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Synthesis of C- α-D-Glucosyl-α-amino Acids

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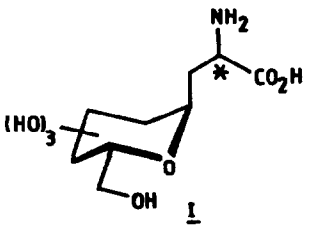
Abstract : The Sharpless asymmetric dihydroxylation of C-allyl-α-D-glucopyranoside with variety of ligands and its application to synthesise C-α -D-glucosyl-α -amino acids have been described.

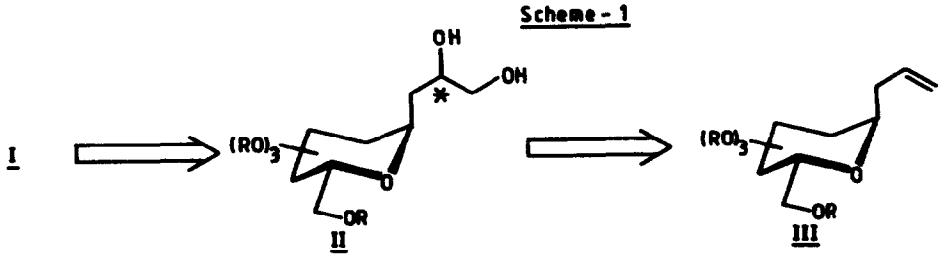
C-Glycosylamino acids (1) arose considerable interest in recent years primarily because of their ability to withstand the biological process of hydrolysis. By the virtue of their high chemical stability, they are accepted as potential glycosidase inhibitors[1]. In spite of many developments[2] that have occurred in the synthesis of O- and N-glycosylamino acids, practically very little work on C-glycosylamino acids has been encountered in literature[3]. Therefore, we believe that there is a significant scope to develop alternate and versatile protocols towards C-glycosylamino acids (I).



I

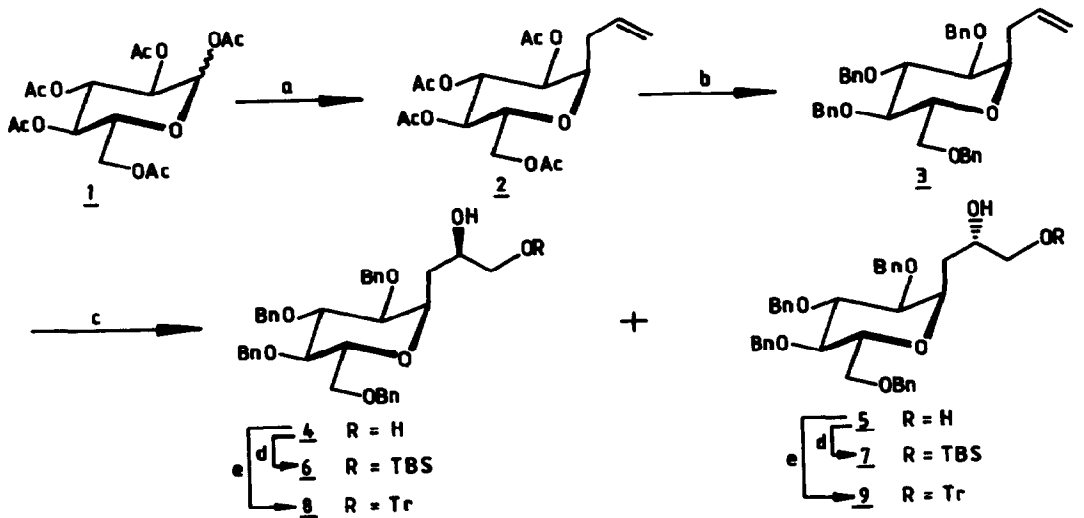
In our previous communication[4], we described the Sharpless asymmetric dihydroxylation (ADH) of allyl D-glucopyranosides to prepare glucosylglycerol derivatives. Since then ADH[5] reaction has been significantly improved in terms of efficiency, simplicity and predictability because of the introduction of reagents such as AD-mix-α and AD-mix-β at the commercial level[6]. In continuation, we planned the retrosynthesis of C-glycosyl-α -amino acid (I) as shown in scheme 1. The proposition to prepare the enantiomerically pure diol (II), serving as an ideal precursor for the target molecule I, was based on the application of ADH on C-allylglycoside (III).

