Asymmetric Synthesis of (+)-CP-99,994 and (+)-L-733,060 from Enantiomerically Pure (3*S*,4*S*)-4-(*tert*-Butylcarbamoyl)-4-phenyl-1-buten-3-ol

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Abstract: Asymmetric syntheses of neurokinin substance P receptor antagonists (+)-CP-99,994 and (+)-L-733,060 have been accomplished starting from enantiomerically pure (3*S*,4*S*)-4-(*tert*-butylcarbamoyl)-4-phenyl-1-buten-3-ol.

Key words: 1,2-amino alcohols, 1,2-diamines, hydroformylations, neurokinin-1 antagonists, piperidines

2,3-Disubstituted piperidines, structural units found in several drug candidates and natural products, have attracted considerable attention as synthetic targets because of their unique biological activities. For example, (+)-CP-99,994 (**1**)[1] and (+)-L-733,060 (**2**)[1g,2] are potent neurokinin substance P receptor antagonists.[3] Febrifugine (**3**)[4] and isofebrifugine (**4**)[4] are well-known antimalarial agents (Figure 1).

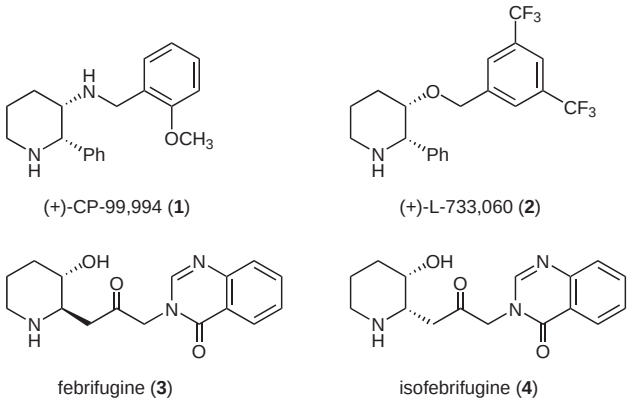
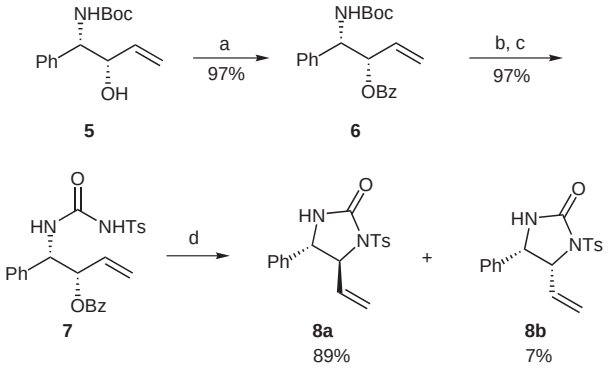


Figure 1 Biologically active 2,3-disubstituted piperidines

Although all these compounds belong to a class of small molecules with simple structural units, efficient synthetic methods for their preparation have not yet been established. In designing the syntheses of such compounds, several points should be taken into consideration. Firstly, it would be absolutely important to synthesize them in enantiomerically pure forms, neither in racemic nor in non-racemic forms, from a biological standpoint. Secondly, the synthetic processes should be flexible and scalable for the syntheses of relevant compounds such as diastereomers, enantiomers and analogues requisite for structure–activity relationship (SAR) study. Thirdly, the efficient processes associated with mild reaction conditions are highly desirable that lead to environmentally benign processes.

We have recently established a practical access to 4-(*tert*-butylcarbamoyl)-1-alken-3-ols with exceedingly high enantiomeric purity by virtue of the lipase-catalyzed kinetic resolution.[5] This protocol has paved a way for man-made chirons having three consecutive functionalities (i.e. amino, hydroxy and vinyl groups) of high synthetic value, otherwise difficult to obtain from natural amino acids. Thus, we envisaged to synthesize **1** and **2** by taking advantage of (3*S*,4*S*)-4-(*tert*-butylcarbamoyl)-4-phenyl-1-buten-3-ol (**5**)[5] (>99% ee) as a common starting material.

