

Asymmetric synthesis of (2*R*,3*S*)-2,3-epoxyamides via camphor-derived sulfonium ylides

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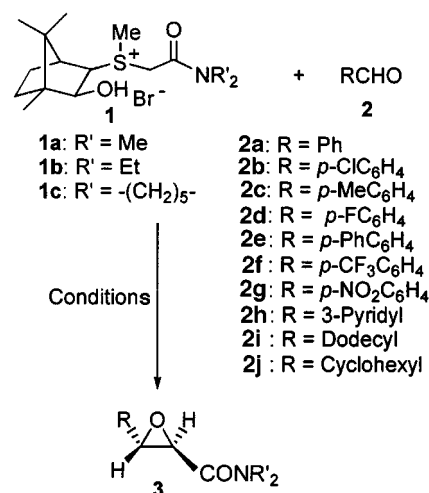
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Enantiomerically enriched *trans*-2,3-epoxyamides **3** were prepared by the reaction of aldehydes **2** with camphor-derived chiral sulfonium ylide **1** in good yields and moderate to good ee values. The absolute configuration of the reaction product is also determined by chemical transformations.

Epoxides are versatile intermediates in organic chemistry. By electrophilic or nucleophilic ring opening reactions, they can be transformed to 1,2-difunctionalized systems or form new C–C bonds.^{1,2} The development of methods for the preparation of this type of compound is always a subject of great challenge. The recorded methods for this aim are chiefly as follows: (a) enantiofacially selective oxidation of a prochiral C=C bond;³ (b) enantioselective alkyldienation of a C=O bond, such as *via* an ylide route or a Darzens reaction. Although the former method has obtained much success, the structure requirements of the substrates and using dangerous oxidative reagents are limiting prerequisites. The latter strategy provides an alternative approach in solving this problem. Enantioselective epoxidation *via* an ylide route is an approach easy to perform but relatively undeveloped to date. At present, only benzylidene transfer has been realized successfully *via* the chiral ylide route.⁴ However synthetically useful 2,3-epoxyesters cannot be prepared by the reaction of ylides and aldehydes because of low reactivity.⁵ In 1966, Ratts and his co-workers reported the reaction of amide-stabilized ylides with aldehydes, and afforded *trans*-2,3-epoxyamides.^{6a} In 1990, Valpuesta-Fernandez and Lopez-Herrera^{6b} reported that the amide-stabilized sulfonium ylide reacted with chiral aldehydes in good stereoselectivities (single *trans* isomers, >92% de) and excellent yields. Subsequently further work⁷ on other substrate-induced and stereoselective ring-opening of products was performed in their laboratory, and high diastereoselectivities were obtained. Our research on the preparation of functionalized optically active epoxides,⁸ combined with our experiences in chiral sulfonium ylide chemistry,⁹ led us to explore enantioselective synthesis of 2,3-epoxyamides by the reaction of aldehydes and a stabilized chiral sulfonium ylide. We disclose herein our methods for preparing (2*R*,3*S*)-epoxyamides through chiral sulfonium ylides with excellent yields, exclusive *trans*-configuration and moderate to good ee values.

In our previous papers on asymmetric epoxidation^{9a} of aromatic aldehydes and aziridination^{9b} of *N*-tosylimines *via* the sulfonium ylide route, we found that camphor-derived sulfides were good chiral reagents, so camphor-derived chiral sulfonium salts **1a**, **1b** and **1c** were easily prepared by the reaction of chiral sulfide (+)-*exo*-3-(methylthio)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol¹⁰ with the corresponding α -bromoacetamides respectively. We then used sulfonium salts **1** to perform this reaction under solid–liquid phase transfer conditions (Scheme 1) (Condition A: KOH, CH₃CN, RT). The model substrate is *p*-chlorobenzaldehyde **2b**. The results are shown in Table 1.

