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A new synthesis of enantiomerically pure α- and β-amino acid derivatives using aziridinyl anions

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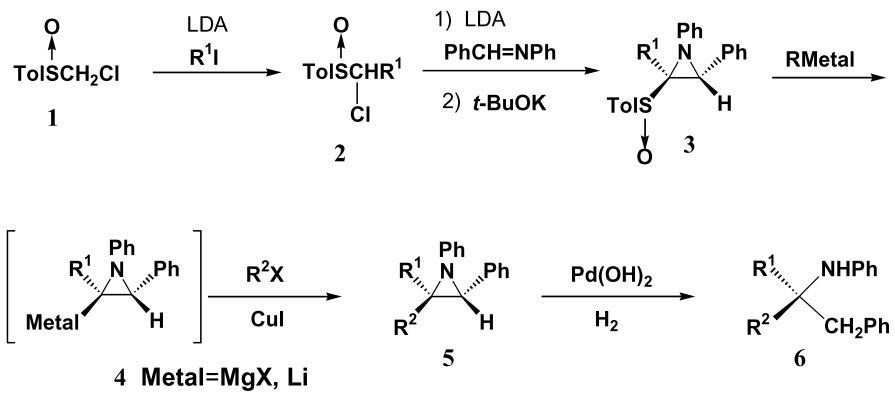
Abstract—Optically active sulfinylaziridines having a 4-methoxyphenyl group on their nitrogen atom were synthesized from optically active 1-chloroalkyl *p*-tolyl sulfoxide and an imine derived from benzaldehyde and *p*-anisidine stereoselectively in good overall yields. The sulfinylaziridines were treated with ethylmagnesium bromide or *tert*-butyllithium to afford aziridinylmagnesiums or aziridinyllithiums, respectively, in quantitative yields. Cross-coupling of the aziridinylmagnesiums with iodoalkanes in the presence of Cu(I) iodide gave tri-substituted aziridines in high yields from which enantiomerically pure β,β-disubstituted β-amino acid derivatives were synthesized. A β-amino acid derivative having deuterium at the stereogenic center was also realized by this method. On the other hand, from the aziridinyllithium, enantiomerically pure quaternary phenylalanine and quaternary aspartic acid derivatives were synthesized.

α-Amino acids and β-amino acids are fundamental compounds in the area of biology, medicine, biochemistry, material science, and synthetic organic chemistry. For this reason, the stereoselective synthesis of natural and unnatural α-amino acids[1] and β-amino acids[2] is of much interest these days. In addition, quaternary amino acids (α,α-disubstituted α-amino acids and β,β-disubstituted β-amino acids) have received considerable recent attention in the area of bioorganic chemistry. In synthetic organic chemistry, the asymmetric synthesis of a stereogenic quaternary carbon center is an interesting and challenging target in its own right.[3]

Over the last few years, we have been studying the generation of aziridinyl anions **4**[4] from sulfinylaziridines **3**, which were synthesized stereoselectively from 1-chloroalkyl *p*-tolyl sulfoxide **2** and benzalaniline in high yields, by a sulfoxide–metal exchange reaction.[5] We also investigated this chemistry of the aziridinyl anions **4** to develop a new method for synthesis of optically active amines **6** by the use of optically active chloromethyl *p*-tolyl sulfoxide **1** (Scheme 1).[6]

In continuation of our interest in the use of the generated aziridinyl anions in organic synthesis, we planned to develop the above-mentioned chemistry to a new synthesis of optically active α- and β-amino acid derivatives starting from the optically active sulfoxide **2** (Scheme 2). The key



Scheme 1.

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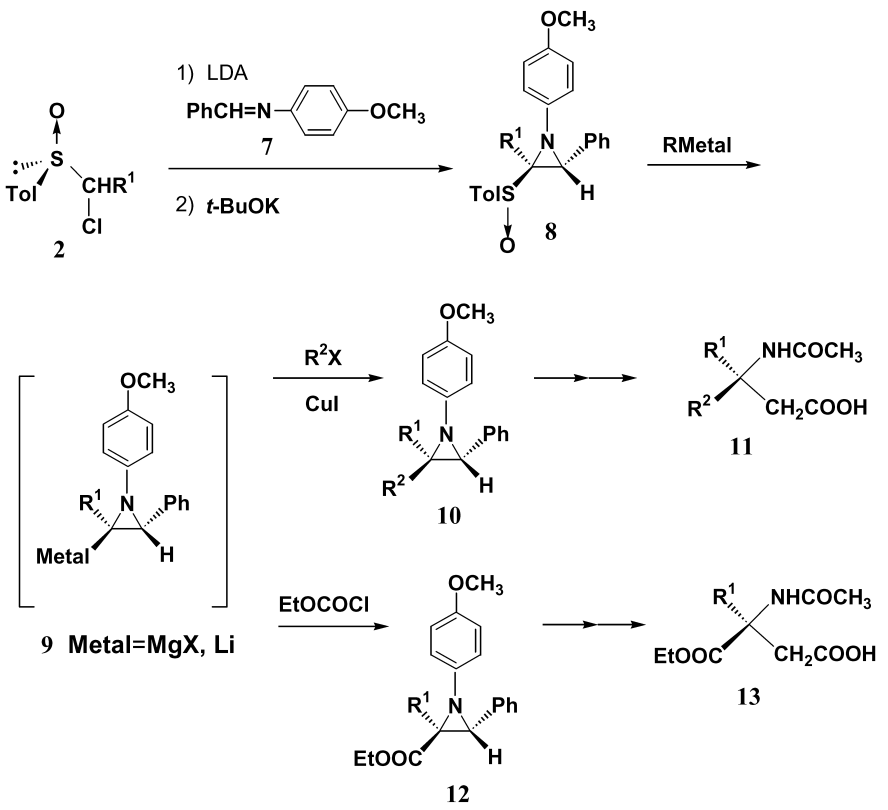


Scheme 2.

improvement step is the use of a *p*-methoxyphenyl group instead of the phenyl group in order to remove the aromatic ring on the nitrogen at a later stage. We also utilized the phenyl group on the aziridine ring as a masked carboxyl group. Herein we report a novel synthesis of both enantiomers of the β,β-disubstituted β-amino acid derivatives **11** and β-amino acid derivatives bearing a deuterium at the stereogenic center **11** (R^2=D), from the aziridinylmagnesium **9** (Metal=MgBr) through the enantiomerically pure tri-substituted aziridine **10**. A synthesis of a quaternary phenylalanine derivative and quaternary aspartic acid derivative **13** through the ethoxycarbonylation of the aziridinyllithium **9** (Metal=Li) is also described.

