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Methods for the Synthesis of Piperazine Derivatives Containing a Chiral Bi-2-naphthyl Moiety

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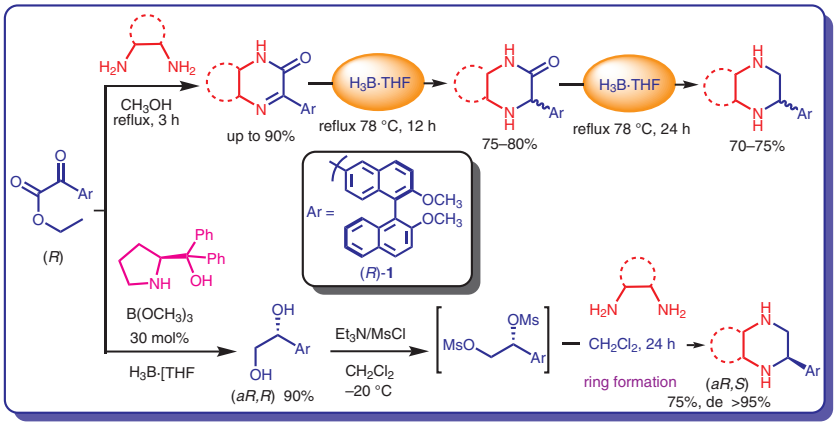

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Abstract Piperazine derivatives containing 1,1′-bi-2-naphthyl moiety were synthesized starting from 2,2′-dimethoxy-1,1′-bi-naphthalene via acylation using ethyl chlorooxoacetate and subsequent condensation with 1,2-diamines followed by reduction of the corresponding dihydro-2-piperazinone intermediate using the $NaBH_4/I_2$ reagent system. The corresponding chiral piperazine derivatives containing bi-2-napthyl moiety was synthesized by asymmetric reduction of ethyl dimethoxy-bi-2-naphthyloxoacetate by chiral oxazoborolidine catalyst prepared in situ using *S*-diphenylprolinol (*S*-DPP), $B(OCH_3)_3$ and H_3B·THF. The resulting diols were mesylated and cyclized using 1,2-diamines to obtain the corresponding chiral piperazine derivatives.

Key words piperazine, 1,2-diamines, bi-2-naphthyl, ethyl chlorooxoacetate

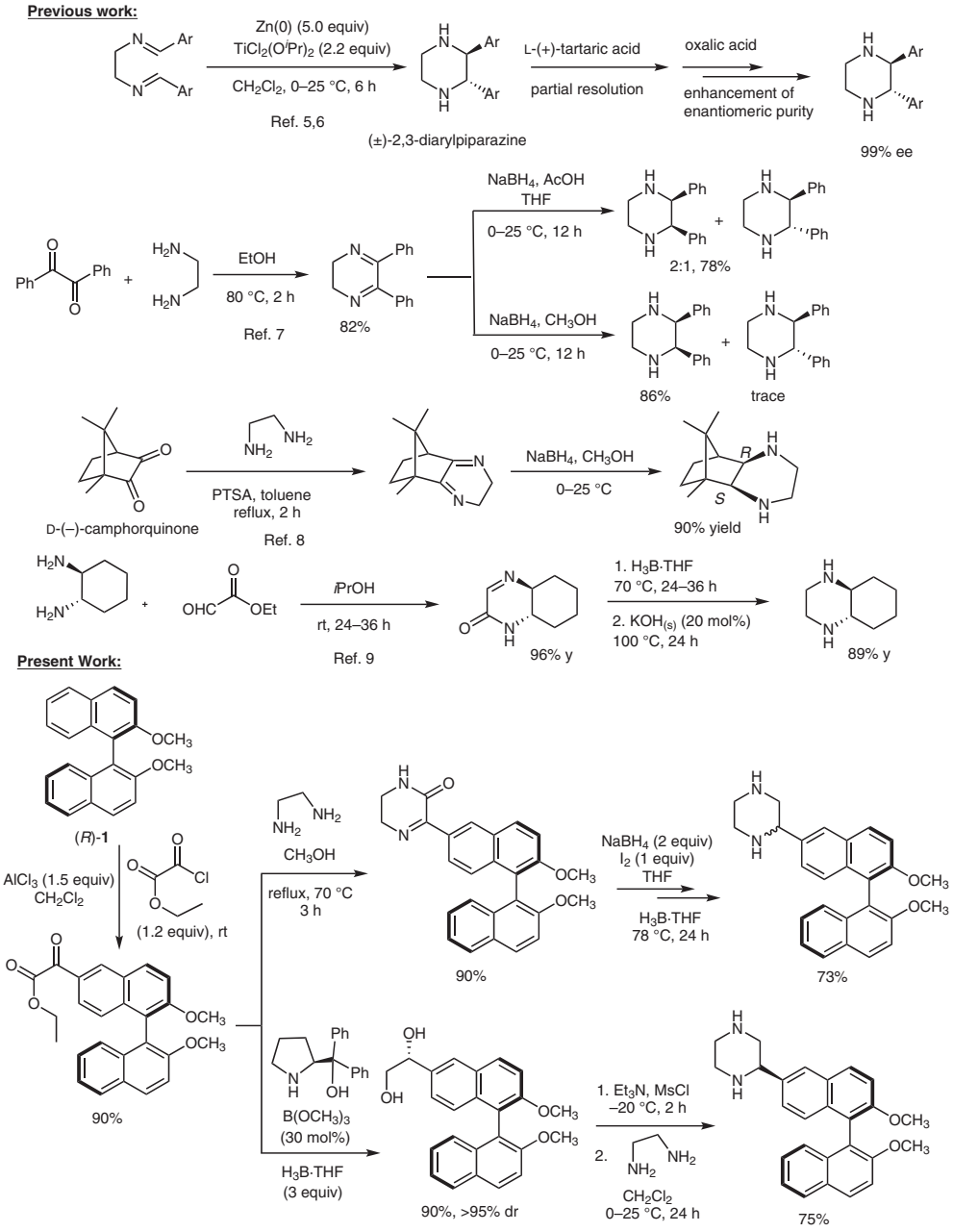
N-Heterocycles are widely present in biologically active molecules. Recently, methods for the synthesis of a variety of chiral N-heterocycles have been reviewed.[1] Among the N-heterocycles, the piperazine derivatives are widely present in life saving drug molecules.[2] Recent reports show that piperazine derivatives are the most commonly used N-heterocycles in pharmaceuticals.[3] Presumably, piperazine moieties enhance the hydrophilic surface area, have additional hydrogen bond accepting and donating nature due to piperazine nitrogen atoms, which improve water solubility, oral bioavailability, absorption in intestine, and smooth excretion properties.[4a,b] Accordingly, efficient synthetic methods with high regio-, stereo-, and enantioselectivity to access piperazine derivatives will be of interest to synthetic and medicinal chemists.

