# (1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium Benzoate, A Versatile Building Block for Chiral 2-Aminoalkanols: Concise Synthesis and Application to Nelfinavir, a Potent HIV-Protease Inhibitor

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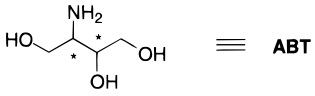
A concise synthesis of a versatile chiral C4 building block for 2-aminoalkanols, (1*S*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium benzoate (**1a**), was described. **1** (**1a** and its enantiomer **1b**) acted as four stereoisomers of optically active 2-amino-1,3,4-butanetriol. The versatility of **1** was demonstrated by its application to the practical synthesis of nelfinavir (**2**), a potent HIV-protease inhibitor, as well as by the stereospecific synthesis of three diastereomers of **2**.

## Introduction

Chiral 2-aminoalkanol components are often seen in many biologically active compounds with all sorts of relative and absolute stereochemical structures. From the point of view of synthetic chemistry, it is rational to consider that optically active 2-amino-1,3,4-butanetriol (ABT) is the smallest suitable retrosynthetic unit for the




chiral 2-aminoalkanol component, because the primary hydroxyl groups at the both ends of ABT act as handles for further extension including carbon−carbon bond formation. In fact, ABT equivalents have been used for the production of biologically important compounds including sphingosines,[1] FR900482 (an antitumor antibiotic),[2] kainic acid,[3] liposidomycins (bacterial peptidoglycan synthesis inhibitors),[4] and glycomimetics.[5] ABT equivalents, used in the above investigations, were prepared from isoascorbic acid,[1h,4c] ascorbic acid,[4b,5b] tartaric acid,[6] chiral aziridino alcohols obtained by enzymatic method,[7] chiral α-keto-β-lactam,[8] erythrulose,[9] and chiral epoxides obtained by Katsuki−Sharpless asymmetric epoxidation,[10] in various protected and unprotected forms. Recently, Sharpless asymmetric aminohydroxylation has been utilized for the preparation of ABT equivalents employing 2-butene-1,4-diol derivatives as substrates.[11] To practically utilize ABT as a versatile building block in various syntheses, ABT should be available on a large scale and in a favorably protected form for the selective treatment of its three hydroxyl groups and an amino group. From this point of view, there still remained problems in generation of versatile ABT equivalents. Herein described is a concise and scalable preparation of favorably protected ABT, i.e., (1*S*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium benzoate (**1a**) and its enantiomer **1b**, which possess three readily differentiated hydroxyls and a free amino group. Application of **1** (**1a** and **1b**) to the synthesis of nelfinavir (**2**, a potent HIV-protease inhibitor)[12] and

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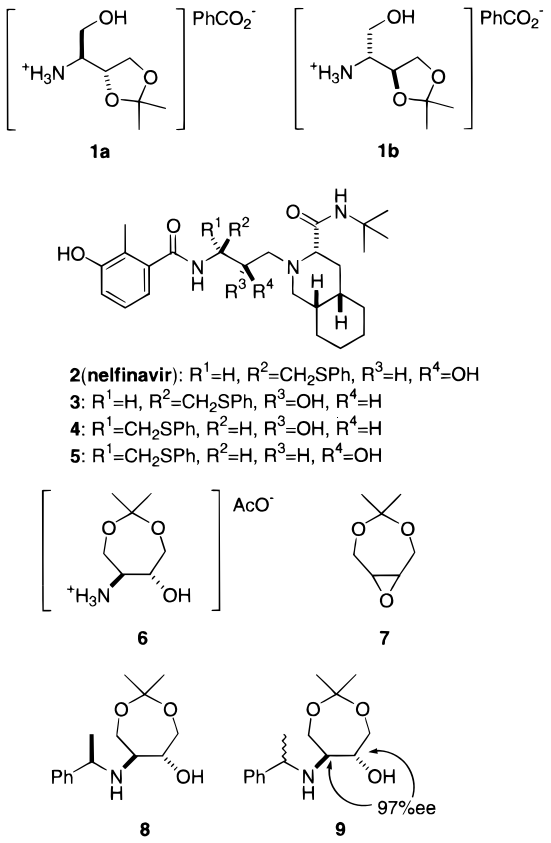
its diastereomers (**3**−**5**), demonstrates the versatility of **1** as ABT equivalent.

