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Stereoselective synthesis of (*R*)-(−)-mianserin

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Abstract—(14b*R*)-2-Methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine, (*R*)-(−)-mianserin **1a** was synthesised in several steps in good enantiomeric purity with the use of (*S*)-(−)-α-methylbenzylamine **5**. The absolute configuration was assigned on the basis of X-ray data.

1. Introduction

Mianserin **1** (Tolvon®, (14b*RS*)-2-methyl-1,2,3,4,10, 14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine) the tetracyclic compound of the piperazine-dibenzepine group, is a drug for the treatment of depressive illness and depression associated with anxiety.[1] Its antidepressant effect is mainly attributed to presynaptic α_2-adrenoreceptor blocking activity and to serotonin receptors antagonism.[2,3] This antidepressant has very little, if any, activity on monoamine re-uptake mechanisms.[4] Based on its undefined mechanism of action, mianserin **1** has been classified as an atypical antidepressant (Fig. 1).[5]

Mianserin **1** is administered as a racemate, although the (*S*)-(+)-enantiomer was more potent than (*R*)-(−)-congener in pharmacological tests for antidepressant activity.[6–8]

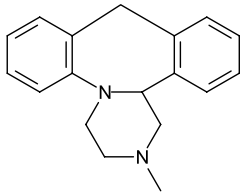

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Figure 1.

The separation of the mianserin **1** enantiomers has been achieved analytically by a GC method[9] and on a larger scale, with the use of chiral preparative HPLC.[10] The absolute configuration of (*S*)-(+)-mianserin was established by X-ray crystallography of its hydrobromide.[11] Only the synthesis of the racemic form of mianserin **1** has been reported.[4] The synthesis of enantiopure chiral compounds represents an important challenge in organic chemistry since numerous classes of compounds undergo 'biodiscrimination' within organisms[12] and reveal biological activity that strongly depends on their stereostructures.

Stereoselective syntheses of compounds having pharmacological importance should preferably start from inexpensive and readily available chiral inductors, preferably accessible in both enantiomeric forms. In this context we decided to use (*S*)-(−)-α-methylbenzylamine **5** as a chiral auxiliary in the synthesis of non-racemic mianserin **1** because it is known to be effective, reasonably priced and easy to remove by reductive methods.[13,14] Also, in our group amine **5**, as well as its enantiomer have been successfully applied for the synthesis of isoquinoline alkaloids[15] and lortalamine derivatives.[16]

2. Results and discussion

In the presented stereoselective synthesis of mianserin **1**, we started with 6-chloromethylmorphanthridine **4**[4] as a precursor for the introduction of chirality adjuvant.

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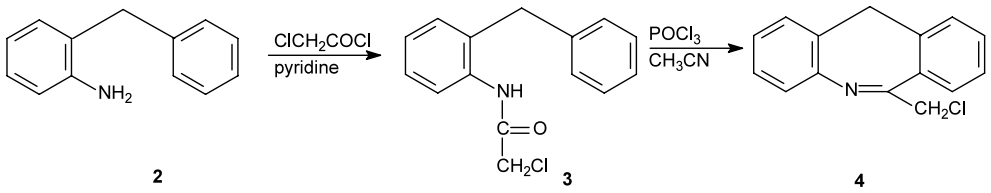
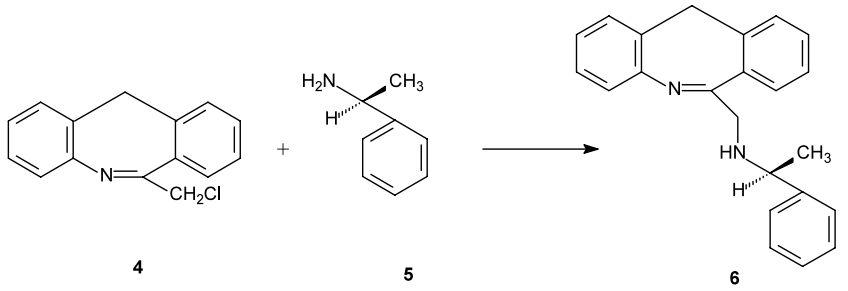
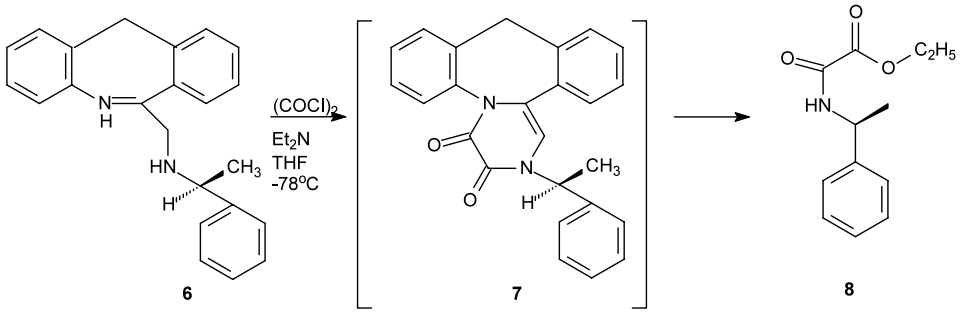


Scheme 1.



