Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 799–811

TETRAHEDRON: *ASYMMETRY*

A new method for the preparation of unsymmetrical 1,4-substituted piperazine derivatives

Aurelio Ortiz,[a] Norberto Farfán,[a,*] Herbert Höpfl,[b] Rosa Santillan,[a] María E. Ochoa [a] and Atilano Gutiérrez [c]

[a]*Departamento de Química, Centro de Investigación y de Estudios Avanzados del IPN, Apdo. Postal 14-740, 07000 Mexico D.F., Mexico*

[b]*Universidad Autónoma del Estado de Morelos, Centro de Investigaciones Químicas, Av. Universidad 1001, Col. Chamilpa C. P. 62210, Cuernavaca, Morelos, Mexico*

[c]*Lab. de RMN, Universidad Autónoma Metropolitana, Av. Michoacan y la Purisima s/n, Col. Vicentina, 09340 Ixtapalapa, Mexico D.F., Mexico*

Received 1 February 1999; accepted 2 February 1999

Abstract

Symmetrical and unsymmetrical *N*,*N*′-piperazine derivatives of (−)-norephedrine and *o*-aminophenol were synthesized stereoselectively in yields >70% by reduction of the corresponding *N*,*N*′-ethylenebisoxazolidine heterocycles. The stereochemistry at the ring fusion carbons was established by NMR spectroscopy and X-ray crystallography.

1. Introduction

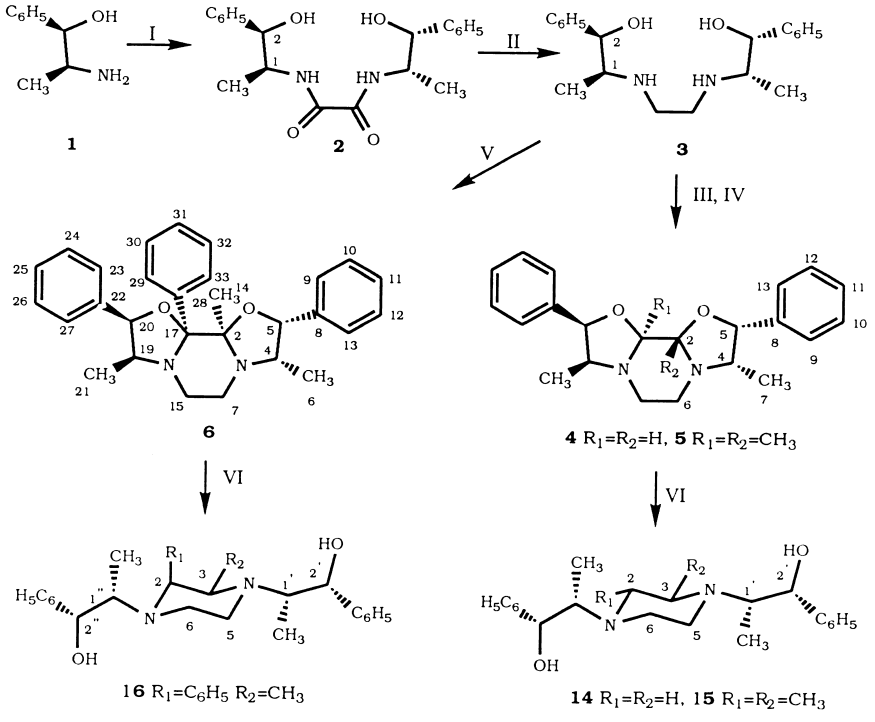
Previously we have described a variety of interesting heterocyclic products obtained by condensation of aminoalcohols with α-diketones.[1–3] Our interest in the synthesis of new bisoxazolidine heterocycles led us to the preparation of five new piperazine derivatives (**14**–**18**) obtained by reaction of β-aminoalcohols with α-dicarbonyls. The piperazine structure is particularly attractive since it is present in a large number of biologically active compounds.[4–15] Common routes described so far include cyclization of different acyclic compounds such as diethylenetriamine, ethylenediamine,[16] diethanolamine,[17] β,β′-dihaloethylamines,[18] as well as β-aminoalcohol *N*-oxides.[19] However, few provide pure optically active compounds.[20] Herein we report a new route to these heterocycles which allowed the preparation of piperazines **14**–**18** (Schemes 1–3).

* Corresponding author. E-mail: jfarfan@mail.cinvestav.mx

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00049-X

2. Results and discussion

Treatment of (1*R*,2*S*)-(−)-norephedrine **1** with diethyl oxalate in a 2:1 molar ratio yielded oxamide **2**, which was reduced with $BH_3 \cdot THF$ to give diamine **3** (Scheme 1). Subsequent condensation with glyoxal or butanedione gave the symmetrical derivatives **4** and **5**, while the reaction with 1-phenyl-1,2-propanedione led to the unsymmetrical ethylenebisoxazolidine **6**. The piperazine compounds **14**–**16** were obtained selectively in yields >70% by reaction with two equivalents of $BH_3 \cdot THF$. Evidence for the formation of these compounds was obtained from their ^{13}C NMR spectra which showed signals at δ 93.77 (**4**), 95.57 (**5**), 101.71 and 94.11 ppm (**6**) for the carbons at the fusion of the heterocycles. Unequivocal ^{1}H and ^{13}C NMR assignments for compounds **4**, **5** and **6** were achieved by 2D ^{1}H–^{13}C correlated experiments. COSY and NOESY spectra allowed the complete assignment of compound **6**.

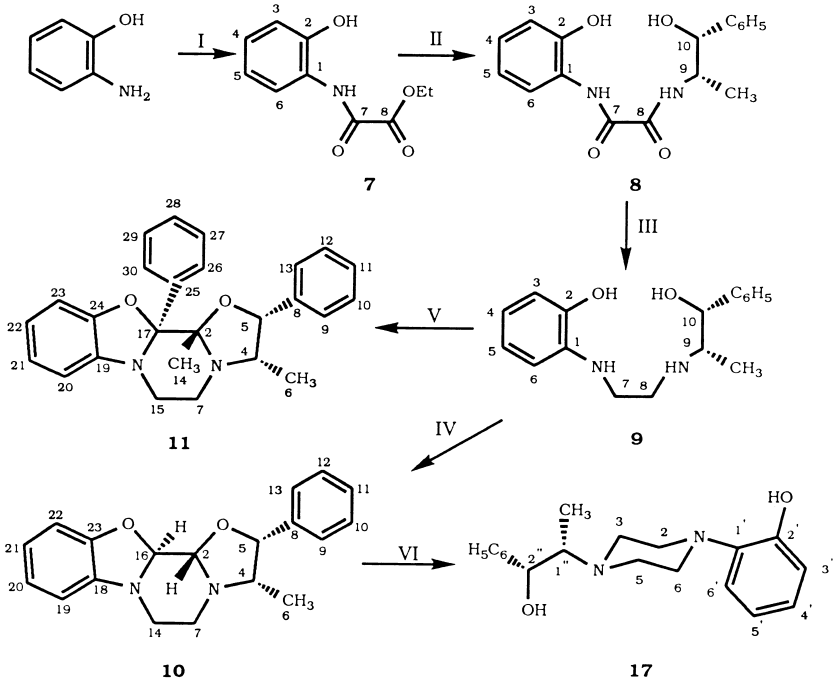


Scheme 1. Reagents: (I) diethyl oxalate, (II) $BH_3 \cdot THF$, (III) glyoxal, (IV) butanedione, (V) 1-phenyl-1,2-propanedione, (VI) $BH_3 \cdot THF$

The synthesis of the unsymmetrical *N*,*N*′-piperazine derivative **17** was achieved by the reaction of ethyl oxalyl chloride with *o*-aminophenol to yield **7**, which was further reacted with (−)-norephedrine to provide the unsymmetrical diamide **8** (Scheme 2). The latter was reduced with $BH_3 \cdot THF$ to obtain ethylenediamine **9**.

