SYNTHESES OF RACEMIC AND ENANTIOMERIC (S)-(+)-4,5,6,7-TETRAHYDRO-5-METHYL-IMIDAZO[4,5,1-*jk*][1,4]BENZODI-AZEPIN-2(1*H*)-ONE DERIVATIVES

Hans Rudolf Pfaendler * and Frank Weisner

Institute of Organic Chemistry, University of Munich,
Karlstrasse 23 D-80333 Munich, Germany

Abstract - Racemic and enantiomeric (S)-(+)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one derivatives were prepared using free amino acids and 3-nitroisatoic anhydride. Simultaneous reduction of two amide functions was efficiently achieved using diborane.

Introduction

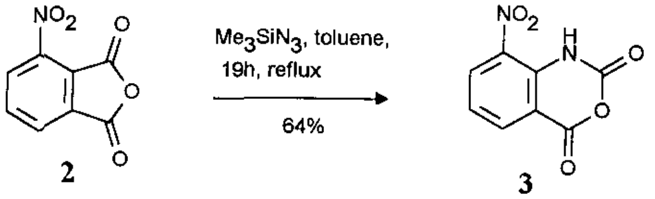
AIDS (acquired immune deficiency syndrome) has become the most threatening infectious disease within ten years of its existence.[1] Although other or additional causes for the development of AIDS have also been suggested,[2] the current theory is that HIV (human immunodeficiency virus)[3] plays a leading role in the etiology of the fatal epidemic. So far, only two broad spectrum antivirals, AZT (3'-azido- 2',3'-dideoxythymidine) and DDI (2',3'-dideoxyinosine) have been fully approved for therapeutic intervention, both with very limited success.

Recently, it was discovered by the Janssen group[4] that TIBO (4,5,6,7-tetrahydro-5-methylimidazo-[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one) derivatives were very active against HIV-1 (a major strain of HIV found in North American and European AIDS patients) in vitro. Similar to the chain terminators AZT or DDI, they interact with reverse transcriptase, essential for the replication of HIV. Certain of the effective derivatives, e. g. **R 82150**, were considerably less cytotoxic than AZT or DDI.[4]

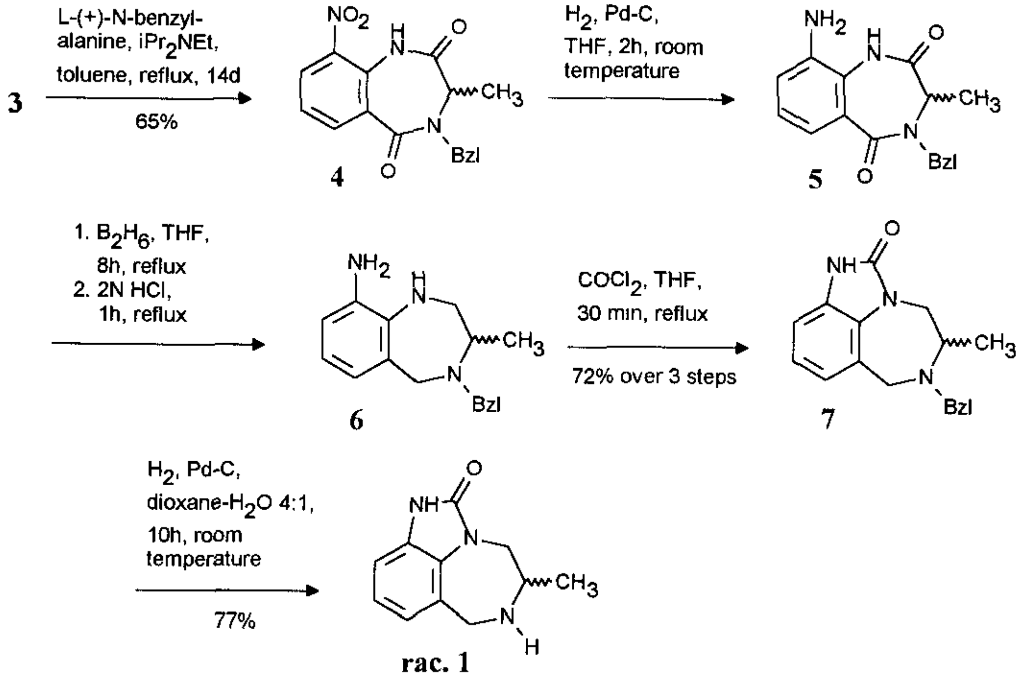
As the chemical synthesis of TIBO derivatives involved up to eleven reaction steps and was difficult to be carried out,[4] we attempted also to prepare these compounds. Very recently, the Janssen synthesis was published,[5] being related to the one reported here.