1. Results and discussion

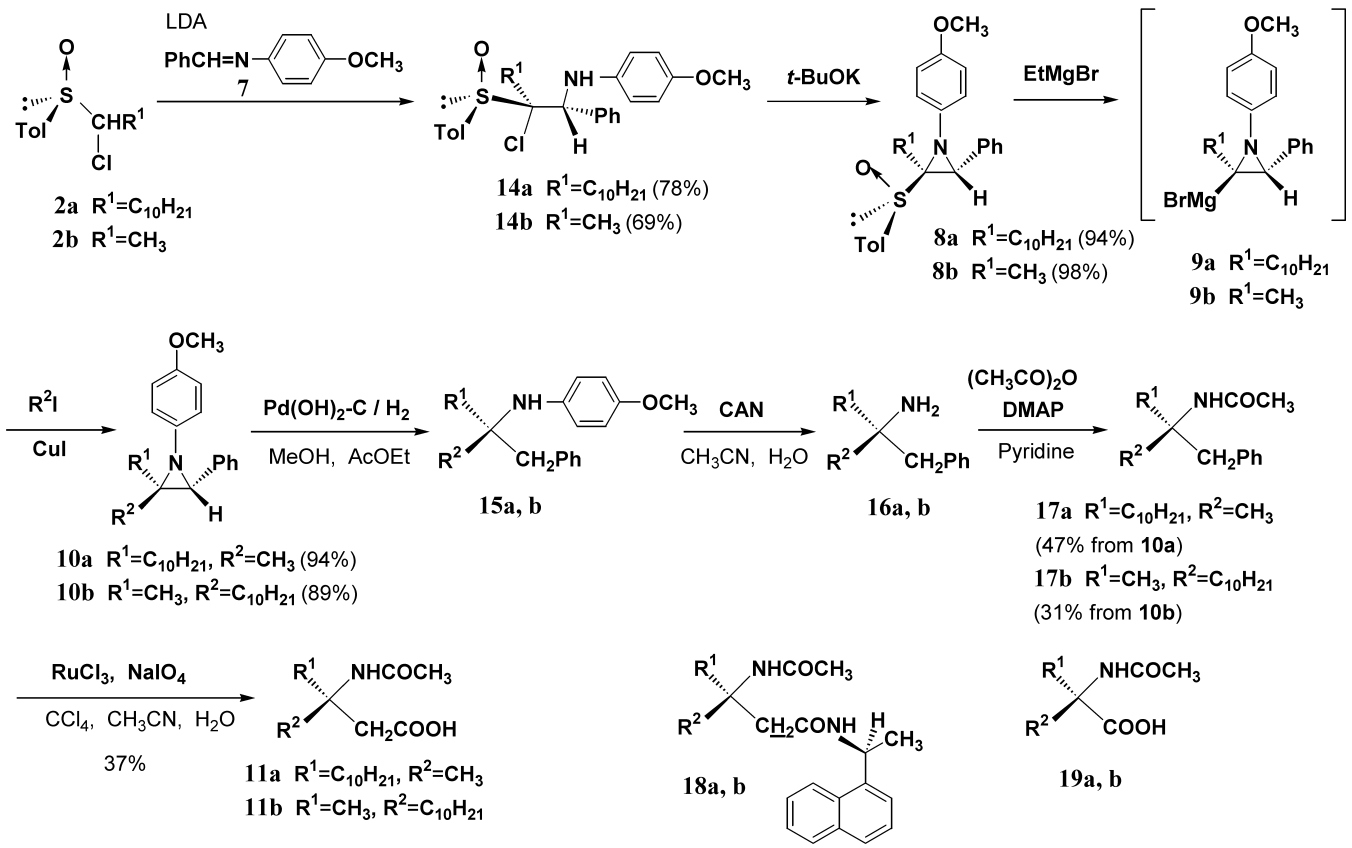
1.1. Synthesis of both enantiomers of β,β-disubstituted β-amino acid derivatives

First, the optically pure 1-chloroundecyl *p*-tolyl sulfoxide **2a**[6d] was treated with LDA at −78°C followed by the imine **7** to give the adduct **14a** in 78% yield as colorless crystals. As already observed in the previous study, the product was a single diastereo isomer even though the adduct has three chiral centers.[5b] The absolute configuration of the adduct **14a** was determined to be as shown in Scheme 3 by comparison of the spectral data with those in the previous studies.[5b,6d] The adduct **14a** was treated with *tert*-BuOK in THF to afford the optically active sulfinylaziridine **8a** in 94% yield. By similar treatment, optically active sulfinylaziridine **8b** was synthesized from **2b**[6d] and the imine **7** through the adduct **14b** in good overall yield (Scheme 3).

A solution of the sulfinylaziridine **8a** in THF was added to a solution of EtMgBr (3.5 equiv.) at −78°C and the reaction mixture was slowly allowed to warm to room temperature to give aziridinylmagnesium **9a**. The aziridinylmagnesium **9a** was found to be stable at room temperature for several hours without decomposition and structural isomerization.

To the solution of **9a**, Cu(I) iodide (10 mol%) was added and after 10 min, iodomethane (3.5 equiv.) was added and the reaction mixture was stirred at room temperature for 30 min to afford the desired tri-substituted aziridine **10a** ($[\alpha]_D$=−87.0, *c* 0.5 in acetone) in 94% yield as a single product. Similar treatment of **8b** with EtMgBr followed by iododecane gave the tri-substituted aziridine **10b** ($[\alpha]_D$=−92.8, *c* 0.5 in acetone) in 89% yield. It is worth noting that **10a** and **10b** are diastereomers of each other.

Next, the synthesized aziridine **10a** was regioselectively cleaved at the benzylic position by catalytic hydrogenation using palladium hydroxide as a catalyst[7] under hydrogen atmosphere to give cleanly the amine **15a**. The amine **15a** was found to be easily adsorbed on silica gel, so without further purification, the amine was treated with ceric (IV) ammonium nitrate (CAN)[8] to afford the free amine **16a**. The produced **16a** was again presumed to be unstable on silica gel; it was successively acetylated to give the acetamide **17a** in 47% overall yield from **10a**. The amide **17a** was a stable compound and showed specific rotation $[\alpha]_D$=+28.9 (*c* 0.5 in acetone). The same treatment of **10b** afforded **17b** in



Scheme 3.

somewhat lower yield. The produced amide **17b** showed the same IR and NMR spectra as those of **17a**; however, the value for the specific rotation was −30.9. These data clearly indicated that **17a** and **17b** are enantiomers to each other. The enantiomeric purity of both **17a** and **17b** was determined to be over 99% by HPLC using chiral column (Daicel, CHIRALCEL OD; hexane–2-propanol=9:1).

