



Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1859–1868

TETRAHEDRON:
ASYMMETRY

Stereochemical course of the hydrogen migration in the boron trifluoride etherate-catalyzed rearrangement of 1,1-disubstituted epoxides

Noriyuki Hara, Akiyoshi Mochizuki, Akinori Tatara and Yoshinori Fujimoto*

Department of Chemistry and Materials Science, Tokyo Institute of Technology, Meguro, Tokyo 152-8551, Japan

Received 24 September 1999; accepted 3 April 2000

Abstract

Mechanistic studies on the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of optically active, regioselectively deuterated 1,1-disubstituted epoxides to aldehydic products revealed that the two hydrogens migrate at the migration terminus with opposite stereochemical preferences, i.e. the hydrogen *anti* to the bulky substituent prefers to migrate with inversion of configuration, whereas the hydrogen *syn* to the bulky substituent prefers to migrate with retention of configuration. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

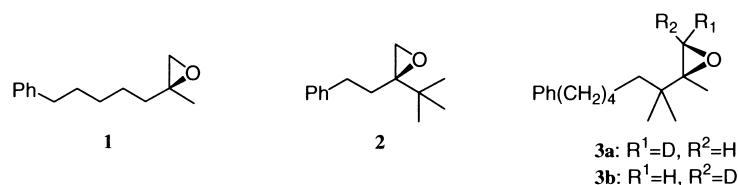
Lewis acid-catalyzed rearrangement of epoxides to carbonyl compounds is a well-known reaction in organic chemistry.¹ It is generally explained that this reaction proceeds by coordination of a Lewis acid molecule on the oxygen atom, fission of a C–O bond to form an electron-deficient carbon center at the more substituted carbon atom, and migration of a substituent to the adjacent carbon center with concomitant formation of a carbonyl compound. A number of examples have been reported on epoxides embedded in cyclic systems such as steroidal epoxides.² In these cases, the structure of the carbonyl product, including the stereochemistry at the migration terminus, seems to be governed by the rigid conformation of the ring system and would be predictable. In contrast, few studies have been done on the stereochemistry at the migration terminus in the rearrangement of acyclic epoxides.^{3–5} We previously reported the unique results that the hydrogen migrates preferentially with retention of configuration at the migration terminus, whereas an alkyl group migrates exclusively with inversion of configuration in the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of acyclic trisubstituted epoxides.⁶ This finding prompted us to study in more detail the mechanism of Lewis acid-catalyzed rearrangement for acyclic epoxides. We describe here our results on the

* Corresponding author. Tel/fax: +81-3-5734-2241; e-mail: fujimoto@cms.titech.ac.jp

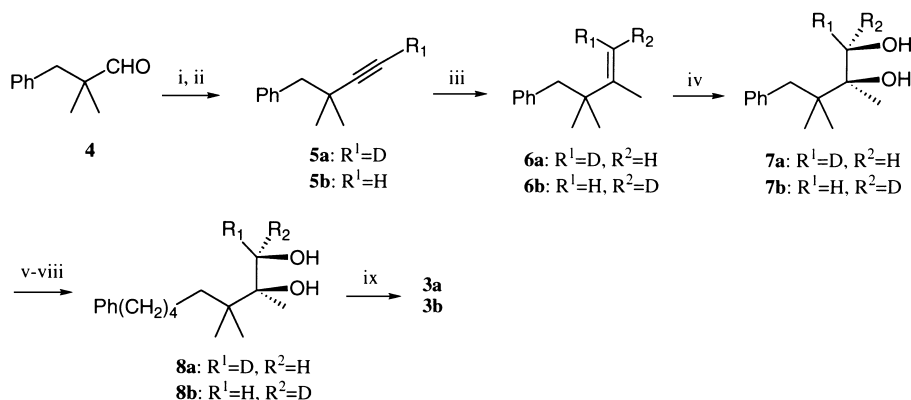
mechanism of and, in particular, the steric course of the hydrogen migration in the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of acyclic 1,1-disubstituted epoxides to aldehydic products.

2. Results and discussion

In our preliminary studies, optically active epoxides **1** and **2** were individually treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2–2.0 equiv.) in CH_2Cl_2 or benzene at room temperature, and the resulting aldehydes were analysed to be essentially racemic.⁷ We, therefore, selected the optically active epoxide **3** which bears the tertiary and methyl substituents. To distinguish the two hydrogens and facilitate the analysis of the steric course of the rearrangement, the regioselectively deuterated substrates, (1*S*,2*S*)-epoxide **3a** and (1*R*,2*S*)-epoxide **3b**, were synthesized.

