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TETRAHEDRON: *ASYMMETRY*

Synthesis of new homochiral 2,3-dialkylpiperazines derived from (*R*)-(−)-phenylglycinol

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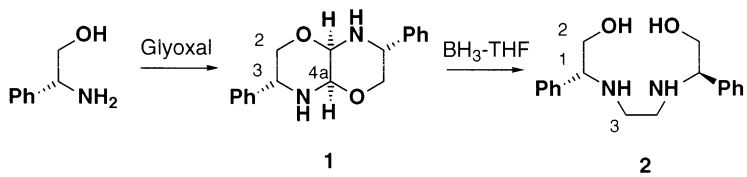
Abstract—The synthesis of four new 2,3-dialkylpiperazines in yields of 70–99% using (*R*)-(−)-phenylglycinol as a chiral inductor is described. The synthesis involved reduction of the oxazino–oxazine type derivatives obtained by condensation of glyoxal and phenylglycinol to give hydroxyethylenediamine precursors which were further condensed with glyoxal, butanedione and 1-phenyl-1,2-propanedione and then reduced to provide the corresponding piperazines. The stereochemical outcome is determined by the configuration of the bisoxazolidine precursors, which is in turn dictated by steric effects exerted by the substituents on the five membered ring. The structures of five derivatives were established by X-ray analysis.

1. Introduction

In the course of our study on the synthesis of dihydro-1,4-oxazine and bisoxazolidine type structures a new route for preparing *N*,*N*′-substituted piperazines diastereoselectively has been found.[1–3] Although studies concerning various aspects of the synthesis and chemistry of this interesting type of compounds have been reported,[4–12] to our knowledge this is the first report describing 2,3-dialkylsubstituted piperazines with *trans*-stereoselectivity.[3] In a recent study[13] the condensation of phenylglycinol with several α-diketones was shown to provide dihydro-1,4-oxazines or oxazino–oxazines depending on the solvent, molar ratios and reaction conditions, in contrast to a previous report where the six-membered fused derivatives could not be obtained.[14] The oxazino–oxazine derivatives have been shown to provide exclusively the *cis*-fused products due to the presence of a stabilising double anomeric effect.[13,16] This fact is important because these heterocycles can be reduced diastereoselectively to obtain symmetrical or unsymmetrical hydroxyethylenediamines depending on the α-diketone used. Moreover, the chiral ligands could be used as catalysts in asymmetric synthesis.[15] In continuation of our studies on the synthesis of piperazines we describe herein four new 2,3-dialkylpiperazines where the hydroxyethylenediamine precursor was obtained by reduction of oxazino–oxazine **1** prepared by condensation of phenylglycinol with glyoxal.



1 **2**

Scheme 1.

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2. Results and discussion

The reaction of (*R*)-(−)-phenylglycinol with glyoxal afforded oxazino–oxazine **1** in 70% yield which was subsequently transformed into dihydroxyethylenediamine **2** by reduction using BH_3–THF, as shown in Scheme 1. The *cis* stereochemistry at the ring fusion for compound **1** is supported by X-ray diffraction analysis (Fig. 1). The selective formation of **2** was evidenced by ^1H and ^{13}C NMR spectroscopy, and the product was used in the next step without purification.

The formation of bisoxazolidines **3a**–**d** was achieved by condensation of **2** with the corresponding α-dicarbonyl compound (Scheme 2). Bisoxazolidine **3a** was obtained diastereoselectively after 5 h under reflux in ethanol. The NMR spectra showed nine ^1H and eight ^{13}C signals consistent with the presence of a C_2 axis and the X-ray diffraction analysis allowed us to establish its structure as well as the (*R*,*R*)- absolute configuration of the ring fusion carbons. In contrast, no stereoselectivity was observed in the reaction with 2,3-butanedione, which under the same reaction conditions afforded two

