantiopure compound by the repetition of the same reaction. Since we can repeat this reaction until the high enantiometic excess we want, this method is very reliable.

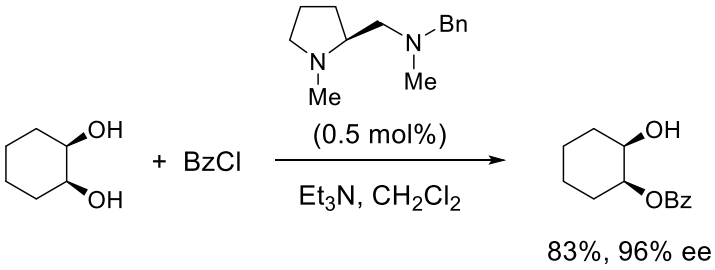
Enzymes such as lipase and esterase have been usually used for asymmetric acylation of alcohols until recent years. However, it has some problems that enzymes are relatively expensive and the substrate scope of the reaction was narrow. On the other hand, *N,N*-dimethyl-4-aminopyridine, so called DMAP are known for the great acylation catalyst but it had been thought that DMAP derivatives could have not easily accomplished the asymmetric acylation. However, in 1996, Vedejs

reported the first kinetic resolution using asymmetric acylation of the racemic secondary alcohols using the chiral amine catalyst (Scheme 1.).[3]



Scheme 1. First Kinetic Resolution Using the Chiral Amino Catalyst.

This methods needs for more than the stoichiometric amount of acylation reagent but Oriyama's group reported the catalytic asymmetric acylation of the diol with desymmetrization using the proline-type diamine catalyst (Scheme 2.)[4].



Scheme 2. Catalytic Asymmetric Acylation Reported by Oriyama's Group.

After that, many catalysts had been developed and the utility had been proved (Figure 2.). Fuji and Kawabata reported the kinetic resolution of racemic 2-hydroxyesters using the chiral

4-pyrrolidinopyridine derivative[5]. And Fu developed the chiral DMAP derivatives possessing the ferrocene moiety[6]. On the other hand, Vedejs's group used the chiral phosphine ligand[7]. Furthermore, Miller[8] and Ishihara[9] groups respectively reported histidine derivative could be used for the asymmetric base catalyst. In addition, Spivey reported the axially chiral pyridine catalyzed asymmetric acylation of the secondary alcohol[10].

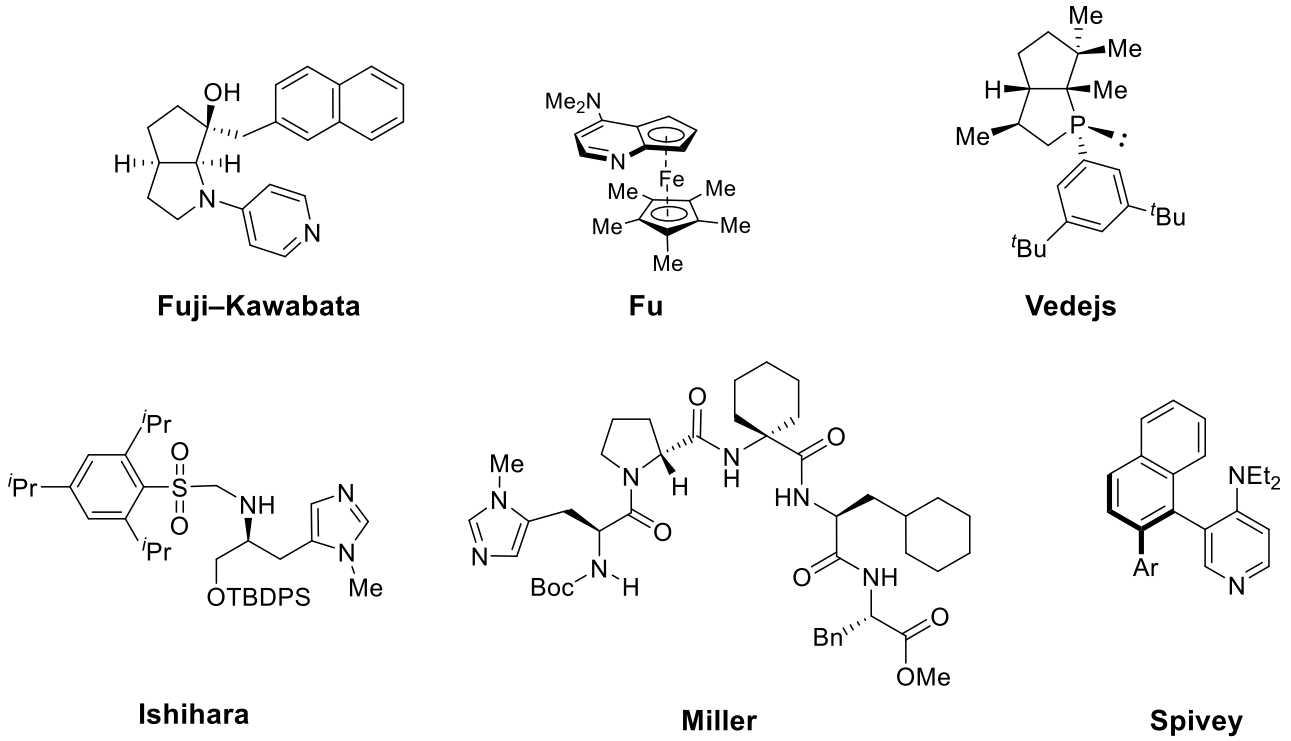
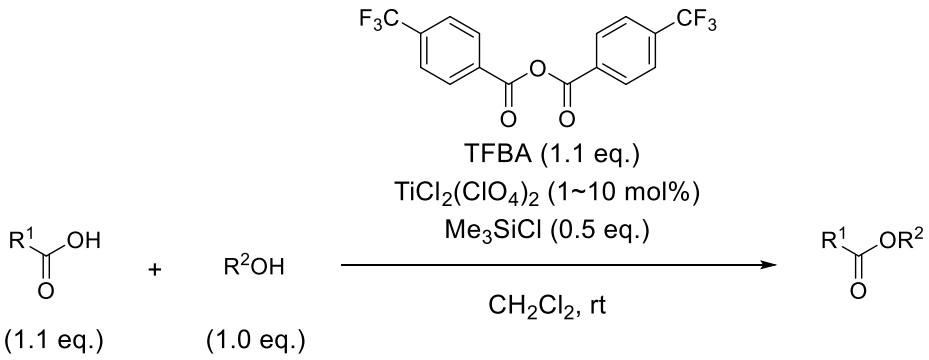


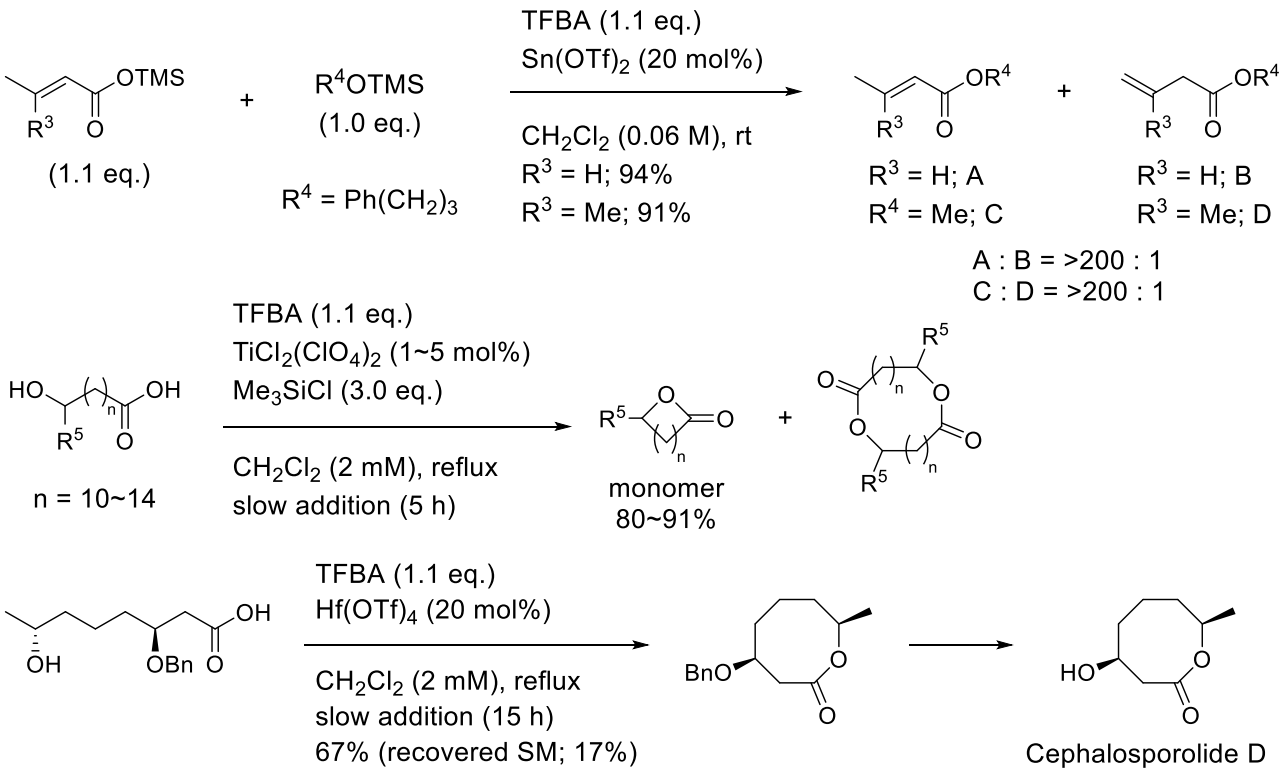
Figure 2. Useful Acylation Catalyst.

On the other hand, we developed the synthesis of esters by dehydrative condensation reaction using substrated benzoic anhydrides[11]. For example, the reaction between carboxylic acid and alcohol gives the corresponding ester in high yield using 4-trifluoromethyl benzoic anhydride (TFBA) as condensation reagent in the presence of a Lewis acid.



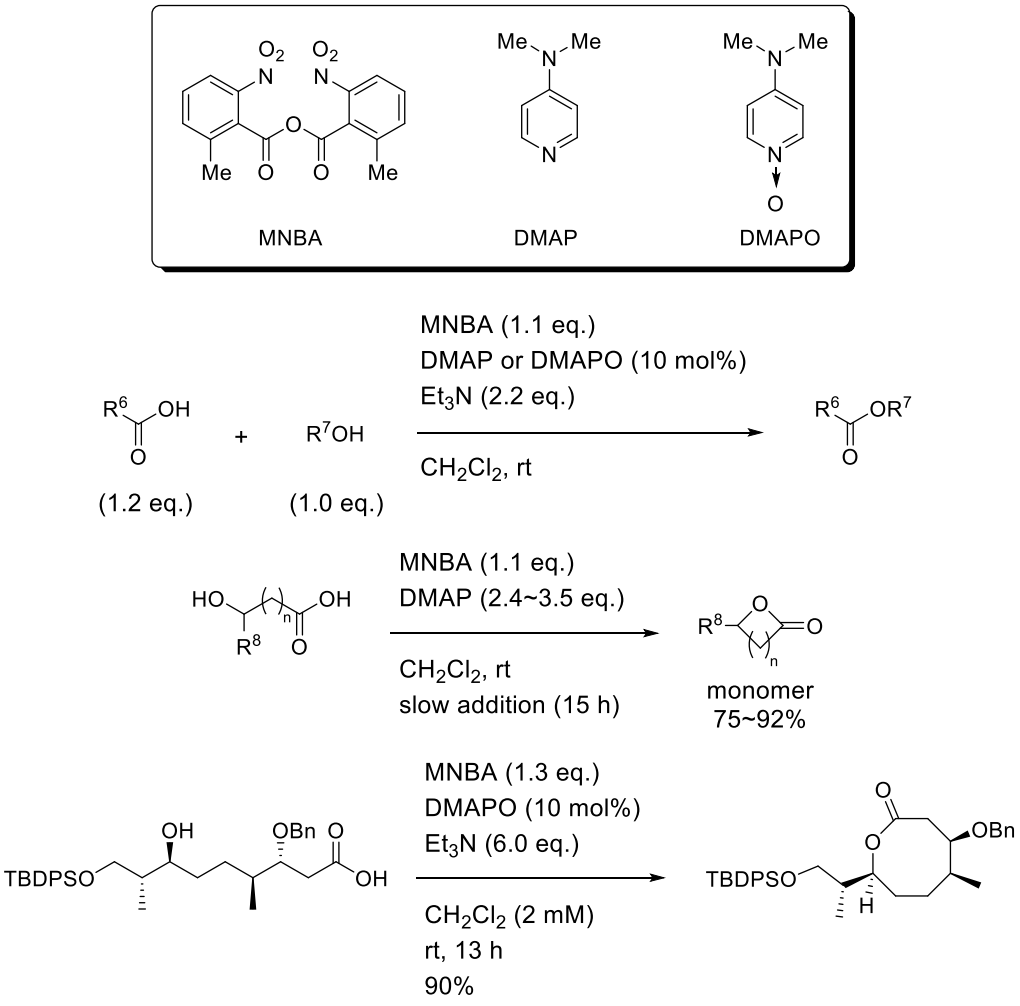
Scheme 3. Condensation Reaction Using TFBA.

Tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) and hafnium(IV) trifluoromethanesulfonate ($Hf(OTf)_4$) can also be used for the reaction as Lewis cocatalyst and the bulky carboxylic acid can be used for this reaction. Since this reaction is proceeded under the acidic condition, it could apply to the α,β-unsaturated ester such as crotonic acid and angelic acid[12]. Furthermore, this reaction can apply not only to intermolecular reaction but also to intramolecular reaction, so we could get a lactone from the corresponding seco acid.



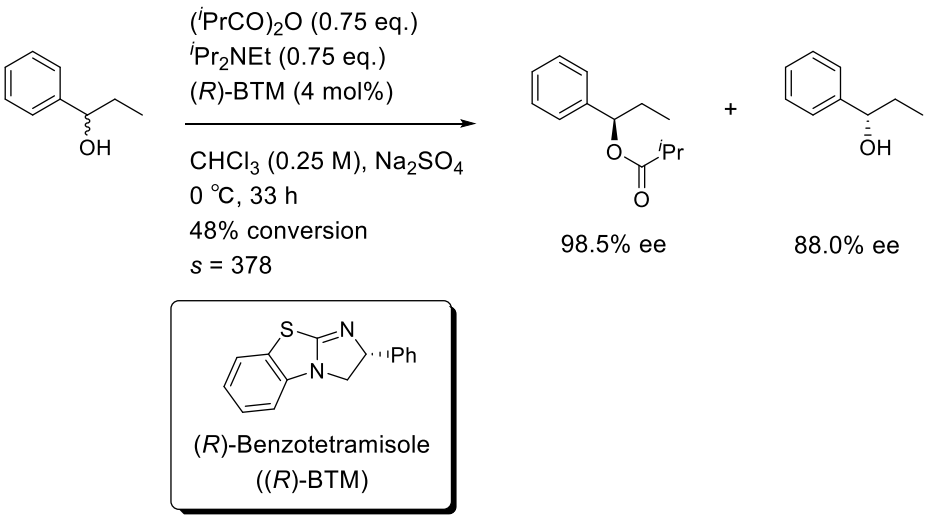
Scheme 4. Various Application of Condensation Reaction Using TFBA.

Generally, in the total synthesis of structurally and functionally complicated natural compounds, it is need for the neural or basic mild esterification and lactonization reaction. So we had done the further investigation and developed the esterification reaction proceeding under the basic condition. That is the method using the *N*,*N*-dimethylaminopyridine (DMAP) or *N*,*N*-dimethylaminopyridine *N*-oxide (DMAPO) as nucleophilic base catalyst and 2-methyl-6-nitro benzoic anhydride (MNBA) as dehydrative condensation reagent (Scheme 4.)[13]. We could conduct the reaction with the easy operation of sequentially addition of carboxylic acid and alcohol to the solution of MNBA and DMAP or DMAPO and we could get the ester in the mild condition at room temperature. Moreover, seco acids can be converted into the large[14] and medium[15] membered lactone with high selectivity and high yield by this method. In fact, we had accomplished the constructed the eight membered ring of the octalactins[16] isolated from a marine microorganism.



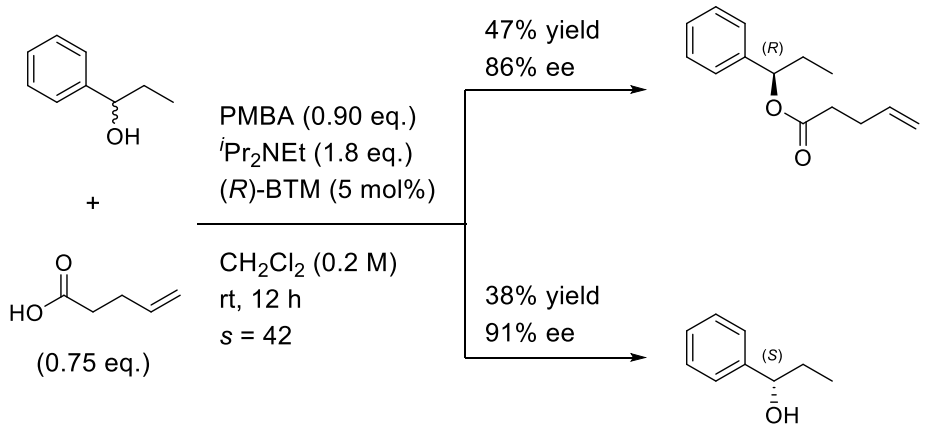
Scheme 5. Condensation Reaction Using MNBA.

After that, we had investigated the asymmetric synthesis using the chiral nucleophilic base catalyst instead of DMAP. Formerly, Birman reported the kinetic resolution of the racemic secondary alcohols using benzotetramisole (BTM) that is used for the insecticide (Scheme 5.)[17].



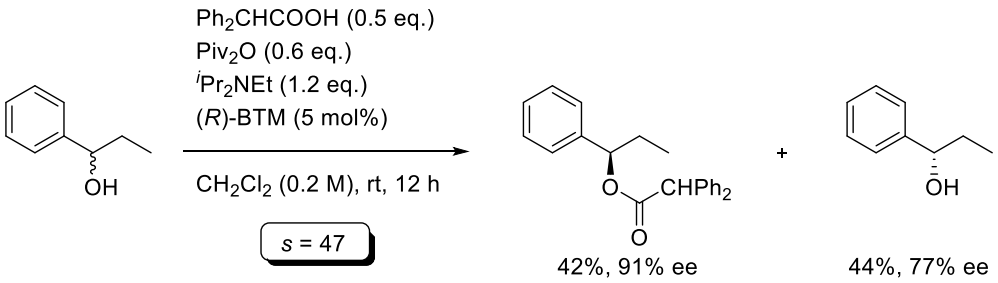
Scheme 6. Kinetic Resolution of Racemic Secondary Alcohol Using BTM.

Then we revealed that we could realize enantioselective esterification that is asymmetric dehydrative condensation reaction between carboxylic acids and alcohols, using the PMBA and BTM. As a result, we achieved the kinetic resolution of the benzylic secondary alcohol with high enantioselectivity and yield (Scheme 7.)[18].



Scheme 7. Kinetic Resolution Using PMBA and BTM.

Then we revealed that pivalic anhydride (Piv_2O) was the effective dehydration reagent in this system[19].



Scheme 8. Kinetic Resolusion of The Benzylic Secondary Alcohol Using Piv_2O.

We could apply this reaction to the various oxygenated substrates such as 2-hydroxyesters[20], 2-hydroxylacotones[21], 2-hydroxyarylketones, 2-hydroxyacetals[22], and 2-hydroxyphosphonates[23] (Figure 3).

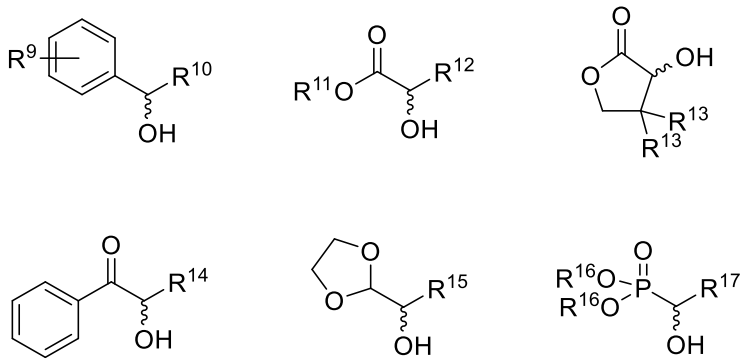
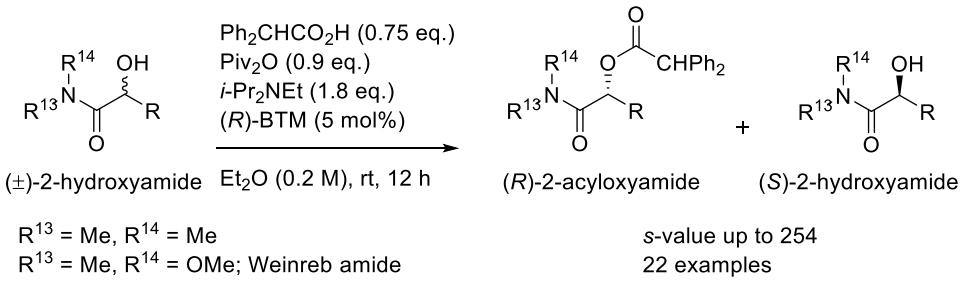


Figure 3. Various Application of Our Kinetic Resolution.

Abstract of Chapter 2

Since we could apply the asymmetric acylation to oxygenenated compound, we tried to apply this reaction to the amides, which is nitrogenated compound in this thesis (Scheme 9.)



Scheme 9. Kinetic Resolution of 2-Hydroxyamides.

Abstract of Chapter 3

We could accomplished the application of our kinetic resolution from oxygenated compounds to nitrogenated compounds, then we tried to apply the reaction from the benzylic secondary alcohol to the benzylic quinol secondary alcohol (Figure 4.).

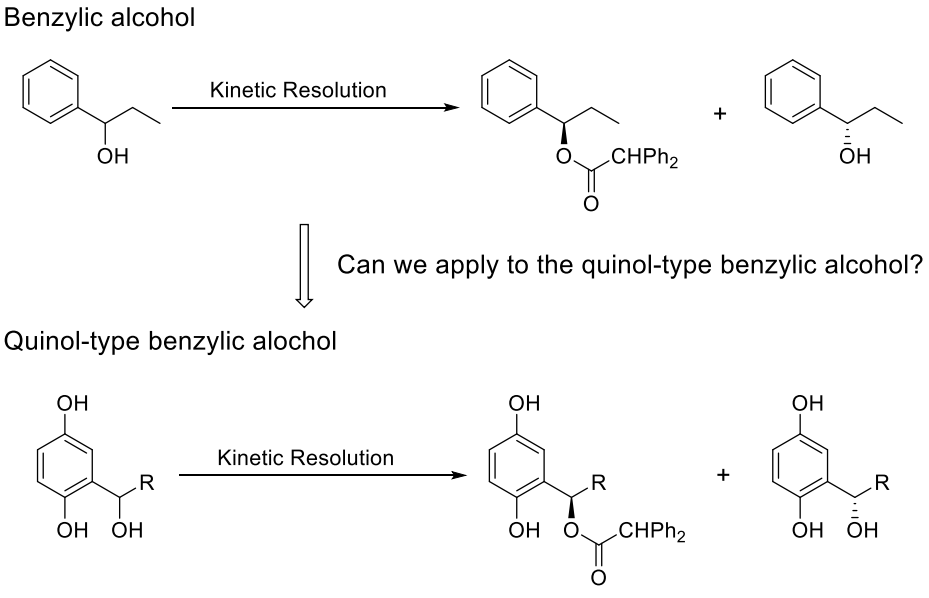


Figure 4. Working Hypothesis.

Then we focused on violaceoids shown in Figure 5.

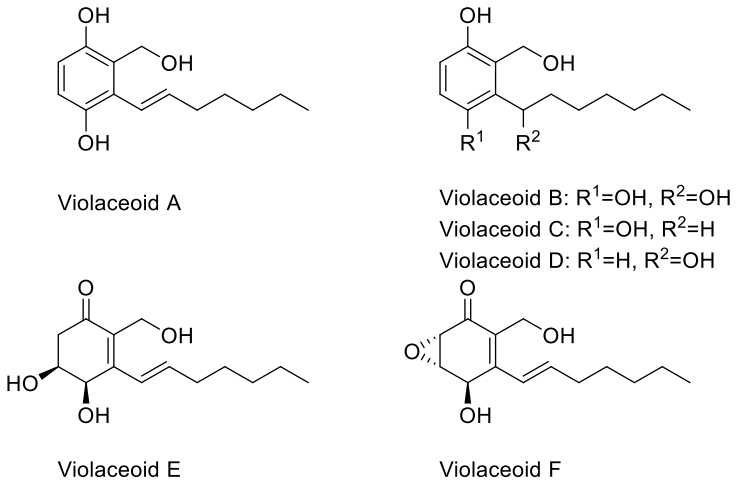


Figure 5. Violaceoids Possessing Quinol Benzylic Alcohol.