The success in the synthesis of **1** seemed to depend strongly upon the regio- and stereoselective introduction of a nitrogen functionality in the C-3 position of **5**, for which we planned to utilize palladium-catalyzed C–O to C–N bond transformation developed by us.[6–8] Thus, *syn* 3-benzoyloxy-4-phenyl-4-(3-tosylureido)-1-buten (**7**) was derived from **5** through a sequence of reactions involving benzoylation, deprotection of the Boc group followed by the amino group protection with *p*-tosyl isocyanate. The palladium-catalyzed intramolecular attack of the nitrogen anion on a π-allylpalladium intermediate took place very smoothly to afford a mixture of *trans* imidazolidin-2-one **8a** (89%) and *cis* isomer **8b** (7%) as shown in Scheme 1.



Scheme 1 Palladium-catalyzed C–O to C–N bond transformation. *Reagents and conditions*: (a) BzCl, pyridine, r.t., 10 h; (b) TFA, CH_2Cl_2, r.t., 1 h; (c) *p*-TsNCO, THF, r.t., 2.5 h; (d) $Pd_2(dba)_3$ (2.5 mol%), dppp (10 mol%), DBU, DMSO, 50 °C, 4 h.

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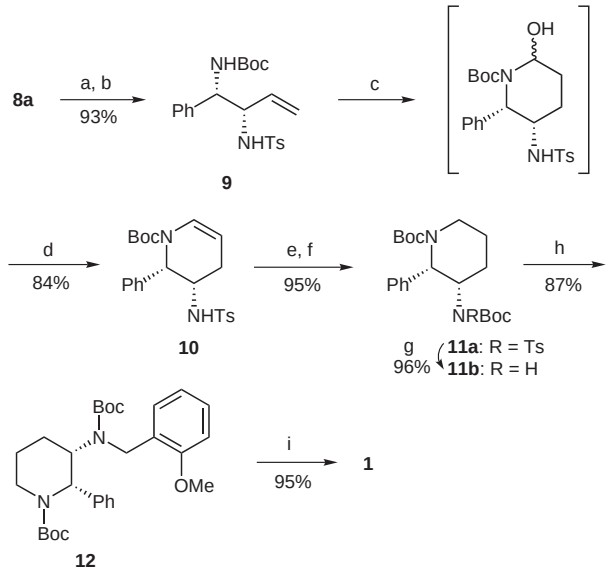
Optimum conditions with regard to the solvent and the base were examined, in which a combination of dimethyl sulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proved to give the satisfactory yield with high diastereoselectivity.[9] It is worth noting that the forerunning fraction **8b** could be easily removed by medium-pressure column chromatography.

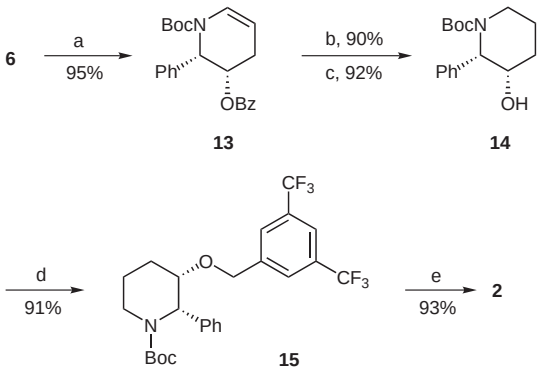


Scheme 2 Synthesis of (+)-CP-99,994. *Reagents and conditions*: (a) Ethylenediamine (50 mol equiv), 160 °C (autoclave), 6 h; (b) Boc_2O, CH_2Cl_2, r.t., 12 h; (c) $Rh(acac)(CO)_2$ (3 mol%), biphephos (6 mol%), THF, $CO–H_2$ (5 atm), 65 °C, 8 h; (d) cat. CSA, THF, r.t., 9 h; (e) H_2 (1 atm), 10% Pd–C, EtOH, r.t., 12 h; (f) Boc_2O, cat. DMAP, THF, r.t., 6 h; (g) Na, naphthalene, THF, –78 °C, 1 h; (h) 2-methoxybenzyl chloride, NaH, TBAI, THF–DMF (1:3), 0 °C, 18 h; (i) TFA, r.t., 2 h; $NaHCO_3$, 95%.