Scheme 2.



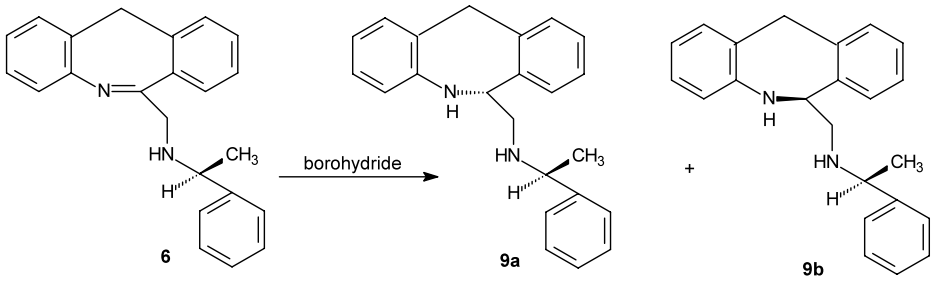
Scheme 3.

This compound was prepared by the reaction of 2-benzylaniline **2** with chloroacetyl chloride in the presence of pyridine to obtain 2-benzylchloroacetanilide **3** in 79% yield (Scheme 1). Bischler–Napieralski condensation of 2-benzylchloroacetanilide **3** with $POCl_3$ in acetonitrile gave 6-chloromethylmorphanthridine **4** in 86%.

Chloroimine **4** was subsequently treated with (*S*)-(−)-α-methylbenzylamine **5** to afford crude compound **6** in approximately 70% yield (Scheme 2). Amidine derivative **6** proved to be very unstable and we were unable to collect all the required spectroscopic data of sufficient quality. However, compound **6** underwent the subsequent steps with reasonable yields. First, we planned to take advantage on the chemistry of acylimmonium ions and compound **6** was subjected to the reaction with oxalyl chloride with the hope of forming cyclic enamide **7**, the more rigid structure of which would possibly allow higher stereoselectivity within the reduction. Unfortunately, compound **7** proved to be extremely unstable and the only product that was obtained in this reaction was **8**, probably as the result of decomposition of **7** and the influence of the solvents. On the other hand, attempts to reduce compound **7** without any purification procedure gave rise to intractable mixtures (Scheme 3).

The prochiral imine moiety in compound **6** was therefore subjected to a series of reductions under different conditions that gave the mixtures of diastereomeric: *N* - [(6*R*) - 6,11 - dihydro - 5*H* - dibenzo[*b*,*e*]azepin - 6-ylmethyl]-*N*-[(1′*S*)-1-phenylethyl]amine **9a** and *N*-[(6*S*)-6,11 - dihydro - 5*H* - dibenzo[*b*,*e*]azepin - 6 - ylmethyl] - *N*-[(1′*S*)-1-phenylethyl]amine **9b**. When sodium borohydride in methanol was used as the reducing agent, almost no stereoselection was observed regardless the temperature. The result is not surprising since the stereoselection is based on 1,4-chirality transfer. Comparable results were obtained in the case of lithium aluminium hydride in THF but the yield was considerably lower. Catalytic hydrogenation (Adams', EtOH/HCl) was also non-selective.

However, when sodium borohydride is treated with a controlled amount of carboxylic acid, a modified reducing agent forms that is weaker, more sterically demanding and therefore more selective.[17] Indeed, when imine **6** was treated with sodium diacetoxy-, triacetoxy- and tri-*i*-butyroylborohydrides an increasing diastereoselectivity, up to 76:24, was observed alas with lowering of the yield (Scheme 4). Attempts to improve the selectivity by temperature or solvent variations were unsuccessful. Selected results are given in Table 1.



Scheme 4.

The diastereomeric composition after the reduction step was established on the basis of ^{1}H NMR spectra taken on crude reaction mixtures. Both isomers **9a** and **9b** showed very similar chromatographic properties and their effective separation required repeated and very careful column chromatography. Moreover, slow decomposition of compounds **9a** and **9b** could be observed. Fortunately, when **9a** or **9b** were treated with oxalyl chloride in the presence of pyridine, stable diketopiperazine derivatives **10a** and **10b** were formed, respectively. Also, both diastereomers **10a** and **10b** showed better separation properties than in the case of **9a** and **9b**. Consequently, we found that the mixture after the reduction could be more efficiently purified and separated after its conversion to the mixture of appropriate diamides (14b*R*)-2-[(1′*S*)-1-phenylethyl]-1,2,10,14b - tetrahydrodibenzo[*c*,*f*]pyrazino[1,2 - *a*]-azepine-3,4-dione **10a** and (14b*S*)-2-[(1′*S*)-1-phenylethyl]-1,2,10,14b-tetrahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]-azepine-3,4-dione **10b** (Scheme 5).

