Preparation of Optically Active Tertiary Alcohols by Enzymatic Methods. Application to the Synthesis of Drugs and Natural Products

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By the catalysis of AK or porcine pancreas lipases, 3-iodo-2-phenyl-1,2-propanediol, 1-(hydroxymethyl)-1-phenyloxirane, 2-(iodomethyl)-4-phenyl-3-butyne-1,2-diol, 2-(iodomethyl)-4-(trimethylsilyl)-3-butyne-1,2-diol, and 5,5-dimethyl-2-(iodomethyl)-3-hexyne-1,2-diol were resolved in very high enantioselectivities ($E \geq 153$). The obtained enantiomerically pure or optically enriched compounds, containing an iodo atom, an oxirane moiety, or an alkynyl group, are versatile building blocks for the synthesis of chiral azido diols, sulfanyl diols, cyano diols, the side chain of a vitamin D_3 metabolite, the ω-chain of a prostaglandin analog, and an aggregation pheromone (1*S*,5*R*)-(−)-frontalin. Models based on the consideration of the importance of size, distance, and electron effect are proposed to interpret the observed stereospecificity in the enzymatic reactions. Thus, the lipase-catalyzed reactions of 1,1-disubstituted 1,2-diols occurred efficiently at the primary hydroxyl groups while the enantioselectivity was controlled by the tertiary carbinyl centers.

Introduction

Tertiary alcohols and their derivatives containing tertiary C−O bonds are useful building blocks for many drugs and natural products (Figure 1), such as prostaglandin analog (**1**),[1] frontalin (**2**),[2] and vitamin D_3 metabolite (**3**).[3] In comparison with the great progress in preparing optically active secondary alcohols, synthesis of enantiomerically pure tertiary alcohols is still a challenging problem. The classical method for preparation of optically active tertiary alcohols is via separation of their properly derivatized diastereomers.[4] For example,[4a] (±)-3-methyl-1-pentyn-3-ol is derivatized with phthalic anhydride, and the resulting acid reacts with a natural alkaloid (−)-brucine to form salts for separation. After several recrystallizations, the separated diastereomers are saponified to give the optically active alcohols in low yields. Another common method to prepare optically active tertiary alcohols involves multistep transformations from chiral pools[5] of natural products such as terpenes, amino acids, hydroxy acids, and carbohydrates. The asymmetric synthesis by addition of chiral organometallic reagents to unsymmetric ketones[6] is a promising approach to obtain optically active tertiary alcohols. The catalytic asymmetric synthesis by dihydroxylation of 1,1-disubstituted olefins[7] is so far the most effective method to prepare optically active tertiary alcohols. The catalytic asymmetric epoxidation of 1,1-disubstituted olefins,[8] followed by treatment with a base or nucleophile, leads to various tertiary alcohols.

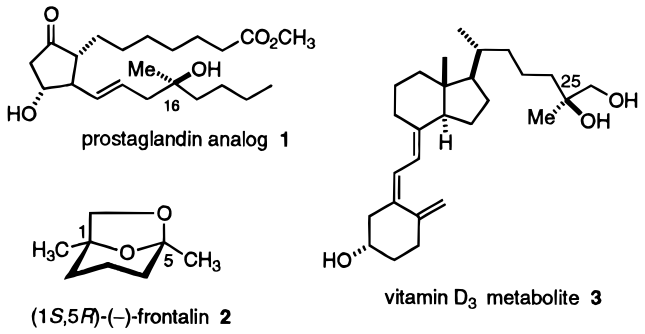

Figure 1. Exemplified natural products and drugs containing tertiary C−O bonds.

Microbial or enzymatic methods have been successfully utilized to prepare some optically active tertiary alcohols, if the substrates are not steric demanding. For example, monooxygenases[9] and chloroperoxidases[9,10] are used to prepare the epoxides of some 2-methylalkenes, but these enzymes fail to catalyze the oxidation of homologous or analogous compounds having the methyl group replaced with other alkyl or phenyl groups. Epoxide hydrolases[11]

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have been used in selective hydrolysis of epoxides, such as the epoxides of fumaric acid and 1-methyl-1-alkyloxiranes. Lipases[12] are generally used to resolve secondary alcohols. Appropriate derivatives of some less hindered tertiary alcohols, such as the cyanohydrin acetates of *n*-alkyl methyl ketones,[13] the acetates of 1-alkyl-1-phenylpropargyl alcohols,[14] the chloroacetates of bicyclo[4.1.0]heptanols,[15] and an isopropyl oxalate of 2-methylbicyclo[2.2.1]heptan-2-ol,[16] have been hydrolyzed by the catalysis of lipases. However, tertiary alcohols of other types are usually too bulky to have access to the active sites of lipases.

As shown in the lipase-catalyzed hydrolysis of the oxalate,[16] the enzymatic reaction obviously occurs at the moiety of the isopropyl ester, while a modest enantioselectivity ($E \leq 7$) is obtained via the stereochemical bias of the tertiary carbinyl center. This is so far the single example that clearly demonstrates a possible way, by extension of the reactive site distal from the tertiary carbinyl center, to circumvent the steric problem in the lipase-catalyzed reactions. We attempted to establish a general enzymatic method for resolution of tertiary alcohols by the similar approach, *i.e.*, to find the derivatives suitable for enantioselective hydrolyses even though the reactive sites are distal from the chiral carbinyl centers.

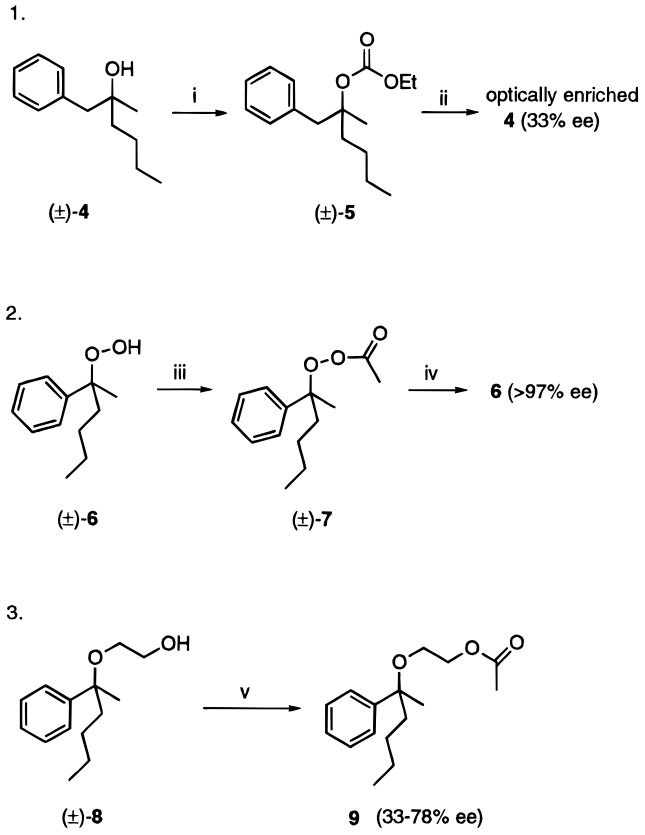
Results and Discussion

Since a carbonate is more apt to hydrolysis than the corresponding ester,[17] we examined whether the carbonate of a tertiary alcohol, (±)-2-benzyl-2-hexanol (**4**), could be hydrolyzed by the catalysis of lipases. Hydrolysis of the ethyl carbonate **5** (Scheme 1) by the catalysis of lipase OF in aqueous DMF solution (5%, pH 7.8) proceeded sluggishly. After the mixture was stirred at room temperature for 12 days, only 1.5% of the carbonate was hydrolyzed to give the optically enriched alcohol (33% ee favoring the more retained enantiomer on a Chiralcel OD column). The enzymatic hydrolysis of the corresponding butyl carbonate or benzyl carbonate under similar conditions was also not efficient.

We prepared a hydroperoxide (±)-**6** from the parent tertiary alcohol, (±)-2-phenyl-2-hexanol (30% H_2O_2, catalytic H_2SO_4; 89% yield). This hydroperoxide exhibited a reactive site (toward lipases) more remote from the carbinyl center. If the hydroperoxide **6** were resolved via the lipase-catalyzed reaction, the obtained optically active products could be reduced to give the parent tertiary alcohols. However, attempts of acetylation of (±)-**6** with vinyl acetate (or isopropenyl acetate) in an organic solvent (*i*-Pr_2O or EtOAc) by the catalysis of lipases (AY, MY, OF, AP-6, MAP, or PPL) failed. The hydroperoxide was then acetylated by a chemical method (Ac_2O, DMAP, THF, 0−30 °C, 30 min) to give the hydroperoxy acetate (±)-**7** in 98% yield. The acetate **7** decomposed in water; however, the enzymatic conversion of **7** to the hydroperoxide **6** was carried out by a PPL-catalyzed transesterification with *n*-BuOH. Due to the instability of **7** in protic solvents, the lipase-catalyzed reaction afforded, after 5 days, only 6% of the enantiomerically pure hydroperoxide **6** according to the HPLC analysis on a Chiralcel OD column. The β-alkoxy alcohol (±)-**8**, a model compound of derivatized tertiary alcohol with a further extended reactive site, was prepared by treatment of the ethyl-enediol acetal of acetophenone with BuLi in the presence of $BF_3{\cdot}OEt_2$. Acetylations of (±)-**8** by the catalysis of MY, AK, PPL, or MAP lipases occurred with reasonable rates to give the acetate **9** in 33−78% ee. The enantioselectivity ($E = 2.4-9.4$) was comparable to that found in the lipase-catalyzed hydrolysis of oxalate;[16] even the reactive site of **8** was more distal from the carbinyl center.

