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PRACTICAL EPC SYNTHESIS OF 1,2- AND 1,3-AMINO ALCOHOLS

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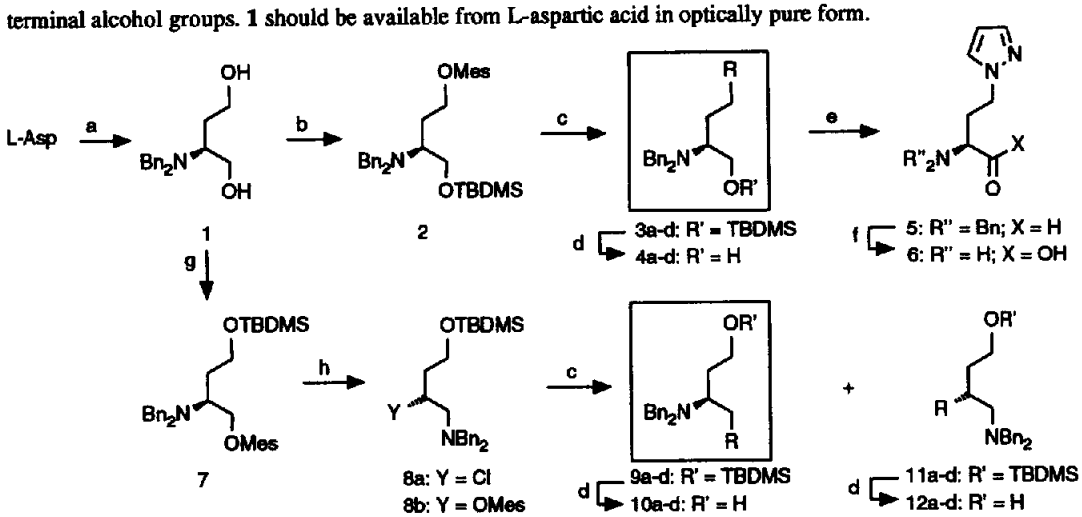
Abstract: An efficient synthesis of enantiomerically pure 1,2- and 1,3-amino alcohols (**4, 10**) through the key intermediates **2** and **8a,b**, obtained from L-aspartic acid, is reported. Using **4d** as an example it is shown that the products can serve as precursors for unusual amino aldehydes and nonproteinogenic amino acids.

In connection with our program on the structure activity relationships of selective dopamine D-2 autoreceptor agonists,[1] we were searching for a flexible strategy to the synthesis of enantiomerically pure 1,2- and 1,3-amino alcohols (**4, 10**), which are also of interest for natural product and amino acid chemistry.[2] It was envisioned to approach to **4** and **10** through the intermediates **2** and **7**, respectively, which were planned to be synthesized from the N,N-dibenzylaminobutanediol **1** by regioselective activation and protection of the terminal alcohol groups. **1** should be available from L-aspartic acid in optically pure form.



a: 1. BnBr, K_2CO_3 / H_2O, 2h, reflux (77%); 2. $LiAlH_4$, THF, 3h, -78 to -55°C (80%). b: 1. MesCl, Et_3N, $CHCl_3$, 1h, -20°C; 2. TBDMSCl, imidazole, DMF, 2h, -20°C (57%). c: see Table. d: NaOH, EtOH / H_2O, 1-48h, 60°C, for R = NPhth: HOAc, THF / H_2O, 20h, RT (95-99%). e: R = 1-pyrazolyl, oxalyl chloride, DMSO, Et_3N, 1h, -60°C (65%). f: 1. $NaClO_2$, 2-methyl-2-butene, ^tBuOH, acetonitrile, 25 min, 0°C (60%); 2. $Pd(OH)_2$-C, H_2, MeOH, 18h, RT, Dowex 50 W x 8 (52%). g: 1. TBDMS-Cl, imidazole, DMF, 2h, RT (66 %); 2. MesX (X = Cl, OMes), Et_3N, CH_2Cl_2, 5 min, 0°C. h: 5h, RT.

