Diastereoselective Synthesis of the C$_2$-Symmetric 2,3-Diaminotetralin via Electrophilic Amination

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Starting from the N,N-dibenzyl protected $\beta$-amino acid 3 a synthesis of the C$_2$-symmetric 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. 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 and as substructures in highly selective bioactive compounds. Thus, the trans-2,3-diaminotetralin template is a major structural unit of the opioid $\kappa$-receptor agonist 1 and is, furthermore, of potential interest in the synthesis of benzo analogues of antineoplastic agents, such as tetraplatin (2).

In this paper, we describe the diastereoselective synthesis of the C$_2$-symmetric diaminotetralin 4 from the $\beta$-amino acid 3 employing cyclization, electrophilic amination and reductive degradation.

The N,N-dibenzyl protected $\beta$-homophenylalanine 3 could be readily prepared in both its racemic and enantiomerically pure form (Scheme 1). Reductive coupling of the $\beta$-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 $\beta$-amino acids. 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.

The elaboration of the following reaction sequence (Scheme 2) the $\beta$-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. For the introduction of the electrophilic nitrogen source, the ketone 9 was deprotonated with BuLi at $-78^\circ$C.

For the elaboration of the following reaction sequence (Scheme 2) the $\beta$-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 $-78^\circ$C.

\[(a) \text{SOCl}_2, \text{DMF}, \text{r. t., 3 h, 86\%}; (b) \text{AlCl}_3, \text{CH}_2\text{Cl}_2, \text{r. t., 0.5 h, 81\%}; (c) 1. \text{BuLi, THF/HMPA, \text{r. t., 2 h; 2. dibenzyl azodicarboxylate, \text{r. t., 2 h; 3. LiEt}_2\text{BH, \text{r. t., 16 h, 56\%}}} (\text{based on 9}); (e) \text{Raney Ni/H}_2, \text{MeOH, \text{r. t., 1 h, 57\%}}; (f) \text{Pd(OH)}_2/\text{H}_2, \text{MeOH, \text{r. t. 2 h, 44\%}}.\]

Scheme 2.
followed by addition of dibenzyl azodicarboxylate. Due to the steric demand of the dibenzylamine substituent the reaction proceeded with high stereoccontrol, resulting in exclusive formation of the trans-product. However, the reaction turned out to be unstable towards β-elimination, producing naphthol as a side product. To circumvent this, the steric demand of the dibenzylamine substituent had to be accomplished. Treatment of the protected β-amino acid with LiEt₃BH (Super-Hydride®) at dry ice temperature. According to the observations we have made recently, this bulky reducing agent attacks the nitrogen atom of the protected β-amino acid with high stereoselectivity to give the corresponding cis-hydrazino alcohol (steric approach control). Since 1,3-diaxial interactions preclude an axial attack. After warming up to room temperature the cis-hydrazino alcohol was converted to the trans-product. It is interesting to note that the cis-hydrazino alcohol is formed in an intramolecular transesterification.

**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/H₂ in MeOH resulted in N-N bond cleavage and hydrogenolysis of the benzyl 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 C₂-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 CH₂Cl₂ from CaH₂, both immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry N₂. Evaporations of final product solutions were done under vacuum with a rotary evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points were determined 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-Dibenzylandio-4-phenylbutyric 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 NaOH (100 mL and 10 mmol) and MgSO₄ to give pure 3 (23.6 g, 99%) as a colorless solid.

**Methyl (RS)-3-Benzylamino-4-phenylbutyric Acid (6a):**

To a solution of 6a (21.4 g, 75.5 mmol) in MeOH (440 mL) was added H₂SO₄ (approx. 80 mL) at 0°C. After addition of NaCNBH₃ (755.1 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 (230 mmol) and stirring under a balloon of H₂ for 2 h. The mixture was filtered through Celite and the filtrate evaporated to give 4 (37 mg, 0.27 mmol) at 0°C and, after 15 min, another portion of AICI₃ (160 mg) was added. The mixture was stirred for 2 h, then filtered, concentrated and again filtered. The combined precipitates were dried (MgSO₄) to give 6b (24.8 g, 88%) as a colorless solid, mp 123°C.

**Methyl (RS)-3-Dibenzylandio-4-phenylbutyric Acid Hydrochloride (8):**

To a solution of 6b (21.4 g, 75.5 mmol) in MeOH (440 mL) was added benzaldehyde (80.14 g, 755.1 mmol) and subsequently NaCNBH₃ (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 (MgSO₄) to give 6b (24.8 g, 88%) as a colorless solid, mp 123°C.

**RS)-3-Dibenzylandio-4-phenylbutylic Acid Chloride Hydrochloride (9):**

To a solution of 3 (21.1 g, 5.87 mmol) and DMF (0.05 mL, 0.65 mmol) in CH₂Cl₂ (60 mL) was added SOCl₂ (0.609 mmol, 7.78 mmol) at 0°C. After stirring at r. t. for 3 h the precipitate was filtered and dried (MgSO₄) to give 8 (21.0 g, 86%) as a colorless solid, mp 161-164°C.

**RS)-3-Dibenzylandio-4-dihydronaphthalene-1(2H)-one (9):**

To a suspension of 8 (115 mg, 0.277 mmol) in CH₂Cl₂ (5 mL) was added AlCl₃ (37 mg, 0.27 mmol) at 0°C and, after 15 min, another portion of AlCl₃ (37 mg, 0.27 mmol). After a further 15 min aq HCl (2 N) and subsequently NaOH (2 N) were added. The mixture...
A mixture of 12 (420 mg, 0.787 mmol) and Raney Ni (50 mg) in MeOH (60 mL) was stirred under a balloon of H₂ at r.t. for 1 h. The mixture was filtered through Celite and the filtrate was evaporated to give 9 (77 mg, 81%) as a colorless solid (mp 93°C).

³¹H NMR (CDCl₃; δ = 2.68 (dd, J = 16.1, 3.7 Hz, 1 H), 3.29 (dd, J = 16.1 Hz, 1 H, Ar), 2.60-2.67 (m, 1 H), 3.13 (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 = 8.4 Hz, 1 H, H-9b), 7.25 (m, 19 H, Ar).

IR (KBr): ν = 3290, 3020, 2940, 1770, 1720 cm⁻¹.

Dibenzyl (2RS, 3SR)-l-(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 hexamethyldisilazane (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 NH₄Cl (100 mL) and Et₂O (200 mL). The organic layer was dried (MgSO₄) and evaporated and the residue purified by flash chromatography (petroleum ether-EtOAc 4:1) to give 10 (77 mg, 81%) as a colorless oil (mp 142°C).

IR (NaCl): ν = 3030, 2930, 1670 cm⁻¹.

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(2) For previous studies on the synthesis of amines by electrophilic amination and reductive degradation, see: Gmeiner, P.; Bollinger, B. Tetrahedron Lett. 1992, 35, 5865.


(4) For previous studies on the synthesis of amines by electrophilic amination and reductive degradation, see: Gmeiner, P.; Bollinger, B. Tetrahedron Lett. 1991, 32, 5977.