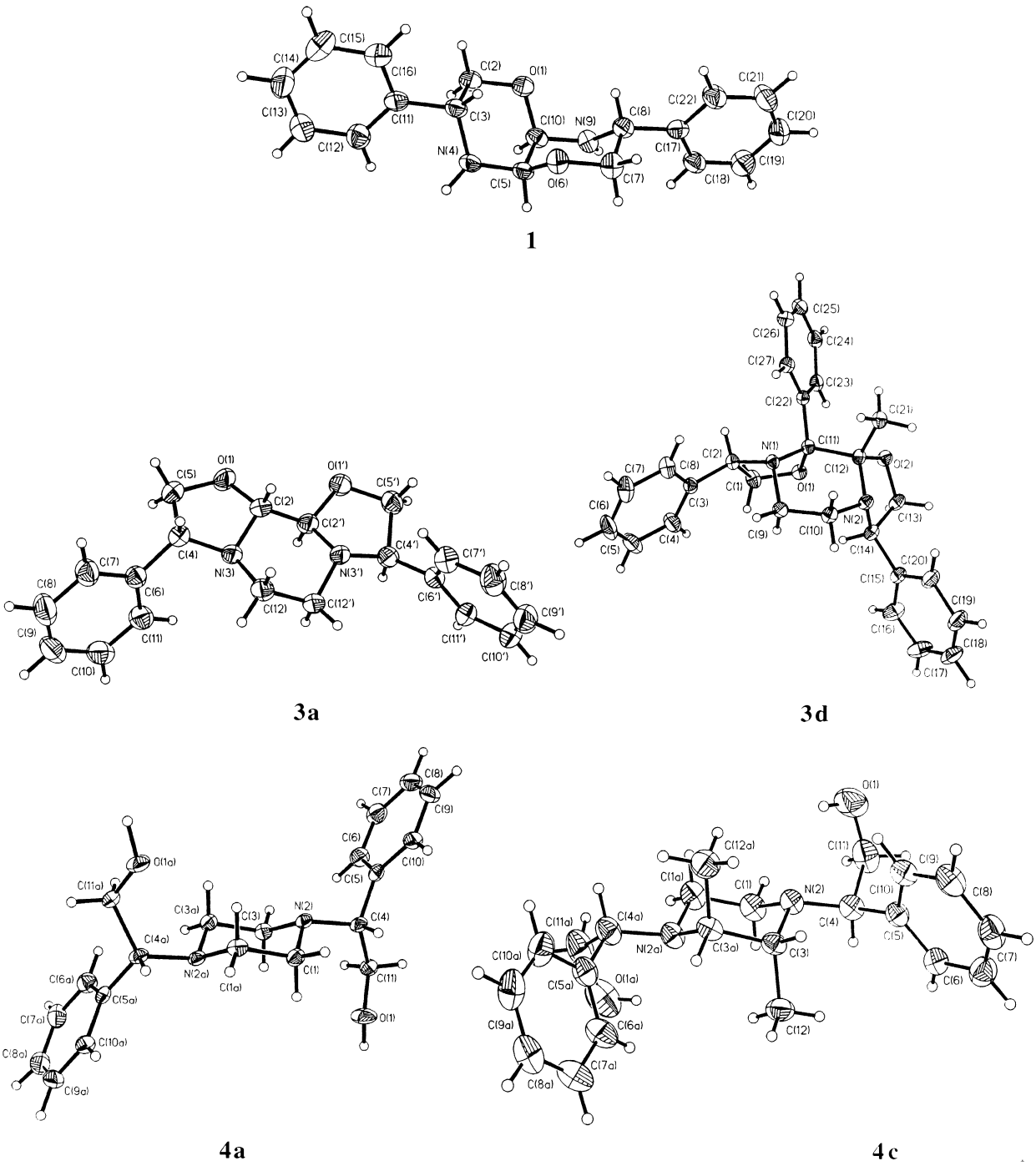
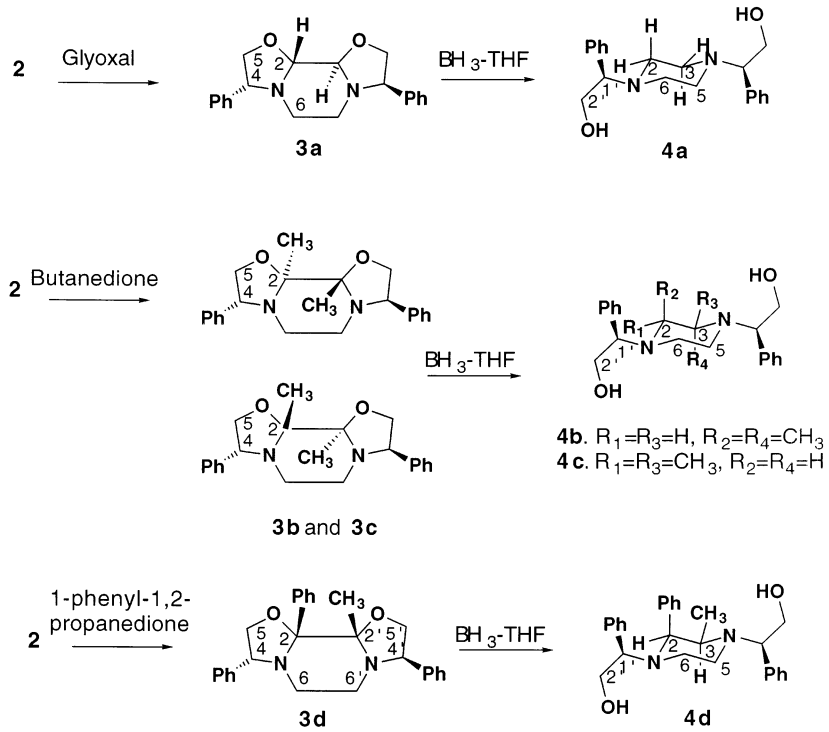


Figure 1. Molecular perspective views for **1**, **3a**, **3d**, **4a** and **4c**.