Results and Discussion

Unlike in the reported[4,5] preparations, we started our synthesis from 3-nitrophthalic anhydride (**2**), a commercially available and inexpensive starting material, which was transformed by trimethylsilyl azide to 3-nitroisatoic anhydride in a single reaction step.[6] Surprisingly, this reaction gave a single (and desired) regioisomer (**3**) after a single crystallization in 64 % yield.[7] The structure of **3** was confirmed by X-ray analysis[8] of a single crystal.



Benzodiazepinediones of type (**8**) have been obtained in moderate yield from isatoic anhydrides and esters of amino acids.[9] Improved yields were reported in the presence of pyridine.[10] In our hands, using the free amino acids, the seven-membered diazepinedione ring was difficult to construct and initial attempts failed to produce the target compound (**8**) by heating L-alanine and **3** in a solvent, with or without base. Interestingly, the analogous model reaction with sarcosine (*N*-methylglycine), instead of alanine, proceeded well in the presence of 2 equivalents of diisopropylethylamine in refluxing toluene for 3 days and afforded the expected bicyclic product in 61 % yield after recrystallization from hot butyl acetate.



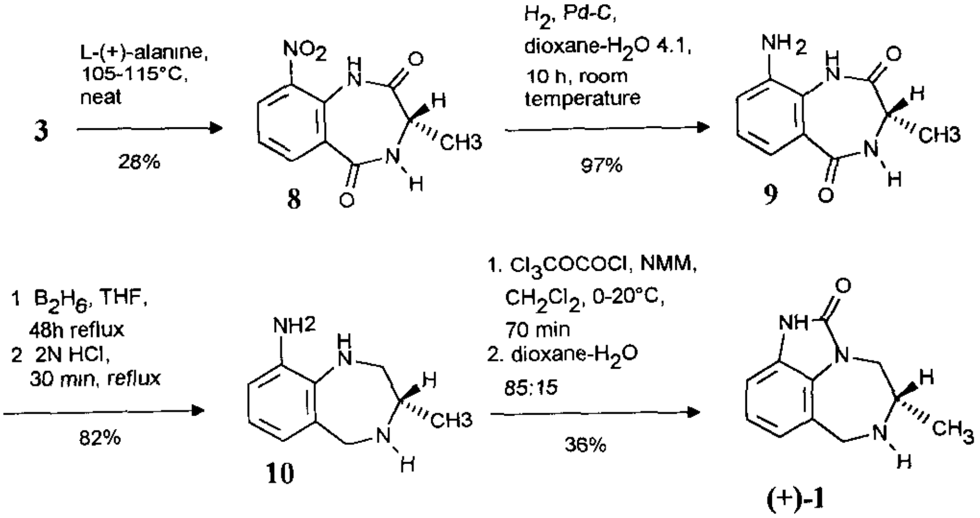
We thought that the improved solubility of the *N*-substituted amino acid was essential in the aforementioned cyclization reaction leading to diazepinediones and, consequently, we chose L-*N*-benzylalanine to achieve step **3** → **4**. It was planned to remove the benzyl protection group at the final stage of the reaction sequence by catalytic hydrogenation.

In our hands diborane was an excellent reducing agent[11] for both amide functions of **5**. The resulting air-sensitive triamine (**6**) was subsequently carbonylated with phosgene to afford stable and crystalline (**7**). Finally, the benzyl protection group was removed by catalytic hydrogenation, to give **1**.

