Catalytic Asymmetric Aminolysis of 3,5,8-Trioxabicyclo[5.1.0]octane Providing an Optically Pure 2-Amino-1,3,4-butanetriol Equivalent

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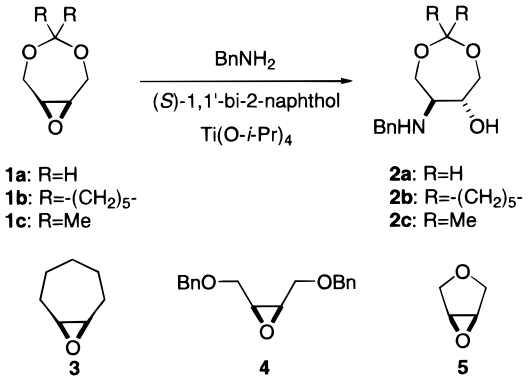
The catalytic asymmetric ring opening of meso epoxides[1] is becoming a powerful tool in the field of synthetic chemistry, and there have been many reports of success using thiols,[2] carboxylic acids,[3] azides,[4] cyanides,[5] halides,[6] phenols,[7] and anilines[2b,8] as nucleophiles. To the best of our knowledge, however, there has been no report employing an alkylamine as a nucleophile irrespective of the utility of the resulting chiral β-amino alcohol for various synthetic purposes.[9] A likely obstacle to achieving a catalytic asymmetric aminolysis of meso epoxides is deactivation of the chiral Lewis acid catalyst, by stable complex formation with an amine used as a nucleophile and/or with a generated β-amino alcohol, resulting in the inability to activate the epoxide.[4a] Nucleophiles employed previously are generally less basic than an alkylamine. Here, we report the catalytic desymmetrization of 3,5,8-trioxabicyclo[5.1.0]octane derivatives **1** using α-substituted or unsubstituted benzylamines as nucleophiles, in which **1** coordinates to a chiral Lewis acid so efficiently in the presence of the amines that very low catalyst loading (<1%) is sufficient for high ee and conversion. The reaction provides optically pure 2-amino-1,3,4-butanetriol equivalents (ABTE), versatile chiral C4 building blocks bearing a substituted or unsubstituted amino group and three hydroxyl groups.

Table 1. Aminolysis[a] of Epoxides with Benzylamine

entry	epoxide	cat.[b] (mol %)	product	convn (%) after 24 h	ee (%)[c]
1	**1a**	1.0	**2a**[d]	55.7[e]	20.0
2	**1b**	1.0	**2b**[d]	79.9[e]	92.0
3	**1c**	1.0	**2c**[d]	94.3[e]	93.2
4	**1c**	0.75	**2c**	93.7[e]	90.6
5	**1c**	0.5	**2c**	85.5[e]	86.2
6	**3**	1.0		<5[f]	
7	**4**	1.0		<5[f]	
8	**5**	1.0		< 5[f]	

[a] All reactions were performed using 1.0 equiv of benzylamine in the presence of 10 mol % of water in toluene at 40 °C. [b] The catalyst was composed of (S)-1,1′-bi-2-naphthol and Ti(O-*i*-Pr)$_4$ (1:1 ratio). [c] Determined by HPLC. [d] The absolute configuration was determined as described in the Supporting Information. [e] HPLC peak area ratio (**2**/(**2**+benzylamine) at 214 nm), calibrated by the molar UV intensity ratio, was used for the conversion. [f] No new peak was observed in the 300 MHz ^{1}H NMR spectrum of the crude extract.

When epoxides **1a**−**c** possessing a ketal group were treated with benzylamine in the presence of catalytic amounts of (*S*)-1,1′-bi-2-naphthol and Ti(O-*i*-Pr)$_4$ and 10 mol % of water[10] relative to epoxide in toluene,[11] smooth reactions took place affording the corresponding amino alcohols **2a**−**c** (Table 1). Particularly, excellent asymmetric induction was observed in the reactions of epoxides (**1b** and **1c**) having alkyl substituents (R) on the ketal carbon (entries 2 to 5, Table 1). In sharp contrast to **1**, when **3**, **4**, and **5** were used as the substrates, no reaction was observed (entries 6−8, Table 1). Molecular modeling studies[12] of **1c** and **5** provided insight into possible reasons for this dramatic difference. The most



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(10) The importance of water in the Lewis acid promoted reaction was previously reported, see: Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. When **1c** was subjected to the similar conditions of entry 3 in Table 1 with exclusion of water (0.01 mol %, Karl Fischer), the conversion of the reaction and ee of product **2c** were 84% and 46%, respectively.