In recent years, methods were reported for the synthesis of several 2,3-diarylpiperazine derivatives (Scheme 1).[5,6] The *trans*-2,3-diphenylpiperazine derivatives were readily accessed via a diastereoselective coupling method using Ti(III) prepared in situ followed by resolution using optically active tartaric acid.[5a] Methods were also reported for the synthesis of *meso*- 2,3-diphenylpiperazine derivatives.[7] Also, the chiral camphorylpiperazine derivatives were prepared by condensation of ethylenediamine with optically active camphorquinone.[8] A similar condensation process with 1,2 diaminocyclohexane was also reported.[9]

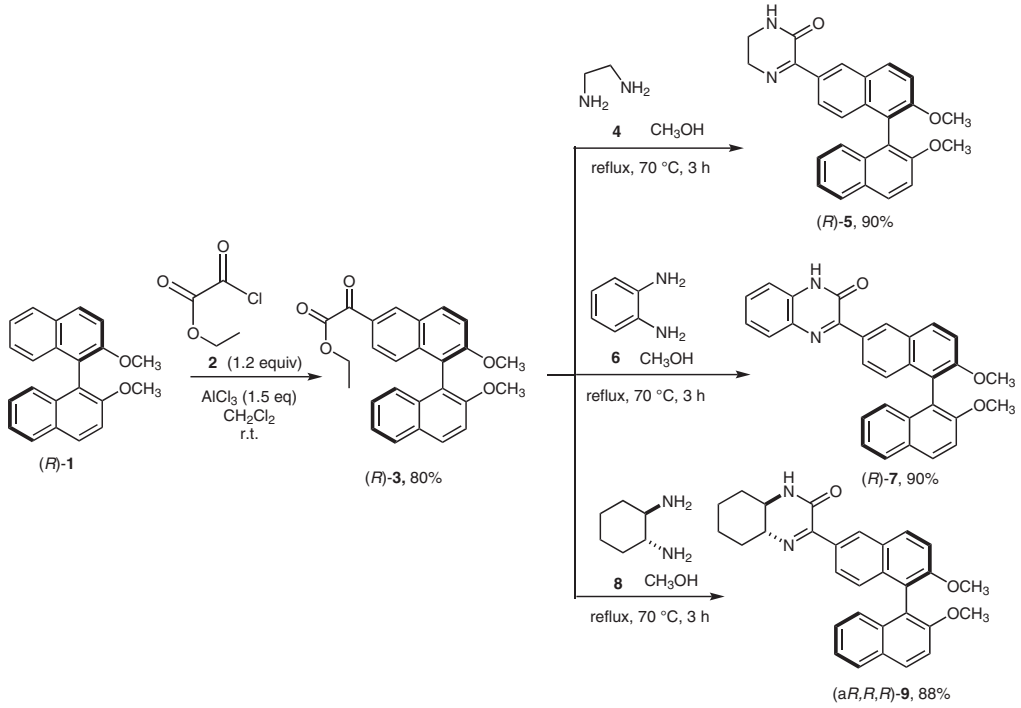
Herein, we report methods for synthesis of piperazine derivatives containing chiral bi-2-napthyl moiety. Initially, the product (*R*)-**3** was prepared in 80% yield by Friedel–Crafts acylation using bi-2-naphthyl derivative (*R*)-**1**, ethyl chlorooxoacetate (**2**; 1.2 equiv), and anhydrous $AlCl_3$ (Scheme 2). Subsequent condensation of this keto ester (*R*)-**3** with ethylenediamine (**4**) in anhydrous methanol gave the product (*R*)-**5** in 90% yield. We have observed that similar condensation reactions of (*R*)-**3** with 1,2-diaminobenzene (**6**) and (2*R*,3*R*)-1,2-diaminocyclohexane (**8**) under reflux conditions furnished cyclic products (*R*)-**7** and (*R*)-**9** in 90% and 88% yield, respectively.

The mechanism and intermediates shown in Scheme 3 may be considered to rationalize these condensation and cyclization processes. Initial reaction of the more reactive keto group with the ethylenediamine (**4**) followed by formation of ketimine and reaction of the amino group with the ester moiety would give the cyclic product (*R*)-**5**. Similar reactions in the case of the diamines **6** and **8** would give the corresponding condensation products (*R*)-**7** and (*R*)-**9**, respectively.