It was found that under the same conditions, ylides generated from chiral sulfonium salts **1** reacted smoothly with aldehyde **2b** to give the optically active *trans*-epoxyamides in good yield. But the yield and ee value of **1c** (entry 2) are lower than those of **1a**



Scheme 1 Condition A: KOH, MeCN, RT; Condition B: NaOH (10% aq), DCM, 0 °C.

and **1b** (entries 1 and 3). In addition, we also examined liquid–liquid phase transfer conditions (Scheme 1) (Condition B: CH₂Cl₂, NaOH 10% aq, 0 °C); the result is also shown in Table 1. From entries 3 and 4 we found that chemical yields and ee values from liquid–liquid and solid–liquid phase transfer condition are the same. When other aldehydes such as **2a** and **2f** were used, we found that the chemical yields from solid–liquid phase conditions are lower than those from liquid–liquid phase conditions, however, the ee values are the same. With regard to *p*-nitrobenzaldehyde (**2g**) and nicotinaldehyde (pyridine-3-carbaldehyde, **2h**), the reaction under solid–liquid phase transfer conditions is complex, and only trace products were obtained. This may be explained by the fact that active aldehydes can undergo side reactions, such as the Cannizzaro reaction, due to contact with strong solid base KOH under solid–liquid phase transfer conditions. However, under liquid–liquid phase transfer conditions, the aldehydes are in the organic phase (CH₂Cl₂), and the base is in the aqueous phase. Therefore, liquid–liquid phase transfer conditions are the best choice. The results for several substrates are summarized in Table 1.

From Table 1 we found that all kind of aldehydes, for example, aryl, heteroaryl and aliphatic, reacted with chiral sulfonium salts under liquid–liquid phase transfer conditions to afford the desired products in good to excellent chemical yields. The asymmetric induction is moderate to good (from 10.9% to 71.5%) and the highest ee (71.5% ee) was obtained in the reaction of benzaldehyde **2a**. Only low ee values are obtained for aliphatic aldehydes (entry 14 and 15). At present, we cannot

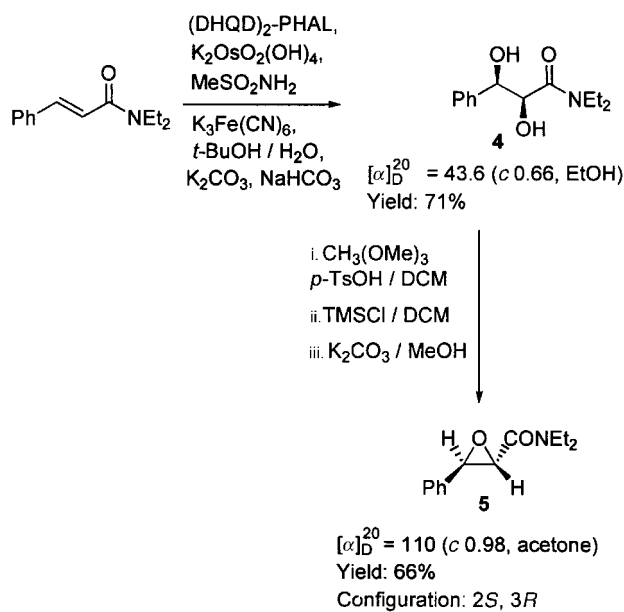
Table 1 Synthesis of chiral **3** by asymmetric epoxidation of aldehydes **2** with sulfonium salts **1** under phase transfer conditions^a