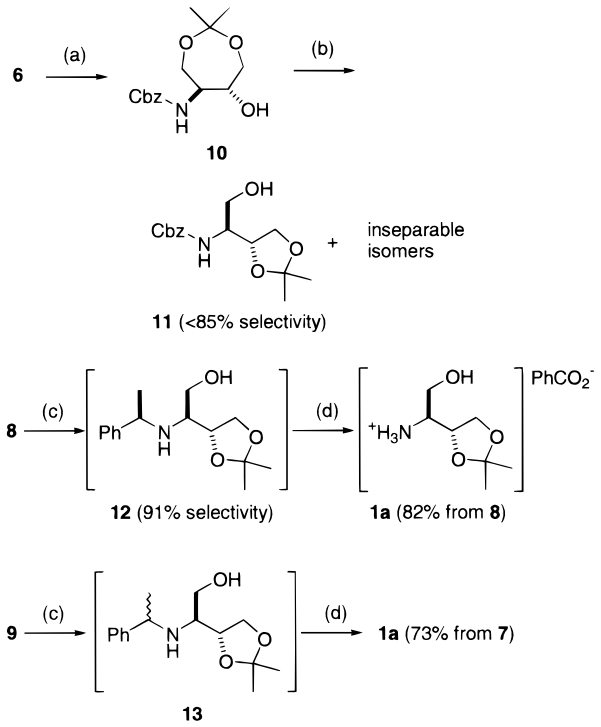



## Results and Discussion

We reported that seven-membered ring amino alcohol **6** was a novel and suitable ABT equivalent in the context of practical synthesis of **2**.[13] In the study, differentiation of the left primary hydroxyl group from the right one of **6**, in which both hydroxyl groups were protected as an acetonide, was carried out by oxazoline formation taking advantage of an amide group introduced on the amino group of **6**. However, **6** seemed to have limitations in its wide use for the production of other compounds possessing chiral 2-aminoalkanol component(s), since the successful differentiation of the two hydroxyl groups was restricted to the cases that the amino group was protected by an amide group. Generally, removal of amide-protection requires strongly acidic conditions, and it could not be applied to highly functionalized compounds. In contrast to **6**, the regioisomer **1a** is expected to be of wider application, since the three hydroxyl groups are favorably differentiated by protection of one of the two primary hydroxyl groups forming acetonide with the neighboring secondary one. By protecting the hydroxyl groups in this fashion, the three hydroxyl groups and the amino group should be selectively handled.

Regarding the preparation of **1**, seven-membered ring compounds **6**, **8**, and **9** were expected to be good precursors of **1a**, because these compounds should effectively migrate to the thermodynamically more favorable five-membered dioxolanes by acid treatment. Moreover, the advantage of using these compounds is that the stereoselective preparation of **8** and **9**, precursors of **6**, have recently become available by means of highly selective asymmetric aminolysis of meso epoxide **7** using Ti−(*S*)-1,1′-bi-2-naphthoxide complex as a chiral catalyst.[14] Initially, isomerization of **10** to **11**, after protection of the amino group of **6** with a Cbz group, was examined. Although isomerization of **10** took place by treatment with PPTS in acetone, the product was an intractable oily isomeric mixture containing desired **11** as a major component (less than 85% selectivity, NMR), which could not be isolated in pure form even by column chromatography (Scheme 1). Direct isomerization of **6** to **1a** was impractical because of the extraction difficulty of the product due to its water-soluble nature, again. In contrast, treatment of **8** with 1.25 equiv of MsOH or dried TsOH in acetone resulted in smooth migration of acetonide[15] and following catalytic hydrogenolysis of the equilibrium mixture in the presence of benzoic acid provided pure **1a** in 82% from **8** after recrystallization. The HPLC analysis indicated that the equilibrium mixture, obtained by the acid treatment, was comprised of desired **12** (91%), **8** (7%), and an unidentified isomer (2%).[16] In addition to the higher selectivity of desired **12** in the isomerization, the advantage of this method is that enantiomerically and diastereomerically pure **1a** can be efficiently obtained by recrystallization. In this hydro-

**Scheme 1**[a]




[a] Reaction conditions: (a) CbzCl, $NaHCO_3$, toluene, $H_2O$; (b) PPTS, acetone; (c) MsOH (1.25 equiv), $Me_2C(OMe)_2$ (10 mol %), acetone; (d) Pd(C), $H_2$, $PhCO_2H$, 2-propanol.

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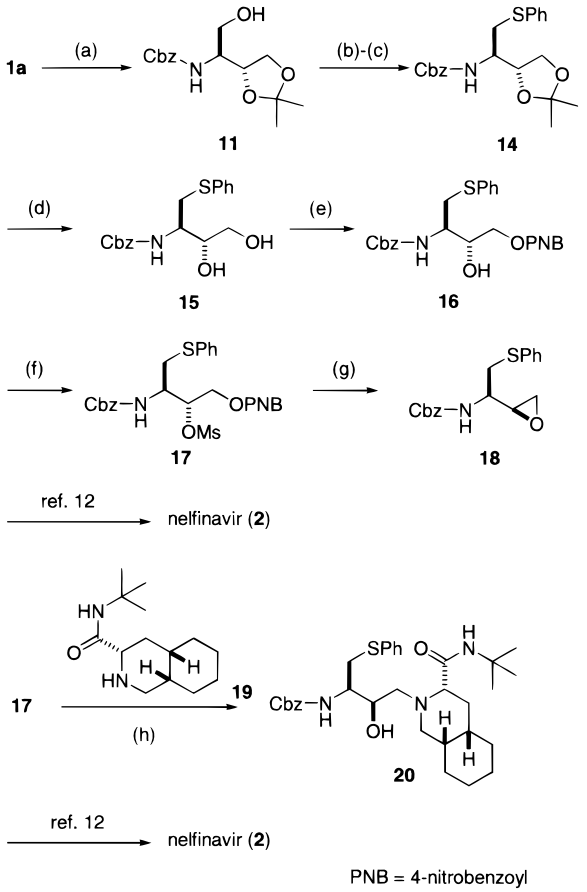
(15) The isomerization was carried out in the presence of 2,2-dimethoxypropane (10 mol %) preventing hydrolysis of acetonide, see Experimental Section.

