First Enantioselective Synthesis of Aptazepine

Piotr Roszkowski,[a] Jan K. Maurin,[b,c] Zbigniew Czarnocki*[a]

[a] Faculty of Chemistry, Warsaw University, Pasteura 1, 02-093, Warsaw, Poland
Fax +48(22)8225996; E-mail: czarnoz@chem.uw.edu.pl

[b] National Medicines Institute, Chełmska 30/34, 00-725 Warsaw, Poland

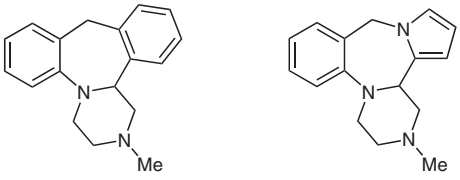
[c] National Centre for Nuclear Research, 05-400 Otwock-Świerk, Poland

Received 6 September 2011; revised 21 November 2011

Abstract: Aptazepine (2-methyl-1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine), a potent tetracyclic antidepressant, was synthesized in both its enantiopure forms by using an asymmetric transfer hydrogenation in a key step. Reduction of the prochiral imine **7** gave the products (*R*)- and (*S*)-**8** in 63% and 61% ee, respectively, but a single crystallization improved the enantiomeric purity to 98% ee. The final (*R*)- and (*S*)-aptazepines were prepared in four subsequent steps. The absolute configuration of intermediate (*S*)-**8** was determined by X-ray crystallography.

Key words: asymmetric synthesis, asymmetric catalysis, total synthesis, reductions, heterocycles

Depressive disorders have become a major public-health problem in recent decades with about 10% of the world's population appearing to be affected by various disorders that fall into this category. The resulting deterioration in human relations and in the daily lives of individuals has widespread social and economic consequences.[1] Therefore, the development of novel antidepressant agents, preferably with few side effects, is of current interest to medicinal chemistry. Fully synthetic tetracyclic antidepressants were successfully developed and introduced in the 1970s as a class of active and relatively safe pharmaceuticals,[2] of which mianserin (**1**) and aptazepine (**2**) are prominent examples (Figure 1). The former is currently being marketed and the latter is undergoing clinical trials.



mianserin (**1**) aptazepine (**2**)

Figure 1

Aptazepine (**2**) is a potent α_2-adrenoreceptor blocking agent and, as such, has been a subject of intensive pharmacological evaluation.[3]

Because mianserin (**1**), the structure of which is similar to that of aptazepine (**2**), exhibits significant 'biostereodiscrimination' in organisms, it is likely that aptazepine will also do so. Surprisingly, only syntheses of racemic aptazepine (*rac*-**2**),[4,5] some of its structural isomers,[6,7] and their derivatives and analogues have been reported. However, enantiomers of aptazepine derivatives and related compounds have recently been separated by HPLC using saccharide-coated chiral stationary phase.[8]

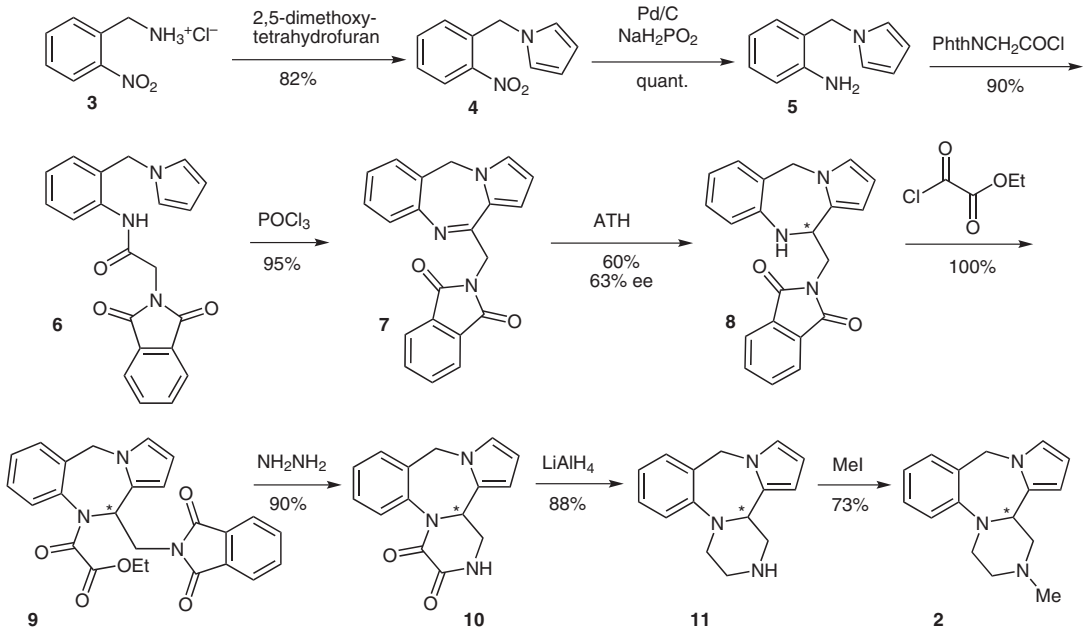
Having already described a stereoselective synthesis of (*R*)-(–)-mianserin,[9] we decided to turn our attention to the aptazepine system. Because asymmetric transfer hydrogenation (ATH) has proven useful in the enantioselective construction of chiral cyclic amines,[10–12] we chose a synthetic scheme that allowed the ATH procedure to be performed on an appropriate prochiral intermediate.

