Diastereoselective Synthesis of the C_2-Symmetric 2,3-Diaminotetralin via Electrophilic Amination

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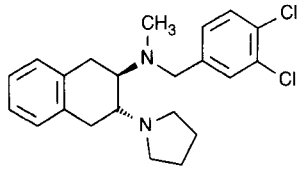
Starting from the *N,N*-dibenzyl protected β-amino acid **3** a synthesis of the C_2-symmetric racemic 2,3-diaminotetralin (**4**; 2,3-diamino-1,2,3,4-tetrahydronaphthalene) is reported. The key step of the procedure is a highly stereocontrolled electrophilic amination by dibenzyl azodicarboxylate.

The ability to stereoselectively generate vicinal diamines constitutes an active area of investigation.[1] This growing interest is due to the importance of this class of compounds as chelating reagents or as building blocks for medicinal chemistry. Vicinal diamines with a C_2-axis of symmetry are emerging as valuable chiral auxiliaries[2] and as substructures in highly selective bioactive compounds. Thus, the *trans*-2,3-diaminotetralin template is a major structural unit of the opioid κ-receptor agonist **1**[3] and is, furthermore, of potential interest in the synthesis of benzo analogues of antineoplastic agents, such as tetraplatin (**2**).[4]



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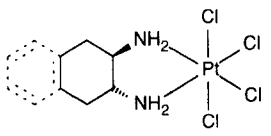

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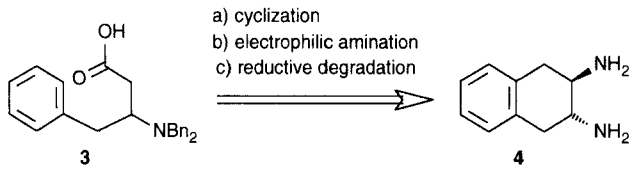
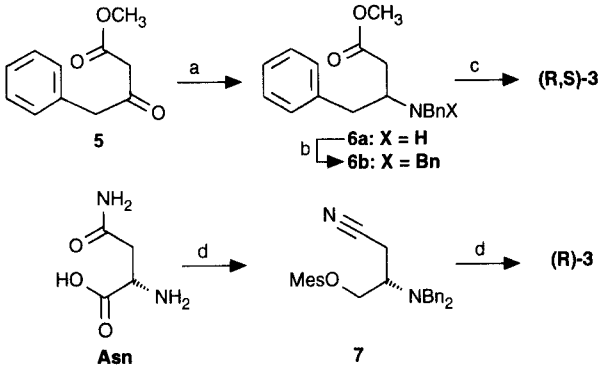
In this paper, we describe the diastereoselective synthesis of the C_2-symmetric diaminotetralin **4**[5] from the β-amino acid **3** employing cyclization, electrophilic amination and reductive degradation.[6]



3 **4**

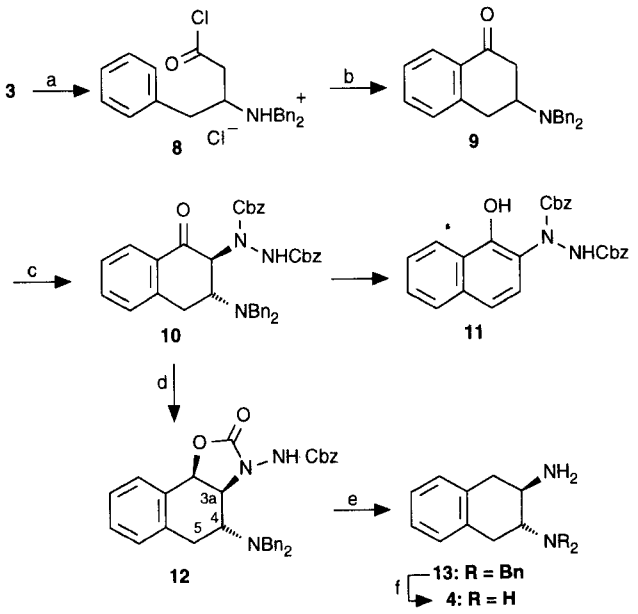
The *N,N*-dibenzyl protected β-homophenylalanine **3** could be readily prepared in both its racemic and enantiomerically pure form (Scheme 1). Reductive coupling of the β-oxo ester **5** and benzylamine afforded the amino ester **6a** which, on treatment with benzaldehyde and $NaCNBH_3$, gave the *N,N*-dibenzyl derivative **6b**. Hydrolysis of **6b** yielded the cyclization precursor **3** in racemic form. Alternatively, **3** can be prepared enantiomerically pure by using our previously described method for the EPC synthesis of β-amino acids.[7] Employing natural asparagine as a starting material, the central intermediate **7** can be synthesized which can be transformed into the amino acid (*R*)-**3** via an organocuprate displacement reaction.



