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

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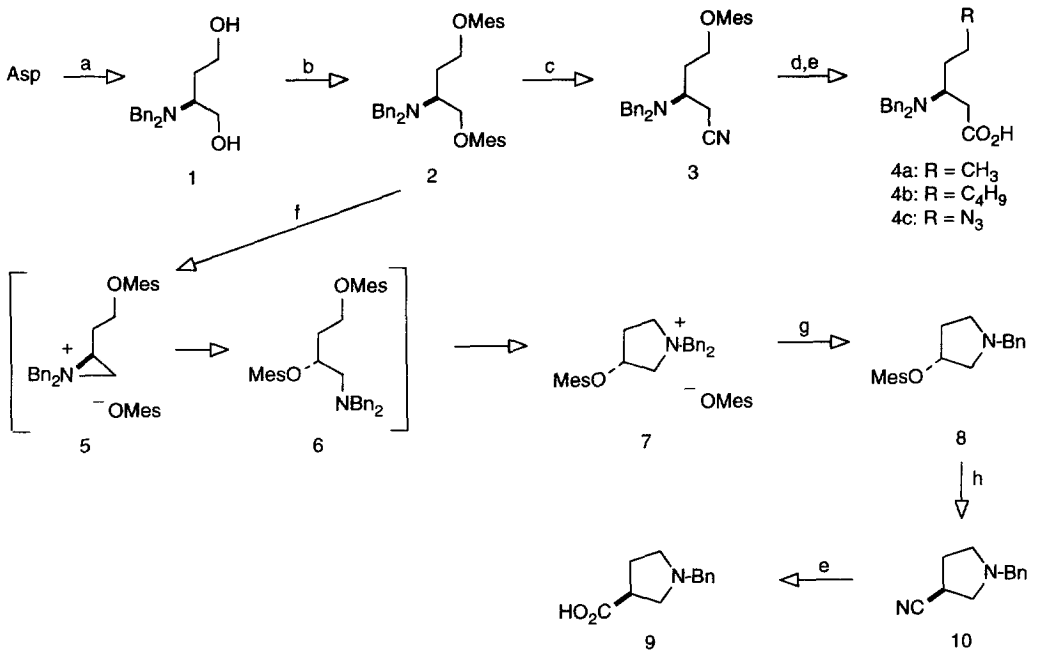
Abstract: Starting from the chiral building block **1**, which is readily available from natural aspartic acid, a concise and versatile synthesis of optically active ß-amino acids including ß-proline derivatives is reported. Regioselective transformations of the 1,4-bis-electrophile **2** are facilitated 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 ß-amino acids employing a chemoselective functionalization of L-asparagine[2] 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 ß-amino acids including ß-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 ^{1}H NMR spectroscopy. Treatment of crude **2** with 1.1 equivalents of LiCN gave a regioselective functionalization of position 1 affording the activated ß-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 Me_2CuLi, Bu_2CuLi or NaN_3 to give the respective displacement products. Subsequent acidic hydrolysis by aqueous HCl resulted in formation of the N-protected ß-amino acids **4a-c**.

For a projected synthesis of ß-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 ($Pd(OH)_2/C$, H_2, 17 min) afforded the tertiary amine **8**.[6] Introduction of the cyanide group gave the ß-proline precursor **10**. Finally, synthesis of the ß-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), Et_3N, 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 Et_2O), CuI (11 eq), Et_2O, 16 h, -20°C (47 %); for **4b**: BuLi (14 eq. 1.6 M in hexane), CuI (7 eq), Et_2O, 23 h, -20°C (48 %); for **4c**: NaN_3, DMF, 16 h, RT (85 %). e: HCl/H_2O (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: $Pd(OH)_2/C$, H_2, MeOH, 17 min, RT (78 %). h: LiCN (4 eq, solution in DMF), 2 d, 60°C (61 %).

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References and Notes

(1) For an example: Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 57-60.

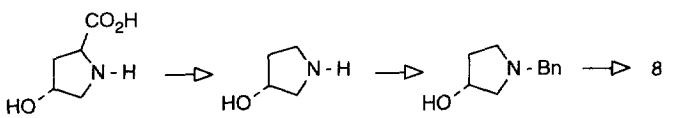
(2) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717-5720.- Gmeiner, P. *Liebigs Ann. Chem.* **1991**, 501-502.- Gmeiner, P. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 551-557.

(3) Gmeiner, P.; Kärtner, A.; Junge, D. *Tetrahedron Lett.* **1993**, *34*, 4325-4326.- Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766-6776.- Gmeiner, P.; Kärtner, A. *Synthesis* **1995**, in press.

(4) Fles, D.; Ghyczy, T. *Croat. Chem. Acta* **1964**, *36*, 27-32.

(5) Analytical data for **7**: $[\alpha]_D^{23}$ -7.2°C (c = 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 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, NCH_2Ph), 5.46 (br-s, 1H, H-3), 7.18-7.58 (m, 10H, ar); attachment of the signals was facilitated by $^1H^1H$COSY spectroscopy.

(6) The structure of **8** was proved by an independent synthesis. Thus, *(R)*-3-hydroxypyrrolidine, which can 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, $NaCNBH_3$). Subsequently, the OH-group was reacted with $MesCl/Et_3N$ 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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