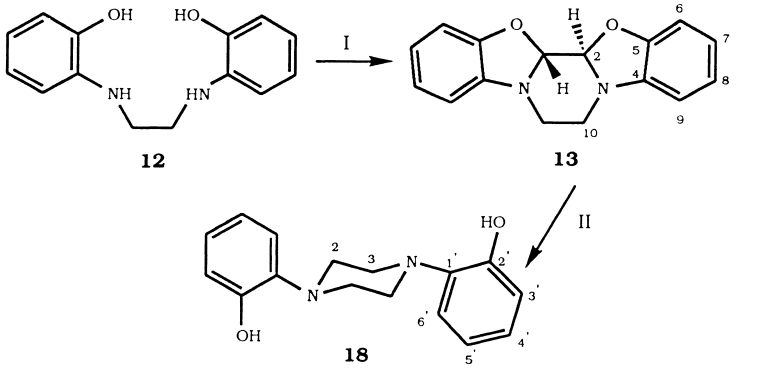
Subsequent condensation of **9** with glyoxal or 1-phenyl-1,2-propanedione allowed the preparation of unsymmetrical *N*,*N*′-ethylenebisoxazolidines **10** and **11**, respectively. The ethylenebisoxazolidine formation was evidenced by ^{13}C NMR with the signals at δ 96.10, 90.83 (**10**) and 103.06, 95.26 ppm (**11**) for the carbon atoms at the ring fusion of the heterocycles. Compound **10** was treated with two equivalents of $BH_3 \cdot THF$ to give the piperazine derivative **17**.

The piperazine derivative **18** was prepared in 70% yield by the reaction of *N*,*N*′-ethylenebisoxazolidine **13** with two equivalents of $BH_3 \cdot THF$, whereby **13** was obtained by condensation of *N*,*N*′-bis-(*o*-



Scheme 2. Reagents: (I) ethyl oxalyl chloride, (II) (−)-norephedrine, (III) $BH_3 \cdot THF$, (IV) glyoxal, (V) 1-phenyl-1,2-propanedione, (VI) $BH_3 \cdot THF$

hydroxyphenylene)ethylenediamine **12**[21] with glyoxal (δ C-2, 92.9 ppm in the ^{13}C NMR spectrum) as can be seen from Scheme 3.



Scheme 3. Reagents: (I) glyoxal, (II) $BH_3 \cdot THF$

It is worthwhile mentioning that the M^+ was not observed for compounds **3** and **14**–**17**, where instead the $M^+ - HOCHC_6H_5$ ion was the base peak.

The $^3J_{H-H}$ coupling constants for the two hydrogen atoms at the ring fusion in **4**, **10** and **13** were extracted from the ^{13}C satellites in the ^1H NMR spectra.[22] These data were used in combination with the generalized Karplus type relationship[23] to determine the dihedral angle between the two hydrogen atoms giving values close to 150° for all three compounds (^3J=6.6 Hz for **4**, 7.3 Hz for **10** and 6.6 Hz for **13**) and, therefore, a *trans*-stereochemistry at the ring fusion can be established. In order to confirm the spectroscopic results, the structure of compound **4** was determined by X-ray crystallography

showing two five-membered rings fused to a six-membered ring in a chair-like conformation with a *trans*-stereochemistry as established by the NMR experiments.

The molecular structures of compounds **4**, **5**, **6** and **11** were determined by X-ray crystallography (Figs. 1 and 2). Compounds **4**, **5** and **11** present a *trans*-fusion, in contrast to compound **6** which possesses a *cis*-stereochemistry. The corresponding torsion angles are H_2–C_2–C_{20}–H_{20}, 170.9° for compound **4**, C_8–C_2–C_{20}–C_{80}, 167.8° for compound **5**, C_{14}–C_2–C_{17}–C_{28}, 46.4° for **6** and C_{14}–C_2–C_{17}–C_{25}, 157.7° for **11**. The bond lengths at the fused five-membered rings are significantly different: the C_2–C_{20} bond length is 1.484 (8) Å for **4**, while C_2–C_{17} is 1.570 (5) Å for **6**. This notable difference between the bond lengths may be attributed to a steric repulsion between the phenyl and methyl groups located at the ring fusion of compound **6**. The corresponding bond lengths in **5** and **11** are within the average values (C_2–C_{20} 1.527 (4) Å, C_2–C_{17} 1.556 (4) Å, respectively).

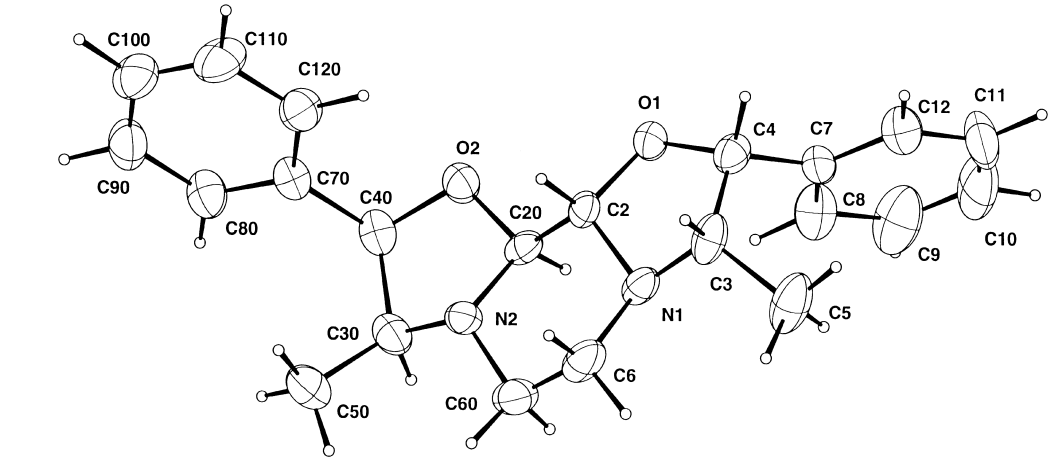
The molecular structures show that the substituents at the fusion of the rings are *anti* to the phenyl group of the norephedrine moiety which is probably the substituent responsible for the asymmetric induction in compounds **4**, **5**, **10** and **11**. On the other hand, compound **6** appears to be an exception since the phenyl group at the fusion is in an *anti*-relationship to the phenyl group of the norephedrine fragment, while the methyl group at C-2 is in a *syn*-relationship to the phenyl substituents at C-17 and C-5 (Figs. 1 and 2).

In general, the reaction of the diamines with glyoxal, butanedione and 1-phenyl-1,2-propanedione occurs by attack of the nitrogen atoms to the *Si* face of each of the carbonyl groups providing a *trans*-stereochemistry, as observed for bisoxazolidines **4**, **5**, **10**, **11** and **13**. However, steric interactions lead to the formation of a *cis*-fusion product, as seen in bisoxazolidine **6**, due to steric repulsion between the phenyl groups.