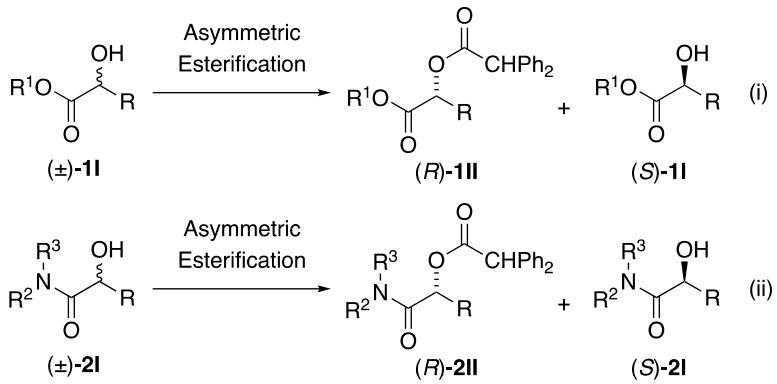
In 2014, Sugawara and coworkers reported a series of unique alkylated hydroquinones, violaceoids A–F (compounds **1**–**6**), which were isolated from a culture broth of *Aspergillus violaceofuscus* Gasperini coexisting with moss[24]. Violaceoids B and D–F are chiral compounds, and the absolute configurations of violaceoids B, D and E have not yet been determined. In addition, violaceoid B has a quinol-type benzylic hydroxy moiety, so we decided to synthesize it and reveal the absolute configuration by the total synthesis using kinetic resolution. We reported the property in this thesis.

Chapter 2

Development of Method for Producing Optically Active Secondary Alcohols Using the Kinetic Resolution of Racemic Compounds

2.1 Introduction

Optically active 2-hydroxyamide derivatives are frequently utilized as chiral building blocks not only for synthesizing biologically active compounds[1–4], but also for preparing asymmetric catalysts and chiral auxiliaries[5,6]. Consequently, considerable effort has been devoted toward developing efficient methods for synthesizing these compounds, including enzymatic[7] and chemical transformations[8–10]. For the purpose of providing chiral alcohols, the kinetic resolution (KR) of racemic alcohols by asymmetric acylation using organocatalysis is widely used as one of the most effective methods[11–13]. However, to the best of our knowledge, a general method for the kinetic resolution of racemic 2-hydroxyamide derivatives has not been reported to date. We recently accomplished the first KR of racemic alcohols with achiral carboxylic acids and of racemic carboxylic acids with achiral alcohols by asymmetric esterification[14–27] via the in situ formation of a mixed anhydride using carboxylic anhydrides as coupling reagents combined with chiral acyl-transfer catalysts. Furthermore, KR of racemic 2-hydroxyalkanoates with diphenylacetic acid was achieved using pivalic anhydride in the presence of (*R*)-benzotetramisole[27,28] ((*R*)-BTM; Scheme 1; (i)). Therefore, it was hypothesized that this KR protocol could be similarly applied to 2-hydroxyamide derivatives (Scheme 1; (ii)). In this article, we report the novel KR of various racemic 2-hydroxyamide derivatives using a diphenylacetyl component as an acyl source, catalyzed by (*R*)-BTM.



Scheme 1. Our previous result (Equation (i)) and working hypothesis for the present study (Equation (ii)).

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)

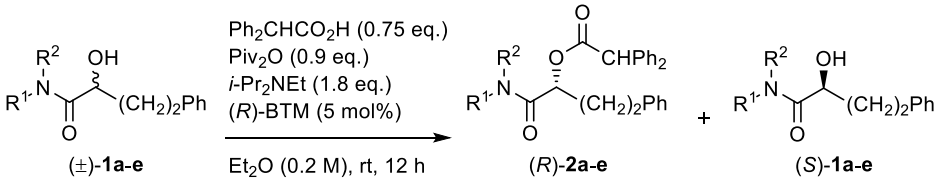
2.2 Results and Discussion

To determine suitable structures for the amide moiety, the KR reactions of a variety of racemic 2-hydroxyamides were using diphenylacetyl sources derived from Ph_2CHCO_2H or $(Ph_2CHCO)_2O$ (DPHAA)[29], catalyzed by (*R*)-BTM in Et_2O at room temperature for 12 h, which were reaction conditions similar to those established in the previous study (Table 1). We first performed KR of the secondary *N*-alkyl amide with methyl (±)-**1a** or benzyl (±)-**1b** and *N*-phenyl amide (±)-**1c** via asymmetric esterification. These substrates were found to be unsuitable for the reaction (Entries 1–3). Conversely, it was found that the tertiary amide yielded high *s*-values under the reaction conditions[30]. The KR of (±)-**1d** smoothly proceeded, affording the corresponding ester (*R*)-**2d** (48%; 92% ee) and the recovered alcohol (*S*)-**1d** (46%; >99% ee) with a high *s*-value (Entry 4; s = 254). It is noteworthy that *N*-methoxy-*N*-methylamide (±)-**1e** (known as Weinreb amide)[31–33] was successfully applied to this protocol with high synthetic utility (Entry 5; s = 156). As the tertiary amide was recognized as a suitable structure high selectivity, we subsequently performed the KR

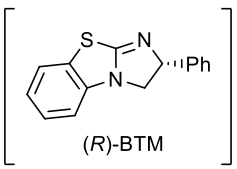
via asymmetric acylation and not via asymmetric esterification for the same reaction. As expected, high selectivity was also achieved by the reaction of (±)-**1d** and **1e** using the asymmetric acylation protocol (Entries 6 and 7).

Table 1. Kinetic Resolution of Various Racemic 2-Hydroxyamide ((±)-**1a–e**).

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)



Entry	R^1, R^2	Yield (**2** ; **1**) [%]	ee (**2** ; **1**) [%]	*s*
1	Me, H (**a**)	45 ; 52	12 ; 14	1
2	Bn, H (**b**)	50 ; 50	17 ; 15	2
3	Ph, H (**c**)	55 ; 45	79 ; 73	18
4[a]	Me, Me (**d**)	48 ; 46	92 ; >99	254
5[a]	Me, OMe (**e**)	50 ; 50	94 ; 99	156
6[b]	Me, Me (**d**)	47 ; 50	91 ; 98	95
7[c]	Me, OMe (**e**)	47 ; 42	94 ; 98	157



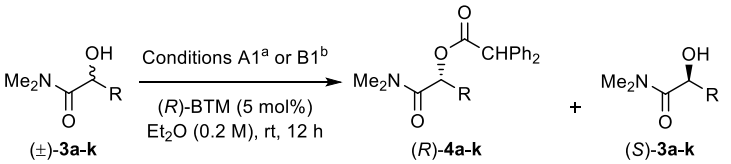
[a] Ph_2CHCO_2H (0.75 eq.), Piv_2O (0.9 eq.), and *i*-Pr_2NEt (1.2 eq.) were used.
[b] $(Ph_2CHCO)_2O$ (DPHAA; 0.60 eq.), and *i*-Pr_2NEt (0.60 eq.) were used.
[c] $(Ph_2CHCO)_2O$ (DPHAA; 0.75 eq.), and *i*-Pr_2NEt (0.75 eq.) were used.

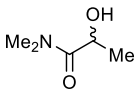
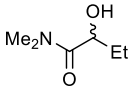
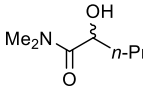
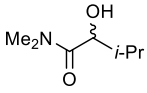
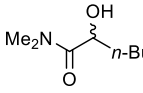
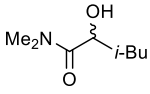
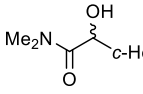
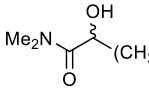
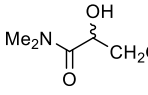
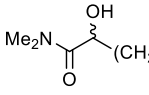
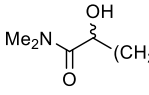
To assess the generality of this novel method, various racemic 2-hydroxy-*N,N*-dimethylamides (±)-**3a**–**3k** with different substituted forms (Table 2) were subjected to asymmetric esterification (condition A1) and asymmetric acylation (condition B1). When the KR of **3a**–**3c**, **3e**, and **3h**, bearing normal aliphatic alkyl chains at the C-2 positions, was performed under the conditions A1 and B1, the reaction successfully proceeded with high *s*-values in all cases. Asymmetric

esterification (condition A1) tended to show better results than asymmetric acylation (condition B1); however, it was revealed that the chiral acylation protocol was also useful for obtaining good *s*-values. In contrast, the reaction of (±)-**3d** and **3g**, bearing branched aliphatic alkyl chains (R = *i*-Pr and *c*-Hex) at the C-2 positions, showed a slight decrease in selectivity, while the reaction of **3f** (R = *i*-Bu) yielded a good *s*-value. We also examined several racemic ω-(*tert*-butyldimethylsiloxy)-2-hydroxy-*N,N*-dimethylamide derivatives (±)-**3i**–**3k**, having different methylene lengths, as shown in Entries 17–22. It was found that the selectivity of the KR of (±)-**3i** was somewhat lowered by the influence of the siloxy group at the C-3 position (Entries 17 and 18). Other reactions yielded high *s*-values, regardless of the length of the alkyl chains possessing *tert*-butyldimethylsiloxy groups under the conditions A1 and B1 (Entries 19–22).

Table 2. Kinetic Resolution of 2-Hydroxy Dimethylamide ((±)-3a–k).

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)



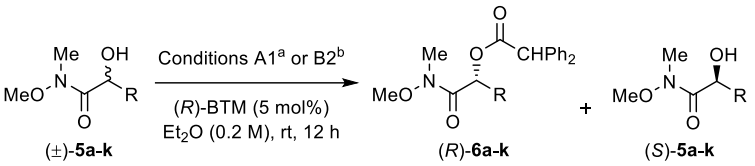
Entry	Substrate		Conditions	Yield (**4** ; **3**) [%]	ee (**4** ; **3**) [%]	*s*
1		(**a**)	A1	52 ; 46	89 ; 82	42
2		(**a**)	B1	37 ; 56	88 ; 57	27
3		(**b**)	A1	40 ; 53	93 ; 54	45
4		(**b**)	B1	37 ; 54	88 ; 62	29
5		(**c**)	A1	41 ; 57	94 ; 65	65
6		(**c**)	B1	45 ; 47	93 ; 74	63
7		(**d**)	A1	13 ; 76	82 ; 14	12
8		(**d**)	B1	25 ; 75	63 ; 21	5
9		(**e**)	A1	41 ; 56	95 ; 69	75
10		(**e**)	B1	36 ; 60	95 ; 74	63
11		(**f**)	A1	47 ; 52	95 ; 78	92
12		(**f**)	B1	48 ; 45	97 ; 94	208
13		(**g**)	A1	7 ; 83	66 ; 6	5
14		(**g**)	B1	43 ; 49	74 ; 68	13
15		(**h**) (=**1d**)	A1	48 ; 46	92 ; >99	254
16		(**h**) (=**1d**)	B1	47 ; 50	91 : 98	95
17		(**i**)	A1	34 ; 66	82 ; 41	15
18		(**i**)	B1	45 ; 49	80 ; 69	18
19		(**j**)	A1	46 ; 50	93 ; 95	103
20		(**j**)	B1	44 ; 51	94 ; 79	81
21		(**k**)	A1	48 ; 51	94 ; 99	151
22		(**k**)	B1	47 ; 46	96 ; 92	176

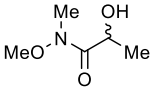
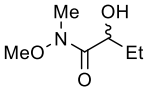
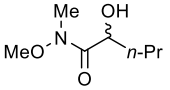
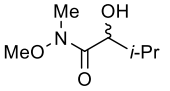
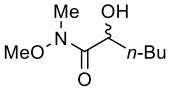
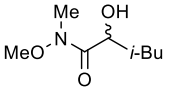
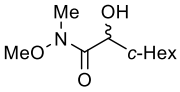
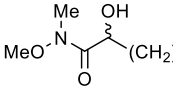
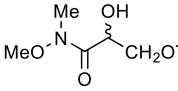
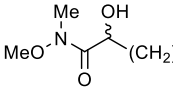
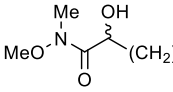
[a] Conditions A1; Ph_2CHCO_2H (0.75 eq.), Piv_2O (0.9 eq.), and *i*-Pr_2NEt (1.2 eq.).
[b] Conditions B1; $(Ph_2CHCO)_2O$ (DPHAA; 0.60 eq.), and *i*-Pr_2NEt (0.60 eq.).

Furthermore, we performed the KR of various racemic 2-hydroxy-Weinreb amides (±)-**5a**–**5k** with substitution patterns corresponding to the *N,N*-dimethylamides (±)-**3a**–**3k** using a similar protocol (Table 3). Consequently, the same tendency was observed. The KR of 2-hydroxy-Weinreb amides **5a**–**5c**, **5e**, **5f**, **5h**, **5j**, and **5k**, bearing normal aliphatic alkyl chains at the C-2 positions, exhibited high *s*-values in all cases under the conditions A1 and B2. Conversely, the reactions of 2-hydroxy-Weinreb amides (±)-**5d**, **5g**, and **5i**, bearing branched aliphatic alkyl chains at the C-2 positions or a siloxy group at the C-3 position, exhibited decreased selectivity.

Table 3. Kinetic Resolution of 2-Hydroxy Weinreb Amide ((±)-**5a**–**k**).

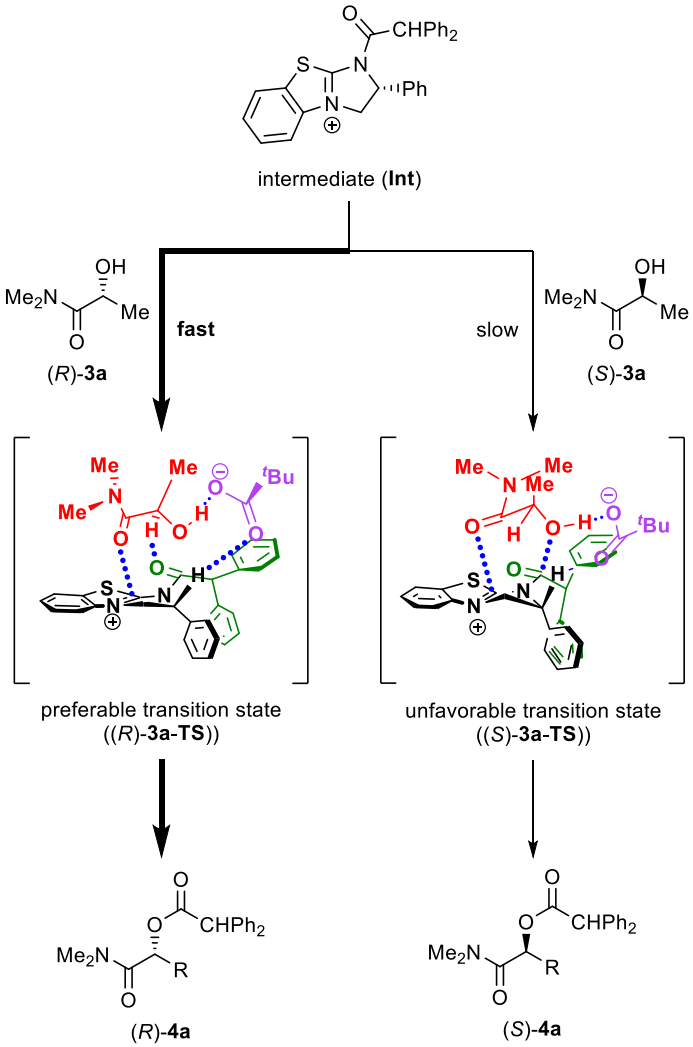
(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)



Entry	Substrate		Conditions	Yield (**4** ; **3**) [%]	ee (**4** ; **3**) [%]	*s*
1		(**a**)	A1	51 ; 44	93 ; 99	130
2		(**a**)	B2	50 ; 50	85 ; 98	57
3		(**b**)	A1	46 ; 51	96 ; 85	118
4		(**b**)	B2	46 ; 49	90 ; 89	57
5		(**c**)	A1	45 ; 55	96 ; 94	176
6		(**c**)	B2	45 ; 42	94 ; 96	118
7		(**d**)	A1	9 ; 91	66 ; 7	5
8		(**d**)	B2	27 ; 65	67 ; 31	7
9		(**e**)	A1	43 ; 56	96 ; 69	113
10		(**e**)	B2	49 ; 50	91 ; 97	89
11		(**f**)	A1	46 ; 49	97 ; 89	168
12		(**f**)	B2	46 ; 44	94 ; 99	168
13		(**g**)	A1	4 ; 91	59 ; 5	4
14		(**g**)	B2	35 ; 61	42 ; 24	3
15		(**h**) (=**1d**)	A1	50 ; 50	94 ; 99	156
16		(**h**) (=**1d**)	B2	47 ; 42	94 : 98	157
17		(**i**)	A1	40 ; 60	86 ; 51	22
18		(**i**)	B2	50 ; 46	73 ; 84	16
19		(**j**)	A1	47 ; 50	95 ; 91	115
20		(**j**)	B2	49 ; 48	90 ; 99	106
21		(**k**)	A1	54 ; 46	94 ; 99	118
22		(**k**)	B2	48 ; 41	87 ; 99	76

[a] Conditions A1; Ph_2CHCO_2H (0.75 eq.), Piv_2O (0.9 eq.), and *i*-Pr_2NEt (1.8 eq.).
[b] Conditions B1; $(Ph_2CHCO)_2O$ (DPHAA; 0.75 eq.), and *i*-Pr_2NEt (0.75 eq.).

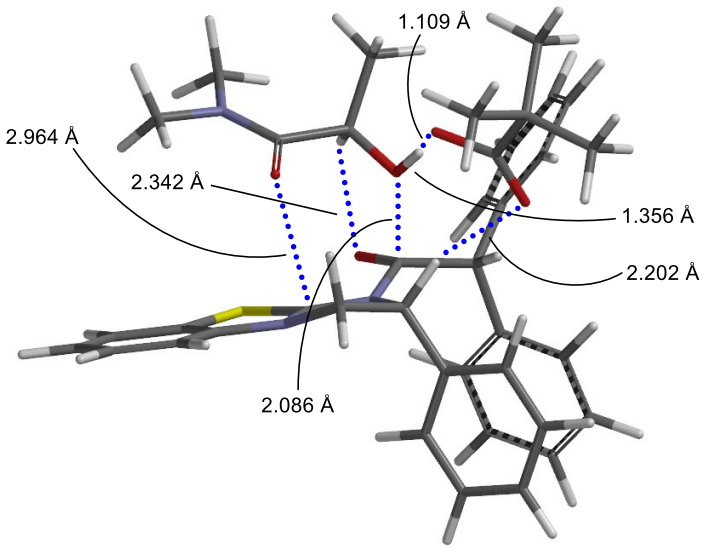
To support the results of the experimental data, we calculated the transition state of each enantiomer in the KR. This was performed using density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level according to a previously reported method[23,27,28]. Initially, we conducted a theoretical study on the KR of 2-hydroxy dimethylamides (Scheme 2)[34].



Scheme 2. Calculated Transition States of Kinetic Resolution of (±)-**3**.

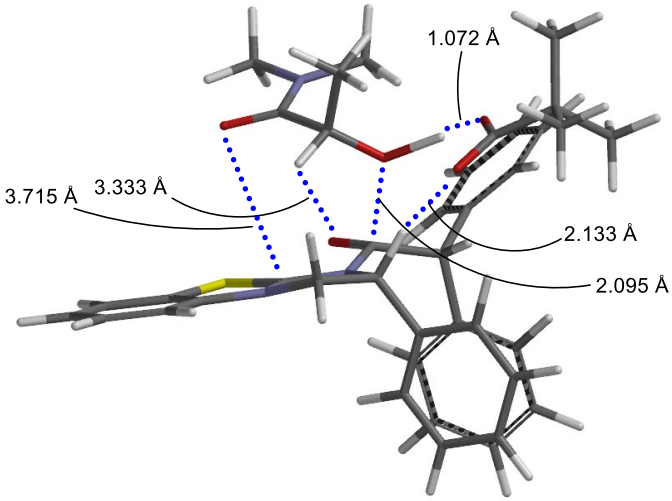
The most stable transition state that affords (*R*)- or (*S*)-2-acyloxy-dimethylamides is shown in Figure 1. It was found that the high selectivity attained in the present KR can be explained by the rapid transformation of (*R*)-**3** into (*R*)-**4** through the stabilized transition state (*R*)-**3**-**TS**, which consists of (*R*)-**3** and the isothiouronium salt derived from the mixed anhydride and (*R*)-BTM. The formation of a C–O bond (between carbonyl carbon of the acid component and oxygen of the hydroxy group) at a distance of 2.086 Å is accompanied by the coordination of oxygen in the carbonyl moiety to hydrogen at the C-2 position of the 2-hydroxydimethylamide at a distance of 2.342 Å, as shown in Figure 1. It was further observed that the length of the cleaved O–H bond (between oxygen and hydrogen in the hydroxyl group) was 1.356 Å. A frequency analysis of (*R*)-**3**-**TS** revealed that the nucleophilic attack of the alcohol to the carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceeded via a concerted reaction mechanism because the C–O bond-forming step and the O–H bond-cleaving process occurred simultaneously.

An attractive interaction occurred between oxygen in the amide carbonyl group and the positive electronic charge on the surface of the thiouronium salt, together with coordination of oxygen in the pivalate anion to hydrogen in the hydroxyl group (1.109 Å) and hydrogen at the C-2 position of the dihydroimidazolium salt (2.964 Å). However, complexation of the thiouronium salt with (*R*)-2-hydroxydimethylamide ((*R*)-**3a**), an enantiomer of (*S*)-2-hydroxydimethylamide ((*S*)-**3a**), produced an unstable structure, i.e., (*S*)-**3a**-**TS**; thus, the formation of (*S*)-**3a**-**TS** proceeded slowly due to an energy gap of 4.02 kcal/mol.



Preferable transition structure ((*R*)-**3a**-**TS**)

E_{rel} = 0.00 kcal/mol



Unfavorable transition state structure ((*S*)-**3a**-**TS**)

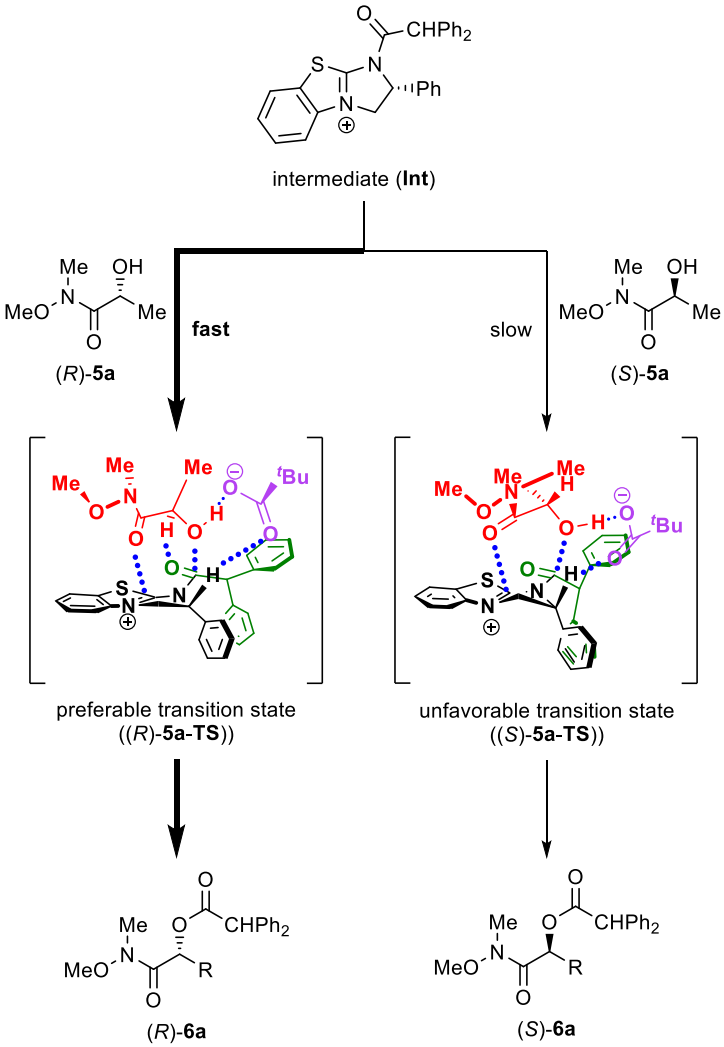
E_{rel} = 4.02 kcal/mol

Figure 1. Three-dimensional structures of the calculated transition states ((*R*)-**3a**-**TS** and (*S*)-**3a**-**TS**).