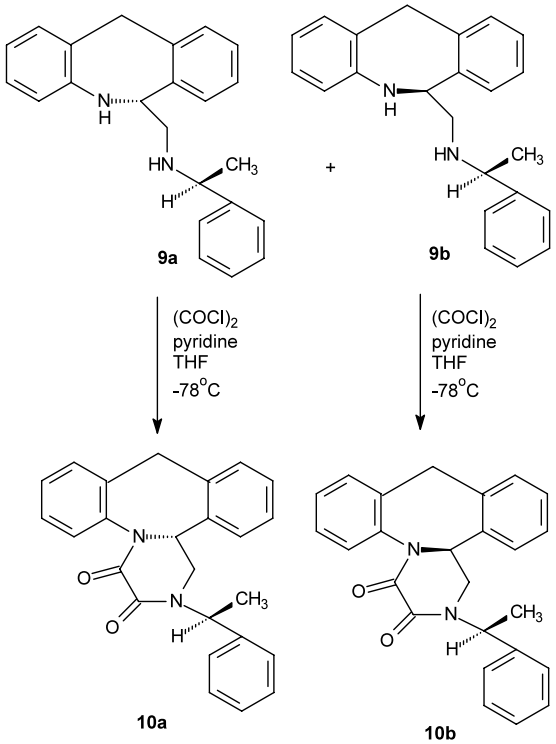
It may be mentioned here that **9b** was the first compound to be eluted during the column chromatography, whereas in case of amides **10a** and **10b** the order of the elution was reversed. In the case of diketopiperazine **10b** we were able to obtain a single crystal suitable for an X-ray study that allowed the assignment of (14b*S*) configuration at the heterocyclic part of the molecule (Fig. 2).

Attempted reduction of compounds **10a** or **10b** with lithium aluminium hydride led to the cleavage of C–N bond and extensive decomposition, whereas with borane–dimethyl sulfide complex (BMS)[18] the reduction of carbonyl groups proceeded smoothly to give products **11a** or **11b** in excellent yields (Schemes 6 and 7).

Final non-racemic (*R*)-(−)-mianserin **1a** was obtained from **11a** in a two step reaction sequence in 58% overall yield. The chiral auxiliary was removed by the hydrogenolysis over palladium-on-carbon and the secondary amine thus formed was subsequently *N*-methylated using formaldehyde-sodium borohydride method to obtain (*R*)-(−)-**1a** in over 92% enantiomeric excess purity. The (*S*)-(+)-**1a** enantiomer could not be detected upon analysis on the chiral GC column.

Table 1.

Reduction conditions	Yield (%)	Diastereomers **9a** and **9b**
1) $NaBH_4$/MeOH/rt	68	48:52
2) $NaBH_4$/MeOH/−70°C	64	57:42
3) $Na(CH_3COO)_2BH_2$/MeOH/rt	67	63:37
4) $Na(CH_3COO)_3BH$/MeOH/rt	57	73:27
5) $Na(i\text{-}C_3H_7COO)_3BH$/MeOH/rt	48	76:24



Scheme 5.

3. Experimental

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 and 200 MHz for ^{1}H NMR and at 125 and 50 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. Chemical shifts were reported in ppm.