(a) $BnNH_2$, $NaCNBH_3$, MeOH/AcOH, r.t., 68 h, 91%; (b) PhCHO, $NaCNBH_3$, MeOH, r.t., 72 h, 88%; (c) conc. HCl, 80 °C, 3 h, 99%; (d) see ref. 7.

Scheme 1.

For the elaboration of the following reaction sequence (Scheme 2) the β-amino acid **3** was used in its racemic form. Activation of **3** for the envisioned ring closure reaction was accomplished by thionyl chloride in dichloromethane. After addition of the reagent the acid chloride **8** precipitated as its ammonium salt. The cyclization precursor **8** was transformed into the aminotetralone derivative **9** using $AlCl_3$ at room temperature. For the introduction of the electrophilic nitrogen source, the ketone **9** was deprotonated with BuLi at −78 °C



(a) $SOCl_2$, CH_2Cl_2 (DMF), r.t., 3 h, 86%; (b) $AlCl_3$, CH_2Cl_2, r.t., 0.5 h, 81%; (c) 1. BuLi, THF/HMPA, −78 °C, 2 h; 2. dibenzyl azodicarboxylate, −78 °C, 2 h; (d) $LiEt_3BH$, −78 °C, 16 h, 56% (based on **9**); (e) Raney Ni/H_2, MeOH, r.t., 1 h, 57%; (f) $Pd(OH)_2$/H_2, MeOH, r.t. 2 h, 44%.

Scheme 2.

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followed by addition of dibenzyl azodicarboxylate. Due to the steric demand of the dibenzylamine substituent the reaction proceeded with high stereocontrol, resulting in exclusive formation of the *trans*-product **10**. However, **10** turned out to be unstable towards β-elimination, producing naphthol **11** as a side product. To circumvent this problem we proceeded in the synthesis by addition of $LiEt_3BH$ (Super-Hydride®) to the crude reaction mixture at dry ice temperature. According to the observations we have made recently,[6] this bulky reducing agent attacks stereoselectively to give the corresponding *cis*-hydrazino alcohol (steric approach control),[8] since 1,3-diaxial interactions preclude an axial attack. After warming up to room temperature the *cis*-oxazolidinone **12** was formed by intramolecular transesterification.

It is interesting to note that **12** exists in a conformation including an axially positioned dibenzylamine substituent (Figure 1). As a consequence, the oxazolidinone moiety is orientated almost perpendicularly to the tetralin ring. This is indicated by diagnostic ^1H NMR coupling constants ($J_{3a,4}$ = 3.7 Hz, $J_{4,5ax}$ = 5.1 Hz, $J_{4,5eq}$ = 4.4 Hz).

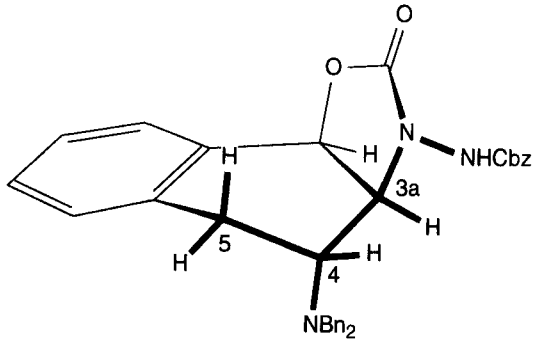

Figure 1. Conformational Representation of **12**

For the final part of the synthesis, a hydrogenolytic degradation had to be accomplished. Treatment of **12** with Raney Ni/H_2 in MeOH resulted in N–N bond cleavage and hydrogenolysis of the benzylic C–O bond of the oxazolidinone fragment to give the monoprotected diamine **13**. Compound **13** could be debenzylated by catalytic hydrogenolysis on $Pd(OH)_2/C$ to furnish the target molecule **4**.