Surprisingly, it was found that the target product (**1**), prepared in this way, was racemic and that racemization had occured in reaction step **3** → **4** Substitution of diisopropylethylamine by *N*-methylmorpholine (a weaker base) led to optically active ($[\alpha]_D$ +50 to +70°, c = 3, $CHCl_3$), but not enantiomerically pure **4**.[12]

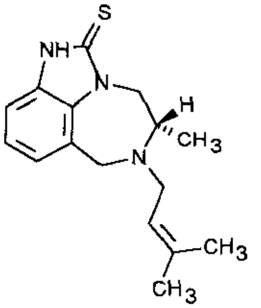
Compound	Reaction time	$[\alpha]_D^{rt}$ (c = 1; THF)	Chemical yields
4	7d	645°	28%
4	14d	561°	31%
4	22d	485°	33%

Table 1: Enantiomeric purity of diazepinediones (4), depending on reaction time of the neat process 3 → 4. Yield and optical rotations refer to chromatographed material (4) after a single crystallization.



Our experience in the synthesis of *N*-benzylated diazepinediones revealed that the use of tertiary amine bases was accompanied by substantial racemization. Therefore, attempts were made to carry out the cyclization reaction **3** → **8** under neutral conditions. Satisfactory results were obtained only by melting together **3** and the amino acid. Using this technique, even L-alanine was converted to **8** in 28 % yield without essential racemization (see Table 1).

Again, diborane reduction **9** → **10** was very successful. The carbonylation of **10**, using diphosgene, has been reported[5] to proceed in 71 % yield (of crude product (+)-**1**). The 4-unsubstituted benzodiazepinedione (**1**) is known[5] to be biologically inactive. However, the conversion of **1** into potent antiviral compounds, such as **R 82150**, involving *N*-alkylation and sulfuration, has already been realized.[14]



R 82150

During our work on the synthesis of TIBO derivatives, it became known that, in spite of their excellent in vitro activity against HIV-1 and their favourable pharmakokinetics, they were not effective in AIDS therapy.[15]

Several investigators[16] have failed to correlate the onset of immune dysfunction with HIV infection, supporting the speculation[17] that HIV may itself be opportunistic. Very recently, progressive acquired immune suppression with no infection by HIV has also become known.[18] Therefore, it seems that further evaluation of TIBO derivatives as therapeutic or prophylactic agents must wait, until the role of HIV in the progression of AIDS is clearly understood or until an other primary immunosuppressive factor is identified without doubt.

We wish to thank Dr. Kurt Polborn for his X-Ray structure determination. This work was supported by Studienstiftung des Deutschen Volkes and Fonds der Chemischen Industrie.

EXPERIMENTAL

Reagents and solvents were of commercial quality from freshly opened containers and were purchased from Fluka Chemical Co..THF was refluxed under N_2 with $LiAlH_4$ and distilled immediately before use. CH_2Cl_2 was refluxed under N_2 with P_2O_5 and distilled immediately before use. Toluene was dried with sodium. The solution of borane in THF we received from the team of Prof. Dr. H. Nöth. *L-N-Benzylalanine* was prepared as described in the original literature.[19] Analytical silica gel tlc plates and silica gel were purchased from E. Merck. The progress of all reactions was monitored by tlc. Melting points were taken on a Büchi 535 apparatus and are uncorrected. Microanalyses were obtained using a Heraeus CHN Standard microanalyzer, ir spectra were obtained using a Perkin-Elmer 1420 ir-spectrophotometer, optical rotations on a Zeiss 0.005° polarimeter at room temperature and nmr spectra using a Varian VXR 400 S (400 MHz) spectrometer.

3-Nitroisatoic anhydride (3).

