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Practical Synthesis of Chiral Emopamil Left Hand as a Bioactive Motif

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Abstract: An asymmetric synthesis of (2*S*)-2-(2-isopropyl)-5-hydroxy-2-phenylpentanenitrile (emopamil left hand, **2**) has been completed by use of the MAD (methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide)-induced rearrangement of a chiral epoxyalcohol as the key reaction. The stereochemistry of the chiral quaternary center was confirmed by transformation of **2** to (*S*)-noremopamil. This method requires minimal purification procedures and affords high chemical and optical yields. Acid-catalyzed isomerization of an allylaldehyde and retro-aldol type racemization at the quaternary carbon of a nitrile-alcohol were encountered.

Introduction

Progress in the use of combinatorial approaches in the drug discovery field has enabled medicinal chemists to search for more druglike templates. We have focused on the phenylalkylamine motif (Figure 1) in L-type calcium channel blockers, such as verapamil (**1a**), emopamil (**1b**), and noremopamil (**1c**), which exhibit a wide range of biological activities.[1−3] A library of compounds that incorporate phenylalkylamine as a bioactive motif has the potential to provide interesting new lead compounds for biological evaluations.

The phenylalkylamine moiety includes a chiral quaternary carbon center, and recent research has indicated that the optical isomers differ significantly in their biological effects.[4,5] Thus, we planned to build a library in which this benzylic center is stereochemically defined. A number of reports have described syntheses of the individual enantiomers. However, a straightforward approach utilizing chiral substrates as starting materials is not suitable for library preparation due to the limited commercial availability and high price of suitable compounds.[6] Separation of diastereomers formed by the introduction of a chiral side chain or with a chiral auxiliary using column chromatography,[7] classical resolution of diastereomeric salts formed with chiral carboxylic acids or amines,[8] or enzymatic resolution of the racemic compound[9] could provide a solution to this problem. However, manipulation to establish the proper conditions is usually time-consuming and would be difficult to standardize because of the variety of target substrates. Although enantioselective synthesis would be more practical, the results reported thus far have shown low enantiomeric excesses.[10] We have explored a novel asymmetric synthesis of the phenylalkylamine locus, and, in this paper, we report our findings on the preparation of the chiral emopamil left hand, **2**.

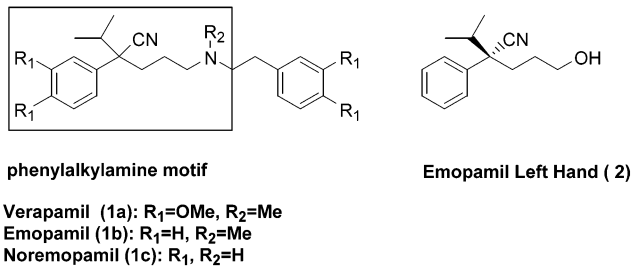

FIGURE 1.

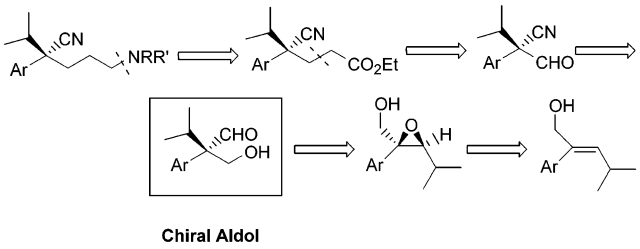

FIGURE 2.

Results and Discussion

Retrosynthetic analysis guided us to a chiral aldol (Figure 2) which could be formed by rearrangement of a chiral epoxyalcohol using the organoaluminum reagent reported by Yamamoto et al.[11]

Phenylacetonitrile was selected as the starting material because of its commercial availability. The acrylonitrile compound **3** was predominantly obtained as the *Z*-isomer by Ladhar's procedure.[12] Reduction of the nitrile **3** using diisobutylaluminum hydride (DIBALH) followed by acid hydrolysis and further reduction gave the allyl alcohol **4** as a mixture of *E*- and *Z*-isomers in preliminary experiments. Since isomerization might have occurred during the hydrolysis step after DIBALH reduction, the process was investigated in detail. When the reduction of **3** by DIBALH was quenched with 3 N H_2SO_4 at −78