We inferred from the above studies that tertiary alcohols containing an adjacent hydroxyl group, such as 1,1-disubstituted 1,2-diols, would be the substrates of choice for the lipase-catalyzed reactions in the sense of both efficacy and enantioselectivity. By analogy to the conventional models[18] for the lipase-catalyzed reactions

Scheme 1. Lipase-Catalyzed Reactions of the Carbonate 5, Hydroperoxy Acetate 7, and β-Alkoxy Alcohol 8[a]



[a] Reagents and conditions: (i) BuLi, 0 °C; $ClCO_2Et$, 0−25 °C, 1 h; 83%; (ii) lipase OF, 5% DMF/H_2O, pH = 7.8, 30 °C, 12 days; 1.5% conversion; (iii) Ac_2O, DMAP, THf, 0−30 °C, 30 min; 98%; (iv) PPL, BuOH, 30 °C, 5 days; 6% yeild; (v) lipase, isopropenyl acetate, *t*-BuOMe, 30 °C, 4−48 h; 9.5−37% conversion.

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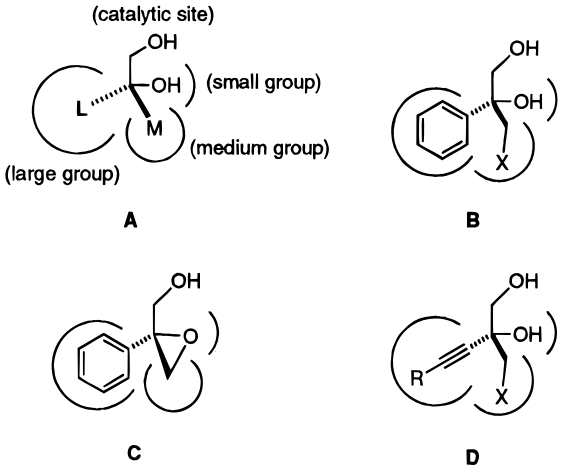

Figure 2. Models for the lipase-catalyzed reactions of 1,1-disubstituted 1,2-diols. (**A**) A putative model: L represents the large substituent, M represents the medium substituent, and the tertiary hydroxyl group is considered as the small substituent. The primary alcohol is the reactive site, while the enantioselectivity is procured by the bias of the tertiary carbinyl center. (**B**) The favorable enantiomers of 2-phenyl-1,2-propanediols (X = H, Cl, Br, or I) for the AK lipase-catalyzed reactions. (**C**) The favorable enantiomer of 2-phenylglycidol for the AK lipase-catalyzed reactions. (**D**) The favorable enantiomers of 2-alkynyl-3-halo-1,2-propanediols (X = H, Cl, Br, or I) for the porcine pancreas lipase-catalyzed reactions.

of secondary and primary alcohols, we conceived that a reaction model **A** (Figure 2) would be appropriate for the reactions of 1,1-disubstituted 1,2-diols, in which the tertiary hydroxyl group was assumed as the small group. High enantioselectivity could be predicted if there is sufficient discrimination of sizes between the L, M, and OH substituents. Since the enzymatic reaction would occur at the primary hydroxyl group, high efficiency is assured.

In order to test this hypothesis, we prepared (±)-2-phenyl-1,2-propanediols **10**−**13** and (±)-2-phenylglycidol **14** (Figure 3) and investigated their lipase-catalyzed acetylations (Table 1). The preliminary survey indicated that most lipases could be used as the catalysts for acetylations of **10**−**14**, and the lipase AK appeared to operate with high enantioselectivity. Most of the enzymatic reactions were monitored by GC or HPLC analyses and quenched at nearly 50% conversions. The lipase-catalyzed acetylation of **10**, (±)-2-phenyl-1,2-propanediol (Table 1, entries 1−3), using isopropenyl acetate as the solvent and acylating agent showed modest enantioselectivities ($E \leq 4.7$). A previous study[19] indicated that no enantioselectivity is found in the lipase-catalyzed acetylations of (±)-2-phenyl-1,2-butanediol or (±)-2-phenyl-1,2-pentanediol by using diisopropyl ether as the solvent. For 1-substituted 1,2-diols,[20] the lipase-catalyzed acetylations occur first at the primary hydroxyl groups with little enantioselectivity, but the subsequent acetylations at the secondary hydroxyl groups exert high enantioselectivity. In the present study of the 1,1-disubstituted 1,2-diols, the lipase-catalyzed acetylations occurred at the primary hydroxyl groups and enantioselectivity was procured simultaneously by the stereochemical bias of the tertiary carbinyl centers. We also found

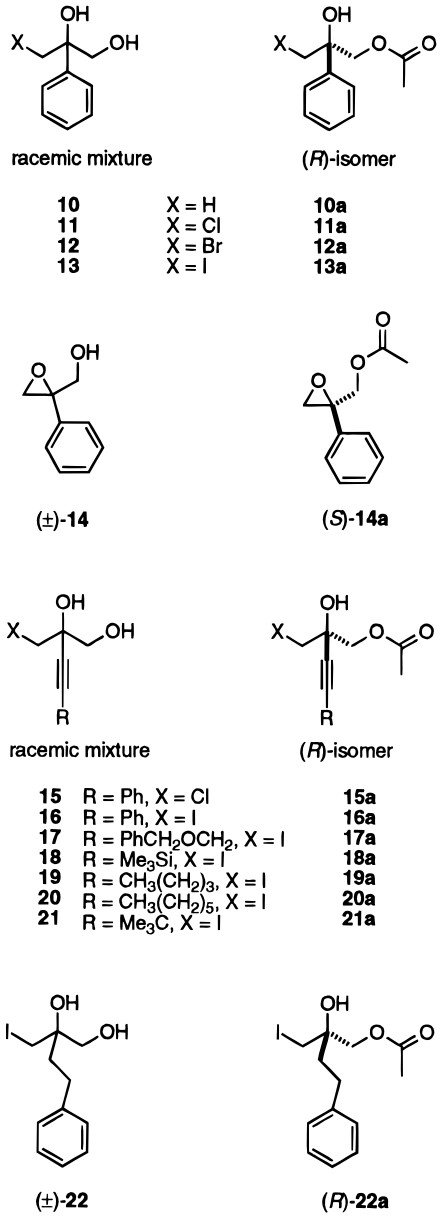

Figure 3. Alcohol substrates and the major products in the lipase-catalyzed acetylations (Tables 1 and 2).

that high enantioselectivity in lipase-catalyzed acetylations could be achieved by introduction of halo substituents, compared the substrates **11**−**13** (X = Cl, Br, and I) with **10** (X = H). As shown in Table 1, these reactions were best conducted with lipase AK using isopropenyl acetate or vinyl acetate as the solvent and acylating agent. Enantioselectivity increased as the size of the halo substituent increased, $E = 11.5$ for the chloro compound **11** (Table 1, entry 4), $E = 13$ for the bromo compound **12** (Table 1, entry 9), and $E = 69$ for the iodo compound **13** (Table 1, entry 10). In this series of lipase AK-catalyzed acetylations, the best result ($E = 153$ at 51% conversion) was obtained with the substrate (±)-2-phenylglycidol (**14**). The reaction using isopropenyl acetate as the solvent and acylating agent proceeded smoothly at room temperature to give the acetate **14a** in 94% ee, accompanied by a recovery of the alcohol **14** in >97% ee (Table 1, entry 12). The immobilized lipase AK was also utilized to catalyze acetylations in good enantioselectivities ($E = 23-101$, Table 1, entries 13−17).