We then carried out the reduction of the compound (*R*)-**5** using H_3B·THF prepared in situ with the $NaBH_4$ and I_2 reagent combination.[10] We observed that the reaction at reflux conditions for 12 hours gave the product 3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]piperzin-2-one [(*R*)-**15**] in 78% yield and further reduction using the $NaBH_4/I_2$ reagent system under reflux conditions for 24 hours gave the corresponding piperazine product *R*-**16** in 73% yield (Scheme 4). Unfortunately, the highly sterically hindered (4a*R*,8a*R*)-3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]-4a,5,6,7,8,8a-hydroquinoxalin-2(1*H*)-one [(*R*)-**7**] failed to undergo reduction under the same conditions. However, the (4a*R*,8a*R*)-3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one [(*R*)-**9**] gave the corresponding reduction products (4a*R*,8a*R*)-3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]-octahydroquinoxalin-2(1*H*)-one [(*R*)-**17**] and (4a*R*,8a*R*)-3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]decahydroquinoxaline [(*R*)-**18**] in 73% and 72% yield, respectively, under the same conditions. Unfortunately, there was no selectivity at the newly formed



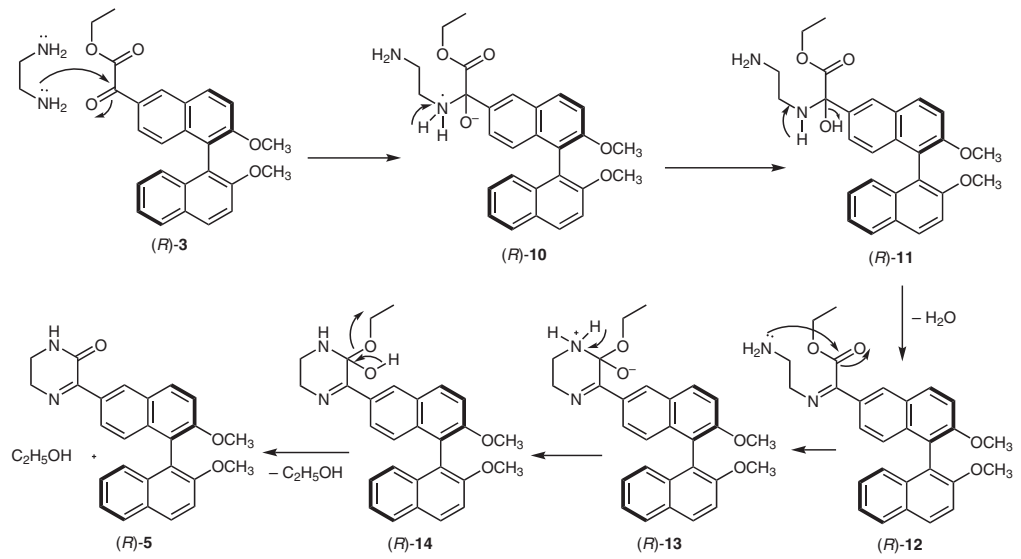
Scheme 1 Synthesis of piperazine derivatives



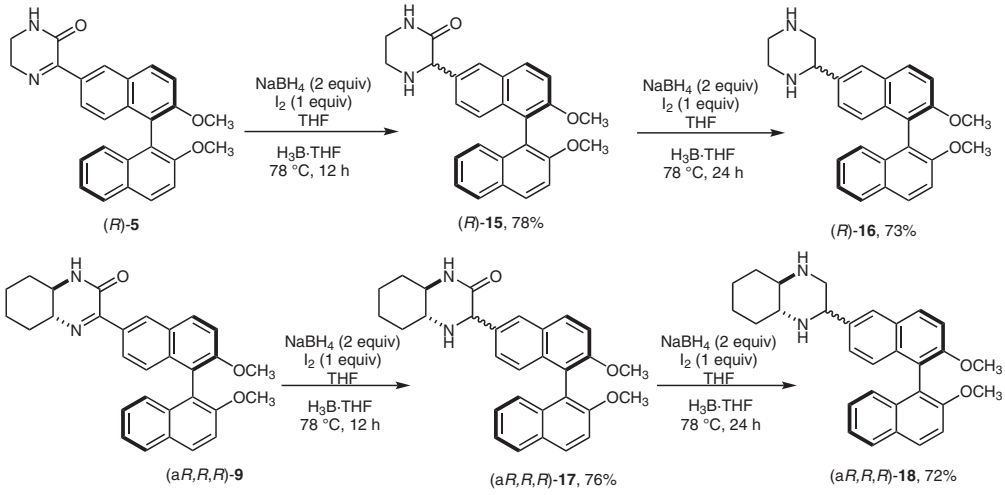
Scheme 2 Protocol for the synthesis of bi-2-naphthyl derivative (*R*)-**3** and its conversion into piperazenone derivatives (*R*)-**5**, (*R*)-**7**, (a*R*,*R*,*R*)-**9**

stereogenic centers in the corresponding piperazine products (*R*)-**15** and (*R*)-**17**. The absence of stereoselectivity in the reduction of piperazenones may be due to remoteness of the atropochiral stereogenic bi-2-naphthyl system.

Next, we turned our attention towards a new protocol involving asymmetric reduction of the carbonyl group in the bi-2-naphthyl derivative (*R*)-**3** involving the CBS-catalyzed process. There have been several reports on the asymmetric reduction of prochiral ketone to corresponding chiral alcohol with 95% ee using (*S*)-DPP and H_3B-Lewis base complexes.[11] In recent years, several borane reagent systems in combination with I_2, benzyl chloride, and (*S*)-diphenylprolinol [(*S*-DPP) **19**] were used in chiral reduction of aryl alkyl ketones to obtain the corresponding secondary alcohol with *R*-configuration with >95% ee.[12] Also, aryl alkyl ketones containing a chiral biaryl moiety were reduced to

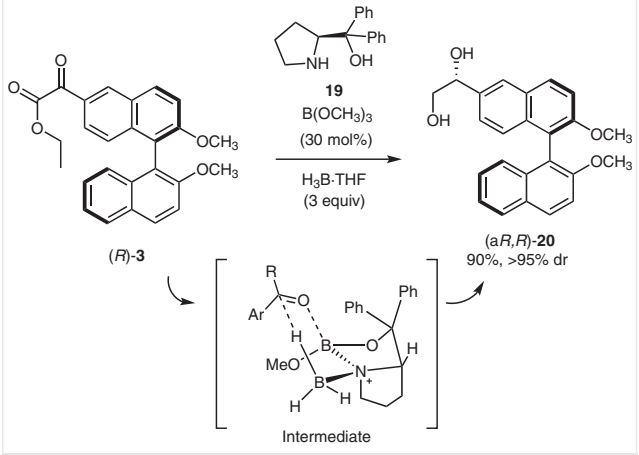


Scheme 3 Tentative mechanism for the condensation of compound (*R*)-**3** with ethylenediamine (**4**)



