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Concise Asymmetric Synthesis of (+)-CP-99,994 and (+)-L-733,060 via Efficient Construction of Homochiral *syn*-1,2-Diamines and *syn*-1,2-Amino Alcohols

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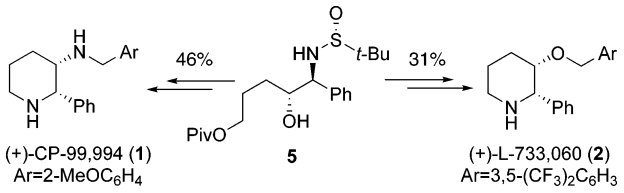

An efficient asymmetric synthesis of human NK-1 SP receptor antagonists (+)-CP-99,994 and (+)-L-733,060 was achieved starting from a common chiral intermediate (**5**). Our route featured the SmI_2-induced reductive coupling of *N-tert*-butanesulfinyl imine (**7**) with aldehyde (**6**) as the key step as well as pivotal transformations of the *anti*-1,2-amino alcohol thus obtained to homochiral *syn*-1,2-amino alcohol and *syn*-1,2-diamine for the asymmetric synthesis of 2,3-disubstituted piperidines.

1,2-Amino alcohol and 1,2-diamine scaffolds are important and ubiquitous structural features in natural products and therapeutical agents possessing a wide variey of biological activities,[1] as well as chiral ligands and auxiliaries for asymmetric synthesis (Figure 1).[2] For example, (+)-CP-99,994 (**1**)[3] and (+)-L-733,060 (**2**)[4] are potent and selective human neuronkinin-1 substance P receptor antagonists. Febrifugine (**3**) is well-known for its antimalarial effect.[5] Recently, Linezolid (**4**)[6] was successfully marketed as a new antibiotic. For (+)-CP-99,994 and (+)-L-733,060, their valuable biological profiles have stimulated immense interests in their syntheses.[7−9] To date, most asymmetric syntheses of **1** and **2** were based on chiron approach, the stereochemical outcomes of which relied more or less on substrate control. It is also noteworthy that only a handful of synthetic routes were applicable to both **1** and **2**,[8d,f,h,i] whereas the majority were devoted to only one of them. Hence, a general, flexible, and efficient synthesis of the two is still highly desirable.

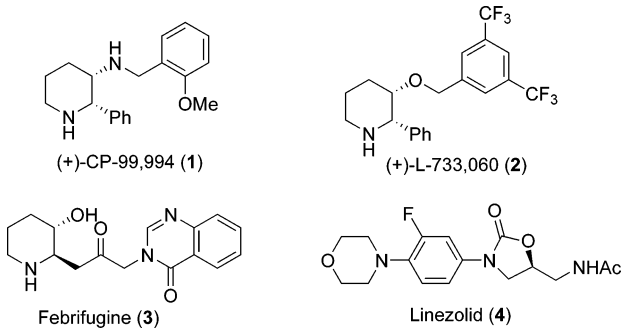

FIGURE 1. Biologically active 1,2-diamines and 1,2-amino alcohols.

One of the most straightforward methods to construct vicinal diamines or vicinal amino alcohols is the direct pinacol-type imine−imine or imine−aldehyde reductive coupling, respectively. Recently we have developed an efficient SmI_2-induced reductive coupling of *N-tert*-butanesulfinyl imines[10] with aldehydes to yield virtually enantiopure *anti*-1,2-amino alcohols.[11]

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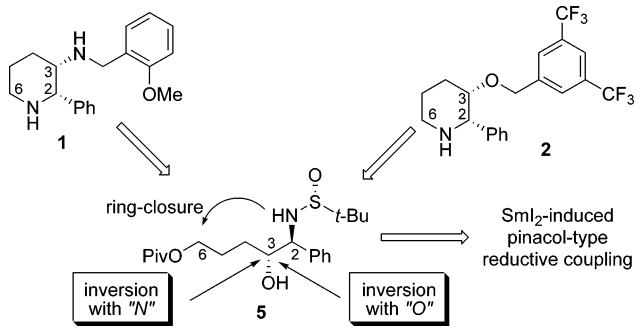