Entry	R in 2	R in 1	Conditions ^b	Yield (%) ^c (product)	Ee (%) ^d	Configuration ^f
1	<i>p</i> -ClC ₆ H ₄	Me	A	88 (3ab)	60.9	(2 <i>R</i> ,3 <i>S</i>)
2	<i>p</i> -ClC ₆ H ₄	-(CH ₂) ₅ -	A	68 (3cb)	54.8	(2 <i>R</i> ,3 <i>S</i>)
3	<i>p</i> -ClC ₆ H ₄	Et	A	89 (3bb)	60.1	(2 <i>R</i> ,3 <i>S</i>)
4	<i>p</i> -ClC ₆ H ₄	Et	B	92 (3bb)	60.2	(2 <i>R</i> ,3 <i>S</i>)
5	C ₆ H ₅	Et	A	61 (3ba)	71.5	2 <i>R</i> ,3 <i>S</i>
6	C ₆ H ₅	Et	B	93 (3ba)	66.4 (90.9 ^e)	2 <i>R</i> ,3 <i>S</i>
7	<i>p</i> -CF ₃ C ₆ H ₄	Et	A	49 (3bf)	63.8	(2 <i>R</i> ,3 <i>S</i>)
8	<i>p</i> -CF ₃ C ₆ H ₄	Et	B	90 (3bf)	63.4	(2 <i>R</i> ,3 <i>S</i>)
9	<i>p</i> -MeC ₆ H ₄	Et	A	93 (3bc)	54.2	(2 <i>R</i> ,3 <i>S</i>)
10	4-Biphenyl	Et	A	96 (3be)	69.7	(2 <i>R</i> ,3 <i>S</i>)
11	3-Pyridyl	Et	B	80 (3bh)	64.7	(2 <i>R</i> ,3 <i>S</i>)
12	<i>p</i> -NO ₂ C ₆ H ₄	Et	B	94 (3bg)	57.1	(2 <i>R</i> ,3 <i>S</i>)
13	<i>p</i> -NO ₂ C ₆ H ₄	Me	B	85 (3ag)	68.8 (95.4 ^e)	(2 <i>R</i> ,3 <i>S</i>)
14	Dodecyl	Et	B	70 (3bi)	10.9	(2 <i>R</i> ,3 <i>S</i>)
15	Cyclohexyl	Et	B	72 (3bj)	1.0	(2 <i>R</i> ,3 <i>S</i>)
16	<i>p</i> -FC ₆ H ₄	Et	B	80 (3bd)	60.6	(2 <i>R</i> ,3 <i>S</i>)

^a All reactions were carried out in a ratio of aldehyde:sulfonium salt = 1:1.2 at a 0.5 mmol scale. ^b Condition A: CH₃CN, KOH, RT; B: CH₂Cl₂, NaOH (10% aq), 0 °C. ^c Isolated yields based on aldehydes; only *trans* isomers were obtained. ^d Determined by chiral HPLC on a Chiralcel OD, OJ or Chiralpak AD column. ^e The ee values refer to those after single recrystallization from *n*-hexane. ^f Determined by chemical transformations. The configuration in parentheses is estimated by comparison with the phenyl analog. Signs of optical rotation of all compounds are (-).

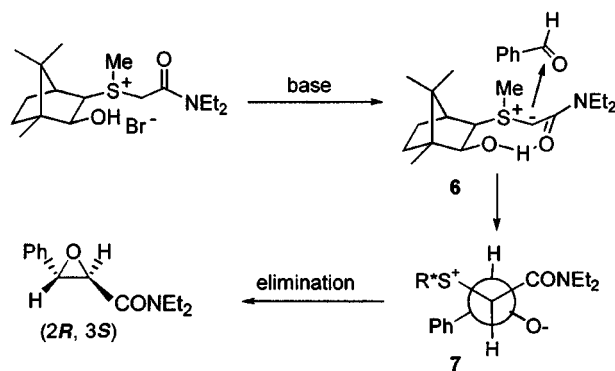
explain this result. Attempts to use ester stabilized ylides in this reaction failed and no sign of the existence of the *cis*-isomer in all products has been revealed.

The absolute configuration of 2,3-epoxyamides **3a** was determined by the following chemical transformations (Scheme 2).