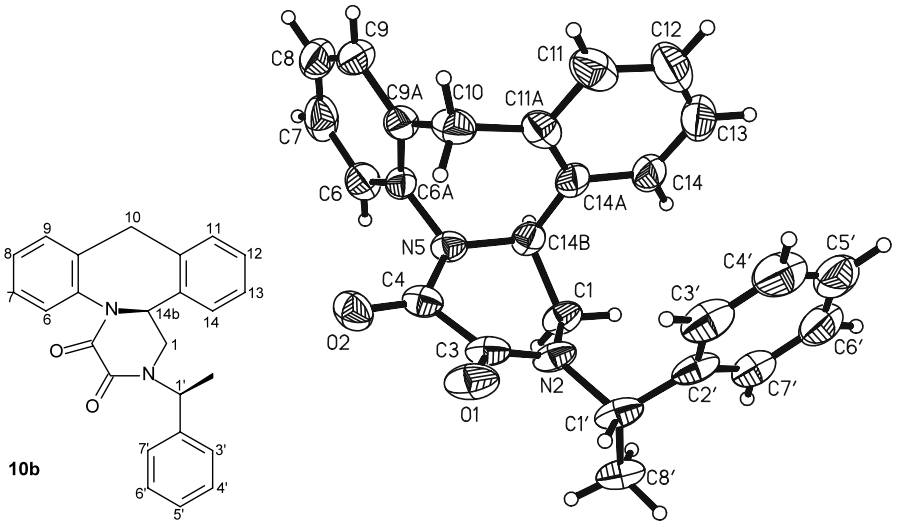
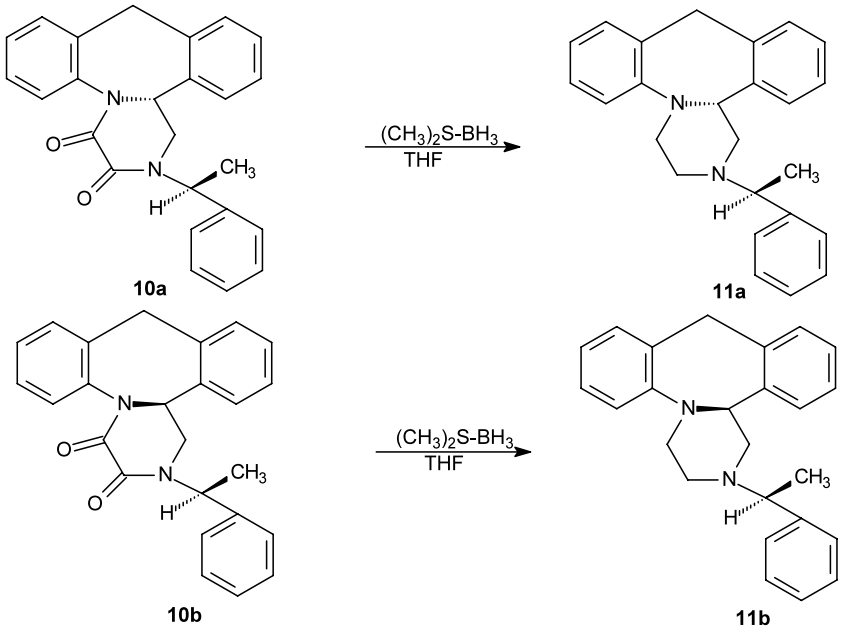
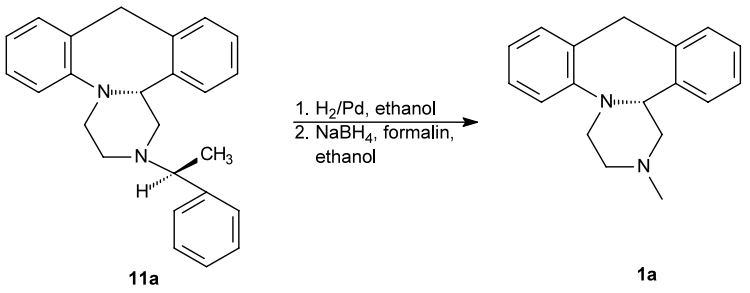


Figure 2. X-Ray diffraction structure (ORTEP diagram) of diketopiperazine **10b**.



Scheme 6.



Scheme 7.

Mass spectra were collected on AMD 604 apparatus; high-resolution mass spectra were acquiring using LSIMS (positive ion mode), GC/MS was done at HP 6890 with a mass detector HP 5973 (oven 280°C, injection 300°C, detector 300°C). ChiraDex β-Dex® 120 30 m/0.25 mm Supelco column was used for analytical enantiomer separations. Optical rotation was measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualised using iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 or under 400 mesh, Merck) or on aluminium oxide (III Brockmann, Merck).

Preparation of 2-benzylchloroacetanilide 3: According to van der Burg procedure,[4] we used a mixture of 25 g (0.14 mol) 2-benzylaniline **2**, 15 mL of pyridine in 125 mL of benzene and 11.9 g (0.11 mol) of chloroacetyl chloride in 20 mL benzene to obtain 28 g (79%) of compound **3** as yellow crystals. Mp 117–119°C, mp[4] 119–120°C.

Preparation of 6-chloromethylmorphanthridine 4: To a suspension of 7.5 g (0.30 mol) 2-benzylochloroacetanilide **3** in 120 mL of acetonitrile a sample of 38 g (0.25 mol) $POCl_3$ was added in one portion. The reaction mixture was stirred and refluxed for 1.5 h. The volatile components were then evaporated in vacuo, the residue was washed with $NaHCO_{3aq}$, extracted with $CHCl_3$ and dried over $MgSO_4$. Column chromatography (silica gel, chloroform) afforded 6.0 g (86%) of compound **4** as yellow crystals. Mp 139–142°C, mp[4] 138–139°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.56–7.16 (m, 8H, H-1, H-2, H-3, H-4, H-7, H-8, H-9, H-10), 4.79 (br.s, 2H, 2H-6a), 3.63 (s, 2H, 2H-11); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 164.5, 144.4, 143.4, 132.6, 131.5, 130.4, 127.1, 127.1, 126.9, 126.5, 125.3, 48.9, 38.8; GC/MS m/z (%): 102 (19), 165 (37), 178 (19), 192(100), 206 (37), 241 (80) M^+.