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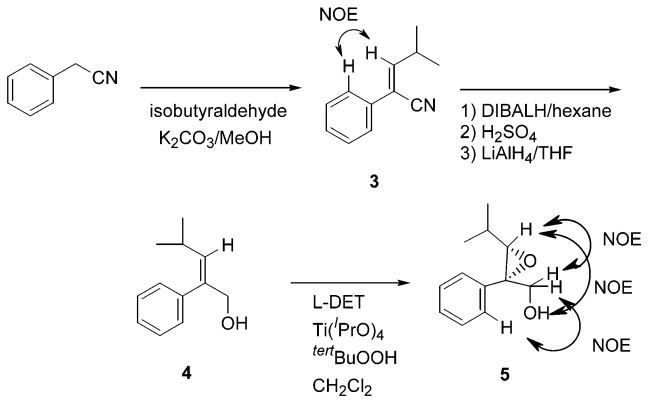
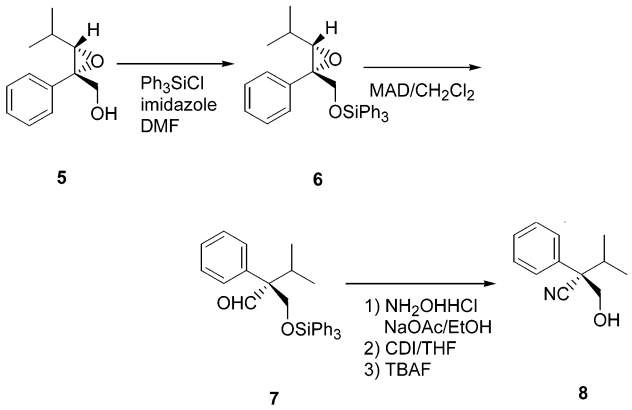
SCHEME 1



SCHEME 2



°C, the *E*/*Z* ratio of the obtained allyl aldehyde was 1:2. Quenching at 0 °C provided a 3:1 mixture of *E*- and *Z*-allyl aldehyde. This result indicates that formation of the *E*-allyl aldehyde is thermodynamically more favorable than that of the *Z*-isomer. Finally, heating at 60 °C for 24 h under acid hydrolysis conditions after the reduction exclusively gave the *E*-allyl aldehyde. Reduction of the *E*-allyl aldehyde with $NaBH_4$ gave the desired *E*-allyl alcohol with the corresponding saturated alcohol as a byproduct. Although reduction by $CeCl_3-NaBH_4$ could be carried out with 1,2-selectivity, the dimethylacetal form of the allyl aldehyde was produced in 30% yield. Complete transformation of the *E*-allyl aldehyde to the *E*-allyl alcohol **4** was accomplished by reduction with lithium aluminum hydride (LAH). The chiral epoxy alcohol **5** was obtained by the standard Sharpless asymmetric epoxidation procedure.[13] This procedure gave the optically pure epoxyalcohol **5** (>99% ee) in crystalline form, circumventing the need for time-consuming column chromatography. The stereochemistry of **5** was directly determined by NOESY study and the data retrospectively confirmed **4** as the *E*-isomer. Transformation from the epoxy alcohol **5** to the corresponding aldol **7** was performed essentially according to Yamamoto's report.[11] The alcohol moiety of **5** was protected as a triphenylsilyl ether, and the resulting epoxide **6** was treated with MAD (methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) to provide the desired aldehyde **7** in quantitative yield. The aldehyde **7** was derivatized to its oxime using hydroxylamine and subsequent dehydrated by reatment with carbonyldiimidazole (CDI) to afford the protected nitrile compound. After desilylation with tetrabutylammonium fluoride (TBAF), the enantiomeric purity of the nitrile-alcohol **8** was evaluated by HPLC using a chiral column. Contrary to our expectation, the isolated material **8** was racemic, although the precursors **6** and **7** showed some degree of optical rotation by polarimetry. Thus, we speculated that compound **8** might have racemized through a retro-aldol type mechanism under the TBAF deprotection conditions.

