An Efficient and Scalable Synthesis of (2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol: A Potent CETP Inhibitor

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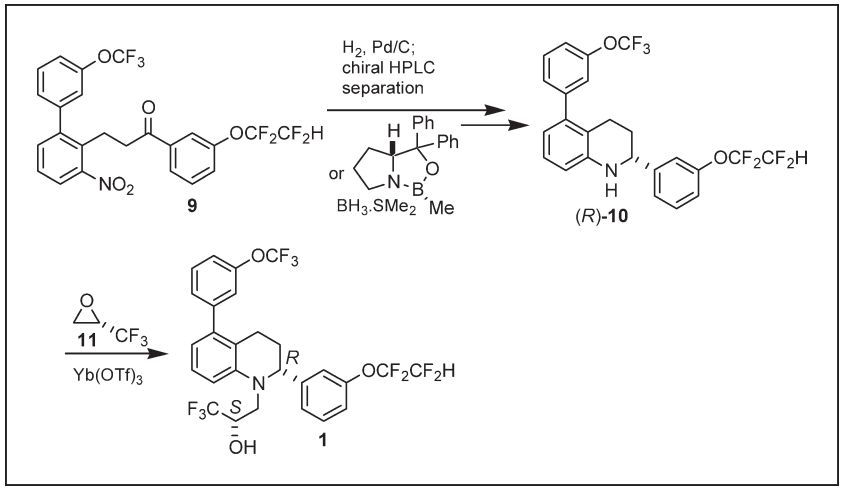

An efficient and scalable synthesis of the potent CETP inhibitor, (2*R*,α*S*)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol **1**, is described. One of the important intermediates, tetrahydroquinoline **10**, was readily prepared by reductive cyclization of nitroketone **9** in high yield. Asymmetric synthesis of **10** with high enantiomeric excess (>80% ee) was also developed.

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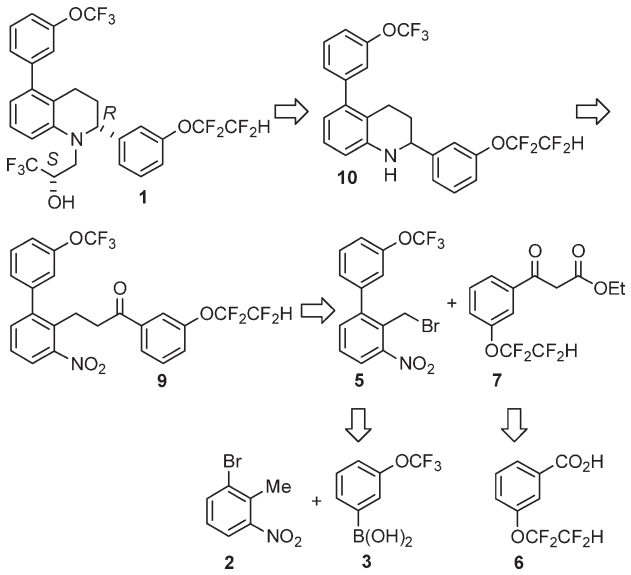
INTRODUCTION

Low levels of high density lipoprotein-cholesterol (HDL-C) and high levels of low density lipoprotein-cholesterol (LDL-C) are independent risk factors for the development of atherosclerosis and eventually coronary heart disease (CHD), which remain the leading cause of death in the developed countries [1–3]. HDL-C plays important role in removal of excess cholesterol from peripheral cells to the liver for metabolic degradation in a reverse cholesterol transport (RCT) process [4–6]. Therefore, the increase in HDL-C level offers a new and promising therapeutical principle for treatment of CHD [7]. Plasma protein cholesteryl ester (CE) transfer protein (CETP) mediates the transfer of CE from HDL to very low density lipoprotein (VLDL) and LDL in exchange for triglyceride [8,9]. As a result, the disadvantage of this action is a reduction in HDL-C level and with increase in VLDL-C and LDL-C levels. Inhibition of CETP has been proposed as a strategy to raise HDL-C level [10], thus increases the efficiency of RCT.

Compound **1** has been identified as a potent CETP inhibitor [11]. It showed IC_{50} in 34–44 n*M* range and increased HDL-C in human CETP transgenic mice. The original preparation of **1** [11c] was lengthy and involved the use of some highly toxic and potentially explosive chemicals. To supply a large quantity of material **1** for further *in vivo* and toxicity studies, an efficient and scalable synthesis was required. In this article, we describe the chemical synthesis that was used successfully in the preparation of multigram quantities of compound **1**.