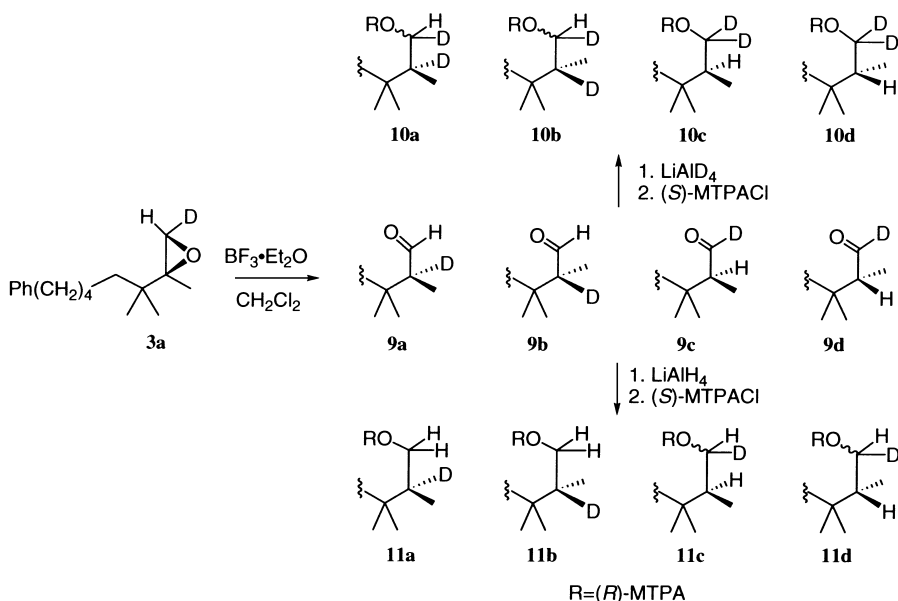


The synthesis of the epoxides **3a** and **3b** is outlined in Scheme 1. The aldehyde **4** was converted into the acetylene **5b** and its deuterated form **5a** via dibromoolefin. Carbozirconation of **5b** by Negishi's protocol⁸ followed by quenching with D_2O gave the *E*-olefin **6a** (*E*:*Z* = 16:1). The corresponding *Z*-olefin **6b** (*Z*:*E* = 21:1) was obtained from **5a** by the same procedure, but by quenching with H_2O . Sharpless asymmetric dihydroxylation⁹ of **6a** and **6b** gave the (1*S*,2*S*)-diols **7a** (55% ee) and (1*R*,2*S*)-**7b** (73% ee), respectively. The enantiomeric excesses of **7a** and **7b** were improved by repeated recrystallization of their phthalic half-esters, followed by hydrolysis to give **7a** (86% ee) and **7b** (92% ee). Extension of the methylene chain of **7a** and **7b** was achieved in seven steps to give the diols **8a** and **8b**, respectively.¹⁰ The diols were finally converted into the epoxides **3a** and **3b** via the corresponding mesylates.



Scheme 1. Synthesis of epoxides **3a** and **3b**. Reagents: (i) CBr_4 , Ph_3P ; (ii) $n\text{BuLi}$, H_2O or D_2O ; (iii) Me_3Al , Cp_2ZrCl_2 , D_2O or H_2O ; (iv) $(\text{DHQD})_2\text{PHAL}$, $\text{K}_2\text{OsO}_2(\text{OH})_4$, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , $\text{CH}_3\text{SO}_2\text{NH}_2$; (v) (a) phthalic anhydride, py, (b) recrystallization, (c) NaOH , MeOH ; (vi) $\text{Me}_2\text{C}(\text{OMe})_2$, $p\text{TsOH}$; (vii) (a) RuCl_3 , NaIO_4 , (b) CH_2N_2 , (c) LiAlH_4 , (d) TsCl , py; (viii) (a) $\text{Ph}(\text{CH}_2)_3\text{MgBr}$, Li_2CuCl_4 , (b) H^+ , MeOH ; (ix) (a) MsCl , py, (b) K_2CO_3 , MeOH

Brief treatment of (1*S*,2*S*)-**3a** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2 equiv.) in CH_2Cl_2 at room temperature afforded a crude product containing aldehyde **9a–d** (21% yield).¹¹ A part of the product was reduced with LiAlD_4 to give the corresponding alcohol which was then converted into the (*R*)-MTPA ester **10a–d**. The other part of the product was reduced with LiAlH_4 and the resulting alcohol was converted into the same ester derivative **11a–d** (Scheme 2).



Scheme 2. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of the epoxide **3a** and analysis of the steric course of the migration of the hydrogen or deuterium atom in the forms of **10** and **11**

The ^1H NMR spectrum of **10a–d** exhibited four broad singlets in the oxymethine/oxymethylene region (δ 4.49, 4.41, 4.03 and 3.95) (Figure 1). Among compounds **10a–10d**, only compounds **10a** and **10b** which arose from the migration of the deuterium atom exhibited the oxymethine signals in this spectrum. The two signals (δ 4.41 and 4.03) were assigned to the oxymethine protons of the diastereomers **10a**, and the remaining two to those of the diastereomers **10b**.¹² The ratio of the compounds, **10a**, **10b** and **10c+10d** (formed by hydrogen migration), was determined to be 31:14:55 on the basis of the signal intensities of the above oxymethine hydrogens by comparison with those of the benzylic methylene hydrogens (δ 2.60). The ^1H NMR spectrum of **11a–d** exhibited eight sets of doublets in the oxymethine region (Figure 1). The two doublets at δ 4.43, 4.05 ($J=10.8$ Hz) were readily assigned to those of **11a** and the two doublets at δ 4.51, 3.97 ($J=10.8$ Hz) to **11b** in comparison with the spectrum of **10a–d**. The two doublets at δ 4.04 ($J=8.8$ Hz) and 4.42 ($J=3.7$ Hz) were assigned to the oxymethine protons of the diastereomers **11c** and the last two doublets at δ 3.95 ($J=8.8$ Hz) and 4.50 ($J=3.7$ Hz) to those of the diastereomers **11d**.⁹ Although the ratio of the signal intensities of these eight doublets could not be accurately obtained due to some overlap of the signals, the ratio (58:42) of ($2 \times \mathbf{11a} + \mathbf{11c}$) and ($2 \times \mathbf{11b} + \mathbf{11d}$) was readily obtained from the integration values of their signals. With the aforementioned two sets of ratios in hand, the ratio for **9a:9b:9c:9d** was calculated to be 31:14:22:33.^{13,14}