To avoid the putative retro-aldol type reaction, the desilylation was performed in the presence of a proton donor such as imidazole. The amended conditions gave optically pure **8** without racemization (>99% ee). In practice, the desilylation step was carried out in one pot following transformation of the oxime to the nitrile, because quenching of excess CDI remaining in the reaction mixture produced sufficient imidazole to prevent scrambling of the stereocenter. Oxidation of the nitrile alcohol **8** followed by treatment with the Horner–Emmons reagent provided the α,β-unsaturated ester **9**, and subsequent hydrogenation led to compound **10**. Reduction of **10** with LAH gave the target alcohol **2** in quantitative chemical and optical yield. To confirm the configuration of the quaternary carbon center, alcohol **2** was transformed to a known derivative, noremopamil (**1c**). Since the isolated product exhibited *levo*-rotation, which is consistent with that of (*S*)-noremopamil reported by Gilmore et al.,[7] the stereogenic center of **2** was concluded to have the expected *S* configuration. This result supports the assignments of all the stereogenic centers of the compounds described here. A chiral phenylalkylamine library was built by coupling of the mesylate of (*S*)-**2** or by reductive amination of the aldehyde of (*S*)-**2** with various amines. The utility of this library has already been confirmed by the discovery of **E-2050**, which is a novel neuronal calcium channel blocker.[14] Evaluation of this library for other biological targets is in progress and will be reported in due course.

Summary

A versatile, high-yield process for the asymmetric synthesis of (2*S*)-2-(2-isopropyl)-5-hydroxy-2-phenylpentanenitrile has been developed. The minimal purification procedures required and the ready availability of the starting materials distinguish this efficient approach from other routes reported to date.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were determined at 400 and 100 MHz, respectively. Mass spectra were recorded by electron spray ionization (ESI) or FAB ionization. Optical rotations were measured using a digital polarimeter with a 10-cm cell. The enantiomeric purity was determined using chiral HPLC analysis by comparison with the

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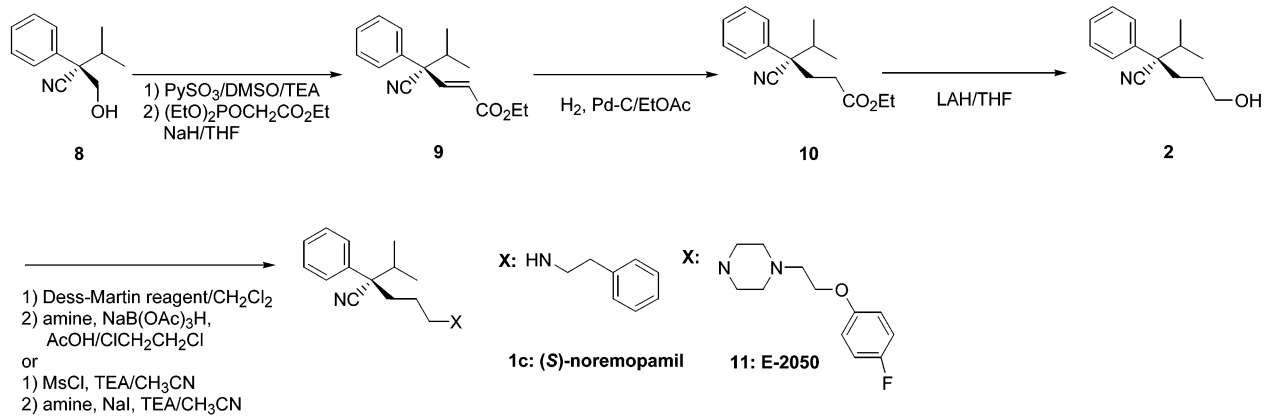
SCHEME 3



corresponding racemic compound (see Supporting Information). Chiral HPLC analysis were performed on a Chiralcel OJ column (250 × 4.6 mm, *n*-hexane/isopropyl alcohol/ethanol 85/10/5, 1 mL/min) for enantiomers of **2**, **5**, **8**, and **11**, and a Chiral OD column (250 × 4.6 mm, *n*-hexane/ethanol 95/5, 1 mL/min) for **1c**. The retention time of each enantiomer is given as t_R. Elemental analyses were performed at the Analytical Chemistry Section of Eisai Tsukuba Research Laboratories.

(*Z*)-2-Phenyl-3-isopropylacrylonitrile (3) was essentially prepared according to the literature procedure[12] and was purified by distillation under reduced pressure (yield 95%. bp 75 °C/0.3 mmHg).

(*E*)-2-Phenyl-3-isopropylallyl alcohol (4). To a solution of **3** (27.4 g, 160 mmol) in hexane (200 mL) at −30 °C was added DIBALH (1.5 M toluene solution, 100 mL) over 20 min. After 2 h at 0 °C, the reaction mixture was slowly poured into ice cold 3 N H_2SO_4 (100 mL), ensuring the mixture remained below 10 °C. The resulting solution was stirred at 0 °C for 0.7 h and then at 60 °C for 19 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with saturated $NaHCO_3$ and dried, filtered, and concentrated in vacuo.