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina,

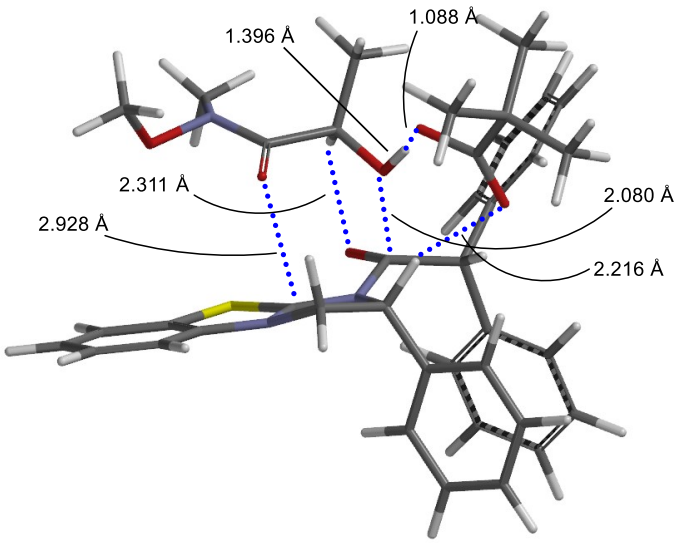
We performed further calculations on the KR of 2-hydroxy-Weinreb amides (Scheme 3). The most stable transition state that affords (*R*)- or (*S*)-2-acyloxy-Weinreb amides is shown in Figure 2[34]. It was found that the high selectivity attained in the present KR can be explained by the rapid transformation of (*R*)-**5** to (*R*)-**6** through the stabilized transition state (*R*)-**5**-**TS**, which consists of (*R*)-**5** and the isothiouronium salt derived from the mixed anhydride and (*R*)-BTM. The formation of a C–O bond (between carbonyl carbon of the acid component and oxygen of the hydroxy group) at a distance of 2.080 Å is accompanied by the coordination of oxygen in the carbonyl moiety to hydrogen at the C-2 position of the 2-hydroxy-Weinreb amide at a distance of 2.311 Å, as shown in Figure 2. It was further observed that the length of the cleaved O–H bond (between oxygen and hydrogen in the hydroxy group) was 1.396 Å. A frequency analysis of (*R*)-**5**-**TS** revealed that the nucleophilic attack of the alcohol to the carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceeded via a concerted reaction mechanism as for the reaction with the 2-hydroxy dimethylamide.

An attractive interaction occurred between oxygen in the amide carbonyl group and the positive electronic charge on the surface of the thiouronium salt, together with coordination of oxygen in the pivalate anion to hydrogen in the hydroxyl group (1.088 Å) and hydrogen at the C-2 position of the dihydroimidazolium salt (2.928 Å). However, complexation of the thiouronium salt with (*R*)-2-hydroxy-Weinreb amide ((*R*)-**5a**), an enantiomer of (*S*)-2-hydroxy-Weinreb amide [(*S*)-**5a**], produced an unstable structure, i.e., (*S*)-**5a**-**TS**; thus, the formation of (*S*)-**5a**-**TS** proceeded slowly due to an energy gap of 3.24 kcal/mol.



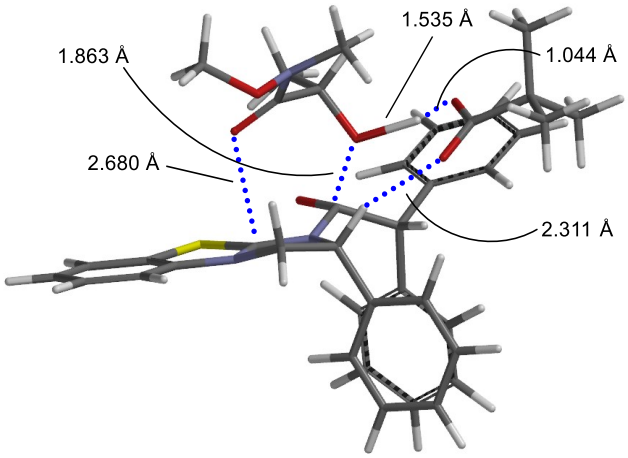
Scheme 3. Calculated Transition States of Kinetic Resolution of (±)-**5**.

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)



Preferable transition structure ((*R*)-**5a**-**TS**)

E_{rel} = 0.00 kcal/mol



Unfavorable transition structure ((*S*)-**5a**-**TS**)

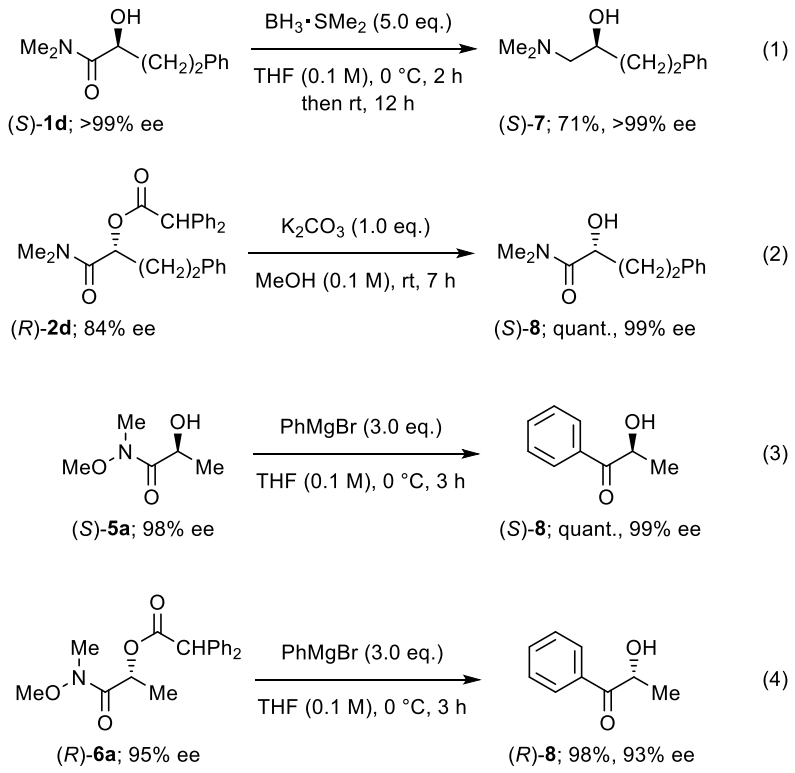
E_{rel} = 3.24 kcal/mol

Figure 2. Three-dimensional Structures of the Calculated Transition States ((*R*)-**5a**-**TS** and (*S*)-**5a**-**TS**).

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a

Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)

Finally, we attempted to transform the obtained chiral 2-hydroxyamides and their esters based on the KR to demonstrate the synthetic utility of this method (Scheme 4). Reduction of chiral 2-hydroxy-*N,N*-dimethylamide (*S*)-**1d** with $BH_3 \cdot SMe_2$ in THF afforded amino alcohol (*S*)-**7** in good yield with no loss of chirality (Equation (i)). When 2-acyloxy-*N,N*-dimethylamide (*R*)-**2d** was subjected to solvolysis with K_2CO_3 in MeOH, 2-hydroxyamide (*R*)-**1d** was produced in good yield (Equation (ii)). Treatment of 2-hydroxy-Weinreb amide (*S*)-**5a** and 2-acyloxy-Weinreb amide (*R*)-**6a** with PhMgBr afforded the corresponding 2-hydroxyketone **8** with opposite stereochemistry (Equations (iii) and (iv), respectively).



Scheme 4. Transformation of Chiral 2-Hydroxyamides and Their Esters.

(Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as Acyl Source and a

Chiral Acyl-Transfer Catalyst. T. Murata, T. Kawanishi, A. Sekiguchi, R. Ishikawa, K. Ono, K. Nakata, I. Shiina, *Molecules*, Vol. 23, issue 8. Copyright © MDPI AG, 2018.)

2.3 Conclusion

In summary, we developed an efficient method for producing optically active 2-hydroxyamides based on the KR of racemic 2-hydroxyamides with diphenylacetyl components using (*R*)-BTM as a nucleophilic chiral acyl-transfer catalyst. The resulting chiral compounds could be converted into the other useful chiral compounds without erosion of the chirality. The transition states were determined by DFT calculations to support the observations in their process.

2.3 Experimental Section for Chapter 2

General Information

Optical rotations were determined using a Jasco P-1020 polarimeter. Infrared (IR) spectra were obtained using a Jasco FT/IR-4600 Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded with chloroform (in $CDCl_3$) on the following instruments: JEOL JNM-AL500 (^{1}H at 500 MHz and ^{13}C at 125 MHz). Mass spectra were determined by a Bruker Daltonics micrOTOF focus (ESI-TOF) mass spectrometer. Thin layer chromatography was performed on Wakogel B5F. HPLC was performed with a Hitachi LaChrom Elite system composed of the Organizer, L-2400 UV Detector, and L-2130 Pump.

Supporting information for 2.2

Typical Procedure for the Preparation of Optically Active 2-Hydroxy-dimethylamides **2d** and **4a**–**4k**

Condition A; Asymmetric esterification of racemic 2-hydroxy-dimethylamide ((±)-**1d**) with diphenylacetic acid by using Piv_2O in the presence of (*R*)-BTM was described (Table 1, entry 4): To a solution of racemic 2-hyroxy-dimethylamide ((±)-**1d**) (41.5 mg, 0.20 mmol) in Et_2O (1.0 mL, 0.20 M) at room temperature were successively added diphenylacetic acid (31.8 mg, 0.15 mmol), Piv_2O (36.5 μL, 0.18 mmol), *i*-Pr_2NEt (62.7 μL, 0.36 mmol) and (*R*)-BTM (2.5 mg, 0.01 mmol). The reaction mixture was stirred for 24 h at the same temperature and then it was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica to afford the corresponding optically active ester (*R*)-**2d** (38.2 mg, 48% yield, 92% ee) and

the recovered optically active alcohol (*S*)-**1d** (19.1 mg, 46% yield, 99% ee) [*s* = 254, Table 1, Entry 4].

Condition B; Asymmetric esterification of racemic 2-hydroxy-dimethylamide ((±)-**1d**) with diphenylacetic anhydride in the presence of (*R*)-BTM was described (Table 1, entry 6): To a solution of racemic 2-hydroxy-dimethylamide ((±)-**1d**) (41.5 mg, 0.20 mmol) in Et_2O (1.0 mL, 0.2 M) at room temperature were successively added diphenylacetic anhydride (48.8 mg, 0.12 mmol), *i*-Pr_2NEt (20.9 μL, 0.12 mmol) and (*R*)-BTM (2.5 mg, 0.011 mmol). The reaction mixture was stirred for 24 h at the same temperature and then it was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica to afford the corresponding optically active ester (*R*)-**2d** (37.4 mg, 47% yield, 91% ee) and the recovered optically active alcohol (*S*)-**1d** (20.7 mg, 50% yield, 98% ee) [*s* = 95, Table 1, Entry 6].

(*S*)-2-Hydroxy-*N*-methyl-4-phenylbutanamide ((*S*)-**1a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/20, flow rate = 1.0 mL/min): t_R = 47.2 min (57.2%), t_R = 54.5 min (42.8%); IR (neat): 3309, 1643, 1619, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.33–7.22 (m, 5H, Ph), 6.85 (brs, 1H, NH), 4.15 (m, 1H, 2-H), 3.92 (d, *J* = 5.5 Hz, 1H, OH), 2.86 (s, 3H, NMe), 2.86–2.79 (m, 2H, 4-H), 2.24–2.12 (m, 1H, 3-H), 2.02–1.95 (m, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 174.8, 141.2, 128.4, 126.0, 71.4, 36.3, 31.2, 25.7; HR MS: calcd for $C_{12}H_{17}NO_2Na$ $[M + Na]^+$ 216.0995, found 216.1004.

(*S*)-*N*-Benzyl-2-hydroxy-4-phenylbutanamide ((*S*)-**1b**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 12.3 min (42.8%), t_R = 14.6 min (57.2%); IR (KBr): 3366, 3252, 1621, 1538, 1496, 1454, 732, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–7.18 (m, 10H, Ph), 7.02 (brs, 1H, NH), 4.46 (dd, *J* = 15.0, 6.0 Hz, 1H, Bn), 4.42

(dd, J = 15.0, 6.0 Hz, 1H, Bn), 4.16 (ddd, J = 8.0, 5.0, 3.5 Hz, 1H, 2-H), 3.47 (brs, 1H, OH), 2.83–2.73 (m, 2H, 4-H), 2.25–2.15 (m, 1H, 3-H), 2.04–1.94 (m, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 173.8, 141.1, 137.8, 128.7, 128.4, 127.6, 127.5, 126.0, 71.5, 43.1, 36.4, 31.2; HR MS: calcd for $C_{17}H_{19}NO_2Na$ $[M + Na]^+$ 292.1308, found 292.1312.

(*S*)-2-Hydroxy-*N*,4-diphenylbutanamide ((*S*)-**1c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 8.2 min (86.6%), t_R = 11.4 min (13.4%); IR (KBr): 3332, 3230, 1656, 1496, 1445, 755, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H, NH), 7.57–7.48 (m, 2H, Ph), 7.31–7.09 (m, 8H, Ph), 4.24 (ddd, J = 8.3, 4.8, 4.0 Hz, 1H, 2-H), 2.89 (brd, J = 4.0 Hz, 1H, OH), 2.82 (d, J = 8.0 Hz, 1H, 4-H), 2.81 (d, J = 9.5 Hz, 1H, 4-H) 2.32–2.22 (m, 1H, 3-H), 2.11–2.01 (m, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 171.6, 140.9, 137.1, 129.1, 128.6, 128.5, 126.2, 124.6, 119.8, 72.1, 36.2, 31.3; HR MS: calcd for $C_{16}H_{17}NO_2Na$ $[M + Na]^+$ 278.1151, found 278.1153.

(*S*)-2-Hydroxy-*N*,*N*-dimethyl-4-phenylbutanamide ((*S*)-**1d**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 29.2 min (100.0%); IR (neat): 3457, 1738, 1498, 1456, 1045, 752, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.31–7.16 (m, 5H, Ph), 4.30 (ddd, J = 9.0, 7.5, 3.0 Hz, 1H, 2-H), 3.78 (dd, J = 7.5, 1.5 Hz, 1H, OH), 2.96 (s, 3H, OMe), 2.87–2.75 (m, 2H, 4-H), 2.80 (s, 3H, NMe), 1.91 (dddd, J = 13.5, 9.0, 8.0, 3.0 Hz, 1H, 3-H), 1.78 (dddd, J = 13.5, 9.0, 8.5, 5.0 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 174.2, 141.3, 128.6, 128.4, 126.0, 66.9, 36.4, 36.1, 35.8, 31.2; HR MS: calcd for $C_{12}H_{17}NO_2Na$ $[M + Na]^+$ 230.1151, found 230.1150.

(*S*)-2-Hydroxy-*N*-methoxy-*N*-methyl-4-phenylbutanamide ((*S*)-**1e**) (=(*S*)-**5h**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 26.7 min (0.8%), t_R = 29.6 min (99.2%); IR (neat): 3439, 1657, 1487, 1450, 753, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.36–7.19 (m, 5H, Ph), 4.38 (dd, J = 7.0, 7.0 Hz, 1H, 2-H), 3.59 (s, 3H, OMe), 3.40 (d, J = 7.0 Hz, 1H, OH), 3.24 (s, 3H, NMe), 2.88 (ddd, J = 14.0, 9.0, 5.0 Hz, 1H, 4-H), 2.83 (ddd, J = 14.0, 8.5, 8.5 Hz,

1H, 4-H), 2.16–2.05 (m, 1H, 3-H), 1.90–1.83 (m, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 175.0, 141.4, 128.6, 128.3, 125.8, 67.7, 61.1, 36.1, 32.4, 31.2; HR MS: calcd for $C_{12}H_{17}NO_3Na$ $[M + Na]^+$ 246.1101, found 246.1106.

(*R*)-2-(Diphenylacetyloxy)-*N*-methyl-4-phenylbutanamide ((*R*)-**2a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 2/3, flow rate = 0.5 mL/min): t_R = 23.6 min (55.9%), t_R = 39.3 min (44.1%); IR (neat): 3424, 3309, 1743, 1673, 1542, 748, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.32–7.20 (m, 10H, Ph), 7.17–7.07 (m, 3H, Ph), 6.99–6.97 (m, 2H, Ph), 5.41 (brs, 1H, NH), 5.23 (dd, *J* = 7.0, 4.0 Hz, 1H, 2-H), 4.99 (s, 1H, $CHPh_2$), 2.52–2.45 (m, 2H, 3-H), 2.49 (s, 3H, NMe), 2.18–2.00 (m, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ 170.7, 169.8, 140.6, 137.8, 137.6, 128.9, 128.7, 128.6, 128.6, 128.4, 128.3, 127.7, 127.6, 126.0, 73.9, 57.1, 33.3, 31.0, 25.7; HR MS: calcd for $C_{26}H_{27}NO_3Na$ $[M + Na]^+$ 410.1727, found 410.1717.

(*R*)-*N*-Benzyl-2-(diphenylacetyloxy)-4-phenylbutanamide ((*R*)-**2b**).

HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 23.1 min (58.6%), t_R = 25.7 min (41.4%); IR (neat): 3308, 1744, 1677, 1496, 1451, 747, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.36–7.18 (m, 16H, Ph), 7.14–7.07 (m, 4H, Ph), 5.88 (t, *J* = 5.5 Hz, 1H, NH), 5.40 (dd, *J* = 7.3, 4.3 Hz, 1H, 2-H), 5.05 (s, 1H, 2′-H), 4.32 (dd, *J* = 14.8, 5.5 Hz, 1H, Bn), 4.24 (dd, *J* = 14.8, 5.5 Hz, 1H, Bn), 2.62 (t, *J* = 8.3 Hz, 2H, 4-H), 2.32–2.17 (m, 2H, 3-H); ^{13}C NMR ($CDCl_3$): δ 170.7, 169.2, 140.6, 137.7, 137.6, 137.6, 128.9, 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 127.7, 127.6, 127.6, 127.5, 126.1, 73.9, 57.1, 43.0, 33.4, 31.0; HR MS: calcd for $C_{31}H_{29}NO_3Na$ $[M + Na]^+$ 486.2040, found 486.2031.

(*R*)-2-(Diphenylacetyloxy)-*N*,4-diphenylbutanamide ((*R*)-**2c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 11.5 min (10.7%), t_R = 25.6 min (89.3%); IR (neat): 3312, 1750, 1670, 1494, 1447, 754, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34–7.00 (m, 21H, Ph, NH), 5.40 (dd, *J* = 6.8, 4.5 Hz, 1H, 2-H), 5.03 (s, 1H, 2’-H), 2.60 (t, *J* = 8.0

Hz, 2H, 4-H), 2.23 (m, 2H, 3-H); ^{13}C NMR ($CDCl_3$): δ 170.6, 167.3, 140.5, 137.7, 137.7, 136.6, 129.2, 128.8, 128.8, 128.7, 128.5, 128.5, 128.3, 127.8, 127.7, 126.1, 124.7, 119.9, 73.9, 57.2, 33.3, 31.0; HR MS: calcd for $C_{30}H_{27}NO_3Na$ $[M + Na]^+$ 472.1883, found 472.1874.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*-dimethyl-4-phenylbutanamide ((*R*)-**2d**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 17.9 min (4.3%), t_R = 40.2 min (95.7%); IR (neat): 1737, 1663, 1496, 744, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.07 (m, 13H, Ph), 6.92–6.85 (m, 2H, Ph), 5.13 (s, 1H, 2′-H), 5.08 (dd, *J* = 10.0, 3.5 Hz, 1H, 2-H), 2.84 (s, 3H, OMe), 2.73 (s, 3H, NMe), 2.59 (ddd, *J* = 14.0, 8.5, 5.0 Hz, 1H, 4-H), 2.41 (ddd, *J* = 14.0, 8.5, 8.5 Hz, 1H, 4-H), 2.11 (dddd, *J* = 14.5, 10.0, 8.5, 5.0 Hz, 1H, 3-H), 1.88 (dddd, *J* = 14.5, 8.5, 8.5, 3.5 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 172.3, 169.4, 140.3, 138.5, 138.4, 128.8, 128.7, 128.5, 128.4, 128.3, 127.4, 127.2, 126.2, 70.1, 56.7, 36.5, 35.9, 32.4, 31.0; HR MS: calcd for $C_{26}H_{27}NO_3Na$ $[M + Na]^+$ 424.1883, found 424.1901.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*-methyl-4-phenylbutanamide ((*R*)-**2e**) (=(*R*)-**6h**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 14.8 min (3.0%), t_R = 41.3 min (97.0%); IR (neat): 1736, 1674, 1496, 1450, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.51–7.19 (m, *J* = 13H, Ph), 7.05–6.99 (m, 2H, Ph), 5.27 (s, 1H, 2'-H), 5.19 (dd, *J* = 9.5, 3.5 Hz, 1H, 2-H), 3.61 (s, 3H, OMe), 3.21 (s, 3H, NMe), 2.74 (ddd, *J* = 14.0, 8.0, 5.0 Hz, 1H, 4-H), 2.53 (ddd, *J* = 14.0, 8.5, 8.5 Hz, 1H, 4-H), 2.22–2.07 (m, 2H, 3-H); ^{13}C NMR ($CDCl_3$): δ 172.5, 170.0, 140.3, 138.5, 138.4, 128.8, 128.8, 128.6, 128.4, 128.4, 128.3, 127.3, 127.1, 126.0, 70.8, 61.1, 56.8, 32.1, 31.7, 31.1; HR MS: calcd for $C_{26}H_{27}NO_4Na$ $[M + Na]^+$ 440.1832, found 440.1852.

(*S*)-2-Hydroxy-*N*,*N*-dimethylpropanamide ((*S*)-**3a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 17.3 min (5.7%), t_R = 26.6 min (93.3%); IR (neat): 3417, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (q, *J* = 6.5 Hz, 1H, 2-H), 3.82 (br s, 1H, OH) 2.95 (s, 3H, NMe), 2.94 (s, 3H, NMe), 1.27 (d, *J* = 6.5 Hz, 3H, 3-H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 64.0, 36.2, 35.8, 20.8; HR MS: calcd for $C_5H_{11}NO_2Na$ [M + Na]$^+$ 140.0682, found 140.0684.

(*S*)-2-Hydroxy-*N*,*N*-dimethylbutanamide ((*S*)-**3b**). HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 15.6 min (3.7%), t_R = 28.2 min (96.3%); IR (neat): 3425, 1642 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (m, 1H, 2-H), 3.68 (d, *J* = 7.5 Hz, 1H, OH), 2.96 (s, 3H, NMe), 2.94 (s, 3H, NMe), 1.67 (m, 1H, 3-H), 1.46 (m, 1H, 3-H), 0.94 (dd, *J* = 7.0, 7.0 Hz, 3H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 68.9, 36,3, 35,7, 27,5, 9.1; HR MS: calcd for $C_6H_{13}NO_2Na$ [M + Na]$^+$ 154.0838, found 154.0845.

(*S*)-2-Hydroxy-*N*,*N*-dimethylpentanamide ((*S*)-**3c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 17.4 min (82.5%), t_R = 36.2 min (17.5%); IR (neat): 3425, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, 1H, 2-H), 3.64 (d, *J* = 7.0 Hz, 1H, OH), 2.90 (s, 3H, NMe), 2.89 (s, 3H, NMe), 1.52–1.47 (m, 1H, 3-H), 1.43–1.32 (m, 3H, 3-H, 4-H), 0.84 (dd, *J* = 7.5, 7.5 Hz, 3H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 67.6, 36.7, 36.2, 35.7, 18.2, 13.6; HR MS: calcd for $C_7H_{15}NO_2Na$ [M + Na]$^+$ 168.0995, found 168.1000.

(*S*)-2-Hydroxy-*N*,*N*,3-trimethylbutanamide ((*S*)-**3d**).

HPLC (CHIRALPAK ID, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 8.7 min (42.8%), t_R = 17.4 min (57.2%); IR (neat): 3425, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (dd, *J* = 7.5, 2.5 Hz, 1H, 2-H), 3.56 (d, *J* = 7.0 Hz, 1H, OH), 2.98 (s, 3H, NMe), 2.97 (s, 3H, NMe), 1.91–1.82 (m, 1H, 3-H), 1.04 (d, *J* = 7.5 Hz, 3H, 4-H), 0.77 (d, *J* = 7.5 Hz, 3H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 72.1, 36.5, 35.8, 31.2, 19.7, 15.0; HR MS: calcd for $C_7H_{15}NO_2Na$ [M + Na]$^+$ 168.0995, found 168.0994.

(*S*)-2-Hydroxy-*N*,*N*-dimethylhexanamide ((*S*)-**3e**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 13.7 min (84.7%), t_R

= 31.2 min (15.3%); IR (neat): 3425, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.32 (ddd, *J* = 7.5, 7.5, 3.5 Hz, 1H, 2-H), 3.67 (d, *J* = 7.5 Hz, 1H, OH), 2.98 (s, 3H, NMe), 2.96 (s, 3H, NMe), 1.64–1.56 (m, 1H, 3-H), 1.48–1.24 (m, 5H, 3-H, 4-H, 5-H), 0.88 (dd, *J* = 7.5, 7.0 Hz, 3H, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 67.9, 36.3, 35.8, 34.3, 27.1, 22.4, 13.9; HR MS: calcd for $C_8H_{17}NO_2Na$ $[M + Na]^+$ 182.1151, found 182.1149.

(*S*)-2-Hydroxy-*N*,*N*,4-trimethylpentanamide ((*S*)-**3f**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 14.6 min (89.2%), t_R = 31.2 min (10.8%); IR (neat): 3425, 1642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.35 (ddd, *J* = 7.0, 2.5 Hz, 1H, 2-H), 3.59 (d, *J* = 7.0 Hz, 1H, OH), 2.96 (s, 3H, NMe), 2.93 (s, 3H, NMe), 1.94 (ddqq, *J* = 2.5, 4.0, 6.0, 7.0 Hz, 1H, 4-H), 1.38 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1H, 3-H), 1.27 (ddd, *J* = 14.0, 10.0, 2.5 Hz, 1H, 3-H), 0.95 (d, *J* = 6.0 Hz, 3H, 5-H), 0.91 (d, *J* = 7.0 Hz, 3H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 66.4, 43.9, 36.2, 35.8, 24.5, 23.5, 21.2; HR MS: calcd for $C_8H_{17}NO_2Na$ $[M + Na]^+$ 182.1151, found 182.1152.