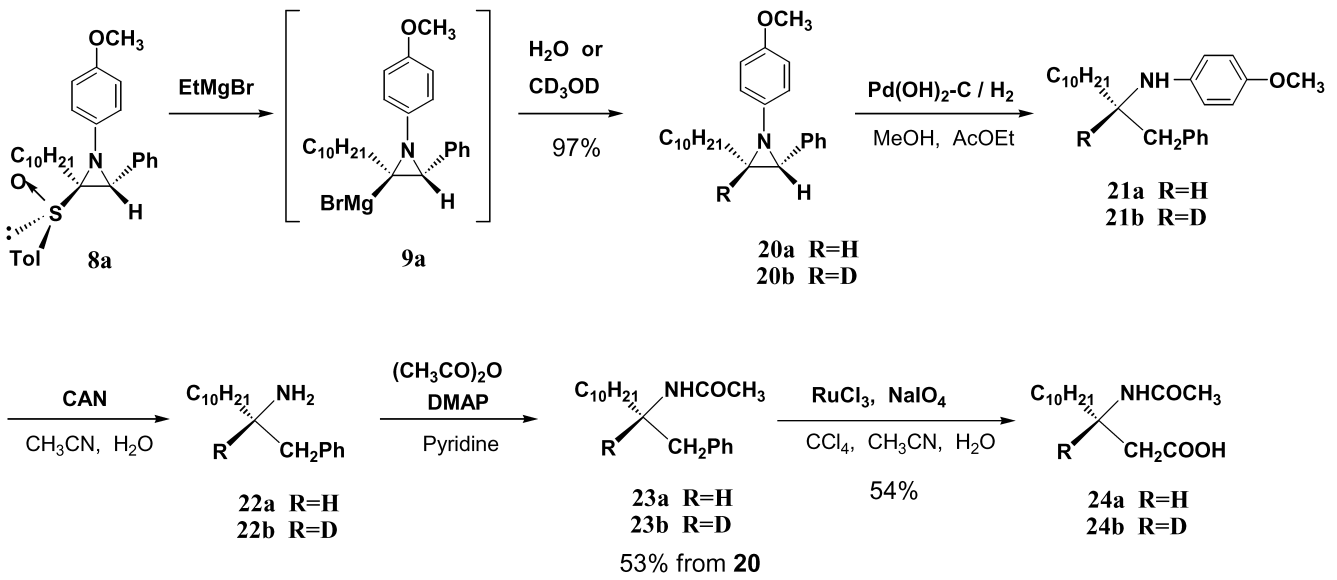
Finally, oxidative degradation of the benzene ring in **17a** and **17b** was carried out under the Sharpless conditions[9] to give the desired quaternary β-amino acids **11a** and **11b**. Interestingly, both **11a** and **11b** showed no specific rotation; however, racemization was quite unlikely in this oxidation step. We determined the enantiomeric purity by using racemic **11** and its methyl ester. Several trials to separate the enantiomers with HPLC and GC (using chiral column) were not successful. Finally, the racemic **11** was derived into its (*S*)-(−)-1-(1-naphthyl)ethylamide **18**.[10] ^{1}H NMR spectroscopy of the produced mixture of two diastereomers was measured and the methylene proton underlined (see Scheme 3) was clearly separated. By this technique, the enantiomeric purity of both **11a** and **11b** was found to be over 99%.

In a detailed inspection of the products for the oxidative degradation of the benzene ring, we found a small amount of α-amino acids **19a** and **19b**. Treatment of **11** with the oxidation conditions ($RuCl_2$–$NaIO_4$) did not give α-amino acid **19**. We are not sure of the mechanism for the formation of the α-amino acids at present. In any event, a synthesis of both enantiomers of the quaternary β-amino acids **11a** and **11b** was successful, in enantiomerically pure form, through the aziridinylmagnesium as the key intermediate.

1.2. A synthesis of a chiral β-amino acid having deuterium at the stereogenic center

As described above, the aziridinylmagnesium **9a** is configurationally highly stable; protonation of **9a** gave diastereomerically pure aziridine **20a** in quantitative yield. In addition, reaction of **9a** with methyl-d_3 alcohol-*d* (CD_3OD) gave deuterated aziridine **20b**. This reaction is quite interesting for a synthesis of deuterium-labeled optically active compounds at the stereogenic center (Scheme 4).

The aziridine **20** was hydrogenated under H_2 atmosphere with $Pd(OH)_2$ as a catalyst to give **21** in good yield. The *p*-methoxyphenyl group of **21** was eliminated with CAN and the produced amine **22** was acetylated without further purification to afford the amide **23**, but the overall yield of the amide **23** was somewhat low. Taking into account the instability of the amine **22**, we conducted the one-pot conversion of the *p*-methoxyphenyl group of **21** to the acetyl group of the amide **23**, which resulted in good overall yield of the amide **23** (53% from **20a**).[11] The enantiomeric purity of this amide **23** could be determined by using HPLC and it was found to be over 99%. Finally, the phenyl ring in **23** was oxidatively converted into a carboxylic acid to give β-amino acid derivative **24a** in moderate yield. The deuterium-labeled enantiomerically pure β-amino acid derivative **24b** was also successfully synthesized.



Scheme 4.