The residue in THF (100 mL) was treated with $LiAlH_4$ (3.1 g, 81.6 mmol) at −78 °C for 30 min. After the reaction was quenched with water and 5 N NaOH, the resulting precipitate was filtered off, and the filtrate was evaporated in vacuo. The residue oil was distilled under reduced pressure to yield **4** (*E*/*Z* 93:7) as a colorless oil (23.6 g, 83.7%). The *E*/*Z* ratio was determined by integration of both vinylic proton signals (*Z*-isomer δ 5.71 ppm).

bp 85 °C/0.4 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.94 (d, 6H, J = 6.6 Hz), 1.45 (brt, 1H), 2.31−2.43 (m, 1H), 4.29 (d, 2H, J = 5.5 Hz), 5.52 (d, 1H, J = 10.1 Hz), 7.19−7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.4, 27.8, 68.4, 127.3, 128.5, 128.8, 136.4, 138.1, 139.1. LRMS (ESI) *m*/*e*: 231 (M + Na + MeOH)$^+$.

(2*S*,3*S*)-3-Isopropyl-2-phenyl-2,3-epoxypropan-1-ol (5). Diethyl L-(+)-tartrate (2.52 mL, 14.8 mmol) and titanium tetraisopropoxide (3.38 mL, 11.4 mmol) were added sequentially to a mixture of powdered activated 4 Å molecular sieves (9 g) and dichloromethane (200 mL) at 0 °C with stirring. The reaction mixture was cooled to −20 °C, *tert*-butyl hydroperoxide (2.7 M in dichloromethane, 109.4 mL, 296.4 mmol) was added dropwise over 0.2 h, and the resulting mixture was stirred at −20 °C for 1 h. Compound **4** (20 g, 114 mmol) dissolved in dichloromethane (100 mL) was then added dropwise over 0.2 h. After stirring for 15 h at −20 °C, the reaction mixture was poured into a freshly prepared ferrous sulfate solution (66 g of $FeSO_4 \cdot 7H_2O$ and 22 g of citric acid in 200 mL of H_2O) at −20 °C and stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was dried, filtered, and concentrated in vacuo. To the residue in Et_2O (300 mL) was added 30% NaOH (20 mL), and the resultant mixture was stirred at 0 °C for 1 h. The two phases were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with brine, dried, filtered, and then concentrated in vacuo. The residue was crystallized from hexane to afford the epoxy alcohol (**5**) as colorless crystals (18.4 g, 84.1%, >99% ee): mp 63 °C. ^{1}H NMR (400 MHz, DMSO): δ (ppm) 0.72 (d, 3H, J = 6.4 Hz), 0.76−0.88 (m, 1H), 0.94 (d, 3H, J = 6.4 Hz), 2.90 (d, 1H, J = 8.8 Hz), 3.68 (dd, 1H, J = 12.4, 6.0 Hz), 3.78 (dd, 1H, J = 12.4, 6.0 Hz), 4.91 (t, 1H, J = 6.0), 7.25−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.1, 20.1, 27.3, 64.9, 66.6, 67.0, 126.9, 128.0, 128.5, 136.2. LRMS (ESI) *m*/*e*: 247 (M + Na + MeOH)$^+$. $[\alpha]^{28}_D$ = −50.1 (*c* 0.78, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_2$ (192.25): C, 74.97; H, 8.39. Found: C, 74.62; H, 8.38. (2*S*,3*S*)-enantiomer of **5**: t_R = 5.0 min. (2*R*,3*R*)-enantiomer of **5**: t_R = 6.5 min.

