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First catalytic enantioselective synthesis of the cocaine abuse therapeutic agent (*S*)-(+)-1-(4-{2-[bis(4-fluorophenyl)methoxy]ethyl}-piperazin-1-yl)-2-phenyl-2-propanol

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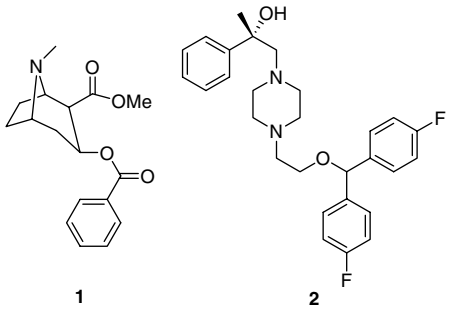
Dedicated to Professor T. Hiyama on occasion of his 60th birthday

Abstract—(*S*)-(+)-1-(4-{2-[Bis(4-fluorophenyl)methoxy]ethyl}piperazin-1-yl)-2-phenyl-2-propanol, which is a promising candidate as a cocaine abuse therapeutic agent, is prepared in several steps. The key asymmetric step is the catalytic enantioselective addition of dimethylzinc to either 2-chloro or 2-bromoacetophenone catalyzed by the use of different chiral isoborneolsulfonamide ligands in the presence of titanium tetraisopropoxide. The synthesis of a new isoborneolsulfonamide ligand bearing a trifluromethyl substituent and its use in this addition is also presented.

1. Introduction

The abuse of cocaine **1** continues to be a major health, social, and economical problem in spite of much governmental effort devoted toward educating the public about the dangers of illicit drug use. The misuse of this potent central nervous system stimulant is linked to numerous health risks, ranging from cardiovascular complications to chronic inflammation, and also infectious diseases.[1] The euphoric and reinforcing properties of cocaine are believed to be primarily associated with a perturbation of the dopaminergic transporter system (DAT),[2] as well as with other neuronal diseases including Parkinson, Huntington, and schizophrenia.[3] However, the level of these perturbations is similar for serotonin (SERT)[4] and norepinephrine (NET)[5] transporter systems.[6]

Although, there are several treatments for cocaine abuse,[7] the regulatory agencies (EMEA, FAD, etc.) have not yet approved any specific medication among the different candidates.[8] (*S*)-(+)-1-(4-{2-[Bis(4-fluorophenyl)methoxy]-ethyl}piperazin-1-yl)-2-phenyl-2-propanol **2** is a promising candidate as a cocaine abuse therapeutic agent. It could decrease the cocaine-maintained response in rhesus monkeys at lower doses than those affecting food-maintained responding, as other related compounds do,[9] which is an important characteristic for a potential treatment agent. Moreover, the hydroxy substituent would allow its further conversion to an oil-soluble prodrug and the presence of the methyl group suggests a possible resistance to metabolism, all these facts making it a good candidate for further development. Finally, it should be pointed out that the absolute configuration of the quaternary stereocenter has a great impact on the DAT and SERT binding affinities, the (*S*)-enantiomer giving the best results.[10]



1 **2**

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Chiral compound **2** has been already obtained either by semi-preparative chiral HPLC followed by recrystallization,[10] or by diastereoselective crystallization of the starting racemic atrolactic acid with chiral 1-phenyl-1-ethylamine.[11]

On the other hand, in our research group, as well as in others, a new family of chiral isoborneolsulfonamide[12–15] ligands **3** has been introduced as excellent chiral ligands for catalytic enantioselective addition[16] of organozinc reagents to ketones[17] in the presence of titanium alkoxides.[18] In this paper, we present the first enantioselective synthesis of compound **2** through a catalytic addition of dimethylzinc **5** to 2-haloacetophenone **4** as the key asymmetric step.