Scheme 2.

diastereomers (**3b** and **3c**) in a 1:1 ratio, as determined by NMR spectroscopy. Finally, bisoxazolidine **3d** was obtained as the only product. The ^{1}H and ^{13}C NMR spectra of **3d** showed signals for each atom because of the absence of molecular symmetry and were assigned based on COSY, NOESY, HETCOR and HMBC experiments. The NOESY experiment revealed that the signal corresponding to the methyl group correlates with the *ortho*-protons of the phenyl group attached to C-(2), this suggests that both the methyl and phenyl groups are on the same side. Additionally the structure of **3d** was established by single-crystal X-ray crystallographic analysis (Fig. 1) which shows that the fusion is *cis*—confirming the stereochemistry suggested by NMR and the absolute configuration with respect to C-(2) and C-(2′) is (*R*,*S*).

Piperazines **4a**–**d** were obtained by reduction of bisoxazolidines **3a**–**d**, respectively (Scheme 2). Piperazine **4a** was obtained as the only product. The ^{1}H NMR spectrum showed a broad multiplet between 2.83 and 2.34 ppm for the ring protons, whereas these carbons give rise to a broad singlet at 49.6 ppm in the ^{13}C NMR spectrum. Moreover, the ^{13}C NMR recorded at 223 K showed two different signals at 52.3 and 45.2 ppm for C-(2) and C-(3), which coalesced at 273 K, allowing us to calculate a $\Delta G^{\neq} = 12.14$ kcal/mol for the ring interconversion process. The structure of **4a** was further established by X-ray diffraction analysis (Fig. 1) which showed that in the solid state the substituents attached to the nitrogen atoms occupy equatorial positions presumably to minimise steric effects.

The mixture of bisoxazolidines **3b** and **3c** was reduced to provide a mixture of diastereomeric piperazines **4b** and **4c** (Scheme 2), which were separated and purified by chromatography on silica gel. The ^{1}H NMR spectrum of **4b** showed a quartet at 3.06 ppm for C-(2)H due to coupling with the methyl group, while the same proton in piperazine **4c** appears as doublet of quartets at 2.22 ppm ($J = 10.9$, 5.4 Hz) due to coupling to the methyl group and the diastereotopic C-(3)H proton. The absence of spin coupling between C-(2)H and C-(3)H in **4b** (dihedral angle $\approx 60°$) and the large spin coupling value in **4c** (dihedral angle $\approx 180°$) are evidence for *trans*-diaxial and *trans*-diequatorial arrangements of the methyl groups in **4b** and **4c**, respectively. Additionally, the ^{1}H NMR signal for **4b** is shifted upfield by 0.84 ppm compared with the equivalent signal in **4c**, and the ^{13}C NMR spectrum showed that the methyl carbon signal in the spectrum of **4b** appears at 11.5 ppm whereas those of **4c** are shifted to 16.0 ppm. Examination of the X-ray diffraction structure of **4c** allowed us to establish the absolute configuration of the carbons at the 2 and 3 positions as (*R*,*R*), respectively. Furthermore, the substituents at the nitrogen atoms were equatorial as observed for piperazine **4a**. It is worth noting that the methyl groups of piperazine **4c** are *trans*-diaxial in contrast to the results found by NMR experiments in solution and is due to the existence of hydrogen bonds between nitrogen and the hydroxyl groups. Piperazine **4d** was obtained with high diasteroselectivity.

3. Conclusions

The outcome of the reaction shows that the condensation of the hydroxyethylenediamine derived from phenylglycinol with glyoxal and butanedione is stereo-

selective, yielding the *trans*-fused bisoxazolidine. The X-ray structure of the bisoxazolidine derived from 1-phenyl-1,2-propanedione shows that the phenyl groups are responsible for steric repulsion that leads to isomeric bisoxazolidines with *cis*-fusion. Reduction of oxazine–oxazine type structures provides access to tetradentate ligands which could find applications as ligands in chiral catalysts. The benzylic groups at the nitrogen atoms can be removed by hydrogenation to obtain new piperazines.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on Jeol-270, Bruker Avance DPX-300 and Jeol Eclipse+400 spectrometers. Chemical shifts (ppm) are relative to $(CH_3)_4Si$. Coupling constants (J) are quoted in Hz. ^{1}H and ^{13}C NMR spectral assignments were supported by 2D NMR techniques (COSY, NOESY, HETCOR and HMBC). Infrared spectra were recorded on a Perkin–Elmer 16F spectrophotometer. Mass spectra were obtained with a HP 5989A mass spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, $[\alpha]_D^{25}$ values are given in deg cm^{-2} g^{-1}. Melting points were obtained on a Gallenkamp MFB-595 apparatus and are uncorrected. The X-ray crystallographic studies for **1**, **3a**, **3d** and **4a** were done on an Enraf Nonius CAD4 diffractometer, $\lambda_{(MoK\alpha)}=0.71069$ Å, graphite monochromator, $T=293$ K, $\omega/2\theta$, range $2<\theta<25°$. The structure of **4c** was determined on a Bruker AXS Smart 6000 with CCD scan type hemisphere, data reduction was done using Saint ver. 6.01. Corrections were made for Lorentz and polarisation effects. The structures were solved by direct methods (SHELXS-86), all non-hydrogen atoms were refined anisotropically by full-matrix least squares using SHELXS-93 for **1**, **3a**, **3d** and **4a** and SHELXTL-97 ver. 5.10 for **4c**. Hydrogen atoms were included in fixed positions. Elemental microanalyses were performed by Oneida Research Services, Whitesboro, NY. The HRMS was determined on a Jeol 102A spectrometer at the Instituto de Química, UNAM.