The ee values and absolute configurations of the acetate products and the remaining alcohols were deter-

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Table 1. Lipase-Catalyzed Acetylations of Alcohols 10−14, Giving Acetates 10a−14a

entry	substrate	lipase	solvent	reaction temp/°C	reaction time/h	convn/%	ee_s, %/ config[a]	ee_p, %/ config[a]	E[a]
1	**10**	MAP	IPA[b]	40	>48	25	5/*S*	15/*R*	1.4
2	**10**	AK	IPA[b]	21	29	35	15/*S*	27/*R*	2.0
3	**10**	AP-6	IPA[b]	40	>48	25	20/*S*	60/*R*	4.7
4	**11**	AK	IPA[b]	25	156	66	97/*S*	50/*R*	11.5
5	**11**	MY[b]	*t*-BuOMe	25	156	32	30/*R*	64/*S*	6.0
6	**11**	AY[b]	*t*-BuOMe	25	156	45	23/*R*	28/*S*	2.0
7	**11**	OF[b]	*t*-BuOMe	25	156	48	60/*R*	66/*S*	8.5
8	**11**	AP-6[b]	*t*-BuOMe	25	156	45	56/*S*	69/*R*	9.3
9	**12**	AK	VA[c]	25	10	55	82/*S*	66/*R*	13
10	**13**	AK	IPA[b]	25	30	43	70/*S*	94/*R*	69
11	**13**	PPL[b,c]	*t*-BuOMe	20	7.5	41	50/*S*	70/*R*	10
12	**14**	AK	IPA[b]	21	4.6	**51**	>**97**[d]**/*S***	**94/*S***	**153**
13	**14**	AK[e]	IPA[b]	25	2	31	43/*S*	97/*S*	101
14	**14**	AK[b,e]	*t*-BuOMe	25	2	56	96/*S*	74/*S*	23
15	**14**	AK[b,e]	THF	25	15	48	87/*S*	93/*S*	76
16	**14**	AK[b,e]	$PhCH_3$	25	3	35	52/*S*	96/*S*	82
17	**14**	AK[e]	VA[c]	25	2	59	>97[d]/*S*	68/*S*	39

[a] The configuration of the major enantiomer. Enantiomeric excess of the remaining substrate, ee_s, and the product, ee_p, were determined by HPLC analysis. See ref 12f and the general part of the Experimental Section for the definition of enantiomeric ratio (*E* value). [b] Isopropenyl acetate (IPA) was used as the acylating agent. [c] Vinyl acetate (VA) was used as the acylating agent. [d] NO enantiomer was found according to the HPLC and NMR analyses. [e] Lipase AK immobilized on Hyflo Supercel was used.

mined by HPLC analyses, optical rotation measurements, and chemical correlations (Scheme 2). The (*S*)-enantiomer of 2-phenyl-1,2-propanediol (**10**) is known to be dextrorotatory;[21] thus, the remaining alcohol **10** in entries 1−3 (Table 1) with dextrorotation should predominate in the (*S*)-enantiomer. The remaining chlorohydrin **11** (97% ee, levorotatory), recovered from the lipase AK-catalyzed acetylation (Table 1, entry 4), was reduced by Bu_3SnH to give (*S*)-(+)-**10** (route 1).[22] Thus, (−)-3-chloro-2-phenyl-1,2-propanediol (**11**) should have the (*S*)-configuration. Treatment of the chlorohydrin (*S*)-**11** with K_2CO_3 in MeOH yielded (*S*)-2-phenylglycidol (**14**), exhibiting levorotation. It should not be overlooked that formation of the oxirane **14** might also involve a Payne rearrangement (route 2).[23] Fortunately, this process was stereogenically degenerative to give the identical glycidol (*S*)-(−)-**14**. Since two enantiomers of **14** (recovered from Table 1, entry 13) were separable on a Chiralcel OD column by elution with 2-propanol/hexane (1:9), the ee value of chlorohydrin **11** was double checked, by correlation with the diol **10** via comparison of the optical rotations or by correlation with the glycidol **14** via the HPLC analysis. The acetates (*R*)-(+)-**11a**, **-12a**, and **-13a** were saponified and converted *in situ* to the oxirane (*R*)-(+)-**14** in alkaline conditions. By this means, the ee values and absolute configurations of the halohydrins **11**−**13** and their corresponding acetates **11a**−**13a** were unambiguously determined.

In order to broaden the scope of this study, we also prepared racemic 2-alkynyl-3-halo-1,2-propanediols **15**−**21** (Figure 3) and investigated their enzymatic reactions (Table 2). The alkynyl substituents were considered to have viable synthetic application. The preliminary study of the lipase AK-catalyzed acetylations of 2-(halomethyl)-4-phenyl-3-butyne-1,2-diols **15** and **16** showed low enantioselectivity, $E = 1.4$ and 3.0, respectively. After several tests, we found that PPL was the proper enzyme for these substrates to be acetylated in a high enantioselective manner. The PPL-catalyzed acetylations of **15** and **16** using vinyl acetate as the solvent and acylating agent (Table 2, entries 4 and 6) resulted in high enantioselectivity with the *E* values 72 and 18. The enantioselectivity was improved dramatically by conducting the acetylation in an aprotic solvent; for instance, acetylation of **16** (R = Ph) was achieved with $E = 211$ in toluene and $E > 1000$ in *tert*-butyl methyl ether (Table 2, entries 7 and 8). The PPL-catalyzed acetylations of the alkynyl compounds **18** (R = Me_3Si) and **21** (R = Me_3C) containing bulky R groups also demonstrated excellent enantioselectivities ($E = 368$ and 751) under similar conditions (Table 2, entries 10 and 13). Therefore, nearly enantiomerically pure alcohol (**16**, **18**, or **21**) and acetate (**16a**, **18a**, or **21a**) were obtained simultaneously by this enzymatic method. The alkynyl compounds **17** (R = (benzyloxy)methyl), **19** (R = *n*-butyl), and **20** (R = *n*-hexyl) containing R groups of medium sizes underwent PPL-catalyzed acetylations in modest to high enantioselectivities, $E = 24$, 47, and 10, respectively. The *E* values of the PPL-catalyzed acetylations decreased when the alkynyl group was replaced with other substituents, such as in the reactions of **13** (having a phenyl substituent, entry 11 of Table 1, $E = 10$) and **22** (having a β-phenylethyl substituent, entry 14 of Table 2, $E = 6.5$).

Enantiomers of the alcohols **15**−**17** and the acetates **15a**−**17a** were resolvable on a Chiralcel OD column, so that the ee values of these compounds in the related enzymatic reactions were readily determined by the HPLC analyses. Otherwise, the diols **18**−**21** and the acetates **18a**−**21a** were treated with K_2CO_3 to give 2-alkynylglycidols **24**−**27** (route 2, Scheme 2), of which ee values were determined by HPLC analyses. In the case of **21**, its enantiomers were also resolvable on a Chiralcel OD column. The measured ee value by this means was in agreement with that deduced from the chemical correlation with glycidol **27**. The experiments also confirmed that no racemization occurred on treating **21** in alkaline conditions to give **27**. The remaining alcohol (−)-**16** recovered from the PPL-catalyzed acetylation (Table 2, entry 8) was determined to have the (*S*)-configuration by correlation with a known compound, 2-methylglycerol acetonide[24] **30** (route 3). Thus, the iodo compound (*S*)-(−)-**16** was reduced with Bu_3SnH or $LiAlH_4$

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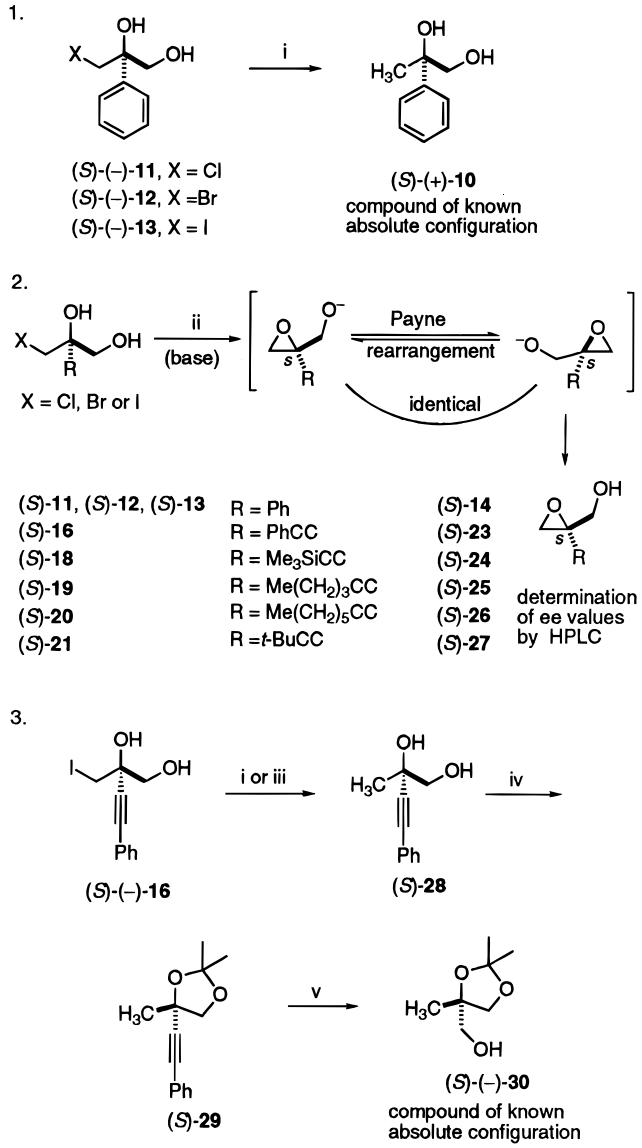
Scheme 2. Determination of Enantiomeric Excesses and Absolute Configurations of 1,1-Disubstituted 1,2-Diols[a]



[a] Reagents and conditions: (i) Bu_3SnH, AIBN, PhH, reflux 4 h; 70%; (ii) K_2CO_3, MeOH, 30 °C, 8 h; 90%; (iii) $LiAlH_4$, Et_2O, 30 °C, 2 h; 74%; (iv) *p*-TsOH, $CuSO_4$, Me_2CO, 25 °C, 4 h; (v) O_3, MeOH, 0 °C (1.5 h), reflux (15 min); then $LiAlH_4$, THF, 25 °C, 12 h; 17% from **28** to **30**.

to give a diol (*S*)-**28**. After protection of the diol as the acetonide, the triple bond was cleaved with ozone, followed by reduction with $LiAlH_4$, to give (*S*)-(−)-**30**, $[\alpha]^{25}_D$ −7.61 (lit.[24] $[\alpha]^{25}_D$ −5.33).