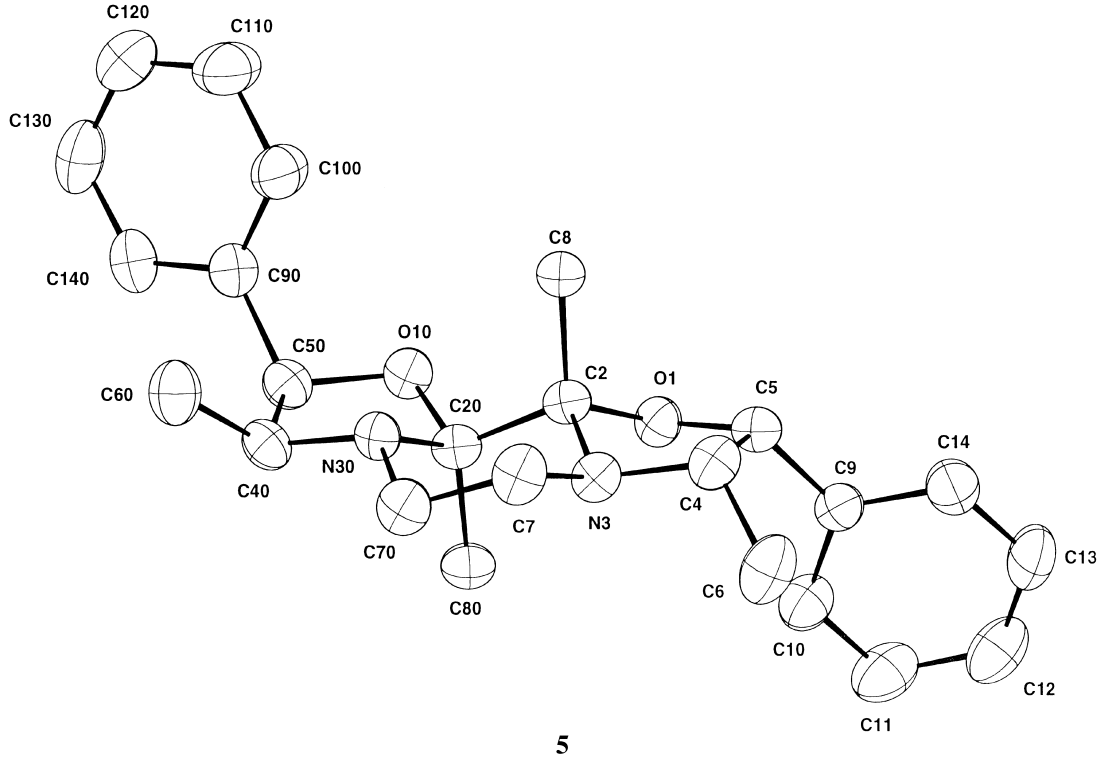
The conformational analysis of *N*-methyl-piperidines has shown that the *N*-methyl group has a preference for the equatorial over the axial orientation[24] and also, the molecular structure of *N*,*N*′-bis-(2-hydroxyethyl)piperazine **14** shows a preference for the hydroxyethyl groups in the equatorial position.[25] The ^{13}C NMR spectrum of **14** at 209 K shows two diastereotopic carbons for the piperazine ring, which coalesce at 263 K ($\Delta G^{\ddagger}$=12.30 kcal mol^{-1}), a dynamic behaviour that may be attributed to ring interconversion.[26] In the case of piperazine **17** the ^{13}C NMR spectrum at room temperature shows two signals at δ 51.02 and 53.0 ppm for carbon atoms 3 and 2. These signals showed an interesting dynamic behaviour, since the signal at δ 51.02 ppm splits into two with a difference of 174 Hz, when the temperature is lowered to 209 K ($\Delta G^{\ddagger}$=12.23 kcal mol^{-1} at 263 K). Also, the signal at δ 53.0 ppm consists of two signals with a difference of 8.8 Hz at 209 K, which gives rise to a single signal at 233 K ($\Delta G^{\ddagger}$=12.16 kcal mol^{-1}) the signals coalesce. This behaviour can be attributed to the fact that at room temperature the piperazine ring is in continuous motion due to the nature of the substituents. Piperazines **15** and **16** are obtained diastereoselectively and it is important to note that this leads to the formation of two piperazine rings with stereogenic centers.

3. Conclusions

In conclusion, the reaction of compounds **3**, **9** and **12** with 1,2-dicarbonyls proceeds with high diastereoselectivity to provide the ethylenebisoxazolidines with a *trans*-stereochemistry, except for compound **6**, due to steric interactions. As a consequence, the subsequent reduction yields only one of the possible diastereomeric piperazine derivatives. The syntheses described herein constitutes a new method for the preparation of symmetrical and unsymmetrical piperazines with chiral carbon atoms in the ring.



4

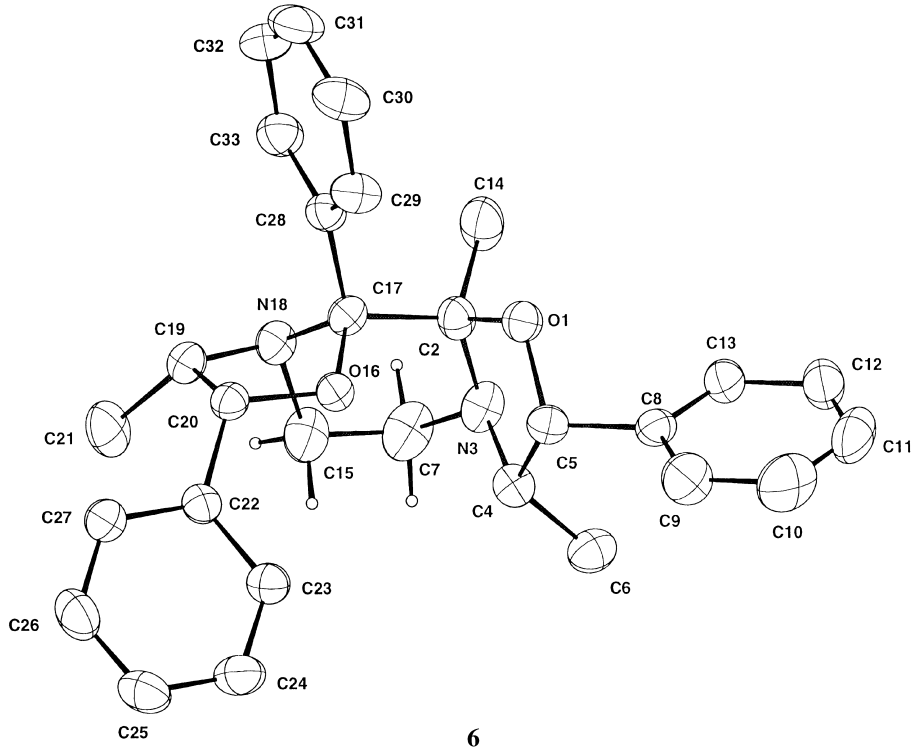


5

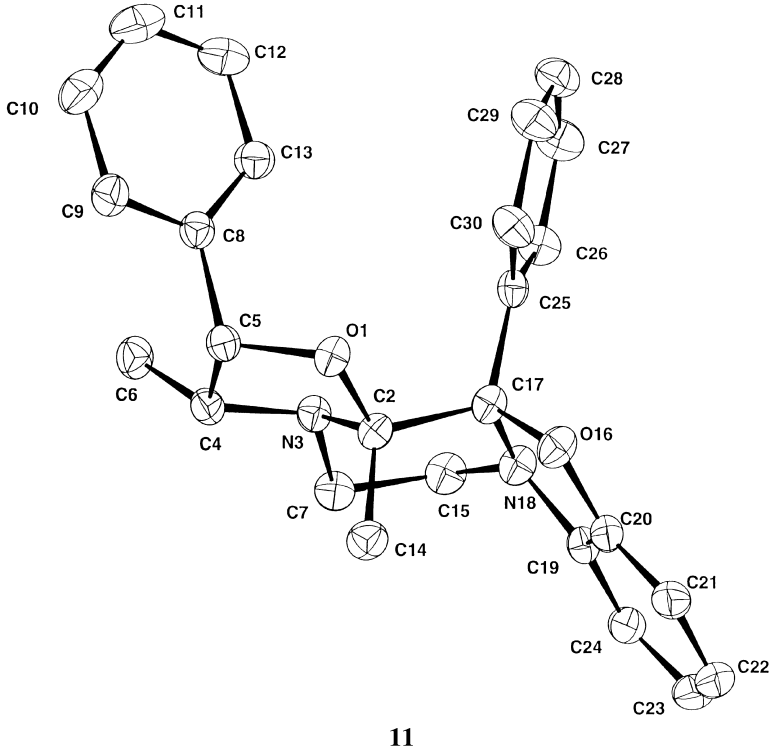
Figure 1. Perspective view of the molecular structures of **4** and **5**. Numbering does not correspond to IUPAC nomenclature

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded with JEOL FX90Q, JEOL GSX 270, and Bruker DMX-500 spectrometers. Chemical shifts (ppm) are relative to $(CH_3)_4Si$. Coupling constants are quoted in hertz. The HETCOR standard pulse sequence, which incorporates quadrature detection in both domains was used. Infrared spectra were recorded on a Perkin–Elmer 16F spectrophotometer. Mass spectra were obtained with a HP5989A equipment. Melting points were obtained on a Gallenkamp MFB-595



6



11

Figure 2. Perspective view of the molecular structures of **6** and **11**

apparatus and are uncorrected. Elemental microanalyses were determined on an EA1108 elemental analyzer Fissons instruments and some were performed by Oneida Research Services, Whitesboro, NY.