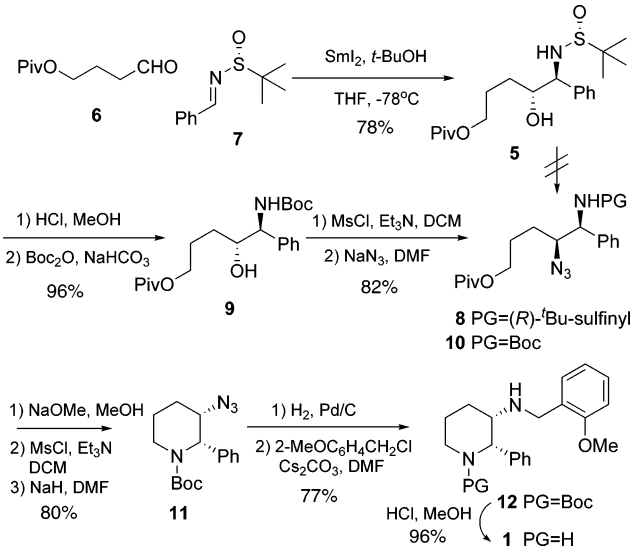
FIGURE 2. Retrosynthetic analysis for **1** and **2**.

With this powerful tool in hand, we envisaged that both **1** and **2** could be readily synthesized from a common intermediate **5**, as outlined in our retrosynthetic analysis (Figure 2). The key to this route lies in the inversion of the configuration of the hydroxyl in **5** by appropriate *N*- and *O*-nucleophiles, respectively, to furnish *syn*-1,2-diamine and *syn*-1,2-amino alcohol structural units. Conceptually, this approach complements the Sharpless asymmetric aminohydroxylation reaction[12] and asymmetric diamination reaction.[13] Moreover, it provides facile access to important 2,3-disubstituted piperidine derivatives[14] of all four possible configurations. Herein we wish to report an efficient asymmetric synthesis of (+)-CP-99,994 and (+)-L-733,060 based on this strategy.

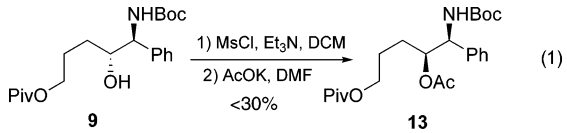
The synthesis of (+)-CP-99,994 was carried out first. Reductive coupling of 4-Pivaloxybutanal (**6**)[15] with (*R*)-Phenyl *N*-*tert*-butanesulfinyl imine (**7**) afforded **5** in 78% yield and excellent *ee*.[16] In view of the difficulty associated with nucleophilic substitution at the C-3 of piperidine,[7d] we decided to invert the hydroxy of **5** to the required configuration at the early stage of the synthesis, that is, before the formation of the piperidine ring. When **5** was subject to conventional Mitsunobu condition (Ph_3P, DEAD, $(PhO)_2PON_3$)[17] or the routine two-step sequence (MsCl/Et_3N, then NaN_3/DMF) to introduce the azide function, complex mixtures resulted due to participation of the electron-rich sulfinyl oxygen. Oxidation of the sulfinyl to sulfonyl[18] did not improve the situation. Thus, the chiral auxiliary was removed under acidic conditions, and the resulting amine was protected with Boc_2O to furnish **9** in 96% yield.