As illustrated by the retrosynthetic analysis in Scheme 1, the feature of our strategy involved efficient construction of the piperidine ring. We envisioned that transforming nitroketone **9** to tetrahydroquinoline **10** would be the key step in achieving our goal. This could be realized by reductive cyclization of nitroketone **9** to a racemic mixture of **10** from which the (*R*)-enantiomer

Scheme 1. Retrosynthetic analysis



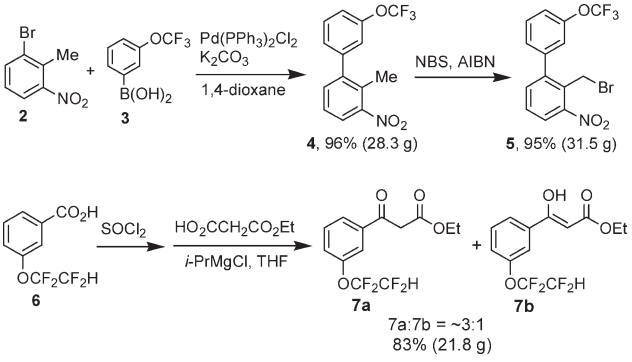
could be isolated by chiral HPLC separation. (*R*)-**10** might also be prepared in a stepwise fashion by asymmetric reductive cyclization of **9**. The nitroketone **9** could be derived from benzyl bromide **5** and β-keto ester **7** by alkylation and decarboxylation. The synthons **5** and **7** should be easily assembled from commercially available 5-bromo-6-methylnitrobenzene **2**, 3-(trifluoromethoxy)phenyl-boronic acid **3**, and 3-tetrafluoroethoxybenzoic acid **6**, respectively.

The preparation of benzyl bromide **5** and β-keto ester **7** is shown in Scheme 2, and the reaction scale is given in parentheses. Suzuki reaction [12] of 5-bromo-6-methylnitrobenzene **2** with 3-(trifluoromethoxy)phenylboronic acid **3** provided 28 g of **4** in 96% yield. In a solvent-free system, bromination [13] of **4** (26 g) with *N*-bromosuccimide and AIBN at 90°C for 5 h gave benzyl bromide **5** in 95% yield. The β-keto ester **7** was synthesized by acylation of ethyl hydrogen malonate with 3-tetrafluoroethoxybenzoyl chloride, followed by decarboxylation during acidic work-up procedure [14]. The product was a mixture of β-keto ester **7a** and its tautomer enol **7b** in ~3:1 ratio.