In a dried 250 ml flask, fitted with reflux condenser, magnetic stirrer and bubbler, containing 3-nitrophthalic anhydride (**2**) (19.31 g, 0.1 mol) in dry toluene (100 ml), trimethylsilyl azide (13.16 ml, 0.1 mol) was added with a syringe at room temperature. The mixture was heated under reflux for 19 h. Then it was cooled to 0°C With stirring, moist ether (120 ml) was added, where upon a pale yellow solid precipitated. The mixture was allowed to stir for additional 30 min at 0°C. It was then filtered and the collected solid washed with cold ether. Drying in an dessicator in vacuo over "Siccapent" (Merck), afforded crude product (**3**) (16.08 g). This was recrystallized from n-butyl acetate (209 ml) to yield pure **3** (13.39 g, 65%), as small yellow needles, mp 170.2-171.8°C; tlc: R_f 0.45 (toluene/EtOAc/AcOH 8:1:1, uv active, I_2 staining). ^{1}HNmr ($CDCl_3$/TMS): $\delta = 7.45$ (t, ^3J = 8.4 Hz, ^3J = 7.8 Hz, 1H), 8.51 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H), 8.67 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 1H), 10.47 (br s, 1H). Ir (CH_2Cl_2): ν = 3345, 3050, 2990, 1807, 1750, 1760, 1623, 1597, 1494, 1540, 1350, 1315, 1048 cm^{-1}. X-Ray structure determination.[8] *Anal.* Calcd for $C_8H_4N_2O_5$: C, 46.17; H, 1.94; N, 13.46. Found: C, 46.36; H, 1.99; N, 13.32.

4-Benzyl-3-methyl-9-nitro-1*H*-[1,4]benzodiazepine-2,5-dione (4).

In a dry 1 l flask, fitted with a water adsorption apparatus, reflux condenser, magnetic stirrer and bubbler, a mixture of **3** (10.4 g, 50 mmol), L-(+)-benzylalanine (9.86 g, 55 mmol) and diisopropylethylamine (17.42 ml, 100 mmol) in dry toluene (400 ml) was heated under reflux for 14 d. After cooling to room temperature, the mixture was diluted with toluene (200 ml) and then filtered. The brick red solution was washed twice with aq. NaCl (10%, 100 ml) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the residue, a brown foam, was dried at 0.001 Torr, yielding crude **4** (14.0 g). It was chromatographed on silica gel (63-200 µm, 700 g) using toluene/THF 19:1 as eluent (27 fractions, 350 ml each) Fractions 11-22 were evaporated in vacuo, the yellow foamy residue dried at 0.001 Torr (11 76 g) It was recrystallized from hot n-butyl acetate (700 ml). Yield: 10.5 g (65%); mp 149.5-149.8 °C; tlc R_f 0 37 (toluene/ EtOAc/AcOH 8:1:1, uv active), 0.34 (toluene/THF 4:1). ^{1}HNmr (DMSO-d_6/TMS, rt): δ = 1.04 and 1.29 (d, ^3J = 6.8 Hz, 3H), 4.34 and 4.48 (q, ^3J = 6.8 Hz, 1H), 4.71 and 4.87 (d, ^2J = 16.0 Hz, 1H), 4.78 and 4.95 (d, ^2J = 16.0 Hz, 1H), 7.30 (m, 5H), 7.50 (t, ^3J = 8.0 Hz, 1H), 8.15 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H), 8.26 (dd, $^3J = 8.0$ Hz, $^4J = 1.5$ Hz, 1H), 10.12 and 10.24 (s, 1H). At room temperature the spectrum of **4** showed a double set of peaks with a ratio of approximately 85:15 for some protons, at 100 C only one set of peaks was observed. In the upper list, the values of the higher intensity are underlined. Ir (CH_2Cl_2): ν = 3350, 3050, 2990, 2940, 1715, 1645, 1605, 1475, 1535, 1340, 1190, 1020, 890, 825 cm^{-1}. *Anal.* Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.66; H, 4.80; N, 12.83.