(2*S*,3*S*)-3-Isopropyl-2-phenyl-2,3-epoxypropan-1-triphenylsilyl Ether (6). To a solution of **5** (5.0 g, 26.0 mmol) in DMF (50 mL) were added imidazole (3.5 g, 51.5 mmol) and triphenylchlorosilane (7.7 g, 26.1 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. After water and hexane were added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layer was dried, filtered, and concentrated in vacuo. The compound **6** (11.8 g, 100%) was enough pure to use in the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.73 (d, 3H, J = 6.4 Hz), 0.90−0.98 (m, 1H), 0.98 (brs, 3H), 2.93 (d, 1H, J = 8.6 Hz), 4.07 (s, 2H), 7.27−7.58 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.2, 20.1, 27.5, 66.5, 67.5, 67.6, 127.6, 127.7, 128.1, 128.2, 130.3, 134.0, 135.7, 136.9. LRMS (ESI) *m*/*e*: 473 (M + Na)$^+$ $[\alpha]^{26}_D$ = −24.8 (*c* 1.83, $CHCl_3$).

(2*S*)-2-Isopropyl-2-phenyl-3-(triphenylsiloxy)propanal (7). To a solution of **6** (9.0 g, 20.0 mmol) in dichloromethane (100 mL) was added methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide) (0.4 M in toluene, 100 mL) at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was poured into cold 2 N HCl (200 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was passed through a silica gel bed and concentrated in vacuo to give **7** (8.90 g, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.80 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.8 Hz), 2.75 (septet, 1H, J = 6.8 Hz), 4.24 (d, 1H, J = 10.4 Hz), 4.27 (d, 1H, J = 10.4 Hz), 7.05−7.53 (m, 20H), 9.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.0, 18.6, 29.2, 62.5, 64.5, 127.4, 128.1, 128.6, 128.9, 130.4, 133.7, 135.6, 136.8, 203.9. HRMS (FAB) *m*/*e* calcd for $C_{30}H_{31}O_2Si$ 451.2094; found 451.2110. $[\alpha]^{26}_D$ = −28.5 (*c* 0.29, $CHCl_3$).

(2*R*)-2-Hydroxymethyl-2-isopropylphenylacetonitrile (8). To a solution of **7** (8.90 g, 19.8 mmol) in ethanol (50 mL) were added hydroxylamine hydrochloride (2.06 g, 28.8 mmol) and sodium acetate (2.44 g, 29.8 mmol), and the reaction mixture was stirred at room temperature for 2 h. After concentration of the reaction mixture in vacuo, EtOAc was added, and the organic phase was washed twice with water, dried, and evaporated in vacuo.

To a solution of the residue in THF (50 mL) was added 1,1′-carbonyldiimidazole (16.0 g, 98.8 mmol). The reaction mixture was refluxed for 2 h and then cooled to 0 °C. After water (1.8 mL) was slowly added, the resulted mixture was stirred until dissipation of gas evolution, and tetrabutylammonium fluoride (1 M solution in THF, 43.6 mL) was added. The reaction mixture was stirred for 1 h at room temperature, and then EtOAc and water were added. The organic phase was washed twice with water, and the aqueous phase was extracted with EtOAc. The combined organic phases were passed through a silica gel bed and evaporated in vacuo. The residue was crystallized from hexane to furnish **8** (2.88 g, 78%, >99% ee) as a white crystalline solid: mp 76−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.83 (d, 3H, J = 6.8 Hz), 1.21 (d, 3H, J = 6.8 Hz), 1.64 (dd, 1H, J = 8.4, 5.5 Hz), 2.30 (septet, 1H, J = 6.8 Hz), 3.99 (dd, 1H, J = 11.2, 5.5 Hz), 4.12 (dd, 1H, J = 11.2, 8.4 Hz), 7.32−7.49 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.7, 19.0, 33.9, 56.6, 67.6, 120.4, 127.0, 128.4, 129.3, 136.2. LRMS (ESI) *m/e*: 190 $(M+H)^+$. $[\alpha]^{29}_D$ = −25.5 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{12}H_{15}NO$ (189.25): C, 76.16; H, 7.99; N, 7.40. Found: C, 75.96; H,8.15; N, 7.35. (2*S*)-enantiomer of **8**: t_R = 5.2 min. (2*R*)-enantiomer of **8**: t_R = 7.6 min.

Ethyl (4*R*)-4-Cyano-4-phenyl-5-methyl-*trans*-2-henxenoate (9). To a solution of **8** (2.77 g, 14.7 mmol) in DMSO (15 mL) were added triethylamine (13.3 mL) and sulfur trioxide−pyridine complex (6.99 g, 44.0 mmol). The reaction mixture was stirred at room temperature for 2 h, and then hexane and 1 N HCl were added. The organic phase was separated, and the aqueous phase was extracted with hexane. The combined organic phases were washed with saturated $NaHCO_3$, dried, and evaporated in vacuo to obtain the crude aldehyde product.