(16) HPLC conditions: column YMC AM-302, 150 × 1.6 mm i.d., S-5 $\mu$m, 120A.; mobile phase acetonitrile/10 mM phosphate buffer (pH 7) = 40/60; detection UV 214 nm; flow rate 1.0 mL/min; column temp. 40 °C, $t_R$ = 5.6 min (**8**, 6.6%), 6.8 min (**12**, 91.4%), 7.5 min (unidentifiable isomer, 2.0%).

**Scheme 2**[a]




[a] Reaction conditions: (a) Cbz-Cl, $K_2CO_3$, toluene, $H_2O$; (b) MsCl, $NEt_3$, toluene; (c) PhSH, NaOH, $Bu_4NBr$, toluene, $H_2O$; (d) HCl, MeOH, $H_2O$; (e) PNB-Cl, 2-picoline, AcOEt; (f) MsCl, $NEt_3$, AcOEt; (g) KOH, 1,4-dioxane, $H_2O$; (h) $K_2CO_3$, $H_2O$, MeOH.

genolysis condition, benzoic acid acts not only as an accelerator of hydrogenolysis but also as an acid that makes the product into a salt of fine crystals, so that removal of other undesired minor isomers is effectively carried out. The production procedure of **1a** does not involve any hazardous reagents, low temperature reaction conditions, strictly dry conditions, or purification by column chromatography. Hence, **1a** has been produced on 1 kg-scale in 74% yield from **7**, which is readily accessible from commercially available *cis*-2-butene-1,4-diol,[17] through a process involving three steps. **1a** was similarly obtained in 73% yield from **7**, through **9** and **13**. The asymmetric centers of **9** were induced from catalytic amount of (*S*)-1,1′-bi-2-naphthol as a sole chiral source.[14] The antipode **1b** was also similarly obtained from the enantiomer of **9** which was obtained using Ti−(*R*)-1,1′-bi-2-naphthoxide complex as a chiral catalyst.

The versatility of **1a** and **1b** was demonstrated by their stereospecific transformation into epoxide **18** and **22**, and into their enantiomers, respectively. **18** was reported to be a key intermediate of nelfinavir **2**.[12] Biologically less active isomers **3**, **4** and **5** were obtained from **22**, enantiomer of **18**, and that of **22**, respectively.

Transformation of **1a** into **18** was performed as shown in Scheme 2. Protection of the amino group of **1a** with CbzCl in a bilayer system gave **11**, which was then

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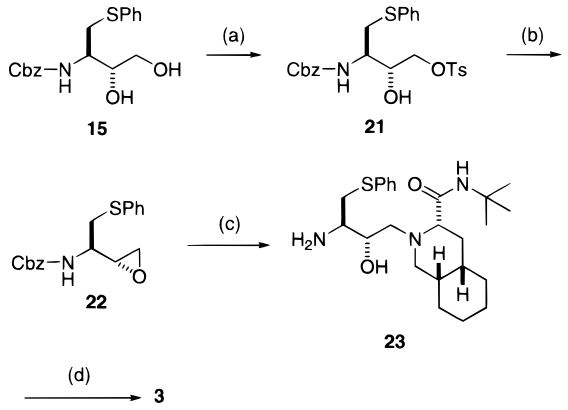
**Scheme 3**[a]




[a] Reaction conditions: (a) TsCl, pyridine; (b) KOH, 2-propanol, $H_2O$; (c) **19**, MeOH, reflux, then KOH; (d) (i) 3-acetoxy-2-methylbenzoyl chloride, $NaHCO_3$, AcOEt, $H_2O$, (ii) $NH_3$, MeOH.

successively treated with MsCl and PhSH providing sulfide **14** in a one-pot fashion. The acetonide protection was removed by the action of HCl in aqueous MeOH to give **15**. Transformation of **1a** into **15** involved no purification procedure, and crude **15** was used for the next reaction. The quantitative HPLC analysis suggested that the yield of **15** was more than 95% from **1a**. Since transformation of **15** into **18** required stereochemical inversion of the secondary hydroxyl group of **15**, this group was converted to a leaving group by treatment with MsCl after protection of the primary hydroxyl group with 4-nitrobenzoyl chloride (PNBCl) in the presence of 2-picoline. These sequential processes were carried out in a one-pot fashion without isolation of the intermediate **16**. The yield of mesylate **17** was 80−84% from **1a** after purification by recrystallization. HPLC indicated that the regioselectivity of the protection of the primary hydroxyl group was 93−95%. The selectivity was lower than 80% when $NEt_3$ or pyridine was used as a base in place of 2-picoline. The advantages of using a PNB group as a protective group were the efficient isolation of **17** by recrystallization and the facile saponification of the ester in the next step. Alkaline treatment of **17** promoted hydrolysis of the PNB group and the spontaneous ring closure giving epoxide **18** in 98%, which was reported to be efficiently converted to nelfinavir **2** through intermediate **20**[18] in three steps.[12] Alternatively, it was also successful to obtain **20** from **17** without isolation of **18**. When **17** was treated with $K_2CO_3$ in the presence of amine **19**[19] in aqueous MeOH, **20** was precipitated out from the reaction mixture as fine crystals in 86% yield.