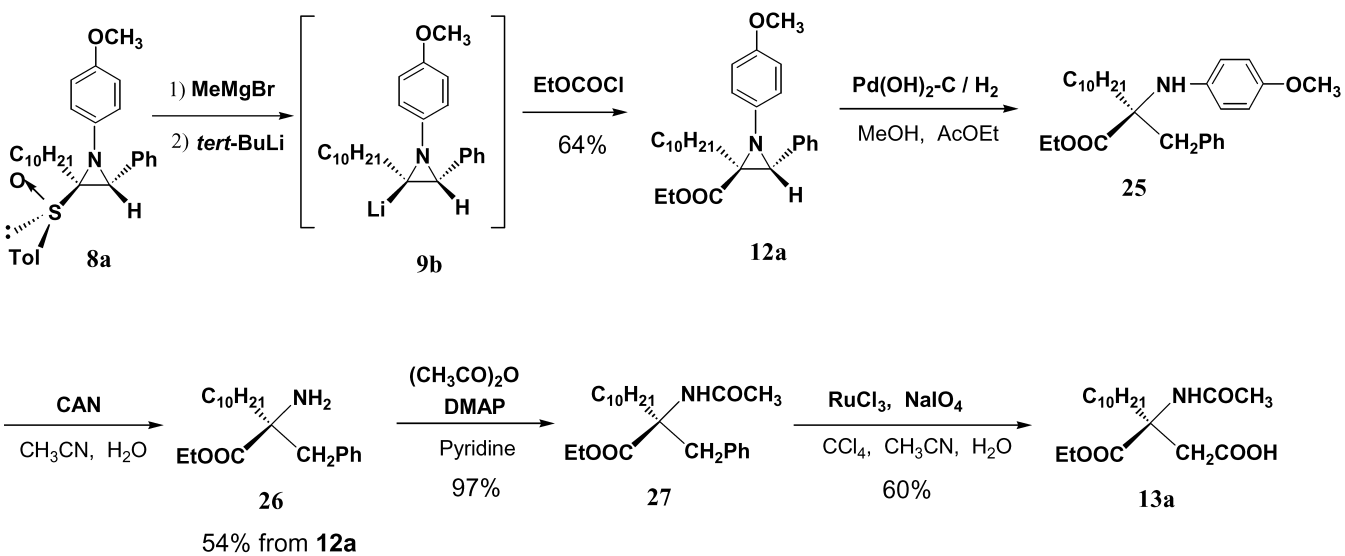
Interestingly, deuterated **24b** showed low value for the specific rotation ($[\alpha]_D$=+0.76, *c* 1.4 in MeOH) although **24a** has specific rotation $[\alpha]_D$=+2.0 (*c* 1.0 in MeOH). This method is found to be useful for the labeled β-amino acid derivatives having deuterium at the stereogenic center.

1.3. Synthesis of enantiomerically pure quaternary phenylalanine derivative and quaternary aspartic acid derivative via aziridinyllithium as the key intermediate

As has been already reported from our research group[6a,b] the sulfinylaziridine **8a** gave the aziridinyllithium **9b** on treatment with *tert*-butyllithium at lower than −30°C. The aziridinyllithum **9b** was found to be reactive with ethyl chloroformate in a stereospecific manner to give ethoxycarbonylated aziridine **12a** without any other diastereomers. Recently, we investigated this reaction in the development of a new synthetic method for quaternary phenylalanine derivative **26** and quaternary aspartic acid derivative **13a** in enantiomerically pure form; herein we report in detail the results (Scheme 5).

First, a solution of **8a** in THF at −78°C was treated with methylmagnesium bromide followed by *tert*-butyllithium to afford the aziridinyllithium **9b**. After 1 min, ethyl chloroformate was added to give the desired optically active ethoxycarbonylated aziridine **12a** in moderate yield. The aziridine **12a** was hydrogenated with $Pd(OH)_2$ to give a quaternary phenylalanine derivative **25** in good yield. The *p*-methoxyphenyl group of **25** was eliminated with CAN to give quaternary phenylalanine ethyl ester **26** in enantiomerically pure form.

Finally, the amino group of **26** was acetylated and the produced amide **27** was oxidized with $RuCl_3$–$NaIO_4$ to give optically pure quaternary aspartic acid derivative **13a** in good yield.



Scheme 5.

In conclusion, we have successfully synthesized several α- and β-amino acid derivatives in enantiomerically pure form from optically active 1-chloroalkyl *p*-tolyl sulfoxides **2** and imine **7** via the enantiomerically pure sulfinylaziridine **8** and the aziridinylmagnesium and aziridinyllithium **9** as the key intermediates. At the same time, we were able to demonstrate that the aziridinyl anions are quite important and versatile intermediates in organic synthesis.

2. Experimental

2.1. General

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 400 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silical gel 60 (MERCK) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, dichloromethane, diisopropylamine, pyridine, and toluene were distilled from CaH_2 and THF was distilled from diphenylketyl. Methanol and liquid N_2 were used for the cooling bath at −100°C.

2.1.1. (1*R*,2*R*,R_S)-2-Chloro-1-(4-methoxyphenylamino)-1-phenyl-2-(*p*-tolylsulfinyl)dodecane (14a). To a solution of LDA (3.6 mmol) in 10 mL of THF at −78°C was added a solution of **2a** (1 g; 3 mmol) in 4 mL of THF dropwise with stirring. After 10 min, a solution of imine **7** (0.76 g; 3.6 mmol) in 2 mL of THF was added to the reaction mixture and the reaction mixture was stirred at −78°C for 30 min. The reaction was quenched by sat. aq. NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. The solvent was evaporated to give colorless crystals, which were collected on a glass filter and washed with a mixture of AcOEt–hexane (10:1) to give pure **14a** (1.26 g; 78%). Colorless crystals; mp 132–133°C (AcOEt–hexane). IR (KBr) 3295 (NH), 2920, 2852, 1510, 1251, 1039 (SO) cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=6.4 Hz), 1.2–2.0 (18H, m), 2.36 (3H, s), 3.68 (3H, s), 4.06 (1H, s), 6.23, 6.60 (each 2H, d, J=9 Hz), 7.1–7.7 (9H, m). $[\alpha]_D^{27}$=−194.6 (*c* 1.0 acetone).

Compound Racemic-**14a**. Colorless crystals; mp 127–130°C (AcOEt–hexane). IR (KBr) 3293 (NH), 1514, 1251, 1039 (SO) cm^{-1}; MS *m/z* (%) 539 (M$^+$, 0.6), 399 (100), 272 (82). Anal. calcd for $C_{32}H_{42}ClNO_2S$: C, 71.15; H, 7.84; Cl, 6.56, N, 2.59; S, 5.94. Found: C, 71.36; H, 7.82; Cl, 6.67; N, 2.41; S, 5.99.

2.1.2. (1*R*,2*R*,R_S)-2-Chloro-1-(4-methoxyphenylamino)-1-phenyl-2-(*p*-tolylsulfinyl)propane (14b). Colorless crystals (69%); mp 170–172°C (AcOEt–hexane). IR (KBr) 3304 (NH), 1511, 1251, 1038 (SO) cm^{-1}; ^{1}H NMR δ 1.84 (3H, s), 2.39 (3H, s), 3.68 (3H, s), 4.36 (1H, d, J=3 Hz), 5.57 (1H, d, J=3 Hz, NH), 6.39, 6.63 (each 2H, d, J=9 Hz), 7.2–7.6 (9H, m). $[\alpha]_D^{30}$=−184.3 (*c* 0.5 acetone).