4.1. Crystal data for 1

$C_{18}H_{20}N_2O_2$, $M=296.36$ g/mol, monoclinic, space group $C2$, with $a=31.597(6)$, $b=5.7510(10)$, $c=20.281(4)$ Å, $\alpha=90$, $\beta=120.59(3)$, $\gamma=90°$, $V=3172.5(10)$ Å^3, $Z=8$, $d_{calc}=1.241$ g cm^{-3}, $\mu=0.082$ mm^{-1}. A total of 3147 reflections were collected from which 3084 were unique (R_{int} 0.038), 1655 were considered observed, $F>4\sigma(F)$, 398 parameters, final $R=0.050$, $R_w=0.133$.

4.2. Crystal data for 3a

$C_{22}H_{22}N_2O_2$, $M=322.40$ g/mol, monoclinic, space group $P2_1$, with $a=10.199(2)$, $b=6.648(10)$, $c=12.803(3)$ Å, $\alpha=90$, $\beta=97.31(3)$, $\gamma=90°$, $V=861.0$ (3) Å^3, $Z=2$, $d_{calc}=1.244$ g cm^{-3}, $\mu=0.081$ mm^{-1}. A total of 3293 reflections were collected from which 1698 were unique (R_{int} 0.038), 1194 were considered observed, $F>4\sigma(F)$, 217 parameters, final $R=0.037$, $R_w=0.093$.

4.3. Crystal data for 3d

$C_{29}H_{35}N_2O_{3.5}$, $M=467.53$ g/mol, orthorhombic, space group $P2_12_12$, with $a=20.393(4)$, $b=20.667(4)$, $c=5.9480(10)$ Å, $\alpha=\beta=\gamma=90°$, $V=2506.9$ (8) Å^3, $Z=4$, $d_{calc}=1.220$ g cm^{-3}, $\mu=0.080$ mm^{-1}. A total of 4963 reflections were collected from which 4392 were unique (R_{int} 0.037), 2889 were considered observed, $F>4\sigma(F)$, 292 parameters, final $R=0.048$, $R_w=0.136$.

4.4. Crystal data for 4a

$C_{20}H_{26}N_2O_2$, $M=326.43$ g/mol, orthorhombic, space group $C222_1$, with $a=5.744(1)$, $b=10.468(2)$, $c=28.218(6)$ Å, $\alpha=\beta=\gamma=90°$, $V=1696.7$ (6) Å^3, $Z=4$, $d_{calc}=1.278$ g cm^{-3}, $\mu=0.083$ mm^{-1}. A total of 1658 reflections were collected from which 1479 were unique (R_{int} 0.028), 1126 were considered observed, $F>4\sigma(F)$, 109 parameters, final $R=0.048$, $R_w=0.131$

4.5. Crystal data for 4c

$C_{22}H_{30}N_2O_2$, $M=354.48$ g/mol, orthorhombic, space group $P2_12_12_1$, with $a=7.8993(4)$, $b=9.1470(5)$, $c=28.2164(13)$ Å, $\alpha=\beta=\gamma=90°$, $V=2038.77$ (18) Å^3, $Z=4$, $d_{calc}=1.155$ g cm^{-3}, $\mu=0.074$ mm^{-1}. A total of 10995 reflections were collected from which 2932 were unique (R_{int} 0.040), 1908 were considered observed, $F>4\sigma(F)$, 236 parameters, final $R=0.037$, $R_w=0.072$.