The synthetic pathway that we adopted is presented in Scheme 1. The reaction of commercially available 2-nitrobenzylamine hydrochloride (**3**) with 2,5-dimethoxytetrahydrofuran by means of a slightly modified Boyer's procedure[5] gave 1-(2-nitrobenzyl)-1*H*-pyrrole (**4**) in 82% yield. Reduction of the nitro group to an amino group proceeded quantitatively.[5] Subsequent acylation with *N*-phthalylglycyl chloride gave the intermediate amide **6** in 90% yield. This amide was converted into the corresponding prochiral endocyclic imine **7** in 95% yield by a Bischler–Napieralski cyclization. Imine **7** then underwent an asymmetric hydrogen-transfer reaction under the classical Noyori conditions.[13]

Unexpectedly, the enantioselective reduction of imine **7** posed a considerable challenge. In contrast to our previous experiences in the ATH reduction of cyclic imines, which gave excellent yields and high enantiomeric excesses of derivatives of tetrahydroisoquinoline and tetrahydro-β-carboline,[11,14] the reduction of compound **7** proceeded with difficulty. Initially, we attempted to use a combination of *N*-tosyl-(1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (TsDPEN)[15] and bis(η^6-benzene)tetrachlorodirhodium, which formed catalyst (*S*,*S*)-**12** in situ (Figure 2). This catalyst was then used at a substrate-to-catalyst ratio of 51 in the presence of a formic acid/triethylamine azeotrope. The desired amine was obtained in only 31% yield and with moderate enantioselectivity (38% ee). When dichloromethane was used as the solvent, the chemical yield increased to 51%, but the stereoselectivity fell to 27% ee.

These unsatisfactory results prompted us to examine another popular (and usually effective) catalyst **13**, which is

SYNTHESIS 2012, 44, 241–246
Advanced online publication: 14.12.2011
DOI: 10.1055/s-0031-1289646; Art ID: T86711SS



Scheme 1 Stereoselective synthesis of stereoisomeric aptazepines **2**

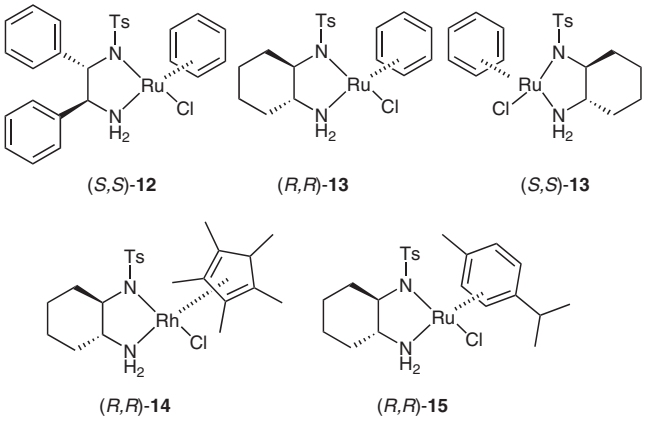


Figure 2 Chiral catalysts for ATH

based on *N*-tosylcyclohexane-1,2-diamine. In this case, we obtained product **8** with superior asymmetric induction (63% ee) and higher chemical yield (60%). A solvent effect similar to that obtained with TsDPEN was observed (Table 1). In a parallel experiment, when *N*-tosyl-(1*R*,2*R*)-cyclohexanediamine and tetrachlorobis(η^5-pentamethylcyclopentadiene)dirhodium was used to prepare catalyst (1*R*,2*R*)-**14**, we obtained product **8** in racemic form in 7% yield, and when we used the complex with tetrachlorobis(η^6-*p*-cymene)dirhodium [(1*R*,2*R*)-**15**], we obtained only traces of the racemic product **8**. In every case, unreacted imine **7** could be recovered from the reaction mixture and reused as a substrate in a repeated ATH procedure; Table 1 therefore also lists yields of amine **8** based on the consumed substrate.