In conclusion, we have shown a highly stereoselective synthesis of the C_2-symmetric diaminotetralin **4** from the protected β-amino acid **3**. Since β-amino acids are also available optically pure this novel approach offers the opportunity to generate vicinal diamines in nonracemic form.

THF was distilled from Na/benzophenone and CH_2Cl_2 from CaH_2, both immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuum with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points were carried out using a Büchi melting point apparatus, and are uncorrected, IR spectra using a Perkin-Elmer 881 spectrometer and mass spectra using a Varian CH7 instrument, the reactant gas for CIMS being methane. NMR spectra were recorded on a Jeol JNM-GX 400 spectrometer at 400 MHz, using tetramethylsilane as an internal standard and elemental analyses using a Heraeus CHN Rapid instrument. Satisfactory microanalyses were obtained: C ± 0.36, H ± 0.38, N ± 0.31.

(*RS*)-3-Dibenzylamino-4-phenylbutanoic Acid (3):
Compound **6b** (24.9 g, 66.7 mmol) was stirred in aq HCl (2 N, 800 mL) at 80 °C for 3 h. The mixture was adjusted to pH 7 by addition of aq NaOH (50 %) at 0 °C. After filtration the precipitate was washed with H_2O (100 mL) and dried ($MgSO_4$) to give pure **3** (23.6 g, 99 %) as a colorless solid, mp 170 °C.

^1H NMR ($CDCl_3$): δ = 2.31 (dd, *J* = 17.6, 3.7 Hz, 1 H), 2.43–2.55 (m, 2 H), 3.30–3.39 (m, 2 H), 3.57 (d, *J* = 13.2 Hz, 2 H), 4.12 (d, *J* = 13.2 Hz, 2 H), 7.06 (d, *J* = 7.3 Hz, 2 H), 7.19–7.41 (m, 8 H).

IR (KBr): ν = 3100, 3020, 2930, 1710 cm^{-1}.

(2*RS*, 3*RS*)-2,3-Diamino-1,2,3,4-tetrahydronaphthalene (4):
A mixture of **13** (82 mg, 0.239 mmol) and 20 % $Pd(OH)_2/C$ (160 mg) in MeOH (10 mL) was stirred under a balloon of H_2 at r.t. for 2 h. The mixture was filtered through Celite and the filtrate evaporated to give **4** (17 mg, 44 %) as a colorless oil.[5]

^1H NMR ($CDCl_3$): δ = 2.61–2.69 (m, 2 H), 2.81–2.88 (m, 2 H), 3.06 (dd, *J* = 17.1, 3.1 Hz, 2 H), 7.06–7.13 (m, 4 H).

IR (NaCl): ν = 3430, 3320, 3030, 2920 cm^{-1}.

Methyl (*RS*)-3-Benzylamino-4-phenylbutanoate (6a):
To a solution of **5** (20.3 g, 105.6 mmol) in MeOH (350 mL) was slowly added benzylamine (114.2 mL, 1055.8 mmol) at 0 °C. After stirring for 19 h at r.t. the solution was adjusted to pH 6 by addition of AcOH (approx. 80 mL) at 0 °C. After addition of $NaCNBH_3$ (14.7 g, 230 mmol) and stirring for further 48 h at r.t. aq HCl (6 N, 250 mL) was slowly added, followed by the addition of aq NaOH (40 %, 125 mL) and H_2O (100 mL). The mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography [petroleum ether (bp 40–56 °C)–EtOAc 1 : 1] to give **6a** (27.2 g, 91 %) as a colorless oil.

^1H NMR ($CDCl_3$): δ = 2.43 (d, *J* = 5.9 Hz, 2 H), 2.74 (dd, *J* = 13.2, 7.0 Hz, 1 H), 2.87 (dd, *J* = 13.2, 6.6 Hz, 1 H), 3.25–3.32 (m, 1 H), 3.65 (s, 3 H), 3.79 (d, *J* = 13.9 Hz, 1 H), 3.82 (d, *J* = 13.9 Hz, 1 H), 7.15–7.35 (m, 10 H).

IR (NaCl): ν = 3330, 3060, 2950, 1730 cm^{-1}.

Methyl (*RS*)-3-Dibenzylamino-4-phenylbutanoate (6b):
To a solution of **6a** (21.4 g, 75.5 mmol) in MeOH (440 mL) was added benzaldehyde (80.14 g, 755.1 mmol) and subsequently $NaCNBH_3$ (11.86 g, 188.7 mmol) at 0 °C. The mixture was stirred at r.t. for 72 h, then filtered, concentrated and again filtered. The combined precipitates were dried ($MgSO_4$) to give **6b** (24.8 g, 88 %) as a colorless solid, mp 123 °C.