**Scheme 2**

The 3-phenyl-2,3-dihydroxypropionamide **4** was synthesized by Sharpless asymmetric dihydroxylation (AD);¹¹ the configuration is known to be (2*S*,3*R*). This compound was then transformed to 2,3-epoxyamide **5** by a known literature method.¹² On the basis of the sign of optical rotation and absolute configuration (2*S*,3*R*) of compound **5**, (-)-**3a** is therefore unambiguously assigned as (2*R*,3*S*). The configurations of other 2,3-epoxyamides are assumed by the same signs of optical rotations and the analogous structural similarity.

The enantiocontrolled reduction observed here can be visualized by the mechanism shown in Scheme 3. Because the hydroxy and the carbonyl of the amide can form an intramolecular hydrogen bond, chiral sulfonium salt **1b** is deprotonated to afford a cyclic chiral sulfonium ylide **6**, then the ylide attacks the *re*-face of benzaldehyde followed by an immediate *anti*-elimination to furnish *trans*-(2*R*,3*S*) 2,3-epoxyamide **3ba**.

**Scheme 3**

There are some examples of chiral, sulfide-catalyzed asymmetric ylide epoxidation.¹³ They are catalytic with respect to the chiral reagents. High ee values (>90%) and de (>98%) were obtained with aromatic aldehydes, but lower de values (*trans/cis* = 2/1) were obtained with aliphatic aldehydes, and the reaction requires strict reaction conditions. The present asymmetric epoxidation is a stoichiometric reaction but may represent a promising practical approach to optically active epoxyamides due to its compatibility with a wide range of substrates, high yields and mild reaction conditions. Furthermore, the ylide precursor could be recovered in higher than 80% yield without loss of optical purity, and could be reused. Although the ee value of the product is not high (maximum 71.5%, entry 5), it could be increased by a single recrystallization from *n*-hexane. For example, the ee values of the products from entries 6 and 13 can be increased from 66.4% to 90.9% and from 68.8% to 95.4%.

In conclusion, we developed a simple and practical approach to optically active 2,3-epoxyamides *via* a chiral sulfonium ylide route under phase transfer conditions. The absolute configuration was assigned as (2*R*,3*S*) by known chemical transformations. As can be seen, the title compound is a very useful intermediate in organic synthesis.

Experimental

The commercially available reagents were used as received without further purification. Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in CDCl₃ at room temperature. Chemical shifts are given in parts per million downfield from tetramethyl-

silane. Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 20 °C (concentration *c* given as g per 100 mL). IR spectra were recorded in KBr and measured in cm⁻¹, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument. Ee values were determined by chiral HPLC on a Chiralcel OD, OJ column or a Chiralpak AD column. Chromatographic separations were achieved using a liquid chromatograph constructed from the following components: a Waters M510 pump operating at 0.7 mL min⁻¹, a M440 UV detector (Waters, UV 254 or 214 nm), a Rheodyne M7725 injector and 250 × 4.6 mm i.d. Chiralpak AD, Chiralcel OJ and Chiralcel OD columns. The detector output was stored and reprocessed using a Perkin-Elmer Nelson 1022. The temperature is about 20 °C. Chiral sulfide (+)-*exo*-3-(methylthio)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol,¹⁰ **4**¹¹ and α -bromo acetamides¹⁴ were prepared according to the literature procedures. Sulfonium bromides **1a**, **1b** and **1c** were prepared by the reaction of the corresponding α -bromo acetamides with the chiral sulfide in a small amount of acetone at room temp. with excellent yields.

General procedure for epoxidation under liquid–liquid phase-transfer conditions

To a solution of aldehyde **2** (0.5 mmol) in dichloromethane (5 mL) was added the chiral sulfonium salt **1** (0.6 mmol) and 10% aqueous NaOH (0.3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Water (2 mL) was then added and the organic phase separated. The aqueous phase was extracted twice with dichloromethane (2 × 5 mL). The organic layers were washed with water, dried with MgSO₄, concentrated and chromatographed on a silica gel with a mixture of petroleum ether and ethyl acetate (3 : 1) to give the pure product **3**.