Scheme 4 Reduction of 3-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]piperzin-2-one derivatives using $NaBH_4/I_2$ reagent system

the corresponding secondary alcohols with >95% ee with the *S*-DPP/B(OCH$_3$)$_3$/H$_3$B·THF with *R*-configuration at the new stereogenic center.[13a,b] Previously, we have also observed that asymmetric reduction of several 6-acyl derivatives prepared using 2,2′-dimethoxy-1,1′-binaphthalene (*R*)-**1** with the *S*-DPP/B(OCH$_3$)$_3$/H$_3$B·THF reagent combination gave the corresponding alcohols with *R*-configuration with >95% ee.[13c] Accordingly, we have carried out the asymmetric reduction of the 2-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]-2-oxoacetate with *S*-DPP (30 mol%) and B(OCH$_3$)$_3$ using H$_3$B·THF (2 M, 3 equiv) at 0 °C to obtain the corresponding 1,2-diol product (*aR*,*R*)-**20** in 90% yield and with >95% dr. In this reaction, alignment of smaller R group with phenyl group in the oxazaborolidine intermediate over the larger bi-2-naphthyl group is expected to result in highly specific transfer of chirality while hydride is transferred to afford the chiral 1,2-diol **20** (Scheme 5).[11]



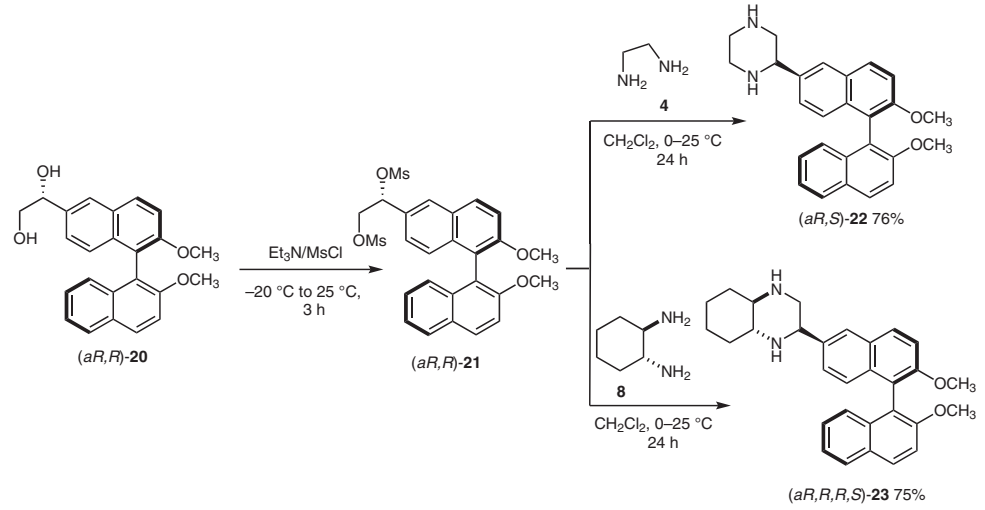
Scheme 5 Asymmetric reduction of bi-2-naphthylmethoxy-6-oxoacetate

Subsequently, we have carried out the preparation of the dimesylate **21** and its reaction with the diamines **4** and **8** (Scheme 6). Whereas, the (2*S*)-2-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]piperazine [(*aR*,*S*)-**22**] was obtained in 76% yield, the (2*R*,4a*S*,8a*R*)-2-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]decahydroquinoxalin [(*R*)-**23**] was obtained in 75% yield. In this reaction, the compounds (*R*)-**22** and (*R*)-**23** were obtained in diastereomerically pure forms and other diastereomer was not detected by ^{1}H and ^{13}C NMR spectral data.

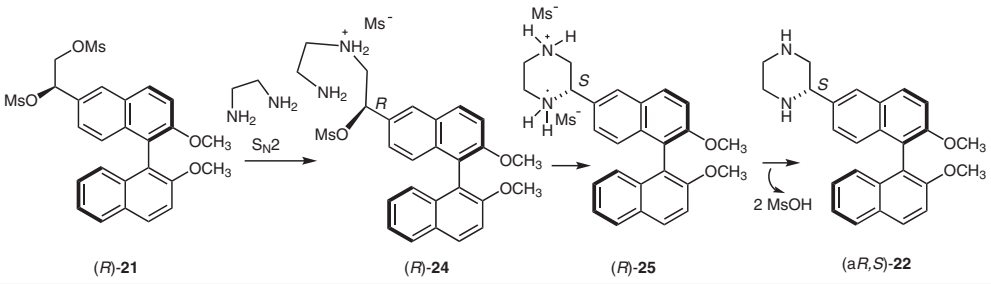
A tentative S$_N$2 type mechanism may be considered for these transformations as outlined in Scheme 7. Accordingly, the stereochemistry of the new stereogenic centers added in the products **22** and **23** are assigned the *S*-configuration.

In summary, convenient methods have been developed for the synthesis of piperazine derivatives containing the bi-2-naphthyl moiety. Since these procedures utilize readily accessible reagent systems, the methods described here open new prospects for the synthesis and study of chiral piperazine derivatives.

Melting points are uncorrected and were determined using a Super fit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer model 5300 and the neat IR spectra were recorded on SHIMADZU FT-IR spectrophotometer model 8300 with polystyrene as reference. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Avance-400 spectrometer in CDCl$_3$ as solvent and TMS as reference (δ = 0). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Elemental analyses were carried out using a PerkinElmer elemental analyzer model-240C and Thermo Finnegan analyzer series Flash EA 1112. Mass spectral analyses were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured with an AUTOPOL-II automatic polarimeter (readability ± 0.01°). Analytical TLC chromatographic tests were carried out on glass plates (3 × 10 cm) coated with 250 mμ Acme's silica gel-G and



Scheme 6 Condensation of 1,2-diamines **4** and **8** with the dimesylate **21**



Scheme 7 Tentative mechanism for the condensation of ethylenediamine **4** with the dimesylate (*aR*,*R*)-**21**

GF-254 containing 13% $CaSO_4$. The spots were visualized by short exposure to I_2 vapor or UV light. Column chromatography was carried out using Acme silica gel (100–200 mesh) or neutral alumina. All anhydrous solvents and reagents (liquids) used were distilled from appropriate drying agents.