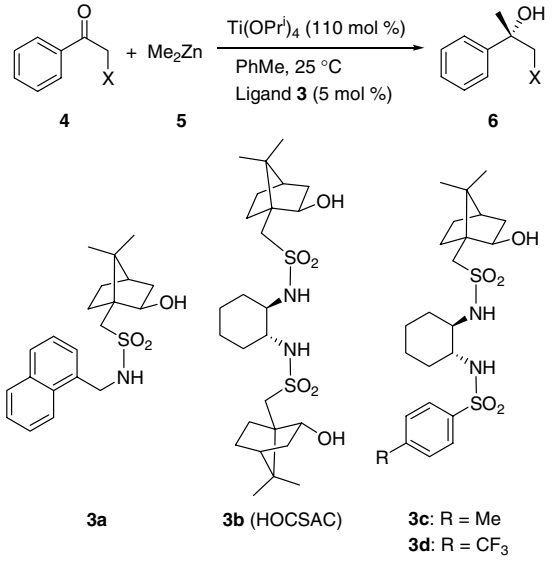
2. Results and discussion

The synthesis started with the study of the asymmetric key step (Table 1).

The enantioselective addition of dimethylzinc **5** to 2-chloroacetophenone **4** (X = Cl) at room temperature catalyzed by the first generation ligand **3a**[12b,2c] gave the expected functionalized tertiary alcohol **6a** with a moderated chemical yield and good enantioselectivity (Table 1, entry 1), the absolute configuration being assigned by correlation with the final product **2**. After this promising initial result, we tested HOCSAC **3b**,[13b,15b] which presented the best enantioselectivities among the second generation ligands due to the beneficial possibility of a double titanium atom complexation[19] (Table 1, entry 2). However, the only significant change took place in the chemical yield, and not in the enantioselectivity. In our previous studies with other simple ketones, the use of the so-called third generation ligands gave the best enantioselectivities. Therefore ligand **3c**[14a,15b] from the third generation set was tested and, surprisingly, the results were worse. This disappointing result could be explained as a consequence of the presence of an extra-coordinating basic functionality. We thought that increasing the acidity of the ligand by the introduction of an electron withdrawing group on the aromatic ring, such as in ligand **3d**, could improve the results (Table 1, entry 3). In fact, the results could be somewhat better than the previous results with the third generation ligand **3c**, but inferior to those obtained using the second generation one HOCSAC. These results pointed out that, although for simple ketones increasing generations gave better results, for a particular functionalized ketone some ligand optimization needs to be done. Finally, the reaction of dimethylzinc with 2-bromoacetophenone catalyzed by HOCSAC **3b** gave the related alcohol **6b** with a disappointing enantioselectivity (compare entries 2 and 5 in Table 1).

Once the chiral part of prodrug **2** was prepared, the achiral part was synthesized starting by a standard[20] double addition of 4-fluorophenylmagnesium bromide **7** to ethyl formate **8** at 0 °C to give the corresponding diaryl methanol **9**[21] with good yield (96%, Scheme 1).

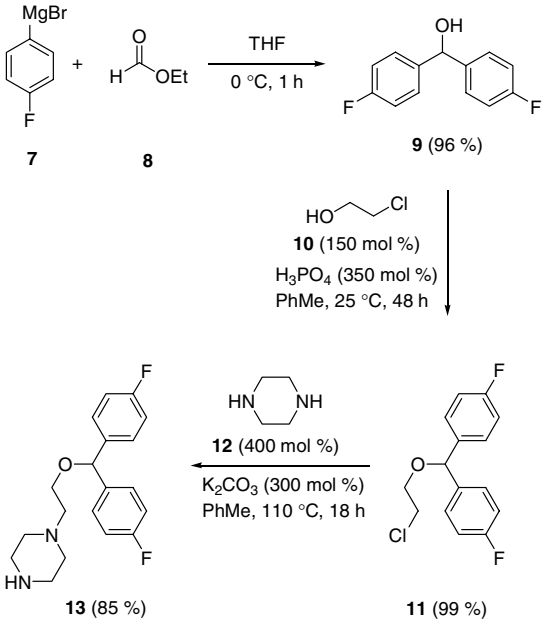
Table 1. Catalytic enantioselective addition of dimethylzinc to ketone **4**



Entry	Ligand	Time (h)	No	X	Yield[a] (%)	ee[b] (%)
1	**3a**	180	**6a**	Cl	60	80
2	**3b**	111	**6a**	Cl	90	78
3	**3c**	180	**6a**	Cl	69	48
4	**3d**	180	**6a**	Cl	81	68
5	**3b**	42	**6b**	Br	83	59