Epoxide **22** was obtained by selective sulfonylation of the primary hydroxyl group of **15** followed by alkaline treatment (Scheme 3). Thus, treatment of **15** with TsCl gave **21** in 75% and subsequent alkaline treatment gave **22** in 92%. Ring-opening of **22** with **19** followed by removal of the Cbz group afforded **23** in 74%. Coupling of **23** with 3-acetoxy-2-methylbenzoyl chloride[13] and successive removal of the acetyl group gave **3** in 74% yield. The stereochemistry of **23** was confirmed by X-ray crystallographic analysis to verify the stereochemistry of

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**22**.[20] The other stereoisomers, i.e., **4** and **5**, were similarly and specifically prepared from the enantiomer of **18** and that of **22** in 69% and 80%, respectively.[21]

## Conclusion

Isomerically pure **1a** was produced on a 1 kg-scale via five steps from commercially available *cis*-2-butene-1,4-diol in more than 60% yield without chromatography purification. **1** was demonstrated to be a versatile chiral C4 building block for 2-amino-1,3,4-butanetriol of a variety of absolute and relative stereochemical structures by selective treatments of its three hydroxyl groups and an amino group. Especially, **1a** was shown to be suitable building block for the construction of 2-aminoalkanol moiety of aspartic protease inhibitors such as an HIV protease inhibitor **2**. It is also expected that **1a** and **1b** will be used for the synthesis of other biologically active compounds containing chiral 2-aminoalkanol component(s).[1−5]

## Experimental Section

**General.** All melting points are uncorrected. The $^1$H NMR spectra were recorded at 300 MHz unless otherwise noted. Solvents, starting materials and reagents were used as purchased without further purification. Silica gel 60 (230−400 mesh, Merck) was used for column chromatography.

**(1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium Benzoate (1a).** To a mixture of **8**[13,14] (1.00 kg, 3.77 mol), 2,2-dimethoxypropane (39.3 g, 377 mmol), and acetone (2.00 L) was added MsOH (435 g, 4.52 mol) over 25 min with stirring (<25 °C). After stirring for 4 h, the reaction mixture was poured into a solution of $K_2CO_3$ (625 g, 4.52 mol) in water (3.00 L), and the product was extracted with toluene (3.00 L). The organic layer was concentrated to give a crude oily residue, which was mainly comprised of **12**. This crude material was diluted with 2-propanol (6.00 L) and hydrogenated (5% Pd−C (100 g, 50% wet type) with $H_2$ (5 kg/cm$^2$), 60 °C, 9 h) in the presence of benzoic acid (460 g, 3.77 mol). Then the catalyst was removed, and then the filtrate was concentrated so that the crude residue contained 1.1 L of 2-propanol. To the residue was added heptane (10.0 L) at 55−60 °C, and the resulting solution was stirred at 0−5 °C for 1 h. Deposited crystals were collected by filtration to give **1a** (879 g, 82% from **8**) as colorless crystals: mp 112−113 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.99 (m, 2H), 7.44 (m, 1H), 7.34 (m, 2H), 6.33 (br s, 3H), 4.18 (td, 1H, $J$ = 6.2, 7.7 Hz), 4.01 (dd, 1H, $J$ = 6.6, 8.4 Hz), 3.78 (dd, 1H, $J$ = 3.7, 12.5 Hz), 3.70 (dd, 1H, $J$ = 5.9, 8.8 Hz), 3.63 (dd, 1H, $J$ = 6.2, 12.5 Hz), 3.12 (m, 1H), 1.32 (s, 3H), 1.24 (s, 3H); IR (KBr) 2983, 1610, 1517, 1393, 1048 cm$^{-1}$; $[\alpha]^{25}_D$ +2.8 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.11; H, 7.65; N, 4.98. **1a** was similarly obtained in 73% form **7** via **9**.[14]

**(2*S*)-2-Benzyloxycarbonylamino-2-[(4*R*)-2,2-dimethyl-1,3-dioxolane-4-yl]ethanol (11).** To a mixture of toluene (3.85 L), water (3.85 L), and $K_2CO_3$ (470 g, 3.40 mol) were successively added **1a** (770 g, 2.72 mol) and CbzCl (488 g, 2.72 mol) with vigorous stirring at a temperature below 25 °C. After stirring at room temperature for 3 h, triethylamine (27.5 g, 270 mmol) and NaCl (578 g) were successively added, and the mixture was stirred for a further 30 min. The organic layer was separated and concentrated to give **11** as oil, which was used for the next reaction without purification. The analytical sample was prepared by column chromatography; $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.29 (m, 5H), 5.32 (br d, 1H, $J$ = 5.5 Hz), 5.15 (d, 1H, $J$ = 12.2 Hz), 5.09 (d, 1H, $J$ = 12.2 Hz), 4.34 (m, 1H), 4.05 (t, 1H, $J$ = 7.5 Hz), 3.84−3.70 (m, 4H), 2.54 (br s, 1H), 1.42 (s, 3H), 1.35 (s, 3H); IR (neat) 3440, 1703, 1530, 1216, 1069 cm$^{-1}$; $[\alpha]^{25}_D$ −23.5 (*c* 1.02, MeOH); HRMS (FAB) calcd for $C_{15}H_{23}NO_5$ 296.1498, found 296.1491.