Scheme - 1



The preparation of C-allyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**2**) from D-glucosepentaacetate (**1**) and allyltrimethylsilane in the presence of BF_3:OEt_2 was a straightforward exercise[7]. Subsequently, **2** was deacetylated under Zemplen condition and then benzylated by employing NaH-BnBr combination in dry DMF to provide **3**. Compounds **2** and **3** formed representative examples of the present ADH study (scheme 2).

Scheme - 2



a) Ref.6, (b) (i) NaOMe, MeOH, RT, 2h, 96%; (ii) DMF, NaH, BnBr, O°-RT, 18h, 92%; (c) OsO_4, $K_3Fe(CN)_6$, t-BuOH-H_2O (1:1), Ligand, 0°-RT, 18h, 70-85%; d) TBS-Cl, Imid., CH_2Cl_2, RT, 3h; 75%; e) TrCl, Py, 70°, 3h, 90%.

Treatment of **3** with AD-mix-β in 1:1 t-BuOH-H_2O at 0°-RT for 18 h gave a diastereomeric mixture of diols (**4/5**). In order to determine the ratio, **4/5** were converted selectively into the mono TBS-ether (**6/7**) or the mono trityl-ethers (**8/9**) by adopting standard procedures. The HPLC analysis of **6/7** on a chiral column (chira-cel OD, 8% isopropanol/n-hexane, UV

Table

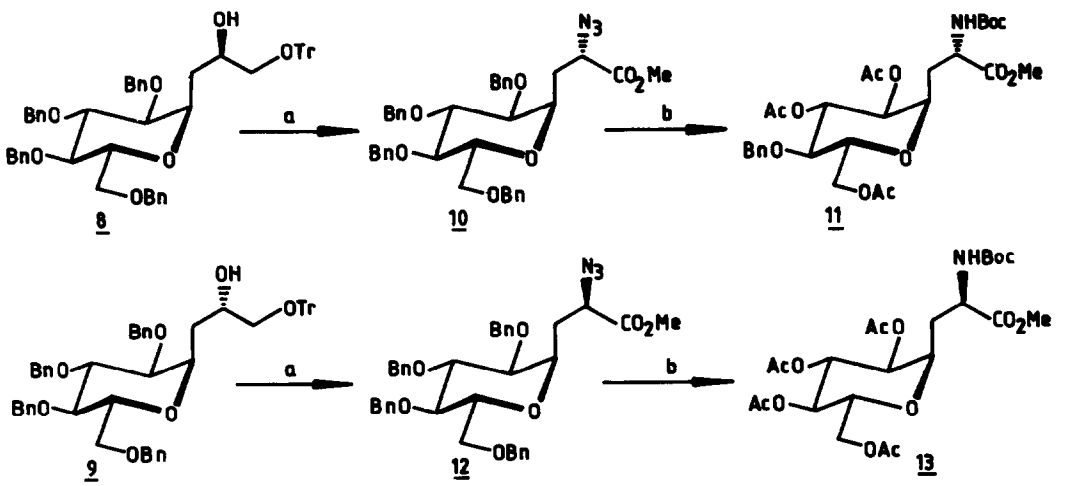
Entry	Substrate	Ligand	Product		Yield
			2R	2S	
1	3	AD-mix-β	61	39	73%
2	3	DHQD-9-O-phenathryl ether	78	22	83%
3	3	DHQD-p-Cl-benzoate	64	36	84%
4	3	DHQ-9-O-phenanthryl ether	41	59	75%
5	2	DHQD-9-O-phenanthryl ether	70	30	70%