As a routine practice, all organic extracts were washed with brine (brine), dried over anhyd Na_2SO_4, and concentrated on Heidolph-rotary evaporator. All yields reported are of isolated materials judged homogeneous by TLC, IR spectroscopy, and NMR spectrometry. CH_2Cl_2 and $CHCl_3$ were distilled over CaH_2 and dried over molecular sieves. (*S*)-DPP was supplied by Gerchem Labs, India and (*S*)-proline was supplied by Lancaster Synthesis Ltd., UK.

Ethyl 2-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]-2-oxoacetate [(*R*)-3]

To a mixture of 2,2′-dimethoxy-1,1′-binaphthalene [(*R*)-**1**; 314 mg, 1 mmol] and anhyd $AlCl_3$ (200 mg, 1.5 mmol) was added ethyl chlorooxoacetate (**2**; 164 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at rt and the reaction mixture was stirred for 3 h. Then, the mixture was poured into ice-cold H_2O, and CH_2Cl_2 (10 mL) was added. The organic layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried (anhyd Na_2SO_4). The solvent was removed and the residue was subjected to column chromatography (silica gel, hexane–EtOAc 80:20); yield: 0.332 g (80%); white solid; mp 92–94 °C; $[\alpha]_D^{25}$ +6.15 (*c* 0.052, $CHCl_3$).

IR (KBr): 3055, 2937, 2839, 1732, 1676, 1614, 1508, 1479, 1265, 1222, 1045, 910, 808, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.60–8.14 (d, *J* = 4.0 Hz, 1 H), 8.12–8.02 (d, *J* = 8.0 Hz, 1 H), 8.0–7.90 (d, *J* = 4.0 Hz, 1 H), 7.88–7.78 (d, *J* = 94.4 Hz, 1 H), 7.78–7.76 (d, *J* = 8.0 Hz, 1 H), 7.76–7.76 (d, *J* = 8.3 Hz, 1 H), 7.55–7.53 (d, *J* = 8.6 Hz, 1 H), 7.48–7.45 (d, *J* = 8.4 Hz, 1 H), 7.34–7.23 (m, 2 H), 7.06–7.06 (d, *J* = 8.0 Hz, 1 H), 4.51–4.41 (q, *J* = 4.0 Hz, 2 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 1.52–1.43 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.4, 164.5, 158.3, 155.1, 137.5, 134.3, 133.9, 132.2, 130.1, 129.3, 128.3, 127.9, 127.8, 126.8, 126.4, 124.8, 124.5, 123.8, 119.9, 118.2, 114.7, 113.9, 62.4, 56.4, 56.2, 14.2.

MS (EI): *m*/*z* = 415 $(M + 1)^+$.

Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35; O, 19.30. Found: C, 75.25; H, 5.20; O, 19.28.

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]-5,6-dihydropiperzin-2(1*H*)-ones (*R*)-5 and (*R*)-7; General Procedure

To a stirred solution of (*R*)-**3** (414 mg, 1 mmol) in CH_3OH (10 mL) was added the respective 1,2-diamine **4** or **6** (1 mmol) and the contents were refluxed at 70 °C for 3 h. The mixture was brought to 25 °C and the solid precipitate was collected by suction filtration. The precipi-

tate was washed thoroughly with sat. aq NH_4Cl (15 mL), H_2O (2 × 10 mL), and brine (10 mL). The products (*R*)-**5** and (*R*)-**7** were dried under vacuum.

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]-5,6-dihydropiperzin-2(1*H*)-one [(*R*)-5]

Yield: 0.370 g (90%); yellow solid; mp 238–240 °C.

IR (KBr): 3270, 3042, 2928, 1682, 1630, 1598, 1460, 1342, 1084, 906, 802 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.61–8.60 (t, *J* = 8.4 Hz, 1 H), 8.07–8.04 (d, *J* = 8.2 Hz, 1 H), 7.99–7.97 (d, *J* = 8.1 Hz, 2 H), 7.87–7.85 (d, *J* = 6.8 Hz, 1 H), 7.75–7.72 (d, *J* = 8.5Hz, 1 H), 7.47–7.44 (m, 2 H), 7.43–7.29 (m, 1 H), 7.22–7.20 (t, *J* = 6.9 Hz, 2 H), 7.18–7.10 (m, 2 H), 7.09–6.23 (m, 2 H), 3.97–3.97 (m, 2 H), 3.85 (br s, 3 H), 3.75 (br s, 3 H), 3.54–3.52 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 158, 156.1, 154.9, 135.1, 133.9, 132, 130, 129.4, 127.9, 126, 125, 123.5, 119.5, 114.5, 56.8, 56.6, 48.2, 39.0.

MS (EI): *m*/*z* = 412 $(M + 1)^+$.

Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82; O, 11.69. Found: C, 76.02; H, 5.28; N, 6.81; O, 11.53.

3-[2,3-Dimethoxy-(1,1′-binaphthlen)-6-yl]quinoxalin-2(1*H*)-one [(*R*)-7]

Yield: 0.412 g (90%); brown solid; mp 258–260 °C.