4,5,6,7-Tetrahydro-6-benzyl-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (7):

In a hydrogenation apparatus, equipped with a magnetic stirrer and a silicon septum, a suspension of Pd on C (10%, 163 mg) in THF (3 ml) was prehydrogenated at room temperature. A solution of **4** (1.627 g, 5.0 mmol) in THF (16 ml) was added by a syringe and the mixture hydrogenated at room temperature until the reaction came to an end (2 h). The consumption was 360 ml (3 equiv.). After adding THF (10 ml), the mixture was filtered under N_2 through a glass filter (No.4) and the catalyst washed with chloroform. The solution was evaporated in vacuo and the residue, a pale yellow solid was dried at 0.001 Torr. Thus crude **5** (1.498 g, >100%) was obtained. It was used without further purification.

In a well-dried 100 ml two-necked flask, fitted with reflux condenser, N_2-balloon, magnetic stirrer and silicon septum, containing a solution of crude **5** (1.498 g, max. 5.0 mmol) in dry THF (40 ml), a solution of borane in THF (2.65 M, 28.3 ml, 75 mmol) was added with a syringe and the mixture heated to reflux for 8 h. The colourless solution was allowed to cool to room temperature, was given then carefully to aq. HCl (2N, 45 ml) by a pipette and the resulting mixture was heated under reflux for 1 h. THF (60 ml) was removed by destillation and the remaining aqueous solution transferred to a separatory funnel. Ethyl acetate (70 ml) and then aq. NaOH (2N, 55ml) were added. After strong shaking, the organic layer was separated and the aqueous layer reextracted with ethyl acetate (30 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. Drying of the resulting resin at 0.001 Torr yielded crude **6** (1.424 g, >100%), which was used without further purification.

In a dried 100 ml two-necked flask, equipped with a silicon septum, magnetic stirrer, reflux condenser and N_2-balloon, containing a solution of crude **6** (1.424 g, max. 5.0 mmol) in dry THF (40 ml), a solution of phosgene in toluene (1.93 M, 5.20 ml, 10 mmol) was added with a syringe. Immediately a white solid precipitated. The mixture was heated to reflux for 30 min., then cooled to room temperature, aq. K_2CO_3 (20%, 40 ml) was added and the resulting solution was transferred to a separatory funnel. Ethyl acetate (50 ml) was added, the organic layer separated and subsequently washed with aq. NaCl (10%, 20 ml). Drying ($MgSO_4$), filtration, evaporation in vacuo and drying of the residue at 0.001 Torr afforded crude **7** (1.41 g, 96%). Recrystallization from hot dry EtOH yielded pure **7** (1.059, 72%) as thin colourless needles.

7: tlc: R_f 0.34 (EtOAc, uv active), 0.17 (toluene/EtOAc 1:1); mp 203.1-206.7 C. ^{1}HNmr (DMSO-d_6/TMS): $\delta = 1.25$ (d, $^3J = 6.8$ Hz, 3H), 3.45 - 3.55 (m, $^3J = 6.8$ Hz, $^3J = 3.2$ Hz, 1H), 3.52 (d,

^2J = 14.0 Hz, 1H), 3.75 (dd, ^2J = 13.9 Hz, ^3J = 9.2 Hz, 1H), 3.82 (d, ^2J = 14.0 Hz, 1H), 3.91 (d, ^2J = 16.9 Hz, 1H), 3.96 (d, ^2J = 16.9 Hz, 1H), 3.96 (dd, ^2J = 13.9 Hz, ^3J = 3.2 Hz, 1H), 6.58 (dd, ^3J = 7.0 Hz, ^4J = 1.7 Hz, 1H), 6.85 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1H), 6.88 (t, ^3J = 7.0 Hz, ^3J = 7.7 Hz, 1H), 7.21 - 7.34 (m, 5H), 10.89 (s, 1H). Ir (CH_2Cl_2): ν = 3460, 3060, 2980, 2940, 2840, 1695, 1620, 1495, 1475, 1455, 1390, 1365, 1135, 1030 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.42; H, 6.56; N, 14.28.