^1H NMR ($CDCl_3$): δ = 2.30 (dd, *J* = 13.9, 5.9 Hz, 1 H), 2.53 (dd, *J* = 13.5, 8.8 Hz, 1 H), 2.62 (dd, *J* = 13.9, 8.8 Hz, 1 H), 3.10 (dd, *J* = 13.5, 5.5 Hz, 1 H), 3.38–3.46 (m, 1 H), 3.54 (s, 3 H), 3.58 (d, *J* = 14.2 Hz, 2 H), 3.72 (d, *J* = 14.2 Hz, 2 H), 7.04–7.29 (m, 15 H).

IR (KBr): ν = 3060, 2950, 1730 cm^{-1}.

(*RS*)-3-Dibenzylamino-4-phenylbutyryl Chloride Hydrochloride (8):
To a mixture of **3** (2.11 g, 5.87 mmol) and DMF (0.05 mL, 0.65 mmol) in CH_2Cl_2 (60 mL) was added $SOCl_2$ (0.609 mL, 7.78 mmol) at 0 °C. After stirring at r.t. for 3 h the precipitate was filtered and dried ($MgSO_4$) to give **8** (2.10 g, 86 %) as a colorless solid, mp 161–164 °C.

^1H NMR ($CDCl_3$): δ = 2.52 (dd, *J* = 16.3, 6.6 Hz, 1 H), 2.88 (dd, *J* = 13.5, 9.5 Hz, 1 H), 3.12 (dd, *J* = 16.3, 4.8 Hz, 1 H), 3.48 (dd, *J* = 13.5, 3.7 Hz, 1 H), 3.82–3.86 (m, 1 H), 4.24 (s, 4 H), 7.11–7.13 (m, 2 H), 7.19–7.26 (m, 3 H), 7.32–7.34 (m, 6 H), 7.49–7.51 (m, 4 H).

IR (KBr): ν = 3030, 2930, 2480, 1800 cm^{-1}.

(*RS*)-3-Dibenzylamino-3,4-dihydronaphthalen-1(2*H*)-one (9):
To a suspension of **8** (115 mg, 0.277 mmol) in CH_2Cl_2 (5 mL) was added $AlCl_3$ (37 mg, 0.27 mmol) at 0 °C and, after 15 min, another portion of $AlCl_3$ (37 mg, 0.27 mmol). After a further 15 min aq HCl (2 N) and subsequently NaOH (2 N) were added. The mixture

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was extracted with Et_2O (50 mL), the organic layer dried ($MgSO_4$) and evaporated to give **9** (77 mg, 81%) as a colorless solid (mp 93°C).

^1H NMR ($CDCl_3$): δ = 2.68 (dd, J = 16.1, 13.2 Hz, 1 H), 2.97 (dd, J = 16.1, 1.8 Hz, 1 H), 3.07–3.14 (m, 2 H), 3.33–3.41 (m, 1 H), 3.69 (d, J = 13.9 Hz, 2 H), 3.80 (d, J = 13.9 Hz, 2 H), 7.19–7.47 (m, 13 H), 7.96 (d, J = 7.3 Hz, 1 H).

IR (KBr): ν = 3030, 2930, 1670 cm^{-1}.

Dibenzyl (2*RS*, 3*SR*)-1-(3-Dibenzylamino-1,2,3,4-tetrahydro-1-oxo-2-naphthyl)-1,2-hydrazinedicarboxylate (10) and Dibenzyl 1-(1-Hydroxy-2-naphthyl)-1,2-hydrazinedicarboxylate (11):

To a mixture of **9** (358 mg, 1.05 mmol) in THF (15 mL) and hexamethylphosphoric triamide (HMPA) (1.76 mL, 10 mmol) was added LDA (4.26 mL, 0.3 M in THF) at −78°C. After 30 min a solution of dibenzyl azodicarboxylate (406 mg, 1.36 mmol) in THF (3 mL) was added. After stirring at −78°C for 1 h the mixture was added to sat. aq NH_4Cl (100 mL) and Et_2O (200 mL). The organic layer was dried ($MgSO_4$) and evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 4:1) to give **10** (300–400 mg, 45–60%) as a colorless oil and **11** (50–130 mg, 11–28%) as a colorless solid, mp 135°C. When stirring of the reaction mixture was continued at r.t. for 24 h only **11** (233 mg, 62%) was isolated after the above described workup.