228 nm) resolved the mixture efficiently to provide the ratio of 61:39 (**6/7**) (entry 1, Table). Since the diastereofacialselectivity with AD-mix-β was only moderate, we decided to utilise other cinchona alkaloids, as chiral ligands, with the hope to improve ADH stereoselectivity[8]. Indeed ADH reaction of **3** with DHQD-9-O-phenanthryl ether (entry 2) followed by derivatisation of TBS-ethers (**6/7**) showed significant improvement in the ratio, 78:22 as judged by HPLC. On the other hand, with DHQ-9-O-phenanthrylether (entry 4) as ligand, **3** demonstrated, as expected, the reverse diastereofacialselectivity with the ratio 41:59 for **6/7**. Other exmaples of ADH reactions with **2** and **3** are included in the Table.

On a preparative and multigram scale, the diastereomeric mixture of trityl ether derivatives (**8/9**) were cleanly separated by silica gel column chromatography, thus providing enantiomerically pure (2R)-**8** and (2S)-**9** isomers. Both these products were then transformed independently into the corresponding C-α-glucosyl-α-amino acid derivatives.

For instance, **8** was first converted into the mesyl derivative with MsCl-Py and then subjected to nucleophilic displacement reaction with NaN_3-DMF at 120°. From the resulting azido derivative, the trityl group was removed by using 80% aqueous acetic acid followed by Jones oxidation and esterification providing the azido ester (**10**). Exhaustive reduction of **10** over 10% Pd-C at 1 atm in methanol containing 1.2 equivalent of Boc_2O was then performed for 36 h, followed by conventional acetylation with Ac_2O-Py to give α-C-glucosyl-α-amino acid derivative (**11**)[9].

Scheme-3



a) (i) Py, MsCl, CH_2Cl_2, 0°-RT, 3h; (ii) NaN_3, DMF, 120°, 3h, 35% (from 8), (iii) 80% AcOH, 80°, 2h, 70%; (iv) Jones reagent, MeCOMe, 0°-RT, 1h; (v) CH_2N_2, EtOEt, 0°, 30 min, 63%, (b) (i) Pd-C, EtOH, BOC_2O, H_2 (1 atm), 36 h, 70%; (ii) Ac_2O-Py, 0°-RT, 18h, 90%.

In a similar fashion, compound **9** was also converted into the C-glycosylamino acid (**13**) via the azido ester substrate **12**, by following essentially identical reaction conditions.

In the preceding lines, we have described a simple and versatile approach to synthesise C-glycosylamino acids. The process in principle could be expanded to other C-glycosylamino acids depending upon the C-alkenylglycosides used as substrates. This study is under progress.

Acknowledgments

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9. a) Data for **13**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.01 (s, 6H), 2.03 (s, 3H), 2.07 (s, 3H), 3.73 (s, 3H), 3.96 (dd, 1H, J = 2.2, 13.5 Hz), 4.21 (dd, 1H, J = 4.4, 13.5 Hz), 4.34 (m, 2H), 4.92 (t, 1H, J = 9.0 Hz), 5.16 (t, 1H, J = 9.0 Hz), 5.28 (d, 1H, J = 6.75 Hz); $[\alpha]_D$ +36 (c 1.0, $CHCl_3$); b) Data for **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.04 (s, 6H), 2.08 (s, 3H), 2.12 (s, 3H), 3.75 (s, 3H), 4.06 (dd, 1H, J = 2.0, 12.5 Hz), 4.23 (m, 2H), 4.39 (m, 1H), 4.91 (t, 1H, J = 8.3 Hz), 5.18 (t, 1H, J = 8.5 Hz); $[\alpha]_D$ +42 (c 1.0, $CHCl_3$).

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