(*S*)-2-Cyclohexyl-2-Hydroxy-*N*,*N*-dimethylacetamide ((*S*)-**3g**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 11.0 min (53.2%), t_R = 32.8 min (46.8%); IR (KBr): 3363, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.19 (d, *J* = 1.5 Hz, 1H, 2-H), 3.54 (br s, 1H, OH), 2.98 (s, 3H, NMe), 2.97 (s, 3H, NMe), 1.77–1.72 (m, 2H, *c*-Hex), 1.62–1.60 (m, 2H, *c*-Hex), 1.50–1.37 (m, 3H, *c*-Hex), 1.26–1.05 (m, 4H, *c*-Hex); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 72.0, 41.4, 36.6, 35.8, 29.8, 26.4, 26.0, 25.9, 25.5; HR MS: calcd for $C_{10}H_{19}NO_2Na$ $[M + Na]^+$ 208.1308, found 208.1311.

(*S*)-3-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*,*N*-dimethylpropanamide ((S)-**3i**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 9.0 min (70.6%), t_R = 13.3 min (29.4%); IR (neat): 3278, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.49 (ddd, *J* = 9.5, 6.0, 2.0 Hz, 1H, 2-H), 3.78 (dd, *J* = 10.0, 5.0 Hz, 1H, 3-H), 3.65 (d, *J* = 7.5 Hz, 1H, OH), 3.63 (dd,

J = 10.0, 7.5 Hz, 1H, 3-H), 3.05 (s, 3H, NMe), 2.99 (s, 3H, NMe), 0.86 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 68.7, 66.3, 36.8, 35.9, 25.8, 18.3, –5.5; HR MS: calcd for $C_{11}H_{25}NO_3SiNa$ $[M + Na]^+$ 270.1496, found 270.1509.

(*S*)-4-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*,*N*-dimethylbutanamide ((*S*)-**3j**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 11.4 min (3.5%), t_R = 25.0 min (96.5%); IR (neat): 3363, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55–4.51 (m, 1H, 2-H), 3.85 (ddd, *J* = 10.0, 10.0, 3.5 Hz, 1H, 4-H), 3.75 (ddd, *J* = 10.0, 10.0, 3.5 Hz, 1H, 4-H), 3.65 (d, *J* = 7.5 Hz, 1H, OH), 2.98 (s, 6H, NMe), 1.85–1.80 (m, 1H, 3-H), 1.58–1.51 (m, 1H, 3-H), 0.88 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6, 64.9, 59.2, 38.3, 36.1, 35.8, 25.8, 18.2, –5.5; HR MS: calcd for $C_{12}H_{27}NO_3SiNa$ $[M + Na]^+$ 284.1652, found 284.1645.

(*S*)-5-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*,*N*-dimethylpentanamide ((*S*)-**3k**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 12.2 min (97.2%), t_R = 30.3 min (2.8%); IR (neat): 3425, 1643 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.36 (m, 1H, 2-H), 3.71 (d, *J* = 7.0 Hz, 1H, OH), 3.69–3.59 (m, 2H, 5-H), 2.98 (s, 3H, NMe), 2.96 (s, 3H. NMe), 1.80–1.73 (m, 1H, 3-H), 1.68–1.62 (m, 2H, 4-H), 1.52–1.44 (m, 1H, 3-H), 0.86 (s, 9H, TBS), 0.01 (s, 6H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 67.6, 62.3, 36.3, 35.8, 30.9, 28.0, 25.8, 18.2, –5.4; HR MS: calcd for $C_{13}H_{29}NO_3SiNa$ $[M + Na]^+$ 298.1809 found 298.1805.

(*R*)-2-(Diphenylaceloxy)-*N*,*N*-dimethylpropanamide ((*R*)-**4a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 17.3 min (5.7%), t_R = 24.0 min (94.3%); IR (neat): 1736, 1666, 1496, 1458, 741, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.21 (m, 10H, Ph), 5.43 (q, *J* = 6.0 Hz, 1H, 2-H), 5.12 (s, 1H, 2'-H), 2.93 (s, 6H, NMe_2), 1.41 (d, *J* = 6.0 Hz, 3H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 169.7, 138.4, 138.3, 128.7, 128.6, 128.5, 128.4, 127.2, 127.1, 67.7, 56.6, 36.6, 35.6, 16.5; HR MS: calcd for $C_{19}H_{21}NO_3Na$ [M

+ Na]$^+$ 334.1414, found 334.1407.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*-dimethylbutanamide ((*R*)-**4b**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 15.6 min (3.7%), t_R = 28.2 min (96.3%); IR (neat): 1736, 1658, 1496, 1458, 741, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.18 (m, 10H, Ph), 5.21 (dd, *J* = 7.5, 5.5 Hz, 1H, 2-H), 5.11 (s, 1H, 2′-H), 2.96 (s, 3H, NMe), 2.91 (s, 3H, NMe) 1.79–1.71 (m, 2H, 3-H), 0.84 (t, *J* = 7.5 Hz, 3H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 169.3, 138.5, 128.7, 128.6, 128.5, 128.4, 127.2, 127.1, 72.5, 56.7, 36.7, 35.8, 24.3, 9.6; HR MS: calcd for $C_{20}H_{23}NO_3Na$ [M + Na]$^+$ 348.1570, found 348.1577.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*-dimethylpentanamide ((*R*)-**4c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 13.8 min (2.9%), t_R = 27.6 min (97.1%); IR (neat): 1736, 1666, 1496, 1458, 741, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.21 (m, 10H, Ph), 5.31 (dd, *J* = 8.5, 4.5 Hz, 1H, 2-H), 5.14 (s, 1H, 2′-H), 3.00 (s, 3H, NMe), 2.94 (s, 3H, NMe), 1.82–1.76 (m, 1H, 3-H), 1.70–1.64 (m, 1H, 3-H), 1.38–1.22 (m, 2H, 4-H), 0.85 (t, *J* = 7.5 Hz, 3H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 169.5, 138.5, 138.5, 128.7, 128.6, 128.5, 128.4, 127.2, 127.1, 71.0, 56.6, 36.7, 35.9, 32.9, 18.4, 13.5; HR MS: calcd for $C_{21}H_{25}NO_3Na$ [M + Na]$^+$ 362.1727, found 362.1733.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*,3-trimethylbutanamide ((*R*)-**4d**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 8.7 min (90.9%), t_R = 18.4 min (9.1%); IR (neat): 1736, 1658, 1496, 1458, 748, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.14 (m, 10H, Ph), 5.08 (s, 1H, 2'-H), 4.99 (d, *J* = 7.5 Hz, 1H, 2-H), 3.00 (s, 3H, NMe), 2.89 (s, 3H, NMe), 2.08 (m, 1H, 3-H), 0.80 (d, *J* = 7.5 Hz, 3H, 4-H), 0.78 (d, *J* = 6.0 Hz, 3H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 169.1, 138.5, 138.5, 128.7, 128.7, 128.5, 128.3, 127.2, 127.1, 75.6, 56.8, 37.0, 35.9, 30.1, 18.4, 17.7; HR MS: calcd for $C_{21}H_{25}NO_3Na$ [M + Na]$^+$ 362.1727, found 362.1710.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*-dimethylhexanamide ((*R*)-**4e**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 13.4 min (2.7%), t_R = 30.0 min (97.3%); IR (neat): 1736, 1666, 1496, 1458, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.21 (m, 10H, Ph), 5.30 (dd, *J* = 5.0, 5.0 Hz, 1H, 2-H), 5.14 (s, 1H, 2′-H), 3.00 (s, 3H, NMe), 2.94 (s, 3H, NMe), 1.80 (m, 1H, 3-H), 1.70 (m, 1H, 3-H), 1.27–1.20 (m, 4H, 4-H, 5-H), 0.77 (t, *J* = 6.5, 6.0 Hz, 3H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 169.6, 138.5, 138.5, 128.7, 128.7, 128.6, 128.4, 127.2, 127.1, 71.2, 56.7, 36.7, 35.9, 30.6, 27.2, 22.1, 13.7; HR MS: calcd for $C_{22}H_{27}NO_3Na$ $[M + Na]^+$ 376.1883, found 376.1898.

(*R*)-2-(Diphenylacetyloxy)-*N*,*N*,4-trimethylpentanamide ((*R*)-**4f**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 14.8 min (2.5%), t_R = 31.3 min (97.5%); IR (neat): 1736, 1666, 1496, 1458, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.18 (m, 10H, Ph), 5.32 (dd, *J* = 10.4, 3.4 Hz, 1H, 2-H), 5.12 (s, 1H, 2′-H), 2.98 (s, 3H, NMe), 2.91 (s, 3H, NMe), 1.79 (ddd, *J* = 14.6, 10.4, 4.6, 1H, 3-H), 1.54–1.51 (m, 1H, 4-H), 1.38 (ddd, *J* = 14.0, 9.2, 3.4 Hz, 1H, 3-H), 0.81 (d, *J* = 6.7 Hz, 3H, 5-H), 0.79 (d, *J* = 6.4 Hz, 3H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 169.8, 138.5, 138.4, 128.7, 128.7, 128.5, 128.4, 127.2, 127.1, 69.9, 56.7, 39.6, 36.6, 35.9, 24.4, 23.0, 21.3; HR MS: calcd for $C_{22}H_{27}NO_3Na$ $[M + Na]^+$ 376.1883, found 376.1873.

(*R*)-2-Cyclohexyl-2-(diphenylacetyloxy)-*N*,*N*-dimethylacetamide ((*R*)-**4g**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 2/3, flow rate = 0.75 mL/min): t_R = 11.2 min (16.8%), t_R = 31.3 min (83.2%); IR (neat): 1736, 1658, 1496, 1450, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.13 (m, 10H, Ph), 5.06 (s, 1H, 2'-H), 5.00 (d, *J* = 7.3 Hz, 1H, 2-H), 3.00 (s, 3H, NMe), 2.88 (s, 3H, NMe), 1.77 (m, 1H, 3-H), 1.58–1.45 (m, 5H, *c*-Hex), 1.17–0.80 (m, 5H, *c*-Hex); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 169.1, 138.6, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 75.0, 56.7, 39.5, 37.1, 35.9, 28.5, 28.2, 26.0, 25.8, 25.5; HR MS: calcd for $C_{24}H_{29}NO_3Na$ $[M + Na]^+$

402.2040, found 402.2047.

(*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(diphenylacetyloxy)-*N*,*N*-dimethylpropanamide ((*R*)-**4i**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 11.4 min (9.0%), t_R = 13.3 min (91.0%); IR (neat): 1743, 1658, 1496, 1458, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 10H, Ph), 5.49 (t, *J* = 6.0 Hz, 1H, 2-H), 5.15 (s, 1H, 2′-H), 3.90 (m, 2H, 3-H), 3.10 (s, 3H, NMe), 2.97 (s, 3H, NMe), 0.85 (s, 9H, TBS), 0.02 (s, 3H, TBS), 0.00 (s, 3H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 168.1, 138.4, 138.4, 128.7, 128.6, 128.5, 127.3, 127.2, 71.6, 62.9, 56.6, 37.0, 36.0, 25.7, 18.1, 5.6, 5.7; HR MS: calcd for $C_{25}H_{35}NO_4SiNa$ $[M + Na]^+$ 464.2228, found 464.2222.

(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-(diphenylacetyloxy)-*N*,*N*-dimethylbutanamide ((*R*)-**4j**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 11.4 min (3.5%), t_R = 25.0 min (96.5%); IR (neat): 1743, 1666, 1496, 1466, 748, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.22 (m, 10H, Ph), 5.54 (dd, *J* = 9.5, 3.0 Hz, 1H, 2-H), 5.17 (s, 1H, 2′-H), 3.60 (dt, *J* = 10.0, 5.0 Hz, 1H, 4-H), 3.48 (dt, *J* = 10.0, 3.5 Hz, 1H, 4-H), 3.08 (s, 3H, NMe), 2.98 (s, 3H, NMe), 1.98 (m, 1H, 3-H), 1.89 (m, 1H, 3-H) 0.86 (s, 9H, TBS), 0.02 (s, 3H, TBS), 0.06 (s, 3H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 169.8, 138.6, 138.5, 128.8, 128.7, 128.6, 128.4, 127.2, 127.1, 68.0, 58.4, 56.7, 36.6, 35.8, 34.2, 25.8, 18.1, 5.6, 5.7; HR MS: calcd for $C_{26}H_{37}NO_4SiNa$ $[M + Na]^+$ 478.2384, found 478.2386.

(*R*)-5-(*tert*-Butyldimethylsiloxy)-2-(Diphenylacetyloxy)-*N*,*N*-dimethylpentanamide ((*R*)-**4k**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 12.2 min (2.4%), t_R = 29.7 min (97.6%); IR (neat): 1751, 1666, 1496, 1458, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.22 (m, 10H, Ph), 5.35 (t, *J* = 6.5 Hz, 1H, 2-H), 5.15 (s, 1H, 2'-H), 3.54 (t, *J* = 6.0 Hz, 2H, 5-H), 3.02 (s, 3H, NMe), 2.95 (s, 3H, NMe), 1.84 (dt, *J* = 6.5, 6.5 Hz, 2H, 3-H), 1.55–1.39 (m, 2H, 4-H), 0.87 (s, 9H, TBS), 0.01 (s, 6H, TBS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 169.5, 138.5,

138.5, 128.8, 128.7, 128.6, 128.4, 127.2, 127.1, 71.1, 62.0, 56.7, 36.7, 35.9, 28.0, 27.3, 25.9, 18.2, 5.4; HR MS: calcd for $C_{27}H_{39}NO_4SiNa$ $[M + Na]^+$ 492.2541, found 492.2554.

(*S*)-2-Hydroxy-*N*-methoxy-*N*-methylpropanamide ((*S*)-**5a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 16.6 min (99.2%), t_R = 27.3 min (0.8%); IR (neat): 3443, 1662 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.42 (dq, *J* = 7.0, 7.0 Hz, 1H, 2-H), 3.65 (s, 3H, OMe), 3.42 (d, *J* = 7.0 Hz, 1H, OH), 2.81 (s, 3H, NMe), 1.29 (d, *J* = 7.0 Hz, 3H, 3-H); ^{13}C NMR ($CDCl_3$): δ 175.6, 64.8, 61.1, 32.2, 20.8; HR MS: calcd for $C_5H_{11}NO_3Na$ $[M + Na]^+$ 156.0631, found 156.0634.

(*S*)-2-Hydroxy-*N*-methoxy-*N*-methylbutanamide ((*S*)-**5b**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 13.6 min (92.4%), t_R = 41.3 min (7.6%); IR (neat): 3448, 1658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.33 (ddd, *J* = 7.5, 7.5, 3.5 Hz, 1H, 2-H), 3.69 (s, 3H, OMe), 3.24 (d, *J* = 7.5 Hz, 1H, OH), 3.22 (s, 3H, NMe), 1.76 (dqd, *J* = 14.5, 7.5, 3.5 Hz, 1H, 3-H), 1.55 (ddq, *J* = 14.5, 7.5, 7.5 Hz, 1H, 3-H), 0.95 (dd, *J* = 7.5, 7.5 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 175.0, 69.6, 61.2, 32.3, 27.6, 9.1; HR MS: calcd for $C_6H_{13}NO_3Na$ $[M + Na]^+$ 170.0788, found 170.0793.

(*S*)-2-Hydroxy-*N*-methoxy-*N*-methylpentanamide ((*S*)-**5c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 13.1 min (96.8%), t_R = 33.4 min (3.2%); IR (neat): 3464, 1658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.43–4.24 (m, 1H, 2-H), 3.66 (dd, *J* = 14.0, 14.0 Hz, 3H, OMe), 3.28–3.20 (m, 1H, OH), 3.19 (dd, *J* = 14.0, 14.0 Hz, 3H, NMe), 1.71–1.57 (m, 1H, 3-H), 1.53–1.35 (m, 3H, 3-H, 4-H), 0.89 (dddd, *J* = 15.0, 15.0, 7.5, 7.5 Hz, 3H, 5-H); ^{13}C NMR ($CDCl_3$): δ 175.2, 68.3, 61.1, 36.8, 36.7, 32.3, 18.2, 18.1, 13.6; HR MS: calcd for $C_7H_{15}NO_3Na$ $[M + Na]^+$ 184.0944, found 184.0941.

(*S*)-2-Hydroxy-*N*-methoxy-*N*,3-dimethylbutanamide ((*S*)-**5d**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 11.1 min (53.4%), t_R

= 31.8 min (46.6%); IR (neat): 3455, 1656 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.23 (dd, *J* = 8.0, 2.5 Hz, 1H, 2-H), 3.67 (s, 3H, OMe), 3.21 (s, 3H, NMe), 3.13 (d, *J* = 8.0 Hz, 1H, OH), 2.05–1.93 (m, 1H, 3-H), 1.00 (d, *J* = 7.0 Hz, 3H, 4-H), 0.78 (d, *J* = 7.0 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 174.6, 72.8, 32.3, 31.3, 19.6, 15.2; HR MS: calcd for $C_7H_{15}NO_3Na$ $[M + Na]^+$ 184.0944, found 184.0949.

(*S*)-2-Hydroxy-*N*-methoxy-*N*-methylhexanamide ((*S*)-**5e**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 10.3 min (84.3%), t_R = 26.1 min (15.7%); IR (neat): 3449, 1658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.37–4.34 (m, 1H, 2-H), 3.68 (s, 3H, OMe), 3.23 (s, 1H, OH), 3.21 (s, 3H, NMe), 1.75–1.64 (m, 1H, 3-H), 1.55–1.21 (m, 3H, 3-H, 4-H), 0.88 (dd, *J* = 7.5, 7.5 Hz, 3H, 5-H); ^{13}C NMR ($CDCl_3$): δ 175.3, 68.6, 61.2, 34.3, 32.3, 27.0, 22.3, 13.8; HR MS: calcd for $C_8H_{17}NO_3Na$ $[M + Na]^+$ 198.1101, found 198.1110.

(*S*)-2-Hydroxy-*N*-methoxy-*N*,4-dimethylpentanamide ((*S*)-**5f**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 20.0 min (82.3%), t_R = 50.9 min (4.8%); IR (neat): 3447, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.39 (dd, *J* = 8.0, 8.0 Hz, 1H, 2-H), 3.68 (s, 3H, OMe), 3.20 (s, 3H, NMe), 3.15 (d, *J* = 8.0 Hz, 1H, OH), 1.95–1.84 (m, 1H, 4-H), 1.48–1.33 (m, 2H, 3-H), 0.93 (d, *J* = 7.0 Hz, 3H, 5-H), 0.91 (d, *J* = 6.5 Hz, 3H, 5-H); ^{13}C NMR ($CDCl_3$): δ 175.7, 67.2, 61.1, 43.9, 32.4, 24.5, 23.5, 21.2; HR MS: calcd for $C_8H_{17}NO_3Na$ $[M + Na]^+$ 198.1101, found 198.1097.

(*S*)-2-Cyclohexyl-2-hydroxy-*N*-methoxy-*N*-methylacetamide ((*S*)-**5h**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 10.2 min (52.5%), t_R = 40.4 min (47.5%); IR (neat): 3451, 1656 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.20 (d, *J* = 4.0 Hz, 1H, 2-H), 3.67 (s, 3H, OMe), 3.21 (s, 3H, NMe), 3.13 (d, *J* = 8.0 Hz, 1H, OH), 1.76–1.53 (m, 5H, *c*-Hex), 1.47–1.30 (m, 2H, *c*-Hex), 1.26–1.03 (m, 4H, *c*-Hex); ^{13}C NMR ($CDCl_3$): δ 174.4, 72.6, 61.1, 41.4, 32.2, 29.6, 26.3, 26.0, 25.9; HR MS: calcd for $C_{10}H_{19}NO_3Na$ $[M + Na]^+$ 224.1257, found 224.1248.

(*S*)-3-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*-methoxy-*N*-methylpropanamide ((*S*)-**5i**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 13.7 min (75.4%), t_R = 20.2 min (24.6%); IR (neat): 3447, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.52–4.35 (m, 1H, 2-H), 3.86 (dd, *J* = 10.0, 3.5 Hz, 1H, 3-H), 3.81 (dd, *J* = 10.0, 3.5 Hz, 1H, 3-H), 3.70 (dd, *J* = 15.0, 15.0 Hz, 3H, OMe), 3.48 (ddd, *J* = 15.0, 15.0, 8.5 Hz, 1H, OH), 3.23 (dd, *J* = 15.0, 15.0 Hz, 3H, NMe), 0.86 (dd, *J* = 15.0, 15.0 Hz, 9H, TBS), 0.04 (dd, *J* = 15.0, 15.0 Hz, 3H, TBS), 0.03 (s, 3H, TBS); ^{13}C NMR ($CDCl_3$): δ 172.3, 70.2, 65.2, 61.2, 32.4, 25.8, 18.3, −5.4, −5.5; HR MS: calcd for $C_{11}H_{25}NO_4SiNa$ $[M + Na]^+$ 286.1445, found 286.1431.

(*S*)-4-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*-methoxy-*N*-methylbutanamide ((*S*)-**5j**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 9.6 min (95.2%), t_R = 23.1 min (4.8%); IR (neat): 3451, 1662, cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.62–4.48 (m, 1H, 2-H), 3.90–3.74 (m, 2H, 4-H), 3.70 (dd, *J* = 15.0, 15.0 Hz, 3H, OMe), 3.28 (d, *J* = 7.0 Hz, 1H, OH), 3.23 (ddd, *J* = 14.5, 14.5, 5.0 Hz, 3H, NMe), 2.05–1.88 (m, 1H, 3-H), 1.68–1.55 (m, 1H, 3-H), 0.89 (dd, *J* = 15.0, 15.0 Hz, 9H, TBS), 0.06 (ddd, *J* = 14.5, 14.5, 5.0 Hz, 3H, TBS), 0.05 (s, 3H, TBS); ^{13}C NMR ($CDCl_3$): δ 175.3, 65.9, 61.3, 59.2, 37.6, 32.5, 25.9, 18.2, −5.4, −5.5; HR MS: calcd for $C_{12}H_{27}NO_4SiNa$ $[M + Na]^+$ 300.1602, found 300.1607.

(*S*)-4-(*tert*-Butyldimethylsiloxy)-2-hydroxy-*N*-methoxy-*N*-methylpentanamide ((*S*)-**5k**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 8.7 min (99.6%), t_R = 21.7 min (0.4%); IR (neat): 3464, 1658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.47–4.33 (m, 1H, 2-H), 3.70 (s, 3H, OMe), 3.64 (td, *J* = 6.0, 2.5 Hz, 1H, 5-H), 3.30 (d, *J* = 8.0 Hz, 1H, OH), 3.23 (s, 3H, NMe), 1.87–1.78 (m, 1H, 3-H), 1.70–1.51 (m, 3H, 3-H, 4-H), 0.87 (s, 9H, TBS), 0.03 (s, 6H, TBS); ^{13}C NMR ($CDCl_3$): δ 175.1, 68.5, 62.7, 61.2, 32.4, 31.2, 28.3, 25.9, 18.3, –5.3; HR MS: calcd for $C_{13}H_{29}NO_4SiNa$ $[M + Na]^+$ 314.1758, found 314.1748.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*-methylpropanamide ((*R*)-**6a**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 18.9 min (26.5%), t_R

= 26.5 in (96.4%); IR (neat): 1736, 1673, 1489, 1458, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.19 (m, 10H, Ph), 5.39 (q, *J* = 6.8 Hz, 1H, 2-H), 5.13 (s, 1H, 2′-H), 3.73 (s, 3H, OMe), 3.18 (s, 3H, NMe), 1.41 (d, *J* = 6.8 Hz, 3H, 3-H); ^{13}C NMR ($CDCl_3$): δ 172.5, 170.6, 138.6, 138.5, 128.8, 128.7, 128.6, 128.4, 127.2, 127.1, 68.3, 56.6, 32.1, 16.3; HR MS: calcd for $C_{19}H_{21}NO_4Na$ $[M + Na]^+$ 350.1363, found 350.1350.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*-methylbutanamide ((*R*)-**6b**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min): t_R = 13.6 min (2.2%), t_R = 30.8 min (97.8%); IR (neat): 1736, 1676, 1486, 1454, 749, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39–7.19 (m, 10H, Ph), 5.25 (t, *J* = 7.0 Hz, 1H, 2-H), 5.16 (s, 1H, 2′-H), 3.76 (s, 3H, OMe), 3.20 (s, 3H, NMe), 1.85–1.76 (m, 2H, 3-H), 0.88 (t, *J* = 7.0 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 172.7, 170.0, 138.6, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 73.0, 61.2, 56.7, 32.0, 24.1, 9.7; HR MS: calcd for $C_{20}H_{23}NO_4Na$ $[M + Na]^+$ 364.1519, found 364.1537.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*-methylpentanamide ((*R*)-**6c**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 13.2 min (1.9%), t_R = 32.7 min (98.1%); IR (neat): 1736, 1678, 1602, 1497, 1459, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35–7.16 (m, 10H, Ph), 5.28 (dd, *J* = 9.0, 3.5 Hz, 1H, 2-H), 5.12 (s, 1H, 2′-H), 3.73 (s, 3H, OMe), 3.16 (s, 3H, NMe), 1.80–1.61 (m, 2H, 3-H), 1.39–1.16 (m, 2H, 4-H), 0.81 (dd, *J* = 7.5, 7.5 Hz, 3H, 5-H); ^{13}C NMR ($CDCl_3$): δ 172.7, 170.2, 138.6, 138.5, 128.8, 128.8, 128.5, 128.4, 127.2, 127.1, 71.6, 61.2, 56.7, 32.6, 32.1, 18.5, 13.4; HR MS: calcd for $C_{21}H_{25}NO_4Na$ $[M + Na]^+$ 378.1676, found 378.1689.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*,3-dimethylbutanamide ((*R*)-**6d**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 11.3 min (17.1%), t_R = 32.5 min (82.9%); IR (neat): 1735, 1674, 1496, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42–7.21 (m, 10H, Ph), 5.17 (s, 1H, 2'-H), 5.17 (d, *J* = 6.5 Hz, 1H, 2-H), 3.79 (s, 3H, OMe), 3.22 (s, 3H, NMe),

2.17 (dqq, J = 7.0, 6.5, 6.5 Hz, 1H, 3-H), 0.88 (d, J = 6.5 Hz, 3H, 4-H), 0.87 (d, J = 6.5 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 172.6, 169.5, 138.6, 138.5, 128.8, 128.8, 128.6, 128.3, 127.2, 127.0, 75.8, 61.1, 56.9, 32.0, 29.9, 18.7, 17.3; HR MS: calcd for $C_{21}H_{25}NO_4Na$ $[M + Na]^+$ 378.1676, found 378.1686.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*-methylhexanamide ((*R*)-**6e**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 10.4 min (1.8%), t_R = 25.4 min (98.2%); IR (neat): 1736, 1678, 1498, 1445, 743, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.35–7.17 (m, 10H, Ph), 5.27 (dd, J = 8.5, 4.0 Hz, 1H, 2-H), 5.13 (s, 1H, 2-H), 3.73 (s, 3H, OMe), 3.16 (s, 3H, NMe), 1.80–1.67 (m, 2H, 3-H), 1.29–1.13 (m, 4H, 4-H, 5-H), 0.79 (ddd, J = 7.0, 7.0, 2.5 Hz, 3H, 6-H); ^{13}C NMR ($CDCl_3$): δ 172.6, 170.2, 138.6, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 71.7, 61.2, 56.7, 21.1, 30.2, 27.2, 22.0, 13.7; HR MS: calcd for $C_{22}H_{27}NO_4Na$ $[M + Na]^+$ 392.1832, found 392.1848.