IR (KBr): 3272, 3057, 2935, 1680, 1628, 1598, 1467, 1340, 1084, 1068, 908, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.60–12.52 (br s, 1 H), 9.19–9.19 (d, *J* = 8.16 Hz, 1 H), 9.18–9.18 (d, *J* = 16 Hz, 1 H), 8.70–8.70 (d, *J* = 16.1 Hz, 1 H), 8.40–8.24 (t, *J* = 8.0 Hz, 1 H), 8.42–8.11 (t, *J* = 12.0 Hz, 1 H), 7.82–7.80 (t, *J* = 4.0 Hz, 1 H), 7.98 (m, 2 H), 7.69–7.65 (m, 2 H), 7.52–7.50 (t, *J* = 12.0 Hz, 1 H), 7.73–7.30 (m, 2 H), 7.08–7.00 (m, 1 H), 6.39–6.37 (t, *J* = 12.0 Hz, 1 H), 4.48–4.67 (m, 1 H), 3.99–3.82 (q, *J* = 4.6 Hz, 1 H), 3.30 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 164.6, 158.5, 156.4, 155.2, 154, 153, 137, 135.4, 134.4, 132.3, 131.1, 130.5, 129.1, 128.3, 127.2, 124.2, 123.8, 118.5, 117.7, 115.5, 114.7, 56.7.

MS (EI): *m*/*z* = 459 $(M + 1)^+$.

Anal. Calcd for $C_{30}H_{22}N_2O_3$: C, 78.59; H, 4.84; N, 6.11; O, 10.47. Found: C, 78.47; H, 4.79; N, 6.09; O, 10.20.

(4a*R*,8a*R*)-3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]-4a,5,6,7,8,8a-hexahydroquinoxalin-2(1*H*)-one [(*R*)-9]

To a stirred solution of (*R*)-**3** (414 mg, 1 mmol) in anhyd CH_3OH (10 mL) was added (*R*,*R*)-cyclohexyldiamine (**8**; 114 mg, 1 mmol) at rt and the reaction mixture was refluxed at 70 °C for 3 h. CH_3OH was removed under rotor evaporator. To the residue was added sat. aq NH_4Cl (5 mL). The contents were extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried (anhyd Na_2SO_4). After removal of the solvent, the residue was subjected to column chromatography (silica gel, hexane–EtOAc 20:80); yield: 0.400 g (88%); brown gum.

IR (Neat): 3272, 3057, 2935, 1680, 1628, 1598, 1467, 1340, 1268, 1084, 1068, 908, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.61–8.60 (d, *J* = 8.2 Hz, 1 H), 8.11–8.08 (d, *J* = Hz, 1 H), 7.91–7.82 (m, *J* = 9.1 Hz, 3 H), 7.43–7.29 (m, *J* = 9.1 Hz, 4 H), 7.25–7.20 (m, *J* = 9.0 Hz, 1 H), 7.04–7.02 (d, *J* = 8.0 Hz, 1 H), 5.03 (br s, 1 H), 3.79 (s, 3 H), 3.10–3.09 (d, *J* = 8.8 Hz, 2 H), 2.40 (d, *J* = 8.8 Hz, 1 H), 1.88–1.77 (m, 2 H), 1.74–1.70 (m, 1 H), 1.48–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 158.6, 156.9, 151.5, 135.1, 133.8, 129.7, 128.6, 126.7, 124.8, 117, 115, 113.9, 62.7, 60.4, 56.4, 53.9, 31.8, 30.8, 25.1, 23.7.

MS (EI): *m*/*z* = 465 $(M + 1)^+$.

Anal. Calcd for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.08; N, 6.03; O, 10.33. Found: C, 77.47; H, 6.05; N, 6.01; O, 10.21.

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]piperzin-2-ones (*R*)-15 and (*R*)-17; General Procedure

$NaBH_4$ (76 mg, 2 mmol) was suspended in anhyd THF (10 mL) under an inert atmosphere in a two-necked septum capped round-bottomed flask. I_2 (127 mg, 1 mmol) dissolved in anhyd THF (5 mL) was taken in an liquid additional funnel and was added dropwise slowly at 0 °C during 1 h to prepare the H_3B·THF complex. Then, the compound (*R*)-**5** or (*R*)-**9** (1 mmol) dissolved in anhyd THF was added dropwise slowly. The mixture was stirred at 0 °C for 1 h and brought to rt and refluxed for 12 h. The contents were brought to rt and carefully quenched by the dropwise addition of 3 N aq HCl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with aq $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL) and dried (anhyd Na_2SO_4). After removal of the solvent, the product was purified by column chromatography (silica gel 100–200 mesh, hexane–EtOAc 20:80).

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]piperzin-2-one [(*R*)-15]

Yield: 0.320 g (78%); yellow solid; mp 237–239 °C; $[\alpha]_D^{25}$ –72.0 (*c* 0.030, $CHCl_3$).

IR (KBr): 3233, 3049, 2932, 1686, 1620, 1589, 1332, 1261, 1080, 910, 816 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.84 (m, 1 H), 7.83–7.77 (m, 3 H), 7.43–7.37 (m, 2 H), 7.34–7.30 (m, 2 H), 7.24–7.20 (m, 1 H), 7.18–7.01 (m, 1 H), 6.99–6.91 (m, 1 H), 4.96–4.63 (m, 2 H), 3.78 (s, 3 H), 3.7 (s, 3 H), 2.72 (br s, 1 H), 1.63 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 155.8, 154.9, 133.9, 133.8, 130, 129.9, 129.2, 128.6, 128.1, 126.5, 126.3, 125.9, 125.7, 125, 123.7, 119.3, 119.1, 118.9, 114.8, 114.3, 67.7, 67.5, 57, 56.8, 56.6, 44.7, 44.3, 37.6, 29.7.

LCMS: *m*/*z* = 413 $(M + 1)^+$.

Anal. Calcd for $C_{26}H_{24}N_2O_3$:C, 76.08; H, 5.40; N, 6.82; O, 11.69. Found: C, 76.02; H, 5.39; N, 6.81; O, 11.63.

(4a*R*,8a*R*)-3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]octahydroquinoxalin-2(1*H*)-one [(*R*)-17]

Yield: 0.350 g (76%); brown gum; $[\alpha]_D^{25}$ –420.1 (*c* 0.212, $CHCl_3$).