4.0.1. X-Ray analysis

A selected monocrystal was set upon an automatic diffractometer, and unit cell dimensions with estimated standard deviations were obtained from least-squares refinements of the setting angles of 24 well centered reflections. Two standard reflections were monitored periodically; they showed no change during data collection. Corrections were made for Lorentz and polarization effects. Empirical absorption corrections (DIFABS)[27] were applied. Computations were performed by using CRYSTALS[28] adapted on a Micro Vax II. Atomic form factors for neutral C, N, O and H were taken from the *International Tables for X-ray Crystallography*.[29]

The structures were solved by direct methods using the SHELXS86 program.[30] Hydrogen atoms were calculated and refined with an overall isotropic temperature factor. Anisotropic temperature factors were introduced for all non-hydrogen atoms, and least-squares refinements were carried out by minimizing $\sum w(|F_o|-|F_c|)^2$, where F_o and F_c are the observed and calculated structure factors. Unit weight was used for structures **4**–**6** and $w=1/\sigma^2$ for **11**. Models reached convergence with $R=\sum(||F_o|-|F_c||)/\sum|F_o|$ and $R_w=[\sum w(|F_o|-|F_c||)^2\sum/w\,(F_o)^2]^{1/2}$. Criteria for a satisfactorily complete analysis were the ratios of rms shift to standard deviation being less than 0.1 and no significant features in the final difference map. There are two independent molecules in the unit cell of **11** and no correlation could be found between the two molecules as expected for an enantiomerically pure compound.

4.0.2. Supplementary material available

Tables of atomic coordinates, thermal parameters, bond lengths and angles as well as observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre.

*4.1. (1*S*,2*R*)-*N,N′*-Bis-[(2-hydroxy-1-methyl-2-phenyl)ethyl]oxamide (**2**)*

Diethyl oxalate (2.4 g, 16.5 mmol) was added to a solution of (−)-norephedrine (5.0 g, 33.0 mmol) in THF (50 ml). The reaction mixture was stirred for 1 h and the oxamide **2** was removed by filtration and obtained as a white solid (4.6 g, 85%), m.p. 233–235°C. $[\alpha]_D^{25}=+25.2$ (*c* 0.11 in EtOH). ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 8.37 (1H, d, J=9.2 Hz, NH), 7.36–7.22 (5H, m, C_6H_5), 5.62 (1H, s, OH), 4.68 (1H, d, J=4.6 Hz, H-2), 3.97 (1H, m, H-1), 0.96 (3H, d, J=6.6 Hz, CH_3-1). ^{13}C NMR (DMSO-d_6, 67.80 MHz) δ: 158.80 (C=O), 142.73 (C_i), 127.78 (C_m), 126.82 (C_p), 126.10 (C_o), 73.66 (C-2), 50.84 (C-1), 14.20 (CH_3-1). MS (EI, 15 eV) m/z: [M^+−OH, 339 (2)], 250 (5), 231 (3), 187 (2), 160 (2), 118 (100), 44 (5). IR ν_{max} (KBr) 3284, 1652, 1522, 1040 cm^{-1}. Anal. calcd for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74; N, 7.86. Found: C, 66.76; H, 6.85; N, 7.67.

*4.2. (1*S*,2*R*)-*N,N′*-Bis-[(2-hydroxy-1-methyl-2-phenyl)ethyl]ethylenediamine (**3**)*

To a solution of **2** (2.0 g, 5.6 mmol) in anhydrous THF (100 ml) a 1.6 M solution of $BH_3\cdot$THF (20 ml) was added. The mixture was refluxed for 5 h and then cooled to room temperature; after addition of water, the THF was removed and the organic phase extracted with ethyl acetate (3×30 ml). The extracts were washed with NaOH solution, dried ($MgSO_4$), and concentrated under vacuum to give diamine **3** as a white solid (1.1 g, 60%), m.p. 115–116°C. $[\alpha]_D^{25}=-6.1$ (*c* 0.41 in EtOH). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46–7.15 (5H, m, C_6H_5), 4.67 (1H, d, J=3.3 Hz, H-2), 2.83–2.61 (3H, m, H-1 and CH_2-N), 0.83 (3H, d, J=6.6 Hz, CH_3-1). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 141.69 (C_i), 127.90 (C_m), 126.90 (C_p), 126.04

(C_o), 73.78 (C-2), 58.41 (C-1), 46.57 (C-N), 14.36 (CH_3-1). MS (EI, 15 eV) m/z: [M^+−$HOCHC_6H_5$, 221 (100)], 203 (4), 160 (2), 146 (3), 105 (1), 72.25 (1). IR ν_{max} (KBr) 2816, 1456, 1344, 1080, 1050 and 1025 cm^{-1}. Anal. calcd for $C_{20}H_{28}N_2O_2$: C, 73.17; H, 8.53; N, 8.53. Found: C, 72.57; H, 8.67; N, 8.49.

*4.3. (4*S,*5*R,*2*S,*4′*S,*5′*R,*2′*S*)*-*N,N′*-*Ethylene(4,4′-dimethyl-5,5′-diphenyl)-2,2′-bisoxazolidine (**4**)*

The procedure described below is representative for the synthesis of compounds **4**–**6**, **10**, **11**, **13**.

To a solution of **3** (1.0 g, 3.0 mmol) in benzene (30 ml), a 40 wt% solution of glyoxal in water (0.17 g, 3.04 mmol) was added dropwise. The reaction mixture was then brought to reflux for 3 h and cooled to room temperature. Removal of the solvent under vacuum followed by crystallization from EtOH provided *N,N′*-ethylenebisoxazolidine **4** as a white crystalline solid (0.8 g, 74%), m.p. 190–192°C. $[\alpha]_D^{25}$=−54.88 (*c* 0.088 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.34–7.20 (5H, m, C_6H_5), 5.10 (1H, d, J=8.0 Hz, H-5), 3.96 (1H, s, H-2), 3.02 (1H, dq, J=8.0, 6.0 Hz, H-4), 2.98 and 2.41 (2H, AB, J=6.6 Hz, CH_2-6), 0.66 (3H, d, J=6.0 Hz, CH_3-4). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 139.60 (C_i), 127.82 (C_m), 127.63 (C_o), 127.50 (C_p), 93.77 (C-2), 83.11 (C-5), 59.92 (C-4), 45.96 (C-6), 14.19 (CH_3-4). MS (EI, 70 eV) m/z: [M^+, 350 (12)], 322 (28), 231 (31), 203 (32), 162 (16), 118 (100), 117 (71), 91 (55), 55 (26). IR ν_{max} (KBr) 2816, 1456, 1344, 1080, 1050, 1025 cm^{-1} Anal. calcd for $C_{22}H_{26}N_2O_2$: C, 75.42; H, 7.43; N, 8.00. Found: C,75.36; H, 7.51; N, 8.00.