(11) Using an aprotic solvent was crucial to prevent the noncatalyzed reaction. No reaction was observed when the epoxides (**1a**, **1c**, and **5**) were treated with the amines (benzylamine and **6**) in the absence of the catalyst in toluene or heptane.

(12) Computational results were obtained using software programs from MSI of San Diego—MD and MM calculations were conducted with the Discover program, using the CFF91 (for **1c** and **5**) and ESFF (for **1c**+**Ti**) force fields. Simulated annealing calculation (via molecular dynamics) was carried out for each compound starting from 100 initial conformations generated by randomizing atom coordinates of the molecules. The structure of **1c**+**Ti** was obtained by the calculation of the **1c**−Ti(OMe)$_4$ complex. The methoxyl groups were omitted for clarity in Figure 1.

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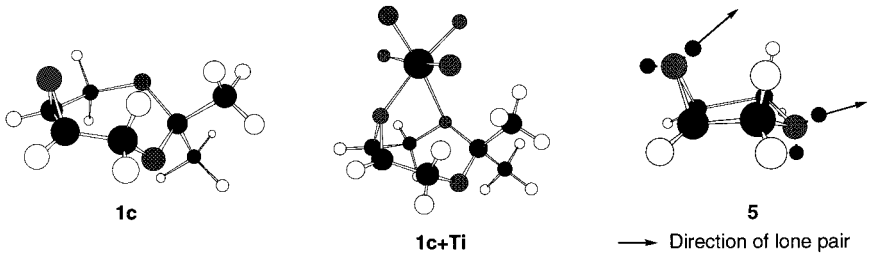
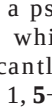


Figure 1. The arrows in **5** are directions of the lone pairs. The structure **1c**+**Ti** was obtained though the calculation of the **1c**−Ti(OMe)$_4$ complex. The four methyl groups were omitted for clarity.

stable conformer, which was obtained through simulated annealing calculation of **1c**, was the twist-boat form (Figure 1 **1c**). It was rational to assume that the structure of **1c** was suitable for interaction with a Ti atom, because the most stable Ti-coordinated structure of **1c** (Figure 1, **1c**+**Ti**) was close to that of **1c** in conformation.[13] The structure of **1c**+**Ti** indicated that the direction of the lone pair on one of the two ketal oxygen atoms and that of the epoxide oxygen fitted well in the geometry of chelating titanium atom, which should assume a typical tetragonal bipyramidal structure.[14] Hence **1c** was considered to preferentially coordinate to a titanium atom in a bidentate fashion to form an activated complex of **1c**+**Ti** leading to **2c**. However, the unreactive compound **3** could not assume such a bidentate coordination because of the absence of a supplementary oxygen atom. The epoxide **4**, which possesses both oxygen atoms could be unreactive because it was speculated not to assume a conformation having an effective bidentate coordination without a severe decrease in entropy. Calculation of unreactive **5** showed that a pseudo-chair form was the most stable conformer in which the directions of the oxygen lone pairs significantly deviated from the assumed O−Ti bonds (Figure 1, **5**+**Ti**). These findings allow us to speculate that bidentate titanium complex formation with the assistance of a ketal oxygen atom is necessary to promote the catalytic asymmetric aminolysis.[15] It is proposed that enantiomeric discrimination of one of two acetal oxygen atoms by the (*S*)-1,1′-bi-2-naphthol−titanium complex is responsible for the asymmetric induction in the reaction of **1**. When R in **1** was a hydrogen atom (**1a**), the discrimination of one of two acetal oxygen atoms seemed to be less effective, resulting in the lower ee of product **2a** (entry 1, Table 1). This fact implies that the alkyl substituents on the ketal carbon favorably interact with the chiral Lewis acid to enhance the stereoselectivity.