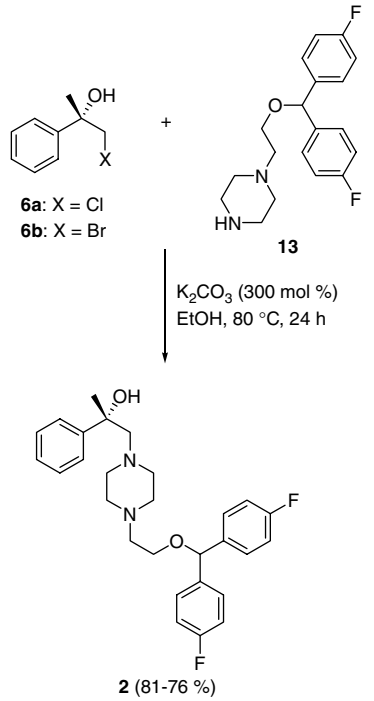
[a] Isolated yield based on the starting ketone **4** after column chromatography (hexane/ethyl acetate).
[b] Enantiomeric excess determined by HPLC using a Chiralcel OJ column.

Then, the reaction of alcohol **9** with an excess of 2-chloroethanol **10** in the presence of a Brønsted acid[22] (phosphoric acid[23]) at room temperature gave the expected ether **11**[9a] in excellent yield, resulting from a classical S_N1 reaction. The final step was an S_N2 substitution reaction between chlorinated derivative **11** and piperazine **12** to yield the final achiral compound **13**[9a] (Scheme 1).



Scheme 1. Synthesis of compound **13**.

Finally, product **2** was synthesized by a S_N2 displacement reaction in the presence of a weak base. So, the reaction of chlorinated alcohol **6a** with piperazine derivative **13** gave the expected compound **2**[11] in 81% yield, after column chromatography purification (Scheme 2). Surprisingly, the enantiomeric excess of the final compound **2** was 91%, whereas the enantiomeric excess of the initial alcohol **6a** was only 78%. The enantiomeric enrichment of different substances through their column chromatography purification has been previously described and associated with the formation of diastereomeric dimers of the chiral compound;[24] therefore, we believe that the same resolution equilibrium occurs in our case.



Scheme 2. Final step in the synthesis of compound **2**.

When the reaction was performed using the brominated derivative **6b**, the corresponding compound **2** was obtained in 76% yield and, as in the previous case, there is an important enantiomeric enrichment from the initial 59% ee of **6b** up to 72% ee of the final compound **2**. In this last case, the enantiomeric excess could be further improved up to 89% simply by recrystallization of the corresponding dimaleate salt[11] from DMF–methanol and final basic extraction to liberate the initial amine **2**.

3. Conclusion

The first catalytic enantioselective synthesis of a promising candidate as a cocaine abuse therapeutic agent (*S*)-(+)-1-(4-{2-[bis(4-fluorophenyl)methoxy]ethyl}piperazin-1-yl)-2-phenyl-2-propanol was accomplished in 59% overall yield by a five-step process, which permits its easy multigram scale-up and avoids the economical and environmental problems associated with the presence of other enantiomer. The key asymmetric step was the catalytic enantioselective addition of dimethylzinc to 2-haloacetophenone in the presence of stoichiometric amounts of titanium tetraisopropoxide and substoichiometric amounts of different isoborneolsulfonamide ligands. The enantiomeric excess of the initially obtained products was further increased by spontaneous enrichment by the column chromatography isolation.

4. Experimental

Melting points were obtained with a Reichert Thermovar apparatus. $[\alpha]_D$ were recorded at room temperature (ca. 25 °C) in a DIP-1000 JASCO polarimeter. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as a solvent and TMS as internal standard; chemical shifts are given in δ (parts per million) and coupling constants (J) in Hertz. Mass spectra (EI) were obtained at 70 eV on a Shimazdu QP-5000 spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. The high resolution mass spectrum was performed by the corresponding Mass Spectrometry Service at the University of Alicante. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and 12 m HP-1 capillary column (0.2 mm diam, 0.33 mm film thickness, OV-1 stationary phase),

using nitrogen (2 mL/min) as a carrier gas, $T_{injector} = 275$ °C, $T_{detector} = 300$ °C, $T_{column} = 60$ °C (3 min) and 60–270 °C (15 °C/min), $P = 40$ kPa; t_R values are given in minutes under these conditions. The enantiomeric ratios (er) for the calculation of enantiomeric excess of tertiary alcohols were determined by HPLC analysis in a HP-1100 or a Jasco P-1030 apparatus by using hexane/2-propanol mixtures as solvents, and Chiralcel OD-H (ODH) and Chiralcel OJ (OJ) as chiral columns, indicating in each case the column and solvent ratio used. The t_R (*R*) and t_R (*S*) values are given in minutes under these conditions. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid [25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2{\cdot}4H_2O$, 60 mL concentrated H_2SO_4 and 940 mL H_2O]; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35–70 mesh. Chiral ligands **3a**[12c] and **3b**,**c**[15b,25] were prepared according to literature procedures. All other reagents were commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.[26]