With enantiomerically pure **8a** in hand, we then tried to cleave the imidazolidinone ring. The attempted known procedures such as acid[10a] or base-mediated[10b,c] hydrolysis, however, had no effect on **8a**. Eventually, the successful ring cleavage of **8a** was accomplished with a large excess of ethylenediamine in an autoclave at 160 °C,[11] giving a mono-*N*-Ts-protected 1,2-diamine.[12] To the best of our knowledge, the ring-cleavage reaction of imidazolidinones through amine-exchange protocol has never been reported, but would be of high synthetic value. The free amine thus obtained was protected by a Boc group to afford **9**.

Next we stepped into the piperidine ring formation, for which we selected a Rh-catalyzed hydroformylation.[13] Compound **9** underwent smooth hydroformylation with a catalytic system of $Rh(acac)(CO)_2$ (3 mol%) and biphephos (6 mol%)[14] under five atmospheres of $CO–H_2$ (1:1), giving a mixture of the *N*-Boc-protected aminal and enamide **10** as major products.[15] The crude reaction mixture was submitted to 10-camphorsulfonic acid (CSA)-catalyzed dehydration to afford **10**[16] in 84% yield. Enamide **10** was hydrogenated in quantitative yield to provide a saturated 3-tosylaminopiperidine, which was subjected to the reductive cleavage of *N*-tosyl group with sodium naphthalenide. This attempt, however, was unsuccessful and a complex mixture was obtained. Thus, the tosylamino group was further protected with $(Boc)_2O$–4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give **11a**, whose *p*-tosyl group was smoothly removed by treatment with sodium naphthalenide in tetrahydrofuran at –78 °C. Carbamate **11b** thus obtained was deprotonated with sodium hydride in tetrahydrofuran–*N*,*N*-dimethylformamide (1:3) at room temperature and carefully treated with 2-methoxybenzyl chloride in the presence of tetrabutylammonium iodide (TBAI) at 0 °C for 18 hours to produce **12** (87%).[17,18] Finally, treatment of **12** with trifluoroacetic acid at room temperature for two hours provided **1**[19] (Scheme 2) in 95% yield {mp (dihydrochloride): 253–254.5 °C; $[\alpha]_D^{24}$ +77.5 (dihydrochloride, *c* = 1.05, MeOH)} {Lit.[1a] mp (dihydrochloride): 255 °C, $[\alpha]_D^{25}$ +77 (dihydrochloride, *c* = 1.0, MeOH); Lit.[1e] mp (dihydrochloride): 254.5 °C, $[\alpha]_D^{23}$ +75.5 (dihydrochloride, *c* = 1.1, MeOH); Lit.[1g] $[\alpha]_D^{16}$ +75.1 (dihydrochloride, *c* = 0.6, MeOH); Lit.[1j] mp: 236 °C, $[\alpha]_D^{20}$ –73.0 (hydrochloride of *ent*-**1**, *c* = 1.0, MeOH)}.

On the other hand, the synthesis of **2** was successfully achieved as shown in Scheme 3, in which the piperidine framework was also constructed through the aforementioned hydroformylation. The hydroformylation of benzoate **6**[20] under the same conditions as that of **9** proceeded smoothly to provide enamide **13**[21,22] (95%). In this case, **13** was obtained in a straightforward manner without the treatment with CSA. Hydrogenation of **13** followed by alkaline hydrolysis gave piperidine **14**.[23] Finally, 3,5-bistrifluoromethylbenzylation provided **15**,[24] whose Boc group was removed to give **2**[25] {yield: 85% for two steps; mp (hydrochloride): 215–217 °C, $[\alpha]_D^{23}$ +87.1 (hydrochloride, *c* = 1.0, MeOH), $[\alpha]_D^{24}$ +73.7 (free base, *c* = 1.3, $CHCl_3$)}{Lit.[1g] mp 213–215 °C, $[\alpha]_D^{28}$ +84.5 (hydrochloride, *c* = 0.8, MeOH); Lit.[2a] 215–216 °C, $[\alpha]_D^{23}$ +87.3 (hydrochloride, *c* = 1, MeOH); Lit.[2d] $[\alpha]_D^{25}$ +34.29 (free base, *c* = 1.32, $CHCl_3$); Lit.[2e] $[\alpha]_D^{25}$ +32.65 (free base, *c* = 1.0, $CHCl_3$); Lit.[1i] mp 200–202 °C, $[\alpha]_D^{20}$ –83.9 (hydro-