General procedure for epoxidation under solid–liquid phase-transfer conditions

A 25 mL flask containing a magnetic stirring bar was charged with aldehyde **2** (1.0 equiv.), sulfonium salt **1** (1.2 equiv.) and acetonitrile (4 mL, reagent grade, it need not be dried before use). Powdered KOH (1.2 equiv.) was subsequently added under stirring. After the reaction was complete according to TLC, the reaction mixture was filtered on a short neutral Al₂O₃ column to remove the inorganic salt. The filtrate was concentrated and chromatographed on a silica gel column with a mixture of light petroleum ether and ethyl acetate (3 : 1) as the eluent to give pure product **3**.

trans-N,N-Diethyl-3-phenyl-2,3-epoxypropionamide 3ba. (Found: C, 71.27; H, 7.86; N, 6.21; C₁₃H₁₇NO₂ requires C, 71.21; H, 7.81; N, 6.39%); [α]_D²⁰ –68.3 (*c*, 1.10, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.16 (3H, t, *J* 7.1, -CH₂CH₃), 1.25 (3H, t, *J* 7.1, -CH₂CH₃), 3.42 (2H, q, *J* 7.1, -CH₂CH₃), 3.56 (2H, q, *J* 7.1, -CH₂CH₃), 3.59 (1H, d, *J* 2.1, CH), 4.09 (1H, d, *J* 2.0, CH), 7.36 (5H, m, ArH); MS *m/z* 220 (M⁺ + 1, 16.6), 219 (M, 54.9), 200 (28.0), 147 (12.7), 100 (91.6), 91 (58.2), 72 (100), 56 (78.5); IR (KBr) 1646 (C=O) cm⁻¹. Chiralcel OD, hexane-*i*-PrOH (80 : 20); 9.9 min (2S,3R), 10.9 min (2R,3S).

trans-N,N-Dimethyl-3-(4-nitrophenyl)-2,3-epoxypropionamide 3ag. (Found: C, 55.75; H, 5.19; N, 11.93; C₁₁H₁₂N₂O₄ requires C, 55.93; H, 5.12; N, 11.86%); [α]_D²⁰ –80.1 (*c*, 1.08, acetone); ¹H NMR (300 MHz, CDCl₃) δ 3.04 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.64 (1H, d, *J* 1.9, CH), 4.23 (1H, d, *J* 1.8, CH), 7.57 (2H, d, *J* 8.7, ArH), 8.24 (2H, d, *J* 8.7, ArH); MS *m/z* 236 (M⁺, 6.2), 89 (20), 72 (100); IR (KBr) 1651 (C=O). Chiralcel OD, hexane-*i*-PrOH (60 : 40); 34.7 min (2S,3R), 36.7 min (2R,3S).

trans-N,N-Diethyl-3-(biphenyl-4-yl)-2,3-epoxypropionamide 3be. (Found: C, 71.27; H, 7.86; N, 6.21; C₁₃H₁₇NO₂ requires C, 71.21; H, 7.81; N, 6.39%); [α]_D²⁰ –87.5 (*c*, 1.40, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.18 (3H, t, *J* 7.3, -CH₂CH₃), 1.25 (3H, t, *J* 7.3, -CH₂CH₃), 3.47 (m, -CH₂CH₃), 3.64 (1H, d, *J* 2.1, CH), 4.14 (1H, d, *J* 1.8, CH), 7.42 (5H, m, ArH), 7.62 (4H, m, ArH); MS *m/z* 296 (M⁺ + 1, 50.5), 295 (M, 82.9), 238 (34.6), 165 (86), 152 (39), 100 (100), 72 (49.5), 56 (52.3); IR (KBr) 1653 (C=O). Chiralcel OD, hexane-*i*-PrOH (90 : 10); 25.3 min (2R,3S), 28.3 min (2S,3R).