With the intention of increasing the stereoselectivity, the reaction of **1c** with α-substituted and disubstituted benzylamines (**6a**−**c**) was investigated (Table 2). Enantioselectivity decreased when **1c** was opened using dimethylbenzylamine (**6a**, 70.8% ee) or benzhydrylamine (**6b**, 89% ee). However, employment of the α-methylbenzylamine ((*R*)- or (*S*)-**6c**) brought about an increase of stereoselectivity (entry 3, Table 2), and using a solvent composed of heptane−toluene (9/1) was effective in retaining excellent conversion (entries 4, 5, and 6, Table 2). It is worth noting that the reaction of **1c** with (*R*)- and (*S*)-**6c** gave **7c**[16] and **7d**, respectively, *with the same stereochemical mode at the newly formed asymmetric centers in >97% de and excellent yield using the 0.5 mol % catalysts* (entries 5 and 6, Table 2). These results indicated that the enantioselectivity was not affected by the configuration of **6c** but rather by that of (*S*)-1,1′-bi-2-naphthol. Use of racemic **6c** gave the same result. Removal of the substituted benzyl group from the product (a 1:1 diastereomeric mixture of **7c** and **7d**) followed by recrystallization gave optically pure **8**[16] in 84% from racemic **6c** (entry 7, Table 2).[17]

Table 2. Aminolysis[a] of 1c with 6

entry	amines	cat.[b] (mol%)	solvent	product	conv.[c] (%)	ee or de[d]
1	 **6a**	1.0	toluene	**7a**[e]	7.4 (42 h)	70.8%ee[f]
2	 **6b**	1.0	toluene	**7b**[e]	97.0 (36 h)	89.8%ee
3	 **(*R*)-6c**	1.0	toluene	**7c**	81.6 (24 h)	97.6%de
4	**(*R*)-6c**	1.0	heptane-toluene (9:1)	**7c**	99.5 (24 h)	97.8%de
5[g]	**(*R*)-6c**	0.5	heptane-toluene (9:1)	**7c**	99.5 (24 h)	97.0%de
6	 **(*S*)-6c**	0.5	heptane-toluene (9:1)	**7d**[e]	96.9 (24 h)	97.6%de
7	 **racemic-6c**	0.5	heptane-toluene (9:1)	**7c** + **7d**	94.9 (24 h)	97.2%ee[f]

[a] All reactions were performed with 1.0 equiv of **6** in the presence of 10 mol % of water at 40 °C. [b] The catalyst was composed of (S)-1,1′-bi-2-naphthol and Ti(O-*i*-Pr)$_4$ (1:1 ratio). [c] HPLC peak area ratio (**7**/(**7**+**6**) at 214 nm), calibrated by the molar UV intensity ratio, was used for the conversion. [d] Determined by HPLC. [e] The absolute configuration was determined as described in the Supporting Information. [f] The ee was that of crude **8** derived from the reaction mixture. [g] When the reaction was performed in the presence of 0.1 mol % of the catalyst, 67.6% de and 6.6% conversion were obtained after 24 h.

(13) The RMS distance between the heavy atoms of **1c** and **1c** in **1c**+**Ti** was 0.26 Å.

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(15) The stable conformations of the products (**2c** and the amino alcohol derived from **5**) indicated that there was no significant difference in the conformation of their β-amino alcohol portions. Therefore, a difference in the dissociation rate of Ti from the products was ruled out as the cause of the dramatic difference in reactivity.

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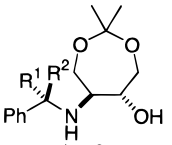
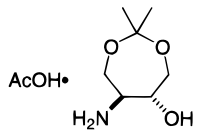


7a: R^1=R^2=Me
7b: R^1=Ph, R^2=H
7c: R^1=H, R^2=Me
7d: R^1=Me, R^2=H



8

In summary, excellent stereoselectivity and yield were observed in the catalytic aminolysis of meso epoxides **1b** and **1c**, which effectively coordinate to a titanium atom. Moreover, this reaction is a practical preparation of optically pure ABTEs, because no hazardous reagents are used and chiral Lewis acid of 0.5 mol % is sufficient to achieve >97% ee as well as excellent conversion. ABTE is a chiral C4 unit, which is expected to be useful in the production of chiral synthetic targets of biological interest.[18]

Experimental Section

General. All melting points are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz. Solvents, starting materials, and reagents were used as purchased without further purification. Silica gel 60 (230−400 mesh, Merck) was used for column chromatography. The enantioselectivity and diastereoselectivity were obtained by HPLC analyses. When reactions became heterogeneous because of the crystallization of products, CH_2Cl_2 was added to obtain clear solutions for HPLC analysis. All HPLC conditions shown below afforded good separations for the determination of ee and de.