*4.4. (5*R,*4*S,*2*S,*5′*S,*4′*S,*2′*S*)*-*N,N′*-*Ethylene(5,5′-diphenyl-4,4′,2,2′-tetramethyl)2,2′-bisoxazolidine (**5**)*

A solution of **3** (1.0 g, 3.0 mmol) in benzene (30 ml), was treated with 2,3-butanedione (0.26 g, 3.04 mmol) to yield *N,N′*-ethylenebisoxazolidine **5** as a white crystalline solid (0.92 g, 80%) m.p. 170–171°C (crystallized from EtOH). $[\alpha]_D^{25}$=−103.59 (*c* 0.612 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.37–7.24 (5H, m, C_6H_5), 5.16 (1H, d, J=8.6 Hz, H-5), 3.28 (1H, dq, J=8.6, 6.6 Hz, H-4), 2.80 and 2.60 (2H, AB, J=6.6 Hz, CH_2-6), 1.54 (3H, s, CH_3-2), 0.60 (3H, d, J=6.6 Hz, CH_3-4). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 139.98 (C_i), 127.81 (C_m), 127.66 (C_o), 127.27 (C_p), 95.57 (C-2), 81.04 (C-5), 55.77 (C-4), 43.62 (CH_2-6), 16.12 (CH_3-4), 9.32 (CH_3-2). MS (EI, 70 eV) m/z: [M^+, 378 (9)], 319 (6), 287 (18), 245 (21), 203 (41), 176 (24), 134. (26), 118 (100), 117 (64), 116 (91), 69 (45), 43 (74). IR ν_{max} (KBr) 2964, 1456, 1368, 1316, 1180, 1132, 1082, 994,746 cm^{-1}. Anal. calcd for $C_{24}H_{30}N_2O_2$: C, 76.19; H, 7.93; N, 7.40. Found: C,75.53; H, 7.93; N, 7.34.

*4.5. (2*R,*4*S,*5*R,*17*S,*19*S,*20*R*)*-*N,N′*-*Ethylene(2,4,19-trimethyl-5,17,20-triphenyl)-2,17-bisoxazolidine (**6**)*

A solution of **3** (1.0 g, 3.04 mmol) in ethyl acetate (30 ml) was treated with 1-phenyl-1,2-propanedione (0.46 g, 3.04 mmol) and refluxed for 5 h to provide *N,N′*-ethylenebisoxazolidine **6** as a white crystalline solid, that was recrystallized from hexane/ethyl acetate, m.p. 190–193°C. $[\alpha]_D^{25}$=−88.65 (*c* 0.097 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.75 (2H, d, J=6.6 Hz, H-29,33), 7.39–7.26 (13H, m, H-9-13, H-23-27, H-30-32), 5.70 (1H, d, J=8.5 Hz, H-5), 4.60 (1H, dq J=8.5, 6.4 Hz, H-4), 4.53 (1H, d, J=9.2 Hz, H-20), 3.70 (1H, dq, J=9.2, 7.3 Hz, H-19), 3.45 (1H, ddd, J=14.7, 13.0, 3.0 Hz, H-7*ax*), 3.14 (1H, dt, J=14.8, 2.5 Hz, H-7*eq*), 3.00 (1H, ddd, J=12.5, 12.4, 3.0 Hz, H-15*ax*), 2.44 (1H, dt, J=11.5, 2.5 Hz, H-15*eq*), 1.27 (3H, s, CH_3-14), 0.87 (3H, d, J=7.3 Hz, CH_3-21), 0.73 (3H, d, J=6.4 Hz, CH_3-6). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 140.86, 140.62, 140.08 (C-8, 22, 28), 128.26, 127.87 (C-10, 12, 24, 26, 30, 32), 127.68, 127.40, 127.27 (C-11, 25, 31), 126.91, 126.22 (C-9, 13, 29, 33, 23, 27), 101.71 (C-17), 94.11 (C-2), 83.36 (C-5), 78.44 (C-20), 60.0 (C-19), 56.74 (C-4), 41.92 (C-7), 36.06 (C-15), 26.59 (CH_3-

14), 16.96 (CH_3-6), 13.43 (CH_3-21). MS (EI, 70 eV) m/z: [M^+, 440 (10)], 349 (16), 334 (12), 333 (19), 322 (20), 264 (13), 189 (20), 176 (29), 118 (100), 117 (58), 116 (78), 115 (21), 105 (74), 91 (27), 88 (36), 43 (38). IR ν_{max} (KBr) 2964, 2836, 1456, 1316, 1180, 1132, 1082, 994, 702 cm^{-1}. Anal. calcd for $C_{29}H_{32}N_2O_2$: C, 79.09; H, 7.27; N, 6.36. Found: C, 77.47; H, 8.00; N, 6.30.

*4.6. (2-Hydroxy)-ethyloxanilate (**7**)*

To a solution of *o*-aminophenol (1.0 g, 9.2 mmol) in THF, 1.5 ml of triethylamine (1.1 g, 11 mmol) and ethyl oxalyl chloride (1.5 g, 11.0 mmol) were added dropwise at 10°C. The reaction mixture was stirred for 1 h at the same temperature, the product was separated by filtration, and washed with acetone to give **6** as a white solid (1.33 g, 70%), m.p. 179–181°C. ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 10.20 (1H, s, OH), 9.60 (1H, s, NH), 7.90 (1H, d, J=8.0 Hz, H-6), 6.700–7.00 (3H, m, H-3,4,5), 4.25 (2H, q, J=7.2 Hz, CH_2), 1.26 (3H, t, J=7.2 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 67.80 MHz) δ: 160.53 (C-7), 154.35 (C-8), 147.54 (C-2), 125.61 (C-5), 124.74 (C-1), 120.84 (C-4), 119.50 (C-3), 119.19 (C-6), 62.66 (CH_2), 13.81 (CH_3). MS (EI, 15 eV) m/z: [M^+, 209 (34)], 165 (10), 137 (9), 136 (100), 135 (22), 108 (15), 80 (10), 79 (6), 29 (11). IR ν_{max} (KBr) 3362, 1654, 1596, 1464, 1350, 1292, 1106, 1026, 752, 744, 504 cm^{-1}. Anal. calcd for $C_{10}H_{11}NO_4$: C, 57.47; H, 5.26; N, 6.69. Found: C, 57.05; H, 5.40; N, 6.43.

4.7. N-*(2′-Hydroxyphenyl)*-N′-*[9*S,*10*R-*(10-hydroxy-9-methyl-1-phenyl)ethyl]oxamide (**8**)*

To a solution of **7** (1.0 g, 4.8 mmol) in anhydrous THF (30 ml), (−)-norephedrine (0.725 g, 4.8 mmol) was added. The reaction mixture was then brought to reflux for 2 h. Removal of the solvent under vacuum afforded a solid which was washed with CH_2Cl_2. Recrystallization from ethyl acetate provided **8** as a white solid (0.9 g, 61%), m.p. 163–165°C. $[\alpha]_D^{25}$=+30.6 (*c* 0.31 in EtOH). ^{1}H NMR (DMSO-d_6, 270 MHZ) δ: 10.33 (1H, s, HO-10), 9.68 (1H, s, HO-2), 8.70 (1H, d, J=8.6 Hz, NH-9), 8.1 (1H, d, J=8.0 Hz, H-3), 7.37–6.80 (8H, m, H-4-6, C_6H_5), 4.70 (1H, d, J=4.6 Hz, H-10), 4.01 (1H, dq, J=6.6, 4.6 Hz, H-9), 1.09 (3H, d, J=6.6 Hz, CH_3-9). ^{13}C NMR (DMSO-d_6, 67.80 MHz) δ: 158.87 (C-7), 157.16 (C-8), 146.86 (C-2), 142.90 (C_i), 128.06 (C_m,), 127.23 (C_p) 126.47 (C_o, C-5), 125.37 (C-1), 124.91 (C-4), 119.56 (C-3), 115.06 (C-6), 73.99 (C-10), 51.47 (C-9), 14.89 (CH_3-9). MS (EI, 15 eV) m/z: [M^+−OH, 296 (13)], 209 (12), 208 (100), 207 (18), 164 (2), 136 (25), 109 (16), 79 (2), 44 (63). IR ν_{max} (KBr) 3383, 1670, 1560, 1522, 1458, 1380, 1044, 750 cm^{-1}. Anal. calcd for $C_{17}H_{18}N_2O_4$: C, 64.93; H, 5.73; N, 8.91. Found: C, 63.48; H, 5.81; N, 8.69.