Preparation of *N*-(11*H*-dibenzo[*b*,*e*]azepin-6-ylmethyl)-*N*-[(1′*S*)-1-phenylethyl]amine 6: The mixture of 3.23 g (13.4 mmol) 6-chloromethylmorphanthridine **4** and 4.05 g (33.5 mmol) (*S*)-(−)-α-methylbenzylamine **5** was stirred at 50°C under argon. After 20 min the reaction mixture was cooled and white crystals of amine hydrochloride were filtered off. The residue consisted of compound **6** as very unstable oil, which could not be effectively purified nor characterised and therefore it had to be used without any further treatment. EI (70 eV) (%): 326 (45), 105(100); LSIMS HR (+) m/z (%): 105 (100), 327[M+H]$^+$(60), 349[M+Na]$^+$(20).

Preparation of ethyl oxo{[(1*S*)-1-phenylethyl]amino}-acetate 8: To a solution of 3.30 g (10.1 mmol) of the crude imine **6**, 2.1 mL (22.0 mmol) of triethylamine in 70 mL of dry THF cooled to −78°C and stirred magnetically under argon, the solution of 1.41 g (9.0 mmol) of oxalyl chloride in 30 mL dry THF was added dropwise. After 24 h of subsequent stirring white crystals were filtered off, washed with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was poured into $NaHCO_{3aq}$, extracted with CH_2Cl_2 and dried over $MgSO_4$. Column chromatography (silica gel, chloroform/ethanol, 9:1) afforded compound **8** in a yield of 1.63 g (78%). $[\alpha]_D^{22}$ −75 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.34–7.28 (m, 5H, $5H_{arom.}$), 5.15 (q, 1H, $J=7.0$ Hz, CH), 4.34 (q, 2H, $J=14.5$ Hz, CH_2), 1.61 (br.s, 1H, NH), 1.57 (d, 3H, $J=6.5$ Hz, CH_3), 1.38 (t, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR (125 MHz), $CDCl_3$, δ (ppm): 160.8, 155.6, 141.7, 128.8, 127.8, 126.2, 63.2, 49.4, 21.2, 14.0.

Reductions with sodium borohydride: A solution of 5.35 g (16.4 mmol) of imine **6** in 250 mL of methanol was treated while stirring with 4.5 g (0.12 mol) of $NaBH_4$, which was added in five portions. After 24 h, the solvent was evaporated in vacuo, the residue was treated with 50 mL of 10% HCl and then made basic with Na_2CO_{3aq}, extracted with $CHCl_3$ and dried over $MgSO_4$. Short-path column chromatography (aluminium oxide III, 98:2 cyclohexane/ethyl acetate) afforded 3.7 g (68%) yield of the mixture of *N*-[(6*R*)-6,11-dihydro-5*H*-dibenzo[*b*,*e*]azepin-6-ylmethyl]-*N*-[(1′*S*)-1-phenylethyl]amine **9a** and *N*-[(6*S*)-6,11-dihydro-5*H*-dibenzo[*b*,*e*]azepin-6-ylmethyl]-*N*-[(1′*S*)-1-phenylethyl]amine **9b** in the ratio 48:52 as calculated from the integration of the signals at 1.41 and 1.45 ppm in ^{1}H NMR. Two diastereomeric forms were separated by means of a very careful column chromatography (silica gel, 99:1 chloroform/methanol). Analytical data for compound **9a**: $[\alpha]_D^{22}$ −89 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.33 and 7.28–7.25 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-7′), 7.20–7.14 and 7.01–6.96 (m, 6H, H-1, H-3, H-7, H-8, H-9, H-10), 6.65 (td, 1H, $J_1=7.5$ Hz, $J_2=1.0$ Hz, H-2), 6.56 (br. d, 1H, $J=8.0$ Hz, H-4), 4.96 (dd, 1H, $J_1=10.0$ Hz, $J_2=4.0$ Hz, H-6), 4.55 and 3.71 (q_{AB}, 2H, $J=15.0$ Hz, 2H-11), 3.91 (q, 1H, $J=14.0$ Hz, H-1′), 3.07 (dd, 1H, $J_1=11.5$ Hz, $J_2=4.0$ Hz, H-6a), 2.90 (td, 1H, $J_1=11.5$ Hz, $J_2=1.5$ Hz, H-6a), 1.65 (br.s, 1H), 1.41 (d, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 145.9, 139.7, 138.1, 129.9, 128.6, 128.4, 127.6, 127.4, 127.2, 126.8, 126.6, 124.9, 118.7, 118.2, 58.0, 54.9, 51.0, 30.2, 26.9.

Analytical data for compound **9b**: $[\alpha]_D^{22}$ +40.5 (*c* 1.2, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.31 and 7.26–7.24 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-7′), 7.19–7.13 and 7.01–6.96 (m, 6H, H-1, H-3, H-7, H-8, H-9, H-10), 6.66 (td, 1H, $J_1=7.5$ Hz, $J_2=1.0$ Hz, H-2), 6.59 (br.d, 1H, $J=8.0$ Hz, H-4), 4.74 (t, 1H, $J=5.5$ Hz, H-6), 4.49 (br.s, 1H), 4.41 and 3.76 (q_{AB}, 2H, $J=15.5$ Hz, 2H-11), 3.86 (q, 1H, $J=13.0$ Hz, H-1′), 3.00 (br.d, 1H, $J=2.0$ Hz, H-6a), 2.99 (br.s, 1H, H-6a), 1.60 (br.s, 1H), 1.45 (d, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 145.9, 139.6, 138.1, 129.9, 128.6, 128.5, 127.5, 127.4, 127.2, 126.8, 126.5, 125.6, 125.3, 118.9, 118.4, 58.9, 55.7, 52.1, 30.2, 26.9. GC/MS m/z (%): 105(33), 134(15), 165(15), 179(2), 194(100), 328(2) M^+.