The deuterium labeled (1*S*,2*S*)-epoxide **3b** was similarly treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and the resulting aldehyde **9** was analyzed in the forms of the (*R*)-MTPA ester derivatives **10** and **11**. The ratio

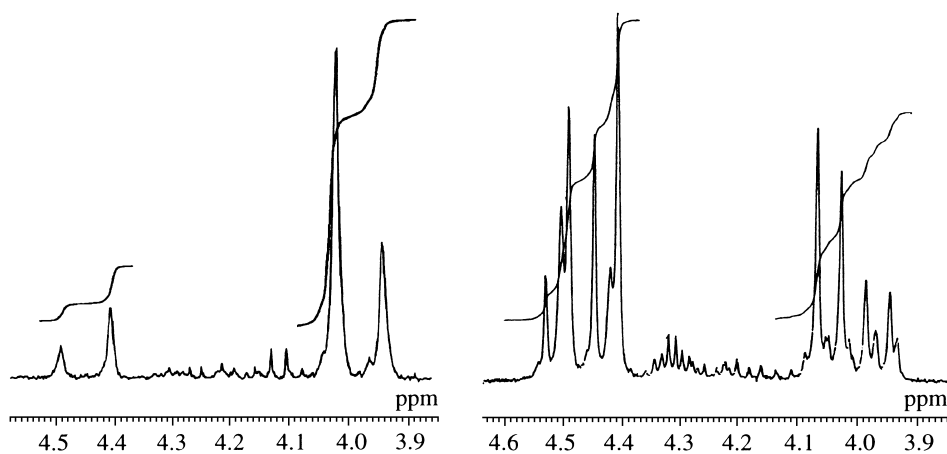
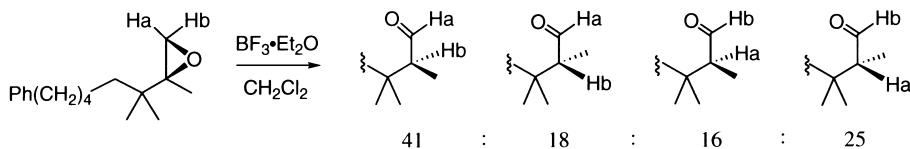


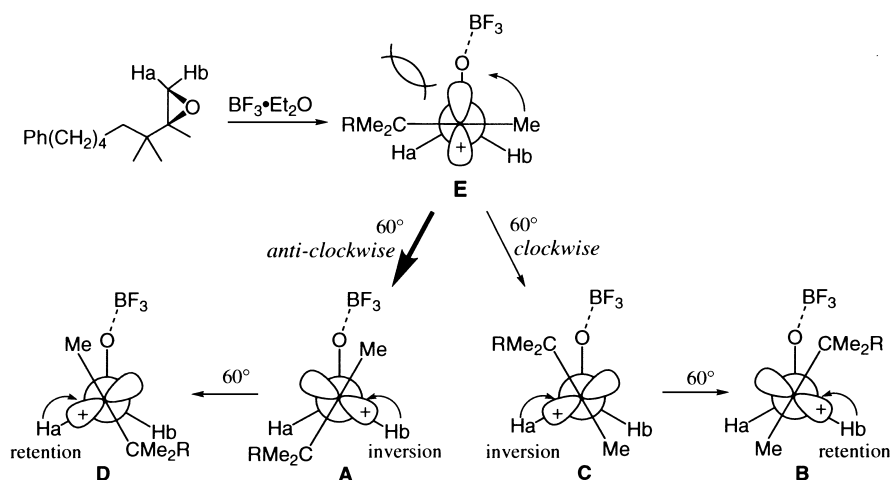
Figure 1. ^1H NMR spectra (270 MHz, CDCl_3) of the oxymethylene/oxymethine protons of **10a–d** (left) and **11a–d** (right) derived from the aldehyde **9a–d** obtained from the epoxide **3a**. The signals at δ 4.15–4.36 in the right spectrum are due to impurities

9a:9b:9c:9d = 11:17:50:22 was obtained.¹⁴ One may suspect racemization of the once-formed aldehyde **9** during the reaction conditions. This racemization was found to be negligible by subjecting a synthetic optically active aldehyde¹⁵ to the reaction conditions.

Based on the above two sets of the data for **9a–d**, it is deduced that the deuterium migration is retarded by 1.77-fold¹⁶ compared to the hydrogen migration. Thus, the ratio of the four rearranged products corresponding to **9a**, **9b**, **9c** and **9d** could be estimated as 41:18:16:25 for non-deuterated epoxide (Scheme 3). This ratio would reflect the relative contribution of four transition conformers **A**, **B**, **C** and **D** in this order, wherein either hydrogen Ha or Hb is placed in the proper orientation for the 1,2-hydride shift (Scheme 4). The unstable carbocation (conformation **E**)¹⁷ generated by the C–O bond fission of the epoxide would rotate along the central C–C⁺ axis to give rise to conformers **A–D**. Out of the two possible directions of the rotation, anti-clockwise rotation seems more preferable than the clockwise, due to the larger non-bonded repulsive interaction between the RCMe_2 and O-BF_3 groups. Among these, conformation **A**, wherein Hb migrates with inversion of stereochemistry, seems most readily accessible, and conformation **D**, which corresponds to the migration of Ha with retention of stereochemistry, might follow as the next accessible one. Blackett et al. reported that Hb (the hydrogen *anti* to the bulky substituent) is more susceptible to the migration (by ca. 1.9 fold) than Ha by considering only two conformations **A** and **D** in the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of a similar 1,1-disubstituted epoxide without information on the steric course of the hydrogen migration.⁴ The reported aptitude was confirmed in the present experiments in which Hb migrated more readily [1.44 (= 59/41) fold] than Ha.