Scheme 3 Synthesis of (+)-L-733,060. *Reagents and conditions*: (a) $Rh(acac)(CO)_2$ (3 mol%), biphephos (6 mol%), $CO–H_2$ (5 atm), THF, 65 °C, 5 h; (b) 10% Pd–C, H_2(1 atm), EtOH, r.t., 20 h; (c) 1 M NaOH–MeOH–1,4-dioxane, (2:3:6), r.t., 1 h; (d) 3,5-$(CF_3)_2C_6H_3CH_2Br$, NaH, THF–DMF (1:3), 0 °C, 6 h; (e) TFA, r.t., 1.5 h, $NaHCO_3$.

chloride of *ent*-**2**, *c* = 0.99, MeOH); Lit.[1j] mp 210 °C, $[\alpha]_D^{20}$ –86.0 (hydrochloride of *ent*-**2**, *c* = 1.0, MeOH)}.

In conclusion, we have successfully established an efficient synthetic method for (+)-CP-99,994 and (+)-L-733,060 from enantiomerically pure (3*S*,4*S*)-4-(*tert*-butylcarbamoyl)-4-phenyl-1-buten-3-ol as a common starting material without loss of optical purity.

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(5) (a) Oshitari, T.; Mandai, T. *Synlett* **2003**, 2374. (b) The enantiomeric purity of **5** was determined to be >99% ee by HPLC [CHIRALCEL OD-H; hexane–*i*-PrOH = 9:1; λ = 220 nm; flow rate: 0.8 mL/min; t_R(**5**) = 6.36 min; t_R(*ent*-**5**) = 8.71 min]. (c) Compound **5** was also prepared from (*S*)-(+)-phenylglycine. See: Denis J.-N., Correa A., Greene A. E.; *J. Org. Chem.;* **1991**, *56*: 6939; Greene and co-workers reported therein that **5** was obtained in moderate yield with complete retention of enantiomeric purity by the addition of the crude Swern-oxidation product of *N*-Boc phenylglycinol to a large excess of vinylmagnesium bromide. Bhaskar et al. adopted this method for the preparation of compound **5** in their synthesis of **2**,[2d] whose enantiomeric purity can be estimated below 50% ee in comparison with our own data. Ham and co-workers also synthesized **2** via an oxazoline derivative starting from *N*-benzoyl phenylglycinol.[2e] The optical rotation of **2** was in agreement with that reported in ref. 2d. These observations clearly imply that special care is required for employing easily racemizable phenylglycinal derivatives as a source of chiron approach.

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(9) In our preliminary investigation, DMSO was proven to be more effective solvent than toluene, THF and DMF. In addition, we found that DBU, soluble in above solvents, was much superior to other bases such as NaH, *t*-BuOK and Cs_2CO_3.

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(11) The reaction under heating at refluxing temperature in a flask overnight provided 4-phenyl-4-(3-aminopropionamido)-3-tosylamino-1-butene as the sole product.

(12) After removal of ethylenediamine in vacuo, a mixture of the mono-*N*-Ts-protected 1,2-diamine and 2-imidazolidone was afforded, which was subjected to the next step without further purification.

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(15) Five-membered *N*-Boc-enamide (2%) and five-membered *N*-Boc-aminals (5%) were also isolated after the treatment with CSA. *N*-Ts-enamide and *N*-Ts-aminals were not obtained at all.

(16) Compound **10**: colorless foam; $[\alpha]_D^{22}$ –206.0 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.21 (br s, 6.3 H), 1.41 (br s, 2.7 H), 1.77–1.85 (m, 1 H), 1.89–2.10 (br m, 1 H), 2.45 (s, 3 H), 3.87 (m, 1 H), 3.97 (d, *J* = 10.1 Hz, 1 H), 4.71 (br, 0.3 H), 4.78 (br, 0.7 H), 4.98 (br, 0.7 H), 5.15 (br, 0.3 H), 6.89–7.22 (m, 2 H), 7.28–7.38 (m, 5 H), 7.78 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 21.6, 25.5, 26.1, 27.9, 28.2, 49.8, 57.5, 58.9, 77.2, 81.3, 81.5, 101.0, 126.2, 126.6, 127.0, 128.0, 128.5, 129.9, 137.3, 137.7, 138.1, 143.7, 152.1. Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.37; H, 6.71; N, 6.54.