Mesylation and subsequent azide displacement proceeded smoothly to afford compound **10** in 82% yield with inversion

SCHEME 1. Total Synthesis of (+)-CP-99,994



of configuration. Deblocking of Piv with NaOMe, mesylation of the terminal hydroxyl and ring closure (NaH, DMF) gave 2,3-disubstituted piperidine derivative **11** in satisfactory yield. The azide function was reduced by hydrogenation, and the primary amine intermediate underwent mono-alkylation with 2-methoxybenzyl chloride to furnish **12** (77%) cleanly, without the contamination of a substantial amount of 2-methoxybenzyl alcohol inevitably formed in the alternative reductive amination using $NaBH_3CN$. Removal of *N*-Boc protection under acidic condition completed the synthesis of (+)-(2*S*,3*S*)-CP-99,994 (**1**), whose spectral data were in agreement with the literature (Scheme 1).[8d,f] The overall yield is 46% in 10 steps under 5 operations from **5**.



Total synthesis of (+)-L-733,060 along the same line was then persued. The direct inversion of the hydroxyl in substrates such as compound **9** with *O*-nucleophiles has not been previously established, and this proved to be non-trivial.[19] Initial attemps to displace the mesylate of **9** with *O*-nucleophiles such as AcOK in DMF resulted in unsatisfactory yield (<30%), due partly to the instability of the mesylate at elevated temperatures and partly to the bulk of the *N*-Boc protection which might favor other reaction pathways over the substitution by the weakly nucleophilic acetate anion (eq 1). Mitsunobu reaction employing several recent modifications[20] was also unsuccessful.

Since all these intermolecular reactions failed to work, we then looked at the possibility of inverting the hydroxyl in an intramolecular manner (Scheme 2). Starting from chiral building block **5**, removal of the chiral auxiliary followed by selective *N*-acylation[11] with 4-methoxy-benzoic anhydride afforded amide

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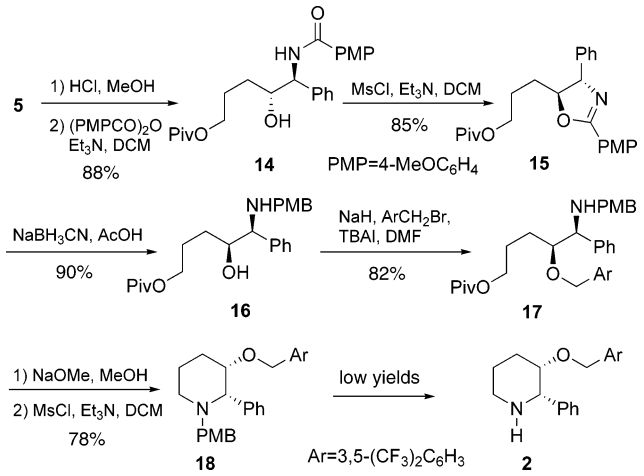
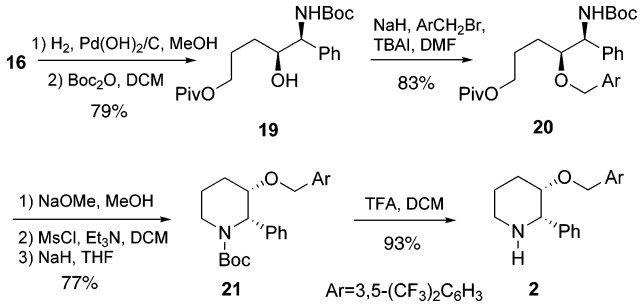
SCHEME 2. Inversion of Hydroxyl and Attemped Synthesis of 2



SCHEME 3. Total Synthesis of (+)-L-733,060



14 (88%). To our delight, upon treatement of **14** with MsCl/Et_3N,[21] oxazoline **15** was obtained smoothly in 85% yield, with complete inversion of configuration at C-2. The stereochemistry of the product **15** was unambiguously established by NOE experiment. Compared to methods employing addition to or reduction of carbonyl, the present approach is free of racemization or epimerization since there is no involvement of α-position of carbonyl. Reductive ring-opening of oxazoline ($NaBH_3CN$, HOAc, 40 °C)[22] gave *syn*-1,2-amino alcohol **16** in excellent yield. Next, selective *O*-alkylation provided **17** uneventfully (82%). Conversion of **17** to piperidine **18** was achieved by sequential removal of Piv, selective *O*-mesylation thanks to the steric demand of PMB, and spontaneous ring-closure without using strong bases such as NaH (78%). However, the removal of *N*-PMB of **18** encountered tremendous difficulty. Although CAN and DDQ led to complex reactions in low yields (15−35%), **18** was inert toward 1-chloroethyl chloroformate.[23] Attempted hydrogenolysis with Pd catalysts under both neutral[24] and acidic[25] conditions was also unfruitful.