IR (Neat): 3273, 3059, 2937, 2841, 1680, 1593, 1508, 1469, 1342, 1267, 1091, 1066, 908, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.90 (d, *J* = 8.6 Hz, 2 H), 7.87–7.75 (m, 4 H), 7.38–7.31 (m, 2 H), 7.29–7.23 (m, 1 H), 7.21–7.20 (m, 9 H), 7.19–7.12 (m, 2 H), 6.90–6.87 (m, 2 H), 4.63 (s, 1 H), 4.16–4.123 (m, 3 H), 3.95 (s, 3 H), 3.7 (s, 3 H), 2.92 (m, 2 H), 2.50 (m, 2 H), 1.67–1.6 5 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171, 156, 151.6, 135.1, 133.9, 133.7, 130.6, 129.5, 129.2, 128.3, 128, 127.4, 126.2, 25.5, 124.8, 123, 118, 116.5, 115.3, 114.1, 64.7, 58.4, 58.4, 58, 56.6, 30.8, 30.3, 29.7, 29.3, 24.5 23.7.

MS (EI): m/z = 467 $(M + 1)^+$.

Anal. Calcd for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00; O, 10.26. Found: C, 77.22; H, 6.37; N, 5.57; O, 10.20.

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]piperzines (*R*)-16 and (*R*)-18; General Procedure

$NaBH_4$ (76 mg, 2 mmol) was suspended in anhyd THF (10 mL) under N_2 atmosphere in a two-necked septum capped round-bottomed flask. I_2 (1 mmol) dissolved in anhyd THF (5 mL) was taken in liquid additional funnel and was added dropwise slowly at 0 °C during 1 h to prepare the H_3B·THF complex. Then, the compound (*R*)-**15** or (*R*)-**17** (1 mmol) dissolved in anhyd THF was added dropwise slowly. The mixture was stirred at 0 °C for 1 h and brought to rt and refluxed for 24 h. The mixture was brought to rt and carefully quenched by slowly adding with 3 N aq HCl (2 mL). The contents were extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with aq $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL) and dried (anhyd Na_2SO_4). After removal of the solvent, the product was purified by column chromatography (silica gel 100–200 mesh, hexane–EtOAc 20:80).

3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]piperzine [(*R*)-16]

Yield: 0.290 g (73%); yellow solid; mp 248–250 °C; $[\alpha]_D^{25}$ –40.0 (*c* 0.140, $CHCl_3$).

IR (KBr): 3320, 3042, 3010, 2952, 2898, 1590, 1332, 1268, 1042, 889, 802 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.87 (d, *J* = 8.3 Hz, 2 H), 7.85–7.84 (d, *J* = 8.8 Hz, 1 H), 7.45–7.43 (m, 2 H), 7.33–7.31 (m, 1 H), 7.29–7.20 (m, 2 H), 7.29–7.07 (m, 2 H), 6.90–6.88 (m, 1 H), 4.67 (s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.50–3.40 (m, 1 H), 3.33–3.30 (m, 1 H), 3.130–3.110 (m, 1 H), 3.09–3.00 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 155, 134.8, 134.1, 133.7, 129.6, 129.5, 129.2, 129.1, 128, 127.8, 127.6, 127.0, 126.9, 126.4, 125.8, 125.3, 123.6, 119.5, 114.3, 114.2, 63.8, 63.6, 56.7, 42.9, 41, 40.8.

MS (EI): m/z = 399 $(M + 1)^+$.

Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; O, 8.03; S, 7.03. Found: C, 78.22; H, 6.51; O, 8.01; S, 7.05.

(4a*S*,8a*R*)-3-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]decahydroquinoxalin [(*R*)-18]

Yield: 0.320 g (72%); brown gum; $[\alpha]_D^{25}$ –782.8 (*c* 0.211, $CHCl_3$).

IR (Neat): 3273, 3059, 2937, 2841, 1680, 1593, 1508, 1469, 1342, 1267, 1091, 1066, 908, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 1 H), 7.99–7.90 (d, *J* = 8.1 Hz, 1 H), 7.88–7.83 (m, 2 H), 7.76–7.75 (d, *J* = 6.8 Hz, 1 H), 7.47–7.45 (d, *J* =8.2 Hz, 1 H), 7.38–7.31 (m, 1 H), 7.38–7.31 (m, 1 H), 7.29–7.21 (m, 1 H), 7.19–7.10 (m, 1 H), 7.09–7.02 (m, 1 H), 3.92 (br s, 1 H), 3.78 (s, 4 H), 3.52–3.43 (m, 1 H), 3.25–3.24 (m, 1 H), 2.39–3.33 (m, 2 H), 2.16–2.15 (s, 1 H), 1.95–1.63 (m, 3 H), 1.30–1.25 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 151.7, 135.6, 133.7, 129.2, 128.3, 127.1, 125.5, 124.3, 122.0, 118.0, 117.0, 114.0, 113.1, 60.8, 60.6, 58.8, 55.8, 51.7, 48.7, 30.8, 30.49, 24.3, 24.09.

MS (EI): m/z = 453 $(M + 1)^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.09; N, 6.19; O, 7.07. Found: C, 79.41; H, 7.09; N, 6.13; O, 7.05.

Chiral (*R*)-1-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]ethane-1,2-diol [(*R*)-20]

$NaBH_4$ (76 mg, 2 mmol) was suspened in anhyd THF (10 mL) under N_2 atmosphere in a two-necked septum capped round-bottome flask. I_2 (127 mg, 1 mmol) dissolved in anhyd THF (5 mL) was taken in liquid additional funnel and was added dropwise slowly at 0 °C during 1 h to prepare the H_3B·THF complex. To this, a solution of (*S*)-DPP (**19**; 76 mg, 0.3 mmol) and $B(OCH_3)_3$ (31 mg, 0.3 mmol) in anhyd THF (5 mL) was added and the contents were stirred for 20 min. Then, the compound (*R*)-**3** (414 mg, 1 mmol) dissolved in anhyd THF (5 mL) was added slowly during 1 h at 10 °C and the contents were further stirred at rt for 1 h. The mixture was carefully quenched with 1 N aq HCl (2 mL) and extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine (5 mL) and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, 100–200 mesh, hexane–EtOAc 20:80); yield: 0.330 g (90%); white solid; mp 112–114 °C; $[\alpha]_D^{25}$ +28.4 (*c* 0.100, $CHCl_3$);.