trans-1-[3-(4-Chlorophenyl)-2,3-epoxypropionyl]piperidine 3cb. (Found: C, 63.36; H, 6.23; N, 5.10; C₁₄H₁₆ClNO₂ requires C, 63.28; H, 6.07; N, 5.27%); [α]_D²⁰ –70.7 (*c*, 0.60, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.55–1.75 (6H, m, -(CH₂)₃-), 3.40–3.70 (4H, m, -NCH₂-), 3.63 (1H, d, *J* 1.9, CH), 4.04 (1H, d, *J* 1.9, CH), 7.29 (4H, m, ArH); MS *m/z* 265 (M⁺, 13), 248 (15), 125 (50), 112 (42), 96 (100), 84 (37), 69 (55); IR (KBr) 1649 (C=O). Chiralcel OJ, hexane-*i*-PrOH (80 : 20); 13.6 min (2S,3R), 16.7 min (2R,3S).

trans-N,N-Diethyl-3-(4-chlorophenyl)-2,3-epoxypropionamide 3bb. (Found: C, 62.36; H, 6.36; N, 5.23; C₁₃H₁₆ClNO₂ requires C, 61.54; H, 6.38; N, 5.52%); [α]_D²⁰ –56.4 (*c*, 1.25, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.16 (3H, t, *J* 7.2, -CH₂CH₃), 1.22 (3H, t, *J* 7.2, -CH₂CH₃), 3.45 (4H, m, -CH₂CH₃), 3.54 (1H, d, *J* 1.5, CH), 4.08 (1H, d, *J* 1.8, CH), 7.27 (2H, d, *J* 8.5, ArH), 7.35 (2H, d, *J* 8.7, ArH); ¹³C NMR (300 MHz, CDCl₃) δ 12.95, 14.95, 40.98, 41.56, 56.99, 57.24, 127.05, 128.89, 165.38; MS *m/z* 255 (M⁺, 8, ³⁷Cl), 253 (M⁺, 27, ³⁵Cl), 195 (50), 165 (43), 149 (58), 100 (59), 72 (97), 56 (87), 44 (100); IR (KBr) 1650 (C=O). Chiralcel OD, hexane-*i*-PrOH (80 : 20); 11.1 min (2S,3R), 13.2 min (2R,3S).

trans-N,N-Diethyl-3-(4-fluorophenyl)-2,3-epoxypropionamide 3bd. (Found: C, 65.62; H, 6.75; N, 5.60; C₁₃H₁₆FNO₂ requires C, 65.81; H, 6.80; N, 5.90%); [α]_D²⁰ –27.0 (*c*, 1.05, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.17 (3H, t, *J* 7.1, -CH₂CH₃), 1.24 (3H, t, *J* 7.3, -CH₂CH₃), 3.45 (4H, m, -CH₂CH₃), 3.55 (1H, d, *J* 2.0, CH), 4.08 (1H, d, *J* 1.8, CH), 7.06 (2H, m, ArH), 7.31 (2H, m, ArH); MS *m/z* 238 (M⁺ + 1, 16), 237 (M⁺, 86), 220 (31), 149 (44), 128 (77), 100 (100), 72 (100), 56 (55); IR (KBr) 1649 (C=O). Chiralcel OD, hexane-*i*-PrOH (90 : 10); 10.9 min (2S,3R), 11.9 min (2R,3S).

trans-N,N-Diethyl-3-(4-methylphenyl)-2,3-epoxypropionamide 3bc. (Found: C, 72.08; H, 8.13; N, 5.65; C₁₄H₁₉NO₂ requires C, 72.07; H, 8.21; N, 6.00%); [α]_D²⁰ –66.7 (*c*, 1.10, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.16 (3H, t, *J* 7.1, -CH₂CH₃), 1.20 (3H, t, *J* 7.2, -CH₂CH₃), 2.35 (3H, s, ArMe), 3.46 (4H, m, -CH₂CH₃), 3.58 (1H, d, *J* 2.1, CH), 4.04 (1H, d, *J* 2.0, CH), 7.20 (4H, m, ArH); MS *m/z* 255 (M⁺ + 1, 17), 233 (M⁺, 76), 216 (18), 176 (30), 100 (92), 72 (100), 56 (99); IR (KBr) 1646 (C=O). Chiralcel OD, hexane-*i*-PrOH (95 : 5); 9.1 min (2S,3R), 10.3 min (2R,3S).