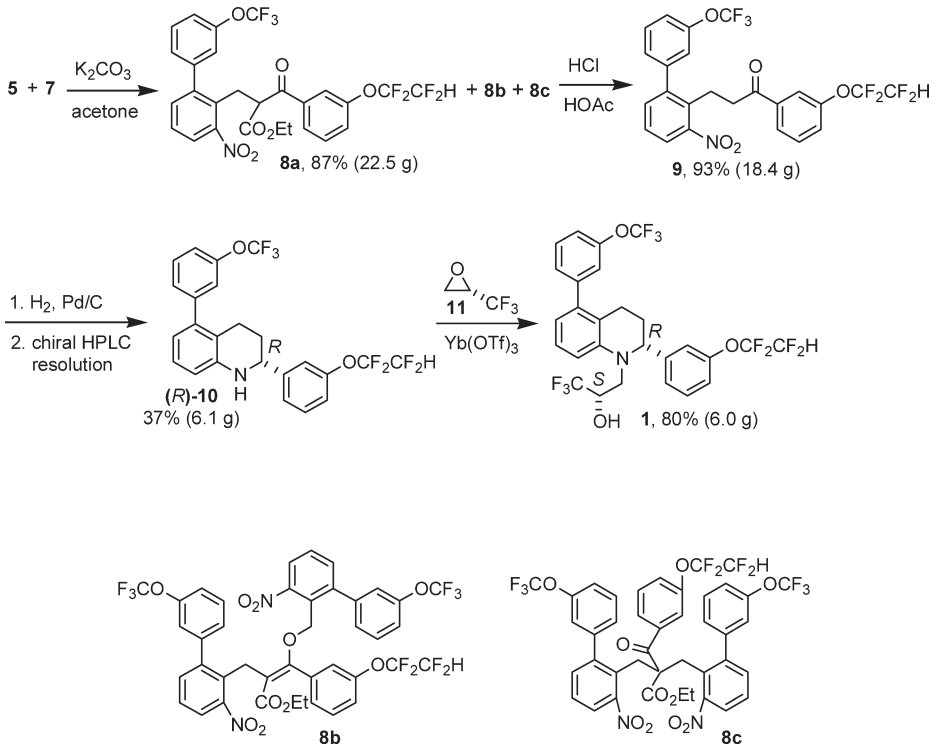
With both building synthons **5** and **7** available, the stage was set to generate the important intermediate **8a** by alkylation of β-keto ester **7** with benzyl bromide **5** (Scheme 3). However, the reaction was complicated by the formation of **8a**, *C*,*O*-dialkylation compound **8b**, and α,α-dialkylation by-product **8c**. Different reaction conditions were explored by varying a variety of bases (such as $NaN(SiMe_3)_2$, NaH, *n*-BuLi, Cs_2CO_3, and K_2CO_3), solvents (such as THF, DMF, CH_3CN, and acetone), reaction temperature, the order of reagent addition. It was found that using K_2CO_3 in acetone was the best conditions tried to give the desired product **8a** in 87% yield, along with 5% of *C*,*O*-dialkylation by-product **8b**. Without separation of the two compounds, the mixture was converted to the same nitroketone **9** upon treatment with hydrochloric acid in hot acetic acid [15]. Under normal catalytic hydrogenation conditions, reductive cyclization of nitroketone **9** occurred to form tetrahydroquinoline **10** in essentially quantitative yield. The (*R*)-**10** was collected by chiral HPLC resolution of the racemic mixture. The *R* configuration at the 2 position of the tetrahydroquinoline ring of (*R*)-**10** was known by comparing its optical rotation, $[\alpha]_D^{20}$ –13.3° (*c*1.0, $CHCl_3$), with that of (*R*)-**10**, $[\alpha]_D^{20}$ –12.9° (*c* 1.0, $CHCl_3$), obtained from an asymmetric synthesis shown below in Scheme 4. In the presence of catalytic amount of Lewis acid ytterbium trifluoromethanesulfonate, N-alkylation of (*R*)-**10** with commercially available ~90% enriched (*S*)-1,1,1-trifluoro-2,3-epoxypropane **11** occurred to produce the target **1** in 80% yield [16]. Under these conditions, the ring opening of the epoxide proceeded with complete regioselectivity.

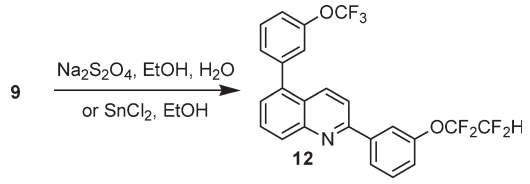
Although this route is attractive due to its simplicity and rapid access to **1**, it suffers from the obvious need for resolution of racemic tetrahydroquinoline **10** and economy of synthesis. We then turned our attention toward the development of an asymmetric approach to (*R*)-**10**. It was hoped that by controlling reaction conditions, the hydrogenation of nitroketone **9** could stop at aminoketone or cyclic-imine stage, and both of the materials could be reduced to (*R*)-**10** in high enantiomeric purity by subjecting to chiral sodium triacyloxyborohydride [17] as demonstrated in our syntheses of similar analogues [18]. However, preliminary investigation by changing H_2 pressure, solvents, and catalysts only yielded a mixture of starting material **9** and partially reduced intermediates. The strategy of stepwise reduction of nitroketone **9** to aminoketone and subsequently enantioselective reductive cyclization of which to (*R*)-**10** was also attempted by using inorganic reducing reagents such as $Na_2S_2O_4$, $SnCl_2$, and $FeSO_3$. Unfortunately, it only resulted in the formation of quinoline **12** (eq. 1):