Scheme 3. The ratio of the rearranged products expected for the non-labeled epoxide



Scheme 4. Four transition conformations **A–D** for the hydrogen migration, arising from the initially formed conformation **E**

Concerning the migration of Hb , the retention:inversion ratio (22:50 or 14:31) indicates that conformation **B** which corresponds to the hydrogen migration with retention of stereochemistry has to be considered as well, although its contribution is less than half of that of conformation **A**. Similarly, it was found that conformation **C**, which is responsible for the migration of Ha with inversion of stereochemistry, cannot be ignored on the basis of the retention:inversion ratio of Ha (33:22 or 17:11). It can be summarized that the relative significance of the four transition conformations is **A**, **D**, **B**, **C** in the decreasing order.

In conclusion, the present study has investigated the steric course of each hydrogen in the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed rearrangement of 1,1-disubstituted epoxide for the first time, and established that the hydrogen *anti* to the bulky substituent prefers to migrate with inversion of configuration at the migrating terminus, whereas the hydrogen *syn* to the bulky substituent prefers to migrate with retention of configuration. The relative contribution of the *four* transition conformers in the rearrangement is also estimated.

3. Experimental

3.1. General

All melting points were measured on a Yazawa hot-stage microscope BY-1 and are reported uncorrected. The IR spectra were measured on a JASCO FT-IR200 spectrometer in CHCl_3 solutions and are reported in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 or EX-270 spectrometer in CDCl_3 solutions and chemical shifts were reported in δ value based on internal tetramethylsilane (δ_{H} 0.0) or the solvent signal (δ_{C} = 77.0). ^2H NMR spectra were recorded on a JEOL GSX-500 (76.8 MHz) spectrometer in CHCl_3 solutions and chemical shifts are referenced to natural abundance CDCl_3 (δ_{D} 7.26). EI-MS (70 eV) and high-resolution FABMS spectra were obtained on a JEOL JMS-AX505HA spectrometer.

3.2. $[1-^2H]$ -3,3-Dimethyl-4-phenyl-1-butyne **5a**

A mixture of PPh_3 (110 g, 419 mmol) and CBr_4 (69.4 g, 209 mmol) in dry CH_2Cl_2 (136 ml) was stirred at 0°C for 10 min. A solution of 2,2-dimethyl-3-phenylpropanal **4** (11.3 g, 69.8 mmol) in CH_2Cl_2 (26 ml) was added and stirring was continued at 0°C for 10 min and then at room temperature overnight. The mixture was filtered by suction and the filtrate was diluted with ether and aq. NaHCO_3 . Extractive (ether) workup and chromatography on silica gel (hexane:benzene, 20:1) afforded the dibromoolefin (19.4 g, 87%) as a colorless oil. IR ν_{max} : 2970, 2930, 1600, 1500, 1470, 1450, 1370. ^1H NMR δ : 1.19 (6H, s, 3- $\text{CH}_3 \times 2$), 2.80 (2H, s, 4- H_2), 6.49 (1H, s, 2-H), 7.13–7.31 (5H, m, Ph). ^{13}C NMR δ : 27.15, 39.98, 46.63, 85.99, 126.27, 127.89, 130.51, 137.99, 145.86. Anal. calcd for $\text{C}_{12}\text{H}_{14}\text{Br}_2$: C, 45.32; H, 4.44. Found: C, 45.16; H, 4.37.

$n\text{BuLi}$ (1.70M hexane solution, 39.1 ml, 66.5 mmol) was added to a solution of the dibromoolefin (10.8 g, 33.9 mmol) in dry THF (45 ml) at -78°C under N_2 and the mixture was stirred for 15 min at the same temperature. D_2O (5.0 ml) was added to this mixture and the whole was stirred for 30 min after removal of the cooling bath. Extractive workup (ether) and chromatography on silica gel (hexane:ether 30:1) gave **5a** (5.07 g, 94%) as an oil. IR ν_{max} : 3300, 3010, 2970, 2930, 2590, 1490, 1450, 1360. ^1H NMR δ : 1.21 (6H, s, 3- $\text{CH}_3 \times 2$), 2.71 (2H, s, 4- H_2), 7.19–7.31 (5H, m, Ph). ^{13}C NMR δ : 28.92, 32.00, 48.68, 68.84 (t, $J=38$ Hz), 90.87 (t, $J=7.4$ Hz) 126.38, 127.57, 127.67, 130.40, 130.51, 137.92. HR-EIMS (70 eV) calcd for $\text{C}_{12}\text{H}_{13}\text{D}$: 159.1157 (M^+). Found: 159.1132.