Alternatively, a suspension of 0.40 g (11.9 mmol) of $NaBH_4$ in 5 mL of methanol was introduced slowly into a solution of 0.50 g (1.5 mmol) of imine **6** in methanol cooled to −78°C and stirred. After 5 h the

cooling bath was removed and the mixture was stirred overnight. The solvent was evaporated in vacuo, the residue was washed with 10% HCl and Na_2CO_{3aq}, extracted with $CHCl_3$ and dried ($MgSO_4$). Column chromatography (aluminium oxide III, 98:2 ethyl cyclohexane/acetate) afforded 0.32 g (64%) of mixture of compounds **9a** and **9b** in the ratio 57:42.

General procedure for the reductions of imine 6 with modified borohydrides: The modified borohydride solution was obtained from $NaBH_4$ in dry THF and the calculated amount of the carboxylic acid.[17]

In the case of $Na(CH_3COO)_2BH_2$, a sample of 1.36 g (22.8 mmol) of glacial acetic acid was added over a period 20 min to a suspension 0.43 g (11.4 mmol) $NaBH_4$ in 25 mL of dry THF and the resulted mixture was then stirred for 0.5 h. After that time, 0.26 g (6.8 mmol) of imine **6** was introduced and the contents of the flash was stirred for 24 h. The mixture was then poured onto 25 mL of 25% aqueous NaOH, stirred for 0.5 h, and extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to leave colourless oil. Column chromatography (aluminium oxide III, 98:2 cyclohexane/ethyl acetate) afforded 0.18 g (67%) mixture of compounds **9a** and **9b** in the ratio 63:37.

In the case of other acyl borohydrides: $Na(CH_3COO)_3BH$ and $Na(i\text{-}C_3H_7COO)_3BH$, respective amounts of 34.1 mmol of glacial acetic acid and 28.6 mmol of *i*-butyric acid were added and the procedure that followed was the same as above. The stereochemical outcome was given in Table 1.

Preparation of (14b*R*)-2-[(1′*S*)-1-phenylethyl]-1,2,10,14b-tetrahydrodibenzo[*c*,*f*] pyrazino[1,2-*a*]azepine-3,4-dione 10a and (14b*S*)-2-[(1′*R*)-1-phenylethyl]-1,2,10,14b-tetrahydro dibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine-3,4-dione 10b: A solution of 0.24 mL (3.0 mmol) of oxalyl chloride in 2 mL of dry CH_2Cl_2 was introduced slowly into a magnetically stirred solution of the mixture of 0.66 g (2.0 mmol) of amines **9a** and **9b** in 15 mL CH_2Cl_2 with 0.38 mL (4.4 mmol) of pyridine at −78°C under argon atmosphere. After 24 h, the white crystals were filtered out and washed with CH_2Cl_2 and the filtrate was concentrated in vacuo. The residue was poured onto a suspension of $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. Two 20 mL portions of xylene were added and then removed in vacuo and the residue was quenched with ethyl acetate, affording the first crop of 30 mg of **10b** in the form of white crystals. Column chromatography of the mother liquor (silica gel, cyclohexane/ethyl acetate, 85:15) allowed the complete separation of the diastereomers in 70 mg (92%) chemical yield.

Analytical data for compound **10a**: $[\alpha]_D^{22}$ −156 (*c* 1.2, $CHCl_3$); mp 228–232°C; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.47–7.35 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-7′), 7.27–7.24 and 7.18–7.11 (m, 6H, H-7, H-9, H-11, H-12, H-13, H-14), 7.05 (td, 1H, $J_1=7.5$ Hz, $J_2=1.5$ Hz, H-8), 6.54 (d, 1H, $J=7.5$ Hz, H-6), 6.01 (q, 1H, $J=14.5$ Hz, H-1′), 4.89 (dd, 1H, $J_1=11.0$ Hz, $J_2=3.5$ Hz, H-14b), 4.50 and 3.42 (q_{AB}, 2H, $J=13.5$ Hz, 2H-10), 3.78 (td, 1H, $J_1=13.5$ Hz, $J_2=2.5$ Hz, H-1), 3.10 (dd, 1H, $J_1=13.5$ Hz, $J_2=3.0$ Hz, H-1), 1.52 (d, 3H, $J=7.5$ Hz, CH_3); ^{13}C NMR (125 MHz), $CDCl_3$, δ (ppm): 157.8, 157.0, 140.4, 139.2, 139.1, 136.2, 132.7, 129.3, 128,9, 128.7, 128.7, 128.4, 128.3, 128.2, 127.7, 127.6, 127.4, 127.3, 61.0, 51.4, 46.4, 38.3, 15.1; GC/MS *m*/*z* (%): 105 (85), 132 (23), 165 (40), 178 (23), 193 (100), 249 (25), 339 (25), 382 (100) M^+.