Scheme 2



Scheme 3

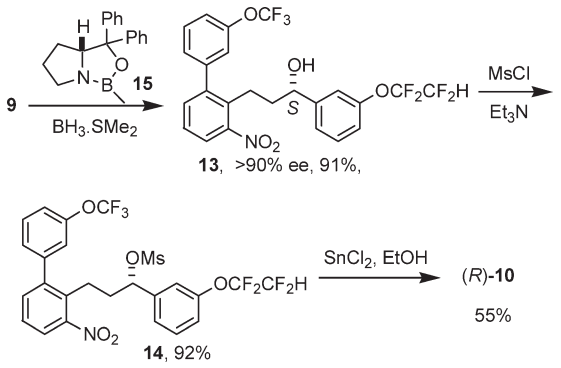




(1)

Alternatively, the required stereocenter was introduced by utilizing Corey's oxazaborolidine-borane methodology [19]. Using the *R*-Me CBS oxazaborolidine reagent **15**, nitroketone **9** was enantioselectively reduced to (*S*)-alcohol **13** in 91% yield and >90% enantiomeric excess (% ee) [20] (Scheme 4). The *S* configuration of alcohol **13** was assigned based upon the precedent illustrated in Corey and Helal's article [19]. The hydroxyl group in **13** was then converted to a good leaving group mesylate **14**. Upon treatment of **14** with $SnCl_2$ in ethanol, the nitro group was reduced to amino functionality [21] and followed by spontaneous intramolecular displacement of the mesylate to yield the ring closed (*R*)-**10** in 80–85% ee [20]. During this transformation, the inversion of the original stereocenter occurred to give the *R* absolute configuration at the 2 position of the tetrahydroquinoline ring of **10**. A small erosion of ee was observed during the cyclization step due to a competitive ionization pathway.

Scheme 4



In conclusion, we have developed a very efficient, scalable, and high yielding synthesis of (2*R*,α*S*)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol **1**. This method provides access to **1** in multigram quantities reliably.

EXPERIMENTAL

2-Methyl-3-nitro-3′-trifluoromethoxy-biphenyl (4). A mixture of 2-bromo-6-nitrotoluene **2** (21.5 g, 99.5 mmol), 3-trifluoromethoxylbenzeneboronic acid **3** (27.0 g, 131.1 mmol), $Pd(PPh_3)_2Cl_2$ (3.50 g, 5.0 mmol), and 2.0*M* K_2CO_3 (120 mL, 240 mmol) in dioxane (330 mL) was degassed with N_2 and then heated at 100°C for 3 h. After cooling to room temperature, the reaction mixture was passed through Celite and partitioned between EtOAc and brine. The combined organic

phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (1–10% EtOAc in hexane) to give 28.27 g (96%) of **4** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 1 H), 7.74–7.38 (m, 3 H), 7.31–7.23 (m, 2 H), 7.19 (s, 1 H), 2.37 (s, 3 H).

2-Bromomethyl-3-nitro-3′-trifluoromethoxy-biphenyl (5). A mixture of **4** (26.1 g, 87.8 mmol), NBS (20.3 g, 114 mmol), and AIBN (1.44 g, 8.77 mmol) was degassed with N_2 and then heated at 85°C. After 20 min, it began to react vigorously. After 2 h, the temperature was raised to 90°C, and the mixture was heated for 3 more hours. After cooling to room temperature, the reaction mixture was diluted with hexane. The solid was filtered off, and the filtrate was concentrated to give 31.47 g (95%) of **5** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, J = 2.0, 2.0, 1 H), 7.58–7.49 (m, 3 H), 7.41–7.28 (m, 3 H), 4.69 (s, 2 H).

3-Oxo-3-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propionic acid ethyl ester (7). To an ice-cooled solution of 3-tetrafluoroethoxy-benzoic acid **6** (40.0 g, 0.168 mol) was added $SOCl_2$ (59.0 mL, 0.809 mol) dropwise. After addition, the ice-bath was removed, and the mixture was stirred at room temperature for 3 h followed by heating at 50°C for 2 h and 75°C for 3 h. The reaction mixture was left stirring at room temperature overnight. After removing of $SOCl_2$ *in vacuo*, to the residue was added dry toluene and concentrated (20 mL × 3). After on high vacuum line for 5 h, the acyl chloride was obtained as a clear oil (41.0 g, 95%).