4.6. (3*R*,7*R*,4a*R*,8a*R*)-3,7-*cis*-Perhydro-[1,4]oxazino-[3,2-*b*]-1,4-oxazine 1

To a solution of (*R*)-(−)-phenylglycinol (2.0 g, 14.36 mmol) in ethanol (30 mL), was added glyoxal (40% in water, 1.04 g). The reaction mixture was stirred under reflux for 3 h and concentrated to give a white solid (1.48 g, 70%) which was recrystallized from chloroform–ethanol to afford a white crystalline product, mp 191–192°C $[\alpha]_D^{25}=-164.6$ ($c=0.1$, CH_2Cl_2); ^{1}H NMR (399.78 MHz, $CDCl_3$): δ 7.44 (2H, d, $J=7.0$ Hz, H-*o*), 7.36 (2H, t, $J=7.0$ Hz, H-*m*), 7.30 (1H, t, $J=7.0$ Hz, H-*p*), 4.55 (1H, s, H-4a), 4.51 (1H, dd, $J=3.3$, 11.0 Hz, H-3), 3.92 (1H, dd, $J=3.3$, 11.0 Hz, H-2eq), 3.60 (1H, t, $J=11.0$ Hz, H-2ax), 2.58 (1H, s, NH); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ 139.9 (C-*i*), 128.6 (C-*o*), 127.9 (C-*p*), 127.4 (C-*m*), 81.5 (C-4a), 72.4 (C-2), 52.5 (C-3); MS, m/z (%): [M$^+$+1, 297 (2)], 265 (2), 162 (14), 161 (100), 148 (9), 136 (9), 120 (19), 104 (48), 91 (3), 70 (7); IR ν_{max} (KBr): 2914, 2898, 2846, 1490, 1452, 1340, 1162, 1102, 1082, 1074, 1064, 1044, 928, 784, 760, 738, 700, 530 cm^{-1}. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.75; N, 9.45. Found: C, 72.73; H, 6.94; N, 9.37.

4.7. (1*R*)-*N*,*N*′-Bis-[(2-hydroxy-1-phenyl)ethyl-ethylenediamine 2

To a solution of **1** (1.0 g, 3.3 mmol) in dry THF (30 mL) was added BH_3–THF (2 M, 6.7 mL, 13.4 mmol), and the mixture stirred under reflux for 5 h. Water (20 mL) was added and the solvent was removed with a Dean–Stark trap. The organic layer was extracted with chloroform (3×15 mL), the organic extract was then evaporated to afford an oil (0.98 g, 97%) which was used in the next step without purification; ^{1}H NMR (399.78 MHz, $CDCl_3$): δ 7.35–7.23 (5H, m, H-*o*,*m*,*p*), 3.80–3.64 (3H, m, CH_2-2 and CH-1), 2.66–2.56 (2H, m, CH_2-3); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ 140.4 (C-*i*), 128.7 (C-*o*), 127.6 (C-*p*), 127.4 (C-*m*), 66.8 (C-2), 64.8 (C-1), 46.7 (C-3).

4.8. (2*R*,2′*R*,4*R*,4′*R*)-*N*,*N*′-Ethylene(4,4′-diphenyl)-2,2′-bisoxazolidine 3a

To a solution of diamine **2** (0.98 g, 3.25 mmol) in ethanol (30 mL) was added glyoxal (40% in water, 0.47 mL), and the reaction mixture stirred under reflux for 5 h. The solvent was removed under reduced pressure and the resulting white solid was recrystallised from chloroform/ethanol to give white crystals of **3a** (0.71 g, 68%). Mp 241–243°C $[\alpha]_D^{25}=-245.79$ ($c=0.107$, CH_2Cl_2); ^{1}H NMR (399.78 MHz, $CDCl_3$): δ 7.39 (2H, d, $J=7.0$ Hz, H-*o*), 7.36 (2H, t, $J=7.0$ Hz, H-*m*), 7.30 (1H, t, $J=7.0$ Hz, H-*p*), 4.32 (1H, t, $J=7.0$ Hz, Ha-5), 3.96 (1H, s, H-2), 3.79 (1H, t, $J=7.0$ Hz, H-4), 3.74 (1H, t, $J=7.0$ Hz, Hb-5), 2.72 (1H, d, $J=7.3$ Hz, Ha-6), 2.39 (1H, d, $J=7.3$ Hz, Hb-6); ^{13}C NMR (100.54 MHz, $CDCl_3$): δ 138.6 (C-*i*), 128.7 (C-*m*), 128.0 (C-*p*), 127.8 (C-*o*), 94.3 (C-2), 75.0 (C-5), 65.5 (C-4), 45.8 (C-6); MS, *m*/*z* (%): [M$^+$+1, 323 (5)], [M$^+$, 322 (12)], 217 (21), 189 (21), 188 (69), 148 (14), 120 (12), 117 (15), 105 (16), 104 (100), 103 (32), 91 (19), 90 (11), 78 (16), 77 (19), 42 (10), 28 (9); IR ν_{max} (KBr): 2956, 2942, 2884, 2850, 2822, 1492, 1356, 1292, 1278, 1268, 1212, 1156, 1108, 1082, 1072, 1056, 1010, 968, 928, 898, 758, 702, 680, 532, 492 cm^{-1}. Anal. calcd for $C_{20}H_{22}N_2O_2$: C, 74.53; H, 6.83; N, 8.62. Found: C, 74.23; H, 6.96; N, 8.66.