In this connection, removal of *N*-PMB of **16** (H_2, $Pd(OH)_2$/C, MeOH), followed by *N*-protection with Boc_2O, circumvented the above difficulty (79%) (Scheme 3). Selective *O*-benzylation of **19** was achieved using NaH (1.0 equiv) as base and TBAI as catalyst to suppress oxazolidone formation (83%). Routine deprotection of Piv and ring-closure gave *N*-Boc protected piperidine **21** (77%). Removal of *N*-Boc afforded **2**, whose spectral data were in full agreement with those reported.[8d,f] The overall yield is 31% in 10 steps under 7 operations from **5**.

In summary, a concise and efficient synthesis of (+)-CP-99,994 and (+)-L-733,060 was accomplished in high overall yields from a common chiral intermediate **5**. These examples illustrated the vast utility of SmI_2-induced reductive coupling of *N*-*tert*-butanesulfinyl imines with aldehydes. Pivotal transformations of the *anti*-1,2-amino alcohols thus obtained provided easy access to a full spectrum of vicinal diamines and amino alcohols with defined stereochemistry. Further application of this versatile strategy to biologically significant molecules of more structural complexity and diversity is in progress.

Experimental Section

Compound 5. To a cooled (−78 °C) solution of SmI_2 (16.9 mmol) in 60 mL THF under Ar was added dropwise a solution of **6** (1.45 g, 8.4 mmol), **7** (1.18 g, 5.6 mmol), and *t*-BuOH (1.06 mL) in THF (60 mL). The mixture was stirred for 5 h at −78 °C, quenched by saturated aq $Na_2S_2O_3$, and extracted with EtOAc (3 × 50 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Hexanes = 1:2) to afford **5** (1.68 g, 78%) as a white solid.

Mp. 87−88 °C; $[\alpha]_D^{23}$ −26.1 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40−7.28 (m, 5H), 4.40 (dd, 1H, *J* = 5.4, 4.2 Hz), 4.06−3.94 (m, 3H), 3.87−3.83 (m, 1H), 2.28−2.21 (m, 1H), 1.90−1.60 (m, 2H), 1.55−1.40 (m, 1H), 1.22 (s, 9H), 1.18 (m, 1H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.5, 138.1, 128.6, 128.2, 73.1, 64.0, 62.3, 56.3, 38.7, 29.6, 27.1, 25.2, 22.6. ESI-MS *m*/*z* 384.2 ($M + H^+$); HR-ESI-MS *m*/*z* Calcd for $C_{20}H_{34}NO_4S$ 384.2209, Found 384.2209.

Compound 9. To a solution of **5** (434 mg, 1.13 mmol) in MeOH (5 mL) was added a methanolic solution of HCl (2M, 2.3 mL) at rt, stirring was continued for 4 h, and the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL); to this was added saturated aq $NaHCO_3$ (2.5 mL) and Boc_2O (295 mg, 1.36 mmol) at rt, and the mixture was stirred overnight and diluted with CH_2Cl_2 (20 mL), and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Hexanes = 1:2) to afford **9** (412 mg, 96%) as a white solid.