To a suspension of NaH (882 mg of 60% oil suspension washed with hexane three times) in THF (20 mL) was added triethyl phosphonoacetate (4.94 g, 22.1 mmol) at room temperature. After stirring for 3 h, a solution of the above aldehyde in THF (30 mL) was added to the reaction mixture. The resultant mixture was stirred for 1 h and then concentrated to dryness. 10% EtOAc in hexane and water were added to the reaction mixture, and the organic phase was separated. The aqueous phase was extracted with the same solvent system, and the combined organic phases were filtered through a silica gel bed (SiO_2, 5 g). The filtrate was evaporated in vacuo to give **9** as a colorless oil (2.72 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.90 (d, 3H, J = 6.8 Hz), 1.13 (d, 3H, J = 6.8 Hz), 1.29 (t, 3H, J = 7.1 Hz), 2.40 (septet, 1H, J = 6.8 Hz), 4.20 (q, 2H, J = 7.1 Hz), 6.31 (d, 1H, J = 15.6 Hz), 7.02 (d, 1H, J = 15.6 Hz), 7.31−7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.4, 18.4, 18.8, 37.3, 56.5, 61.1, 118.5, 122.9, 126.3, 128.6, 129.5, 137.4, 145.6, 165.9. LRMS (ESI) *m/e*: 312 (M + Na + MeOH)$^+$. $[\alpha]^{26}_D$ = +11.3 (*c* 0.63, $CHCl_3$).

Ethyl (4*S*)-4-Cyano-4-phenyl-5-methyl-hexanoate (10). Compound **9** (2.6 g, 10.1 mmol) was dissolved in EtOAc (50 mL) and stirred in the presence of 10% Pd on carbon under an atmosphere of hydrogen (1 atm) for 16 h. The mixture was filtered through Celite and concentrated in vacuo to obtain **10** as a colorless oil (2.54 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.79 (d, 3H, J = 6.8 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.23 (d, 3H, J = 6.8 Hz), 1.94 (ddd, 1H, J = 16.5, 11.9, 4.6 Hz), 2.15 (septet, 1H, J = 6.8 Hz), 2.19 (ddd, 1H, J = 16.5, 11.9, 4.8 Hz), 2.40 (ddd, 1H, J = 16.3, 11.9, 4.6 Hz), 2.50 (ddd, 1H, J = 16.3, 11.9, 4.8 Hz), 3.98−4.12 (m, 2H), 7.29−7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 18.8, 19.2, 30.9, 33.0, 38.1, 53.4, 60.8, 120.8, 126.6, 128.1, 129.2, 137.4, 172.7. LRMS (ESI) *m/e*: 282 (M + Na)$^+$, 542 (2M + Na)$^+$. $[\alpha]^{26}_D$ = −37.2 (*c* 0.83, $CHCl_3$).

(2*S*)-2-(2-Isopropyl)-5-hydroxy-2-phenylpentanenitrile (2). To a solution of **10** (2.51 g, 9.69 mmol) in THF (20 mL) was added $LiAlH_4$ (740 mg, 19.5 mmol) portionwise at 0 °C, and the reaction mixture was stirred at the same temperature. After 1 h, water (0.8 mL), 5 N NaOH (0.8 mL), and water (2.4 mL) was added into the reaction mixture sequentially. The precipitate was filtered off, and the filtrate was concentrated in vacuo to give **2** as a colorless oil (2.54 g, 97%, >99% ee): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.79 (d, 3H, J = 6.8 Hz), 1.18−1.28 (m, 1H), 1.21 (d, 3H, J = 6.8 Hz), 1.55−1.66 (m, 2H), 1.98 (ddd, 1H, J = 13.5, 12.1, 4.6 Hz), 2.13 (septet, 1H, J = 6.8 Hz), 2.24 (ddd, 1H, J = 13.5, 12.1, 4.6 Hz), 3.59 (q, 2H, J = 5.5 Hz), 7.27−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.6, 19.0, 28.9, 34.2, 37.9, 53.6, 62.3, 121.3, 126.4, 127.6, 128.8, 138.0. LRMS (ESI) *m/e*: 240 (M + Na)$^+$, 272 (M + Na + MeOH)$^+$, 457 (2M + Na)$^+$. $[\alpha]^{26}_D$ = −12.4 (*c* 1.2, $CHCl_3$). (2*S*)-enantiomer of **2**: t_R = 7.6 min. (2*R*)-enantiomer of **2**: t_R = 9.5 min.