5: tlc: R_f 0.33 (EtOAc, uv active), 0.11 (toluene/EtOAc 1:1); mp 202.3 -203.4 C. ^{1}HNmr (DMSO-d_6/TMS): δ = 0.92 and 1.24 (d, ^3J = 7.2 Hz, 3H), 4.12 and 4.26 (q, ^3J = 7.2 Hz, 1H), 4.70 and 4.79 (t, ^2J = 16.8 Hz, 2H), 5.22 (s, 2H), 6.89 (dd, ^3J = 6.5 Hz, ^4J = 2.6 Hz, 1H), 6.99 (dd partially covered, ^3J = 7.5 Hz, ^4J = 2.6 Hz, 1H), 7.01 (t partially covered, ^3J= 7.8 Hz, 1H), 9.46 and 9.55 (s, 1H). Similarly to 4, the spectrum of 5 showed a double set of peaks with a ratio of approximately 82:18 for some protons. At 100 C only one set of peaks was observed. In the upper list, the values of the higher intensity are underlined. Ir (CH_2Cl_2): ν = 3450, 3360, 3050, 2980, 2950, 1685, 1635, 1590, 1485, 1430, 1410 cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.88; H, 5.89; N, 14.12.

6: tlc: R_f 0.26 (EtOAc, uv active). ^{1}HNmr (DMSO-d_6/TMS): δ= 1.17 (d, ^3J = 6.4 Hz, 3H), 2.84 -2.98 (m, 1H), 2.90 (d, ^2J = 12.5 Hz, 1H), 3.07 (d, ^2J = 12.5 Hz, 1H), 3.40 - 4.00 (m, 4H), 4.42 (s, 1H), 4.67 (s, 2H), 6.10 (d, ^3J = 6.8 Hz, 1H), 6.45 (t, ^3J = 7.0 Hz, 1H), 6.51 (d, ^3J = 7.5 Hz, 1H), 7.18 -7.34 (m, 5H). Ir (CH_2Cl_2): ν = 3420, 3350, 3040, 2970, 2940, 2850, 1625, 1605, 1490, 1455, 1380, 1370 cm^{-1}.

4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (rac.1).

In a hydrogenation apparatusequipped with magnetic stirrer and rubber septum, a suspension of Pd on C (10%, 117 mg) in dioxane/water (4:1, 5 ml) was prehydrogenated at room temperature. A solution of 7 (586.8 mg, 2.0 mmol) in dioxane/water (4:1, 23 ml) was added by a syringe and the mixture hydrogenated at room temperature until the reaction came to an end (10 h). The mixture was filtered through a glass filter (No.4), the catalyst washed with THF (20 ml), the solvent removed in a rotary evaporator and the solid residue dried in vacuo over “Siccapent” (Merck). Crude **rac.-1** (393 mg, 97%) was recrystallized from n-butyl acetate, yielding pure **rac.-1** (311 mg, 77%). tlc: R_f 0.24 (MeCN/H_2O 9:1, uv active). mp 196.1-197.4. ^{1}HNmr (DMSO-d_6/TMS): δ = 1.18 (d, ^3J = 6.6 Hz, 3H), 2.58 (br s, 1H), 3.01 (m, ^3J = 2.2 Hz, ^3J = 6.6 Hz, 1H), 3.16 (dd, ^2J = 12.9 Hz, ^3J = 9.9 Hz, 1H), 3.96 (d, ^2J= 16.5 Hz, 1H), 4.07 (dd, ^2J = 12.9 Hz, ^3J = 2.2 Hz, 1H), 4.09 (d, ^2J= 16.5 Hz, 1H), 6.72 (d, ^3J = 7.6 Hz, 1H), 6.81 (d, ^3J = 7.6 Hz, 1H), 6.87 (t, ^3J = 7.6 Hz, 1H). Ir (KBr): ν = 3260, 2970, 2910, 2870, 2820, 2750, 2670, 1700, 1610, 1500, 1470, 1440, 1385, 1365, 720 cm^{-1}. *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N 20.67. Found: C, 65.18; H, 6.51; N, 20.87.

(+)-(S)-3-Methyl-9-nitro-1*H*-[1,4]benzodiazepine-2,5-dione (8).