In practice, natural aspartic acid was treated with an excess of benzyl bromide to give the tetrabenzyl derivative, which could be reduced to **1** by $LiAlH_4$.[3] Due to the bulky dibenzylamino group the two primary alcohols could be differentiated very efficiently. Thus, treatment of **1** with methanesulfonic chloride resulted in selective activation of the less hindered pos.4. Subsequent protection of pos.1 by t-butyldimethylsilyl chloride yielded 57% of the key intermediate **2** ($[\alpha]_D^{20}$ -34°, c = 1, $CHCl_3$). Reversing the order of activation and protection should give access to the regioisomer **7**. Treatment of the diol **1** with TBDMS-Cl resulted in preferred attack at the less hindered pos. 4.[4] Subsequent activation by MesCl afforded the projected

intermediate **7**. However, **7** could be only detected in pure form (by NMR) immediately after addition of the reagents since, in a following reaction step, rearrangement occurred. After 5 h the secondary chloride **8a** which was obviously formed through an aziridinium intermediate was isolated as a single product in 94 % yield ($[\alpha]_D^{20}$ +18°, c = 1.0, $CHCl_3$). By analogy, the rearranged methanesulfonic ester **8b** could be prepared employing Mes_2O.[5]

To demonstrate the versatility of the method **2** and **8** were reacted with representative nucleophiles (Table). Starting from **2**, the anticipated substitutions were observed to give **3a-d** in 51-62 % yield. In the course of surveying the reactivity of **8a,b** we discovered that the displacement reactions proceeded again through an aziridinium intermediate resulting in migration of the dibenzylamine group.[6] Treatment of **8a** with phthalimide-K or NaCN resulted in preferred ring opening at the less crowded aziridinium position, when the protected 1,3-amino alcohols **9b,c** were formed as the main products, besides the regioisomers **11b,c**. For substitutions with organocuprates the chloride **8a** was not reactive enough. However, the more electrophilic mesylate **8b** gave a smooth reaction with Me_2CuLi to afford the protected 1,3-amino alcohol **9a**, exclusively. On the other hand, employment of nucleophiles with leaving group character, allowing thermodynamic control, resulted in formation of 1,4-amino alcohols. For example, treatment of **8b** with LiBr afforded **11d**. For cleavage of the TBDMS protecting group **3a-d**, **9a-c** and **11b,c** were treated with aqueous NaOH or HOAc to yield the N,N-dibenzylamino alcohols **4a-d**, **10a-c** and **12b,c**, respectively.[7]

Using **4d** (R = 1-pyrazolyl) as an example it was shown that the N,N-dibenzylamino alcohols can serve as precursors for unusual amino aldehydes and nonproteinogenic amino acids. Thus, **4d** was oxidized to the amino aldehyde **5** which could be converted into the α-amino acid **6** ($[\alpha]_D^{20}$ +9°, c = 0.175, MeOH) upon treatment with $NaClO_2$, followed by hydrogenolytic debenzylation.

Table

educt	reagent	solvent	temp [°C]	time [h]	product	yield [%]
2	Me_2CuLi	Et_2O	-50	20	3a (R = Me)	51
2	Ph_2CuLi	Et_2O	-20	3	3b (R = Ph)	58
2	NPhth-K	DMF	20	20	3c (R = NPhth)	61
2	1-pyrazolyl-K	THF	20	40	3d (R = 1-pyrazolyl)	62
8b	Me_2CuLi	Et_2O	-20	20	9a (R = Me)	46
8a	NPhth-K	DMF	50	42	9b, 11b (R = NPhth)	52, 19
8a	NaCN	DMF	50	120	9c, 11c (R = CN)	73, 7
8b	LiBr	CH_2Cl_2	20	20	11d (R = Br)	68

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References and Notes

Dedicated to Professor H.-D. Stachel on the occasion of his 65th birthday.

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2 For examples, see: Sibi, M.P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115. Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A.L. *J. Org. Chem.* **1992**, *57*, 1219 and references cited therein.

3 For previous syntheses, see: Gmeiner, P. *Arch. Pharm. (Weinheim)* **1991**, *324*, 551. Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1029.

4 Besides 66% product, 2% regioisomer and 11% bis-protected derivative were formed. Both by-products could be easily separated by chromatography.

5 **8b** is unstable towards chromatography and was used as a solution in CH_2Cl_2.

6 For examples of related migration reactions, see: Shanzer, A.; Somekh, L. *J. Am. Chem. Soc.* **1982**, *104*, 5836. Setoi, H.; Takeno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261.

7 Using **9b** and **11b** as examples, the optical integrity of the synthesis was proved by hydrazinolysis and subsequent derivatization of the primary amines with optically pure (R)-1-phenylethylisocyanate.

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