To a solution of $EtOCOCH_2CO_2H$ (16.1 g, 0.122 mol) in THF (120 mL) at –78°C was added *i*-PrMgCl (2.0*M* in THF, 122 mL, 0.244 mol) dropwise through an additional funnel. After stirring at –78°C for 1 h, the above prepared acyl chloride (20.9 g, 0.0815 mol) in THF (80 mL) was added via an addition funnel. The reaction mixture was stirred at –78°C for 1 h and RT for 2 h. The reaction flask was cooled in an ice-bath, and ∼100 mL of 1*N* HCl was added dropwise until pH < 1. Upon addition of 1*N* HCl, some precipitate formed and stirring became difficult. The precipitated solid gradually dissolved during further addition of 1*N* HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried, concentrated, and purified by flash column chromatography (5–10% EtOAc in hexane) to give 21.8 g (83%) of **7** as a yellow oil.

7a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 1 H), 7.80 (s, 1 H), 7.56–7.51 (m, 1 H), 7.48–7.45 (m, 1 H), 5.95 (tt, J = 53.0, 2.5 Hz, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 3.98 (s, 2 H), 1.27 (t, J = 7.2 Hz, 3 H); MS (ES) m/z: 331 ($M+Na^+$); HRMS (ESI) calcd for $C_{13}H_{12}F_4O_4$ ($M + H^+$) m/z 309.0750, found m/z 309.0751.

7b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.6 (s, 1 H), 7.71–7.68 (m, 1 H), 7.63 (s, 1 H), 7.45–7.42 (m, 1 H), 7.34–7.31 (m, 1 H), 5.94 (tt, J = 53.0, 2.5 Hz, 1 H), 5.68 (s, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 1.35 (t, J = 7.2 Hz, 3 H); MS (ES) m/z: 331 ($M+Na^+$).

2-(3-Nitro-3′-trifluoromethoxy-biphenyl-2-ylmethyl)-3-oxo-3-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propionic acid ethyl ester (8a). To a mixture of β-keto ester **7** (13.5 g, 43.8 mmol) and benzyl bromide **5** (15.7 g, 41.7 mmol) in 270 mL of acetone was added K_2CO_3 (8.66 g, 62.6 mmol). After stirring at room temperature for 1 h, TLC (15% EtOAc in hexane) showed the completion of reaction. The reaction mixture was filtered through Celite and the solid was washed with EtOAc. The filtrate was concentrated and purified by flash column chromatography (5–15% EtOAc in hexane) to give 22.5 g (87%) of **8a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 6.5, 2.7 Hz, 1 H), 7.59–7.54 (m, 2 H), 7.48–7.36 (m, 5 H), 7.26–7.21 (m, 2 H), 7.14 (s, 1 H), 5.92 (tt, J = 53.0, 2.5 Hz, 1 H), 4.21 (t, J = 7.0 Hz, 1 H), 4.02–3.82 (m, 2 H), 3.74–3.59 (m, 2 H), 0.96 (t, J = 7.1 Hz, 3 H); MS (ES) m/z: 626 ($M+Na^+$). Anal. Calcd for $C_{27}H_{20}F_7NO_7$: C, 53.74; H, 3.34; N, 2.32. Found: C, 54.00; H, 3.02; N, 2.36.

3-(3-Nitro-3′-trifluoromethoxy-biphenyl-2-yl)-1-[3-(1, 1,2,2-tetrafluoro-ethoxy)-phenyl]-propan-1-one (9). A solution of **8a** (22.5 g, 37.3 mmol) in concentrated HCl (85 mL) and HOAc (140 mL) was heated at 100°C for 9 h. TLC (20% EtOAc in hexane) showed the completion of reaction. After cooling down to room temperature, HOAc was evaporated through a rotary evaporator. The residue was diluted with water (200 mL) and cooled in an ice-bath. To the mixture was added 6*N* NaOH (∼80 mL) until basic judged by pH paper. The aqueous solution was extracted with EtOAc (×3), and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (10–20% EtOAc in hexane) to give 18.4 g (93%) of **9** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.84 (m, 1 H), 7.71–7.64 (m, 2 H), 7.50–7.37 (m, 5 H), 7.28–7.22 (m, 2 H), 7.17 (s, 1 H), 5.91 (tt, J = 53.0, 2.7 Hz, 1 H), 3.21–3.08 (m, 4 H); MS (ES) m/z: 554 ($M+Na^+$); HRMS (ESI) calcd for $C_{24}H_{16}F_7NO_5$ ($M + H^+$) m/z 532.0995, found m/z 532.0989. Anal. Calcd for $C_{24}H_{16}F_7NO_5$: C, 54.25; H, 3.01; N, 2.64. Found: C, 54.38; H, 2.59; N, 2.89.