These experiments showed that the enantioselectivity strongly depends on the structure of the catalyst that is used. The sterically demanding complexes **14** and **15** cannot effectively reduce the C=N bond, probably because of the steric density of the substituents in the complexes and in the region of the substrate molecule surrounding the C=N bond. Furthermore, the structure of the reduced sub-

Table 1 Optimization of the catalyst for the ATH Reaction of Imine **7**

Catalyst	S/C[a]	Solvent	Time (h)	Yield[b] (%) of **8**	Yield based on consumed substrate (%)	ee (%)
(*S*,*S*)-**12**	51	MeCN	72	31	91	38
(*S*,*S*)-**12**	54	CH_2Cl_2	96	51	89	27
(*R*,*R*)-**13**	27	MeCN	96	60	90	63 (*R*)
(*S*,*S*)-**13**	27	MeCN	96	58	86	61 (*S*)
(*R*,*R*)-**13**	26	CH_2Cl_2	96	55	87	38 (*R*)
(*R*,*R*)-**14**	37	MeCN	72	7	–	–
(*R*,*R*)-**15**	19	MeCN	72	1	–	–

[a] Substrate-to-catalyst ratio.
[b] Isolated yield.

strate also affects the ease of the reaction. The prochiral C=N double bond in imine **7** appears to be less accessible to the reaction sphere of the ruthenium complex (Figure 2).

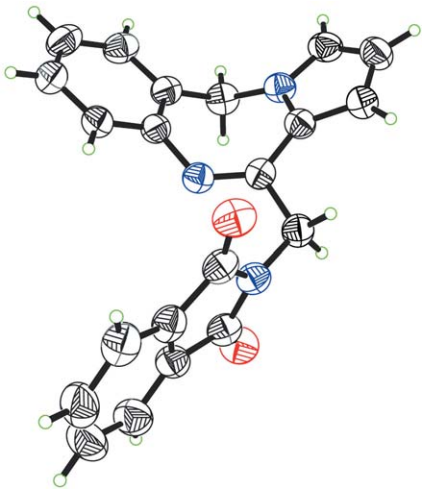


Figure 3 ORTEP diagram from X-ray analysis of compound **7**

Although amine **8** was initially formed with only moderate enantiomeric enrichment (63% ee), it was effectively transformed into the enantiopure form upon one recrystallization from chloroform–diethyl ether–methanol mixture. This process afforded a optically pure enantiomers of $[\alpha]_D^{23}$ +42.3 and $[\alpha]_D^{23}$ –41.9. The values remained unchanged upon repeated crystallizations. The optical purity of these samples was further confirmed by means of HPLC using a column with a chiral stationary phase (Daicel OD-H).

The absolute configuration of amine **8** obtained by reduction of **7** using (*S*,*S*)-**13** as a catalyst was determined by means of X-ray analysis to be that of (*S*)-**8** (Figure 4).

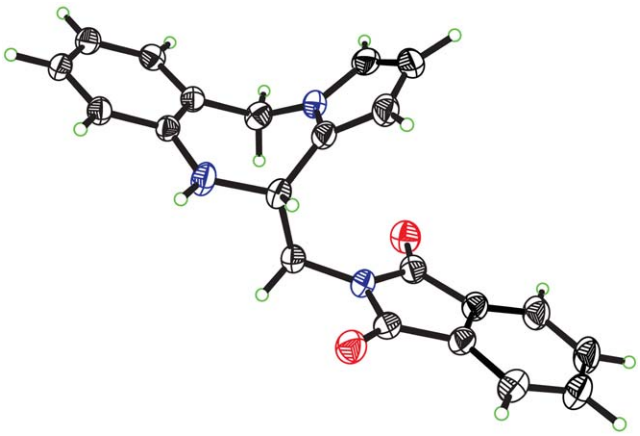


Figure 4 The ORTEP diagram for X-ray analysis of compound (*S*)-**8**

Subsequent treatment of amine **8** with ethyl chloro(oxo)acetate in refluxing chloroform in the presence of triethylamine gave the amide **9** in quantitative yield. Treatment of amide **9** with hydrazine in refluxing ethanol gave the dioxopiperazine derivative **10** in 90% yield without the isolation of an intermediate with a free amino group. Reduction of carbonyl groups in diamide **10** by using a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran gave intermediate **11** in 88% yield. Finally, methylation of intermediate **11** with methyl iodide gave enantiopure (*R*)-(+)- or (*S*)-(–)-aptazepine **2** (as confirmed by HPLC) in 73% yield.

In summary, we developed the first enantioselective preparation of (*R*)-(+)- and (*S*)-(–)-aptazepine, starting from easily available 2-nitrobenzylamine hydrochloride, 2,5-dimethoxytetrahydrofuran, and phthaloyl glycine. Chirality was induced in a key step through asymmetric transfer hydrogenation.