3.3. 3,3-Dimethyl-4-phenyl-1-butyne **5b**

The dibromoolefin (7.92 g, 24.9 mmol) was similarly treated with $n\text{-BuLi}$ and the reaction mixture was quenched by the addition of water (4.0 ml) in place of D_2O . Extractive workup and chromatography on silica gel gave **5b** (3.62 g, 92%) as a colorless oil. IR ν_{max} : 3305, 3005, 2970, 2930, 2110, 1490, 1460. ^1H NMR δ : 1.20 (6H, s, 3- $\text{CH}_3 \times 2$), 2.10 (1H, s, 1-acetylene), 2.70 (2H, s, 4- H_2), 7.18–7.30 (5H, m, Ph). ^{13}C NMR δ : 28.88, 31.97, 48.61, 69.09, 91.23, 126.38, 127.64, 130.37, 130.48, 137.84. HR-EIMS (70 eV) calcd for $\text{C}_{12}\text{H}_{14}$: 158.1096 (M^+). Found: 158.1081.

3.4. $[1-^2H]$ -(1R,2S)-2,3,3-Trimethyl-4-phenyl-1,2-butanediol **7a**

Trimethylaluminum (2.0 M toluene solution, 18.2 ml, 36.3 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (5.33 g, 18.2 mmol) in dry 1,2-dichloroethane (82 ml) at room temperature and the mixture was stirred for 10 min. A solution of acetylene **5a** (2.91 g, 18.3 mmol) in dry 1,2-dichloroethane (15 ml) was added and stirring was continued for 2 days. Extractive (ether) workup and chromatography on silica gel (hexane) afforded a mixture (2.47 g, 77%) of *Z*-olefin **6a** (*E*:*Z* = 1:21) and *trans*-1,2-disubstituted olefin as a colorless oil.

A mixture of $(\text{DHQ})_2\text{PHAL}$ (590 mg, 0.76 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (13.4 g, 40.6 mmol), K_2CO_3 (5.61 g, 40.6 mmol), $\text{CH}_3\text{SO}_2\text{NH}_2$ (1.29 g, 13.5 mmol) in *t*BuOH (63 ml) and water (68 ml) was vigorously stirred at room temperature for 5 min, and then cooled to 0°C . $\text{K}_2\text{OsO}_2(\text{OH})_4$ (30 mg, 0.081 mmol) was added and the mixture was further stirred for 40 min. The above olefin (2.37 g, 13.5 mmol) in *t*BuOH (5.0 ml) was added dropwise and stirring was continued at 0°C for 3 days and at room temperature for 2 days. $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (40 g) was added and stirring was continued for 0.5 h. Extractive (AcOEt) workup and chromatography on silica gel (hexane:AcOEt, 4:1) afforded **7a** (1.70 g, 60%) and 4,4-dimethyl-5-phenylpentane-2,3-diol (1.10 g, 39%) as a white solid. **7a**: mp

45–48°C. IR ν_{max} : 3620, 3560, 3450, 3010, 2970, 1370, 1080, 1040. ^1H NMR δ : 0.84, 0.85 (3H each, s, 3- $\text{CH}_3 \times 2$), 1.30 (3H, s, 4- CH_3), 2.68 (2H, s, 4- H_2), 3.51 (1H, brs, 1-H), 7.13–7.29 (5H, m, Ph). ^{13}C NMR δ : 19.88, 21.35, 21.41, 40.21, 42.19, 65.54 ($J=21.8$ Hz), 76.85, 125.83, 127.61, 131.09, 138.85. Anal. calcd for $\text{C}_{13}\text{H}_{19}\text{DO}_2$: C, 74.60; H+D, 10.11. Found: C, 74.31; H+D, 10.08. The ee of **7a** was determined to be 56% by ^1H NMR analysis of the mono-(*R*)-MTPA ester. ^1H NMR δ : 0.86 (6H, s, 3- $\text{CH}_3 \times 2$), 1.25 (3H, s, 2- CH_3), 1.61–1.71 (1H, br, OH), 2.69 (2H, s, 4- H_2), 3.58 (3H, s, OMe), 4.25 (1H, s, 1- H_1 , for (*2S*)-isomer), 4.32 (1H, s, 1- H_1 , for (*2R*)-isomer), 7.11–7.59 (10H, Ph).

A mixture of the diol **7a** (1.64 g, 7.85 mmol) and phthalic anhydride (1.26 g, 8.51 mmol) in pyridine was stirred at room temperature overnight. Addition of ice chips and extractive (ether) workup followed by chromatography on silica gel (hexane:AcOEt, 4:1) afforded phthalate half-ester as a white solid, mp 128–130°C. The ester was repeatedly recrystallized from hexane and ether to afford an optically enriched ester (1.10 g). Hydrolysis of the ester by treating with 5N aq. NaOH (1.5 ml) in MeOH (10 ml) followed by chromatography on silica gel furnished **7a** (580 mg, 35%, 86% ee).

3.5. [*1*-²H]-(*1S,2S*)-2,3,3-Trimethyl-4-phenyl-1,2-butanediol **7b**

The acetylene **5b** (2.88 g, 18.2 mmol) was subjected to the carbozirconation as described for **5a** and the reaction was quenched by addition of D_2O in place of H_2O . Extractive workup and purification gave a mixture (2.30 g, 72%) of **6b** (*E:Z* = 16:1) and *trans*-1,2-disubstituted olefin as an oil.