IR (KBr): 3402, 2935, 2837, 1622, 1593, 1506, 1462, 1263, 1064, 895, 808 cm^{-1}.

^{1}H NMR (400 MHz, $CHCl_3$): δ = 7.99–7.97 (d, *J* = 8.0 Hz, 1 H), 7.89–7.87 (d, *J* = 8.1 Hz, 2 H), 7.45–7.49 (d, *J* = 7.8 Hz, 2 H), 7.20–7.18 (d, *J* = 8.0 Hz, 2 H), 6.97–6.95 (d, *J* = 4.4 Hz, 2 H), 4.80–4.77 (t, *J* = 12.0 Hz, 2 H), 3.79–3.76 (s, 8 H), 2.57 (br s, 1 H), 2.09 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 155.1, 154.9, 135.5, 133.9, 133.7, 129.5, 129.2, 128.9, 128, 126.4, 125.6, 125.2, 124.7, 123.6, 119.4, 114.5, 114.1, 74.6, 67.8, 56.8.

MS (EI): m/z = 375 $(M + 1)^+$.

Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92; O, 17.09. Found: C, 76.02; H, 5.62; O, 16.86.

(2*S*)-2-(2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl)piperazines (*R*)-22 and (*R*)-23; General Procedure

To a stirred solution of the compound (*R*)-**20** (374 mg, 1 mmol, 99% ee) and Et_3N (252 mg, 2.2 mmol) in CH_2Cl_2 (5 mL) was added MsCl (2.2 mmol) at –20 °C. The reaction mixture was stirred for 2 h at –20 °C and then quenched with sat. aq NH_4Cl (2 mL). The contents were brought to 25 °C. The organic layer was washed with H_2O (5 mL), sat. aq $NaHCO_3$ (2 mL), and brine (5 mL). The organic extract was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to approximately 3 mL. This crude dimesylate (*R*)-**21** was added to ethylenediamine **4** or **8** (0.5 mL) at 0 °C and stirred at rt for 24 h. The excess amine was removed under reduced pressure. The residue was dissolved in Et_2O (5 mL) and washed successively with sat. aq $NaHCO_3$ (2 mL), H_2O (5 mL), and brine (5 mL). The organic extract was dried (anhyd Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel 100–200 mesh, EtOAc 95:5).

(2*S*)-2-[2,2′-Dimethoxy-(1,1′-binaphthalen)-6-yl]piperazine [(*R*)-22]

Yield: 0.310 g (76%); yellow solid; mp 251–253 °C; $[\alpha]_D^{25}$ –43.4 (*c* 0.140, $CHCl_3$).

IR (KBr): 3320, 3031, 3012, 2952, 2898, 1596, 1328, 1268, 1062, 889, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.87 (d, *J* = 8.3 Hz, 2 H), 7.85–7.84 (d, *J* = 8.8 Hz, 1 H), 7.45–7.43 (m, 2 H), 7.33–7.31 (m, 1 H), 7.29–7.20 (m, 2 H), 7.29–7.07 (m, 2 H), 6.90–6.88 (m, 1 H), 4.67 (s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.50–3.40 (m, 1 H), 3.33–3.30 (m, 1 H), 3.13–3.11 (m, 1 H), 3.09–3.0 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 155, 134.8, 134.1, 133.7, 129.6, 129.5, 129.2, 129.1, 128, 127.8, 127.6, 127.0, 126.9, 126.4, 125.8, 125.3, 123.6, 119.5, 114.3, 114.2, 63.8, 63.6, 56.7, 42.9, 41, 40.8.

MS (EI): *m*/*z* = 399 $(M + 1)^+$.

Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; O, 8.03; S, 7.03. Found: C, 78.20; H, 6.47; O, 8.01; S, 7.05.

(2*S*,4a*R*,8a*R*)-2-[2,2′-dimethoxy-(1,1′-binaphthalen)-6-yl]decahydroquinoxalin [(*R*)-23]

Yield: 0.330 g (75%); brown gum; $[\alpha]_D^{25}$ –823.05 (*c* 0.210, $CHCl_3$).

IR (Neat): 3273, 3059, 2937, 2841, 1680, 1593, 1508, 1469, 1342, 1267, 1091, 1066, 908, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 1 H), 7.99–7.90 (d, *J* = 8.1 Hz, 1 H), 7.88–7.83 (m, 2 H), 7.76–7.75 (d, *J* = 6.8 Hz, 1 H), 7.47–7.45 (d, *J* = 8.2 Hz, 1 H), 7.38–7.31 (m, 1 H), 7.38–7.31 (m, 1 H), 7.29–7.21 (m, 1 H), 7.19–7.10 (m, 1 H), 7.09–7.02 (m, 1 H), 3.92 (br s, 1 H), 3.78 (s, 4 H), 3.52–3.43 (m, 1 H), 3.25–3.24 (m, 1 H), 2.39–3.33 (m, 2 H), 2.16–2.15 (s, 1 H), 1.95–1.63 (m, 3 H), 1.30–1.25 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD): δ = 155.0, 151.7, 135.6, 133.7, 129.2, 128.3, 127.1, 125.0, 124.0, 122.0, 118.0, 117.0, 114.0, 113.1, 60.89, 60.6, 58.8, 55.89, 51.7, 30.8, 30.49, 24.3, 24.0.

MS (EI): *m*/*z* = 453 $(M + 1)^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.09; N, 6.19; O, 7.07. Found: C, 79.37; H, 7.01; N, 6.11; O, 7.05.

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Supporting Information

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