(5*R*,6*S*)-2,2-Dimethyl-6-benzylamino-1,3-dioxepan-5-ol (2c). To a solution of (*S*)-1,1′-bi-2-naphthol (19.9 mg, 0.0694 mmol) in toluene (2.0 mL) was added titanium tetraisopropoxide (19.7 mg, 0.0694 mmol) under a nitrogen atmosphere at room temperature. After this mixture was stirred for 10 min, benzylamine (744 mg, 6.94 mmol), water (10 mg), and **1c** (1.00 g, 6.94 mmol) were successively added to the solution and the reaction mixture was stirred at 40 °C for 24 h. There was 94.3% conversion after 24 h according to HPLC (YMC Co., Ltd., AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 17/83, 214 nm, 1.0 mL/min, t_R(benzylamine) = 2.1 min, t_R(**2c**) = 11.7 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.72 (benzylamine/**2c**). The reaction mixture was washed with aqueous 1.0 M NaOH (1.8 mL) and concentrated to dryness. Purification by silica gel column chromatography (hexane−AcOEt) gave **2c** (1.60 g, 92% yield, 93.2% ee) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.33−7.23 (m, 5H), 3.92 (d, 1H, J = 13.2 Hz), 3.82−3.76 (m, 2H), 3.78 (d, 1H, J = 13.2 Hz), 3.59−3.49 (m, 3H), 2.56 (m, 1H), 2.04 (br s, 1H), 1.33 (s, 3H), 1.32 (s, 3H); IR ($CHCl_3$) 3416, 1219, 1047 cm^{-1}; $[\alpha]^{25}_D$ +50.6 (*c* 0.5, MeOH); HRMS (Fab) calcd for $C_{14}H_{22}NO_3$ (M^+ + 1) 252.1594, found 252.1591. t_R(**2c**) = 25.5 min (96.6%), t_R(anti-**2c**) = 23.9 min (3.4%), Shinwa Chemical Industries, Ltd., ULTRON ES-PhCD, 45 °C, MeCN/phosphate buffer (pH 7) = 20/80, 214 nm, 1.0 mL/min. The compound **2c** thus obtained was converted to **9** via **8** to determine its absolute configuration.[19]

(5*R*,6*S*)-6-Benzylamino-1,3-dioxepan-5-ol (2a). This compound was similarly obtained from the reaction of **1a** with benzylamine as pale yellow crystals (51% yield, 20.0% ee): mp 56−58 °C; ^{1}H NMR ($CDCl_3$) δ 7.34−7.24 (m, 5H), 4.75 (d, 1H, J = 4.8 Hz), 4.73 (d, 1H, J = 4.8 Hz), 3.94 (d, 1H, J = 13.2 Hz), 3.88 (dd, 1H, J = 2.2, 10.3 Hz), 3.84 (dd, 1H, J = 2.6, 10.3 Hz), 3.81 (d, 1H, J = 13.2 Hz), 3.77−3.64 (m, 2H), 3.61 (dt, 1H, J = 2.6, 5.1 Hz), 2.86 (dt, 1H, J = 2.2, 5.1 Hz), 2.02 (brs, 1H); IR (KBr) 3134, 1132, 1049 cm^{-1}; $[\alpha]^{25}_D$ +10.3 (*c* 1.0, MeOH). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.64; H, 7.91; N, 6.28. t_R(**2a**) = 8.0 min (60.0%), t_R(anti-**2a**) = 10.1 min (40.0%), Daicel Chemical Industries, Ltd., CHIRAL AGP, 35 °C, 2-propanol/phosphate buffer (pH 7) = 0.5/99.5, 214 nm, 0.5 mL/min. There was 55.7% conversion after 24 h according to HPLC (AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 17/83, 214 nm, 1.0 mL/min, t_R(benzylamine) = 2.1 min, t_R(**2a**) = 5.1 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.70 (benzylamine/**2a**).