2-[3-(1,1,2,2-Tetrafluoro-ethoxy)-phenyl]-5-(3-trifluoromethoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (10). A mixture of **9** (5.70 g, 10.7 mmol) and 10% Pd/C (615 mg) in EtOAc (∼100 mL) was shaken in a par-shaker under 50 psi H_2 for 19 h. The reaction mixture was filtered through Celite and the solid was washed with EtOAc. The filtrate was concentrated and dried under vacuum to give 5.20 g (100%) of **10** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 3 H), 7.28–7.23 (m, 2 H), 7.20–7.05 (m, 4 H), 6.61 (d, J = 7.8 Hz, 2 H), 5.92 (tt, J = 53.0, 2.8 Hz, 1 H), 4.50 (dd, J = 8.9, 3.3 Hz, 1 H), 2.75 (ddd, J = 16.4, 10.6, 5.1 Hz, 1 H), 2.51 (dt, J = 16.5, 4.9 Hz, 1 H), 2.10–2.02 (m, 1 H), 1.91–1.81 (m, 1 H); MS (ES) m/z: 486 ($M+H^+$). Anal. Calcd for $C_{24}H_{18}F_7NO_2$: C, 59.39; H, 3.74; N, 2.89. Found: C, 59.80; H, 3.50; N, 2.80.

(2*R*)-1,2,3,4-Tetrahydro-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-5-[3-(trifluoromethoxy)phenyl]quinoline (10). Chiral HPLC resolution of racemate (±)-**10**: 16.5 g of (±)-**10** was separated by using Chiralcel OJ eluting with 80% heptane–20% ethanol at 80 mL/min and wavelength 220 nm. A total of 6.46 g of (*R*)-**10** and 5.91 g of (*S*)-**10** were obtained in 99.99% and 99.5% ee, respectively. (*R*)-**10**: $[\alpha]_D^{20}$ –13.3° (*c*1.0, $CHCl_3$).

Cyclization of (*S*)-**14**: A solution of **14** (105 mg, 0.172 mmol) and EtOH (2 mL) was degassed under vacuum and then filled with N_2 for three times. To the solution $SnCl_2{\cdot}2H_2O$ (244 mg, 1.08 mmol) was added and the reaction mixture was stirred at room temperature under N_2 for 4.5 h. After removal of EtOH under vacuum, to the residue were added CH_2Cl_2 and saturated NH_4OH. The precipitated solid was filtered through Celite, and rinsed with CH_2Cl_2 and EtOAc. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried, concentrated *in vacuo*, and purified by flash column chromatography (10–15% EtOAc in hexane) to give 46 mg (55%) of (*R*)-**10** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.42–7.30 (m, 3 H), 7.29–7.23 (m, 2 H), 7.21–7.07 (m, 4 H), 6.61 (d, J = 7.8 Hz, 2 H), 5.91 (tt, J = 53.1, 2.8 Hz, 1 H), 4.51 (dd, J = 9.0, 3.4 Hz, 1 H), 4.20 (brs, 1 H), 2.76 (ddd, J = 16.3, 10.6, 5.2 Hz, 1 H), 2.53 (dt, J = 16.6, 5.0 Hz, 1 H), 2.11–2.04 (m, 1 H), 1.93–1.83 (m, 1 H); MS (ES) m/z: 486 ($M+H^+$); HRMS (ESI) calcd for $C_{24}H_{18}F_7NO_2$ m/z 485.1226, found m/z 485.1219. $[\alpha]_D^{20}$ –12.9° (c 1.0, $CHCl_3$). A total of 80–85% ee was analyzed by chiral HPLC (Chiralcel OJ; isocratic elution 10/90 isopropanol/hexane, 0.8 mL/min, area integration at 210 nm).