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm) relative to TMS. Mass spectra were recorded on Quatro LC Micromass and LCT Micromass TOF HiRes instruments. Optical rotations were measured on a Perkin-Elmer 247 MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized by UV irradiation or exposure to I_2 vapor. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck) with $CHCl_3$ or $CHCl_3$–MeOH as the eluent. Melting points were determined on a Boetius hot-plate microscope and are uncorrected. All solvents used in the reactions were anhydrous.

1-(2-Nitrobenzyl)-1*H*-pyrrole (4)

A stirred suspension of (2-nitrobenzyl)amine hydrochloride (**3**; 3.0 g, 15.90 mmol) in toluene (90 mL) was mixed with 2% aq HCl (15 mL) to adjust the pH to 2–3. A first portion of 2,5-dimethoxytetrahydrofuran (1.98 mL, 15.28 mmol) was added and the pH of the reaction mixture was adjusted to 1 with concd HCl (0.6 mL). After 1 h, a second portion of 2,5-dimethoxytetrahydrofuran (1.73 mL, 13.35 mmol) was added and, after 48 h, the mixture was basified with 10% aq NaOH (15 mL). The layers were separated and the aqueous layer was extracted with toluene (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by a column chromatography (silica gel, $CHCl_3$) to give an olive-colored solid; yield: 2.64 g (82%); mp 39–40 °C (Lit.[4] 38–40 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (s, 2 H, CH_2), 6.25 (t, *J* = 2.0 Hz, 2 H, pyrrole), 6.59–6.61 (m, 1 H, Ar), 6.70 (t, *J* = 2.0 Hz, 2 H, pyrrole), 7.41–7.44 (m, 1 H, Ar), 7.50–7.54 (m, 1 H, Ar), 8.09–8.11 (m, 1 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.6, 109.3, 121.7, 124.9, 128.3, 128.4, 134.2, 135.2, 146.8.

LRMS (ESI): *m/z* = 225.1 $[M + Na]^+$.

1-(2-Aminobenzyl)-1*H*-pyrrole (5)

H_2O (5 mL), K_2CO_3 (1.97 g, 14.24 mmol) and 5% Pd/charcoal (67 mg) were added to a stirred soln of nitro compound **4** (4.0 g, 19.78 mmol) in THF (4 mL). The mixture was heated to 60 °C and a soln of NaH_2PO_2 (7.97 g, 75.16 mmol) in H_2O (15 mL) was added dropwise over 1 h. When the addition was complete, the mixture was refluxed for a further 3.5 h, cooled to r.t., and neutralized with solid $KHCO_3$. Toluene (100 mL) was added, the layers were separated, and the aqueous layer was extracted with toluene (50 mL). The combined organic layers were dried ($MgSO_4$) and the resulting soln of amino compound **5** was used in the next step without further pu-

rification. TLC analysis confirmed the complete conversion of the nitro derivative **4** into amino compound **5**.

LRMS (ESI): *m/z* = 195.1 $[M + Na]^+$.

2-(*N*-Phthalimido)-*N*-[2-(1*H*-pyrrol-1-ylmethyl)phenyl]acetamide (6)

A soln of $PhthNCH_2COCl$ (4.86 g, 21.76 mmol) in toluene (25 mL) was added during 20 min to a stirred soln of amino compound **5** (3.40 g, 19.78 mmol) and Et_3N (9.10 mL, 65.28 mmol) in toluene (150 mL). The mixture was stirred at r.t. for 20 min, and then toluene was evaporated. $CHCl_3$ (250 mL) and 5% aq NaOH (50 mL) were added successively, the phases were separated, and the H_2O layer was extracted with $CHCl_3$ (2 × 70 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by crystallization from $CHCl_3$–Et_2O to give a beige solid; yield: 6.40 g (90%); mp 218–220 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.35 (s, 2 H), 5.07 (s, 2 H), 6.05 (s, 2 H, pyrrole), 6.62 (s, 2 H, pyrrole, 6.99 (s, 1 H, CO-NH), 7.15–7.19 (m, 2 H, Ar), 7.32–7.34 (m, 1 H, Ar), 7.68–7.70 (m, 1 H, Ar), 7.76–7.78 (m, 2 H, Phth), 7.88–7.90 (m, 2 H, Phth).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3, 51.1, 109.4, 120.8, 123.7, 125.0, 126.2, 129.1, 129.4, 129.7, 132.0, 134.4, 135.3, 164.7, 167.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{17}N_3O_3Na$: 382.1168; found: 382.1169.