10: ^1H NMR (DMSO-d_6, 100°C): δ = 3.11 (dd, J = 16.1, 3.7 Hz, 1 H), 3.29 (dd, J = 16.1 Hz, 11 Hz, 1 H), 3.60–3.67 (m, 1 H), 3.71 (d, J = 13.9 Hz, 2 H), 3.96 (d, J = 13.9 Hz, 2 H), 5.02 (d, J = 11.0 Hz, 1 H), 5.14 (s, 2 H), 5.17 (s, 2 H), 7.11–7.39 (m, 23 H), 7.80 (d, J = 8.1 Hz, 1 H).

IR (NaCl): ν = 3030, 2920, 1760, 1730, 1680 cm^{-1}.

11: ^1H NMR (DMSO-d_6, 140°C): δ = 5.14 (s, 2 H), 5.17 (s, 2 H), 7.16–7.34 (m, 14 H), 7.38–7.53 (m, 2 H).

IR (KBr): ν = 3290, 3030, 2960, 1710, 1690 cm^{-1}.

Benzyl (3a*RS*, 4*SR*, 9b*SR*)-*N*-(4-Dibenzylamino-2,3,3a,4,5,9b-hexahydro-2-oxonaphth[2,1-*d*]oxazol-3-yl)carbamate (12):

To a mixture of **9** (547 mg, 1.6 mmol) in THF (45 mL) and HMPA (2.6 mL, 14.8 mmol) was added BuLi (1.33 mL, 1.6 M in hexane) at −78°C. After 2 h a solution of dibenzyl azodicarboxylate (718 mg, 2.4 mmol) in THF (5 mL) was added. After stirring at −78°C for 2 h $LiEt_3BH$ (2.4 mL, 1 M in THF) was slowly added. After stirring at −78°C for a further 16 h, the mixture was allowed to warm up to 10°C when it was added to sat. aq NH_4Cl (100 mL) and Et_2O (300 mL). The organic layer was dried ($MgSO_4$), evaporated and the residue purified by flash chromatography (petroleum ether–EtOAc 4:1) to give **12** (478 mg, 56%) as a colorless solid, mp 142°C.

^1H NMR (DMSO-d_6, 140°C)): δ = 2.90 (dd, J = 16.1, 5.1 Hz, 1 H, H-5ax), 3.02 (dd, J = 16.1, 4.4 Hz, 1 H, H-5eq), 3.33–3.37 (m, 1 H, H-4), 3.51 (d, J = 13.9 Hz, 2 H, NCH_2Ph), 3.68 (d, J = 13.9 Hz, 2 H, CH_2Ph), 4.55 (dd, J = 8.4, 3.7 Hz, 1 H, H-3a), 5.08–5.14 (m, 2 H, OCH_2Ph), 5.61 (d, J = 8.4 Hz, 1 H, H-9b), 7.25 (m, 19 H, Ar).

IR (KBr): ν = 3290, 3020, 2940, 1770, 1720 cm^{-1}.

(2*RS*, 3*RS*)-2-Amino-3-dibenzylamino-1,2,3,4-tetrahydronaphthalene (13):

A mixture of **12** (420 mg, 0.787 mmol) and Raney Ni (50 mg) in MeOH (60 mL) was stirred under a balloon of H_2 at r.t. for 1 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 3:2) to give **13** (154 mg, 57%) as a colorless oil.

^1H NMR ($CDCl_3$): δ = 2.50 (dd, J = 16.1, 10.5 Hz, 1 H), 2.77 (dt, J = 10.5, 5.4 Hz, 1 H), 2.94 (dd, J = 16.1, 10.5 Hz, 1 H), 3.05 (dd, J = 16.1, 5.1 Hz, 1 H), 3.13 (dd, J = 16.1, 5.1 Hz, 1 H), 3.21 (dt, J = 10.5, 5.1 Hz, 1 H), 3.54 (d, J = 13.5 Hz, 2 H), 3.92 (d, J = 13.5 Hz, 2 H), 7.02–7.38 (m, 14 H).

IR (NaCl): ν = 3380, 3060, 2920 cm^{-1}.

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