Compound Racemic-**14b**. Colorless crystals; mp 165–168°C (AcOEt–hexane); IR (KBr) 3302 (NH), 1509, 1252, 1037 (SO) cm^{-1}; MS *m/z* (%) 413 (M$^+$, 9), 361 (4), 273 (74), 238 (78), 212 (84), 122 (100). Anal. calcd for $C_{23}H_{24}ClNO_2S$: C, 66.74; H, 5.84; Cl, 8.56; N, 3.38; S, 7.75. Found: C, 66.49; H, 5.72; Cl, 8.72; N, 3.18; S, 7.80.

2.1.3. (2*R*,3*R*,R_S)-2-Decyl-1-(4-methoxyphenyl)-3-phenyl-2-(*p*-tolylsulfinyl)aziridine (8a). To a solution of **14a** (550 mg; 1.02 mmol) in THF (25 mL) at 70°C was added a suspension of *t*-BuOK (285 mg; 2.55 mmol) in 5 mL of *t*-BuOH. The reaction mixture was stirred at 70°C for 40 min. After cooling the reaction mixture to room temperature, the reaction was quenched by sat. aq. NH_4Cl. The whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give **8a** (482 mg; 94%) as a colorless oil; IR (neat) 2926, 2854, 1507, 1242, 1084, 1056 (SO) cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=7 Hz), 1.0–1.3 (16H, m), 1.6–1.8 (2H, m), 2.41 (3H, s), 3.78 (3H, s), 4.62 (1H, s), 6.87, 7.05 (each 2H, d, J=9 Hz), 7.2–7.7 (9H, m). MS *m/z* (%) 503 (M$^+$, trace), 478 (1.4), 364 (28), 274 (100). Calcd for $C_{32}H_{41}NO_2S$: M, 503.2858. Found: *m/z* 503.2869. $[\alpha]_D^{25}$=−307.1 (*c* 0.5 acetone).

2.1.4. (2*R*,3*R*,R_S)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(*p*-tolylsulfinyl)aziridine (8b). Colorless oil (98%); IR (neat) 3034, 2997, 2833, 1597, 1505, 1452, 1399, 1241, 1040, 909, 811, 759, 702 cm^{-1}; ^{1}H NMR δ 1.03 (3H, s), 2.41 (3H, s), 3.78 (3H, s), 4.51 (1H, s), 6.86, 6.98 (each 2H, d, J=9 Hz), 7.2–7.7 (9H, m). $[\alpha]_D^{30}$=−348.4 (*c* 0.5 acetone).

Compound Racemic-**8b**. Colorless crystals; mp 88–91°C (AcOEt–hexane). IR (KBr) 1505, 1238, 1228, 1046 (SO) cm^{-1}; MS *m/z* (%) 377 (M$^+$, 7), 361 (25), 238 (52), 212 (63), 148 (100). Anal. calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71; S, 8.49. Found: C, 73.31; H, 6.01; N, 3.52; S, 8.51.

2.1.5. (2*S*,3*R*)-2-Decyl-2-methyl-1-(4-methoxyphenyl)-3-phenylaziridine (10a). To a solution of EtMgBr (15.43 mmol) in 20 mL of THF at −78°C was added a solution of **8a** (2.22 g; 4.41 mmol) in 4 mL of THF dropwise with stirring. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm up to room temperature at once and was stirred at room temperature for 30 min. Cu(I) iodide (209 mg; 1.1 mmol) was then added to the reaction mixture and after 10 min, iodomethane (1.09 mL; 17.63 mmol) was added successively and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by sat. aq. NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel flash chromatography to afford **10a** (1.57 g; 94%) as colorless oil; IR (neat) 2925, 2854, 1507, 1465, 1239 cm^{-1}; ^{1}H NMR δ 0.87 (3H, t, J=7 Hz), 1.10 (3H, s), 1.16–1.28 (18H, m), 3.10 (1H, s), 3.77 (3H, s), 6.79, 6.84 (each 2H, d, J=9 Hz), 7.24–7.43 (5H, m). MS *m/z* (%) 379 (M$^+$, 40), 365 (10), 322 (4), 308 (3), 280 (21), 266 (82), 253 (29), 238 (14), 197 (100), 148 (74), 134 (24), 121 (17), 91 (80). Calcd for $C_{26}H_{37}NO$: M, 379.2875. Found: *m/z* 379.2860. $[\alpha]_D^{29}$=−87.0 (*c* 0.5 acetone).

2.1.6. (2*R*,3*R*)-2-Decyl-2-methyl-1-(4-methoxyphenyl)-3-phenylaziridine (10b). Colorless oil (89%); IR (neat) 2926, 2855, 1506, 1464, 1238 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7 Hz), 1.07 (3H, s), 1.24–1.46 (18H, m), 3.09 (1H, s), 3.77 (3H, s), 6.79, 6.85 (each 2H, d, J=9 Hz), 7.27–7.41 (5H, m). MS m/z (%) 379 (M^+, 73), 364 (4), 336 (3), 280 (22), 266 (87), 197 (100), 148 (62), 91 (76). Calcd for $C_{26}H_{37}NO$: M, 379.2875. Found: m/z 379.2881. $[\alpha]_D^{29}=-92.8$ (c 0.5 acetone).

2.1.7. *N*-(1-Benzyl-1-methylundecyl)acetamide (17a,b). Palladium hydroxide (20 wt% Pd (dry basis) on carbon; 3.05 g, 300 wt%) was added to a solution of **10a** (1.05 g; 2.77 mmol) in 50 mL of a mixture of MeOH and AcOEt. The reaction mixture was stirred for 30–60 min under hydrogen atmosphere. The catalyst was filtered off and the solvent was evaporated under vacuum to afford the secondary amine **15a**. Without further purification, a solution of CAN (6.07 g; 11.1 mmol) in 13 mL of water was added to a solution of **15a** in 25 mL of CH_3CN at 0°C with stirring. The reaction mixture was stirred at 0°C for 30 min, then the solution was neutralized with 5% aq. $NaHCO_3$. Na_2SO_3 (1.4 g) was added to the reaction mixture with stirring and after 10 min, the reaction mixture was filtered through a celite pad. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with sat. aq. $NaHCO_3$, 10% aq. Na_2SO_3, and brine, and then dried over $MgSO_4$. After concentration, obtained crude **16a** was successively added pyridine (11 mL), acetic anhydride (5.2 mL) and 4-(dimethylamino)pyridine (67 mg; 0.55 mmol). The reaction mixture was stirred at room temperature for 1 h. The acetic anhydride and pyridine were evaporated under vacuum and the residue was purified by silica gel column chromatography to give (*S*)-(+)-**17a** (412 mg; 47% from **10a**) as colorless oil; IR (neat) 3298, 2925, 2855, 1652, 1558, 1465, 1371, 1031 cm^{-1}; $[\alpha]_D^{29}=+28.9$ (c 0.5 acetone).

