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## 2-DIBENZYLAMINO BUTANE-1,4-DIOL: A VERSATILE INTERMEDIATE FOR A CHIROSPECIFIC $\beta$ -AMINO ACID SYNTHESIS

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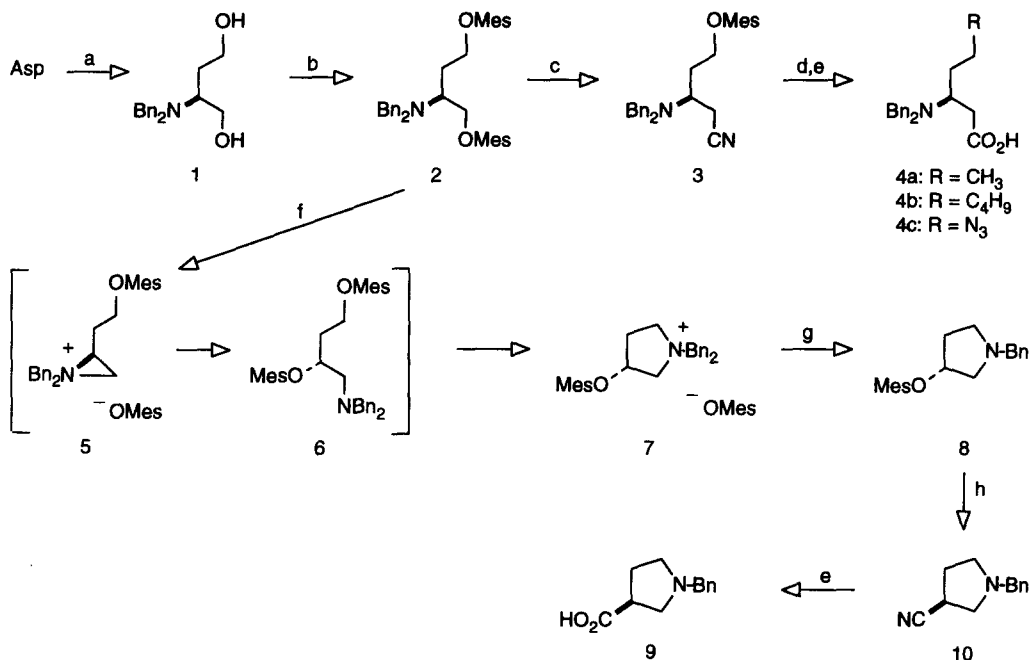
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**Abstract:** Starting from the chiral building block **1**, which is readily available from natural aspartic acid, a concise and versatile synthesis of optically active  $\beta$ -amino acids including  $\beta$ -proline derivatives is reported. Regioselective 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,<sup>1</sup> we have developed methodology for an 8-step synthesis of enantiomerically pure  $\beta$ -amino acids employing a chemoselective functionalization of L-asparagine<sup>2</sup> as well as regioselective transformations of L-aspartic acid yielding enantiomerically pure 1,2- and 1,3-amino alcohols.<sup>3</sup> Combining these strategies, we herein report a concise and flexible synthesis of  $\beta$ -amino acids including  $\beta$ -proline derivatives.<sup>4</sup>

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.<sup>3</sup> 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 <sup>1</sup>H NMR spectroscopy. Treatment of crude **2** with 1.1 equivalents of LiCN gave a regioselective functionalization of position 1 affording the activated  $\beta$ -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<sub>2</sub>CuLi, Bu<sub>2</sub>CuLi or NaN<sub>3</sub> to give the respective displacement products. Subsequent acidic hydrolysis by aqueous HCl resulted in formation of the N-protected  $\beta$ -amino acids **4a-c**.

For a projected synthesis of  $\beta$ -proline derivatives we envisioned to utilize the previously observed tendency of  $\alpha$ -dibenzylamino mesylates to undergo rearrangement via an aziridinium intermediate.<sup>3</sup> 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**.<sup>5</sup> Subsequent hydrogenolytic mono-debenzylation (Pd(OH)<sub>2</sub>/C, H<sub>2</sub>, 17 min) afforded the tertiary amine **8**.<sup>6</sup> Introduction of the cyanide group gave the  $\beta$ -proline precursor **10**. Finally, synthesis of the  $\beta$ -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.

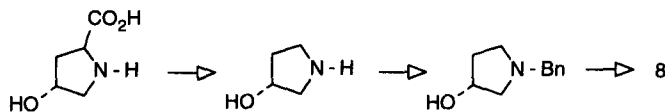


a: see ref. 3. b: MesCl (2.5 eq), Et<sub>3</sub>N, THF, 25 min, -20°C. c: LiCN (1.1 eq, solution in DMF), 3 h, RT (74 %, based on 1). d: for 4a: MeLi (20 eq, 1.6 M in Et<sub>2</sub>O), CuI (11 eq), Et<sub>2</sub>O, 16 h, -20°C (47 %); for 4b: BuLi (14 eq, 1.6 M in hexane), CuI (7 eq), Et<sub>2</sub>O, 23 h, -20°C (48 %); for 4c: NaN<sub>3</sub>, DMF, 16 h, RT (85 %). e: HCl/H<sub>2</sub>O (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)<sub>2</sub>/C, H<sub>2</sub>, 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<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) = 2.14-2.18 (m, 1H, H-4<sub>a</sub>), 2.48-2.57 (m, 1H, H-4<sub>b</sub>), 2.75 (s, 3H, OMe), 3.00 (s, 3H, OMe), 3.73-3.80 (m, 2H, H-5<sub>a,b</sub>), 3.94 (br-d, J = 13.9 Hz, 1H, H-2<sub>a</sub>), 4.18 (dd, J = 13.9, 5.9, 1H, H-2<sub>b</sub>), 4.76-4.92 (m, 4H, NCH<sub>2</sub>Ph), 5.46 (br-s, 1H, H-3), 7.18-7.58 (m, 10H, ar); attachment of the signals was facilitated by <sup>1</sup>H<sup>1</sup>H 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<sub>3</sub>). Subsequently, the OH-group was reacted with MesCl/Et<sub>3</sub>N 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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