11-(*N*-Phthalimidomethyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (7)

A soln of amide **6** (4.0 g, 11.13 mmol) and $POCl_3$ (10.37 mL, 11.13 mmol) in anhyd toluene (100 mL) was heated at reflux using a Dean–Stark apparatus for 4 h. The solvent was then evaporated and $CHCl_3$ (200 mL) and 12% aq NH_3 (40 mL) were added to the residue. The aqueous layer was extracted with several portions of $CHCl_3$ (100 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, $CHCl_3$) to give colorless crystals; yield: 3.6 g (95%); mp 178–180 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.90 (s, 2 H), 4.97 (s, 2 H), 6.21 (dd, J_1 = 2.5 Hz, J_2 = 4 Hz, 1 H, pyrrole), 6.68 (dd, J_1 = 2.0 Hz, J_2 = 4.0 Hz, 1 H, pyrrole), 6.82 (dd, J_1 = 2.0 Hz, J_2 = 2.5 Hz, 1 H, pyrrole), 7.01–7.03 (m, 1 H, Ar), 7.10–7.16 (m, 2 H, Ar), 7.18–7.22 (m, 1 H, Ar), 7.72–7.76 (m, 2 H, Phth), 7.88–7.92 (m, 2 H, Phth).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.9, 51.6, 109.2, 112.0, 123.4, 124.1, 126.2, 127.4, 127.6, 128.0, 128.6, 128.6, 132.4, 133.9, 146.8, 153.4, 168.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{15}N_3O_2Na$: 364.1062; found: 364.1060.

(11*R*)-11-(*N*-Phthalimidomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine [(*R*)-8]; Typical Procedure

The catalyst (*R*,*R*)-**13** was prepared from $[Ru_2Cl_4(\eta^6\text{-benzene})_2]$ (20 mg, 78 μmol), *N*-tosyl-(1*R*,2*R*)-cyclohexane-1,2-diamine (30.0 mg, 117 μmol), and Et_3N (100 μmol) in MeCN (4 mL). A 5:2 mixture of HCO_2H and Et_3N mixture (2.5 mL) and the catalyst soln were added successively to a soln of imine **7** (3.0 g, 8.79 mmol) in MeCN (60 mL). The mixture was then stirred at r.t. for 96 h and, after 24, 48, and 72 h, additional portions of the catalyst and azeotrope were added. The solvents were then evaporated and the residue was dissolved in CH_2Cl_2 (100 mL) and basified with aq K_2CO_3. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by column chromatography (silica gel, $CHCl_3$) to give a colorless solid; yield: 1.83 g (60%); $[\alpha]_D^{23}$ +26.8 (*c* 1; $CHCl_3$). Recrystallization from $CHCl_3$–Et_2O–MeOH (1:1:0.5) gave the pure enantiomer; yield: 670 mg; mp 224–225 °C, $[\alpha]_D^{23}$ +42.2 (*c* 1, $CHCl_3$). The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane–*i*-PrOH (70:30), 1 mL/min]; the *R*-isomer eluted at 18.3 min.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.17 (dd, J_1 = 9.5 Hz, J_2 = 14.0 Hz, 1 H), 4.36 (dd, J_1 = 5.0 Hz, J_2 = 14.0 Hz, 1 H), 4.54–4.56 (m, 1 H, NH), 4.89 (d, *J* = 15.5 Hz, 1 H, methylene bridge), 5.109–5.13 (m, 1 H, methine), 5.46 (d, *J* = 15.5 Hz, 1 H, methylene bridge), 6.02–6.03 (m, 2 H, pyrrole), 6.51–6.53 (m, 1 H, Ar), 6.61–6.64 (m, 1 H, Ar), 6.68–6.67 (m, 1 H, pyrrole), 6.97–7.01 (m, 2 H, Ar), 7.72–7.76 (m, 2 H, Phth), 7.85–7.89 (m, 2 H, Phth).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 50.7, 51.6, 104.6, 106.3, 118.3, 118.5, 120.8, 121.1, 123.5, 128.8, 129.5, 130.7, 131.8, 134.3, 145.5, 168.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}N_3O_2$: 344.1399; found: 344.1397.

(11*S*)-11-(*N*-Phthalimidomethyl)-10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine [(11*S*)-8]

The corresponding reaction using the (*S*,*S*)-**13** catalyst formed from $[Ru_2Cl_4(\eta^6\text{-benzene})_2]$ and *N*-tosyl-(1*S*,2*S*)-cyclohexane-1,2-diamine gave *S*-enantiomer of (*S*)-**8** as colorless crystals; $[\alpha]_D^{23}$ –25,8. Recrystallization from $CHCl_3$–Et_2O–MeOH (1:1:0.5) gave the pure enantiomer; mp 223–224 °C; $[\alpha]_D^{23}$ –41.8 (*c* 1, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis [Chiracel OD-H, hexane–*i*-PrOH (70:30), 1 mL/min]; the *S*-isomer eluted at 29.6 min.