On the basis the assumption that the PPL-catalyzed acetylations proceeded in a consistent mechanism, all the remaining alcohols **16**−**22** were considered to predominate in the (*S*)-enantiomers and the major products **16a**−**22a** should predominate in the (*R*)-enantiomers. These assignments were supported by the eluting orders on a Chiralcel OD column. For example, the (*S*)-alcohol **16** (major enantiomer) and (*S*)-acetate **16a** (minor enantiomer) were more retained than their corresponding (*R*)-enantiomers. The similar eluting order for the enantiomeric pairs of **15**, **15a**, **17**, **17a**, and **21** was observed.

The acetylations of (±)-2-phenyl-1,2-propanediols **10**−**13**, (±)-2-phenylglycidol (**14**), and (±)-2-alkynyl-1,2-propanediols **15**−**21** using lipases AK, PPL, MAP, and AP-6 as the catalysts exhibited a consistent enantiotopic preference for the formation of (*R*)-acetates **10a**−**13a**, (*S*)-**14a** (noting the different *S*-notation for **14a** according to the convention of Cahn−Ingold−Prelog sequence rule[25]), and (*R*)-acetates **15a**−**21a**. The model **A**, which was hypothesized at the outset of this study, seems appropriate to explain the observed enantiotopic preference in the lipase-catalyzed reactions of 1,1-disubstituted 1,2-diols. For **11**−**13** (Figure 2, model **B**), the phenyl, halomethyl, and hydroxyl groups of the substrate are placed in the large, medium, and small pockets, respectively. The glycidol **14** fits the model **C** very well and shows the utmost enantiotopic preference. For **15**−**21** (model D), we assume the alkynyl group is closer to the stereogenic center due to the sp hybrid nature of the triple bond. This substituent, especially that in **16**, **18**, or **21** containing a bulky phenyl, trimethylsilyl, or *tert*-butyl moiety at the terminal of the triple bond, is thus the most steric demanding and placed in the large pocket of the enzyme. The C−I bond is rather long, and the iodomethyl group is considered to be located in the medium pocket. The hydroxyl group is in the small pocket to cope with the observed high enantioselectivity. The previous study[19] also shows that enantioselectivity of lipase-catalyzed acetylations can be determined by the subtle effect of a double bond in the substrates. For example,[19] the lipase-catalyzed acetylation of (±)-2-phenylhexane-1,2-diol proceeds without any enantiomeric preference, whereas the reaction of (±)-2-phenyl-4-hexene-1,2-diol shows a modest enantioselectivity ($E = 16$). By comparison of the excellent E value in the PPL-catalyzed hydrolysis of 2-(iodomethyl)-4-phenyl-3-butyne-1,2-diol (**16**) ($E > 1000$) with those of 2-(iodomethyl)-4-phenylbutane-1,2-diol (**22**) ($E = 6.5$) and 3-iodo-2-phenyl-1,2-propanediol (**13**) ($E = 10$), the enhancement of enantioselectivity in **16** by the effect of a triple bond is dramatic.

It is noted that acetylations of **11** and **15** using *Candida cylindracea* lipases MY, AY, or OF as catalysts (entries 5−7 in Table 1 and entries 2−3 in Table 2) showed the opposite enantiotopic preference. This result may reflect the different nature of the lipases of *Candida* genus, but the elucidation of the real mechanism awaits further investigation.

Synthetic Application. The optically active tertiary alcohols containing halo atoms or oxirane moieties are especially useful for functional group transformation and C−C bond formation. The glycidol (*S*)-**14** was subjected to nucleophilic substitutions with NaN_3, PhSH, and HCN (generated from the cyanohydrin of acetone) to give, respectively, the azido diol (*R*)-**31**, the sulfanyl diol (*S*)-**32**, and the cyano diol (*S*)-**33** in a stereospecific manner (Scheme 3, route 1). The methyl ether of (*S*)-**14** reacted with PhLi in the presence of CuCN to afford the tertiary alcohol (*S*)-**41** in 88% yield. Treatment of the iodohydrin (*R*)-**16** with NaN_3 in DMF at 70 °C yielded the azido diol (*S*)-**34** in 94% yield. The product might be obtained directly by an S_N2 mechanism or via the intermediacy of the glycidol (*R*)-**23** (route 2). Indeed, (*R*)-**23** was found when the reaction of (*R*)-**16** with NaN_3 was performed at a lower reaction temperature (25 °C). The glycidol (*R*)-**23** was isolated from the reaction of (*R*)-**16** with PhSNa and subsequently converted to the sulfanyl diol (*R*)-**35** on treatment with PhSH−Et_3N. As phenylsulfanyl group is known to be a good leaving group, (*R*)-**23** and (*R*)-**35** might be interconvertible, and the equilibrium was dependent of the reaction conditions. The nucleophilic

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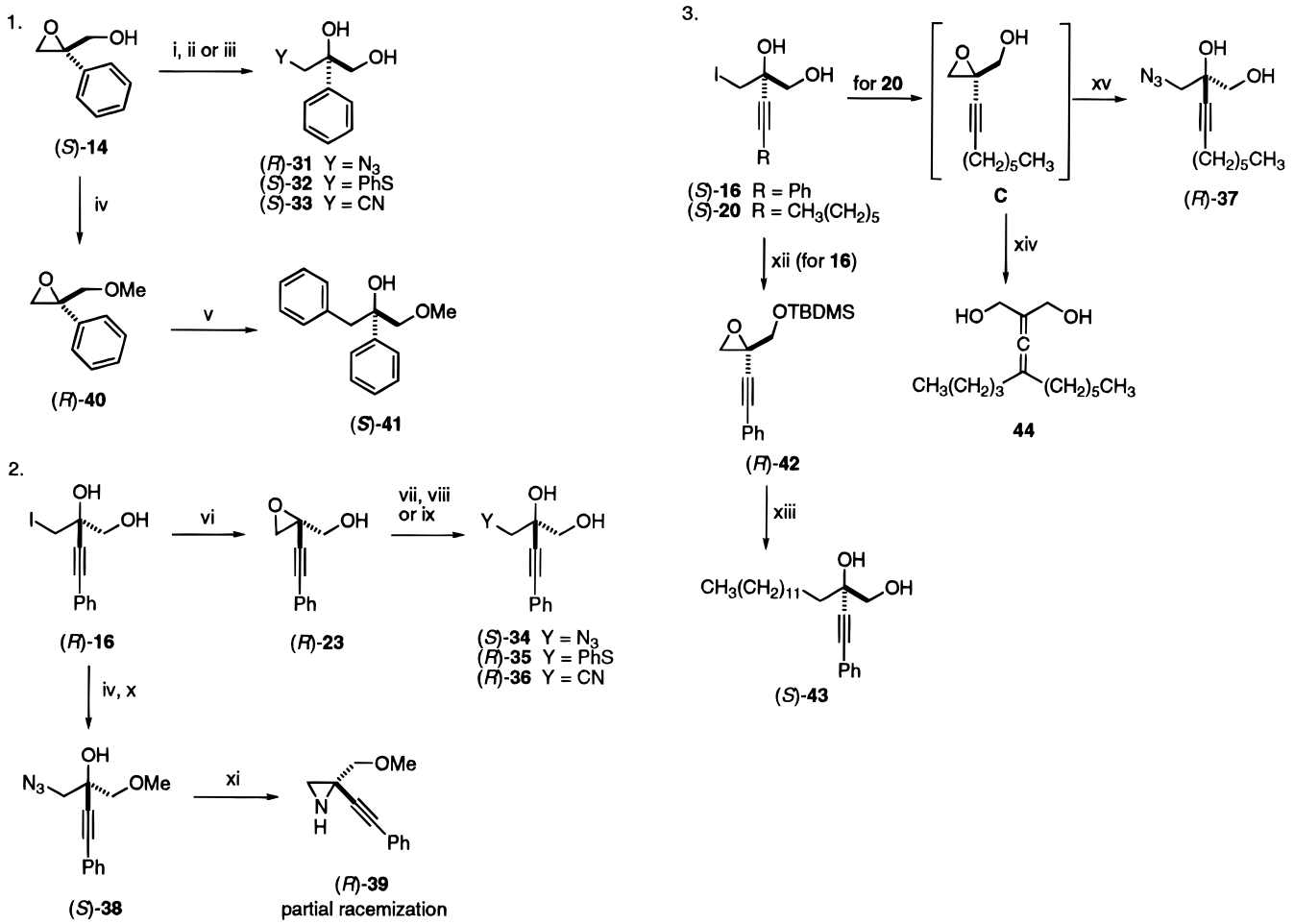
Table 2. Lipase-Catalyzed Acetylations of Alcohols 15−22 with Vinyl Acetate, Giving Acetates 15a−22a