4.8. N-*(2′-Hydroxyphenyl)*-N′-*[9*S,*10*R-*(10-hydroxy-9-methyl-10-phenyl)ethyl]ethylenediamine (**9**)*

To a solution of **8** (1.0 g, 3.2 mmol) in anhydrous THF (50 ml), a 1.6 M solution of $BH_3\cdot$THF (8 ml) was added. This mixture was refluxed for 5 h and then cooled to room temperature. After addition of water, the THF was removed and the organic phase was extracted with ethyl acetate (3×30 mL). The extracts were washed with brine, dried ($MgSO_4$) and concentrated under vacuum to give the diamine **9** as a red oil (0.4 g, 50%). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.31–6.57 (9H, m, arom.), 4.80 (1H, d, J=3.3 Hz, H-10), 3.20 (2H, m, CH_2-7), 2.90 (3H, m, H-9, CH_2-8), 0.83 (3H, d, J=6.7 Hz, CH_3-9). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 145.57 (C-2), 141.20 (C_i), 137.04 (C-1), 128.08 (C_m), 127.11 (C_p), 126.01 (C_o), 120.65 (C-5), 118.85 (C-4), 115.34 (C-3), 113.55 (C-6), 73.53 (C-10), 58.30 (C-9), 45.75 (CH_2-7), 44.53 (CH_2-8), 13.50 (CH_3-9). IR ν_{max} (KBr) 3240, 2985, 1636, 1110, 765 cm^{-1}.

*4.9. (5R,4S,2R,16R)-N,N′-Ethylene(4-methyl-5-phenyl-18,23-phenylene)-2,16-bisoxazolidine (**10**)*

A solution of **9** (1.0 g, 3.5 mmol) in toluene (30 ml) was treated with 40% aq. glyoxal (0.2 g, 3.5 mmol). The solid was washed with MeOH and crystallized from a $CHCl_3$:EtOH mixture (1:1) to provide compound **10** as a white crystalline solid (0.7 g, 70%), m.p. 190–193°C. $[\alpha]_D^{25}$=−155.56 (*c* 0.0655 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.32–7.25 (5H, m, C_6H_5), 6.77 (1H, t, J=7.3 Hz, H-20), 6.71 (1H, d, J=6.6 Hz, H-22), 6.60 (1H, t, J=7.3 Hz, H-21), 6.39 (1H, d, J=6.6 Hz, H-19), 5.63 (1H, d, J=7.3 Hz, H-16), 5.04 (1H, d, J=8.0 Hz, H-5), 3.84 (1H, d, J=7.3 Hz, H-2), 3.68 (1H, dd, J=16.5, 2.7 Hz, H-14*eq*), 3.40 (1H, ddd, J=13.9, 11.9, 4.0 Hz, H-14*ax*), 2.87 (2H, m, H-7*eq*, H-4), 2.30 (1H, ddd, J=15.2, 11.9, 4.0 Hz, H-7*ax*), 0.68 (3H, d, J=6.6 Hz, CH_3-6). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 139.00 (C-23), 138.60 (C_i), 127.87 (C_m), 127.83 (C_o), 121.58 (C-20), 118.34 (C-21), 108.48 (C-22), 105.07 (C-19), 96.10 (C-16), 90.83 (C-2), 82.51 (C-5), 60.90 (C-4), 45.75 (C-7), 42.83 (C-14), 13.75 (CH_3-6). MS (EI, 70 eV) m/z: [M^+, 308 (75)], 280 (6), 189 (46), 146 (16), 116 (100), 91 (33), 55 (71), 28 (47). IR ν_{max} (KBr) 1772.0, 1740, 1492.0, 1456, 1306, 1176 cm^{-1}. Anal. calcd for $C_{19}H_{20}N_2O_2 \cdot H_2O$: C, 69.95; H, 6.74; N, 8.58. Found: C, 70.99; H, 6.85; N, 8.27.

*4.10. (2S,4S,5R,17S)-N,N′-Ethylene(2,4-dimethyl-5,17-diphenyl-19,24-phenylene)-2,17-bisoxazolidine (**11**)*

A solution of **9** (1.0 g, 3.5 mmol) in benzene (30 ml) was treated with 1-phenyl-1,2-propanedione (0.5 g, 3.5 mmol) and refluxed for 2 h. The product was crystallized from a 2:1 $CHCl_3$:hexane mixture to yield **11** as a white crystalline solid (0.9 g, 65%), m.p. 184–186°C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.78 (2H, d, J=2.0 Hz, H-26, 30), 7.34–7.23 (3H, m, H-27–H-29), 7.08 (1H, t, J=7.3 Hz, H-11), 6.97 (2H, t, J=7.3 Hz, H-10, 12), 6.72 (1H, t, J=7.3 Hz, H-21), 6.68 (1H, d, J=7.3 Hz, H-23), 6.50 (1H, t, J=7.3 Hz, H-22), 6.35 (3H, d, J=7.3 Hz, H-20, 9, 13), 5.03 (1H, d, J=8.6 Hz, H-5), 4.00 (1H, ddd, J=13.9, 6.0, 12.5 Hz, H-15*ax*), 3.74 (1H, dd, 13.2, 4.0 Hz, H-15*eq*), 3.18 (1H, dq, J=8.6, 6.0 Hz, H-4), 2.98 (1H, dd, J=6.0, H-7*eq*), 2.78 (1H, ddd, J=11.2, 11.2, 5.3 Hz, H-7*ax*), 1.42 (3H, s, CH_3-14), 0.47 (3H, d, J=6.0 Hz, CH_3-6). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 149.69 (C-24), 140.72 (C-25), 138.85 (C-19), 138.59 (C-8), 128.82 (C-10, 12), 127.78 (C-27, 29), 127.66 (C-11), 127.40 (C-28), 127.21 (C-9, 13), 126.93 (C-26, 30), 120.98 (C-21), 117.33 (C-22), 107.03 (C-23), 104.04 (C-20), 103.06 (C-17), 95.26 (C-2), 80.75 (C-5), 56.76 (C-4), 44.27 (C-15), 42.94 (C-7), 15.44 (CH_3-6), 11.59 (CH_3-14). MS (EI, 70 eV) m/z: [M^+, 398 (19)], 265 (10), 222 (15), 205 (18), 203 (100), 202 (16), 196 (17), 195 (22), 167 (13), 160 (22), 118 (24), 117 (33), 116 (95), 115 (15), 44 (31), 42 (18). IR ν_{max} (KBr) 1772, 1654, 1636, 1492, 1458, 1068 cm^{-1}.

4.11. N,N′-*Ethylene-2,2′-bisbenzoxazolidine (**13**)*

A solution of *N,N′*-bis-(*o*-hydroxyphenyl)ethylenediamine[21] **12** (3.0 g, 12.3 mmol) in 350 mL THF was treated with 40% aq. glyoxal (0.89 g, 15.36 mmol) and refluxed for 24 h at 45°C to yield **13** as a white solid (43%). The product was recrystallized from acetone, m.p. 179–182°C. ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 6.79 (1H, td, J=7.6, 1.3 Hz, H-8), 6.75 (1H, dd, J=7.3, 1.3 Hz, H-6), 6.65 (1H, dd, J=7.3, 1.3, H-9), 6.58 (1H, td, J=7.6,1.3 Hz, H-7), 5.48 (1H, s, H-2), 3.73 (1H, d, J=9.3 Hz, H-10a), 3.23 (1H, d, J=9.3 Hz, 10b). ^{13}C NMR (DMSO-d_6, 67.80 MHz) δ: 149.2 (C-5), 137.5 (C-4), 121.9 (C-8), 118.6 (C-7), 107.9 (C-6), 106.2 (C-9), 92.9 (C-2), 41.4 (C-10). MS (EI, 70 eV) m/z [M^+, 266 (38)], 147 (29), 120 (12), 119 (100), 91 (8), 65 (1). IR ν_{max} (KBr) 3056, 2926, 1650, 1400, 1250 cm^{-1}. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.01; H, 5.35; N, 10.51. Found: C, 72.01; H, 5.28; N, 10.51.