**(1*R*)-1-Benzyloxycarbonylamino-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-phenylthioethane (14).** To a mixture of crude **11** (prepared from **1a** (770 g, 2.72 mol)), toluene (7.00 L), and triethylamine (330 g, 3.26 mol) was added MsCl (342 g, 2.99 mol) at a temperature below 10 °C over 30 min, and the mixture was stirred at this temperature for 1.5 h. Then, thiophenol (335 mL, 3.26 mol), NaOH (250 g, 3.25 mol), $Bu_4$-NBr (17.5 g, 54.4 mmol), and water (3.08 L) were successively added under a nitrogen atmosphere. The mixture was stirred at 55 °C for 2.5 h and cooled to room temperature, and the aqueous layer was split off. The organic layer was successively washed with 1 M NaOH and 1 M HCl, and concentrated to give **14** as colorless oil (1.93 kg), which was used for the next reaction without purification. An analytically pure sample was prepared by recrystallization from hexane/diethyl ether: mp 64−65 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.43−7.15 (m, 10H), 5.16 (d, 1H, $J$ = 12.5 Hz), 5.12 (br s, 1 H), 5.98 (d, 1H, $J$ = 12.5 Hz), 4.50 (td, 1H, $J$ = 6.9, 1.8 Hz), 3.99 (m, 1H), 3.86 (m, 1H), 3.66 (dd, 1H, $J$ = 8.1, 7.0 Hz), 3.24 (dd, 1H, $J$ = 13.8, 5.9 Hz), 3.04 (dd, 1H, $J$ = 13.8, 8.6 Hz), 1.42 (s, 3H), 1.30 (s, 3H); IR (KBr) 3308, 2986, 1688, 1540, 1262 cm$^{-1}$; $[\alpha]^{25}_D$ −78.6 (*c* 0.99, EtOH). Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.12; H, 6.56; N, 3.56.

**(2*R*,3*R*)-3-Benzyloxycarbonylamino-4-phenylthio-1,2-butanediol (15).** To a solution of crude **14**, prepared from **1a** (770 g, 2.72 mol), in MeOH (4.20 L) were successively added water (1.05 L) and concd HCl (11.3 mL, 136 mmol). The resultant bilayer system was heated to reflux for 3.5 h, affording a clear solution. Then the reaction mixture was concentrated and mixed with water (3.16 L) containing $NaHCO_3$ (9.13 g, 109 mmol) and NaCl (790 g). The deposited oily product was extracted with AcOEt (5.27 L). Then the organic phase was concentrated to give a residue, which was diluted with AcOEt (3.00 L) and concentrated again to remove MeOH and moisture, affording **15** as colorless oil. This crude material was used for the next reaction without purification. An analytically pure sample was obtained by recrystallization from toluene: mp 73−74 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.51−7.22 (m, 10H), 5.27 (br d, 1H, $J$ = 8.8 Hz), 5.09 (s, 2H), 4.01 (m, 1H), 3.86 (m, 1H), 3.54−3.53 (m, 2H), 3.21 (dd, 1H, $J$ = 13.7, 6.7 Hz), 3.12 (dd, 1H, $J$ = 13.7, 7.5 Hz), 2.58 (br s, 1H), 2.47 (br s, 1H); IR (KBr) 3306, 2934, 1693, 1428, 1049 cm$^{-1}$; $[\alpha]^{25}_D$ −46.9 (*c* 1.00, EtOH). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.39; H, 6.09; N, 3.99.

**(2*R*,3*R*)-3-Benzyloxycarbonylamino-4-phenylthio-2-methanesulfonyloxy-1-(4-nitrobenzoyloxy)butane (17).** To a solution of crude **15**, prepared from **1a** (770 g, 2.72 mol), in AcOEt (6.61 L) were successively added 2-picoline (329 g, 3.53 mol) and 4-nitrobenzoyl chloride (605 g, 3.26 mol) at a temperature below 10 °C. The mixture was stirred at 5−10 °C for 8.5 h under a nitrogen atmosphere, and methanesulfonyl chloride (374 g, 3.26 mol) was added. Then, triethylamine (660 g, 6.52 mol) was added dropwise to the mixture at a temperature below 15 °C, and the mixture was stirred for 30 min. The reaction was stopped by the addition of MeOH (87.1 g, 2.27 mol), followed by stirring at ambient temperature for 1.5 h. The mixture was successively washed with 1 M HCl (5.67 L), 8% aqueous $NaHCO_3$ (5.67 L), and water (2.83 L) and was refluxed for 1 h in the presence of activated carbon (46.9 g). Insoluble material was removed, and the filtrate was concentrated to give a yellow solid. Recrystallization of this material from AcOEt (3.0 L)/heptane (12.0 L) followed by rinsing with MeOH (4.72 L) gave **17** (1.31 kg, 84.0% yield from **1a**) as pale yellow crystals: mp 117−118 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.24 (d, 2H, $J$ = 8.7 Hz), 8.12 (d, 2H, $J$ = 8.7 Hz), 7.44−7.21 (m, 10H), 5.44 (ddd, 1H, $J$ = 6.9, 5.1, 2.3 Hz), 5.11 (s, 2H), 5.09 (br d, 1H, $J$ = 9.5 Hz), 4.57 (dd, 1H, $J$ = 12.0, 6.9 Hz), 4.50 (dd, 1H, $J$ = 12.0, 5.1 Hz), 4.21 (m, 1H), 3.25 (dd, 1H, $J$ = 14.0, 6.2 Hz), 3.05 (s, 3H), 3.05 (dd, 1H, $J$ = 14.0, 8.2 Hz); IR (KBr) 1725, 1699, 1531, 1349, 1283 cm$^{-1}$; $[\alpha]^{25}_D$ −13.4 (*c* 1.00, $CHCl_3$).