Asymmetric dihydroxylation of the mixture, as described for **6a**, afforded **7b** (1.71 g, 62%, 74% ee) and 4,4-dimethyl-5-phenylpentane-2,3-diol (603 mg, 24%) as white solids. Compound **7b**: mp 44–47°C. IR ν_{max} : 3630, 3560, 3450, 3010, 2980, 1450, 1370, 1100, 1030. ^1H NMR δ : 0.84, 0.85 (3H each, s, 3- $\text{CH}_3 \times 2$), 1.30 (3H, s, 4- CH_3), 2.68 (2H, s, 4- H_2), 3.81 (1H, brs, 1-H), 7.12, 7.30 (5H, m, Ph). ^{13}C NMR δ : 19.93, 21.37, 21.44, 40.24, 42.21, 65.57 ($J=22.0$ Hz), 76.82, 125.88, 127.64, 131.09, 138.85. Anal. calcd for $\text{C}_{13}\text{H}_{19}\text{DO}_2$: C, 74.60; H+D, 10.11. Found: C, 74.31; H+D, 10.00. The ee of the diol **7b** was increased in the manner as described for **7a**, furnishing **7b** (727 mg, 43%, ee 92%).

3.6. [*1*-²H]-(*1R,2S*)-2,3,3-Trimethyl-8-phenyl-1,2-octanediol **8a**

A solution of the diol **7a** (515 mg, 2.46 mmol) and acetone dimethylacetal (0.35 ml, 2.86 mmol) in dry CH_2Cl_2 (5 ml) containing *p*-TsOH (3 mg) was stirred at room temperature for 15 min. Addition of NaHCO_3 (powder, 5 mg), removal of the solvent under reduced pressure and chromatography of the residue on silica gel (hexane:AcOEt, 10:1) afforded the acetonide (580 mg, 95%). NaIO_4 (9.6 g, 45 mmol) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (44–45% Ru, 26 mg, 0.12 mmol) was added to a solution of the acetonide (561 mg, 2.25 mmol) in $\text{CCl}_4:\text{CH}_3\text{CN}$ (1:1 v/v, 11.2 ml) and phosphate buffer ($\text{NaH}_2\text{PO}_4:\text{Na}_2\text{HPO}_4 = 1:1$, 11 ml) was added and the mixture was stirred at room temperature for 36 h. Extractive (CH_2Cl_2) workup and chromatography on silica gel (hexane:AcOEt, 2:1) gave a crude acid. This was treated with excess of ethereal CH_2N_2 and the resulting methyl ester was reduced with LiAlH_4 in dry ether in the usual manner. Extractive (AcOEt) workup and chromatography on silica gel (hexane:AcOEt, 2:1) afforded the alcohol (270 mg, 59%) as a colorless oil.

The alcohol (255 mg, 1.25 mmol) in pyridine (0.90 ml) was treated with TsCl (310 mg, 1.63 mmol) at 0°C for 1.5 h. Extractive (ether) workup and chromatography on silica gel (hexane:AcOEt, 7:1) afforded the tosylate (380 mg, 85%) as a colorless oil.

To a solution of 3-phenylpropylmagnesium bromide, prepared from 3-phenylpropylbromide (1.06 ml, 6.97 mmol), magnesium (170 mg, 6.99 mmol) and THF (5.0 ml), was added Li_2CuCl_4 (0.1 M THF solution; 1.0 ml, 0.10 mmol) and the tosylate (359 mg, 1.00 mmol) in THF (2.0 ml) at -78°C . After removal of the cooling bath, the mixture was stirred for 4 h. Extractive (ether) workup and chromatography (benzene) on silica gel gave a coupling product (216 mg, 71%) as a colorless oil.

A solution of the coupling product (201 mg, 0.66 mmol) in MeOH (50 ml) and 2N HCl (1.0 ml, 2.0 mmol) was heated at 55°C for 1.5 h. Removal of the solvent under reduced pressure and chromatography of the residue on silica gel afforded **8a** (108 mg, 62%) as a white solid, mp $63\text{--}65^\circ\text{C}$. IR ν_{max} : 3630, 3470, 3010, 2970, 2940, 2870, 1460, 1370, 1030. ^1H NMR δ : 0.87, 0.88 (each 3H, s, 3- $\text{CH}_3 \times 2$), 1.17 (3H, s, 2- CH_3), 1.28 (6H, m, 4,5,6- H_2), 1.63 (2H, m, 7- H_2), 2.08, 2.39 (each 1H, br, OH $\times 2$), 2.60 (2H, t, $J=7.6$ Hz, 8- H_2), 3.38 (1H, brs, 1-H), 7.16–7.30 (5H, m, Ph). ^{13}C NMR δ : 19.57, 21.37, 24.17, 30.35, 31.50, 35.96, 36.75, 38.94, 65.46 ($J=22.0$ Hz), 77.00, 125.55, 128.18, 128.36, 142.73. Anal. calcd for $\text{C}_{17}\text{H}_{27}\text{DO}_2$: C, 76.93; H+D, 11.01. Found: C, 76.73; H+D, 11.16.

3.7. $[1\text{-}^2\text{H}]\text{-}(1\text{S},2\text{S})\text{-}2,3,3\text{-Trimethyl-}8\text{-phenyl-}1,2\text{-octanediol } \mathbf{8b}$

Diol **7b** (707 mg, 3.38 mmol) was converted, in the same manner as described for **7a**, into **8b** (125 mg, 14%), mp $71\text{--}74^\circ\text{C}$. IR ν_{max} : 3630, 3460, 3010, 2970, 2940, 2870, 1460, 1380, 1030, 940. ^1H NMR δ : 0.87, 0.88 (each 3H, s, 3- $\text{CH}_3 \times 2$), 1.17 (3H, s, 2- CH_3), 1.28 (6H, m, 4, 5, 6- H_2), 1.63 (2H, m, 7- H_2), 1.90, 2.10 (each 1H, br, OH $\times 2$), 2.60 (2H, t, $J=7.9$ Hz, 8- H_2), 3.67 (1H, brs, 1-H), 7.15–7.30 (5H, m, Ph). ^{13}C NMR (67.5 MHz, CDCl_3) δ : 19.59, 21.37, 24.19, 30.37, 31.52, 35.98, 36.75, 38.94, 65.48 ($J=21.4$ Hz), 77.05, 125.55, 128.19, 128.37, 142.75. Anal. calcd for $\text{C}_{17}\text{H}_{27}\text{DO}_2$: C, 76.93; H+D, 11.01. Found: C, 76.89; H+D, 11.01.