(α*S*)-3-Nitro-α-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-3′-(trifluoromethoxy)-[1,1′-biphenyl]-2-propanol (13). To a solution of THF (0.2 mL) and 1.0*M* (*R*)-2-methyl-CBS-oxazaborolidine (0.186 mL, 0.186 mmol) in toluene was added 2.0*M* $BH_3{\cdot}SMe_2$ (0.137 mL, 0.274 mmol) in THF. After stirring at room temperature for 15 min, the mixture was cooled to –25°C and to which a solution of **9** (132 mg, 0.249 mmol) in THF (2 mL) was added. The reaction mixture was stirred from –20°C to –10°C for 3.5 h and then quenched with a few drops of MeOH followed by a few drops of 1*N* HCl. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was dried, concentrated, and purified by flash column chromatography (10–20% EtOAc in hexane) to provide 114 mg (86%) of **13** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.77 (m, 1 H), 7.43–7.37 (m, 3 H), 7.28–7.23 (m, 2 H), 7.14–6.99 (m, 5 H), 5.90 (tt, J = 53.1, 2.8 Hz, 1 H), 4.54 (brs, 1 H), 2.89–2.79 (m, 1 H), 2.73–2.63 (m, 1 H), 1.92–1.76 (m, 2 H), 1.73 (brs, 1 H); MS (ES) m/z: 556 ($M+Na^+$). Anal. Calcd for $C_{24}H_{18}F_7NO_5$: C, 54.04; H, 3.40; N, 2.63. Found: C, 54.10; H, 2.89; N, 2.50. $[\alpha]_D^{20}$ –10.6° (c 1.0, $CHCl_3$). A total of >90% ee was determined by chiral HPLC (Chiralcel OJ; isocratic elution 10/90 isopropanol/hexane, 0.8 mL/min, area integration at 210 nm).

(α*S*)-3-Nitro-α-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-3′-(trifluoromethoxy)-[1,1′-biphenyl]-2-propanol methanesulfonate (14). To a solution of **13** (220 mg, 0.413 mmol) and CH_2Cl_2 (3 mL) was added methanesulfonyl chloride (0.040 mL, 0.52 mmol) and Et_3N (0.086 mL, 0.62 mmol). After stirring at room temperature for 2 h, water was added and the mixture was acidified with 1*N* HCl until acidic by pH paper. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated to give 250 mg (99%) of **14** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.83 (m, 1 H), 7.49–7.45 (m, 1 H), 7.42 (d, J = 4.6 Hz, 2 H), 7.36–7.29 (m, 2 H), 7.20–7.15 (m, 2 H), 7.09–7.07 (m, 2 H), 7.03 (s, 1 H), 5.92 (tt, J = 53.0, 2.7 Hz, 1 H), 5.38 (dd, J = 7.3, 5.8 Hz, 1 H), 2.85 (td, J = 12.6, 4.8 Hz, 1 H), 2.72 (s, 3 H), 2.67 (dd, J = 13.1, 4.8 Hz, 1 H), 2.18–1.98 (m, 2 H); MS (ES) m/z: 634 ($M+Na^+$).

(2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol (1). To a mixture of (*R*)-**10** (6.10 g, 10.2 mmol) and 1,1,1-trifluoro-2,3-epoxypropane **11** (5.71 g, 51.0 mmol) in CH_2Cl_2 (60 mL) under N_2 was added $Yb(OTf)_3$ (1.58 g, 2.55 mmol). The reaction mixture was heated at 50°C for 48 h and then cooled to ambient temperature. EtOAc was added and the mixture was washed with saturated $NaHCO_3$, H_2O and brine, dried, concentrated and purified by flash column chromatography (5–15% EtOAc in hexane) to give 6.00 g (80%) of **1** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.40–7.34 (m, 2 H), 7.25–7.12 (m, 6 H), 7.05 (s, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 6.68 (d, J = 7.3 Hz, 1 H), 5.89 (tt, J = 53.1, 2.8 Hz, 1 H), 4.90 (t, J = 4.4 Hz, 1 H), 4.46–4.41 (m, 1 H), 3.92 (d, J = 15.4 Hz, 1 H), 3.32 (dd, J = 15.4, 9.6 Hz, 1 H), 2.49 (dt, J = 16.2, 4.6 Hz, 1 H), 2.41–2.34 (m, 2 H), 2.19–2.10 (m, 1 H), 2.00–1.94 (m, 1 H); MS (ES) m/z: 598 ($M+H^+$); HRMS (ESI) calcd for $C_{27}H_{21}F_{10}NO_3$ m/z 597.1362, found m/z 597.1378. Anal. Calcd for $C_{27}H_{21}F_{10}NO_3$: C, 54.28; H, 3.54; N, 2.34. Found: C, 54.10; H, 3.40; N, 1.99. $[\alpha]_D^{20}$ –112.0° (c1.0, $CHCl_3$).

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