(20) See Supporting Information. The atomic coordinates have been deposited with Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(21) The enantiomer of **18** and that of **22** were obtained from **1b** by the identical methods to those used in the preparation of **18** and **22** from **1a**, respectively.

Anal. Calcd for $C_{26}H_{26}N_2O_9S_2$: C, 54.35; H, 4.56; N, 4.88. Found: C, 54.47; H, 4.42; N, 4.90.

**(2*S*,3*R*)-3-Benzyloxycarbonylamino-4-phenylthio-1-buteneoxide (18).**[12] To a solution of **17** (3.78 g, 6.58 mmol) in 1,4-dioxane (30 mL) was added 2 M aqueous KOH (7.30 mL), and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with water (50 mL) and extracted with toluene (50 mL). The organic layer was separated, successively washed with aqueous $NaHCO_3$ and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a colorless solid. Column chromatography purification afforded **18** (2.12 g, 98%) as colorless crystals: mp 61−62 °C (ether/hexane); $^1$H NMR ($CDCl_3$−$D_2O$) $\delta$ 7.40−7.17 (m, 10H), 5.11 (d, 1H, $J$ = 12.1 Hz), 5.06 (d, 1H, $J$ = 12.1 Hz), 3.70 (m, 1H), 3.22 (d, 2H, $J$ = 5.6 Hz), 2.99 (m, 1H), 2.80−2.71 (m, 2H); IR (KBr) 3302, 1694, 1538, 1256, 1028 cm$^{-1}$; $[\alpha]^{25}_D$ −26.2 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.36; H, 5.85; N, 4.33.

**(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(2*R*,3*R*)-3-benzyloxycarbonylamino-2-hydroxy-4-(phenylthio)butyl]decahydroisoquinoline-3-carboxamide (20).**[12,18] To a suspension of **17** (1.30 kg, 2.26 mol) in 67% MeOH (11.7 L) were successively added **19**[19] (539 g, 2.26 mol) and $K_2CO_3$ (641 g, 4.64 mol) at room temperature. The mixture was stirred at 60 °C for 7 h, water (3.90 L) was added to the suspension at 60−55 °C. After cooling to room temperature, deposited crystals were collected by centrifugation, washed successively with 33% MeOH (3.90 L) and water (3.90 L), and dried to give **20** (1.102 kg, 86% yield from **17**) as colorless crystals: mp 138−140 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.39−7.13 (m, 10H), 5.91 (br d, 1H, $J$ = 8.1 Hz), 5.68 (s, 1H), 5.08 (d, 1H, $J$ = 12.5 Hz), 5.03 (d, 1H, $J$ = 12.5 Hz), 4.05−3.94 (m 2H), 3.42 (br s, 1H), 3.39 (br s, 1H), 3.13 (br s, 1H), 2.91 (br d, 1H, $J$ = 11.4 Hz), 2.60 (dd, 1H, $J$ = 7.7, 13.2 Hz), 2.50 (dd, 1H, $J$ = 2.9, 11.0 Hz), 2.22 (dd, 1H, $J$ = 5.5, 13.2 Hz), 2.19 (dd, 1H, $J$ = 2.6, 11.6 Hz), 1.96 (q, 1H, $J$ = 12.5 Hz), 1.80−1.18 (m, 11H), 1.30 (s, 9H); IR (KBr) 3333, 2927, 1711, 1638, 1543 cm$^{-1}$; $[\alpha]^{25}_D$ −82.3 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{32}H_{45}N_3O_4S$: C, 67.69; H, 7.99; N, 7.40. Found: C, 67.84; H, 8.18; N, 7.48.

**(2*R*,3*R*)-1-(4-Methylbenzenesulfonyloxy)-3-benzyloxycarbonylamino-2-hydroxy-4-(phenylthio)butane (21).** To a solution of **15** (21.8 g, 62.7 mmol) in pyridine (140 mL) was added *p*-toluenesulfonyl chloride (12.0 g, 62.7 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and at room temperature for 4 h. Then the mixture was concentrated to give a viscous residue that was diluted with AcOEt (300 mL). The mixture was successively washed with 2 M aqueous HCl (300 mL), water (200 mL), aqueous $NaHCO_3$ (200 mL), and brine (200 mL), dried over $MgSO_4$, and evaporated to dryness. Recrystallization of the residue from hexane/AcOEt gave **21** (21.1 g, 67%) as colorless crystals: mp 113−114 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.75 (d, 2H, $J$ = 8.2 Hz), 7.42−7.19 (m, 12H), 5.19 (br d, 1H, $J$ = 8.7 Hz), 5.07 (d, 1H, $J$ = 10.3 Hz), 5.05 (d, 1H, $J$ = 10.3 Hz), 4.27 (br s, 1H), 4.06−3.93 (m, 2H), 3.72 (br q, 1H, $J$ = 7.9 Hz), 3.19 (dd, 1H, $J$ = 5.9, 13.9 Hz), 3.09 (dd, 1H, $J$ = 8.2, 13.5 Hz), 2.93 (br s, 1H), 2.44 (s, 3H); IR (KBr) 3529, 3313, 1692, 1347, 1265, 1172 cm$^{-1}$; $[\alpha]^{25}_D$ −16.0 (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{25}H_{27}NO_6S_2$: C, 59.86; H, 5.43; N, 2.79. Found: C, 60.32; H, 5.40; N, 2.79. The additional amount of **21** (2.52 g, 8%) was isolated from the filtrate by column chromatography.