3.8. $[1\text{-}^2\text{H}]\text{-}(1\text{S},2\text{S})\text{-}1,2\text{-Epoxy-}2,3,3\text{-trimethyl-}8\text{-phenyl-}1\text{-octane } \mathbf{3a}$

MsCl (35 μl , 0.45 mmol) was added to a solution of the diol **8a** (100 mg, 0.38 mmol) in pyridine (0.8 ml) at 0°C and the mixture was stirred for 1 h at the same temperature. Extractive (ether) workup gave a crude mesylate which was treated with sat. K_2CO_3 in methanol (1 ml) at room temperature for 5 min. Extractive (ether) workup and chromatography on silica gel (hexane:AcOEt, 10:1) afforded the epoxide **3a** (78 mg, 84%) as a colorless oil. IR ν_{max} : 3020, 2970, 2940, 2860, 1460, 1380. ^1H NMR δ : 0.83, 0.90 (each 3H, s, 3- $\text{CH}_3 \times 2$), 1.26 (3H, s, 2- CH_3), 1.32 (6H, m, 4,5,6- H_2), 1.64 (2H, m, 7- H_2), 2.60 (2H, t, $J=7.9$ Hz, 8- H_2), 2.72 (1H, s, 1-H), 7.14–7.30 (5H, m, Ph). ^2H NMR δ : 2.46 (*pro-R*- ^2H). ^{13}C NMR δ : 18.46, 23.17, 23.42, 23.99, 30.14, 31.39, 35.96, 39.73, 50.80 ($J=25.7$ Hz), 61.08, 125.55, 128.18, 128.36, 142.73. HR-FABMS calcd for $\text{C}_{17}\text{H}_{26}\text{DO}$: 248.2146 (MH^+). Found: 248.2108.

3.9. $(1\text{R},2\text{S})\text{-}[1\text{-}^2\text{H}]\text{-}1,2\text{-Epoxy-}2,3,3\text{-trimethyl-}8\text{-phenyl-}1\text{-octane } \mathbf{3b}$

The diol **8b** (120 mg, 0.45 mmol) was converted, in the same manner as described for **8a**, into the epoxide **3b** (103 mg, 92%) as a colorless oil. IR ν_{max} : 3020, 2970, 2940, 2860, 1460, 1380. ^1H NMR δ : 0.83, 0.90 (each 3H, s, 3- $\text{CH}_3 \times 2$), 1.26 (3H, s, 2- CH_3), 1.31 (6H, m, 4,5,6- H_2), 1.63 (2H, m, 7- H_2), 2.37 (1H, s, 1-H), 2.60 (2H, t, 8- H_2 , $J=8.0$ Hz), 7.13–7.30 (5H, m, Ph). ^2H NMR δ : 2.80 (*pro-S*- ^2H). ^{13}C NMR δ : 18.53, 23.20, 23.45, 24.03, 30.17, 31.43, 35.99, 39.77, 50.87 ($J=26.9$ Hz), 61.12, 125.59, 128.21, 128.39, 142.77. HR-FABMS calcd for $\text{C}_{17}\text{H}_{26}\text{DO}$: 248.2146 (MH^+). Found: 248.2105.

3.10. Treatment of the epoxides **3a** and **3b** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (69 μl , 0.55 mmol) was added to a solution of the epoxide **3a** (68 mg, 0.28 mmol) in dry CH_2Cl_2 (6.8 ml) at room temperature and the mixture was stirred for 3 min. Ether and sat. NaHCO_3 were added at once and extractive (ether) workup and chromatography on silica gel (hexane:benzene, 10:1) gave a fraction (30 mg) containing aldehyde **9**. Half of this was reduced with LiAlD_4 in THF in the usual manner. Chromatography of the crude product on silica gel (hexane:AcOEt, 10:1) afforded an alcohol (7 mg). The other half was similarly reduced with LiAlD_4 to give another alcohol (7 mg). Treatment of the two alcohols with (*S*)-MTPA chloride in pyridine followed by purification by *p*-tlc gave the corresponding (*R*)-MTPA esters **10a–d** (7 mg) and **11a–d** (7 mg). Compound **10a–d**: $^1\text{H NMR } \delta$: 0.78–0.92 (9H, m, CH_3), 1.05–1.42, 1.53–1.75 (10.55H, m, CH_2 and CH), 2.60 (2H, t, $J = 8.1$ Hz, PhCH_2), 3.56 (3H, s, OCH_3), 7.23–7.62 (10H, m, Ph). The signals of the oxymethine and oxymethylene region are illustrated in Fig. 1. HR-FABMS calcd for $\text{C}_{27}\text{H}_{34}\text{D}_2\text{O}_3\text{F}_3$: 467.2742 (MH^+). Found: 466.2739. Compound **11a–d**: $^1\text{H NMR } \delta$: 0.79–0.92 (9H, m, CH_3), 1.05–1.40, 1.50–1.76 (10.55H, m, CH_2 and CH), 2.60 (2H, t, $J = 8.1$ Hz, PhCH_2), 3.56 (3H, s, OCH_3), 7.13–7.58 (10H, m, Ph). The signals of the oxymethine and oxymethylene region are illustrated in Fig. 1. HR-FABMS calcd for $\text{C}_{27}\text{H}_{35}\text{DO}_3\text{F}_3$: 466.2679 (MH^+). Found: 466.2673.