In a mortar, **3** (10.41 g, 50 mmol) and L-(+)-alanine (6.68 g, 75 mmol) were well-powdered and well-mixed. The mixture was transferred into a flask, the flask stoppered with glass wool and the mixture heated to 105-115 C for 7 d. The mixture was allowed to cool to room temperature, THF was added (150 ml) and the suspension stirred for 30 min. Filtration, removing of the solvent and drying at 0.001 Torr afforded an orange foam (12.62 g). Chromatography on silica gel (40-63 µm, 630 g), using toluene/EtOAc/AcOH (38:1:1) as eluent (40 fractions, 630 ml each) afforded crude **8** (4.17 g, after evaporating fractions 17-29). Recrystallization from hot isopropanol yielded pure **8** (3.34 g, 28%). mp 135-137 C; tlc: R_f 0.29 (toluene/EtOAc/ AcOH 8:1:1 uv active), 0.31 (EtOAc); $[\alpha]_D^{20°}$ = 645 (c = 1, THF). ^{1}HNmr (DMSO-d_6/TMS): δ = 1.26 (d, ^3J = 6.7 Hz, 3H), 3.97 (dq, ^3J = 6.7 Hz, ^3J = 5.7 Hz, 1H), 7.47 (dd, ^3J = 7.9 Hz, ^3J = 8.1 Hz, 1H), 8.07 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H), 8.22 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H), 8.78 (d, ^3J = 5.5 Hz, 1H), 10.03 (s, 1H). Ir (KBr): ν = 3305, 3180, 3070, 2900, 1720, 1670, 1605, 1575, 1475, 1540, 1355, 1460, 1395, 1300, 1245, 835, 745 cm^{-1}. *Anal.* Calcd for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 51.25; H, 4.04; N, 17.74.

(+)-(S)-9-Amino-3-methyl-1*H*-[1,4]benzodiazepine-2,5-dione (9).

In a hydrogenation apparatus, equipped with a rubber septum and magnetic stirrer, a suspension of Pd on C (10%, 280 mg) in dioxane/water (4:1,10 ml) was prehydrogenated at room temperature. A solution of **8** (941 mg, 4.0 mmol) in dioxane/water (4:1, 20 ml) was added with a syringe and the mixture hydrogenated until the reaction came to an end (2 h). The product partly precipitated. Hydrogen was removed and replaced by nitrogen. Subsequently, the mixture was heated to 50 C, then filtered through a glass filter (No. 4) and the catalyst washed with hot dioxane/ water (4:1, 100 ml). The solvent was removed in vacuo and the solid residue dried in vacuo (0.001 Torr) over "Siccapent" (Merck). Yield: 791 mg (97%) analytically pure 9. mp >290 C; tlc: R_f 0.11 (toluene/EtOAc/AcOH, uv active), 0.56 (MeCN/H_2O 9:1); $[a]_D^{23}$ = 147 (c = 0.5; 6N HCl). 1HNmr (DMSO-d_6/TMS): δ = 1.21 (d, ^3J = 6.7 Hz, 3H), 3.73 (dq, ^3J = 6.7 Hz, ^3J = 5.6 Hz, 1H), 5.21 (s, 2H), 6.86 (dd, ^3J = 7.6 Hz, ^4J = 1.7 Hz, 1H), 6.91 (dd, ^3J = 7.6 Hz, ^4J= 1.7 Hz, 1H), 6.97 (t, ^3J = 7.6 Hz, 1H), 8,33 (d, ^3J = 5.6 Hz, 1H), 9.30 (s, 1H). Ir (KBr): ν = 3410, 3350, 3300, 3170, 3040, 2920, 1690, 1665, 1590, 1490, 1470, 1385, 1415, 1305, 1265, 745 cm^{-1}. *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.78; H, 5.51; N, 20.33.

(S)-2,3,4,5-Tetrahydro-3-methyl-1*H*-[1,4]benzodiazepine-9-amine (10).