4.12. 1,4-Bis-[(1′S,2′R)-(2′-hydroxy-1′-methyl-2′-phenyl-)]ethylpiperazine (**14**)

The procedure described below is representative for the synthesis of compounds **14**–**16**.

To a solution of **4** (0.5 g, 1.4 mmol) in anhydrous THF (100 ml) a 1.6 M solution of $BH_3 \cdot THF$ (3.6 ml) was added. This mixture was refluxed for 3 h, cooled to room temperature, and water then added, the THF removed and the organic phase extracted with CH_2Cl_2 (3×30 ml). The extracts were washed with NaOH, dried ($MgSO_4$) and concentrated under vacuum to give piperazine **14** as a white solid (0.4 g, 79%), m.p. 169–171°C. $[\alpha]_D^{25}$=+5 (*c* 0.08 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.36–7.21 (5H, m, C_6H_5), 4.91 (1H, d, J=3.3 Hz, H-2′), 2.73–2.61 (5H, m, CH_2-2,6 and H-1′), 0.84 (3H, d, J=6.6 Hz, CH_3-1′). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 142.00 (C_i), 127.98 (C_m), 126.85 (C_p), 125.93 (C_o), 71.87 (C-2′), 64.32 (C-1′), 50.83 (C-2), 10.12 (CH_3-1′). MS (EI, 70 eV) m/z: [M^+−$HOCHC_6H_5$, 247 (100)], 113 (10), 112 (12), 111 (12), 107 (4), 84 (22), 43 (17), 28 (17). IR ν_{max} (KBr) 3428, 2984, 2362, 1684, 1430, 1380 cm^{-1}. Anal. calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.42; H, 8.67; N, 7.87.

4.13. 1,4-Bis-[(1′S,2′R)-(2′-hydroxy-1′-methyl-2′-phenyl-)ethyl]-2,3-dimethylpiperazine (**15**)

A solution of **5** (0.5 g, 1.3 mmol) in anhydrous THF (100 ml) was treated with a 1.6 M solution of $BH_3 \cdot THF$ (3.30 ml) to give piperazine **15** as a white solid (0.3 g, 70%), m.p. 114–116°C. $[\alpha]_D^{25}$=−16.9 (*c* 0.39 in EtOH). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.34–7.22 (5H, m, C_6H_5), 4.68 (1H, d, J=4.6 Hz, H-2′), 2.97–2.91 (2H, m, H-1′, H-2), 2.68 (1H, d, J=8.0 Hz, H-5*ax*), 2.19 (1H, d, J=8.0 Hz, H-5*eq*), 1.26 (3H, d, J=6.6 Hz, CH_3-2), 0.87 (3H, d, J=7.3 Hz, CH_3-1′). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 141.72 (C_i), 127.92 (C_m), 126.93 (C_p), 126.12 (C_o), 73.14 (C-2′), 60.52 (C-2), 58.95 (C-1′), 41.69 (C-5), 12.36 (CH_3-1′), 11.63 (CH_3-2). MS (EI, 70 eV) m/z: [M^+−$HOCHC_6H_5$, 275 (100)], 153 (17), 98 (11), 79 (16), 70 (16), 56 (13). IR ν_{max} (KBr) 3419, 2950, 2390, 1650, 1430, 1378 cm^{-1}. Anal. calcd for $C_{24}H_{34}N_2O_2 \cdot 2H_2O$: C, 71.62; H, 9.45; N, 6.96. Found: C, 70.22; H, 9.20; N, 6.76.

4.14. 1,4-Bis[(2′R,2″R,1′S,1″S)-(2′,2″-dihydroxy-1′,1″-dimethyl-2′,2″-diphenyl)diethyl]-3-methyl-2-phenylpiperazine (**16**)

A solution of **6** (0.5 g, 1.3 mmol) in anhydrous THF (100 ml) was treated with a 1.6 M solution of $BH_3 \cdot THF$ (1.62 ml), to give piperazine **16** as a white solid (0.4 g, 75%), m.p. 182–184°C. $[\alpha]_D^{25}$=+59.6 (*c* 0.17 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 50°C: 7.41–7.03 (15H, m, arom.), 4.78 (1H, d, J=4.0 Hz, H-2′), 4.71 (1H, d, J=8.0 Hz, H-2), 3.68 (1H, d, J=4.0 Hz, H-2″), 3.21 (1H, dq, J=8.0, 6.6 Hz, H-3), 3.10 (1H, dq, J=4.0, 6.6 Hz, H-1′), 2.92 (1H, dq, J=4.0, 6.6 Hz, H-1″), 2.80–2.67 (3H, m, CH_2-5, H-6), 2.23 (1H, m, H-6), 1.06 (3H, d, J=6.6 Hz, CH_3-3), 0.75 (3H, d, J=6.6 Hz, CH_3-1′), 0.45 (3H, d, J=6.6 Hz, CH_3-1″). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ (50°C): 143.62, 142.84, 138.20, 130.90, 128.51, 127.86, 127.65, 127.53, 126.90, 126.79, 126.70, 125.97 (arom.), 76.12 (C-2), 72.15 (C-2′), 68.81 (C-2″), 59.78 (C-1′), 58.32 (C-3), 56.81 (C-1″), 46.00 (CH_2-6), 43.17 (CH_2-5), 15.09 (CH_3-3), 11.27 (CH_3-1′), 8.00 (CH_3-1″). MS (EI, 70 eV) m/z: (%) [M^+−$HOCHC_6H_5$, 337 (100)], 321 (2.25), 266 (1.56), 215 (1.12), 117 (0.6). IR ν_{max} (KBr) 3566, 3086, 2970, 1472, 1430 cm^{-1}. Anal. calcd for $C_{29}H_{36}N_2O_2 \cdot 2HCl$: C, 67.32; H, 7.35; N, 5.41. Found: C, 68.96; H, 7.77; N, 5.53.

4.15. 1-(2′-Hydroxyphenyl)-4-[(2″R,1″S)(2″-hydroxy-1″methyl-2″-phenyl)ethyl]piperazine (**17**)

A solution of **10** (0.5 g, 1.6 mmol) in anhydrous THF (100 ml) was treated with a 1.6 M solution of $BH_3 \cdot THF$ (3.0 ml), to give piperazine **17** as a white solid (0.3 g, 70%), m.p. 116–117°C. ^1H NMR ($CDCl_3$, 270 MHz) δ: 7.40–7.23 (5H, m, C_6H_5), 7.17 (1H, d, J=8.0 Hz, H-6′), 7.08 (1H, t, J=8.0 Hz, H-4′), 6.94 (1H, d, J=8.0 Hz, H-3′), 6.87 (1H, t, J=8.0 Hz, H-5′), 4.95 (1H, d, J=2.6 Hz, H-2″), 2.90–2.80 (5H, m, H-2-H-3, H-1″), 0.91 (3H, d, J=6.6 Hz, CH_3-1″). ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ: 151.44 (C-2′), 141.87 (C_i), 138.77 (C-1′), 128.05 (C_m), 126.98 (C_p), 126.48 (C-5′), 125.91 (C_o), 121.34 (C-4′), 120.06 (C-3′), 114.05 (C-6′), 72.21 (C-2″), 64.53 (C-1″), 53.00 (C-2), 51.01 (C-3), 10.07 (CH_3-1″). MS (EI, 70 eV) m/z: [M^+−$HOCHC_6H_5$, 205 (100), 176 (10), 148 (14), 120 (22), 84 (37), 79 (17), 77 (16), 65 (6), 56 (12), 42 (10) 28 (11). IR ν_{max} (KBr) 3630, 3422, 2816, 2360, 1500, 1450, 1380, 1230 cm^{-1}. Anal. calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.37; N, 8.96. Found: C, 72.62; H, 7.72; N, 8.96.