entry	substrate	lipase	solvent	reaction temp/°C	reaction time/h	convn/%	ee_s, %/ config[a]	ee_p, %/ config[a]	*E*
1	**15**	AK	VA[b]	25	n.a.[c]	48	11/*S*	12/*R*	1.4
2	**15**	AY	VA[b]	25	n.a.[c]	26	22/*R*	62/*S*	5.2
3	**15**	OF	VA[b]	25	n.a.[c]	35	24/*R*	45/*S*	3.3
4	**15**	PPL	VA[b]	25	4	41	67/*S*	95/*R*	72
5	**16**	AK	VA[b]	15	3.5	21	12/*S*	46/*R*	3.0
6	**16**	PPL	VA[b]	19	3	63	97/*S*	56/*R*	18
7	**16**	PPL	$PhCH_3$	19	7.7	51	>97[d]/*S*	96/*R*	211
8	**16**	PPL	*t*-BuOMe	19	9	**50**	>**97**[d]**/*S***	>**97**[d]**/*R***	>**1000**
9	**17**	PPL	*t*-BuOMe	19	21	64	>97[d]/*S*	55/*R*	24
10	**18**	PPL	*t*-BuOMe	30	23	**51**	>**97**[d]**/*S***	**94/*R***	**368**
11	**19**	PPL	*t*-BuOMe	30	4	49	88/*S*	89/*R*	47
12	**20**	PPL	*t*-BuOMe	30	5	64	93/*S*	51/*R*	10
13	**21**	PPL	*t*-BuOMe	20	5.3	**49**	**94/*S***	>**97**[d]**/*R***	**751**
14	**22**	PPL	*t*-BuOMe	18	3	51	59/*S*	57/*R*	6.5

[a] The configuration of the major enantiomer. [b] Vinyl acetate was used as the solvent and acylating agent. [c] The degree of acetylation was monitored by GC analysis; however, the data of reaction times are not available. [d] No enantiomer was found according to the HPLC and NMR analyses.

Scheme 3. Nucleophilic Substitution Reactions of Iodohydrins and Glycidols[a]

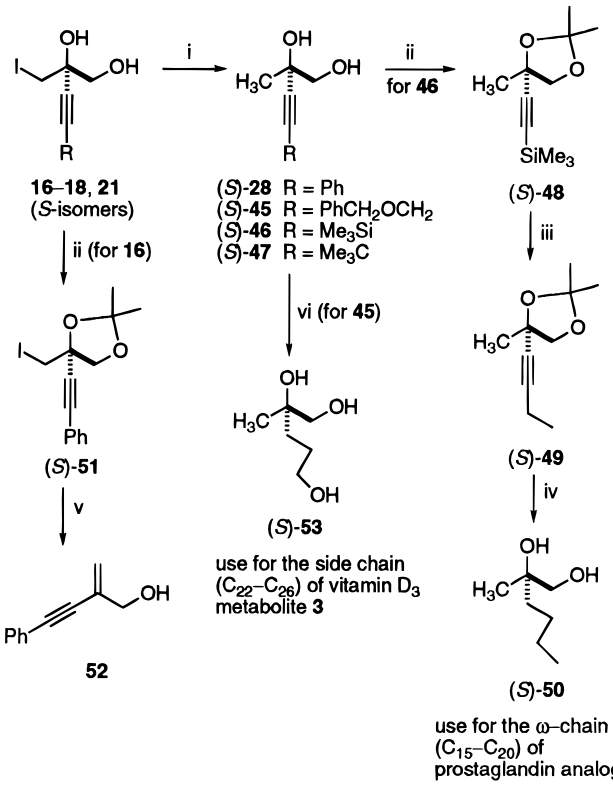


[a] Reagents and conditions: (i) for **31**, NaN_3, NH_4Cl, MeOH, H_2O, reflux, 5.5 h; 57%; (ii) for **32**, PhSH, Et_3N, 25 °C, 15 h; 71%; (ii) for **33**, $Me_2C(OH)CN$, cat. KCN, 25 °C, 24 h; 42%; (iv) NaH, THF, Me_2SO_4, 25 °C, 1 h; 99%; (v) PhLi (3 equiv), CuCN (1.5 equiv), THF, Et_2O, hexane, −78 to 0 °C, 1.5 h; 88%; (vi) PhSNa, DMSO, 60 °C, 5 h; 87%; (vii) for **34**, treating **16** with NaN_3 in DMF−H_2O, 70 °C, 2 h; 94%; (viii) for **35**, treating **23** with PhSH, Et_3N, 25 °C, 15 h; 75%; (ix) for **36**, treating **16** with KCN in DMSO, 25 °C, 13 h; 86%; (x) NaN_3, MeOH, H_2O, reflux 2 h; 75%; (xi) Ph_3P, CH_3CN, 23 °C, 5 h; 71%; (xii) NaH, THF, *t*-$BuMe_2SiCl$, 25 °C, 3 h; 88%; (xiii) $CH_3(CH_2)_{11}MgBr$, THF, 0 °C, 2 h; then Bu_4NF, THF, 25 °C, 10 h; 70%; (xiv) $Bu_2Cu(CN)Li_2$, THF, −78 to 0 °C, 2 h; 60%; (xv) NaN_3, MeOH, reflux, 2 h; 70%.

substitutions of iodohydrins (*R*)-**16** with KCN and (*S*)-**20** with NaN_3 were also carried out smoothly to give the cyano diol (*R*)-**36** and the azido diol (*R*)-**37**. The possibility of Payne rearrangements[23] in the above-mentioned reactions was not overlooked. Nevertheless, the degenerative Payne rearrangements should not change the stereochemical outcomes, as that demonstrated in the transformation of (*S*)-**21** to (*S*)-**27**.

The iodohydrin (*R*)-**16** reacted with Me_2SO_4 and NaN_3 subsequently to give the β-azido alcohol (*S*)-**38**, which was treated with triphenylphosphine to give the aziridine **39** (56% ee favoring the *R*-enantiomer) with partial racemization. The analogous transformation of β-azido alcohols is known to yield the corresponding aziridines with inverse chirality.[26] Due to the nature of the tertiary propargyl alcohol **38**, its transformation to the aziridine

Scheme 4. Reductive Removal of Iodine Atom and Application to the Synthesis of Vitamin D_3 Metabolite and Prostaglandin Analog[a]



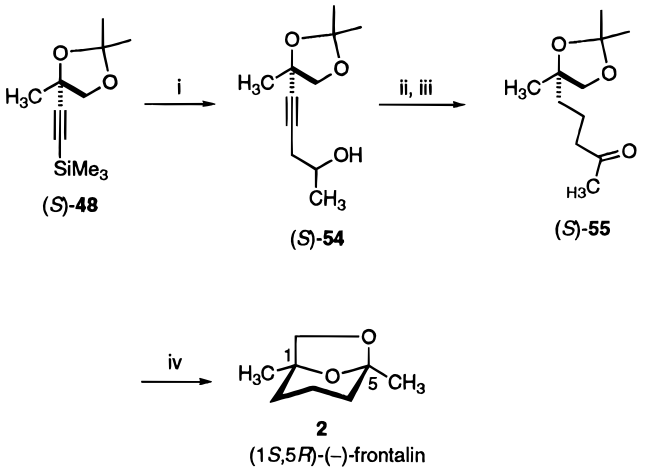
[a] Reagents and conditions: (i) Bu_3SnH, AIBN, PhH, reflux; or $LiAlH_4$, Et_2O, 25 °C, 2 h; **28**, 74%; **45**, 56%; **46**, 83%; **47**, 80%; (ii) Me_2CO, $CuSO_4$, *p*-TsOH, 25 °C, 4 h; 80%; (iii) MeLi, THF, 0−25 °C, 2 h, then EtI, HMPA, 25 °C, 15 h; 40%; (iv) H_2, Pd/C, *p*-TsOH, MeOH, 25 °C, 10 h; 43%; (v) $Bu_2Cu(CN)Li_2$, THF, −78 °C, 2 h; or $CH_3(CH_2)_{11}MgBr$, Li_2CuCl_4, THF, −78 to +25 °C, 12 h; 80%; (vi) H_2, Pd/C, EtOH, 25 °C, 15 h; 40%.

39 might involve both the S_N2 and S_N1 processes to different degrees and eventually led to partial racemization. The iodohydrin (*S*)-**16** was treated with NaH, followed by *t*-$BuMe_2SiCl$, to give the glycidol silyl ether (*R*)-**42**. The reaction of (*R*)-**42** with a Grignard reagent (route 3) afforded a diol (*S*)-**43** after removal of the silyl group. The reaction of the iodohydrin (*S*)-**20** with a cuprate reagent $Bu_2Cu(CN)Li_2$ proceeded in a different fashion to give the allenediol **44**. The product was obtained presumably via an S_N2' mechanism, in which the cuprate reagent attacked the triple bond of the glycidol intermediate.

