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2-DIBENZYLAMINOBUTANE-1,4-DIOL: A VERSATILE INTERMEDIATE FOR A CHIROSPECIFIC β-AMINO ACID SYNTHESIS

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<u>Abstract:</u> Starting from the chiral building block 1, which is readily available from natural aspartic acid, a concise and versatile synthesis of optically active β -amino acids including β -proline derivatives is reported. Regioselective transformations of the 1,4-bis-electrophile 2 are facilitated by an anchimeric participation.

In connection with our program on the structure activity relationships of selective dopamine D-2 autoreceptor agonists,¹ we have developed methodology for an 8-step synthesis of enantiomerically pure β -amino acids employing a chemoselective functionalization of L-asparagine² as well as regioselective transformations of L-aspartic acid yielding enantiomerically pure 1,2- and 1,3-amino alcohols.³ Combining these strategies, we herein report a concise and flexible synthesis of β -amino acids including β -proline derivatives.⁴

The method depends on activation of both hydroxyl groups of the building block 1, which was prepared from L-aspartic acid by perbenzylation and subsequent reduction.³ Reaction of 1 with 2.5 equivalents of methanesulfonic chloride resulted in formation of the 1,4-bis-electrophile 2 which could be characterized by immediately performed ¹H NMR spectroscopy. Treatment of crude 2 with 1.1 equivalents of LiCN gave a regioselective functionalization of position 1 affording the activated β-amino nitrile 3 in 74 % yield. This shows that an activating neighboring group participation of the dibenzylamino group overrides its protecting steric effect. Modification of the amino nitrile side chain could be achieved by treatment of 3 with Me₂CuLi, Bu₂CuLi or NaN₃ to give the respective displacement products. Subsequent acidic hydrolysis by aqueous HCl resulted in formation of the N-protected β-amino acids **4a-c**.

For a projected synthesis of β -proline derivatives we envisioned to utilize the previously observed tendency of α -dibenzylamino mesylates to undergo rearrangement via an aziridinium intermediate.³ Thus, migration of the dibenzylamino group via **5** was expected to give the 1,4-amino mesylate **6** which was anticipated to react intramolecularly. In fact, separation of a colorless oil was observed after flash chromatography of the dimesylate **2** and subsequent storage of the product solution for 12 h at room temperature. The product which crystallized after removal of the solvent proved to be the pyrrolidinium salt **7**.⁵ Subsequent hydrogenolytic mono-debenzylation (Pd(OH)₂/C, H₂, 17 min) afforded the tertiary amine **8**.⁶ Introduction of the cyanide group gave the β -proline precursor **10**. Finally, synthesis of the β -amino acid **9** was accomplished by acidic hydrolysis. Optical purity studies of **9** including esterification, N-deprotection and subsequent coupling with (*R*)- and (*R*,*S*)-1-phenylethyl isocyanate revealed the synthetic material to be isomerically pure.



a: see ref. 3. b: MesCl (2.5 eq), Et₃N, THF, 25 min, -20°C. c: LiCN (1.1 eq, solution in DMF), 3 h, RT (74 %, based on 1). d: for 4a: MeLi (20 eq. 1.6 M in Et₂O), CuI (11 eq), Et₂O, 16 h, -20°C (47 %); for 4b: BuLi (14 eq. 1.6 M in hexane), CuI (7 eq), Et₂O, 23 h, -20°C (48 %); for 4c: NaN₃, DMF, 16 h, RT (85 %). e: HCl/H2O (conc.), 2-4 h, 80°C (30-79 %). f: 1. flash chromatography (silica gel, petroleum ether - EtOAc 1:1); 2. 12 h, RT (60 %, based on 1). g: Pd(OH)₂/C, H₂, MeOH, 17 min, RT (78 %). h: LiCN (4 eq, solution in DMF), 2 d, 60°C (61 %).

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References and Notes

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- Analytical data for 7: $[\alpha]_D^{23}$ -7.2°C (c = 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 2.14-2.18 (m, 1H, H-4_a), 2.48-2.57 (m, 1H, H-4_b), 2.75 (s, 3H, OMes), 3.00 (s, 3H, OMes), 3.73-3.80 (m, 2H, H-5_{a,b}), 3.94 (br-d, J = 13.9 Hz, 1H, H-2_a), 4.18 (dd, J = 13.9, 5.9, 1H, H-2_b), 4.76-4.92 (m, 4H, (5) NCH₂Ph), 5.46 (br-s, 1H, H-3), 7.18-7.58 (m, 10H, ar); attachment of the signals was facilitated by ¹H¹HCOSY spectroscopy.
- The structure of **8** was proved by an independent synthesis. Thus, (R)-3-hydroxypyrrolidine, which can (6) be prepared by decarboxylation of hydroxyproline (Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. Chem. Lett. 1986, 893-896), was subjected to reductive benzylation (benzaldehyde, NaCNBH₃). Subsequently, the OH-group was reacted with MesCl/Et₃N to give 8.



The products obtained by both routes turned out to be identical by NMR spectroscopical means and optical rotation ($[\alpha]_D^{23}$ +11.5 ° and +11.3°, respectively).

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