X-ray Crystallography of Compounds 7 and (*S*)-8

The single-crystal X-ray measurements for compounds **7** and (*S*)-**8** were performed on an Oxford Diffraction Excalibur R CCD κ-axis diffractometer using monochromatic CuKα radiation. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine structures by using the SHELXS97 and SHELXSL97 programs.[16]

Single crystals of **7** suitable for crystallographic measurements were obtained by slow evaporation of $CHCl_3$–Et_2O solns. Although compound **7** is achiral, it crystallizes in a chiral space group $P2_12_12_1$. As a result, the asymmetric part of the unit cell contains two independent molecules with slightly different geometries. The conformation of one of these is shown in Figure 3; that of the second molecule is an approximate mirror image of this.

Single crystals of (*S*)-**8** suitable for crystallographic measurements were obtained by slow evaporation of a $CHCl_3$–Et_2O soln. The absolute structure of the crystal, and hence the absolute configuration of the compound was determined from the value of the Flack parameter.[17] Because the value of this parameter for the structure shown in Figure 4 was close to zero, the molecular structure has the configuration shown.

Crystallographic data for compounds **7** and (*S*)-**8** have been deposited with the accession numbers CCDC 837569 and CCDC 827019, respectively, and they can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

Ethyl [(11*R*)-11-(*N*-Phthalimidomethyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-yl](oxo)acetate [(11*R*)-9]; Typical Procedure

A soln of EtO_2CCOCl (0.27 mL, 2.45 mmol) in $CHCl_3$ (5 mL) was added over 8 min to a stirred soln of (*R*)-(+)-**8** (0.70 g, 2.94 mmol) and Et_3N (0.57 mL, 4.08 mmol) in anhyd $CHCl_3$ (20 mL) at 50 °C. After 30 min, the mixture was cooled to r.t., H_2O (15 mL) was add-

ed, and the mixture was basified with solid Na_2CO_3. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (50 mL). The combined organic layers was washed successively with 2% aq HCl (15 mL) and distilled H_2O (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by column chromatography (silica gel, $CHCl_3$) to give colorless crystals; yield: 0.90 g (quant); mp 171–172 °C; $[\alpha]_D^{23}$ –199 (*c* 1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.89 (q, *J* = 7.0 Hz, 2 H), 4.03–4.05 (m, 2 H), 4.65 (d, *J* = 13.5 Hz, 1 H, methylene bridge), 5.42 (d, *J* = 13.5 Hz, 1 H, methylene bridge), 6.08–6.10 (m, 1 H, methine), 6.27–6.28 (m, 1 H, pyrrole), 6.52–6.54 (m, 1 H, pyrrole), 6.66–6.67 (m, 1 H, pyrrole), 7.36–7.38 (m, 2 H, Ar), 7.41–7.45 (m, 1 H, Ar), 7.73–7.76 (m, 2 H, Phth), 7.82–7.84 (m, 1 H, Ar), 7.90–7.93 (m, 2 H, Phth).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 41.4, 50.6, 52.3, 61.7, 107.6, 110.1, 122.5, 123.4, 124.7, 128.2, 129.4, 129.8, 130.8, 132.1, 134.1, 135.9, 138.1, 161.6, 162.5, 168.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{21}N_3O_5Na$: 466.1379; found: 466.1397.

Ethyl [(11*S*)-11-(*N*-Phthalimidomethyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-10(11*H*)-yl](oxo)acetate [(11S*R*)-9] (9)

The enantiomer (*S*)-**9** was similarly prepared as colorless crystals; $[\alpha]_D^{23}$ +204 (*c* 1, $CHCl_3$); mp 171–172 °C.

(14b*R*)-1,14b-Dihydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-3,4-dione [(*R*)-10]; Typical Procedure