The epoxide **3b** (93 mg, 0.38 mmol) was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in the same manner as described for **3a** and the aldehyde was converted into **10a–d** (9 mg) and **11a–d** (11 mg). Compound **10a–d**: $^1\text{H NMR } \delta$: 0.79–0.89 (9H, m, CH_3), 1.04–1.38, 1.53–1.75 (10.72H, m, CH_2 and CH), 2.60 (2H, t, $J = 8.1$ Hz, PhCH_2), 3.55 (3H, s, OCH_3), 3.92–4.05 (0.06H, m, CH_2 and CDH), 4.38–4.56 (0.01H, m, CH_2 and CDH), 7.12–7.56 (10H, m, Ph). HR-FABMS calcd for $\text{C}_{27}\text{H}_{34}\text{D}_2\text{O}_3\text{F}_3$: 467.2742 (MH^+). Found: 466.2744. Compound **11a–d**: $^1\text{H NMR } \delta$: 0.80–0.88 (9H, m, CH_3), 1.05–1.38, 1.55–1.75 (10.72H, m, CH_2 and CH), 2.60 (2H, t, $J = 8.1$ Hz, PhCH_2), 3.56 (3H, s, OCH_3), 3.92–4.10 (0.10H, m, CH_2 and CDH), 4.38–4.56 (0.21H, m, CH_2 and CDH), 7.12–7.56 (10H, m, Ph). HR-FABMS calcd for $\text{C}_{27}\text{H}_{35}\text{DO}_3\text{F}_3$: 466.2679 (MH^+). Found: 466.2651.

References

1. For Lewis acid-mediated epoxide rearrangements, see: Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827–3829; Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515–3518; Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 5607–5610; Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983–6998.
2. Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier Publishing Co.: Amsterdam, 1968; pp. 353–372.
3. Coxon, J. M.; Lim, C. *Aust. J. Chem.* **1977**, *30*, 1137–1143; Bach, R. D.; Lucast, D. H. *J. Chem. Soc., Chem. Commun.* **1979**, 593–594.
4. Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *J. Am. Chem. Soc.* **1970**, *92*, 2574–2575.
5. Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303–3312.
6. Fujimoto, Y.; Kanzawa, Y.; Ikuina, Y.; Kakinuma, K.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1989**, 1107–1109; Fujimoto, Y.; Ikuina, Y.; Kanzawa, Y.; Nagakari, M.; Kakinuma, K.; Ikekawa, N. *Heterocycles* **1990**, *30*, 275–278.
7. For example, treatment of (*S*)-**1** with 0.2 equiv. of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 afforded 2-methyl-7-phenylpentanal with (*2R*):(*2S*) = 52:48.
8. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Moriyama, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
10. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ treatment of the epoxide which was prepared from **7a** in two steps (mesylation and K_2CO_3 treatment) afforded a mixture of products, probably formed by benzyl group participation. The ee of compound **8a** could not be increased by recrystallization via the phthalic half-ester derivative. The detour route was selected due to these reasons.
11. The epoxide was consumed under this reaction condition. Attempts to increase the yield of the aldehyde were not successful. For example, when the reaction was carried out at a lower temperature (0°C), an increased amount of fluorohydrin was produced. Use of a reduced amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2 equiv.) led to a similar result.
12. The chemical shifts were assigned by comparing the ^1H NMR data with those of stereochemically defined synthetic compounds; (2*R*)-5-phenyl-2,3,3-trimethylpentanol (*R*)-MTPA ester showed oxymethylene proton signals at δ 4.62 (dd, $J=11.0, 3.7$ Hz), 4.07 (dd, $J=11.0, 8.7$ Hz), while the (2*S*)-counterpart showed the corresponding proton signals at δ 4.54 (dd, $J=11.0, 3.7$ Hz), 4.14 (dd, $J=11.0, 8.7$ Hz). The ^1H NMR data for the (*R*)-MTPA ester of non-deuterated racemic **10**: (2*R*)-isomer δ : 4.52 (dd, $J=10.7, 3.7$ Hz), 3.97 (dd, $J=10.7, 9.2$ Hz); (2*S*)-isomer δ : 4.54 (dd, $J=10.7, 3.7$ Hz), 4.05 (dd, $J=10.7, 9.2$ Hz).
13. The percentages of **10c** ($x=22$) and **10d** ($y=33$) were obtained by solving the following two simultaneous equations: $x+y=55$ and $42 \times (31 \times 2 + x) = 58 \times (14 \times 2 + y)$.
14. The presence of the antipode in the epoxide substrate was not considered.
15. (2*R*)-5-Phenyl-2,3,3-trimethylpentanal was subjected to the reaction conditions.
16. The deuterium isotope parameter z was determined to satisfy $31z:14z:22:33 = 50:22:11z:17z$.
17. White, J. C.; Cave, R. J.; Davidson, E. R. *J. Am. Chem. Soc.* **1988**, *110*, 6308–6314; Nakamura, K.; Osamura, Y. *J. Phys. Org. Chem.* **1990**, *3*, 737–745.