4.9. (2*R*,2′*R*,4*R*,4′*R*)- and (2*S*,2*S*,4*R*,4′*R*)-*N*,*N*′-Ethylene(2,2′-dimethyl-4,4′-diphenyl)-2,2′-bisoxazolidine 3b and 3c

To a solution of diamine **2** (2.0 g, 6.6 mmol) in toluene (30 mL) was added (0.61 mL, 7 mmol) of 2,3-butanedione. The reaction mixture was heated to boiling and stirred under reflux for 12 h. The solvent was removed under reduced pressure and the residue purified by chromatography over silica gel with *n*-hexane/ethyl acetate (95:5). The main band to elute was evaporated to afford a white solid of the diastereomeric mixture of **3b** and **3c** (1.94 g, 84%) which could not be separated. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 7.28–7.48 (10H, m, H-arom.), 4.31 (1H, t, $J=7.6$ Hz, H-5), 4.30 (1H, dd, $J=8.6$, 7.4 Hz, H-5), 4.00 (1H, dd, $J=10.4$, 7.2 Hz, H-4), 3.99 (1H, t, $J=7.8$ Hz, H-4), 3.74 (1H, dd, $J=9.9$, 8.2 Hz, H-5), 3.66 (1H, t, $J=7.6$ Hz, H-5), 3.03 and 2.79 (2H, AB, $J=17.4$ Hz, CH_2-6), 2.52 (2H, m, CH_2-6), 1.50 (6H, s, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 140.5 and 139.8 (C-*i*), 129.0, 128.9, 128.3, 128.2, 128.1, 127.0, 98.5 and 96.7 (C-2), 74.5 and 73.4 (C-5), 70.0 and 62.4 (C-4), 46.8 and 42.9 (C-6), 28.0 and 10.9 (C-7).

4.10. (2*R*,2′*S*,4*R*,4′*R*)-*N*,*N*′-Ethylene(2′-methyl-2,4,4′-triphenyl)-2,2′-bisoxazolidine 3d

To a solution of diamine **2** (2.0 g, 6.6 mmol) in benzene (30 mL), was added 1-phenyl-1,2-propanedione (0.942 mL, 7 mmol) and the reaction mixture heated to boiling and stirred under reflux for 24 h. The solvent was removed under reduced pressure and the resulting product was washed with methanol at −78°C to afford a white solid of **3d** (1.90 g, 70%), mp 182–184°C; $[\alpha]_D^{25}=-145$ ($c=0.94$, CH_2Cl_2); ^{1}H NMR (399.78 MHz, $CDCl_3$): δ 7.85 (2H, d, $J=7.3$ Hz, H-*o*″) 7.43 (2H, t, $J=7.3$ Hz, H-*m*″), 7.39–7.26 (11H, m, H-arom.), 4.66 (1H, dd, $J=8.4$, 7.3 Hz, H-4′), 4.64 (1H, dd, $J=9.9$, 8.4 Hz, H-4), 4.56 (1H, t, $J=7.3$ Hz, Ha-5′), 4.26 (1H, dd, $J=9.9$, 7.7 Hz, Ha-5), 3.90 (1H, t, $J=7.7$ Hz, Hb-5), 3.75 (1H, dd, $J=8.4$, 7.3 Hz, Hb-5′), 3.09 (1H, ddd, $J=12.8$, 8.4, 4.0, Hz, Ha-6′), 3.75 (1H, ddd, $J=12.8$, 8.4, 4.0, Hz, Hb-6′), 2.70 (1H, ddd, $J=13.9$, 8.1, 4.0 Hz, Ha-6), 2.56 (1H, ddd, $J=13.9$, 8.1, 4.0 Hz, Hb-6), 1.30 (s, CH_3); ^{13}C NMR (100.53 MHz, $CDCl_3$): δ 142.3, 140.3, 135.8 (C-*i*, C-*i*′, C-*i*″), 128.9, 128.6, 128.5, 128.9, 127.8, 127.7, 127.6, 127.5, 127.4 (C-arom.), 103.6 (C-2), 95.3 (C-2′), 74.1 (C-5′), 66.7 (C-4′), 66.3 (C-4), 62.9 (C-5), 44.8 (C-6′), 38.2 (C-6), 27.2 (CH_3); MS, *m*/*z*; (%): [M$^+$+1, 413 (1)], [M$^+$, 412 (2)], 250 (13), 189 (32), 188 (10), 187 (24), 162 (46), 104 (100), 91 (10), 77 (18), 56 (15), 43 (14); IR ν_{max} (KBr): 3026, 2950, 2942, 2880, 1448, 1474, 1326, 1198, 1092, 1060, 1044, 1028, 932, 768, 758, 702, 678 cm^{-1}. HRMS calcd for $C_{27}H_{29}N_2O_2$: 413.2216. Found: 413.2216, error 3.0 ppm.