A mixture of ester **9** (0.5 g, 1.13 mmol) and N_2H_4 (0.21 mL, 6.77 mmol) in 99.8% EtOH (15 mL) was refluxed for 2 h. After evaporation of volatile components, the residue was purified by column chromatography (silica gel, 0–1.5% MeOH–$CHCl_3$) to give a light-beige solid: yield: 274 mg (90%); mp 320 °C (dec); $[\alpha]_D^{23}$ +152.8 [*c* 0.25, CH_2Cl_2–MeOH (3:1)].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (dt, J_1 = 3.5 Hz, J_2 = 13.5 Hz, 1 H), 3.87–3.92 (m, 1 H), 5.02 (d, *J* = 14.5 Hz, 1 H, methylene bridge), 5.21 (d, *J* = 14.5 Hz, 1 H, methylene bridge), 5.31–5.33 (m, 1 H, methine), 5.89 (dd, J_1 = 2.5 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 6.05 (dd, J_1 = 2.0 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 6.85 (dd, J_1 = 2.0 Hz, J_2 = 2.5 Hz, 1 H, pyrrole), 7.26–7.29 (m, 1 H, Ar), 7.35–7.40 (m, 2 H, Ar), 7.44–7.60 (m, 1 H, Ar), 8.87 (s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.8, 49.1, 55.9, 106.8, 108.7, 123.3, 126.4, 127.5, 128.3, 128.5, 128.8, 134.9, 138.9, 157.1, 157.6.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}N_3O_2Na$: 290.0905; found: 290.0908.

(14b*S*)-1,14b-Dihydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-3,4-dione [(*S*)-10]

The enantiomer (*S*)-**10** was similarly prepared as a light-beige solid; mp 320 °C (dec); $[\alpha]_D^{23}$ –152 [*c* 0.25, CH_2Cl_2–MeOH (3:1)].

(14b*R*)-1,3,4,14b-Tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine [(*R*)-11]; Typical Procedure

A 1.0 M soln of $LiAlH_4$ in THF (1.0 mL) was added to a stirred suspension of dione **10** (50 mg, 0.19 mmol) in anhyd Et_2O (5 mL) and the mixture was refluxed for 1 h then cooled to r.t. Et_2O (50 mL) and H_2O (0.3 mL) were added, the precipitate was filtered off, and the organic layer was dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography (alumina, 0–2% MeOH–$CHCl_3$) to give a solidifying oil; 40 mg (88%); $[\alpha]_D^{23}$ +313 (*c* 0.5, $CHCl_3$). The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane–*i*-PrOH–Et_2N (88:12:0.1), 1 mL/min]; the *R*-isomer eluted at 16.9 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.83 (s, 1 H, NH), 2.97–3.12 (m, 4 H), 3.21–3.27 (m, 2 H), 4.10 (dd, J_1 = 5.5 Hz, J_2 = 9.5 Hz, 1 H, methine), 4.51 (d, *J* = 13.0 Hz, 1 H, methylene bridge), 5.51 (d, *J* = 13.0 Hz, 1 H, methylene bridge), 5.89 (dd, J_1 = 2.0 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 5.97 (dd, J_1 = 2.5 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 6.57 (dd, J_1 = 2.0 Hz, J_2 = 2.5 Hz, 1 H, pyrrole), 6.88–6.92 (m, 1 H, Ar), 7.04–7.06 (m, 1 H, Ar), 7.13–7.16 (m, 1 H, Ar), 7.23–7.27 (m, 1 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.6, 50.8, 52.9, 56.2, 63.7, 107.1, 108.1, 119.7, 120.4, 122.4, 127.3, 129.3, 129.8, 134.6, 150.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}N_3$: 240.1501; found: 240.1521.

(14b*S*)-1,3,4,14b-Tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine [(*S*)-11]

The enantiomer (*S*)-**11** was similarly prepared as a solidifying oil; $[\alpha]_D^{23}$ –318 (*c* 0.5, $CHCl_3$). The enantiomeric purity was determined by HPLC [Chiracel OD-H, hexane–*i*-PrOH–Et_2N (88:12:0.1), 1 mL/min]; the *S*-isomer eluted at 15.5 min.

(14b*R*)-2-Methyl-1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine [(*R*)-2; (+)-Aptazepine]; Typical Procedure