(5*R*,6*S*)-2,2-Cyclohexylidene-6-benzylamino-1,3-dioxepan-5-ol (2b). This compound was similarly obtained from the reaction of **1b** with benzylamine as pale yellow crystals (82% yield, 92.0% ee): mp 96−98 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.24 (m, 5H), 3.94 (d, 1H, J = 13.2 Hz), 3.82−3.77 (m, 3H), 3.59−3.48 (m, 3H), 2.56 (br t, 1H, J = 4.0 Hz), 1.90 (brs, 1H), 1.58−1.39 (m, 10H); IR (KBr) 3167, 1118, 1066 cm^{-1}; $[\alpha]^{25}_D$ +45.4 (*c* 1.0, MeOH). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.37; H, 9.05; N, 4.92. t_R(**2b**) = 11.7 min (96.0%), t_R(anti-**2b**) = 15.5 min (4.0%), CHIRAL AGP, 35 °C, 2-propanol/phosphate buffer (pH 7) = 5/95, 214 nm, 0.5 mL/min. There was 79.9% conversion after 24 h according to HPLC (AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 25/75, 214 nm, 1.0 mL/min, t_R(benzylamine) = 2.0 min, t_R(**2b**) = 24.0 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.69 (benzylamine/**2b**).

(5*R*,6*S*)-2,2-Dimethyl-6-(1-methyl-1-phenylethylamino)-1,3-dioxepan-5-ol (7a). This compound was similarly obtained (42 h reaction) from the reaction of **1c** with **6a** as pale yellow crystals (5% yield, 70.8% ee): mp 62−64 °C; ^{1}H NMR ($CDCl_3$) δ 7.49−7.46 (m, 2H), 7.33−7.18 (m, 3H), 3.92 (dd, 1H, J = 0.9, 13.2 Hz), 3.61 (dd, 1H, J = 1.5, 13.2 Hz), 3.46 (ddd, 1H, J = 0.9, 4.2, 12.9 Hz), 3.32 (br t, 1H, J = 4.2 Hz), 3.08 (dd, 1H, J = 4.2, 12.9 Hz), 2.38 (br t, 1H, J = 4.2 Hz), 1.83 (brs, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H); IR (KBr) 3497, 1054, 1030 cm^{-1}; $[\alpha]^{25}_D$ +24.6 (*c* 1.0, MeOH). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.82; H, 9.31; N, 5.10. There was 7.4% conversion after 42 h according to HPLC (AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 25/75, 214 nm, 1.0 mL/min, t_R(**6a**) = 2.5 min, t_R(**7a**) = 13.0 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.67 (**6a**/**7a**). The compound **7a** thus obtained was converted to **9**[19] via **8** to measure its enantiomeric purity: t_R (**9**) = 22.6 min (85.4%), t_R (anti-**9**) = 30.5 min (14.6%), Daicel Chemical Industries, Ltd., CHIRALCEL OD, 35 °C, hexane/2-propanol = 95/5, 210 nm, 1.0 mL/min.

(5*R*,6*S*)-2,2-Dimethyl-6-diphenylmethylamino-1,3-dioxepan-5-ol (7b). This compound was similarly obtained (36 h reaction) from the reaction of **1c** with **6b** as pale yellow crystals (95% yield, 89.8% ee): mp 106−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.44−7.17 (m, 10H), 5.00 (s, 1H), 4.02 (ddd, 1H, J = 3.0, 14.4, 17.1 Hz), 3.82 (d, 1H, J = 11.4 Hz), 3.77 (dd, 1H, J = 1.8, 13.2 Hz), 3.60−3.51 (m, 3H), 2.54 (dt, 1H, J = 1.2, 4.5 Hz), 1.82 (br s, 1H), 1.32 (s, 3H), 1.31 (s, 3H); IR (KBr) 3345, 1218, 1050 cm^{-1}; $[\alpha]^{25}_D$ +42.8 (*c* 0.5, MeOH). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.61; H, 8.05; N, 4.24. t_R(**7b**) = 16.2 min (94.9%), t_R(anti-**7b**) = 14.1 min (5.1%), CHIRAL AGP, 35 °C, 2-propanol/phosphate buffer (pH 7) = 5/95, 214 nm, 0.5 mL/min. There was 97.0% conversion after 36 h according to HPLC (AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 25/75, 214 nm, 1.0 mL/min, t_R(**6b**) = 10.2 min, t_R(**7b**) = 41.8 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.91 (**6b**/**7b**). The compound **7b** thus obtained was converted to **9** via **8** to determine its absolute configuration.[19]