In a well-dried 100 ml two-necked flask, fitted with reflux condenser, N_2-balloon, magnetic stirrer and silicon septum, containing a suspension of 9 (410 mg, 2.0 mmol) in dry THF (20 ml), under vigorous stirring a solution of borane in THF (2.65 M, 13.6 ml, 36 mmol) was added with a syringe and the mixture heated to reflux for 48 h. The colourless solution was allowed to cool to room temperature. Aq. HCl (2N, 30 ml) was added and the resulting mixture was heated to reflux for 30 min and was again cooled to room temperature. Aq. NaOH (2N, 30 ml) was added, the solvent removed in vacuo and the resulting colourless solid dried overnight in vacuo over "Siccapent" (Merck) in an dessicator. The dessicator was ventilated with nitrogen, the white solid crushed, ethyl acetate (100 ml) added, the suspension vigorously stirred under nitrogen for 10 min, powdered $MgSO_4$ added, stirred for additional 5 min, filtered under nitrogen, the solvent removed in vacuo and the resulting residue dried at 0.001 Torr. Yield: 291 mg (82%) crude **10**, a pale yellow oil, which became partially crystalline upon standing. Crude **10** was used without further purification. tlc: R_f 0.05 ($MeCN/H_2O$ 9:1, uv active), 0.1 ($MeCN/NEt_3$ 49:1). Ir (CH_2Cl_2): ν = 3410, 3340, 3035, 2960, 2930, 2880, 2830, 1625, 1605, 1485, 1435, 1380 cm^{-1}.

(+)-(S)-4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one ((+)-1).
In a dried 25 ml Schlenk flask, equipped with a magnetic stirrer, N_2-balloon and silicon septum, containing a solution of **10** (213 mg, 1.202 mmol) and *N*-methylmorpholine (398 µl, 3.606 mmol) in dry methylene chloride (5 ml), a solution of diphosgene (160 ml, 1.322 mmol) in dry methylene chloride (5 ml) was added with a syringe at 0 C within 5 min. The mixture was allowed to stir for 20 min at 0 C and for 50 min at room temperature, while a white precipitate was formed. Subsequently the solvent was removed in vacuo, the residue redissolved in dioxane/water (85:15, 8 ml) and the solution heated to reflux for 45 min. The solvent was removed in vacuo, the resulting solid redissolved in aq. $NaHCO_3$ (saturated, 10 ml) and the solution evaporated in vacuo again The white solid was dried overnight in vacuo over "Siccapent" (Merck), then it was extracted with THF (20 ml) with stirring for 5 min. The mixture was filtered, the collected solid washed with THF (10 ml), the filtrate evaporated in vacuo and the resulting residue dried at 0.001 Torr. A slightly brown oil was obtained, which crystallized upon standing. Crude (+)-**1** was recrystallized twice from isopropanol, yielding pure (+)-**1** (89 mg, 36%). mp 200-202 C; tlc: R_f 0.24 ($MeCN/H_2O$ 9:1, uv active); $[a]_D23$ = 60 (c = 1, MeOH).[20] ^{1}HNmr (DMSO-d_6/TMS): δ = 1.18 (d, ^3J = 6.6 Hz, 3H), 2.58 (br s, 1H), 3.01 (m, ^3J = 2.2 Hz, ^3J = 6.6 Hz, 1H), 3.16 (dd, ^2J = 12.9 Hz, ^3J = 9.9 Hz, 1H), 3.96 (d, ^2J= 16.5 Hz, 1H), 4.07 (dd, ^2J = 12.9 Hz, ^3J = 2.2 Hz, 1H), 4.09 (d, ^2J= 16.5 Hz, 1H), 6.72 (d, ^3J = 7.6 Hz, 1H), 6.81 (d, ^3J = 7.6 Hz, 1H), 6.87 (t, ^3J = 7.6 Hz, 1H). Ir (KBr): ν = 3260, 2970, 2910, 2870, 2820, 2750, 2670, 1700, 1610, 1500, 1470, 1440, 1385, 1365, 775, 720 cm^{-1}. *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45, N, 20.67. Found: C, 65.18; H, 6.51; N, 20.85.

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20. The enantiomeric purity of (+)-**1** was established by recording the 1H-nmr spectra of (+)-**1** and rac. **1** with 2 equivalents of (S)-9-anthryl-2,2,2-trifluoroethanol in $CDCl_3$.

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