Solid K_2CO_3 (29 mg, 0.21 mmol) and a soln of MeI (13.0 L, 0.21 mmol) in $CHCl_3$ (0.2 mL) were added successively to a stirred soln of tetracycle **11** (50 mg, 0.21 mmol) in anhyd $CHCl_3$ (5 mL). The suspension was refluxed for 2 h, cooled to r.t., and $CHCl_3$ (20 mL) and H_2O (10 mL) were added. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a brown oil that was purified by column chromatography (alumina, 0–1% MeOH–$CHCl_3$) to give a solidifying oil; yield: 39 mg (73%); $[\alpha]_D^{23}$ +462 (*c* 0.5, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis [Chiracel OD-H, hexane–*i*-PrOH–Et_2N (90:10:0.1), 1 mL/min]; the *R*-isomer eluted at 11.9 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27–2.32 (m, 1 H), 2.35 (s, 3 H, N-CH_3), 2.38–2.42 (m, 1 H), 2.92–2.96 (m, 2 H), 3.26 (dt, J_1 = 2.5 Hz, J_2 = 11.5 Hz, 1 H), 3.36–3.41 (m, 1 H), 4.25 (dd, J_1 = 2.5 Hz, J_2 = 10.5 Hz, 1 H, methine), 4.51 (d, *J* = 13.0 Hz, 1 H, methylene bridge), 5.48 (d, *J* = 13.0 Hz, 1 H, methylene bridge), 5.91 (dd, J_1 = 2.0 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 5.97 (dd, J_1 = 2.5 Hz, J_2 = 3.5 Hz, 1 H, pyrrole), 6.57 (dd, J_1 = 2.0 Hz, J_2 = 2.5 Hz, 1 H, pyrrole), 6.89–6.92 (m, 1 H, Ar), 7.06–7.08 (m, 1 H, Ar), 7.13–7.15 (m, 1 H, Ar), 7.23–7.27 (m, 1 H, Ar).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.9, 50.8, 51.3, 55.5, 61.8, 65.1, 107.1, 108.2, 119.8, 120.4, 122.5, 127.3, 129.3, 129.7, 134.5, 150.2.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{19}N_3Na$: 276.1477; found: 276.1469.

(14b*R*)-2-Methyl-1,3,4,14b-tetrahydro-2*H*,10*H*-pyrazino[1,2-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine [(*S*)-2; (–)-Aptazepine]

The enantiomer (*S*)-**2** was similarly prepared as a solidifying oil; $[\alpha]_D^{23}$ –448 (*c* 0.5, $CHCl_3$).

The enantiomeric purity was determined by HPLC analysis [Chiracel OD-H, hexane–*i*-PrOH–Et_2N (90:10:0.1), 1 mL/min]; the *S*-isomer eluted at 8.5 min.

Acknowledgment

We acknowledge financial support from the Polish Ministry of Science and Higher Education in the form of grant N N204 2117939.

References

(1) Hirschfeld, R. M.; Keller, M. B.; Panico, S.; Arons, B. S.; Barlow, D.; Davidoff, F.; Endicott, J.; Froom, J.; Goldstein, M.; Gorman, J. M.; Marek, R. G.; Maurer, T. A.; Meyer, R.;

Phillips, K.; Ross, J.; Schwenk, T. L.; Sharfstein, S. S.; Thase, M. E.; Wyatt, R. J. *JAMA, J. Am. Med. Assoc.* **1997**, *277*, 333.
(2) Tatsumi, M.; Groshan, K.; Blakely, R. D.; Richelson, E. *Eur. J. Pharmacol.* **1997**, *340*, 249.
(3) Gower, A. J.; Broekkamp, C. L.; Rijk, H. W.; Van Delft, A. M. *Arch. Int. Pharmacodyn. Ther.* **1988**, *291*, 185.
(4) Ong-Lee, A.; Sylvester, L.; Wasley, J. W. F. *J. Heterocycl. Chem.* **1983**, *20*, 1565.
(5) Boyer, S. K.; Fitchett, G.; Wasley, J. W. F.; Zaunius, G. *J. Heterocycl. Chem.* **1984**, *21*, 833.
(6) Massa, S.; Mai, A.; Artico, M. *Tetrahedron* **1989**, *45*, 2763.
(7) Massa, S.; Artico, M.; Mai, A.; Corelli, F.; Botta, M.; Tafi, A.; Pantaleoni, G. K.; Giorgi, R.; Coppolino, M. F.; Cagnotto, A.; Skorupska, M. *J. Med. Chem.* **1992**, *35*, 4533.
(8) Pawłowska, J.; Czarnocki, Z.; Wojtasiewicz, K.; Maurin, J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 3335.
(9) Cirilli, R.; Orlando, V.; Ferretti, R.; Turchetto, L.; Silvestri, R.; De Martino, G.; La Torre, G. *Chirality* **2006**, *18*, 621.
(10) Roszkowski, P.; Czarnocki, Z. *Mini-Rev. Org. Chem.* **2007**, *4*, 190.
(11) Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2007**, *18*, 406.
(12) Czarnocki, S. J.; Wojtasiewicz, K.; Jóźwiak, A. P.; Maurin, J. K.; Czarnocki, Z.; Drabowicz, J. *Tetrahedron* **2008**, *64*, 3176.
(13) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.
(14) Roszkowski, P.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Lis, T.; Czarnocki, Z. *J. Mol. Catal. A: Chem.* **2005**, *232*, 143.
(15) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem.* **2000**, 2247.
(16) Sheldrick, G. M. *SHELX97 [Includes SHELXS97, SHELXL97 and CIFTAB]: Programs for Crystal Structure Analysis (Release 97-2)*; Institüt für Anorganische Chemie der Universität Göttingen: Germany, **1998**.
(17) Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876.