(17) In the absence of TBAI, the N-alkylation was very slow at 0 °C. Compound **12**, however, was afforded in 81% yield at r.t. in 5 h with the significant loss of enantiomeric purity (77% ee), which was probably caused by the elimination–addition sequence of the *N*-2-methoxybenzyl-*tert*-butyl carbamoyl group.

(18) Compound **12**: colorless foam; $[\alpha]_D^{21}$ –105.2 (*c* = 1.32, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.19–1.70 (m, 21 H), 1.85 (br m, 1 H), 3.14 (br m, 1 H), 3.33 (br m, 1 H), 3.65 (s, 3 H), 3.75 (br m, 0.45 H), 3.99–4.10 (m, 1.65 H), 4.25 (br m, 0.45 H), 4.50 (br m, 0.45 H), 5.45 (br s, 0.9 H), 5.64 (br s, 0.1 H), 6.71 (m, 1 H), 6.86 (m, 1 H), 7.03 (m, 1 H), 7.12 (m, 1 H), 7.37–7.25 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ = 22.4, 24.6, 28.2, 41.0, 41.6, 42.1, 55.1, 56.2, 57.0, 57.5, 77.2, 79.6, 109.8, 120.2, 126.4, 127.0, 128.0, 128.4, 140.2, 141.2, 155.9. Anal. Calcd for $C_{29}H_{40}N_2O_5$: C, 70.13; H, 8.12; N, 5.64. Found: C, 69.90; H, 8.28; N, 5.54. The enantiomeric purity of **12** was determined to be >99% ee by HPLC [CHIRALCEL OD; hexane–*i*-PrOH = 30:1; λ = 220 nm; flow rate: 1.0 mL/min; t_R(**12**) = 6.8 min; t_R(*ent*-**12**) = 11.0 min].

(19) (+)-CP-99,994 (**1**): ^1H NMR (free base, $CDCl_3$): δ = 1.40 (br d, *J* = 13.2 Hz, 1 H), 1.60 (m, 1 H), 1.76 (br s, 2 H), 1.93 (m, 1 H), 2.14 (br d, *J* = 13.1 Hz, 1 H), 2.76–2.83 (m, 2 H), 3.27 (m, 1 H), 3.41 (d, *J* = 13.8 Hz, 1 H), 3.44 (s, 3 H), 3.67 (d, *J* = 13.8 Hz, 1 H), 3.88 (d, *J* = 2.1 Hz, 1 H), 6.68 (br d, *J* = 8.2 Hz, 1 H), 6.80 (br t, *J* = 7.3 Hz, 1 H), 6.97 (dd, *J* = 1.5, 7.3 Hz, 1 H), 7.15 (dt, *J* = 1.5, 8.2 Hz, 1 H), 7.20–7.31 (m, 5 H). ^{13}C NMR (free base, $CDCl_3$): δ = 20.4, 28.2, 46.7, 47.8, 54.7, 54.8, 64.0, 109.8, 120.0, 126.3, 126.5, 127.8, 128.2, 129.6, 142.4, 157.6.

(20) Protection of C3-hydroxyl group as a benzoate was of choice for the subsequent hydroformylation.

(21) Compound **13**: colorless viscous oil; $[\alpha]_D^{24}$ –152.3 (*c* = 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.25 (br s, 6 H), 1.40–1.55 (br m, 3 H), 2.05–2.25 (m, 1 H), 2.40 (m, 1 H), 4.83 (br m, 0.33 H), 4.93 (br m, 0.67 H), 5.40 (br m, 0.33 H), 5.46–5.63 (m, 1.67 H), 7.00–7.35 (m, 6 H), 7.40 (m, 2 H), 7.55 (m, 1 H), 7.90 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 23.7, 24.0, 27.9, 28.2, 56.0, 57.3, 69.2, 81.3, 100.4, 126.1, 126.4, 127.5, 127.6, 128.0, 128.35, 128.38, 129.69, 129.71, 129.8, 133.1, 138.6, 152.3, 165.6. Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.76; H, 6.84; N, 3.66.

