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CHIROSPECIFIC SYNTHESIS OF AMINO ACIDS, AMINO ALDEHYDES AND AMINO ALCOHOLS FROM D-GLUCOSAMINE HYDROCHLORIDE. A MULTIGRAM SYNTHESIS OF N-BOC-L-SERINAL

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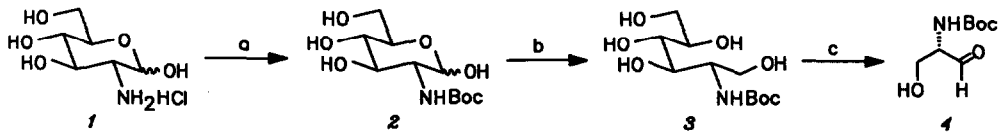
Abstract: N-tert.-butyloxycarbonyl-L-serinal 4 was readily prepared from D-glucosamine hydrochloride 1 in three steps. The versatile synthetic intermediate 4 is chemically and configurationally stable for prolonged time and reacts with various stabilized phosphorus ylides to produce the enantiomerically pure (ee > 95 %) allylamino alcohols 6 in high yields.

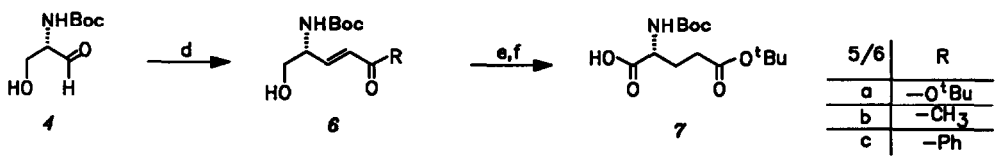
Optically active amino alcohols, amino aldehydes and amino acids with highly functionalized side chains are constituents of many biologically and pharmacologically important compounds, e.g. inhibitors of renin, angiotensin converting enzyme, HIV-1 protease or PLP-dependent enzymes, as well as immunomodulators, cytostatic drugs, peptide antibiotics, etc.[1] Accordingly, interest in synthesis of these compounds grew rapidly in recent years[2].

In the course of our project on synthesis of inhibitors and modulators of glycosphingolipid biosynthesis[3,4], we developed new ways to the chirospecific synthesis of amino alcohols, amino aldehydes and amino acids from inexpensive and readily available D-glucosamine hydrochloride 1 (Scheme I). D-glucosamine hydrochloride 1 (10.78g, 50 mmol) was converted to its N-tert.-butyloxycarbonyl derivative[5] 2 (12.56 g, 90%) by treatment with NaOH/Boc_2O in methanol. Reduction of 2 with excess of $NaBH_4$ in ethanol afforded aminopolyol 3, which, without further purification, was treated with an aqueous solution of $NaIO_4$ (3 eq) to give analytically pure N-tert.-butyloxycarbonyl-L-serinal[6] 4 (6.71 g, 80%, soft.p. 57°C, mp 71-75°C, $[\alpha]^{20}_D$ -10.8°, c=2.18, Me_2SO) after continuous extraction with ether. We were pleased to find out that the crystalline and hihgly functionalized aldehyde 4 is chemically and configurationally stable at room temperature. Its physical data remains unchanged for at least 6 months. The reason for the unusual stability of this versatile synthetic intermediate is its

Scheme I

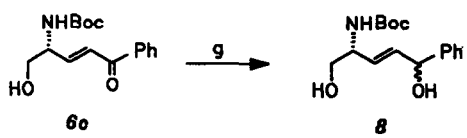


Scheme II



5/6	R
a	$-O^tBu$
b	$-CH_3$
c	-Ph

Scheme III



a:NaOMe, Boc_2O, MeOH, b:$NaBH_4$, EtOH, 20° C, 24h, c:$NaIO_4$, H_2O, 4° C, d:Ph_3P=CHCOR (5a-c), CH_3CN, e: H_2/PtO_2, f: ref. 10, g: ref. 11.

oligomeric / polymeric structure as determined by ^{1}H- and ^{13}C-NMR spectroscopical investigations[7].

Treatment of 4 with various stabilized phosphorus ylides 5 afforded the enantiomerically pure[8] and highly functionalized allylamino alcohols 6a-c in high yields (80-87 %, Scheme II).The E/Z ratio varies from 5:1 (6a) to >95:5 (6b and 6c).

The derivative of D-glutamic acid[9] 7, $[\alpha]^{20}_{D}$ +9.5°(c=0.5,MeOH), mp 101-102°C could be produced from the GABA- analogon 6a after hydrogenation of the double bond and subsequent $RuO_2/NaIO_4$ - oxidation[10] (85% yield , Scheme II). This example demonstrates the suitability of amino aldehyde 4 for the synthesis of D-amino acids.

Finally reduction of compound 6c with $NaBH_4$ / $CeCl_3$[11] gave the amino diol 8 as 1:1 diastereomeric mixture (92% yield , Scheme III).

As D-glucosamine hydrochloride 1 is inexpensive, the N-Boc-L-serinal 4- readily prepared from it in multigram amounts - is stable and reacts smoothly with various phosphorus ylides to chiral compounds 6 in high yields, we think that our system will be widely used in the synthesis of several polyfunctionalized amino alcohols and amino acids [12-14].

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12. Starting from N-benzyloxycarbonyl-D-glucosamine we have prepared N-Z-L-serinal. Similarly N-Z-D-serinal was prepared starting from N-benzyloxycarbonyl-D-mannosamine. Both amino aldehydes are also chemically and configurationally stable at room temperature for at least one year:
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13. Typical procedure: A solution of N-tert.-butyloxycarbonyl-L-serinal 4 (400 mg, 2.11 mmol) and benzoyl-methylenetriphenylphosphorane 5c (1g, 2.63 mmol) in dry acetonitrile (30 ml) is stirred under an atmosphere of nitrogen at 60° C for 2 h. Upon removal of the solvent, the crude product is chromatographed over silica gel (eluent : hexane / ethyl ester 1:1) providing 517 mg(84 %) of pure allylamino alcohol 6c. ^{1}H-NMR (200 MHz, d_6-Me_2SO): δ= 1.42 (s, 9H), 3.48 (m, 2H), 4.3 (m, 1H), 4.95 (t, 1H), 6.90 (dd, 1H, ^{3,4}J= 16 Hz and ^{2,3}J= 5.1 Hz), 7.10 (dd, 1H, ^{3,4}J = 16 Hz and ^{2,4}J= 1.4 Hz), 7.11 (d, J=9 Hz, 1H ,-NH), 7.50- 7.71 (m , 3H), 7.92- 8.00 (m, 2H); mp 113 - 115 °C, $[a]^{20}_D$ -2.16° (c= 1.29, MeOH).
14. All new compounds gave satisfactory C,H,N analyses and appropriate spectra.

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