Compound (*R*)-(−)-**17b**. Colorless oil (31% yield); $[\alpha]_D^{30}=-30.9$ (c 0.5 acetone). Racemic-**17**: Colorless crystals; mp 82–83°C (AcOEt–hexane). IR (KBr) 3277, 3088, 2918, 2848, 1643, 1568, 1470, 1371 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7 Hz), 1.19 (3H, s), 1.26–1.55 (17H, m), 1.51 (1H, m), 1.91 (3H, s), 2.89, 3.19 (each 1H, d, J=13 Hz), 4.86 (1H,s), 7.12–7.29 (5H, m). MS m/z (%) 317 (M^+, 3), 302 (5), 274 (0.5), 258 (6), 226 (60), 184 (100), 176 (6), 134 (6), 91 (11), 70 (7). Calcd for $C_{21}H_{35}NO$: M, 317.2719. Found: m/z 317.2715. Anal. calcd for $C_{21}H_{35}NO$: C, 79.43; H, 11.12; N, 4.41. Found: C, 79.27; H, 11.08; N, 4.35.

2.1.8. 3-Acetamino-3-methyltridecanoic acid (11a,b). A mixture of **17a** (50 mg; 0.16 mmol), ruthenium trichloride hydrate (1.6 mg; 0.00785 mmol) and sodium periodate (600 mg; 2.82 mmol) in a mixture of CCl_4 (1.5 mL), CH_3CN (1.5 mL) and water (1 mL) was stirred at room temperature for 2 days. The mixture was extracted with AcOEt and the organic layer was washed with brine and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography to give **11a** (16.6 mg; 37%) as colorless oil; IR (neat) 3335, 2926, 2855, 1714, 1659, 1549, 1466, 1376, 1221 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7 Hz), 1.25–1.29 (16H, m), 1.38 (3H, s), 1.70, 1.85 (each 1H, m), 1.95 (3H, s), 2.65, 2.91 (each 1H, d, J=14.5 Hz), 5.80 (1H, s). MS m/z (%) 285 (M^+, 0.4), 271 (8), 226 (54), 184 (100), 131 (24), 88 (62), 60 (78). Calcd for $C_{16}H_{31}NO_3$: M, 285.2304. Found: m/z 285.2319.

2.1.9. (*S*)-3-Acetamino-3-methyltridecanoic acid *N*-{1-(1-naphthyl)ethyl}amide (18a). To a solution of **11a** (28.5 mg; 0.1 mmol) in CH_2Cl_2 (4 mL), EDC (23 mg; 0.12 mmol) and HOBt (16.4 mg; 0.12 mmol) were added at 0°C with stirring. After stirring for 1 h at 0°C, (*S*)-(−)-1-(1-naphthyl)ethylamine (32 μL; 0.2 mmol) was added to the reaction mixture and stirred for 3 h. The reaction mixture was washed with 5% aq. HCl twice and sat. aq. $NaHCO_3$ then dried over $MgSO_4$. The solvent was evaporated under vacuum to afford 43 mg (98%) of pure **18a** as colorless oil; IR (neat) 3298, 3053, 2926, 2854, 1652, 1525, 1449, 1372, 799, 778, 756 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7 Hz), 1.15 (3H, s), 1.10–1.31 (18H, m), 1.34 (3H, s), 1.65 (3H, d, J=6.7 Hz), 2.28, 2.89 (each 1H, d, J=12.8 Hz), 5.41 (1H, s), 5.95–6.01 (1H, m), 6.09 (1H, d, J=8.9 Hz), 7.12–8.17 (7H, m). MS m/z (%) 438 (M^+, 28), 268 (35), 209 (11), 170 (100), 155 (54). Calcd for $C_{28}H_{42}N_2O_2$: M, 438.3246. Found: m/z 438. 3249. $[\alpha]_D^{25}=-2.4$ (c 0.73 acetone).

2.1.10. (*R*)-3-Acetamino-3-methyltridecanoic acid *N*-{1-(1-naphthyl)ethyl}amide (18b). Colorless oil (94%); IR (neat) 3299, 3053, 2927, 2855, 1645, 1525, 1449, 1372, 1239, 799, 777, 756 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7 Hz), 1.26–1.40 (18H, m), 1.32 (3H, s), 1.46 (3H, s), 1.63 (3H, d, J=6.7 Hz), 2.55, 2.60 (each 1H, d, J=13 Hz), 5.68 (1H, s), 5.92–5.98 (1H, m), 6.11 (1H, d, J=8.6 Hz), 7.43–8.13 (7H, m). MS m/z (%) 438 (M^+, 26), 268 (34), 209 (11), 170 (100), 155 (54). Calcd for $C_{28}H_{42}N_2O_2$: M, 438.3246. Found: m/z 438.3250. $[\alpha]_D^{21}=-1.6$ (c 0.7 acetone).

2.1.11. (*dl*)-2-Acetamino-2-methyldodecanoic acid (19a,b). Colorless crystals (14%); IR (KBr) 3339, 2921, 2851, 2604, 1701, 1631, 1555, 1469, 1372, 1326, 1254, 1238, 1143 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7 Hz), 1.10–1.32 (16H, m), 1.58 (3H, s), 1.84 (1H, m), 2.04 (3H, s), 2.14 (1H, m), 6.07 (1H, s). MS m/z (%) 271 (M^+, 5), 226 (52), 184 (100), 144 (22), 130 (19), 113 (15), 102 (30), 88 (50), 60 (71). Calcd for $C_{15}H_{29}NO_3$: M, 271.2147. Found: m/z 271.2141.