**(2*R*,3*R*)-3-Benzyloxycarbonylamino-4-phenylthio-1-buteneoxide (22).** To a solution of **21** (20.6 g, 41.1 mmol) in 2-propanol (210 mL) was added 2 M aqueous KOH (41 mL) at room temperature. After the reaction was stirred for 1 h, water (200 mL) was added and the product was extracted with toluene (250 mL × 2). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated to a give a viscous residue. This material was purified by column chromatography (hexane:AcOEt = 4:1−3:1) to give **22** (12.4 g, 92%) as a colorless solid: mp 58−59 °C (ether/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.43−7.16 (m, 10H), 5.09 (s, 2H), 4.88 (br s, 1H), 4.11 (m, 1H), 3.30−3.23 (m, 2H), 3.11 (dd, 1H, $J$ = 7.6, 13.6 Hz), 2.75 (t, 1H, $J$ = 4.2 Hz), 2.62 (dd, 1H, $J$ = 2.6, 4.3 Hz); IR (KBr) 3306, 2954, 1694, 1537, 1245 cm$^{-1}$; $[\alpha]^{25}_D$ +54.3 (*c* 1.00, EtOH). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.73; H, 5.75; N, 4.20.

**(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(2*S*,3*R*)-3-amino-2-hydroxy-4-(phenylthio)butyl]decahydroisoquinoline-3-carboxamide (23).** A mixture of **22** (6.84 g, 20.8 mmol) and **19** (4.95 g, 20.8 mmol) in 2-propanol (100 mL) was stirred at 80 °C for 4 h. Then 2 M aqueous KOH (48 mL) was added, and the mixture was again stirred at 80 °C for 18 h. The reaction mixture was concentrated to 1/3 volume and diluted with water (100 mL). The deposited product was extracted with AcOEt (100 mL × 2). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Purification of the residue by column chromatography ($CHCl_3$:MeOH = 10:1) gave **23** (6.68 g, 74%) as colorless crystals. Recrystallization from a mixed solvent (hexane and toluene) gave fine crystals that were used for X-ray crystallographic analysis:[20] mp 150−152 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.37−7.33 (m, 2H), 7.30−7.24 (m, 2H), 7.19 (m, 1H), 6.21 (br s, 1H), 3.70 (ddd, 1H, $J$ = 3.0, 3.3, 10.5 Hz), 3.41 (br s, 1H), 3.16 (dd, 1H, $J$ = 4.6, 13.4 Hz), 2.88 (dd, 1H, $J$ = 8.5, 13.3 Hz), 2.84 (dd, 1H, $J$ = 2.0, 11.5 Hz), 2.71−2.59 (m, 3H), 2.13 (dd, 1H, $J$ = 3.3, 11.5 Hz), 1.98 (dd, 1H, $J$ = 2.6, 12.7 Hz), 1.94−1.70 (m, 4H), 1.68−1.15 (m, 7H), 1.34 (s, 9H); IR (KBr) 3277, 2928, 1640, 1479, 1454 cm$^{-1}$; $[\alpha]^{25}_D$ −119.3 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{24}H_{39}N_3O_2S$: C, 66.47; H, 9.06; N, 9.69. Found: C, 66.87; H, 9.29; N, 9.57.