By a procedure similar to that described for the transformation of the iodohydrin (*S*)-**16** to the diol (*S*)-**28**, the iodohydrins (*S*)-**17**, (*S*)-**18**, and (*S*)-**21** were reduced (Scheme 4) with Bu_3SnH to give the alkynyl diols (*S*)-**45**, (*S*)-**46**, and (*S*)-**47**, respectively. Catalytic hydrogenation of (*S*)-**45** caused a simultaneous saturation of the triple bond and cleavage of the benzyl group to give (*S*)-2-methyl-1,2,5-pentanetriol,[3] which is a precursor for construction of the side chain of a vitamin D_3 metabolite **3**. The acetonide (*S*)-**51**, derived from (*S*)-**16**, reacted with $Bu_2Cu(CN)Li_2$ or with a mixed reagent of *n*-$C_{12}H_{25}MgBr/Li_2CuCl_4$ to afford an allyl alcohol **52** in 80% yield. The organometallic reagents appeared to attack the iodine atom instead of undergoing a nucleophilic substitution.

(26) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790.
(27) Fujimoto, Y.; Yadav, J. S.; Sih, C. J. *Tetrahedron Lett.* **1980**, *21*, 2481.

Scheme 5. Synthesis of (1*S*,5*R*)-(−)-Frontalin[a]



[a] Reagents and conditions: (i) MeLi, THF, 25 °C, 2 h; $BF_3{\cdot}OEt_2$, −78 °C, 10 min; 2-methyloxirane, −78 °C, 30 min; 81%; (ii) PDC, molecular sieves, CH_2Cl_2, 25 °C, 4 h; (iii) H_2, Pd/C, EtOAc, 25 °C, 4 h; 61% for two steps; (iv) HCl (10 N), Et_2O, 25 °C, 15 h; 60%.

The alkynyl alcohol (*S*)-**18** is a versatile building block. Compound (*S*)-**18** was reduced by Bu_3SnH, giving the diol (*S*)-**46**, and protected as the acetonide (*S*)-**48**. The silyl group in (*S*)-**48** was removed by MeLi to generate an alkynyllithium intermediate, which was subsequently alkylated with iodoethane to give (*S*)-**49**. By the assistance of *p*-toluenesulfonic acid, hydrogenation of **49** in MeOH also effected a hydrolysis of the acetonide moiety to give a single product, (*S*)-2-methyl-1,2-hexanediol[27] (**50**), which has been utilized to synthesize the ω-chain of a potent prostaglandin analog (**1**). Attempts to trap the alkynyllithium intermediate with propylene oxide failed. Fortunately, alkylation with propylene oxide was carried out successfully by a prior treatment of the alkynyllithium intermediate with $BF_3{\cdot}OEt_2$ (Scheme 5), giving the desired homopropargyl alcohol (*S*)-**54** in 81% yield. Oxidation of (*S*)-**54** with pyridinium dichromate, followed by hydrogenation, afforded the ketone (*S*)-**55**. Hydrolysis of (*S*)-**55** under acidic conditions gave a dihydroxy ketone, which underwent intramolecular acetalization to yield an aggregation pheromone (1*S*,5*R*)-(−)-frontalin.[2]

Conclusion

Although a general enzymatic resolution of tertiary alcohols by extension of their reactive sites, as that in the hydroperoxy acetate **7** and β-alkoxy alcohol **8**, was not achieved, we demonstrate a more successful approach by adding CH_2OH tethers to tertiary alcohols, as that shown in the substrates of **11**−**22**, for efficient resolution with the catalysis of lipases. Thus, the lipase-catalyzed reactions occur at the primary hydroxyl groups while the enantioselectivity is controlled by the tertiary C−O centers. By selection of appropriate substituents, such as iodine atom, phenyl, and alkynyl groups, extremely high enantioselectivity is realized. The obtained enantiomerically pure compounds are versatile building blocks for the synthesis of drugs and natural products. We also propose a model to show the importance of size, distance, and electron effect of substituents in lipase-catalyzed reactions. The great enhancement of enantioselectivity by a triple bond in the substrate is most remarkable.

Experimental Section

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a cuvette of 1 cm

length. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. Tetramethylsilane ($\delta = 0$ ppm) was used as internal standard in ^{1}H NMR spectra. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. GC was performed on a gas chromatograph equipped with a flame ionization detector. High-pressure liquid chromatography was carried out on a liquid chromatograph equipped with UV (254 nm) and refractive index detectors. Enantiomeric excesses of the remaining substrate, ee_s, and the product, ee_p, were determined by HPLC analysis using a Chiralcel OB or OD column (25 cm × 0.46 cm i.d.) with the indicated flow rate of elution. The *E* value was calculated according to $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where *c* is conversion [$c = ee_s/(ee_s + ee_p)$].[12f] The reaction was monitored either by GC analysis on an OV-1 column (2% on Chromosorb WHP/80−100 mesh, 2 m × 0.32 cm i.d.) with 30 mL/min flow rate of N_2 or by HPLC analysis on a Nucleosil 100−7 (7 μm) column (15 cm × 0.46 cm i.d.) with the indicated eluent.

Lipase AK (*Pseudomonas* sp.), lipase AP-6 (*Aspergillus niger*), lipase AY (*C. cylindracea*), and lipase MAP (*Mucor meihei*) were purchased from Amano Pharm. Co., Ltd., Japan. Lipase OF (*C. cylindracea*) and lipase MY (*C. cylindracea*) were from Meito-Sangyo Co., Ltd., Japan. Porcine pancreas lipase (PPL, type II) was from Sigma, USA. These crude enzymes were often used for enzymatic reactions without further purification, and lipase AK was occasionally immobilized on Hyflo Supercel (Fluka, 2−25 μm) for the reactions. The reagents and solvents (isopropenyl acetate, vinyl acetate, *t*-BuOMe, THF, and toluene) were dried according to standard procedure and stored over molecular sieves (4 Å) before use.

General Procedure for Lipase-Catalyzed Acetylation and Stereochemical Assignment (Tables 1 and 2). Procedure A. The alcohol (±)-**13** (384 mg, 1.4 mmol) was stirred (800−1000 rpm) with isopropenyl acetate (11 mL) and lipase AK (390 mg) at 25 °C for 30 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (3:7) to give 193 mg (43%) of the acetate **13a** (94% ee favoring the *R*-isomer) and to recover 222 mg (57%) of the alcohol **13** (70% ee favoring the *S*-isomer). The recovered alcohol **13** was treated with K_2CO_3 in MeOH at 30 °C for 8 h to give glycidol **14**, of which the ee value was determined by HPLC analysis. The recovered alcohol **13** was treated with Bu_3SnH (1 equiv) and AIBN (catalytic amount) in refluxing benzene for 4 h to give (*S*)-(+)-**10**.[21] This experiment indicated that the predominant enantiomer of **13** had the (*S*)-configuration. The ee value of the product **13a** and the absolute configuration of its major enantiomer were determined by the procedure similar to that for **13**.

Procedure B. The alcohol (±)-**16** (710 mg, 2.35 mmol) was treated with vinyl acetate (0.65 mL, 3 mmol) by catalysis of PPL (710 mg) in *t*-BuOMe (12 mL) at 19 °C for 9 h to give 405 mg (50%) of the acetate **16a** (>97% ee favoring the *R*-isomer) and to recover 355 mg (50%) of the alcohol **16** (>97% ee favoring the *S*-isomer). The ee values were determined by HPLC analysis. The absolute configuration of the major enantiomers were determined by correlation with 2-methylglycerol 1,2-acetonide **30** (Scheme 2) as follows.

(*S*)-(−)-**16** (350 mg, 1.12 mmol) was treated with Bu_3SnH (0.46 mL, 1.68 mmol) and AIBN (36 mg) in refluxing benzene (25 mL) for 2 h to give (*S*)-2-methyl-4-phenyl-3-butyne-1,2-diol (**28**) (151 mg, 74%). The sample was treated with acetone (20 mL), $CuSO_4$ (3 g), and *p*-TSA (catalytic amount) at 25 °C for 4 h to give the acetonide (*S*)-**29**. The crude acetonide was dissolved in MeOH (8 mL) and treated with ozone at 0 °C. The reaction was monitored by TLC analysis. After completion of the ozonolysis during a period of 1.5 h, the mixture was purged with N_2 to remove the remaining ozone. The mixture was heated for 15 min, concentrated, dissolved in anhydrous THF (10 mL), and treated with $LiAlH_4$ (95 mg, 2.5 mmol) at 25 °C for 12 h. The reaction was quenched by addition of water at 0 °C. The mixture was extracted with EtOAc and chromatographed on a silica gel column (EtOAc/hexane (1:1)) to give (*S*)-2-methylglycidol acetonide (**30**) (20.6 mg, 17% from **28**): $[\alpha]^{25}_D$ −7.61 (*c* 1.05, CH_2Cl_2) (lit.[24] $[\alpha]^{25}_D$ −5.33 (*c* 0.3, CH_2Cl_2)).