Analytical data for compound **10b**: $[\alpha]_D^{22}$ +85 (*c* 1.2, $CHCl_3$); mp 143–150°C; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.36–7.25 and 7.32–7.26 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-7′), 7.24–7.23 and 7.20–7.11 (m, 6H, H-7, H-9, H-11, H-12, H-13, H-14), 7.04 (td, 1H, $J_1=8.0$ Hz, $J_2=2.0$ Hz, H-8), 6.83 (d, 1H, $J=7.5$ Hz, H-6), 6.01 (q, $J=14.0$ Hz, 1H, H-1′), 5.11 (dd, 1H, $J_1=10.5$ Hz, $J_2=3.5$ Hz, H-14b), 4.41 and 3.40 (q_{AB}, 2H, $J_1=14.0$ Hz, 2H-10), 3.46 (td, 1H, $J_1=10.5$ Hz, $J_2=3.5$ Hz, H-1), 3.30 (dd, 1H, $J_1=13.0$ Hz, $J_2=4.0$ Hz, H-1), 1.71 (d, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 157.8, 156.9, 140.1, 139.1, 137.8, 136.6, 132.8, 129.5, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.7, 127.5, 127.4, 60.9, 51.3, 46.1, 38.4, 15.7.

X-Ray intensity data for **10b** were measured at $T=293$ K on a Kuma KM4 κ-axis diffractometer using MoKα radiation ($\lambda=0.71073$ Å). The structure was solved using direct methods from SHELXS-97 program[19] and refined by application of SHELXL-97 software.[20]

Crystal data for **10b**: $C_{25}H_{22}N_2O_2$, M = 382.45, monoclinic space group $P2_1$; $a=8.7300(17)$, $b=11.359(2)$, $c=10.270(2)$ Å, $\beta=91.26(3)°$, $V=1018.2(4)$ Å^3, $Z=2$ and $D_x=1.247$ Mg/m^3. Clear colourless columnar crystal, μ(MoKα) = 0.080 mm^{-1}, 3236 reflections measured, 3062 independent ($R_{int}=0.0252$), 1221 observed [$I>2\sigma(I)$]. The least squares on F^2 (all reflections), $R=0.0534$, $wR=0.1708$ (all). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated with the deposition number CCDC 212929. Apart from crystal structure reported here we obtained also the structure of its solvate in which **10b** crystallised in the orthorhombic space group $P2_12_12$ with $a=12.241(7)$, $b=18.053(7)$, $c=10.459(6)$ Å and $\alpha=\beta=\gamma=90°$. The asymmetric part of the unit cell was composed of one molecule of **10b** and one disordered ethanol molecule. These crystals were however of much worse quality with the *R* of 0.081 for observed reflections.

Preparation of (14b*R*)-2-[(1′*S*)-1-phenylethyl]-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*] pyrazino[1,2-*a*]azepine 11a: A sample of 30 mg (0.4 mmol) of borane dimethyl sulphide complex (BMS) was introduced slowly into a magnetically stirred solution of the solution of 0.30 g (0.8 mmol) of diastereomer **10a** in 10 mL of dry THF. The mixture was then heated at reflux while dimethyl sulfide distilled off. After 4 h, the product was hydrolysed with 12% HCl and heated for 2 h. After cooling, the product was neutralised with 20% NaOH to pH 11, extracted with CH_2Cl_2 and dried over

$MgSO_4$. Column chromatography (silica gel, chloroform) afforded colourless oil 0.26 g (94%) of compound **11a**.Analytical data for compound **11a**: $[\alpha]_D^{22}$ −341.8 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.35–7.30 and 7.25 and 7.22 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-7′), 7.17–7.12 and 7.09–7.07 and 7.02–6.96 (m, 6H, H-7, H-9, H-11, H-12, H-13, H-14), 6.96 (br d, $J=7.0$ Hz, 1H, H-6), 6.84 (td, $J_1=7.5$ Hz, $J_2=1.0$ Hz, 1H, H-8), 4.79 and 3.27 (q_{AB}, 2H, $J_1=12.5$ Hz, 2H-10), 4.11 (br d, 1H, $J=9.0$ Hz, H-14b), 3.44 (q, 1H, $J=13.0$ Hz, H-1′), 3.15-3.10 (m, 2H, H-1, H-4), 2.86 (dd, 1H, $J_1=11.0$ Hz, $J_2=1.5$ Hz, H-1), 2.44 (t, 1H, $J=11.0$ Hz, H-4), 2.22 (td, 2H, $J_1=11.0$ Hz, $J_2=2.5$ Hz, 2H-3), 1.41 (d, 3H, $J=6.5$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.7, 143.6, 139.7, 139.4, 137.9, 129.6, 128.2, 128.1, 127.6, 127.1, 126.9, 126.8, 126.4, 122.1, 118.9, 66.8, 64.8, 60.3, 51.3, 51.1, 38.8, 19.9.