(*R*)-2-(Diphenylacetyloxy)-*N*-methoxy-*N*,4-dimethylpentanamide ((*R*)-**6f**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 10.1 min (1.8%), t_R = 24.7 min (98.2%); IR (neat): 1733, 1678, 1491, 752, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34–7.17 (m, 10H, Ph), 5.31 (dd, J = 10.3, 3.0 Hz, 1H, 2-H), 5.12 (s, 1H, 2′-H), 3.74 (s, 3H, OMe), 3.15 (s, 3H, NMe), 1.73 (ddd, J = 14.0, 10.0, 4.0 Hz, 1H, 3-H), 1.58–1.48 (m, 1H, 4-H), 1.45 (ddd, J = 14.0, 9.5, 3.5 Hz, 1H, 3-H), 0.80 (d, J = 6.0 Hz, 3H, 5-H), 0.76 (d, J = 6.5 Hz, 5-H); ^{13}C NMR ($CDCl_3$): δ 172.7, 170.6, 138.5, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 70.6, 61.2, 56.7, 39.2, 32.2, 24.5, 23.1, 21.1; HR MS: calcd for $C_{22}H_{27}NO_4Na$ $[M + Na]^+$ 392.1832, found 392.1847.

(*R*)-2-Cyclohexyl-2-(diphenylacetyloxy)-*N*-methoxy-*N*-methylacetamide ((*R*)-**6g**).

HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 10.3 min (20.4%), t_R = 40.0 min (79.6%); IR (neat): 1736, 1672, 1495, 1451, 752, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.35–7.16 (m, 10H, Ph), 5.13 (d, J = 6.5 Hz, 1H, 2-H), 5.11 (s, 1H, 2′-H), 3.75 (s, 3H, OMe), 3.17 (s, 3H,

NMe), 1.84–1.75 (m, 1H, *c*-Hex), 1.68–1.41 (m, 5H, *c*-Hex), 1.24–0.92 (m, 5H, *c*-Hex); ^{13}C NMR ($CDCl_3$): δ 172.6, 169.5, 138.6, 138.5, 128.8, 128.6, 128.3, 127.2, 127.0, 75.4, 61.1, 56.9, 39.3, 31.9, 28.7, 27.8, 26.0, 25.7; HR MS: calcd for $C_{24}H_{29}NO_4Na$ $[M + Na]^+$ 418.1989, found 418.2003.

(*R*)-3-(*tert*-Butyldimethylsiloxy)-2-(diphenylacetyloxy)-*N*-methoxy-*N*-methylpropanamide ((*R*)-**6i**). HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 13.7 min (93.0%), t_R = 21.2 min (7.0%); IR (neat): 1741, 1670, 1496, 1469, 737, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.36–7.21 (m, 10H, Ph), 5.48 (dd, *J* = 7.0, 4.0 Hz, 1H, 2-H), 5.17 (s, 1H, 2'-H), 3.91 (dd, *J* = 11.0, 4.0 Hz, 1H, 3-H), 3.88 (dd, *J* = 11.0, 7.0 Hz, 1H, 3-H), 3.80 (s, 3H, OMe), 3.20 (s, 3H, NMe), 0.83 (s, 9H, TBS), –0.00 (s, 3H, TBS), –0.03 (s, 3H, TBS); ^{13}C NMR ($CDCl_3$): δ 172.6, 167.7, 138.5, 138.4, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 73.3, 62.0, 61.3, 56.7, 32.1, 25.7, 18.2, −5.5, −5.6; HR MS: calcd for $C_{25}H_{35}NO_5SiNa$ $[M + Na]^+$ 480.2177, found 480.2174.

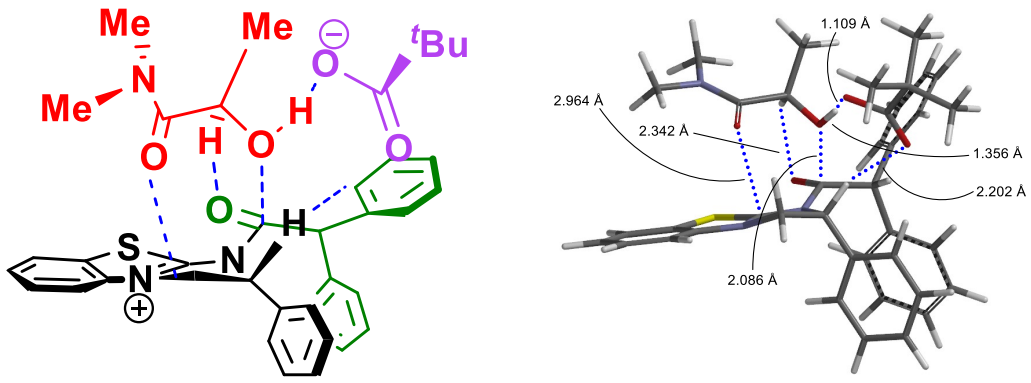
(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-(diphenylacetyloxy)-*N*-methoxy-*N*-methylbutanamide ((*R*)-**6j**). HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 9.8 min (2.7%), t_R = 23.4 min (97.3%); IR (neat): 1738, 1673, 1496, 1469, 762, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.21 (m, 10H, Ph), 5.25 (d, *J* = 8.5 Hz, 1H, 2-H), 5.16 (s, 1H, 2'-H), 3.78 (s, 3H, OMe), 3.59 (ddd, *J* = 10.0, 6.0, 4.0 Hz, 1H, 4-H), 3.50 (ddd, 10.0, 10.0, 5.0 Hz, 1H, 4'-H), 3.21 (s, 3H, NMe), 2.04–1.84 (m, 2H, 3-H), 0.85 (s, 9H, TBS), –0.03 (s, 3H, TBS), –0.07 (s, 3H, TBS); ^{13}C NMR ($CDCl_3$): δ 172.5, 170.4, 138.6, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 68.7, 61.2, 58.3, 56.8, 33.6, 32.2, 25.8, 18.1, −5.5, −5.6; HR MS: calcd for $C_{26}H_{37}NO_5SiNa$ ($M + Na^+$) 494.2333, found 494.2321.

(*R*)-4-(*tert*-Butyldimethylsiloxy)-2-(diphenylacetyloxy)-*N*-methoxy-*N*-methylpentanamide ((*R*)-**6k**). HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 8.8 min (3.0%), t_R = 21.4 min (97.0%); IR (neat): 1739, 1680, 1496, 1469, 735, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.39–7.20 (m, 10H, Ph), 5.34 (dd, *J* = 8.5, 4.5 Hz, 1H, 2-H), 5.16 (s, 1H, 2'-H), 3.77 (s, 3H, OMe), 3.54

(t, J = 6.0 Hz, 2H, 5-H), 3.20 (s, 3H, NMe), 1.93–1.77 (m, 2H, 3-H), 1.58–1.42 (m, 2H, 4-H), 0.87 (s, 9H, TBS), 0.01 (s, 6H, TBS); ^{13}C NMR ($CDCl_3$): δ 172.6, 170.1, 138.6, 138.5, 128.8, 128.8, 128.6, 128.4, 127.2, 127.1, 71.8, 62.3, 61.2, 56.7, 32.1, 28.4, 27.2, 25.9, 18.2, −5.4; HR MS: calcd for $C_{27}H_{39}NO_5SiNa$ $[M + Na]^+$ 508.2490, found 508.2514.

(Cartesian Coordinates of (*S*)-**3a-TS**, (*R*)-**3a-TS**, (*S*)-**5a-TS** and (*R*)-**5a-TS**)

All calculations were performed with the program package *Spartan '10* 1.1.0 of Wavefunction Inc. (http://www.wavefun.com). All structures were optimized and subjected to frequency analysis with the B3LYP/6-31G* method, followed by single point calculations to provide the thermodynamic properties.



Preferable transition structure ((*R*)-**3a-TS**)

E(B3LYP/6-31G*) = –2450.63466 au

ν_{TS} = 258*i* cm^{-1}

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	0.276033	0.407742	1.269097
C	1.797699	0.498867	1.156432
H	2.073283	0.217362	0.138101
O	-0.340336	0.410035	2.333515
N	-0.466607	0.949403	0.123524
C	-1.782791	1.092369	0.208050
N	-2.395278	1.122479	-0.984420
C	-1.458850	0.670358	-2.026805
C	-0.080252	0.885098	-1.323416
C	0.643398	2.130599	-1.804712
C	1.693502	1.979696	-2.719048
C	2.328325	3.103160	-3.251763
C	1.927775	4.383752	-2.869534
C	0.892555	4.538368	-1.944933
C	0.252535	3.418201	-1.416885
H	-0.534512	3.549662	-0.679294
H	0.587800	5.532156	-1.627942
H	2.426533	5.257955	-3.279673
H	3.145241	2.973968	-3.956839
H	2.026439	0.980438	-2.986031
H	0.554396	0.012257	-1.467842
H	-1.653258	-0.387735	-2.221687

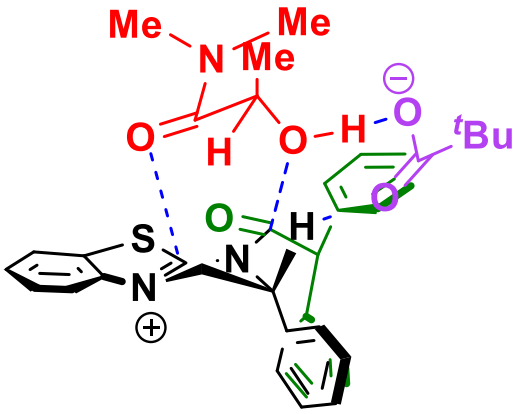
H	-1.553505	1.272820	-2.931429
O	0.165337	-1.522964	0.492982
C	-0.644206	-2.320415	1.283339
C	-2.116792	-2.266667	0.784289
N	-3.110375	-2.782827	1.583094
O	-2.390759	-1.761886	-0.309324
H	-0.630343	-1.914090	2.308680
C	-0.113202	-3.771634	1.313511
H	0.926691	-3.747488	1.652302
H	-0.682650	-4.425860	1.982661
H	-0.135502	-4.203962	0.308213
H	0.427653	-2.083652	-0.713887
O	0.636715	-2.642349	-1.648839
C	1.710637	-2.232619	-2.274664
C	2.161429	-3.169965	-3.412358
O	2.319666	-1.191281	-2.001109
S	-2.853343	1.238951	1.558084
C	-3.781397	1.211298	-0.921692
C	-4.219366	1.330363	0.410049
C	-5.573899	1.456824	0.701878
H	-5.916015	1.547375	1.728597
C	-4.685780	1.212470	-1.981923
H	-4.341315	1.114814	-3.006311
C	-6.042179	1.334824	-1.681714

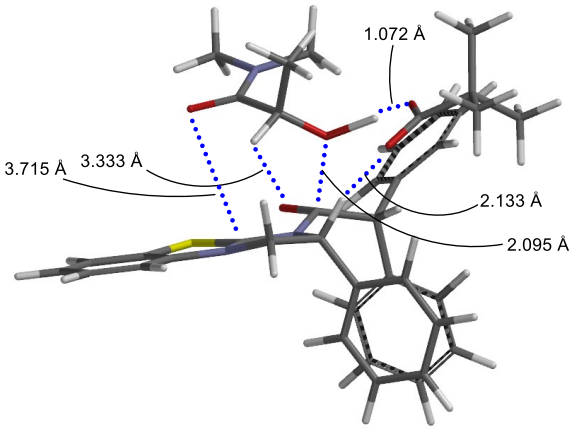
H	-6.766176	1.333523	-2.490921
C	-6.483135	1.459960	-0.358167
H	-7.544180	1.559102	-0.150565
C	0.981571	-3.383419	-4.384091
H	1.271236	-4.079454	-5.180921
H	0.681809	-2.439659	-4.856739
H	0.114615	-3.792886	-3.858752
C	2.561830	-4.524257	-2.786373
H	2.864607	-5.227632	-3.571798
H	1.726096	-4.959964	-2.231533
H	3.405674	-4.404022	-2.096685
C	3.358132	-2.559301	-4.155701
H	3.702225	-3.242651	-4.941638
H	4.190775	-2.365761	-3.473066
H	3.089496	-1.606814	-4.624459
C	2.500581	-0.484685	2.091980
C	3.862480	-2.302976	3.748426
C	3.267759	-1.517163	1.538466
C	2.427051	-0.370359	3.485626
C	3.099686	-1.276013	4.307132
C	3.946288	-2.418667	2.359794
H	3.319091	-1.615476	0.457726
H	1.839422	0.424631	3.931618
H	3.029076	-1.175444	5.387566

H	4.539211	-3.212964	1.912678
H	4.389818	-3.004799	4.389814
C	2.275377	1.939352	1.392772
C	3.298100	4.528971	1.819554
C	1.647588	2.818403	2.285653
C	3.420627	2.380852	0.714756
C	3.930128	3.660568	0.926995
C	2.155107	4.102856	2.495282
H	0.757227	2.497192	2.817003
H	3.917334	1.712497	0.016082
H	4.819545	3.980679	0.390276
H	1.653018	4.769634	3.192204
H	3.692964	5.528109	1.984812
C	-2.934946	-3.291896	2.933649
H	-1.949331	-3.048055	3.323924
H	-3.069249	-4.382279	2.972372
H	-3.683212	-2.836106	3.595484
C	-4.480166	-2.800593	1.092722
H	-5.121220	-2.148197	1.703320
H	-4.888960	-3.819170	1.134579
H	-4.482894	-2.445006	0.063444

Requested basis set is 6-31G(d)

There are 279 shells and 810 basis functions





Unfavorable transition structure ((*S*)-**3a**-**TS**)

E(B3LYP/6-31G*) = –2450.62825 au

ν_{TS} = 95*i* cm^{-1}

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	-0.207745	-0.302275	1.069726
C	1.166811	0.272135	1.426100
H	1.640542	0.613352	0.502855
O	-0.856159	-1.008563	1.836484
N	-1.038343	0.496332	0.148310
C	-2.342133	0.229429	0.080987
N	-2.934700	0.743126	-1.011597

C	-1.932567	1.272381	-1.941200
C	-0.634697	1.293053	-1.061223
C	-0.198170	2.711908	-0.751493
C	0.877193	3.254210	-1.465617
C	1.250669	4.585579	-1.268936
C	0.556788	5.382589	-0.358226
C	-0.516007	4.844568	0.356610
C	-0.895538	3.518866	0.156503
H	-1.719415	3.104802	0.731798
H	-1.054835	5.455813	1.075274
H	0.851105	6.416991	-0.202013
H	2.087047	4.997098	-1.827984
H	1.408801	2.629665	-2.178802
H	0.157886	0.748861	-1.576908
H	-1.837442	0.605455	-2.804825
H	-2.205654	2.273937	-2.278968
O	0.556780	-1.473989	-0.489881
C	-0.413027	-2.250796	-1.122715
H	1.741191	-1.179031	-1.258294
O	2.689909	-1.016151	-1.730246
C	2.624762	-0.191519	-2.754828
C	3.970656	-0.004377	-3.478089
O	1.596850	0.389059	-3.109370
S	-3.410236	-0.646372	1.114183

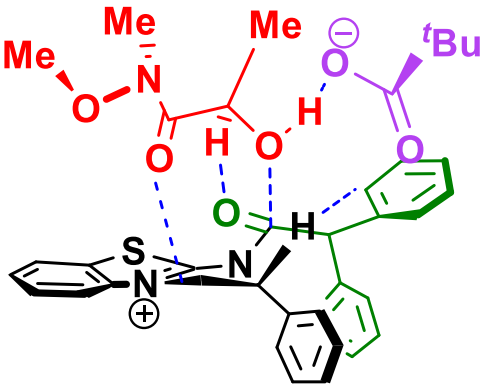
C	-4.296343	0.472328	-1.118908
C	-4.744177	-0.265734	-0.008135
C	-6.079750	-0.644167	0.092818
H	-6.429468	-1.223770	0.941825
C	-5.165468	0.847764	-2.141853
H	-4.811494	1.415198	-2.997017
C	-6.502315	0.466305	-2.030303
H	-7.199312	0.743625	-2.815337
C	-6.955950	-0.268511	-0.927139
H	-8.001180	-0.555305	-0.863988
C	4.492743	-1.385949	-3.927485
H	5.457341	-1.276951	-4.438050
H	3.794953	-1.863443	-4.625695
H	4.626108	-2.053139	-3.071566
C	4.973770	0.628028	-2.487617
H	5.942543	0.776183	-2.979671
H	5.125945	-0.014693	-1.615632
H	4.624613	1.607068	-2.136196
C	3.782675	0.914200	-4.694392
H	4.738250	1.050005	-5.214707
H	3.411342	1.899595	-4.395893
H	3.061062	0.493185	-5.401482
H	-1.286922	-1.635721	-1.408502
C	0.106351	-2.878725	-2.433757

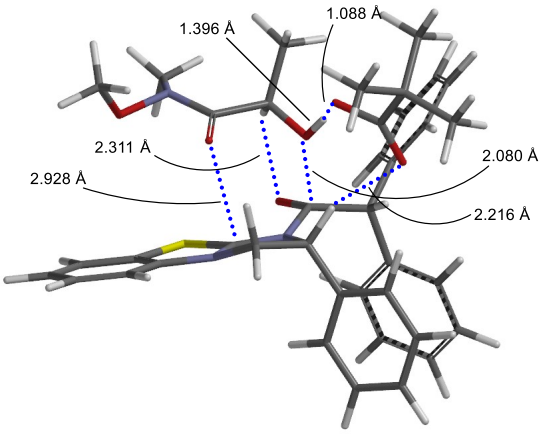
H	0.388247	-2.085896	-3.134242
H	-0.676971	-3.490969	-2.894701
H	0.983242	-3.509218	-2.254573
C	1.030376	1.489837	2.353637
C	0.937185	3.724935	4.064779
C	0.045415	1.590102	3.345669
C	1.967102	2.525392	2.235720
C	1.924101	3.631988	3.081557
C	-0.000865	2.700539	4.191589
H	-0.691555	0.800784	3.456158
H	2.737764	2.462384	1.471650
H	2.661262	4.423048	2.970433
H	-0.773727	2.759802	4.954149
H	0.901019	4.587093	4.725728
C	2.087840	-0.771128	2.063474
C	3.882719	-2.576937	3.266096
C	3.333015	-1.037549	1.483177
C	1.754272	-1.418635	3.261441
C	2.641744	-2.317461	3.852695
C	4.224718	-1.932537	2.077746
H	3.598702	-0.563259	0.543821
H	0.794009	-1.228868	3.725820
H	2.364022	-2.811651	4.780549
H	5.184588	-2.126361	1.605605

H	4.574939	-3.273470	3.732327
C	-1.094660	-3.352881	-0.265317
O	-2.324158	-3.460911	-0.348232
N	-0.344580	-4.207497	0.491390
C	1.106278	-4.193380	0.605032
H	1.509233	-3.289301	0.157494
H	1.541286	-5.084051	0.127188
H	1.391762	-4.200307	1.664073
C	-1.018251	-5.254937	1.241243
H	-0.673863	-6.246464	0.914453
H	-2.090408	-5.167802	1.070607
H	-0.802300	-5.153435	2.313361

Requested basis set is 6-31G(d)

There are 279 shells and 810 basis functions





Preferable transition structure ((*R*)-**5a-TS**)

E(B3LYP/6-31G*) = –2525.79242 au

ν_{TS} = 172*i* cm^{-1}

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
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O	-0.245390	0.567904	2.286722
N	-0.298397	1.014262	0.055040
C	-1.600228	1.268461	0.112971
N	-2.188665	1.318656	-1.090555
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C	0.103239	0.868320	-1.381424
C	0.953396	2.020432	-1.887746

C	2.001885	1.740216	-2.772773
C	2.746953	2.781207	-3.330445
C	2.457918	4.106320	-3.003478
C	1.424055	4.388937	-2.107964
C	0.674096	3.351886	-1.555642
H	-0.114834	3.581748	-0.844640
H	1.204983	5.417317	-1.833690
H	3.042327	4.915464	-3.433544
H	3.561931	2.552440	-4.012158
H	2.246780	0.705826	-2.997224
H	0.648793	-0.068567	-1.485436
H	-1.566478	-0.256894	-2.312282
H	-1.296739	1.383922	-3.017363
O	0.173592	-1.486172	0.564648
C	-0.740868	-2.147900	1.359971
C	-2.176412	-1.948354	0.794157
N	-3.242490	-2.306546	1.604215
O	-2.375510	-1.518769	-0.338655
H	-0.726970	-1.691443	2.363984
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H	0.628698	-3.726874	1.879919
H	-1.068776	-4.184780	2.161887
H	-0.421377	-4.131398	0.509400
H	0.440708	-2.172842	-0.621306

O	0.642692	-2.809397	-1.480722
C	1.723706	-2.461881	-2.136010
C	2.152925	-3.485889	-3.203446
O	2.350244	-1.416794	-1.932662
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C	-5.360222	1.935726	0.525809
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C	-6.245790	1.994488	-0.552264
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H	1.238764	-4.502840	-4.901286
H	0.669172	-2.839093	-4.681486
H	0.096085	-4.116669	-3.593034
C	2.541189	-4.794465	-2.479398
H	2.833814	-5.559008	-3.209417
H	1.704273	-5.178914	-1.889298
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C	2.413751	-0.395488	3.516417
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H	1.841214	0.430297	3.924062
H	2.908055	-1.187881	5.454358
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C	3.673453	4.395015	1.722078
C	1.908911	2.810406	2.215145
C	3.662520	2.214583	0.675446
C	4.253871	3.463071	0.859098
C	2.498824	4.063478	2.396646
H	0.994258	2.563325	2.744613
H	4.119688	1.497015	-0.000993
H	5.167426	3.708822	0.323648
H	2.035845	4.780134	3.070769

H	4.132498	5.369842	1.865327
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H	-2.283878	-2.799041	3.398355
H	-4.045974	-2.996982	3.393367
H	-3.336625	-1.363237	3.499320
O	-4.494392	-1.801067	1.178685
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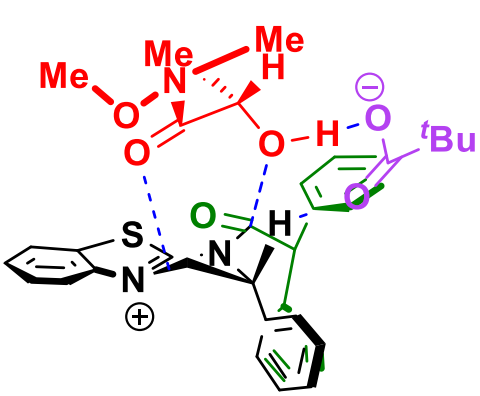
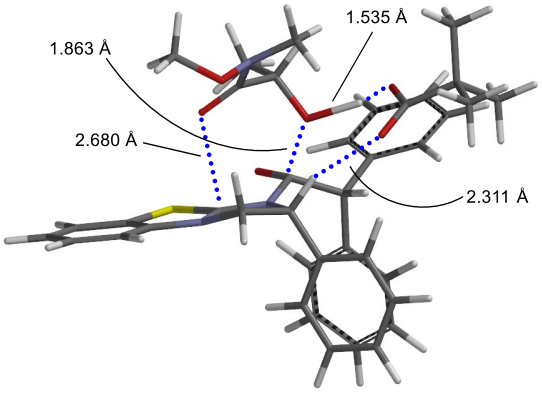
H	-6.089863	-2.266031	0.047625
H	-5.272884	-3.696619	0.752558