trans-N,N-Diethyl-3-(3-pyridyl)-2,3-epoxypropionamide 3bh. [α]_D²⁰ –70.6 (*c*, 0.59, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.09 (3H, t, *J* 7.2, -CH₂CH₃), 1.15 (3H, t, *J* 7.2, -CH₂CH₃), 3.36 (4H, m, -CH₂CH₃), 3.57 (1H, d, *J* 1.8, CH), 4.06 (1H, d, *J* 1.8, CH), 7.25 (1H, m, ArH), 7.55 (1H, m, ArH), 8.50 (2H, m, ArH); MS *m/z* (EI) 222 (M⁺ + 2, 17.9), 221 (M⁺ + 1, 100), 220.1212 (M⁺, C₁₂H₁₆N₂O₂ requires 220.1254, 2.5), 163 (3), 110 (10), 72 (10); IR (KBr) 1650 (C=O). Chiralcel OD, hexane-*i*-PrOH (80 : 20); 18.6 min (2S,3R), 23.7 min (2R,3S).

trans-N,N-Diethyl-3-(4-nitrophenyl)-2,3-epoxypropionamide 3bg. (Found: C, 58.75; H, 5.75; N, 10.47; C₁₃H₁₆N₂O₄ requires C, 59.08; H, 6.10; N, 10.6%); [α]_D²⁰ –56.4 (*c*, 1.03, acetone); ¹H

NMR (300 MHz, CDCl₃) δ 1.11 (3H, t, *J* 7.2, -CH₂CH₃), 1.16 (3H, t, *J* 7.2, -CH₂CH₃), 3.40 (4H, m, -CH₂CH₃), 3.51 (1H, d, *J* 1.8, CH), 4.17 (1H, d, *J* 1.8, CH), 7.44 (2H, d, *J* 8.7, ArH), 8.16 (2H, d, *J* 8.7, ArH); MS *m/z* 265 (M⁺ + 1, 100), 264 (M⁺, 22), 192 (29), 100 (48), 99 (31), 72 (49); IR (KBr) 1655 (C=O). Chiralcel OD, hexane-*i*-PrOH (80:20); 23.9 min (2*S*,3*R*), 27.1 min (2*R*,3*S*).

trans-N,N-Diethyl-3-(4-trifluoromethylphenyl)-2,3-epoxypropionamide 3bf. (Found: C, 58.34; H, 5.74; N, 4.64; C₁₄H₁₆F₃O₂ requires C, 58.53; H, 5.64; N, 4.88%); [α]_D²⁰ -42.1 (*c*, 1.00, acetone); ¹H NMR (300 MHz, CDCl₃) δ 1.04 (3H, t, *J* 7.2, -CH₂CH₃), 1.11 (3H, t, *J* 7.2, -CH₂CH₃), 3.36 (4H, m, -CH₂CH₃), 3.48 (1H, d, *J* 1.8, CH), 4.06 (1H, d, *J* 1.6, CH), 7.36 (2H, d, *J* 8.2, ArH), 7.53 (2H, d, *J* 8.3, ArH); MS *m/z* 288 (M⁺ + 1, 10), 264 (M⁺, 30), 270 (53), 195 (28), 173 (32), 159 (62), 100 (74), 72 (100), 56 (60); IR (KBr) 1647 (C=O). Chiralcel OD, hexane-*i*-PrOH (80:20); 11.6 min (2*S*,3*R*), 15.8 min (2*R*,3*S*).