4.1. Synthesis of (1*S*,2*R*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}-4″-trifluoromethylbenzenesulfonamide 3d

To a solution of (1*R*,2*R*)-*trans*-(+)-diaminocyclohexane (1.37 g, 12 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added an aqueous solution of NaOH (2 M, 15 mL) at 0 °C. To the former strongly stirred biphasic mixture was slowly added a solution of 4-trifluoromethylbenzenesulfonyl chloride (2.94 g, 12 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL), allowing the temperature to rise to 25 °C for 6 h. The reaction was quenched by addition of a 2 M solution of HCl up to acid pH and the organic layer was decanted. The acid aqueous layer was basified by addition of an aqueous 6 M solution of NaOH and extracted with CH_2Cl_2 (4×50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the expected highly pure ketone (6.4 g, 99%). This solid was dissolved in MeCN (25 mL) at 0 °C, subsequently adding 4-DMAP (0.73 g, 6 mmol, 0.5 equiv) and Et_3N (7.6 mL, 54 mmol, 4.5 equiv). Then, a solution of (1*S*)-(+)-(10)-camphorsulfonyl chloride (4.51 g, 18 mmol, 1.5 equiv) in MeCN (25 mL) was slowly added to the above solution at 0 °C. After 24 h allowing the temperature to rise to 25 °C, the reaction mixture was quenched by addition of a 3 M aqueous solution of NaOH (50 mL) and extracted with ethyl acetate (4×40 mL). The organic layers were washed with a 2 M solution of HCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was dissolved in ethanol (50 mL) at 0 °C and $NaBH_4$ (2.27 g, 60 mmol, 6 equiv) was added. The reaction mixture was stirred for 24 h allowing the temperature to rise to 25 °C. Then, the reaction mixture was quenched with 10 mL of a saturated solution of NH_4Cl and extracted with ethyl acetate (4×40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate) to give the title compound (3.0 g, 46%). White solid, mp 80–82 °C (ethyl acetate/hexane); $R_f = 0.56$ (hexane/ethyl acetate: 1/1); $[\alpha]_D = +1.0$ (*c* 1.3, $CHCl_3$); ^{1}H NMR $\delta = 0.86$ and 1.08 [2s, 3H each; $C(CH_3)_2$], 1.10–2.10 [m, 17H; $CH(CH_2)_4CH$ and $(CH_2)_2CHCH_2$], 2.90–2.95 and 3.10–3.15 (2m, 1H each; $2 \times$ CHN), 2.95 and 3.55 (2d, $J = 13.6$ Hz, 1H each; CH_2S), 3.48 (d, $J = 3.8$ Hz, 1H; CHO), 4.10 (s, 1H; OH), 5.08 (d, $J = 8.1$ Hz, 1H; NH), 5.90 (d, $J = 7.6$ Hz, 1H; NH), 7.77 and 8.02 (2d, $J = 8.1$ Hz, 2H each; Ar); ^{13}C NMR $\delta = 14.1$, 19.9, 20.4, 24.4, 27.3, 30.5, 33.2, 34.65, 39.0, 44.4, 48.75, 50.5, 53.9, 57.2, 57.6, 60.4, 126.25 (2C), 126.3 (2C), 127.4, 144.6; IR (KBr): $\nu = 3551$, 3288 (NH, OH), 1062 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 323 (14), 145 (13), 113 (64), 108 (10), 96 (100), 93 (10), 69 (10). HRMS: calcd for $C_{23}H_{33}F_3N_2O_5S_2$–H_2O: 520.1677; found: 520.1669.