**(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(2*S*,3*R*)-2-hydroxy-3-(3-hydroxy-2-methylbenzoylamino)-4-(phenylthio)butyl]-decahydroisoquinoline-3-carboxamide (3).** To a solution of **23** (3.04 g, 7.02 mmol) in AcOEt (30 mL) were added water (30 mL) and $NaHCO_3$ (3.40 g, 40.5 mmol). A solution of 3-acetoxy-2-methylbenzoyl chloride (freshly prepared from 3-acetoxy-2-methylbenzoic acid (1.56 g, 8.04 mmol))[13] in AcOEt (20 mL) was added to the bilayer system with stirring at 0 °C. After the reaction was stirred at room temperature for 1.5 h, the organic phase was diluted with AcOEt (20 mL) and separated. The organic phase was washed with aqueous NaCl (30 mL), dried over $MgSO_4$, and then evaporated to dryness. The colorless amorphous material was dissolved in MeOH (50 mL), and 28% aqueous $NH_3$ (6.2 mL) solution was added at room temperature. After stirring for 3 h, the mixture was evaporated. The residue was suspended in water (50 mL) and extracted with $CHCl_3$ (50 mL × 2). The combined organic layers were dried over $MgSO_4$ and evaporated to give a viscous residue that was then purified by column chromatography ($CHCl_3$:MeOH = 50:1) to give a colorless amorphous material. This material was suspended in AcOEt (50 mL), refluxed for 1 h, and cooled to room temperature. Deposited crystals were collected by filtration to give **3** (2.84 g, 74%) as colorless crystals: mp 193−195 °C; $^1$H NMR ($CD_3OD$) $\delta$ 7.46−7.41 (m, 2H), 7.33−7.26 (m, 2H), 7.23−7.17 (m, 1H), 7.00 (t, 1H, $J$ = 7.8 Hz), 6.82−6.78 (m, 2H), 4.12−4.02 (m, 2H), 3.26 (dd, 1H, $J$ = 6.0, 13.8 Hz), 3.18 (dd, 1H, $J$ = 8.1, 13.8 Hz), 2.88 (dd, 1H, $J$ = 2.1, 11.4 Hz), 2.62 (dd, 1H, $J$ = 3.3, 11.1 Hz), 2.51 (dd, 1H, $J$ = 10.2, 12.9 Hz), 2.22 (s, 3H), 2.19 (dd, 1H, $J$ = 3.0, 11.4 Hz), 2.07 (dd, 1H, $J$ = 2.4, 13.2 Hz), 2.00−1.20 (m, 12H), 1.25 (s, 9H); IR (KBr) 3422, 2928, 1643, 1538, 1361 cm$^{-1}$; $[\alpha]^{25}_D$ −149.9 (*c* 0.99, MeOH). Anal. Calcd for $C_{32}H_{45}N_3O_4S$: C, 67.62; H, 7.99; N, 7.40. Found: C, 67.51; H, 8.11; N, 7.28.

**(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(2*S*,3*S*)-2-hydroxy-3-(3-hydroxy-2-methylbenzoylamino)-4-(phenylthio)butyl]-decahydroisoquinoline-3-carboxamide (4).** The similar procedure, used in the preparation of **3**, gave **4** (69% from the enantiomer of **18**) as a colorless amorphous material: $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.36 (m, 2H), 7.30−7.14 (m, 3H), 7.18 (br s, 1H), 6.95 (t, 1H, $J$ = 7.7 Hz), 6.84 (dd, 1H, $J$ = 1.1, 8.1 Hz), 6.81 (dd, 1H, $J$ = 1.1, 7.3 Hz), 6.38 (br d, 1H, $J$ = 8.8 Hz), 6.16 (br s, 1H), 4.20 (br s, 1H), 4.15 (m, 1H), 3.91 (m, 1H), 3.28−3.18 (m, 2H), 2.80 (br d, 1H, $J$ = 11.4 Hz), 2.63 (br d, 1H, $J$ = 11.0 Hz), 2.54 (br t, 1H, $J$ = 11.0 Hz), 2.16 (s, 3H), 2.18−2.12 (m, 2H), 1.99−1.14 (m, 12H), 1.35 (s, 9H); IR (KBr) 3304, 2926, 1648, 1528, 1285 cm$^{-1}$; $[\alpha]^{25}_D$ −2.29 (*c* 1.09, MeOH). HRMS (FAB) calcd for $C_{32}H_{46}N_3O_4S$ 568.3209, found 568.3217.

**(3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyl-2-[(2*R*,3*S*)-2-hydroxy-3-(3-hydroxy-2-methylbenzoylamino)-4-(phenylthio)butyl]-

**decahydroisoquinoline-3-carboxamide (5).** The similar procedure, used in the preparation of **3**, gave **5** (80% from the enantiomer of **22**) as a colorless amorphous material: $^1$H NMR ($CDCl_3$) $\delta$ 7.46−7.41 (m, 2H), 7.32−7.25 (m, 2H), 7.16 (m, 1H), 7.02 (br d, 1H, $J$ = 8.3 Hz), 6.96 (t, 1H, $J$ = 7.6 Hz), 6.92 (dd, 1H, $J$ = 1.5, 7.6 Hz), 6.79 (dd, 1H, $J$ = 1.4, 7.7 Hz), 5.81 (br s, 1H), 4.13 (br t, 1H, $J$ = 7.0 Hz), 4.02 (br q, 1H, $J$ = 7.5 Hz), 3.53 (dd, 1H, $J$ = 6.9, 13.9 Hz), 3.34 (dd, 1H, $J$ = 7.5, 13.9 Hz), 2.72 (dd, 1H, $J$ = 2.5, 11.7 Hz), 2.53 (dd, 1H, $J$ = 3.0, 10.8 Hz), 2.49 (dd, 1H, $J$ = 6.6, 13.2 Hz), 2.33−2.21 (m, 2H), 2.24 (s, 3H), 1.92 (m, 1H), 1.76−1.05 (m, 11H), 1.27 (s, 9H); IR (KBr) 3339, 2925, 1647, 1585, 1519 cm$^{-1}$; $[\alpha]^{25}_D$ +10.9 (*c* 1.09, MeOH). HRMS (FAB) calcd for $C_{32}H_{46}N_3O_4S$ 568.3209, found 568.3197.

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**Supporting Information Available:** Crystal structure data for **23** and 300 MHz $^1$H NMR spectra of **4**, **5**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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