Mp. 88−89 °C; $[\alpha]_D^{23}$ +10.8 (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40−7.24 (m, 5H), 5.539−5.37 (m, 1H), 4.69−4.57 (m, 1H), 4.11−3.97 (m, 2H), 3.95−3.82 (m, 1H), 2.11 (d, 1H, *J* = 6.9 Hz), 1.88−1.40 (m, 3H), 1.41 (br s, 9H), 1.19 (m, 1H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.6, 155.5, 139.2, 128.5, 127.6, 126.5, 79.7, 73.7, 63.9, 59.2, 38.6, 29.9, 28.3, 27.1, 24.9. ESI-MS *m*/*z* 402.2 ($M + Na^+$); HR-ESI-MS *m*/*z* Calcd for $C_{21}H_{34}NO_5$ ($M + H^+$) 380.2437, Found 380.2455.

Compound 12. A suspension of **11** (83 mg, 0.27 mmol) and 10% Pd/C (10 mg) in MeOH (3 mL) was stirred under H_2 atmosphere at rt for 1 h, filtered through celite, and concentrated under reduced pressure. To a suspension of the crude amine, Cs_2CO_3 (264 mg, 0.81 mmol), and TBAI (20 mg, 0.054 mmol) in DMF (5 mL) was added 2-methoxybenzyl chloride (84 mg, 0.54 mmol) at rt, and the mixture was stirred for 2 days, diluted with water, and extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Hexanes = 1:8) to afford **12** (84 mg, 77%) as a colorless oil.

$[\alpha]_D^{23}$ +17.7 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.57 (d, 2H, *J* = 7.5 Hz), 7.42−6.78 (m, 7H), 5.48 (br s, 1H), 3.99−3.89 (m,

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1H), 3.90−3.75 (AB, 2H, J_{AB} = 13.2 Hz), 3.69 (s, 3H), 3.10−3.00 (m, 1H), 2.96 (td, 1H, J = 12.9, 3.0 Hz), 1.90−1.50 (m, 4H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 157.5, 155.2, 139.1, 129.5, 129.2, 128.4, 128.0, 126.9, 120.3, 110.1, 79.6, 57.2, 55.0, 46.6, 39.4, 28.4, 26.8, 24.3. ESI-MS *m*/*z* 397.2 (M + H$^+$); HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{33}N_2O_3$ 397.2491, Found 397.2476.

Compound 1. To a cooled (0 °C) solution of **21** (53 mg, 0.13 mmol) in MeOH (2.0 mL) was added a methanolic solution of HCl (2M, 0.25 mL, 0.5 mmol), and the mixture was stirred at rt overnight, basified with saturated aq $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (aq NH_3/MeOH/$CHCl_3$ = 1:10:200) to afford **1** (38 mg, 96%) as a colorless oil.

Dihydrochloride: $[\alpha]_D^{23}$ +76.4 (*c* 0.72, MeOH). Free base: $[\alpha]_D^{23}$ +67.3 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.19 (m, 5H), 7.14 (td, 1H, J = 7.8, 1.8 Hz), 6.96 (dd, 1H, J = 7.2, 1.2 Hz), 6.79 (td, J = 7.2, 0.9 Hz), 6.66 (d, 1H, J = 8.1 Hz), 3.87 (d, 1H, J = 2.1 Hz), 3.66−3.41 (AB, 2H, J_{AB} = 14.1 Hz), 3.42 (s, 3H), 3.27 (m, 1H), 2.83−2.75 (m, 2H), 2.13 (br d, 1H, J = 13.3 Hz), 1.93 (m, 1H), 1.77 (br s, 2H), 1.59 (m, 1H), 1.39 (br d, 1H, J = 13.3 Hz); ^{13}C NMR ($CDCl_3$) δ 157.6, 142.4, 129.6, 128.1, 127.8, 126.5, 126.3, 119.9, 109.8, 63.9, 54.72, 54.67, 47.7, 46.7, 28.2, 20.3. ESI-MS *m*/*z* 297.1 (M + H$^+$); HR-ESI-MS *m*/*z* Calcd for $C_{19}H_{25}N_2O$ 297.1967, Found 297.1999.