4.11. (1′*R*)-1,4-Bis-[(2′-hydroxy-1′-phenyl)ethyl]-piperazine 4a

To a solution of bisoxazolidine **3a** (0.25 g, 7.76 mmol) in dry THF (30 mL), was added a solution of BH_3–THF (2 M, 1.55 mL, 3.10 mmol). The reaction mixture was heated to boiling and stirred under reflux for 5 h. After cooling to rt, water (20 mL) was added and the solvent was removed using a Dean–Stark trap. The organic phase was extracted with chloroform (3×10 mL). The solvent was evaporated under vacuum and the product precipitated with ethyl ether to yield a white solid (0.177 g, 70%), mp 129–130°C; $[\alpha]_D^{25}=21.77$ ($c=0.107$, CH_2Cl_2); ^{1}H NMR (270.17 MHz, $CDCl_3$): δ 7.36–7.26 (3H, m, H-*m*,*p*), 7.14 (2H, dd, $J=6.9$, 1.7 Hz, H-*o*), 3.90 (1H, t, $J=11.0$ Hz, H-2′), 3.69–3.51 (2H, m, H-1′, 2′), 2.83–2.34 (4H, m, CH_2-2); ^{13}C NMR (67.94 MHz, $CDCl_3$): δ 135.8 (C-*i*), 128.9 (C-*o*), 128.4 (C-*m*), 128.1 (C-*p*), 70.0 (C-1′), 60.5 (C-2′), 49.6 (s broad, C-2); MS, *m*/*z* (%): [M$^+$+1, 327 (1)], 296 (23), 295 (100), 278 (10), 277 (22), 175 (39), 132 (26), 121 (20), 104 (12), 77 (24), 56 (29), 43 (11), 42 (15), 28 (11); IR ν_{max} (KBr): 3198, 3178, 3152, 3144, 3128, 3122, 3102, 3094, 3088, 3056, 3044, 3026, 2938, 2890, 2874, 2840, 2822, 1128,

1072, 1038, 1016, 942, 794, 756, 700, 532 cm^{-1}. Anal. calcd for $C_{20}H_{26}N_2O_2$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.26; H, 7.95; N, 8.54.

4.12. Piperazines 4b and 4c

To a solution of the diastereomeric mixture of **3b** and **3c** (1.0 g, 2.85 mmol) in dry THF (30 mL), was added a solution of BH_3–THF (1.2 M, 9.5 mL, 11.4 mmol) at −78°C. The reaction mixture was stirred for 30 min, allowed to warm to room temperature and stirred for a further 30 min then heated to boiling and stirred under reflux for 6 h. After cooling to rt, water (20 mL) was added and the solvent removed with a Dean–Stark trap. The aqueous layer was extracted with chloroform (3×10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to yield a white solid of the diastereomeric mixture of piperazines **4b** and **4c**, which was separated by chromatography on silica gel with *n*-hexane/ethyl acetate (9:1) for piperazine **4b** and (8:2) for piperazine **4c**.

4.13. (1′*R*,2*S*)-1,4-Bis-[(2′-hydroxy-1′-phenyl)ethyl]-2,3-dimethylpiperazine 4b

Mp 81–83°C; $[\alpha]_D^{25}=-28.2$ (0.156, $CHCl_3$); ^1H NMR (270.17 MHz, $CDCl_3$): δ 7.34–7.25 (5H, m, H-*o*,*m*,*p*), 3.76–3.58 (3H, m, H-1′, H-2′), 3.06 (1H, q, $J=6.4$ Hz, H-2), 2.52 and 2.33 (2H, AB, $J=13.4$ Hz, H-5), 1.21 (3H, d, $J=6.4$ Hz, CH_3); ^{13}C NMR (67.94 MHz, $CDCl_3$): δ 140.4 (C-*i*), 128.7 (C-*o*), 128.5 (C-*m*), 127.7 (C-*p*), 67.7 (C-1′), 62.9 (C-2′), 57.9 (C-2), 42.5 (C-5), 11.5 (C-7); MS, *m*/*z* (%): [M^++1, 355 (1)], 324 (25), 323 (100), 305 (18), 233 (22), 203 (15), 146 (35), 132 (17), 121 (26), 113 (99), 103 (65), 77 (40), 70 (59), 55 (53), 43 (70), 42 (36), 41 (60), 29 (42); IR ν_{max} (KBr): 3256, 2954, 2916, 2850, 2360, 2342, 1472, 1456,1364, 1056, 1036, 708, 700 cm^{-1}. HRMS calcd for $C_{22}H_{31}N_2O_2$: 355.2386. Found: 355.2391.