4.16. 1,4-Bis-(2′-hydroxyphenyl)piperazine (**18**)

A solution of **5** (0.5 g, 1.8 mmol) in anhydrous THF (100 ml) was treated with a 1.6 M solution of $BH_3 \cdot THF$ (4.69 ml) to give piperazine **18** as a white solid (0.3 g, 70%), m.p. 263–267°C. ^1H NMR (DMSO-d_6, 270 MHz) δ: 8.95 (1H, s, OH), 6.93 (1H, d, J=7.3 Hz, H-6′), 6.83–6.73 (3H, m, H-4′, H-5′, H-6′), 3.10 (4H, s, CH_2-2). ^{13}C NMR (DMSO-d_6, 67.80 MHZ) δ: 150.04 (C-2′), 139.90 (C-1′), 122.70 (C-5′), 119.33 (C-4′), 118.56 (C-3′), 115.45 (C-6′), 50.27 (C-2). MS (EI, 70 eV) m/z: [M^+, 270 (57)], 255 (32), 149 (2), 148 (50), 136 (26), 134 (38), 120 (100), 93 (17), 65 (20), 39 (11). IR ν_{max} (KBr) 2986, 2846, 1596, 1450, 1378, 1264, 1154 cm^{-1}. Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.66; N, 10.37. Found: C, 70.19; H, 6.57; N, 10.30.

Acknowledgements

We are grateful to CONACYT for financial support and Ing. Guillermo Uribe for NMR spectra.

References

1. Farfán, N.; Santillan, R.; Guzmán, J.; Castillo, B.; Ortíz, A.; Daran, J. C.; Robert, F.; Halut, S. *Tetrahedron* **1994**, *50*, 9951–9960.
2. Ortíz, A.; Farfán, N.; Santillan, R.; Rosales, M. J.; García-Baéz, E.; Daran, J. C.; Halut, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2715–2722.
3. Ortíz, A.; Carrasco, J.; Höpfl, H.; Santillan, R.; Farfán, N., *Synth. Commun.* **1998**, *28*, 1293–1297.
4. Romero, D. L.; Olmsted, R. A.; Poel T. J.; Morge, R. A.; Biles, C.; Keiser, B. J.; Kopta, L. A.; Friis, J. M.; Hosley J. D.; Stefanski, K. J.; Wishka, D. G.; Evas, D. B.; Morris J.; Stehle G.; Sharma, S. K.; Yagi, Y.; Voorman, R. L.; Adams, W. J.; Tarpley W. G.; Thomas, R. C. *J. Med. Chem*. **1996**, *39*, 3769–3789.
5. Orjales, A.; Alonso-Cires, L.; Labeaga, L.; Corcóstegui, R. *J. Med. Chem*. **1995**, *38*, 1273–1277.
6. Kuipers, W.; Wijngaarden, I. V.; Kruse, C. G.; Horst-van-Amstel, M.; Tulp, M. Th. M.; Ijzerman, A. P. *J. Med. Chem*. **1995**, *38*, 1942–1954.
7. Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. *J. Med. Chem.* **1995**, *38*, 942–949.
8. Bøgesø, K. P.; Arnt, J.; Frederiksen, K.; Hansen, H. O.; Hyttel, J.; Pedersen, H. *J. Med. Chem.* **1995**, *38*, 4380–4392.
9. Reitz, A. B.; Baxter, E. W.; Bennet, D. J.; Codd, E. E.; Jordan, A. D.; Malloy, E. A.; Maryanoff, B. E.; McDonnell, M. E.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Sherrill, R. G.; Vaught, J. L.; Wustrow, D. J. *J. Med. Chem.* **1995**, *38*, 4211–4222.

10. Vadodaria, D. J.; Deliwala, C. V.; Mandrekar, S. S.; Sheth, U. K. *J. Med. Chem.* **1969**, *12*, 860–865.
11. Regnier, G. L.; Canevari, R. J.; Laubie, M. J.; Le Douarec, J. C. *J. Med. Chem.* **1968**, *11*, 1151–1155.
12. Norman, M. H.; Rigdon, G. C.; Hall, W. R.; Navas III, F. *J. Med. Chem.* **1996**, *39*, 1172–1188.
13. Giardinà, D.; Gulini, U.; Massi, M.; Piloni, M. G.; Pompei, P.; Rafaiani, G; Melchiorre, C. J. *J. Med. Chem.* **1993**, *36*, 690–698.
14. Oh, Y.-S.; Cho, S.-H. *J. Heterocyclic. Chem.* **1998**, *35*, 17–23.
15. William, T. M.; Ciccarone, T. M.; MacTough, S. C.; Bock, R. L.; Conner, M. W.; Davide, J. P.; Hamilton, K.; Koblan, K. S.; Kohl, N. E.; Kral, A. M.; Mosser, S. D.; Omer, C. A.; Pompliano, D. L.; Rands, E.; Schaber, M. D.; Shah, D.; Willson, F. R.; Gibbs, J. B.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Smith, R. L. *J. Med. Chem.* **1996**, *39*, 1345–1348.
16. Martin, W. B.; Martell, A. E. *J. Am. Chem. Soc*. **1948**, *70*, 1817–1818.
17. Rauscher, W. H.; Goldstein, I. S.; Breslau, M. *J. Am. Chem. Soc*. **1949**, *71*, 358–359.
18. Prelog, V.; Blazek, Z. *Collect. Czech. Chem. Commun.* **1934**, *6*, 211–224.
19. Roussi, G.; Zhang, J. *Tetrahedron* **1991**, *47*, 5161–5172.
20. Abdel-Jalil, R.; Al-Qawasmeh, R. A.; Al-Abed, Y.; Voelter, W. *Tetrahedron Lett.* **1998**, *39*, 7703–7704.
21. Mancilla, T.; Farfán, N.; Castillo, D.; Molinero, L.; Merim, A.; Willen, R.; Mahieu, B.; Gielen, G. *Main Group Met. Chem*. **1989**, *12*, 213.
22. Farfán, N.; Santillan, R. L.; Castillo, D.; Cruz, R.; Joseph-Nathan, P.; Daran, J. C. *Can. J. Chem*. **1992**, 70, 2764–2770.
23. Cerda-García-Rojas, C. M.; Zepeda, L. G. Joseph-Nathan, P. *Tetrahedron Comput. Methodol*. **1990**, *3*, 113.
24. Anet, F. A. L.; Yavari, I. *Tetrahedron Lett*. **1976**, *25*, 2093–2096.
25. Okamoto, K.; Fujii, S.; Tomita, K. I.; Arai, S.; Tsutsumi, Y. *Acta Cryst*. **1992**, *C48*, 1518–1519.
26. Katritzky, A. R.; Patel, R. C.; Riddell, F. G. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 521–529.
27. Walker, N.; Stewart, D. *Acta Crystallogr*. *A* **1983**, *39*, 158–166.
28. Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. In CRYSTALS, *An Advanced Crystallographic Program System*; Chemical Crystallography Laboratory, University of Oxford, 1988.
29. *International Tables for X-Ray Crystallography*, Vol IV; Kynoch Press, Birmingham, 1974.
30. Sheldrick, G. M. In SHELXS86, *A Program for Crystal Structure Determination*; University of Göttingen, 1986.