2.1.12. (2*S*,3*R*)-2-Decyl-1-(4-methoxyphenyl)-3-phenylaziridine (20a). To a solution of EtMgBr (2.07 mmol) in 20 mL of THF at −78°C was added a solution of **8a** (300 mg; 0.59 mmol) in 4 mL of THF dropwise with stirring. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm up to room temperature at once and was stirred at room temperature for 30 min. The reaction was quenched by sat. aq. NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel flash chromatography to afford **20a** (210 mg; 97%) as colorless oil; IR (neat) 2924, 2854, 1506, 1464, 1455, 1241, 1180, 1041 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7 Hz), 1.21–1.53 (18H, m), 1.56 (3H, s), 2.35 (1H, dt, J=6.4, 6.7 Hz), 3.24 (1H, d, J=6.4 Hz), 3.76 (3H, s), 6.79, 6.96 (each 2H, d, J=8.8 Hz), 7.27–7.42 (5H, m). MS m/z (%) 365 (M^+, 100), 308 (7), 294 (11), 274 (25), 252 (94), 238 (40), 224 (22), 211 (31), 197 (21), 162 (5), 134

(82), 91 (38). Calcd for $C_{25}H_{35}NO$: M, 365.2719. Found: *m/z* 365.2728. $[\alpha]_D^{25}=-170.7$ (*c* 0.5 acetone).

2.1.13. (2*S*,3*R*)-2-Decyl-2-deuterio-1-(4-methoxyphenyl)-3-phenylaziridine (20b). Colorless oil (97%); IR (neat) 2924, 2853, 1604, 1506, 1464, 1454, 1239, 1180, 1106, 1141 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.8 Hz), 1.21–1.56 (18H, m), 3.23 (1H, s), 3.76 (3H, s), 6.79, 6.96 (each 2H, d, *J*=8.8 Hz), 7.26–7.42 (5H, m). MS *m/z* (%) 366 (M^+, 100), 323 (4), 309 (7), 295 (12), 274 (18), 253 (80), 239 (39), 211 (36), 197 (21), 135 (67), 91 (33), 77 (13). Calcd for $C_{25}H_{34}DNO$: M, 366.2780. Found: *m/z* 366.2784. $[\alpha]_D^{26}=-151.8$ (*c* 1.05 acetone).

2.1.14. (*S*)-*N*-(1-Benzylundecyl)acetamide (23a). Palladium hydroxide (20 wt% Pd (dry basis) on carbon; 1.2 g, 300 wt%) was added to a solution of **20a** (400 mg; 1.1 mmol) in 20 mL of a mixture of MeOH and AcOEt. The reaction mixture was stirred for 30–60 min under hydrogen atmosphere. The catalyst was filtered off and the solvent was evaporated under vacuum to afford the secondary amine **21a**. Without further purification, a solution of CAN (1.21 g; 2.2 mmol) in 5 mL of water was added to a solution of **21a** in 10 mL of CH_3CN at 0°C with stirring. The reaction mixture was stirred at 0°C for 30 min and at room temperature for 2 h, and then was added successively 10% aq. NaOH (1 mL) and acetic anhydride (2.6 mL; 28 mmol) at 0°C. After stirring overnight, the reaction mixture was filtered through a celite pad. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with sat. aq. $NaHCO_3$, 10% aq. Na_2SO_3, and brine, and then dried over $MgSO_4$. Concentration of the solution followed by purification by silica gel column chromatography gave **23a** (176 mg; 53% from **20a**) as colorless crystals; mp 94–96°C (AcOEt–hexane). IR (KBr) 3295, 2917, 2850, 1646, 1555, 1372 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.15–1.55 (18H, m), 1.92 (3H, s), 2.78 (2H, m), 4.18 (1H, m), 5.14 (1H, d, *J*=8.9 Hz), 7.15–7.30 (5H, m). $[\alpha]_D^{22}=-6.6$ (*c* 0.5 acetone).

Compound Racemic-**23**. Colorless crystals; mp 100–102°C (AcOEt–hexane); IR (KBr) 3300, 2917, 2850, 1646, 1550, 1466, 1370 cm^{-1}. MS *m/z* (%) 303 (M^+, 0.5), 244 (8), 212 (56), 170 (100), 120 (6), 91 (14). Calcd for $C_{20}H_{33}NO$: M, 303.2562. Found: *m/z* 303.2571. Anal. calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.62. Found: C, 79.22; H, 11.18; N, 4.64.

2.1.15. (*S*)-*N*-(1-Benzyl-1-deuterioundecyl)acetamide (23b). Colorless crystals (43% from **20b**); mp 94–95°C (AcOEt–hexane). IR (KBr), 3293, 2917, 2850, 1644, 1547 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.15–1.55 (18H, m), 1.92 (3H, s), 2.73 (2H, m), 5.24 (1H, s), 7.15–7.30 (5H, m). MS *m/z* (%) 304 (M^+, 0.5), 245 (10), 213 (72), 171 (100), 91 (13). Calcd for $C_{20}H_{32}DNO$: M, 304.2624. Found: *m/z* 304.2622. Anal. calcd for $C_{20}H_{32}DNO$: C, 78.89; H, 10.92; N, 4.60. Found: C, 78.99; H, 11.20; N, 4.52. $[\alpha]_D^{25}=-7.3$ (*c* 0.5 acetone).

2.1.16. (*S*)-3-Acetaminotridecanoic acid (24a). Colorless crystals (54%); mp 84–86°C (AcOEt–hexane). IR (KBr) 3286, 2919, 2850, 1721, 1649, 1552, 1376, 1238 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.15–1.60 (18H, m), 2.00 (3H, s), 2.48–2.63 (2H, m), 4.22 (1H, m), 6.16 (1H, d, *J*=8.8 Hz). $[\alpha]_D^{23}=+2.0$ (*c* 1.0 MeOH).

Compound Racemic-**24a**. Colorless crystals; mp 109–110°C (AcOEt–hexane); IR (KBr) 3326, 2919, 2851, 1730, 1651, 1605, 1559, 1412, 1375 cm^{-1}. MS *m/z* (%) 271 (M^+, 11), 256 (4), 228 (42), 212 (14), 170 (25), 130 (67), 88 (100), 60 (28). Calcd for $C_{15}H_{29}NO_3$: M, 271.2147. Found: *m/z* 271.2153. Anal. calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 65.48; H, 10.49; N, 4.94.