2-(Iodomethyl)-4-phenyl-3-butyne-1,2-diol (16): solid; mp 94−95 °C; $[\alpha]^{25}_D$ −8.0 (*c* 2.5, EtOH; *S*-isomer); HPLC (Chiralcel OD, 2-propanol/hexane (10:90), 1 mL/min) t_R 12.3 min (*R*-isomer), 15.0 min (*S*-isomer); IR (KBr) 3341, 2314 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.45 (2H, m), 7.28−7.31 (3H, m), 3.92 (1H, d, $J = 11.1$ Hz), 3.83 (1H, d, $J = 11.1$ Hz), 3.59 (1H, d, $J = 10.2$ Hz), 3.54 (1H, d, $J = 10.2$ Hz), 2.93 (1H, s, OH)), 2.21 (1H, br s, OH); ^{13}C NMR (75 MHz, acetone-d_6) δ 132.6, 129.6, 129.4, 123.6, 90.5, 85.7, 71.3, 68.5, 14.7; MS *m*/*z* (rel intensity) 302 (3, M^+), 144 (100); HRMS calcd for $C_{11}H_{12}O_2I$ (M^+) 301.9803, found 301.9809.

1-Acetoxy-2-(iodomethyl)-4-phenyl-3-butyn-2-ol (16a): oil; $[\alpha]^{25}_D$ −10.2 (*c* 2.5, EtOH; >97% ee favoring the *R*-isomer); HPLC (Chiralcel OD, 2-propanol/hexane (10:90), 0.5 mL/min) t_R 15.4 min (*R*-isomer), 17.2 min (*S*-isomer); IR (neat) 3417, 2230, 1737 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.44 (2H, m), 7.27−7.32 (3H, m), 4.43 (1H, d, $J = 11.3$ Hz), 4.36 (1H, d, $J = 11.3$ Hz), 3.53(2H, s), 3.19 (1H, s, OH), 2.11 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.2, 131.8, 128.9, 128.2 121.4, 86.6, 86.3, 68.9, 67.9, 20.8, 13.4; MS *m*/*z* (rel intensity) 344 (5, M^+), 271 (100); HRMS calcd for $C_{13}H_{13}OI$ (M^+) 344.9909, found 344.9919.

1-(Hydroxymethyl)-1-(phenylethynyl)oxirane (23). The iodohydrin (*S*)-**16** (205 mg, 0.67 mmol; >97% ee) in THF (10 mL) was treated with NaH (750 mg, 30 mmol) at 0 °C for 30 min to give the oxirane (*S*)-**23** (116 mg, 99%): oil; $[\alpha]^{25}_D$ −11.7 (*c* 4.8, EtOH; *S*-isomer, >97% ee); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 128.9, 128.2, 121.4, 84.8, 84.7, 62.9, 51.5, 51.4; HRMS calcd for $C_{11}H_{10}O_2$ (M^+) 174.0680, found 174.0679 .

3-Azido-2-phenyl-1,2-propanediol (31). A mixture of oxirane (*S*)-**14** (74 mg, 0.49 mmol; >97% ee), NaN_3 (162 mg, 2.45 mmol), and NH_4Cl (57 mg) in H_2O/MeOH (1:8) solution (5 mL) was refluxed for 5.5 h. The mixture was concentrated and taken up with EtOAc. The organic phase was washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and filtered. The filtrate was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (30:70) to give the azido compound (*R*)-**31** (54 mg, 57%): oil; $[\alpha]^{25}_D$ −55.81 (*c* 2.65, EtOH; *R*-isomer, >97% ee); IR (neat) 3413, 2104 (N_3) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44−7.26 (5H, m), 3.80 (1H, d, $J = 11.5$ Hz), 3.72 (1H, d, $J = 11.5$ Hz), 3.64 (1H, d, $J = 13.0$ Hz), 3.57 (1H, d, $J = 13.0$ Hz) , 3.34 (1H, br s), 2.52 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 128.5, 127.9, 125.2, 76.3, 67.5, 57.7; MS *m*/*z* (rel intensity) 194 (1, M^+), 137 (100); HRMS calcd for $C_8H_8ON_3$ ($M^+ - CH_2OH$) 162.0667, found 162.0675.

3-(Phenylthio)-2-phenylpropane-1,2-diol (32). The oxirane (*S*)-**14** (79 mg, 0.52 mmol; >97% ee) was treated with PhSH (0.08 mL, 0.78 mmol) and Et_3N (2 mL, 1.75 mmol) at 25 °C for 15 h to give (*S*)-**32** (98 mg, 71%): solid; mp 105−106 °C; $[\alpha]^{25}_D$ +15.2 (*c* 4.2, EtOH; *S*-isomer, >97% ee); IR (KBr) 3171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.13 (10H, m), 3.77 (1H, d, $J = 11.3$ Hz), 3.72 (1H, d, $J = 11.3$ Hz), 3.58 (1H, d, $J = 13.3$ Hz), 3.52 (1H, d, $J = 13.3$ Hz), 3.37 (1H, br s), 2.31 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 136.0, 129.9, 128.9, 128.9, 128.3, 127.6, 126.4, 125.4, 76.4, 69.3, 44.1; MS *m*/*z* (rel intensity) 260 (2, M^+), 124 (100); HRMS calcd for $C_{15}H_{16}O_2S$ (M^+) 260.0871, found 260.0873.

3,4-Dihydroxy-3-phenylbutanenitrile (33). The oxirane (*S*)-**14** (75 mg, 0.50 mmol; >97% ee) was treated with KCN (6.5 mg, 0.09 mmol) and acetone cyanohydrin (2 mL, 21.9 mmol) at 25 °C for 24 h to give (*S*)-**33** (38 mg, 42%): solid; 117−118 °C; $[\alpha]^{25}_D$ −9.26 (*c* 1.2, EtOH; *S*-isomer, >97% ee); IR (KBr) 3437, 2217 (CN) cm^{-1}; ^{1}H NMR (200 MHz, acetone-d_6) δ 7.60−7.55 (2H, m), 7.40−7.27 (3H, m), 3.78 (1H, d, $J = 11.0$ Hz), 3.68 (1H, d, $J = 11.0$ Hz), 3.11 (1H, d, $J = 16.8$ Hz), 3.01 (1H, d, $J = 16.8$ Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 143.4, 128.8, 128.1, 126.2, 118.3, 75.3, 69.5, 32.5; MS *m*/*z* (rel intensity) 177 (2, M^+), 105 (100); HRMS calcd for $C_{10}H_{11}O_2N$ (M^+), 177.0789, found 177.0795.

1-(Methoxymethyl)-1-(phenylethynyl)aziridine (39). The iodo compound (*R*)-**16** (280 mg, 0.92 mmol; >97% ee) was treated with NaH (750 mg, 30 mmol) and Me_2SO_4 (0.13 mL, 1.4 mmol) in THF (5 mL) at 23 °C for 1 h to give a crude product of the methyl ether. The crude product was treated

with NaN_3 (59 mg, 9.2 mmol) in refluxing MeOH/H_2O (10:1) solution (11 mL) for 2 h to give (*S*)-**38** (160 mg, 75%): oil; $[\alpha]^{24}_D$ +58.22 (*c* 7.5, EtOH; *S*-isomer, >97% ee).

The azido compound (*S*)-**38** (95 mg, 0.44 mmol) was treated with PPh_3 (126 mg, 0.48 mmol) in MeCN (10 mL) at 23 °C for 5 h to give **39** (54 mg, 71%; 56% ee favoring the *R*-isomer): oil; $[\alpha]^{25}_D$ −12.5 (*c* 0.68, EtOH; 56% ee favoring the *R*-isomer); HPLC (Chiralcel OD, 2-propanol/hexane (10:90), 1 mL/min) t_R 13.6 min (*S*-isomer), 15.0 min (*R*-isomer); IR (neat) 3282, 2240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.42−7.37 (2H, m), 7.27−7.22 (3H, m), 3.55 (2H, s), 3.42 (3H, s), 2.20 (1H, br s), 1.96 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.7, 128.1, 128.0, 122.3, 89.1, 80.3, 75.9, 59.0, 32.0, 29.3; MS *m*/*z* (rel intensity) 187 (5, M^+), 155 (100); HRMS calcd for $C_{12}H_{13}O_1N$ (M^+) 187.0997, found 187.0992.

1-Methoxy-2,3-diphenyl-2-propanol (41). The oxirane (*S*)-**14** (450 mg, 3 mmol; >97% ee) was treated with NaH (750 mg, 30 mmol) and Me_2SO_4 (mL, 3.3 mmol) in THF (15 mL) at 23 °C for 1 h to give (*S*)-1-(methoxymethyl)-1-phenyloxirane **40** (501 mg, 99%). The ether (*S*)-**40** (487 mg, 2.97 mmol) was treated with PhLi (2.96 mL of 3 M solution in cyclohexane/Et_2O) and CuCN (400 mg, 4.45 mmol) in THF (3 mL) at −78 °C and then at 0 °C for 1.5 h to give (*S*)-**41** (632 mg, 88%): oil; $[\alpha]^{30}_D$ −26.3 (*c* 0.05, EtOH; *S*-isomer, >97% ee); IR (neat) 3450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34−6.78 (10H, m) 3.66 (1H, d, J = 9.2 Hz), 3.60 (1H, d, J = 9.2 Hz), 3.38 (3H, s, OCH_3), 3.13 (2H, s, CH_2Ph), 2.83 (1H, s, OH); MS *m*/*z* (rel intensity) 242 (1, M^+), 91 (100); HRMS calcd for $C_{16}H_{18}O_2$ (M^+) 242.1306, found 242.1300.