Compound **11b** was obtained from diastereoisomer **10b** in a similar procedure.

Analytical data for compound **11b**: $[\alpha]_D^{22}$ +157.7 (*c* 0.91, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.35–7.30 and 7.25 and 7.22 (m, 5H, H-3′, H-4′, H-5′, H-6′ H-7′), 7.17–7.12 and 7.09–7.07 and 7.02–6.96 (m, 6H, H-7, H-9, H-11, H-12, H-13, H-14), 6.85 (td, 1H, $J_1=7.5$ Hz, $J_2=1.0$ Hz, H-8), 6.81 (dd, 1H, $J_1=8.5$ Hz, $J_2=2.0$ Hz, H-6), 4.77 and 3.26 (q_{AB}, 2H, $J=12.5$ Hz, 2H-10), 4.01 (dd, 1H, $J_1=10.0$ Hz, $J_2=1.5$ Hz, H-14b), 3.51 (q, 1H, $J_1=14.0$ Hz, H-1′), 3.38 (td, 1H, $J_1=12.0$ Hz, $J_2=3.0$ Hz, H-1), 3.29-3.24 (m, 1H, H-4), 3.13 (dd, 1H, $J_1=11.5$ Hz, $J_2=2.0$ Hz, H-1), 2.81 (dt, 1H, $J_1=11.5$ Hz, $J_2=2.0$ Hz, H-4), 2.38 (td, 2H, $J_1=11.0$ Hz, $J_2=3.0$ Hz, 2H-3), 1.42 (d, $J=7.0$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.7, 143.5, 139.7, 139.3, 137.7, 129.5, 128.2, 127.9, 127.6, 127.1, 126.9, 126.7, 126.4, 126.4, 122.1, 118.9, 66.8, 64.4, 60.5, 51.4, 50.2, 38.8, 19.2; GC/MS *m*/*z* (%): 105 (20), 165 (10), 179 (15), 193 (35), 249 (100), 354 (31) M^+.

Preparation of (*R*)-(−)-mianserin 1a: A solution of 200 mg (0.5 mmol) of compound **11a** in 10 mL of EtOH that contained 0.5 mL of concentrated HCl_{aq} and 60 mg of 10% Pd/C was hydrogenated under atmospheric pressure of hydrogen for 3 h. Longer reaction time promoted extensive decomposition of the product. The mixture was then filtered, made basic with 20% $NaOH_{aq}$ and evaporated. The residue was taken up into CH_2Cl_2, washed with brine and evaporated after drying over $MgSO_4$. Column chromatography (silica gel, 99:1 chloroform/methanol) of the residue gave 175 mg of pure, recovered substrate **11a** and 15 mg of *N*-nor-mianserin. Repeated hydrogenation of the recovered substrate allowed its conversion into the product in 85% final yield.

A sample of 40 mg (0.16 mmol) of *N*-nor-mianserin was dissolved in 3 mL of EtOH that contained three drops of formalin and was left to stand overnight at 10°C. The mixture was then treated with 80 mg (2.1 mmol) of $NaBH_4$, added in four portions while stirring. After subsequent evaporation of the solvent, the mixture was taken up into CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated to leave the residue that after column chromatography (silica gel, chloroform) afforded final (*R*)-(−)-mianserin **1a** as a white powder (25 mg, 58% yield). $[\alpha]_D^{22}$ −421 (*c* 1, C_2H_5OH); mp 114–119°C; ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.18–6.99 (m, H-6, H-7, H-9, H-11, H-12, H-13, H-14), 6.87 (td, 1H, $J_1=7.5$ Hz, $J_2=1.0$ Hz, H-8), 4.82 and 3.30 (q_{AB}, 2H, $J=13.0$ Hz, 2H-10), 4.08 (dd, 1H, $J_1=10.5$ Hz, $J_2=2.5$ Hz, H-14b), 3.37 (td, 1H, $J_1=12.0$ Hz, $J_2=3.0$ Hz, H-1), 3.27–3.24 (m, 1H, H-4), 2.97 (dd, 1H, $J_1=11.5$ Hz, $J_2=2.0$ Hz, H-1), 2.88 (dt, 1H, $J_1=11.0$ Hz, $J_2=2.0$ Hz, H-4), 2.42 (t, 1H, $J=10.5$ Hz, H-3), 2.36 (s, 3H, CH_3), 2.33 (dd, 1H, $J_1=11.0$ Hz, $J_2=3.5$ Hz, H-3). Lit.[21] $[\alpha]_D^{22}$ for compound (*R*)-(−)-**1a** −457.6 (C_2H_5OH).

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