2.1.17. (*S*)-3-Acetamino-3-deuteriotridecanoic acid (24b). Colorless crystals (54%); mp 71–73°C (AcOEt–hexane). IR (KBr) 3286, 2918, 2851, 1703, 1648, 1544, 1466, 1435, 1373, 1051 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.9 Hz), 1.25–1.55 (18H, m), 2.00 (3H, s), 2.50, 2.60 (each 1H, d, *J*=15.9 Hz), 6.23 (1H, s). MS *m/z* (%) 272 (M^+, 4), 257 (3), 229 (24), 213 (17), 171 (32), 131 (61), 89 (100), 71 (13), 60 (35). Calcd for $C_{15}H_{28}DNO_3$: M, 272.2209. Found: *m/z* 272.2216. Anal. calcd for $C_{15}H_{28}DNO_3{\cdot}0.8H_2O$: C, 62.82; H, 10.75; N, 4.88. Found: C, 62.81; H, 10.39; N, 4.78. $[\alpha]_D^{27}=+0.76$ (*c* 1.4 MeOH).

2.1.18. (2*R*,3*R*)-2-Decyl-2-ethoxycarbonyl-1-(4-methoxyphenyl)-3-phenylaziridine (12a). To a solution of **8a** (300 mg; 0.59 mmol) in 25 mL of dry THF in a flame-dried flask was added MeMgBr (0.77 mmol) at −50°C with stirring. The reaction mixture was stirred at −50°C for 15 min, then the solution was cooled to −80°C. *t*-BuLi (1.2 mmol) was added to the reaction mixture dropwise with stirring and after 1 min, ethyl chloroformate (0.23 mL; 2.4 mmol) was added. The reaction mixture was stirred for 1 min, then the reaction was quenched by adding sat. aq. NH_4Cl. The whole was extracted with ether–benzene. The product was purified by silica gel flash chromatography to afford **12a** (165 mg; 64%) as a colorless oil. IR (neat) 1724 (CO), 1507, 1241, 1177 cm^{-1}. ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.02 (3H, t, *J*=7 Hz), 1.08–1.70 (18H, m), 3.76 (3H, s), 3.93–4.02 (2H, m), 4.13 (1H, s), 6.77, 6.82 (each 2H, d, *J*=8.8 Hz), 7.28–7.44 (5H, m). MS *m/z* (%) 437 (M^+, 52), 408 (31), 364 (45), 276 (100), 274 (58). Calcd for $C_{28}H_{39}NO_3$: M, 437.2929. Found: *m/z* 437.2924. $[\alpha]_D^{27}=-44.4$ (*c* 1.1 acetone).

2.1.19. (*S*)-Ethyl 2-amino-2-benzyldodecanoate (26). To a solution of **12a** (0.24 g; 0.54 mmol) in distilled methanol (15 mL) was added 60 mg of $Pd(OH)_2$ (10% on carbon). The reaction mixture was stirred under hydrogen atmosphere for 1 h. The catalyst was filtered off and the methanol was evaporated to give crude **25**. A solution of CAN (1.48 g; 2.7 mmol) in 10 mL of water was added to a crude solution of **25** in 15 mL of CH_3CN at 0°C with stirring. The reaction mixture was stirred at 0°C for 30 min, then the solution was neutralized with 5% aq. $NaHCO_3$. Na_2SO_3 (340 mg) was added to the reaction mixture with stirring and after 10 min, the reaction mixture was filtered through a celite pad and the whole was extracted with ethyl acetate. The product was purified by silica gel column chromatography to afford 99 mg (54% from **12a**) of **26** as colorless oil. IR (neat) 3388 (NH), 1732 (CO), 1182, 1031 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.10–1.70 (22H, m), 1.85–1.95 (1H, m), 2.76, 3.18 (each 1H, d, *J*=13 Hz), 4.09–4.23 (2H, m), 7.10–7.40 (5H, m). MS (FAB) *m/z* (%) 334 ($[M+H]^+$, 100), 260 (51),

242 (21), 91 (15). Calcd for $C_{21}H_{36}NO_2$: M, 334.2746. Found: *m*/*z* 334.2734. $[\alpha]_D^{24}=-15.4$ (*c* 1.0 acetone).

2.1.20. (*S*)-Ethyl 2-acetamino-2-benzyldodecanoate (27). Colorless oil (97%); IR (neat) 3410, 3299, 2926, 2855, 1737, 1680, 1658, 1497, 1455, 1374, 1201 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 0.98 (1H, m), 1.24–1.31 (15H, m), 1.33 (3H, t, *J*=7.2 Hz), 1.83 (1H, m), 1.96 (3H, s), 2.63 (1H, m), 3.07, 3.75 (each 1H, d, *J*=13.4 Hz), 4.16–4.29 (2H, m), 6.18 (1H, s), 7.01–7.24 (5H, m). MS *m*/*z* (%) 375 (M^+, 4), 316 (24), 302 (5), 284 (76), 242 (100), 168 (12), 91 (20). Calcd for $C_{23}H_{37}NO_3$: M, 375.2773. Found: *m*/*z* 375.2770. $[\alpha]_D^{25}=+7.88$ (*c* 1.0 acetone).

2.1.21. (*S*)-2-Acetamino-2-decylsuccinic acid-1-ethyl ester (13a). Colorless crystals (60%); mp 65–66°C (Hexane); IR (KBr) 3361, 2959, 2923, 2853, 2490, 1740, 1720, 1620, 1536, 1377, 1206, 1016 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=6.9 Hz), 1.00 (1H, m), 1.15–1.24 (15H, m), 1.27 (3H, t, *J*=7.2 Hz), 1.63 (1H, m), 1.99 (3H, s), 2.45 (1H, m), 2.92, 3.66 (each 1H, d, *J*=16.6 Hz), 4.24 (2H, m), 6.73 (1H, s). Anal. calcd for $C_{18}H_{33}NO_5$: C, 62.95; H, 9.68; N, 4.08. Found: C, 62.63; H, 9.62; N, 4.08.. $[\alpha]_D^{29}=-11.0$ (*c* 0.5 MeOH).

Compound Racemic-**13a**. Colorless oil; IR (neat) 3360, 2926, 2855, 1739, 1659, 1526, 1466, 1374, 1211, 1024 cm^{-1}; MS *m*/*z* (%) 343 (M^+, 4), 300 (10), 284 (6), 270 (84), 228 (100), 203 (25), 160 (29), 142 (8), 114 (10), 99 (8), 60 (9). Calcd for $C_{18}H_{33}NO_5$: M, 343.2359. Found: *m*/*z* 343.2367.

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