Compound 15. To a cooled (0 °C) solution of **14** (550 mg, 1.33 mmol) and Et_3N (1.2 mL, 8.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise MsCl (0.14 mL, 2.0 mmol), and the mixture was stirred at rt for 4 h and quenched with saturated aq $NaHCO_3$, and the aq phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Hexanes = 1:6) to afford **15** (447 mg, 85%) as a colorless oil.

$[\alpha]_D^{21}$ −40.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2H, J = 9.0 Hz), 7.40−7.24 (m, 5H), 6.94 (d, 2H, J = 9.0 Hz), 4.87 (d, 1H, J = 6.9 Hz), 4.48 (m, 1H), 4.14 (m, 2H), 3.86 (s, 3H), 1.95−1.80 (m, 4H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.5, 163.8, 162.3, 142.4, 130.2, 128.7, 127.6, 126.7, 120.1, 113.7, 87.2, 75.7, 63.8, 55.4, 38.7, 31.8, 27.1, 24.8. ESI-MS *m*/*z* 396.2 (M + H$^+$); HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{30}NO_4$ 396.2175, Found 396.2210.

Compound 16. To a solution of **15** (403 mg, 1.02 mmol) in HOAc (4.0 mL) was added carefully $NaBH_3CN$ (190 mg, 3.06 mmol), and the solution was stirred at 45 °C overnight, cooled to rt, diluted with water, basified by adding solid Na_2CO_3, and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Hexanes = 1:2 to 1:1) to afford **16** (366 mg, 90%) as a colorless oil.

$[\alpha]_D^{21}$ +45.8 (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.24 (m, 3H), 7.21−7.13 (m, 4H), 6.83 (d, 2H, J = Hz), 3.95 (t, 2H, J = 6.6 Hz), 3.78 (s, 3H), 3.64−3.42 (AB, 2H, J_{AB} = 12.6 Hz), 3.60−3.52 (m, 1H), 3.30 (d, J = 9.0 Hz), 1.86−1.69 (m, 1H), 1.67−1.51 (m, 1H), 1.30−1.17 (m, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.4, 158.7, 140.6, 131.8, 129.4, 128.7, 127.6, 127.5, 113.8, 73.8, 67.8, 64.0, 55.2, 50.4, 38.6, 29.6, 27.0, 24.9. ESI-MS *m*/*z* 400.2 (M + H$^+$); HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{34}NO_4$ 400.2488, Found 400.2486.

Compound 2. To a cooled (0 °C) solution of **21** (67 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added dropwise TFA (0.10 mL, 1.3 mmol), and the mixture was stirred at rt overnight, quenched with saturated aq $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 1:9) to afford **2** (50 mg, 93%) as a colorless oil.

Hydrochloride: Mp. 215−217 °C; $[\alpha]_D^{23}$ +87.5 (*c* 0.74, MeOH); Free base: $[\alpha]_D^{25}$ +73.9 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.69 (br s, 1H), 7.44 (br s, 2H), 7.40−7.22 (m, 5H), 4.52 (d, 1H, J_{AB} = 12.5 Hz), 4.13 (d, 1H, J_{AB} = 12.5 Hz), 3.84 (d, 1H, J = 1.2 Hz), 3.68 (d, 1H, J = 1.5 Hz), 3.29 (dt, 1H, J = 12.2, 2.1 Hz), 2.85 (ddd, 1H, J = 12.5, 12.5, 3.1 Hz), 2.22 (br d, 1H, J = 13.7 Hz), 1.88 (m, 1H), 1.76−1.64 (m, 1H), 1.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.9, 141.2, 131.2 (q, J = 32.6 Hz), 128.1, 127.4, 127.1, 126.7, 123.2 (q, J = 271 Hz), 121.1 (m), 77.3, 70.0, 64.2, 47.1, 28.4, 20.5. ESI-MS *m*/*z* 404.0 (M + H$^+$); HR-ESI-MS *m*/*z* Calcd for $C_{20}H_{20}F_6NO$ 404.1449, Found 404.1498.

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Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds **5**, **9**−**12**, **1**, **14**−**16**, **19**−**21**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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