(22) Five-membered aminals (4%) were also isolated.

(23) Compound **14**: colorless viscous oil; $[\alpha]_D^{22}$ +56.7 (*c* = 1.3, $CHCl_3$) {Lit.[1g] $[\alpha]_D^{15}$ +53.77 (*c* = 1.0, $CHCl_3$); Lit.[2d] $[\alpha]_D^{25}$ +38.30 (*c* = 1.92, $CHCl_3$)}. ^1H NMR ($CDCl_3$): δ = 1.37 (s, 9 H), 1.54–1.62 (m, 1 H), 1.69 (m, 1 H), 1.76–1.87 (m, 3 H), 3.04 (m, 1 H), 4.01 (dd, *J* = 5.8, 12.8 Hz, 1 H), 4.09 (m, 1 H), 5.32 (d, *J* = 5.8 Hz, 1 H), 7.27 (m, 1 H), 7.37–7.32 (m, 2 H), 7.45 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 23.1, 27.7, 28.3, 39.5, 59.3, 70.1, 79.9, 127.2, 128.4, 138.5, 155.4. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.21; H, 8.59; N, 4.77. The enantiomeric purity of **14** was determined to be >99% ee by HPLC [CHIRALCEL OJ-H; hexane–*i*-PrOH = 9:1; λ = 220 nm; flow rate: 1.0 mL/min; t_R(**14**) = 4.80 min; t_R(*ent*-**14**) = 5.75 min].

(24) Compound **15**: colorless oil; $[\alpha]_D^{23}$ +43.3 (*c* = 1.60, $CHCl_3$) {Lit.[1g] $[\alpha]_D^{28}$ +36.90 (*c* = 1.0, $CHCl_3$)}. ^1H NMR ($CDCl_3$): δ = 1.46 (s, 9 H), 1.58–1.76 (m, 2 H), 1.94–2.05 (m, 2 H), 2.77 (ddd, *J* = 3.3, 13.4, 13.4 Hz, 1 H), 3.88 (m, 1 H), 3.95 (dd, *J* = 3.3, 13.4 Hz, 1 H), 4.71 (d, *J* = 12.5 Hz, 1 H), 4.75 (d, *J* = 12.5 Hz, 1 H), 5.70 (br s, 1 H), 7.25–7.36 (m, 3 H), 7.54 (br s, 1 H), 7.56 (br s, 1 H), 7.71 (br s, 2 H), 7.78 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 24.2, 25.8, 28.4, 39.2, 55.4, 69.1, 78.7, 80.1, 121.4 (m), 123.3 (q, *J* = 272 Hz), 127.0, 127.2, 128.28, 128.32, 131.6 (q, *J* = 32.9 Hz), 138.0, 141.0, 155.3. The enantiomeric purity of **15** was determined to be >99% ee by HPLC [CHIRALPAK IA; hexane–*i*-PrOH = 30:1; λ = 220 nm; flow rate: 0.3 mL/min; t_R(**15**)= 14.1 min; t_R(*ent*-**15**) = 16.6 min)].

(25) L-733,060 (**2**): ^1H NMR (free base, $CDCl_3$): δ = 1.53 (m, 1 H), 1.66–1.75 (m, 1 H), 1.88 (m, 1 H), 2.22 (br d, *J* = 14.0 Hz, 1 H), 2.85 (ddd, *J* = 3.1, 12.5, 12.5 Hz, 1 H), 3.29 (m, 1 H), 3.68 (br m, 1 H), 3.85 (d, *J* = 1.2 Hz, 1 H), 4.13 (d, *J* = 12.5 Hz, 1 H), 4.52 (d, *J* = 12.5 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.30–7.35 (m, 2 H), 7.35–7.39 (m, 2 H), 7.44 (br s, 2 H), 7.69 (br s, 1 H). ^{13}C NMR (free base, $CDCl_3$): δ = 20.5, 28.4, 47.1, 64.2, 70.0, 77.3, 121.1 (hept, *J* = 4.1 Hz), 123.2 (q, *J* = 271 Hz), 126.7, 127.0, 127.4 (m), 128.1, 131.2 (q, *J* = 32.9 Hz), 141.2, 141.9.