4.2. General procedure for the enantioselective addition of dimethylzinc to 2-haloacetophenone

To a solution of corresponding chiral ligand **3** (0.25 mmol, 0.05 equiv) in toluene (10 mL) was added a solution of dimethylzinc in toluene (2.0 M, 6 mL, 12 mmol, 2.4 equiv) under argon atmosphere. After 5 min stirring at 25 °C, a solution of $Ti(OPr^i)_4$ (1.6 mL, 5.5 mmol, 1.1 equiv) was added, followed by the corresponding 2-haloacetophenone **4** (5 mmol, 1 equiv). The reaction mixture was stirred for several hours (see Table 1) at the same temperature and finally quenched by successively addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL). The mixture was filtered through Celite and the resulting solution was extracted with ethyl acetate (3×40 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate) to give chiral tertiary alcohols **6**. Yields and enantiomeric excesses are included in Table 1. Physical and spectroscopic data, as well as literature references, follow.

4.2.1. (*S*)-1-Chloro-2-phenylpropan-2-ol 3a.[27] Pale yellow oil. $R_f = 0.57$ (hexane/ethyl acetate: 7/3); t_R (GC) = 9.6; HPLC (OJ, UV 215 nm, hexane/2-propanol: 97/3, flow 1 mL/min) t_R (*R*) 26.9, t_R (*S*) 28.8; $[\alpha]_D = +14.9$ [*c* 3.7, $CHCl_3$; er (*R*/*S*): 10.0/90.0]; ^{1}H NMR $\delta = 1.62$ (s, 3H; CH_3), 2.71 (br s, 1H; OH), 3.77 (q, $J = 11.1$ Hz, 2H; CH_2), 7.25–7.45 (m, 5H; Ph); ^{13}C NMR $\delta = 27.2$, 55.3, 73.8, 124.9 (2C), 127.5, 128.35 (2C), 144.1; IR (film): $\nu = 3420$ (OH), 1066 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 170 $[M]^+$ (<1), 121 (100), 91 (10), 77 (17).

4.2.2. (*S*)-1-Bromo-2-phenylpropan-2-ol 3b.[28] Pale yellow oil. $R_f = 0.65$ (hexane/ethyl acetate: 7/3); t_R (GC) = 10.4; HPLC (OJ, UV 206 nm, hexane/2-propanol: 98/2, flow 0.8 mL/min) t_R (*R*) 36.1, t_R (*S*) 39.3; $[\alpha]_D = +15.3$ [*c* 11.5, $CHCl_3$; er (*R*/*S*): 20.5/79.5]; ^{1}H NMR $\delta = 1.66$ (s, 3H; CH_3), 2.72 (br s, 1H; OH), 3.70 (q, $J = 10.4$ Hz, 2H; CH_2), 7.25–7.45 (m, 5H; Ph); ^{13}C NMR $\delta = 27.9$, 46.1, 73.1, 124.8 (2C), 127.4, 128.3 (2C), 144.1; IR (film): $\nu = 3451$ (OH), 1067 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 214 $[M]^+$ (<1), 121 (100), 77 (10).

4.3. Synthesis of bis(4-fluorophenyl)methanol 9

To a solution of ethyl formate (2.4 mL, 30 mmol, 1.0 equiv) in THF (60 mL) a 2 M solution of 4-fluorophenylmagnesium bromide in diethyl ether (37.5 mL, 75 mmol, 2.5 equiv) was slowly added at 0 °C. After 1 h allowing the temperature to rise to 25 °C, the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (40 mL). The mixture was filtered through Celite and the resulting solution was extracted with ethyl acetate (3×50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give pure title compound (6.3 g, 96%):[21] white needles, mp 47–49 °C (ethyl acetate/hexane); $R_f = 0.61$ (hexane/ethyl acetate: 7/3); ^{1}H NMR $\delta = 2.64$ (s, 1H; OH), 5.71 (s, 1H; CH), 6.95–7.00 and 7.25–7.30 (2m, 4H each; Ar); ^{13}C NMR $\delta = 74.8$, 115.2 (2C), 115.5 (2C), 128.1 (2C), 128.2 (2C), 139.3, 139.35, 160.5, 163.8; IR (KBr): $\nu = 3244$ (OH), 1610, 1514 cm^{-1} (C=C); MS (EI): m/z (%): 221 $[M+H]^+$ (2), 220 $[M]^+$ (18), 219 $[M-H]^+$ (12), 201 (12), 125 (13), 124 (11), 123 (100), 97 (18), 96 (11), 95 (19).