3-(Hydroxymethyl)-1-phenyl-1-heptadecyn-3-ol (43). The iodo compound (*S*)-**16** (151 mg, 0.50 mmol; >97% ee) was treated with NaH (125 mg, 5 mmol) and *t*-$BuMe_2SiCl$ (0.75 mL of 1 M THF solution) in THF (5 mL) at 25 °C for 3 h to give a silyl ether (*S*)-**42** (127 mg, 88%). The silyl ether was treated with dodecylmagnesium bromide (6 mL of 1 M THF solution) in THF at 0 °C for 2 h to give a crude product. The product was subsequently treated with Bu_4NF (172 mg, 0.66 mmol) in THF (10 mL) to give (*S*)-**43** (110 mg, 70%): oil; $[\alpha]^{23}_D$ −32.1 (*c* 2.0, EtOH; *S*-isomer, >97% ee); IR (neat) 3338, 2240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.39 (2H, m), 7.30−7.27 (3H, m), 3.74 (1H, d, J = 11.0 Hz), 3.57 (1H, d, J = 11.0 Hz), 2.25 (2H, br s), 1.73−1.54 (4H, m), 1.22 (22H, br s), 0.85 (3H, t, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 128.5, 128.2, 122.5, 89.5, 85.4, 72.3, 69.7, 37.9, 31.9, 29.7, 29.6, 29.5, 29.3, 24.1, 22.6, 14.1; MS *m*/*z* (rel intensity) 341 (3), 327 (100, $M^+ - CH_2OH$); HRMS calcd for $C_{23}H_{35}O_2$ ($M^+ - CH_2OH$) 327.2687, found 327.2692.

4-Butyl-2-(hydroxymethyl)-2,3-decadien-1-ol (44). The iodo compound (*S*)-**20** (99 mg, 0.32 mmol) in THF (1.5 mL) was treated with $Bu_2Cu(CN)Li_2$ (3 mL of 0.43 M solution in THF) at −78 °C for 1 h and then at 0 °C for an additional 1 h to give **44** (46 mg, 60%): oil; IR (neat) 3352, 1955 (allene) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.16 (4H, s), 1.99−1.92(6H, m, 2 CH_2, 2 OH), 1.39−1.24 (12H, m) 0.89−0.81 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.5, 109.9, 105.6, 62.7, 32.8, 32.5, 31.7, 30.0, 28.9, 27.8, 22.6, 22.3, 13.9, 13.8; MS *m*/*z* (rel intensity) 240 (3, M^+), 109 (100); HRMS calcd for $C_{15}H_{28}O_2$ (M^+) 240.2089, found 240.2089.

2-Methyl-1,2-hexanediol (50). The diol (*S*)-**46** (487 mg, 2.83 mmol; >97% ee) was treated with acetone (20 mL) by the catalysis of $CuSO_4$ (6 g) and *p*-TsOH (2 grains) at 25 °C for 4 h to give the corresponding acetonide (*S*)-**48** (483 mg, 80%): oil; $[\alpha]^{25}_D$ −5.21 (*c* 2.5, $CHCl_3$; *S*-isomer, >97% ee). The acetonide (*S*)-**48** (200 mg, 0.9 mmol; >97% ee) was treated with MeLi (0.89 mL of 1.5 M of hexane solution) at 25 °C for 2 h. EtI (0.4 mL, 0.9 mmol) and HMPA (1 mL) were added. The mixture was stirred at 25 °C for 18 h to give a crude product **49** (57 mg). The product was subjected to hydrogenation by the catalysis of Pd/C (5%, 100 mg) and *p*-TsOH (catalytic amount) in MeOH (10 mL) at 25 °C for 10 h to give (*S*)-**50** (19 mg, 43%): oil; $[\alpha]^{25}_D$ −4.8 (*c* 0.95, $CHCl_3$; *S*-isomer, >97% ee) (lit.[27] $[\alpha]^{25}_D$ −3.0 (*c* 0.7, $CHCl_3$)).

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2-Methylene-4-phenyl-3-butyn-1-ol (52). The iodo compound (*S*)-**16** (152 mg, 0.5 mmol; >97% ee) was treated with acetone (20 mL) by the catalysis of $CuSO_4$ (2 g) and *p*-TsOH (2 grains) at 25 °C for 4 h to give the corresponding acetonide (*S*)-**51** (136 mg, 78%). The acetonide in THF (4 mL) was treated $Bu_2Cu(CN)Li_2$ (6 mL of 0.33 M solution in THF) at −78 °C for 2 h to give **52** (49 mg, 80%): oil; IR (neat) 3358, 2205 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36−7.29 (2H, m), 7.22−7.16 (3H, m), 5.49−5.46 (2H, m), 4.11 (2H, s), 2.18 (1H, br s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.5, 131.1, 128.3, 128.2, 122.6, 120.2, 90.6, 87.0, 65.0; MS *m*/*z* (rel intensity) 158 (100, M^+); HRMS calcd for $C_{11}H_{10}O$ (M^+) 158.0731, found 158.0722.

2-Methyl-1,2,5-pentanetriol (53). The diol (*S*)-**45** (220 mg, 1 mmol; >97% ee) was subjected to hydrogenation by the catalysis of Pd/C (5%, 100 mg) in EtOH at 25 °C for 15 h to give (*S*)-**53**[3] (55 mg, 40%): oil; ^{13}C NMR (50 MHz, acetone-d_6) δ 72.5, 70.3, 63.2, 35.9, 27.8, 24.1.

5-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-4-pentyn-2-ol (54). The acetonide (*S*)-**48** (212 mg, 1 mmol; >97% ee) was treated with MeLi (1 mL, 1.6 M of hexane solution) in THF (5 mL) at 25 °C for 2 h. The mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (0.13 mL, 1 mmol) was added. After 10 min, 1-methyloxirane (116 mg, 2 mmol) was added. The mixture was stirred for 30 min, and the reaction was quenched by addition of Et_3N and saturated $NaHCO_3$. The mixture was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated and chromatographed on a SiO_2 column by elution with EtOAc/hexane (20:80) to give (*S*)-**54** (160 mg, 81%): oil; $[\alpha]^{25}_D$ −9.44 (*c* 9.0, $CHCl_3$; *S*-isomer, >97% ee); IR (neat) 3424, 2236 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.05 (1H, d, J = 8.1 Hz), 3.91−3.82 (1H, m), 3.70 (1H, d, J = 8.1 Hz), 2.35 (1H, br s, OH), 2.31 (2H, d, J = 5.9 Hz), 1.48 (3H, s), 1.46 (3H, s), 1.33 (3H, s), 1.18 (3H, d, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.4, 84.5, 80.4, 75.7, 73.7, 66.1, 29.1, 26.9, 26.9, 26.1, 22.2; MS *m*/*z* (rel intensity) 183 (51, $M^+ - CH_3$), 72 (100); HRMS calcd for $C_{10}H_{15}O_3$ ($M^+ - CH_3$) 183.1021, found 183.1019.

5-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pentan-2-one (55). The alcohol (*S*)-**54** (289 mg, 1.45 mmol; >97% ee) was treated with pyridinium dichromate (1.36 g, 3.62 mmol) in the presence of molecular sieves (4 Å) in CH_2Cl_2 at 25 °C for 4 h. The mixture was filtered and rinsed with Et_2O. The filtrate was concentrated to give a crude product, which was subjected to hydrogenation (1 atm) by the catalysis of Pd/C (5%, 150 mg) in EtOAc (15 mL) at 25 °C for 4 h to give (*S*)-**55** (176 mg, 61%; >97% ee): oil; IR (neat) 2981, 1707 $cm^{-1;}$ ^1H NMR (200 MHz, $CDCl_3$) δ 3.75 (1H, d, J = 8.3 Hz), 3.66 (1H, d, J = 8.3 Hz), 2.42 (2H, t, J = 6.9 Hz), 2.10 (3H, s), 1.67−1.39 (4H, m), 1.35 (3H, s), 1.34 (3H, s), 1.24 (3H, s); MS *m*/*z* (rel intensity) 200 (1, M^+), 185 (45), 72 (100); HRMS calcd for $C_{11}H_{20}O_3$ (M^+) 200.1412, found 200.1432.

(1*S*,5*R*)-(−)-Frontalin (2). Compound (*S*)-**55** (176 mg, 0.88 mmol; >97% ee) was treated with HCl (10 N, 0.5 mL) in Et_2O (2 mL) at 25 °C for 15 h. After addition of $NaHCO_3$, Na_2SO_4 and Et_2O, the mixture was filtered. The solvent was evaporated, the residue was distilled (Kugelrohr, 95−100 °C, 100 mmHg) to give (1*S*,5*R*)-frontalin (76 mg, 60%; >97% ee). $[\alpha]^{23}_D$ −52.5 (*c* 2.0, Et_2O) [lit.[28] $[\alpha]^{22}_D$ −52.8 (*c* 1.64, Et_2O). ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (1H, d, J = 6.3 Hz), 3.45 (1H, d, J =6.3 Hz), 1.26−2.02 (6H, m), 1.44 (3H, s), 1.34 (3H, s).

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Supporting Information Available: Additional experimental procedures, spectral data, and authentic NMR spectra of new compounds (64 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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