Requested basis set is 6-31G(d)

There are 283 shells and 825 basis functions





Unfavorable transition structure ((*S*)-**5a-TS**)

E(B3LYP/6-31G*) = –2525.78725 au

ν_{TS} = 136*i* cm^{-1}

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	0.006980	0.812077	1.144269
C	1.328094	1.482134	0.717279
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O	-0.577688	1.135441	2.186467
N	-0.950485	0.600978	-0.002543
C	-2.249553	0.579353	0.249458
N	-2.978080	0.021585	-0.734241
C	-2.091522	-0.679788	-1.671787
C	-0.706237	-0.024344	-1.345554
C	-0.288717	0.974466	-2.412901
C	0.741252	0.628540	-3.296652
C	1.092754	1.490398	-4.338328
C	0.422206	2.701994	-4.505193
C	-0.602725	3.053241	-3.623481
C	-0.957103	2.194337	-2.584855
H	-1.740191	2.491740	-1.892664
H	-1.121125	4.001214	-3.738474
H	0.699478	3.373540	-5.313619
H	1.895061	1.213136	-5.017394

H	1.264998	-0.313391	-3.160309
H	0.062581	-0.787854	-1.224766
H	-2.119307	-1.750818	-1.447776
H	-2.388476	-0.494705	-2.705728
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H	2.004886	-1.429557	0.572756
O	2.899375	-1.869082	0.286354
C	2.911174	-2.176525	-1.001017
C	4.247239	-2.782777	-1.460230
O	1.958840	-1.998317	-1.755756
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C	-4.341144	-0.064740	-0.472883
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H	5.519722	-4.457825	-0.907288

H	3.792633	-4.795937	-0.715739
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H	6.322396	-2.132707	-1.579192
H	5.431954	-1.429743	-0.209877
H	5.158828	-0.826551	-1.858472
C	4.154597	-3.178548	-2.941212
H	5.105281	-3.613944	-3.270671
H	3.935035	-2.311608	-3.571893
H	3.362344	-3.915857	-3.106173
H	0.952077	-2.697670	2.103693
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H	-0.322200	3.418605	1.866734
H	2.516594	2.837548	-1.300610
H	2.330394	5.217946	-1.917267

H	-0.527017	5.802906	1.243586
H	0.800462	6.722616	-0.650221
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C	4.559895	1.324487	3.621286
C	3.733896	1.087747	1.362760
C	2.209777	1.670712	3.131844
C	3.264969	1.631016	4.043925
C	4.790907	1.054584	2.272845
H	3.926278	0.870621	0.315499
H	1.207459	1.904539	3.469217
H	3.072295	1.846777	5.092190
H	5.792994	0.814958	1.925347
H	5.379238	1.298407	4.335260
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O	-2.144729	-2.028370	1.225063
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C	0.382301	-4.388126	0.114367
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H	0.612707	-4.099215	-0.916273
H	0.266586	-5.475049	0.171316
O	-1.888981	-4.098331	-0.343289
C	-2.939244	-4.796754	0.333278
H	-3.439524	-4.139275	1.048671
H	-2.553167	-5.690542	0.838609

H -3.634743 -5.093231 -0.456665

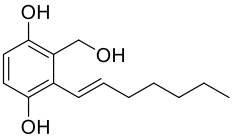
Requested basis set is 6-31G(d)

There are 283 shells and 825 basis functions

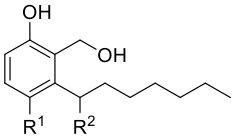
Chapter 3

the Total Synthesis of Naturally Occuring Polyoxy-compounds, Violaceoids A and B

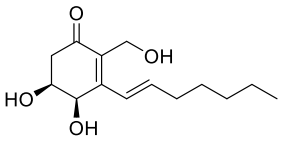
3.1 Introduction



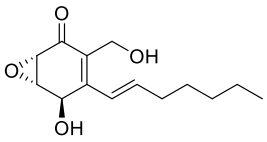
Violaceoid A (**1**)



Violaceoid B (**2**): R^1=OH, R^2=OH
Violaceoid C (**3**): R^1=OH, R^2=H
Violaceoid D (**4**): R^1=H, R^2=OH



Violaceoid E (**5**)



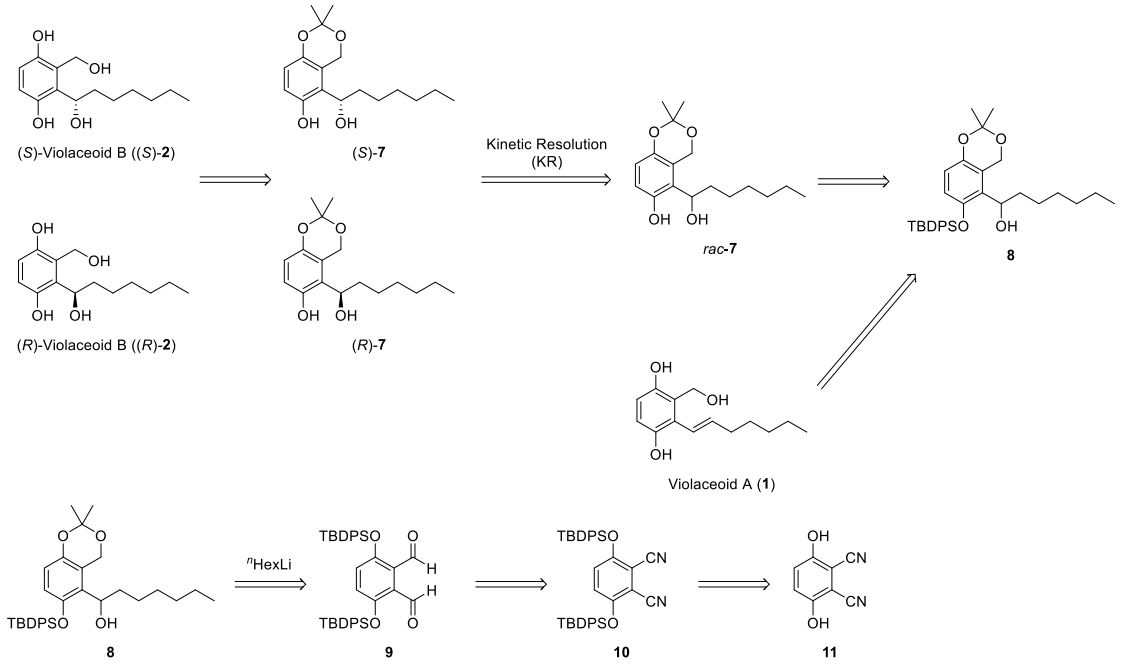
Violaceoid F (**6**)

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

In 2014, Sugawara and coworkers reported a series of unique alkylated hydroquinones, violaceoids A–F (compounds **1**–**6**), which were isolated from a culture broth of *Aspergillus violaceofuscus* Gasperini coexisting with moss.[1] Violaceoids B and D–F are chiral compounds, and the absolute configurations of violaceoids B, D and E have not yet been determined. Sugawara's group also reported that violaceoids exhibit cytotoxicity. Among them, violaceoid A (**1**) inhibited the growth of several human cancer cell lines. In addition, neither the total synthesis nor the synthetic approach for violaceoids A–E has ever been reported to the best of our knowledge.[2] Considering this, we initiated a program to synthesize **1** and **2**, and the details are presented in this chapter.

3.2 Total Synthesis of Violaceoid A and *rac*-Violaceoid B

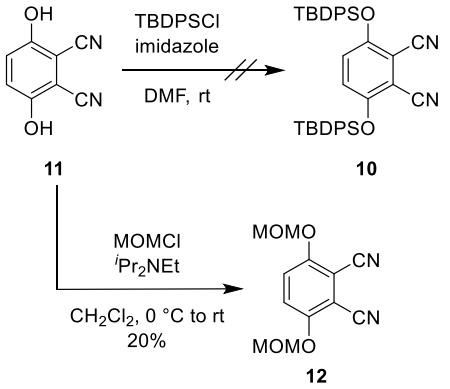
The retrosynthetic analysis of **1** and **2** is shown in Scheme 1.



Scheme 1. Retrosynthetic Analysis of **1** and **2**.

(Total Synthesis of Violaceoid A and (–)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

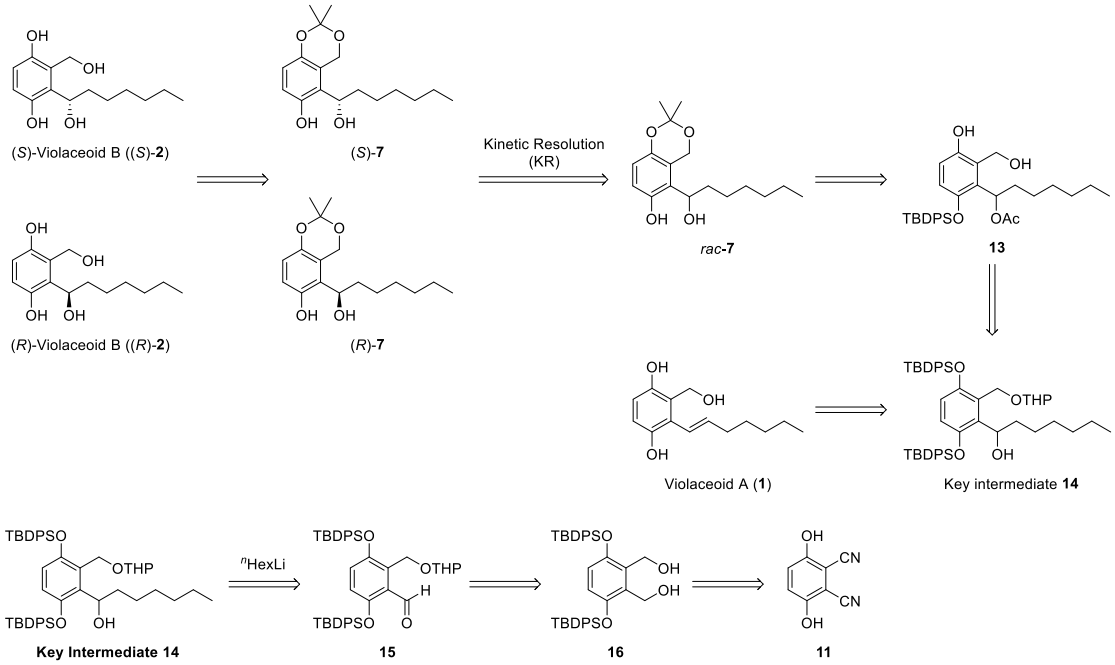
Optically active (*S*)- or (*R*)-violaceoid B (**2**) can be obtained by the deprotection of the acetonide group from (*S*)- or (*R*)-**7**, respectively. Diols (*S*)- and (*R*)-**7** can be separated by using a kinetic resolution method of racemic compound (*rac*-**7**) that our group has already reported.[3] The substrate for kinetic resolution can be obtained from the racemic secondary alcohol **8**, which can be prepared from 3,6-dihydroxyphthalonitrile (**11**) via direct protection of **11**.



Scheme 2. Protection of 3,6-Dihydroxyphtalonitrile (**11**).

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

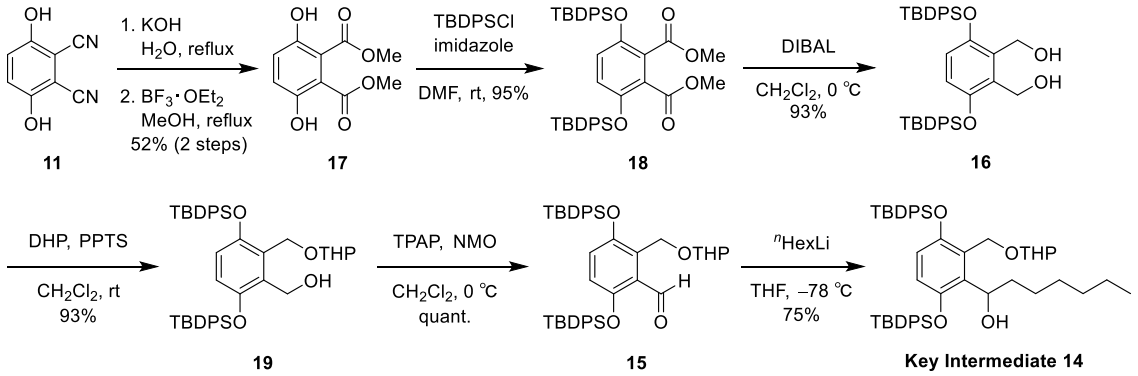
Following this strategy, we first tried to protect two hydroxy groups of 3,6-dihydroxyphthalonitrile as *tert*-butyldiphenylsilyl (TBDPS) ether depicted in Scheme 2. However, we could not obtain the desired phthalonitrile **10**. Then we conducted the protection transforming into methoxymethyl (MOM) ether groups but we could get the desired compound **12** in low yield. On the basis of the above results, we decided to change the synthetic plan for providing violaceoids A and B as shown in Scheme 3.



Scheme 3. Revised Retrosynthetic Analysis of **1** and **2**.

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

In the revised synthetic plan, *rac*-**7**, the substrate for kinetic resolution can be obtained from the racemic secondary alcohol **14** by several functional transformations. Violaceoid A (**1**) can also be derived from **14**. The key intermediate **14** can be prepared from **11** via reduction of a derivative of **11**.

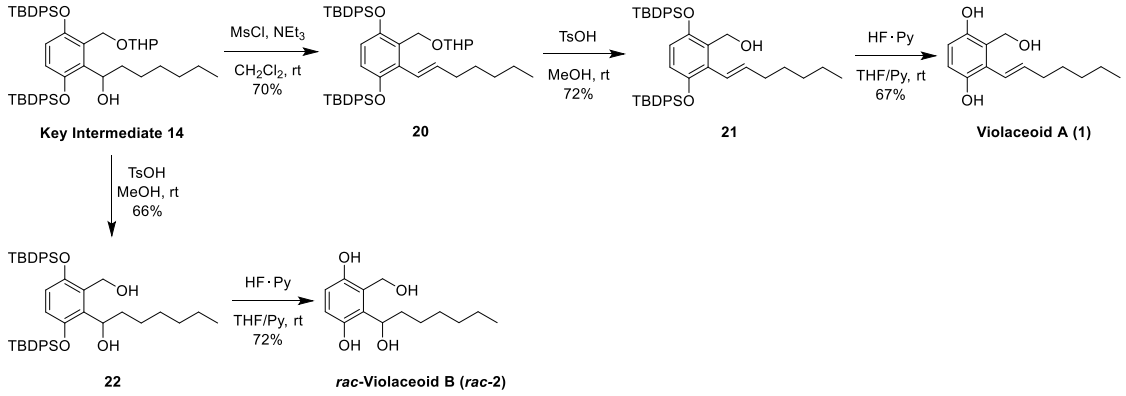


Scheme 4. Synthesis of Key Intermediate **14**.

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

The preparation of **14** was carried out as depicted in Scheme 4. The hydrolysis of **11** followed by esterification gave the dimethyl ester **17**.[4] The two hydroxy groups of **17** were protected with TBDPS groups to afford **18**. The symmetric diol **16** was obtained by the reduction of diester **18**. Mono-tetrahydropyranylation gave the unilateral protected alcohol **19**. After the oxidation of alcohol **19** to aldehyde **15** followed by alkylation with an alkyl lithium reagent, we obtained the key intermediate **14**.

We next attempted to synthesize **1** and *rac*-**2** (Scheme 5).



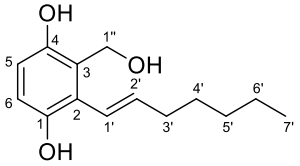
Scheme 5. Synthesis of **1** and *rac*-**2**.

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

The double bond in **20** was generated by mesylation of **14**. Then, the THP group was removed, and we obtained the alcohol **21**. Finally, by deprotection of the two TBDPS groups, we accomplished the total synthesis of violaceoid A (**1**). In addition, by sequential deprotection of the THP and TBDPS groups of **14**, we achieved the synthesis of *rac*-violaceoid B (*rac*-**2**). We compared the ^{1}H and ^{13}C NMR data of the synthetic **1** and **2** with those of naturally occurring violaceoids A and B reported in the literature to determine the true structure. The results are shown in Tables 1 and 2. As a result, the ^{1}H and ^{13}C NMR data of synthetic **1** and **2** were shown to be in accordance with those reported for the natural compounds.

Table 1. Comparison of the ^{1}H and ^{13}C NMR Data of Naturally Occurring Violaceoid A with Those of Synthetic **1** in CD_3OD.

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)



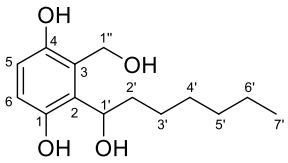
position	natural violaceoid A[a] δ_C	natural violaceoid A[a] δ_H (J in Hz)	position	synthetic violaceoid A[b] δ_C	synthetic violaceoid A[b] δ_H (J in Hz)
1	148.8		1	148.8	
2	127.6		2	127.6	
3	125.9		3	125.9	
4	150.6		4	150.6	
5	115.0	6.57, d (8.7)	5	114.9	6.54, d (8.7)
6	116.3	6.60, d (8.7)	6	116.2	6.59, d (8.7)
1'	124.6	6.45, dt (16.1, 6.9)	1'	124.6	6.50-6.42, m
2'	137.9	6.06, dt (16.1, 6.9)	2'	137.8	6.08, dt (15.6, 6.9)
3'	34.9	2.24, tdd (6.9, 6.9, 1.5)	3'	34.9	2.32-2.19, m
4'	30.3	1.51, m	4'	30.4	1.61-1.43, m
5'	32.7	1.37, m	5'	32.7	1.43-1.30, m
6'	23.6	1.37, m	6'	23.7	1.43-1.30, m
7'	14.4	0.93, t (7.1)	7'	14.5	0.94, t (7.2)
1"	58.5	4.72, s	1"	58.4	4.71, s

a : 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. See Ref 1.

b : 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR using JNM-AL300.

Table 2. Comparison of the ^{1}H and ^{13}C NMR Data of Naturally Occurring Violaceoid B with Those of Synthetic **2** in CD_3OD.

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)



	natural violaceoid B[a]			synthetic violaceoid B	
position	δ_C	δ_H (J in Hz)	position	δ_C[b]	δ_H (J in Hz)[c]
1	150.1		1	150.1	
2	130.4		2	130.5	
3	125.1		3	125.0	
4	150.1		4	150.0	
5	115.8	6.57, d (8.7)	5	115.6	6.63, d (8.4)
6	117.5	6.60, d (8.7)	6	117.5	6.60, d (8.4)
1'	72.0	5.15, dd (9.0, 4.6)	1'	71.9	5.19, dd (9.2, 4.4)
2'	38.2	1.89, m, 1.71, m	2'	38.2	2.00-1.83, 1.80-1.67, m
3'	27.2	1.55, m	3'	27.2	1.67-1.43, m
4'	30.3	1.33, m	4'	30.4	1.43-1.25, m
5'	33.1	1.33, m	5'	33.1	1.43-1.25, m
6'	23.7	1.33, m	6'	23.7	1.43-1.25, m
7'	14.4	0.89, t (6.8)	7'	14.5	0.93, t (6.8)
1"	56.6	4.71, d (11.7), 4.68, d (11.7)	1"	56.5	4.75, d (11.6), 4.71, d (11.6)

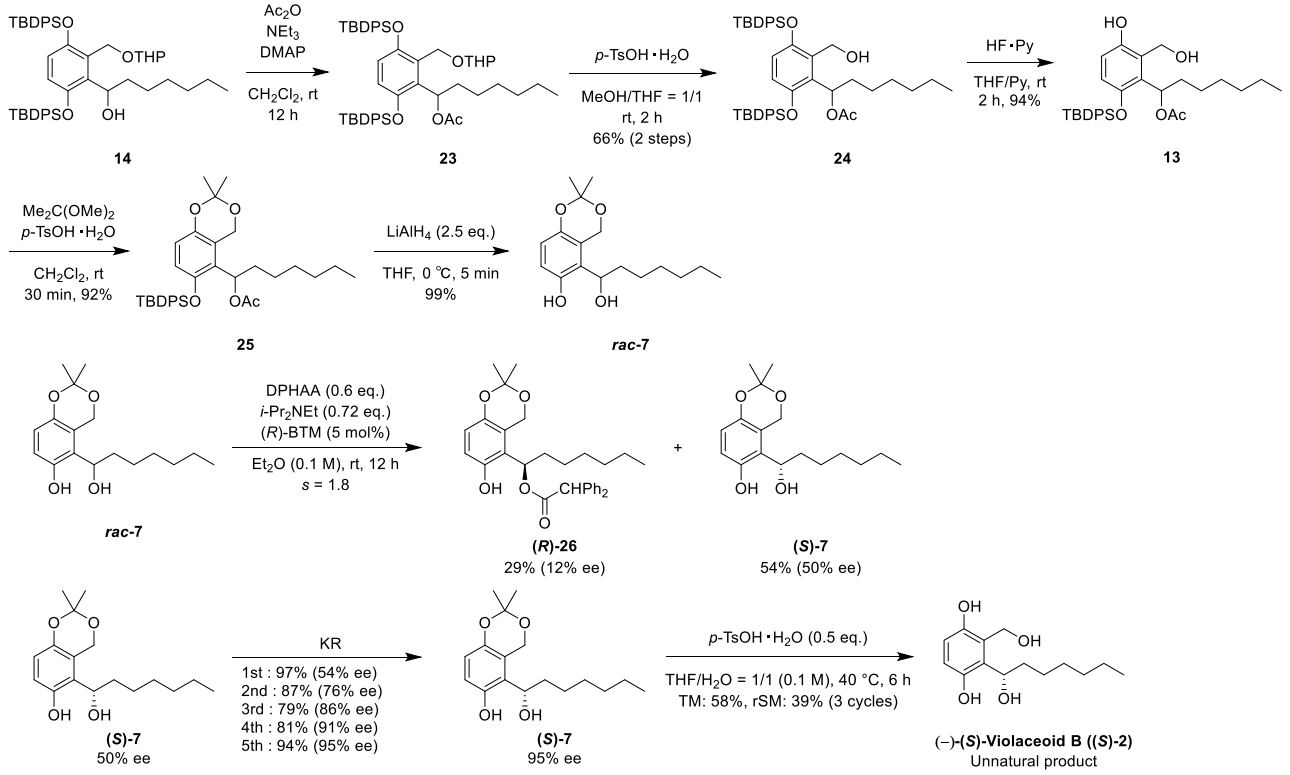
a : 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. See Ref 1.

b : 125 MHz using JNM-LA500.

c : 400 MHz using AVANCE 400M.

3.3 Asymmetric Total synthesis of (*R*)- and (*S*)-Violaceoid B

Subsequently, we attempted to determine the absolute configuration of naturally occurring violaceoid B (**2**), as depicted in Scheme 6.

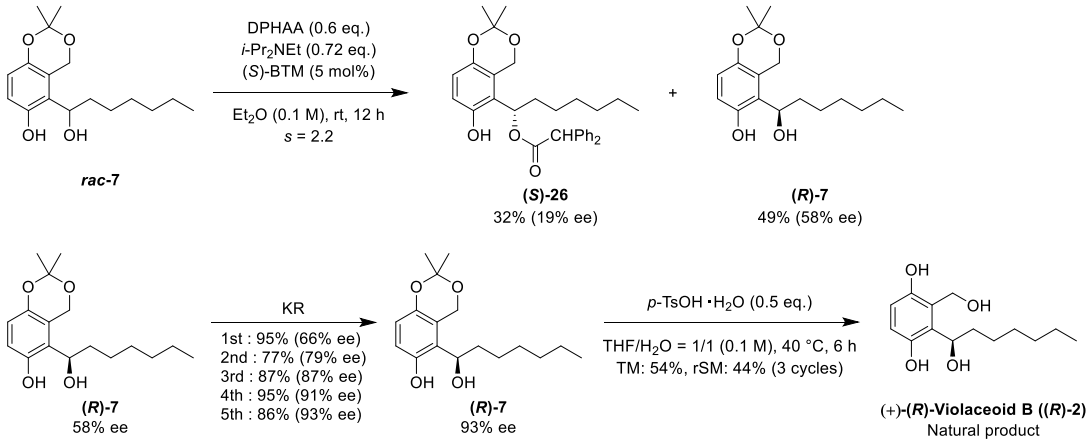


Scheme 6. Synthesis of (*S*)-Violaceoid B ((*S*)-**2**).

(Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B. T. Murata, T. Kuboki, R. Ishikawa, T. Saito, S. Taguchi, K. Takeuchi, E. Hatano, M. Shimonaka, I. Shiina, *J. Nat. Prod.*, Vol. 81, issue 11. Copyright © 2018 American Chemical Society and American Society of Pharmacognosy. https://pubs.acs.org/articlesonrequest/AOR-C5h3rsu2PRptZ6WVZRBk)

We obtained the alcohol **24** by acetylation of **14** followed by deprotection of the THP group. Next, deprotection of the TBDPS group was conducted to afford the 1,3-diol **13**. The acetyl and TBDPS

groups were reductively removed together to yield *rac*-**7**, which is the substrate for kinetic resolution.[2] The kinetic resolution was conducted to afford the enantiorich ester (*R*)-**26**[5] and enantiorich alcohol (*S*)-**7**. Further, the same reaction was repeated five times to obtain the enantiorich alcohol in 95% ee. Finally, by deprotection of the acetonide group, we accomplished the asymmetric total synthesis of (*S*)-violaceoid B ((*S*)-**2**). However, the optical rotation of (*S*)-**2** was not consistent with the natural product, which motivated us to synthesize the enantiomer, (*R*)-violaceoid B ((*R*)-**2**) (Scheme 7).



Scheme 7. Synthesis of (*R*)-Violaceoid B ((*R*)-**2**).

As for enantiopure (*S*)-**7**, we conducted the kinetic resolution procedure. Using the recovered enantiorich alcohol, the same reaction was then repeated five times to obtain the enantiorich alcohol in 93% ee. Finally, deprotection of the acetonide group was conducted, and we accomplished the asymmetric total synthesis of (*R*)-violaceoid B ((*R*)-**2**). The optical rotation of synthetic (*R*)-**2** was consistent with that reported for naturally occurring violaceoid B.

To evaluate the anti-proliferative effect of violaceoids on human breast cancer cells, MCF-7 cells or Hs 578T cells were incubated with synthetic violaceoid A and (*S*)- and (*R*)-violaceoid B, and cell numbers were estimated using WST-8 reagent. Violaceoid A (**1**) inhibited the growth of MCF-7 cells and Hs 578T cells between the concentrations of 10−100 μM in a dose-dependent manner. The GI_{50} values of **1** in MCF-7 cells and Hs 578T cells were 61.5 ± 18.0 μM, and 59.7 ± 10.0 μM, respectively. On the other hand, (*S*)- violaceoid B ((*S*)-**2**) and (*R*)-violaceoid B ((*R*)-**2**) did not inhibit the growth of these cells within the same range. The GI_{50} values of (*S*)-**2** and (*R*)-**2** in these cells were therefore estimated as >100 μM.

3.4 Conclusion

In conclusion, we have accomplished the first total synthesis of violaceoids A and B and successfully elucidated the absolute configuration of the naturally occurring violaceoid B. The cytotoxicity of the synthetic violaceoid A, (*S*)- or (*R*)-violaceoid B against human cancer cells was assessed using MCF-7 cells or Hs 578T cells, and it was shown that violaceoid A inhibited the growth of both breast cancer cell lines at concentrations of less than 100 μM (with GI_{50} values of 61.5 ± 18.0 μM for MCF-7 and 59.7 ± 10.0 μM for Hs 578T).

3.5 Experimental Section for Chapter 3

General Information.

Optical rotations were determined using a Jasco P-1020 polarimeter. Infrared (IR) spectra were obtained using a Jasco FT/IR-4600 Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded with chloroform (in $CDCl_3$) or methanol (in CD_3OD) on the following instrument: JEOL JNM-AL300 (^{1}H at 300 MHz and ^{13}C at 75 MHz), JEOL JNM-LA500 (^{1}H at 500 MHz and ^{13}C at 125 MHz), Bruker Biospin AVANCE 400M (^{1}H at 400 MHz and ^{13}C at 100 MHz). Mass spectra were determined by a Bruker Daltonics micrOTOF focus (ESI-TOF) mass spectrometer. Thin-layer chromatography was performed on Wakogel B-5F. HPLC was performed with a Hitachi LaChrom Elite system composed of the organizer, L-2400 UV detector, and L-2130 pump.

All reactions were carried out under an argon atmosphere in dried glassware unless otherwise noted. CH_2Cl_2 was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å. All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc., or Aldrich Chemical Co., Inc. and used without further purification unless otherwise noted. Carbon atoms of all compounds are numbered according to IUPAC nomenclature.

3,6-Bis(methoxymethoxy)phthalonitrile (12).

To a solution of 3,6-dihydroxyphthalonitrile (**11**) (400 mg, 2.56 mmol) in CH_2Cl_2 (25.6 mL), diisopropylethylamine (1.76 mL, 10.24 mmol) and methyloxymethyl chloride (0.77 mL, 10.24 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h, and warmed up to rt and stirred for 12 h. The solution was diluted with water, extracted with CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtrated, concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 4:1). Compound **12** (127 mg, 20%) was obtained as a

white solid.

Mp 108 °C; IR (KBr) 1496, 1288, 1165, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 2H, H-4 and H-5), 7.07 (s, 2H, OH), 3.89 (s, 6H, CO_2Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (*C*O_2Me), 152.3 (C-3 and C-6), 124.0 (C-4 and C-5), 112.5 (C-1 and C-2), 52.7 (CO_2*Me*); HR MS m/z 271.0680 $[M + Na]^+$ (calcd for $C_{12}H_{12}N_2O_4Na$, 271.0689).

Dimethyl 3,6-dihydroxyphthalate (17).

To a solution of KOH (32.0 g, 570 mmol) in water (32.0 mL), 3,6-dihydroxyphthalonitrile (**11**) (5.00 g, 31.2 mmol) was added at room temperature (rt). The reaction mixture was refluxed for 1 h. Aqueous 20% H_2SO_4 (100 mL) was slowly poured into the reaction mixture, and extracted with Et_2O, $CHCl_3$ sequentially. The organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacuo, gave 3,6-dihydroxyphtalic acid (6.20 g) as the crude product including starting material **11**. The mixture was used for the next reaction without further purification.

To a solution of the crude 3,6-dihydroxyphtalic acid (6.20 g) in MeOH (240 mL), boron trifluoride diethyl etherate (12.8 mL, 100 mmol) was added at room temperature, and reaction mixture was refluxed for 15 h. The solution was cooled into rt and concentrated in vacuo, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtrated, concentrated in vacuo to yield dimethyl 3,6-dihydroxyphthalate (**17**) (3.69 g, 52% in 2 steps) as a white solid.

Mp 141 °C; IR (KBr) 3425, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 2H, H-4 and H-5), 7.07 (s, 2H, OH), 3.89 (s, 6H, CO_2Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (*C*O_2Me), 152.3 (C-3 and C-6), 124.0 (C-4 and C-5), 112.5 (C-1 and C-2), 52.7 (CO_2*Me*); HR MS m/z 249.0370 $[M + Na]^+$ (calcd for $C_{10}H_{10}O_6Na$, 249.0374).

Dimethyl 3,6-bis((*tert*-butyldiphenylsilyl)oxy)phthalate (18).

3,6-Dihydroxyphthalate (**17**) (500 mg, 2.21 mmol) was dissolved in CH_2Cl_2 (22 mL) and cooled

into 0 °C. Imidazole (1.20 g, 17.68 mmol) and TBDPSCl (2.27 mL, 8.84 mmol) were added to the solution, the reaction mixture had been stirred for 2 h at rt. The mixture was quenched by saturated aqueous $NaHCO_3$ at 0 °C, extracted with EtOAc, washed with brine, and concentrated. The residue was purified by silica gel column chromatography (gradient, *n*-hexane:EtOAc = 20:1 ~ 5:1). Compound **18** (1.61 g, 95%) was obtained as a white solid.

Mp 193 °C; IR (KBr): 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.65-7.63 (m, 8H, TBDPS), 7.40-7.37 (m, 4H, TBDPS), 7.33-7.30 (m, 8H, TBDPS), 6.06 (s, 2H, H-4 and 5-H), 3.93 (s, 6H, CO_2Me), 1.02 (s, 18H, TBDPS); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3 (*C*O_2Me), 147.1 (C-3 and C-6), 135.7 (TBDPS), 132.3 (TBDPS), 130.3 (TBDPS), 128.1 (TBDPS), 124.5 (C-4 and C-5), 122.2 (C-1 and C-2), 52.8 (CO_2*Me*), 26.4 (TBDPS), 19.6 (TBDPS); HR MS m/z 725.2725 [M + Na]$^+$ (calcd for $C_{42}H_{46}O_6Si_2Na$, 725.2706).

(3,6-Bis((*tert*-butyldiphenylsilyl)oxy)-1,2-phenylene)dimethanol (16).

To a solution of **18** in CH_2Cl_2, diisobutylalminium hydride (42.7 mL, 42.7mmol) was added at −78 °C and stirred at 0 °C for 2 h. The reaction mixture was quenched by MeOH and saturated aqueous Rochell's salt, extracted with CH_2Cl_2, wash with brine, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 10:1). Compound **16** (1.60 g, 93%) was obtained as a colorless solid.

Mp: 163 °C (recrystallization, hexane/EtOAc); IR (KBr): 3309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65-7.62 (m, 8H, TBDPS), 7.42-7.37 (m, 4H, TBDPS), 7.34-7.30 (m, 8H, TBDPS), 6.13 (s, 2H, H-4 and H-5), 4.98 (s, 4H, C*H*$_2$OH), 2.56 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7 (C-3 and C-6), 135.4 (TBDPS), 132.5 (TBDPS), 130.9 (TBDPS), 129.9 (C-1 and C-2), 127.7 (TBDPS), 119.1 (C-4 and C-5), 57.3 (CH_2OH), 26.6 (TBDPS), 19.5 (TBDPS); HR MS m/z 669.2827 [M + Na]$^+$ (calcd for $C_{40}H_{46}O_4Si_2Na$, 669.2799).

(3,6-Bis((*tert*-butyldiphenylsilyl)oxy)-2-(((tetrahydro-2*H*-pyran-2'-yl)oxy)methyl)phenyl)meth

anol (19).

To a solution of **16** (1.16 g, 1.79 mmol) in CH_2Cl_2 (44.8 mL, 0.04 M), pyridinium *p*-toluenesulfonate (90.4 mg, 0.36 mmol) and 3,4-dihydro-2*H*-pyran (0.23 mL, 2.69 mmol) were added and stirred for 4 h at rt. The reaction mixture was quenched by saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and concentrated. The residue was purified by the silica gel column chromatography (gradient, *n*-hexane:EtOAc = 20:1 ~ 1:1). Compound **19** (1.22 g, 93%) was obtained as a white solid.

Mp: 48 °C; IR (KBr): 3478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.58 (m, 8H, TBDPS), 7.40-7.32 (m, 4H, TBDPS), 7.32-7.24 (m, 8H, TBDPS), 6.06 (d, *J* = 9.2 Hz, 1H, H-5), 6.02 (d, *J* = 9.2 Hz, 1H, H-5), 5.13 (d, *J* = 10.8 Hz, 1H, C*H*$_2$OTHP), 5.03-4.88 (m, 2H, C*H*$_2$OH), 4.96 (d, *J* = 10.8 Hz, 1H, C*H*$_2$OTHP), 4.83 (t, *J* = 3.2 Hz, 1H, THP), 4.06-3.85 (m, 1H, THP), 3.61-3.46 (m, 1H, THP), 1.90-1.69 (m, 2H, THP), 1.69-1.49 (m, 4H, THP), 1.08 (s, 9H, TBDPS), 1.06 (s, 9H, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0 (C-3), 147.9 (C-6), 135.5 (TBDPS or C-1 or C-2), 135.5 (TBDPS or C-1 or C-2), 135.4 (TBDPS or C-1 or C-2), 135.4 (TBDPS or C-1 or C-2), 132.8 (TBDPS or C-1 or C-2), 132.7 (TBDPS or C-1 or C-2), 132.7 (TBDPS or C-1 or C-2), 132.6 (TBDPS or C-1 or C-2), 132.2 (TBDPS or C-1 or C-2), 129.2 (TBDPS or C-1 or C-2), 127.7 (TBDPS or C-1 or C-2), 127.4 (TBDPS or C-1 or C-2), 119.2 (C-5), 118.5 (C-4), 98.5 (THP), 62.2 (CH_2OH), 61.6 (CH_2OTHP), 57.1 (THP), 30.6 (THP), 26.5 (TBDPS), 25.4 (THP), 19.5 (THP or TBDPS), 19.3 (THP or TBDPS), 19.3 (THP or TBDPS); HR MS m/z 753.3402 $[M + Na]^+$ (calcd for $C_{45}H_{54}O_5Si_2Na$, 753.3400).

3,6-Bis((*tert*-butyldiphenylsilyl)oxy)-2'-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)benzaldehyde (15).

To a solution of **19** (198 mg, 0.271 mmol) in CH_2Cl_2 (5.42 mL, 0.05 M), tetrapropylammonium perruthenate (28.6 mg, 0.0813 mmol) and 4-methylmorpholine *N*-oxide (95.5 mg, 0.813 mmol)

were added and stirred for 2 h at 0 °C. The reaction mixture was filtrated through short pad silica gel with EtOAc and the filtrate was concentrated. Compound **15** (197 mg, quant.) was obtained as a white solid.

Mp: 49 °C; IR (KBr): 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (s, 1H, CHO), 7.67-7.58 (m, 8H, TBDPS), 7.42-7.24 (m, 12H, TBDPS), 6.20 (d, *J* = 9.2 Hz, 1H, H-5), 6.03 (d, *J* = 9.2 Hz, 1H, H-5), 5.34 (d, *J* = 10.0 Hz, 1H, C*H*$_2$OTHP), 4.94 (d, *J* = 10.0 Hz, 1H, C*H*$_2$OTHP), 4.90 (t, *J* = 3.2 Hz, 1H, THP), 4.08-3.96 (m, 1H, THP), 3.62-3.51 (m, 1H, THP), 1.90-1.76 (m, 1H, THP), 1.76-1.44 (m, 5H, THP), 1.05 (s, 9H, TBDPS), 1.04 (s, 9H, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7 (CHO), 152.4 (C-6), 148.4 (C-3), 135.4 (TBDPS or C-1 or C-2), 135.4 (TBDPS or C-1 or C-2), 132.4 (TBDPS or C-1 or C-2), 132.0 (TBDPS or C-1 or C-2), 132.0 (TBDPS or C-1 or C-2), 130.0 (TBDPS or C-1 or C-2), 129.9 (TBDPS or C-1 or C-2), 128.4 (TBDPS or C-1 or C-2), 127.8 (TBDPS or C-1 or C-2), 128.8 (TBDPS or C-1 or C-2), 127.7 (TBDPS or C-1 or C-2), 126.8 (TBDPS or C-1 or C-2), 124.2 (C-4), 120.5 (C-5), 98.9 (THP), 61.7 (CH_2OTHP), 60.0 (THP), 30.5 (THP), 26.4 (TBDPS), 26.4 (TBDPS), 25.6 (THP), 19.5 (THP or TBDPS), 19.5 (THP or TBDPS), 19.2 (THP or TBDPS); HR MS m/z 751.3245 $[M + Na]^+$ (calcd for $C_{45}H_{52}O_5Si_2Na$, 751.3279).

1-(3',6'-Bis((*tert*-butyldiphenylsilyl)oxy)-2'-(((tetrahydro-2*H*-pyran-2''-yl)oxy)methyl)phenyl) heptan-1-ol (14).

To a solution of **15** (457 mg, 0.628 mmol) in THF (12.6 mL, 0.05 M), 1.15 M hexyllithium solution in *n*-hexane was added at −78 °C and stirred 5 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, concentrated. The residue was purified by the silica gel column chromatography (*n*-hexane:EtOAc = 5/1). Compound **15** (382 mg, 75%) was obtained as a white solid.

Mp: 41 °C; IR (KBr): 3556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.54 (m, 16H, TBDPS),

7.41-7.21 (m, 24H, TBDPS), 6.00-5.93 (m, 2H, H-5'), 5.92-5.87 (m, 2H, H-4'), 5.26-5.10 (m, 2H, H-1), 5.22 (d, *J* = 10.4 Hz, 1H, C*H*$_2$OTHP), 5.01 (s, 2H, C*H*$_2$OTHP), 4.85 (t, *J* = 3.2 Hz, 1H, THP), 4.80 (t, *J* = 3.2 Hz, 1H, THP), 4.74 (d, *J* = 10.4 Hz, 1H, THP), 4.12 (d, *J* = 9.6 Hz, 1H, THP), 4.05-3.94 (m, 2H, THP), 3.68-3.52 (m, 2H, THP), 2.25-2.22 (m, 2H, THP), 1.95-1.20 (m, 30H, H-2, H-3, H-4, H-5, H-6, THP), 1.05 (s, 18H, TBDPS), 1.04 (s, 18H, TBDPS), 0.89 (t, *J* = 6.8 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5 (C-6'), 148.2 (C-6'), 147.2 (C-3'), 135.5 (TBDPS or C-1' or C-2' or C-4'), 135.4 (TBDPS or C-1' or C-2' or C-4'), 135.4 (TBDPS or C-1' or C-2' or C-4'), 135.3 (TBDPS or C-1' or C-2' or C-4'), 124.2 (4), 135.0 (TBDPS or C-1' or C-2' or C-4'), 133.0 (TBDPS or C-1' or C-2' or C-4'), 132.9 (TBDPS or C-1' or C-2' or C-4'), 132.6 (TBDPS or C-1' or C-2' or C-4'), 132.1 (TBDPS or C-1' or C-2' or C-4'), 131.8 (TBDPS or C-1' or C-2' or C-4'), 131.8 (TBDPS or C-1' or C-2' or C-4'), 129.9 (TBDPS or C-1' or C-2' or C-4'), 129.7 (TBDPS or C-1' or C-2' or C-4'), 127.8 (TBDPS or C-1' or C-2' or C-4'), 127.6 (TBDPS or C-1' or C-2' or C-4'), 119.6 (C-5'), 117.2 (C-5'), 98.9 (THP), 98.5 (THP), 62.2 (C-1), 62.0 (C-1), 60.8 (THP), 37.2 (C-2), 37.6 (C-2), 32.0 (C-3), 31.9 (C-3), 30.6 (THP), 29.5 (C-4), 29.4 (C-4), 26.7 (TBDPS), 26.6 (TBDPS), 25.5 (THP), 25.5 (THP), 22.7 (C-6), 19.5 (THP or TBDPS), 19.5 (THP or TBDPS), 19.4 (THP or TBDPS), 19.2 (THP or TBDPS), 19.1 (THP or TBDPS), 14.1 (C-7); HR MS m/z 837.4341 $[M + Na]^+$ (calcd for $C_{51}H_{66}O_5Si_2Na$, 837.4358).

(*E*)-((2-(Hept-1'-en-1'-yl)-3-(((tetrahydro-2*H*-pyran-2"-yl)oxy)methyl)-1,4-phenylene)bis(oxy)bis(*tert*-butyldiphenylsilane) (20).

To a solution of **14** (180 mg, 0.220 mmol) in CH_2Cl_2 (4.35 mL, 0.05 M), methanesulfonyl chloride (0.047 mL, 0.660 mmol) and triethylamine (0.186 mL, 1.321 mmol) were added at 0 °C and stirred for 3 h at rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted CH_2Cl_2, concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5/1). Compound **20** (122 mg, 70%) was obtained as a white solid.

Mp: 45 °C; IR (KBr): 1473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.53 (m, 8H, TBDPS), 7.42-7.21 (m, 12H, TBDPS), 6.63 (d, *J* = 16.0 Hz, 1H, H-1'), 6.22 (dt, *J* = 16.0, 6.8 Hz, 1H, H-2'), 5.98 (d, *J* = 8.8 Hz, 1H, H-6), 5.91 (d, *J* = 8.8 Hz, 1H, H-5), 4.96 (d, *J* = 9.6 Hz, 1H, C*H*$_2$OTHP), 4.83 (t, *J* = 3.6 Hz, 1H, THP), 4.74 (d, *J* = 9.6 Hz, 1H, C*H*$_2$OTHP), 3.99 (ddd, *J* = 10.2, 10.2, 2.8 Hz, 1H, THP), 3.56 (ddd, *J* = 10.2, 5.6, 4.4 Hz, 1H, THP), 2.30-2.25 (m, 1H, THP), 1.92-1.84 (m, 1H, H-3'), 1.75-1.47 (m, 6H, H-4' or H-5' or H-6' or THP), 1.42-1.22 (m, 6H, H-4' or H-5' or H-6' or THP), 1.05 (s, 18H, TBDPS), 1.03 (s, 9H, TBDPS), 0.91 (t, *J* = 7.2 Hz, 3H, H-7'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5 (C-6), 146.9 (C-3), 136.8 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.5 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.4 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.3 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.3 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.2 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.1 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.0 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.0 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.0 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 129.7 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 129.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 129.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.7 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 124.2 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 118.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 116.8 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 98.8 (THP), 62.7 (THP), 62.1 (CH_2OTHP), 33.9 (C-3'), 31.7 (C-5'), 30.7 (THP), 29.0 (C-4'), 26.6 (THP), 26.6 (THP), 26.5 (C-6'), 25.7 (THP), 22.6 (TBDPS), 22.6 (TBDPS), 19.5 (TBDPS), 19.5 (TBDPS), 19.4 (TBDPS), 14.1 (C-7'); HR MS m/z 819.4235 $[M + Na]^+$ (calcd for $C_{51}H_{64}O_4Si_2Na$, 819.4218).

(*E*)-(3,6-Bis((*tert*-butyldiphenylsilyl)oxy)-2-(hept-1'-en-1'-yl)phenyl)methanol (21).

To a solution of **20** (84.0 mg, 0.106 mmol) in MeOH (4.24 mL, 0.025 M), *p*-toluenesulfonic acid monohydrate (30.0 mg, 0.158 mmol) was added at 0 °C and stirred for 2 h at rt. The reaction mixture was diluted with water, extracted with chloroform, concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5/1). Compound **21** (53.8 mg, 72%) was obtained as a colorless oil.

IR (neat): 3594, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.53 (m, 8H, TBDPS), 7.43-7.22 (m, 12H, TBDPS), 6.63 (d, *J* = 16.4 Hz, 1H, H-1'), 6.02 (dt, *J* = 16.4, 6.8 Hz, 1H, H-2'), 6.02-5.93 (m, 2H, 4-H, H-5), 4.91 (d, *J* = 6.0 Hz, 2H, CH_2OH), 2.34-2.23 (m, 2H, H-3'), 1.59-1.48 (m, 2H, H-5'), 1.44-1.17 (m, 4H, H-4', H-6'), 1.08 (s, 9H, TBDPS), 1.03 (s, 9H, TBDPS), 0.91 (t, *J* = 6.8 Hz, 3H, H-7'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (C-6), 147.2 (C-3), 137.4 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.4 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 135.4 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 133.0 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 132.5 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 131.0 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 129.9 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 129.1 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.8 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 127.6 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 124.2 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 118.1 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 116.9 (TBDPS or C-1 or C-2 or C-4 or C-5 or C-1' or C-2'), 58.9 (CH_2OH), 33.8 (C-3'), 31.6 (C-5'), 29.0 (C-4'), 26.6 (TBDPS), 26.6 (TBDPS), 26.5 (C-6'), 22.6 (TBDPS), 19.5 (TBDPS), 19.4 (TBDPS), 14.1 (C-7'); HR MS m/z 735.3660 $[M + Na]^+$ (calcd for $C_{46}H_{56}O_3Si_2Na$, 735.3697).

(*E*)-2-(Hept-1'-en-1'-yl)-3-(hydroxymethyl)benzene-1,4-diol (Violaceoid A (1)).

To a solution of **21** (18.5 mg, 0.026 mmol) in THF/pyridine (1.7 mL, v/v = 1/1, 0.015 M), hydrogen

fluoride pyridine complex (0.60 mL) was added at 0 °C and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, washed with saturated aqueous copper sulfate, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 2/1). Violaceoid A (**1**) (4.1 mg, 67%) was obtained as a white solid.

Mp: 63 °C; IR (KBr): 3410, 3194, 2923, 1473, 1381, 1265 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 6.59 (d, *J* = 8.7 Hz, 1H, H-6), 6.54 (d, *J* = 8.7 Hz, 1H, H-5), 6.50-6.42 (m, 1H, H-1'), 6.08 (dt, *J* = 15.6, 6.9 Hz, 1H, H-2'), 4.71 (s, 2H, C*H*$_2$OH), 2.32-2.19 (m, 2H, H-3'), 1.61-1.43 (m, 2H, H-4'), 1.43-1.30 (m, 4H, H-5', H-6'), 0.94 (t, *J* = 7.2 Hz, 3H, H-7'); ^{13}C NMR (125 MHz, CD_3OD): δ 150.6 (C-4), 148.8 (C-1) 137.8 (C-2'), 127.6 (C-2), 125.9 (C-3), 124.6 (C-1'), 116.2 (C-6), 114.9 (C-5), 58.4 (CH_2OH), 34.9 (C-3'), 32.7 (C-5'), 30.4 (C-4'), 23.7 (C-6'), 14.5 (C-7'); HR MS m/z 259.1305 $[M + Na]^+$ (calcd for $C_{14}H_{20}O_3Na$, 259.1340).

1-(3',6'-Bis((*tert*-butyldiphenylsilyl)oxy)-2'-(hydroxymethyl)phenyl)heptan-1-ol (22).