4.4. Synthesis of 1-bis(4-fluorophenyl)methoxy-2-chloroethane 11

To a solution of bis(4-fluorophenyl)methanol **9** (5.5 g, 25 mmol, 1 equiv) and 2-chloroethanol **10** (2.5 mL, 37.5 mmol, 1.5 equiv) in toluene (50 mL) was slowly added dropwise 5 mL of phosphoric acid (85%) at 25 °C. The mixture was strongly stirred for 48 h at the same temperature, quenched by addition of brine and extracted with ethyl acetate (3×50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate) to give the title compound **11**:[9a] pale yellow oil. $R_f = 0.43$ (hexane/ethyl acetate: 9/1); t_R (GC) = 14.8; ^{1}H NMR $\delta = 3.67$–3.70 (m, 4H; CH_2CH_2), 5.39 (s, 1H; CHO), 7.00–7.05 and 7.25–7.30 (2m, 4H each; Ar); ^{13}C NMR $\delta = 43.0$, 69.0, 82.6, 115.3 (2C), 115.5 (2C), 128.6 (2C), 128.65 (2C), 137.2, 137.3, 161.05, 163.5; IR (film): $\nu = 3077$, 3043 (C=CH), 1606, 1513 cm^{-1} (C=C); MS (EI): m/z (%):285 $[M+3H]^+$ (1), 284 $[M+2H]^+$ (7), 283 $[M+H]^+$ (4), 282 $[M]^+$ (23), 204 (17), 203 (100), 201 (27), 187 (16), 183 (27), 123 (38), 95 (12), 63 (12).

4.5. Synthesis of 1-{2-[bis(4-fluorophenyl)-methoxy]-ethyl}piperazine 13

To a mixture of piperazine **12** (8.0 g, 93.2 mmol, 4 equiv) and potassium carbonate (9.7 g, 69.9 mmol, 3 equiv) in toluene (20 mL), 1-bis(4-fluorophenyl)methoxy-2-chloroethane **11** (6.6 g, 23.3 mmol, 1 equiv) was slowly added dropwise at reflux, keeping the temperature for 18 h, quenched with water and extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were extracted with an aqueous 3 M solution of citric acid (3×50 mL). Then, the combined acid aqueous layers were basified with a solution of ammonium hydroxide (25%) and extracted with CH_2Cl_2 (3×80 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the pure title compound **13**:[9a] pale yellow oil. $R_f = 0.57$ (ethyl acetate/methanol: 9/1); t_R (GC) = 17.8; ^{1}H NMR $\delta = 2.22$ (br s, 1H; NH), 2.45–2.50 and 2.85–2.90 [2 m, 4H each; $N(CH_2CH_2)_2$], 2.64 (t, $J = 6.0$ Hz, 2H; OCH_2CH_2N), 3.56 (t, $J = 6.0$ Hz, 2H; OCH_2CH_2N), 5.33 (s, 1H; CHO), 6.95–7.00 and 7.25–7.30 (2m, 4H each; Ar); ^{13}C NMR $\delta = 45.95$ (2C), 54.75 (2C), 58.4, 66.8, 82.5, 115.1 (2C), 115.3 (2C), 128.5 (2C), 128.6 (2C), 137.7, 137.8, 160.9, 163.3; IR (film): $\nu = 3412$ (NH), 1610, 1508 cm^{-1} (C=C); MS (EI): m/z (%): 332 $[M]^+$ (<1), 203 (18), 201 (11), 183 (12), 99 (100), 86 (15) 70 (10) 56 (16).

4.6. General procedure for the synthesis of (*S*)-(+)-1-(4-{2-[bis(4-fluorophenyl)methoxy]ethyl}piperazin-1-yl)-2-phenyl-2-propanol 2