4.14. (1′*R*,2*R*)-1,4-Bis-[(2′-hydroxy-1′-phenyl)ethyl]-2,3-dimethylpiperazine 4c

Mp 131–133°C; $[\alpha]_D^{25}=-47.17$ ($c=0.106$, $CHCl_3$); ^1H NMR (270.17 MHz, $CDCl_3$): δ 7.37–7.25 (3H, m, H-*m*,*p*), 7.16 (2H, dd, $J=2.0$, 7.7 Hz, H-*o*), 4.11 (1H, dd, $J=9.2$, 5.2 Hz, H-1′), 3.88 (1H, t, $J=10.4$, 9.2 Hz, H-2′), 3.59 (1H, dd, $J=10.4$, 5.2 Hz, H-2′), 2.82 and 2.16 (2H, AB, $J=13.4$, H-5), 2.22 (1H, dq, $J=10.9$, 5.4 Hz, H-2), 1.19 (3H, d, $J=5.4$ Hz, CH_3); ^{13}C NMR (67.94 MHz, $CDCl_3$): δ 136.0 (C-*i*), 128.9 (C-*o*), 128.4 (C-*m*), 128.0 (C-*p*), 62.3 (C-1′), 60.3 (C-2′), 57.6 (C-2), 44.4 (C-6), 16.0 (CH_3); MS, *m*/*z* (%): [M^++1, 355 (9)], [M^+, 354 (1)], 324 (45), 323 (100), 306 (20), 305 (32), 294 (21), 233 (42), 203 (20), 178 (17), 146 (22), 121 (18), 113 (62), 103 (47), 91 (46), 77 (26), 70 (25), 56 (19); IR ν_{max} (KBr): 3446, 3026, 2982, 2962, 2928, 2872, 2850, 1492, 1384, 1366, 1294, 1186, 1174, 1144, 1080, 1066, 1058, 1032, 1024, 1004, 998, 838, 772, 708 cm^{-1}. Anal. calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.57; H, 8.42; N, 7.90.

4.15. (1′*R*,2*S*,3*R*)-1,4-Bis-[(2′-hydroxy-1′-phenyl)ethyl]-2-phenyl-3-methylpiperazine 4d

To a solution of bisoxazolidine **3d** (1.80 g, 4.37 mmol) in dry THF (30 mL), was added a solution of BH_3–THF (1.2 M, 14.56 mL, 16.2 mmol) at −78°C. The reaction mixture was stirred for 30 min at −78°C, allowed to warm to room temperature and stirred for a further 30 min then heated to reflux and stirred for 6 h. After cooling, water (20 mL) was added, and the solvent was removed using a Dean–Stark trap. The aqueous phase was extracted with chloroform (3×10 mL). The solvent was evaporated under reduced pressure and the resulting product was purified by chromatography on silica gel with *n*-hexane/ethyl acetate (95:5), the main fraction to elute was evaporated to afford an oil (1.80 g) d.e. (99%); $[\alpha]_D^{25}=-81.1$ ($c=0.172$, $CHCl_3$); ^1H NMR (270.17 MHz, $CDCl_3$): δ 7.44–7.09 (13H, m, H-arom.), 6.92 (2H, d, $J=3.5$ Hz, H-*o*), 4.09 (1H, dd, $J=9.2$, 4.5 Hz, H-2′ or H-2″), 3.98 (1H, dd, $J=10.1$, 9.7 Hz, H-2′ or H-2″), 3.93 (1H, d, $J=3.5$ Hz, H-2), 3.81–3.61 (3H, m, H-2′ or H-2″, H-1′ or H-1″), 3.05 (1H, dq, $J=3.5$, 6.7 Hz, H-3), 2.99–2.90 (2H, m, CH_2-5 and CH_2-6), 2.62–2.56 and 2.28–2.20 (2H, m, CH_2-5 and CH_2-6), 0.97 (3H, d, $J=6.7$ Hz, CH_3); ^{13}C NMR (67.94 MHz, $CDCl_3$): δ 139.3, 138.5, 135.7 (C-*i*), 130.2, 128.9, 128.7, 128.5, 128.1, 128.0, 127.9 (C-arom.), 69.2 (C-2), 65.8 and 61.9 (C-1′ and C-1″), 61.3 and 60.9 (C-2′ and C-2″), 56.8 (C-3), 45.7 and 43.8 (C-5 and C-6), 16.2 (CH_3); MS, *m*/*z* (%): [M^++2, 418 (1)], [M^++1, 417 (2)], 385 (23), 296 (22), 295 (100), 175 (64), 162 (15), 103 (24), 91 (26), 77 (12), 71 (17); IR ν_{max} (KBr): 3408, 3058, 3026, 2929, 2850, 1492, 1452, 1370, 1140, 762, 702 cm^{-1}; HRMS calcd for $C_{27}H_{33}O_2N_2$: 417.2542. Found 417.2546.

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