To a solution of **14** (200 mg, 0.246 mmol) in MeOH (5.00 mL, 0.05 M), *p*-toluenesulfonic acid monohydrate (56.0 mg, 0.295 mmol) was added at 0 °C and stirred for 2 h at rt. The reaction mixture was diluted with water, extracted with chloroform, concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5/1). Compound **22** (119 mg, 66%) was obtained as a white solid.

Mp: 114-118 °C; IR (KBr): 3394, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (m, 8H, TBDPS), 7.41-7.18 (m, 12H, TBDPS), 6.01 (d, *J* = 8.8 Hz, 1H, H-5'), 5.98 (d, *J* = 8.8 Hz, 1H, H-4'), 5.40 (dd, *J* = 9.6, 5.2 Hz, 1H, H-1), 5.06 (d, *J* = 11.6 Hz, 1H, C*H*$_2$OTHP), 4.93 (d, *J* = 11.6 Hz, 1H, C*H*$_2$OTHP), 2.18-2.01 (m, 1H, H-2), 1.92-1.78 (m, 1H, H-2), 1.76-1.59 (m, 1H, H-3), 1.42-1.22 (m, 7H, H-3, H-4, H-5, H-6), 1.08 (s, 9H, TBDPS), 1.06 (s, 9H, TBDPS), 0.89 (t, *J* = 6.8 Hz, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (C-6), 146.3 (C-3), 135.4 (TBDPS or C-1 or

C-2 or C-1’ or C-2’ or C-4’ or C-5), 135.4 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 135.4 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 135.3 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 133.7 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 132.6 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 132.4 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 132.2 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 132.0 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 129.9 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 129.8 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 129.8 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 129.5 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 127.8 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 127.7 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 127.7 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 119.0 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 117.7 (TBDPS or C-1 or C-2 or C-1’ or C-2’ or C-4’ or C-5), 70.7 (C-1), 58.9 (CH_2OH), 37.9 (C-3), 31.9 (C-5), 29.3 (C-4), 26.6 (TBDPS), 26.6 (TBDPS), 22.6 (C-6), 19.4 (TBDPS), 19.2 (TBDPS), 14.1 (C-7); HR MS m/z 753.3766 $[M + Na]^+$ (calcd for $C_{46}H_{58}O_4Si_2Na$, 753.3750).

2-(1’-Hydroxyheptyl)-3-(hydroxymethyl)benzene-1,4-diol (*rac*-Violaceoid B (2)).

To a solution of **22** (77 mg, 0.105 mmol) in THF/pyridine (5.25 mL, v/v = 1/1, 0.02 M), hydrogen fluoride pyridine complex (2.00 mL) was added at 0 °C and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, washed with saturated aqueous copper sulfate, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 2/1). *rac*-Violaceoid B (**2**) (19.2 mg, 72%) was obtained as a white solid.

Mp: 101 °C; IR (KBr): 3370, 2931, 2854, 1735, 1473, 1380, 1257 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 6.63 (d, *J* = 8.4 Hz, 1H, 5-H), 6.60 (d, *J* = 8.4 Hz, 1H, 6-H), 5.19 (dd, *J* = 9.2, 4.4 Hz, 1H, H-2’), 4.75 (d, *J* = 11.6 Hz, 1H, C*H*$_2$OH), 4.71 (d, *J* = 11.6 Hz, 1H, C*H*$_2$OH), 2.00-1.83 (m, 1H,

H-2'), 1.80-1.67 (m, 1H, H-2'), 1.67-1.43 (m, 1H, H-3'), 1.43-1.25 (m, 7H, H-3', H-4', H-5', H-6'), 0.94 (t, J = 6.8 Hz, 3H, H-7'); ^{13}C NMR (125 MHz, CD_3OD): δ 150.1 (C-1), 150.0 (C-4) 130.5 (C-2), 125.0 (C-3), 117.5 (C-6), 115.6 (C-5), 71.9 (C-1'), 56.5 (CH_2OH), 38.2 (C-2'), 33.1 (C-5'), 30.4 (C-4'), 27.2 (C-3'), 23.7 (C-6'), 14.5 (C-7'); HR MS m/z 277.1410 $[M + Na]^+$ (calcd for $C_{14}H_{20}O_3Na$, 277.1412).

1-(3',6'-Bis((*tert*-butyldiphenylsilyl)oxy)-2'-(hydroxymethyl)phenyl)heptyl acetate (24).

To a solution of **14** (32.4 mg, 0.040 mmol) in CH_2Cl_2 (2.00 mL, 0.02 M), acetic anhydride (7.5 μL, 0.0796 mmol), triethylamine (22.2 μL, 0.159 mmol), and *N*,*N*-dimethylpyridin-4-amine (1.0 mg, 0.00796 mmol) were added at rt and stirred for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted CH_2Cl_2×2, EtOAc×2, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 5/1). The crude product **23** was used for the following reaction without further purification.

To a solution of the crude product **23** in MeOH/THF (3.35 mL, v/v = 1:1, 0.01 M), *p*-toluenesulfonic acid monohydrate (9.6 mg, 0.0503 mmol) was added at 0 °C and stirred for 2 h at rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted CH_2Cl_2×2, EtOAc×2, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 5/1). Compound **24** (20.4 mg, 66% in 2 steps) was obtained as a white solid.

Mp: 45 °C; IR (KBr): 3548, 2931, 1735, 1473 cm^{-1}; H NMR (500 MHz, $CDCl_3$): δ 7.67-7.54 (m, 8H, TBDPS), 7.43-7.23 (m, 12H, TBDPS), 6.05 (d, J = 9.0 Hz, 1H, H-5'), 5.93 (d, J = 9.0 Hz, 1H, H-4'), 5.49 (d, J = 11.5 Hz, 1H, CH_2OH), 5.41 (d, J = 11.5 Hz, 1H, CH_2OH), 5.10 (brs, 1H, 1-H), 3.67 (brs, 1H, OH), 2.22-2.10 (m, 1H, H-2), 2.06 (s, 3H, CH_3CO), 1.92-1.80 (m, 1H, H-2), 1.77-1.60 (m, 1H, H-3), 1.46-1.20 (m, 7H, H-3, H-4, H-5, H-6), 1.07 (s, 9H, TBDPS), 1.04 (s, 9H,

TBDPS), 0.91 (t, J = 6.0 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0 (CH_3CO), 149.1 (C-6'), 146.9 (C-3'), 135.3 (TBDPS or C-1' or C-2' or C-4' or C-5'), 134.6 (TBDPS or C-1' or C-2' or C-4' or C-5'), 132.6 (TBDPS or C-1' or C-2' or C-4' or C-5'), 132.4 (TBDPS or C-1' or C-2' or C-4' or C-5'), 131.8 (TBDPS or C-1' or C-2' or C-4' or C-5'), 131.5 (TBDPS or C-1' or C-2' or C-4' or C-5'), 130.0 (TBDPS or C-1' or C-2' or C-4' or C-5'), 129.8 (TBDPS or C-1' or C-2' or C-4' or C-5'), 127.8 (TBDPS or C-1' or C-2' or C-4' or C-5'), 127.6 (TBDPS or C-1' or C-2' or C-4' or C-5'), 123.4 (TBDPS or C-1' or C-2' or C-4' or C-5'), 120.3 (TBDPS or C-1' or C-2' or C-4' or C-5'), 117.3 (TBDPS or C-1' or C-2' or C-4' or C-5'), 71.2 (C-1), 58.8 (CH_2OH), 37.9 (C-2), 31.9 (C-3), 31.6 (C-5), 29.4 (C-4), 26.5 (TBDPS), 26.5 (TBDPS), 22.6 (C-6), 21.0 (CH_3CO) 19.4 (TBDPS), 19.1 (TBDPS), 14.1 (C-7'); HR MS m/z 795.3871 $[M + Na]^+$ (calcd for $C_{48}H_{60}O_5Si_2Na$, 795.3883).

1-(6'-((*tert*-Butyldiphenylsilyl)oxy)-3'-hydroxy-2'-(hydroxymethyl)phenyl)heptyl acetate (13). To a solution of **24** (1.45 g, 1.70 mmol) in THF/pyridine (34.0 mL, v/v = 2:1, 0.050 M), hydrogen fluoride pyridine complex (1.0 mL) was added at 0 °C and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc and concentrated. Pyridine was removed by using azetrope with benzene and the residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 3/1). Compound **13** (851 mg, 94%) was obtained as a white solid.

Mp: 45 °C; IR (KBr): 3370, 2931, 1736, 1473 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 3.0 Hz, 1H, 3'-OH), 7.77-7.63 (m, 10H, TBDPS), 6.46 (d, J = 7.5 Hz, 1H, H-4'), 6.32 (d, J = 7.5 Hz, 1H, H-5'), 5.35 (d, J = 10.5 Hz, 1H, CH_2OH), 5.25 (d, J = 10.5 Hz, 1H, CH_2OH), 5.25-5.18 (m, 1H, H-1), 3.03-2.89 (brs, 1H, CH_2OH), 2.09-1.94 (m, 1H, H-2), 2.03 (s, 3H, CH_3CO), 1.79-1.65 (m, 1H, H-2), 1.64-1.49 (m, 1H, H-3), 1.42-1.22 (m, 7H, H-3, H-4, H-5, H-6), 1.09 (s, 9H, TBDPS), 0.90 (t, J = 7.0 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2 (CH_3CO), 149.1 (C-3'), 146.9

(C-6'), 135.4 (TBDPS or C-1' or C-2' or C-4' or C-5'), 132.6 (TBDPS or C-1' or C-2' or C-4' or C-5'), 132.5 (TBDPS or C-1' or C-2' or C-4' or C-5'), 129.9 (TBDPS or C-1' or C-2' or C-4' or C-5'), 128.4 (TBDPS or C-1' or C-2' or C-4' or C-5'), 127.8 (TBDPS or C-1' or C-2' or C-4' or C-5'), 121.6 (TBDPS or C-1' or C-2' or C-4' or C-5'), 118.8 (TBDPS or C-1' or C-2' or C-4' or C-5'), 118.3 (TBDPS or C-1' or C-2' or C-4' or C-5'), 72.7 (C-1), 58.2 (CH_2OH), 36.5 (C-2), 31.8 (C-3), 31.6 (C-5), 29.1 (C-4), 26.4 (TBDPS), 26.1 (C-5'), 22.6 (CH_3CO), 20.9 (C-6'), 19.4 (TBDPS), 14.1 (C-7'); HR MS m/z 557.2694 $[M + Na]^+$ (calcd for $C_{32}H_{42}O_5SiNa$, 557.2688).

1-(6'-((*tert*-Butyldiphenylsilyl)oxy)-2',2'-dimethyl-4*H*-benzo[*d*][1',3']dioxin-5'-yl)heptyl acetate (25).

To a solution of **13** (851 mg, 1.59 mmol) in CH_2Cl_2 (53.1 mL, 0.03 M), 2,2-dimethoxypropane (0.49 mL, 3.98 mmol) and *p*-toluenesulfonic acid monohydrate (1.5 mg, 0.0796 mmol) were added and stirred for 30 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 3/1). Compound **25** (838 mg, 92%) was obtained as a colorless oil.

IR (neat): 3370, 2931, 1736, 1473 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77-7.63 (m, 4H, TBDPS), 7.47-7.27 (m, 6H, TBDPS), 6.41 (d, *J* = 9.0 Hz, 1H, H-7'), 6.33 (d, *J* = 9.0 Hz, 1H, H-8'), 5.31 (d, *J* = 12.5 Hz, 1H, H-4'), 5.15-5.07 (m, 1H, H-1), 5.03 (d, *J* = 12.5 Hz, 1H, H-4'), 2.02 (s, 3H, H-2), 1.90-1.78 (m, 1H, H-2), 1.78-1.65 (m, 1H, H-2), 1.54 (s, 3H, 2'-Me), 1.45-1.17 (m, 8H, H-3, H-4, H-5, H-6), 1.36 (s, 3H, 2'-Me), 1.09 (s, 9H, TBDPS), 0.89 (t, *J* = 7.5 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1 (CH_3CO), 149.4 (C-6'), 145.7 (C-8'a), 135.4 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 135.4 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 132.8 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 132.5 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 129.9 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 129.9 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 127.8 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 127.7 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 125.4 (TBDPS or C-4'a or C-5' or

C-7' or C-8'), 120.6 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 118.3 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 118.3 (TBDPS or C-4'a or C-5' or C-7' or C-8'), 98.5 (C-1), 69.4 (C-4'), 59.0 (C-2'), 36.8 (C-2), 31.8 (C-3), 29.4 (C-5), 28.4 (C-4), 26.4 (TBDPS), 24.3 (C-6), 22.7 (2'-Me), 21.7 (2'-Me), 20.9 (CH$_3$CO), 19.4 (TBDPS), 14.1 (C-7); HR MS m/z 597.3007 $[M + Na]^+$ (calcd for $C_{35}H_{46}O_5SiNa$, 597.3015).

5-(1'-Hydroxyheptyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-ol (*rac*-7).

To a solution of **25** (422 mg, 0.734 mmol) in THF (24.5 mL, 0.03 M), 1.0 M lithium aluminium hydride in THF (1.84 mL) was added at 0 °C and stirred at 5 min. The reaction mixture was quenched with MeOH and saturated aqueous Rochell's salt, extracted with EtOAc, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 3/1). Compound *rac*-**7** (214 mg, 99%) was obtained as a white solid.

HPLC analysis: DAICEL CHIRALPAK, IA-3, UV 254 nm, temperature 25 °C, hexane/*i*PrOH = 95/5, flow rate 0.75 mL/min, $t_R(R)$ = 20.0 min, $t_R(S)$ = 22.8 min; Mp: 77 °C; IR (KBr): 3409, 3286, 2931, 1473 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H, 6-OH), 6.73 (d, J = 8.5 Hz, 1H, H-7), 6.66 (d, J = 8.5 Hz, 1H, H-8), 4.81 (d, J = 15.5 Hz, 1H, H-4), 4.75 (ddd, J = 3.5, 3.0, 2.0 Hz, 1H, H-4), 4.65 (d, J = 15.5 Hz, 1H, H-4), 2.55 (d, J = 3.0 Hz, 1H, 1'-OH), 2.05-1.90 (m, 1H, H-2'), 1.78-1.63 (m, 1H, H-2'), 1.52 (s, 3H, 2-Me), 1.42-1.21 (m, 8H, H-3', H-4', H-5', H-6'), 1.50 (s, 3H, 2-Me), 0.88 (t, J = 7.0 Hz, 3H, H-7'); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4 (C-6), 143.8 (C-8a). 122.9 (C-5), 117.2 (C-4a), 117.2 (C-7), 115.7 (C-8), 98.4 (C-2), 70.8 (C-1'), 59.3 (C-4), 36.0 (C-2'), 31.7 (C-3'), 29.0 (C-5'), 25.8 (C-4'), 25.0 (C-6'), 23.7 (2-Me), 22.6 (2-Me), 14.1 (C-7'); HR MS m/z 317.1723 $[M + Na]^+$ (calcd for $C_{17}H_{26}O_5Na$, 317.1724).

(*R*)-1-(6'-Hydroxy-2',2'-dimethyl-4*H*-benzo[*d*][1',3']dioxin-5'-yl)heptyl 2,2-diphenylacetate ((*R*)-26) and **(*S*)-5-(1'-Hydroxyheptyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-ol ((*S*)-7).**

To a solution of *rac*-**7** (69.3 mg, 0.235 mmol) in Et_2O (2.3 mL, 0.1 M), *N*,*N*-diisopropylethylamine (0.030 mL, 0.169 mmol), (*R*)-benzotetramisole (3.0 mg, 0.0118 mmol) and diphenylacetic anhydride (57.0 mg, 0.141 mmol) were added and stirred for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted EtOAc, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 4/1, then CH_2Cl_2). Compound (*R*)-**26** (33.1 mg, 29%, 12% ee) was obtained as a colorless oil and compound (*S*)-**7** (37.1 mg, 54%, 50% ee) was obtained as a white solid.

(*R*)-**26** (12% ee)**;** $[\alpha]_D^{26}$ + 0.02° (*c* 1.01, $CHCl_3$); IR (neat): 3432, 2931, 1727, 1457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39- 7.16 (m, 10H, Ph), 6.66 (d, *J* = 1.5 Hz, 1H, H-7'), 6.66 (d, *J* = 1.5 Hz, 1H, H-8'), 5.87 (t, *J* = 6.5 Hz, 1H, H-4), 5.35 (brs, 1H, 6'-OH), 5.09 (d, *J* = 16.0 Hz, 1H, H-7'), 5.07 (s, 2H, H-4'), 4.70 (d, *J* = 16.0 Hz, 1H, H-8'), 2.07-1.88 (m, 1H, H-2'), 1.83-1.73 (m, 1H, H-2), 1.52 (s, 3H, 2'-Me), 1.48 (s, 3H, 2'-Me), 1.40-1.10 (m, 8H, H-3, H-4, H-5, H-6), 0.86 (t, *J* = 7.5 Hz, 3H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4 (CH_3CO), 147.9 (C-6'), 144.9 (C-8'a). 138.0 (C-5'), 137.7 (C-4'a), 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 127.5 (Ph), 127.4 (Ph), 118.0 (C-7'), 117.7 (C-8'), 98.4 (C-2'), 72.5 (C-1), 59.5 (C-2), 57.2 (C-4'), 33.0 (C-2), 31.6 (C-3), 28.7 (C-5), 25.6 (C-4), 24.7 (2-Me), 24.2 (2-Me), 22.5 (C-6), 14.0 (C-7); HR MS m/z 511.2455 $[M + Na]^+$ (calcd for $C_{31}H_{36}O_5Na$, 511.2456).

(*S*)-5-(1'-Hydroxyheptyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-ol ((*S*)-7) (95% ee).

To a solution of **(*S*)-7** (37.1 mg, 0.126 mmol, 50% ee) in Et_2O (1.3 mL, 0.1 M), *N*,*N*-diisopropylethylamine (0.014 mL, 0.0339 mmol), (*R*)-benzotetramisole (1.6 mg, 0.00628 mmol) and diphenylacetic anhydride (13.8 mg, 0.0339 mmol) were added and stirred for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted EtOAc, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 4/1, then CH_2Cl_2). Compound (*S*)-**7** (35.9 mg, 97%, 54% ee)

was obtained as a white solid.

The chiral enriched (*S*)-**7** (18.8 mg, 95% ee) was obtained by the same kinetic resolution after 4 repetitions from the above (*S*)-**7** (35.9 mg, 0.126 mmol, 54% ee).

(*S*)-**7** (95% ee); $[\alpha]_D^{25}$ $-46.3°$ (*c* 1.12, $CHCl_3$). Other spectrum are the same with *rac*-**7**.

(*S*)-2-(1'-Hydroxyheptyl)-3-(hydroxymethyl)benzene-1,4-diol ((*S*)-Violaceoid B, (*S*)-2)).

To a solution of (*S*)-**7** (69.5 mg, 0.236 mmol, 95% ee) in THF/H_2O (2.36 mL, v/v = 1/1, 0.1 M), *p*-toluenesulfonic acid monohydrate (22.4 mg, 0.118 mmol) was added and stirred for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 3/1) to afford (*S*)-violaceoid B (9.2 mg, 15%) as a white solid, and (*S*)-**7** (59.6 mg, 86%) was recovered.

Additionally, (*S*)-violaceioid B (25.7 mg) and (*S*)-**7** (27.1 mg) were obtained by the same reaction after 2 repetitions from the recovered (*S*)-**7** (59.6 mg, 0.202 mmol). Therefore, 34.9 mg (total amount) of (*S*)-violaceoid (58%) was prepared from the starting 69.5 mg of (*S*)-**7**.

(*S*)-Violaceoid B ((*S*)-**2**) (95% ee); $[\alpha]_D^{23}$ $-17.0°$ (*c* 0.093, $CHCl_3$), $[\alpha]_D^{23}$ $-22.5°$ (*c* 0.667, MeOH). Other spectrum are the same with *rac*-**2**.

(*S*)-1-(6'-Hydroxy-2',2'-dimethyl-4*H*-benzo[*d*][1',3']dioxin-5'-yl)heptyl 2,2-diphenylacetate ((*S*)-26) and **(*R*)-5-(1'-Hydroxyheptyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-ol ((*R*)-7).**

To a solution of *rac*-**7** (123.7 mg, 0.420 mmol) in Et_2O (4.2 mL, 0.1 M), *N*,*N*-diisopropylethylamine (0.050 mL, 0.303 mmol), (*S*)-benzotetramisole (5.0 mg, 0.0210 mmol) and diphenylacetic anhydride (102 mg, 0.252 mmol) were added and stirred for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted EtOAc, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 4/1, then CH_2Cl_2). Compound (*S*)-**26** (65.9 mg, 32%, 19% ee) was obtained as a colorless oil and compound (*R*)-**7** (60.1 mg, 49%, 58% ee) was obtained as a white solid.

(*S*)-**26** (19% ee); $[\alpha]_D^{26}$ $-0.20°$ (*c* 2.39, $CHCl_3$). Other spectrum are the same with (*R*)-**26**.

(*R*)-5-(1'-hydroxyheptyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-ol ((*R*)-7) (93% ee).

To a solution of (*R*)-**7** (60.1 mg, 0.204 mmol, 58% ee) in Et_2O (2.0 mL, 0.10 M), *N*,*N*-diisopropylethylamine (9.6 μL, 0.0550 mmol), (*S*)-benzotetramisole (2.6 mg, 0.0118 mmol) and diphenylacetic anhydride (22.3 mg, 0.0550 mmol) were added and stirred for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted EtOAc, dried over with Na_2SO_4. The organic layer was filtrated and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 4/1, then CH_2Cl_2). Compound (*R*)-**7** (56.8 mg, 95%, 66% ee) was obtained as a white solid.

The chiral enriched (*R*)-**7** (31.0 mg, 93% ee) was obtained by the same kinetic resolution after 4 repetitions from the above (*R*)-**7** (56.8 mg, 0.193 mmol, 66% ee).

(*R*)-**7** (93% ee); $[\alpha]_D^{25}$ $+44.6°$ (*c* 1.87, $CHCl_3$). Other spectrum are the same with *rac*-**7**.

(*R*)-2-(1'-Hydroxyheptyl)-3-(hydroxymethyl)benzene-1,4-diol ((*R*)-Violaceoid B, (*R*)-2)).

To a solution of (*R*)-**7** (25.1 mg, 0.0853 mmol, 93% ee) in THF/H_2O (1.71 mL, v/v = 1/1, 0.05 M), *p*-toluenesulfonic acid monohydrate (8.1 mg, 0.0426 mmol) was added and stirred for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, and concentrated. The residue was purified by silica gel chromatography (*n*-hexane:EtOAc = 3/1) to afford (*R*)-violaceoid B (4.6 mg, 21%) as a white solid, and (*R*)-**7** (19.6 mg, 78%) was recovered.

Additionally, (*R*)-violaceoid B (4.6 mg) and (*R*)-**7** (12.2 mg) were obtained by the same reaction after 2 repetitions from the recovered (*R*)-**7** (19.6 mg, 0.0618 mmol). Therefore, 9.2 mg (total amount) of (*R*)-violaceoid (54%) was prepared from the starting 25.1 mg of (*R*)-**7**.

(*R*)-Violaceoid B ((*R*)-**2**) (93% ee); $[\alpha]_D^{23}$ $+15.9°$ (*c* 0.087, $CHCl_3$), $[\alpha]_D^{23}$ $+22.9°$ (*c* 0.667, MeOH). Other spectrum are the same with *rac*-**2**.

Biological Assay. Human breast cancer cell lines MCF-7 and Hs 578T were obtained from Japanese Collection of Research Bioresources (JCRB) Cell Bank (Osaka, Japan) and American Type Culture Collection (Manassas, VA), respectively. Cells were cultured with Dulbecco's modified Eagle's medium supplemented with Antibiotic-Antimycotic (100 U/ml penicillin, 100 μg/ml streptomycin, 0.25 μg/ml amphotericin B; Thermo Fisher Scientific, Inc., Waltham, MA, USA), gentamicin (10 μg/ml, Thermo Fisher Scientific, Inc.) and 10% heat-inactivated fetal bovine serum. MCF-7 cells or Hs 578T cells were seeded in 96-well plates (1000 cells/well) and incubated for 48 h at 37 ˚C. Cells were then incubated with violaceoid A or (*S*)- and (*R*)-violaceoid B (10–100 μM) for 48 h, and cell number was estimated by WST-8 reagent (Cell Counting Kit-8, Dojindo Laboratories, Japan).

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Publication List

1. Kinetic Resolution of Racemic 2-Hydroxyamides Using a Diphenylacetyl Component as an Acyl Source and a Chiral Acyl-Transfer Catalyst

   （速度論的光学分割法を用いる光学活性第二級アルコールの製造法の開発）

   Takatsugu Murata, Tatsuya Kawanishi, Akihiro Sekiguchi, Ryo Ishikawa, Keisuke Ono, Kenya Nakata and Isamu Shiina

   Molecules, 23(8), 2003, August 2018

   DOI: 10.3390/molecules23082003

2. Total Synthesis of Violaceoid A and (−)- and (+)-Violaceoid B

   （天然ポリオキシ化合物ビオールアセオイド A および B の全合成）

   Takatsugu Murata, Teppei Kuboki, Ryo Ishikawa, Takahiro Saito, Shotaro Taguchi, Kazuma Takeuchi, Emiko Hatano, Motoyuki Shimonaka and Isamu Shiina

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