A suspension of compound **13** (0.33 g, 1.1 mmol, 1 equiv), chiral tertiary alcohol **6** (1.2 mmol, 1.1 equiv), and K_2CO_3 (0.46 g, 3.3 mmol, 3 equiv) in absolute ethanol (9 mL) was heated at reflux for 24 h. The solvent was removed under reduced pressure to afford a crude oil. Then, H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate) to give the pure title compound **2**.[11] Yields and enantiomeric excesses are included in Scheme 2 and text: pale yellow oil. $R_f = 0.67$ (ethyl acetate/methanol: 9/1); t_R (GC) = 36.5; HPLC (OD-H, UV 225 nm, hexane/2-propanol: 99.7/0.3, flow 0.3 mL/min) t_R (*S*) 45.8, t_R (*R*) 52.7; $[\alpha]_D = +2.9$ [*c* 7.1, $CHCl_3$; er (*R*/*S*): 4.5/95.5]; ^{1}H NMR $\delta = 1.45$ (s, 3H; CH_3), 1.63 (br s, 1H; OH), 2.30–2.40 [m, 8H; $2 \times N(CH_2)_2$], 2.58 (t, $J = 6.1$ Hz, 2H; OCH_2CH_2N), 2.61 and 2.82 (2d, $J = 13.1$ Hz, 1H each; NCH_2CO), 3.49 (t, $J = 6.1$ Hz, 2H; OCH_2CH_2N), 5.29 (s, 1H; CHO), 6.95–7.00, 7.20–7.35, and 7.40–7.45 (3m, 4, 7, and 2H, respectively; Ar); ^{13}C NMR $\delta = 29.5$, 53.7 (2C), 54.5 (2C), 57.6, 66.7, 69.0, 71.5, 82.5, 115.1 (2C), 115.3 (2C), 124.6 (2C), 126.2, 128.05 (2C), 128.5 (2C), 128.55 (2C), 128.8, 137.7, 148.1, 160.9, 163.3; IR (film): $\nu = 3417$ (OH), 3062 (C=CH), 1606, 1514 (C=C), 1217 cm^{-1} (C–O); MS (EI): m/z (%): 448 $[M-H_2O]^+$ (5), 346 (22), 345 (97), 215 (26), 204 (15), 203 (100), 202 (10), 201 (15), 183 (22), 142 (15), 111 (10), 97 (10), 70 (17), 56 (10).

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References

1. See for instance: (a) Friedman, H.; Pross, S.; Klein, T. W. *FEMS Immunol. Med. Microbiol.* **2006**, *47*, 330–342; (b) Tashkin, D. P. *J. Neuroimmunol.* **2004**, *147*, 26–27.
2. See for instance: (a) Ikegami, A.; Duvauchelle, C. L. *Int. Rev. Neurobiol.* **2004**, *62*, 45–94; (b) Anderson, S. M.; Pierce, R. C. *Pharmacol. Ther.* **2005**, *106*, 389–403.