(5*R*,6*S*)-2,2-Dimethyl-6-[(*R*)-1-phenylethylamino]-1,3-dioxepan-5-ol (7c).[16] To a 1 L four-necked round-bottomed flask were added (*S*)-1,1′-bi-2-naphthol (993 mg, 3.47 mmol) and heptane−toluene (9:1, 350 mL). To the suspension was added titanium tetraisopropoxide (986 mg, 3.47 mmol) under a nitrogen atmosphere at room temperature; after the solution was stirred for 10 min, (*R*)-**6c** (84.1 g, 694 mmol), water (1.25 g, 69.4 mmol), and **1c** (100 g, 694 mmol) were added to the solution successively. After stirring at 40 °C for 24 h, toluene (280 mL) was added to

(17) To avoid the problems related to the preferential hydrogenation of some diastereomer, the completion of the reaction was confirmed by TLC.

(18) The ABTE, **8**, was used for the practical synthesis of nelfinavir, a potent HIV protease inhibitor, see ref 16.

(19) (a) The compound **9**, (5*R*,6*S*)-6-benzyloxycarbonylamino-2,2-dimethyl-5-hydroxy-1,3-dioxepan, was obtained by treatment of **8** with Cbz-Cl. See the Supporting Information. (b) **2c**, **7a**, **7b**, and **7d** were converted into **8** using the similar conditions described in the preparation of **8** from the mixture of **7c** and **7d**.

the reaction mixture, which was then stirred at 40 °C for 1 h and at 5 °C for 1 h. Filtration of the deposited crystals gave crude **7c** as bright yellow crystals, which contained trace amounts of (*S*)-1,1′-bi-2-naphthol and titanium. This material was suspended in toluene (526 mL) and was heated to reflux in the presence of 1 M aqueous sodium hydroxide (175 mL) for 1 h. After removal of the aqueous layer while hot (>50 °C), the organic layer was refluxed in the presence of charcoal (3.0 g) for 1 h. The insoluble material in the mixture was removed by filtration while hot (>50 °C), and then the filtrate was concentrated to dryness, affording **7c** (157.1 g, 90% yield and >99%de (HPLC)) as pale yellow crystals. The analytical sample was prepared by recrystallization from heptane/2-propanol: mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 7.33−7.22 (m, 5H), 3.95 (q, 1H, J = 6.5 Hz), 3.75 (dd, 1H, J = 1.8, 12.1?Hz), 3.74 (dd, 1H, J = 2.0, 12.5?Hz), 3.52 (dd, 1H, J = 5.5, 12.5 Hz), 3.48 (ddd, 1H, J = 0.5, 5.9, 12.1 Hz), 3.37 (dt, 1H, J = 1.4, 5.6 Hz), 2.44 (brs, 1H), 2.34 (dt, 1H, J = 1.7, 5.5 Hz), 1.34 (d, 3H, J = 6.5 Hz), 1.34 (s, 3H), 1.31 (s, 3H); IR (KBr) 3214, 1219, 1052 cm^{-1}; $[\alpha]^{25}_D$ +96.2 (*c* 1.00, MeOH). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.90; H, 9.01; N, 5.31. The de (97.0%) and conversion ratio (99.5%) were determined by HPLC analysis of an independent smaller run using identical conditions to those shown above, in which the reaction mixture was converted to a clear solution by addition of CH_2Cl_2 after 24 h. t_R(**7c**) = 16.4 min (98.5%), t_R(corresponding diastereomer of **7c**) = 17.7 min (1.5%), AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 17/83, 214 nm, 1.0 mL/min. The % conversion was calibrated by the relative molar UV intensity ratio of 0.65 ((*R*)-**6c** (t_R = 2.5 min)/**7c**). The relative molar UV intensity ratio (**7c**/corresponding diastereomer of **7c**) was 1.00.