trans-N,N-Dimethyl-3-(4-chlorophenyl)-2,3-epoxypropionamide 3ab. [α]_D²⁰ -14.2 (*c*, 1.25, acetone); ¹H NMR (300 MHz, CDCl₃) δ 2.99 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.58 (1H, d, *J* 2.0, CH), 3.96 (1H, d, *J* 2.0, CH), 7.26 (5H, m, ArH). Chiralcel OD, hexane-*i*-PrOH (80:20); 18.2 min (2*S*,3*R*), 19.5 min (2*R*,3*S*).

trans-N,N-Diethyl-3-dodecyl-2,3-epoxypropionamide 3bi. ¹H NMR (300 MHz, CDCl₃) δ 0.78 (3H, t, *J* 6.7, -CH₂CH₃), 1.03 (3H, t, *J* 7.1, -CH₂CH₃), 1.10-1.60 (23H, m, -(CH₂)₁₀CH₃), 3.04 (1H, dt, *J* 2.5 and 5.6, CH), 3.22 (1H, d, *J* 2.1, CH), 3.43 (4H, m, -CH₂CH₃); MS *m/z* 299 (M⁺ + 2, 26.7), 298.2746 (M⁺ + 1, C₁₉H₃₇NO₂ requires 298.2746, 100), 270 (53), 195 (28), 173 (32), 159 (62), 100 (74), 72 (100), 56 (60); IR (KBr) 1656 (C=O). Chiralcel OD, hexane-*i*-PrOH (95:5); 10.8 min (2*S*,3*R*), 12.1 min (2*R*,3*S*).

trans-N,N-Diethyl-3-cyclohexyl-2,3-epoxypropionamide 3bj. ¹H NMR (300 MHz, CDCl₃) δ 1.10-1.40 (12H, m, -CH₂CH₂-CH₂- and CH₃CH₂-), 1.50-1.80 (5H, m, -CH₂CHCH₂-), 2.93 (1H, dd, *J* 2.1 and 6.6, CH), 3.40-3.60 (5H, m, -CH₂CH₃ and CH); MS *m/z* 226 (M⁺ + 1, 100), 225.1726 (M⁺, C₁₃H₂₃NO₂ requires 225.1729, 208 (45), 142 (8), 100 (15), 72 (25); IR (KBr) 1660 (C=O). Chiralcel OD, hexane-*i*-PrOH (95:5); 6.5 min (2*S*,3*R*), 7.5 min (2*R*,3*S*).

The determination of absolute configuration of reaction product

Trimethyl orthoacetate (0.383 mL, 3.0 mmol) was added to a stirred solution of **4** (475 mg, 2.0 mmol) and toluene-*p*-sulfonic acid monohydrate (10 mg) in dichloromethane (12 mL). After 15 min, the mixture was evaporated and the residual MeOH was removed at *ca.* 0.5 mmHg for 5 min. The residue was taken up in dichloromethane (5 mL), to which TMSCl (0.41 mL, 2.83 mmol) was added. After 100 min, TLC showed almost complete absence of orthoacetate, the mixture was heated to reflux for 60 min, and then allowed to cool. Evaporation under reduced pressure gave the crude acetoxy chloride as an oil. Potassium carbonate (355 mg, 2.52 mmol) was added in 2 portions over 10 min to a vigorously stirred solution of the crude acetoxy chloride in MeOH (12 mL) at -20 °C. After 2 h, the mixture was poured into a saturated aqueous NH₄Cl solution (12 mL) and extracted with dichloromethane (3 × 30 mL), dried over Na₂SO₄. Purification of the residue by flash chromatography (petroleum ether-ethyl acetate 3:1) afforded epoxyamide **5** as a white solid 288 mg (66%). [α]_D²⁰ = 110° (*c* 0.98, acetone). The absolute configuration of compounds **5** is (2*S*,3*R*). On the basis of the sign of optical rotation and absolute configuration (2*S*,3*R*) of compound **5**, (-)-**3a** is therefore unambiguously assigned as (2*R*,3*S*).

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