3. Hashimoto, K.; Ishiwata, K. *Curr. Pharm. Des.* **2006**, *12*, 3857–3876.
4. Mueller, C. P.; Carey, R. J.; Huston, J. P. *Drugs Today* **2003**, *39*, 497–511.
5. Rocha, B. A. *Eur. J. Pharmacol.* **2003**, *479*, 107–115.
6. Greiner, E.; Boos, T. L.; Prisinzano, T. E.; De Martino, M. G.; Zeglis, B.; Dersch, C. M.; Marcus, J.; Partilla, J. S.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2006**, *49*, 1766–1772.
7. See for instance: (a) Rounsaville, B. J. *Biol. Psychiatry* **2004**, *56*, 803–809; (b) Kreek, M. J.; Bart, G.; Lilly, C.; Laforge, K. S.; Nielsen, D. A. *Pharmacol. Rev.* **2005**, *57*, 1–26; (c) Dickerson, T. J.; Janda, K. D. *AAPS J.* **2005**, *7*, E579–E586.
8. (a) Dackis, C. A. *Drug Discovery Today: Ther. Strategies* **2005**, *2*, 79–86; (b) Herman, B. H.; Elkashef, A.; Vocci, F. *Drug Discovery Today: Ther. Strategies* **2005**, *2*, 87–92.
9. van der (a) Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. *Eur. J. Med. Chem.* **1980**, *15*, 363–370; (b) Glowa, J. R.; Wojnicki, F. H. E.; Matecka, D.; Rice, K. C.; Rothman, R. B. *Exp. Clin. Psychopharmacol.* **1995**, *3*, 232–239; (c) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321–1329.
10. Hsin, L.-W.; Prisinzano, T.; Wilkerson, C. R.; Dersch, C. M.; Horel, R.; Jacobson, A. E.; Rothman, R. B.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 553–556.
11. Prisinzano, T.; Hsin, L.-W.; Folk, J. E.; Flippen-Anderson, J. L.; George, C.; Jacobson, A. E.; Rice, K. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3285–3289.
12. For ligands bearing only one isoborneolsulfonamide moiety (first generation), see: (a) Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479–2496; (b) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239–1242; (c) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651–5666; (d) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057–5058; (e) Gadenne, B.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron Lett.* **2004**, *45*, 8157–8160; (f) Hui, X.-P.; Chen, C.-A.; Gau, H.-M. *Chirality* **2005**, *17*, 51–56; (g) Lu, G.; Li, X.; Li, Y.-M.; Kwong, F. Y.; Chang, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 1926–1933; (h) Hui, A. L.; Zhang, J.-T.; Wang, Z.-Y. *Arkivoc* **2006**, *xiii*, 41–56; (i) Gadenne, B.; Hesemann, P.; Polshettiwar, V.; Moreau, J. J. E. *Eur. J. Inorg. Chem.* **2006**, 3697–3702.
13. For ligands bearing two isoborneolsulfonamide moieties (second generation), see: (a) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971; (b) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291–2293; (c) Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745–2748; (d) Yus, M.; Ramón, D. J. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114; (e) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544–9545; (f) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957; (g) Bauer, T.; Gajewiak, J. *Tetrahedron* **2003**, *59*, 10009–10012; (h) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641–3644; (i) Mukaiyama, T.; Ikegai, K. *Chem. Lett.* **2004**, *33*, 1522–1523; (j) Li, H.; García, C.; Walsh, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425–5427; (k) de Parrodi, C. A.; Walsh, P. J. *Synlett* **2004**, 2417–2420; (l) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; (m) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *70*, 448–455; (n) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361; (o) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425; (p) Hui, A.; Zhang, J.; Fan, J.; Wang, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 2101–2107; (q) Liu, L.; Wang, R.; Kang, Y.-F.; Cai, H.-Q.; Chen, C. *Synlett* **2006**, 1245–1249.
14. For ligands bearing one isoborneolsulfonamide and another different sulfonamide moiety (third generation), see: (a) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344; (b) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2054–2058.
15. For a comparison on the enantioselective addition of organozinc reagents to aryl alkyl ketones between different ligand generations, see: (a) Yus, M.; Ramón, D. J. *Pure Appl. Chem.* **2005**, *77*, 2111–2119; (b) Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem. Eur. J.* **2006**, *12*, 4431–4445, corrigendum: *Chem. Eur. J.* **2006**, *12*, 6727.
16. Yus, M.; Ramón, D. J. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 297–378.
17. (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287; (b) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183; (c) Ramón, D. J.; Yus, M. In *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005; Chapter 8, pp 207–241; (d) García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849–1889.
18. (a) Ramón, D. J.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 489–523; (b) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208.
19. Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 1573–1579.
20. See for instance: (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1990**, *31*, 3763–3766; (b) Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 10103–10110; (c) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 7115–7118; (d) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 3437–3446; (e) Alonso, E.; Guijarro, D.; Martínez, P.; Ramón, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027–11038; (f) Yus, M.; Ramón, D. J.; Gómez, I. *Tetrahedron* **2002**, *58*, 5163–5172; (g) Yus, M.; Ramón, D. J.; Gómez, I. *J. Organomet. Chem.* **2002**, *663*, 21–31; (h) Yus, M.; Ramón, D. J.; Gómez, I. *Tetrahedron* **2003**, *59*, 3219–3225.
21. Streitwieser, A.; Vorpagel, E. A.; Chen, C. C. *J. Am. Chem. Soc.* **1985**, *107*, 6970–6975.
22. Boos, T. L.; Greiner, E.; Calhoun, W. J.; Prisinzano, T. E.; Nightingale, B.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2006**, *14*, 3967–3973.
23. (a) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 9535–9546; (b) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 7307–7314.
24. For examples of enantiomeric enrichment of chiral compounds during a column chromatography isolation by a dimerization equilibrium, see: (a) Tsai, W. L.; Hermann, K.; Hug, E.; Rohde, B.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 2238–2243; (b) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370–373; (c) Suchý, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentová, E. *J. Org. Chem.* **2001**, *66*, 3940–3947; (d) Baciocchi, R.; Zenobi, G.; Valentini, M.; Mazzotti, M.; Morbidelli, M. *J. Phys. Chem. A* **2002**, *106*, 10461–10469.
25. HOCSAC ligand **3b** has been recently incorporated to the Aldrich catalogue (no. 673315).
26. Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1989.
27. El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168–176.
28. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504.