(5*R*,6*S*)-2,2-Dimethyl-6-[(*S*)-1-phenylethylamino]-1,3-dioxepan-5-ol (7d). This compound was similarly obtained from the reaction of **1c** with (*S*)-**6c** as a pale yellow oil (94% yield, 97.6% de): ^{1}H NMR ($CDCl_3$) δ 7.32−7.20 (m, 5H), 3.92−3.83 (m, 2H), 3.67 (dd, 1H, J = 2.0, 12.5 Hz), 3.59−3.40 (m, 2H), 3.30 (dd, 1H, J = 5.3, 12.5 Hz), 2.52 (br t, 1H, J = 4.0 Hz), 2.10 (brs, 1H), 1.34 (d, 1H, J = 6.5 Hz), 1.31 (s, 6H); IR (KBr) 3416, 1218, 1048 cm^{-1}; $[\alpha]^{25}_D$ +12.0 (*c* 1.0, MeOH). HRMS Calcd for $C_{15}H_{24}NO_3$ (M^+ + 1): 266.1757,found 266.1749. t_R(**7d**) = 17.0 min (98.8%), t_R(corresponding diastereomer of **7d**) = 15.9 min (1.2%), AM-302 (achiral), 45 °C, 2-propanol/phosphate buffer (pH 7) = 17/83, 214 nm, 1.0 mL/min. There was 96.9% conversion after 24 h according to HPLC under identical conditions (t_R((*S*)-**6c**) = 2.8 min). The % conversion was calibrated by the relative molar UV intensity ratio of 0.65 ((*S*)-**6c**/**7d**). The relative molar UV intensity ratio (**7d**/corresponding diastereomer of **7d**) was 1.00. The compound **7d** thus obtained was converted to **9** via **8** to determine its absolute configuration.[19]

Preparation of a Mixture of 7c and 7d and Successive Conversion to (5*R*,6*S*)-2,2-Dimethyl-5-hydroxy-1,3-dioxepan-6-ylammonium Acetate (8). To a 500 mL three-necked round-bottomed flask were added (*S*)-1,1′-bi-2-naphthol (283 mg, 0.99 mmol) and heptane−toluene (9:1, 105 mL). To the suspension was added titanium tetraisopropoxide (281 mg, 0.99 mmol) under a nitrogen atmosphere at room temperature, and the solution was stirred for 10 min. Racemic **6c** (24.0 g, 198 mmol), water (300 mg, 16.7 mmol), and **1c** (28.6 g, 198 mol) were added to the solution successively. After stirring at 40 °C for 24 h, the reaction mixture was diluted with toluene (84 mL) and heated to reflux in the presence of 1 M aqueous sodium hydroxide (29 mL) for 1 h. The aqueous layer was removed, and the organic layer was stirred in the presence of charcoal (300 mg) for 1 h. The insoluble material in the mixture was removed by filtration, and the filtrate was concentrated to give a crude mixture containing **7c** and **7d** (1:1, **7c** and **7d** had the same molar UV intensity at 214 nm) as a pale yellow oil. To a suspension of 5% Pd(C) (5.30 g, 55% wet type) in 2-propanol (316 mL) were added the mixture thus obtained, AcOH (11.3 mL, 198 mmol), and water (9.8 mL). Then the mixture was stirred at room temperature for 24 h under an H_2 atmosphere (3 atm). After the catalyst was removed, the filtrate was concentrated to 1/2 volume, diluted with heptane (263 mL), and then stirred at room temperature for 0.5 h. Filtration of the deposited crystals followed by drying at 50 °C in vacuo gave **8** (36.7 g, 84% yield, ee >99%) as colorless crystals: mp 133−134 °C; ^{1}H NMR (CD_3OD) δ 3.84 (dd, 1H, J = 2.5, 12.7 Hz), 3.74 (dd, 1H, J = 2.5, 12.5 Hz), 3.67−3.53 (m, 3H), 2.98 (dt, 1H, J = 2.4, 6.5 Hz), 1.91 (s, 3H), 1.33 (s, 6H); IR (KBr) 3178, 1561, 1087 cm^{-1}; $[\alpha]^{25}_D$ +29.6 (*c* 1.05, MeOH). Anal. Calcd for $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33. Found: C, 48.98; H, 8.70; N, 6.36. The crude **8** obtained before recrystallization was converted into **9**[19a] to measure the stereoselectivity of the reaction: t_R(**9**) = 23.7 min (98.6%), t_R(anti-**9**) = 31.7 min (1.4%), CHIRALCEL OD, 35 °C, hexane/2-propanol = 95/5, 210 nm, 1.0 mL/min.

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Supporting Information Available: Absolute stereochemical assignment of all new chiral compounds, molecular modeling procedure and coordinates of the most stable conformer of **1c**, **5**, and **1c**+**Ti**, HPLC charts from Table 1, entry 6 and from Table 2, entry 4, and 300 MHz ^{1}H NMR spectra of **2c** and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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