1-[(4*S*)-(4-Cyano-5-methyl-4-phenyl)hexyl]-4-[2-(4-fluorophenoxy)ethyl]piperazine dihydrochloride (E2050; 11). To a solution of **2** (2.10 g, 9.68 mmol) in acetonitrile (20 mL) were added triethylamine (2.15 g, 21.3 mmol) and methanesulfonyl chloride (1.22 g, 10.7 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was concentrated in vacuo, and Et_2O and brine were added. The organic layer was separated, dried, and evaporated in vacuo.

To a solution of the residue in acetonitrile (30 mL) were added 4-fluorophenoxypiperazine (2.4 g, 10.7 mmol), NaI (1.6 g, 10.7 mmol), and triethylamine (1.08 g, 10.7 mmol), and the resulting mixture was stirred at 70 °C for 3 h. After the reaction mixture was cooled to room temperature, Et_2O and 5 N HCl were added, and the quenched reaction was stirred vigorously for 10 min. The aqueous layer was separated, and the organic layer was extracted with 5 N HCl. The combined aqueous layer was neutralized with $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried, and evaporated in vacuo to obtain the oily product (3.51 g, 86%, >99% ee): ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) 0.77 (d, 3H, J = 6.8 Hz), 1.05−1.17 (m, 1H), 1.20 (d, 3H, J = 6.8 Hz), 1.50−1.60 (m, 1H), 1.88 (dt, 1H, J = 4.4, 12.4 Hz), 2.06−2.19 (m, 2H), 2.24−2.30 (m, 2H), 2.30−2.43 (m, 4H), 2.46−2.62 (m, 4H), 2.77 (t, 2H, J = 5.8 Hz), 4.04 (t, 2H, J = 5.8 Hz), 6.80−6.85 (m, 2H), 6.91−6.99 (m, 2H), 7.25−7.32 (m, 1H), 7.32−7.40 (m, 4H). [a]$^{26}_D$ = −6.5 (c 0.93, $CHCl_3$). (*S*)-enantiomer of **11** (free salt): t_R = 5.2 min. (*R*)-enantiomer of **11** (free salt): t_R = 6.3 min.

Dissolution of the oil in EtOAc and acidification with 2 equivalents of 1N HCl in EtOAc gave a solid. Recrystallization from 1-propanol provided the hydrochloride salt of **11** as white crystals: mp 184−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6); δ (ppm) 0.68 (d, 3H, J = 6.6 Hz), 1.11 (d, 3H, J = 6.6 Hz), 1.22−1.34 (m, 1H), 1.58−1.62 (m, 1H), 2.06−2.30 (m, 3H), 3.00−3.25 (m, 2H), 3.30−3.80 (m, 10H), 4.36 (brs, 2H), 6.98−7.07 (m, 2H), 7.11−7.20 (m, 2H), 7.32−7.40 (m, 1H), 7.40−7.50 (m, 4H).^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 18.8, 19.1, 21.0, 35.0, 38.4, 48.6, 49.6, 54.2, 56.6, 56.9, 63.5, 116.5, 116.6, 121.3, 126.9, 128.7, 129.7, 137.6, 154.1, 158.7. LRMS (ESI) *m/e*: 424 (M + H)$^+$. $[\alpha]^{26}_D$ = −5.5 (*c* 1.1, EtOH). Anal. Calcd for $C_{26}H_{36}N_3OCl_2F$ (496.49): C, 62.90; H, 7.31; N, 8.46. Found: C, 63.22; H,7.55; N, 8.51.

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Supporting Information Available: Experimental procedures for compounds **1c**, (DL)- **2**, (DL)-**5**, and (DL)-**8**; spectral data (^{1}H NMR including NOE) for **3**; spectral data (^{1}H NMR, ^{13}C NMR, and LRMS) for **4**, **6**, **9**, and **10**; spectral data (^{1}H NMR including NOESY, ^{13}C NMR, and LRMS) and HPLC data for **5**; spectral data (^{1}H NMR, ^{13}C NMR, LRMS, and HRMS) for **7**; spectral data (^{1}H NMR, ^{13}C NMR, and LRMS) and HPLC data for **1c**, **2**, **8**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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