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Synthesis of 2-Amino-2-deoxy-D-hexopyranosides from 4-*O*-Trichloroacetimidyl-D-hex-2-enopyranoside by [3,3]-Sigmatropic Rearrangement

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Summary: 2-Amino-2-deoxysugars, D-mannosamine and D-altrosamine derivatives were synthesized together with D-idosamine and D-talosamine ones from a 2-deoxy-2-trichloroacetamido-hex-3-enopyranoside. This key intermediate was prepared by regio- and stereoselective [3,3]-sigmatropic rearrangement of 4-*O*-trichloroacetimidyl-hex-2-enopyranoside.

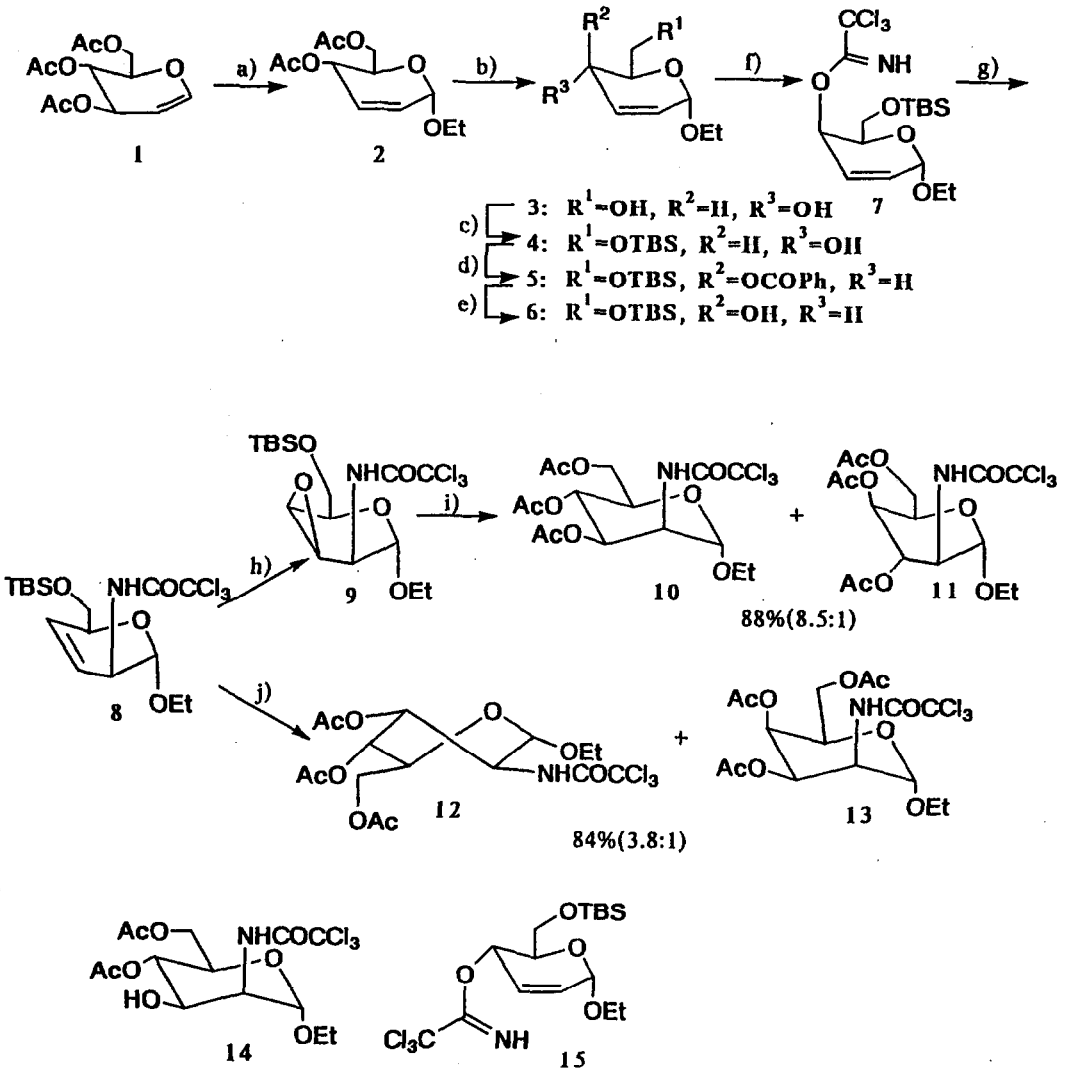
2-Amino-2-deoxy-D-mannopyranose (D-mannosamine) and its derivatives play important role as substrate for a type-specific immunogeneity in various bacteria associated with invasive diseases[1,2].

A wide range of methods are available for the synthesis of 2-aminosugars[3]. However, few syntheses[4] of 2-aminosugars employing [3,3]-sigmatropic rearrangement of 2-enopyranoside have appeared.

Now we wish to report[5] the regio- and stereoselective synthesis of 2-amino-2-deoxy sugars such as D-mannosamine and D-altrosamine derivatives by the 1,3-rearrangement of allylic functionality of hex-2-enopyranoside. A key step in the present synthesis is the [3,3]-sigmatropic rearrangment of a trichloroacetimidyloxy residue[6] on the allylic position of 2-enopyranoside.

The construction of the key compound for the 1,3-rearrangement, 4-*O*-trichloroacetimidyl-2-enopyranoside 7, started with 2-enopyranoside 2 obtained by Ferrier rearrangement[7] of 3,4,6-tri-*O*-acetyl-D-glucal(1)[8] with ethanol (80%) (Scheme I). After *O*-deacetylation of 2 with sodium methoxide in methanol (86%), selective *tert*-butyldimethylsilylation (TBS) of *O*-6 was carried out to give 4 in 95% yield. 4-Benzoate 5 prepared by inversion of the 4-hydroxyl group of 4 *via* Mitsunobu reaction[9] (85%) was treated with sodium methoxide to give a 4-epimer(6) of 4 (quant). The 2-enoside 6 was treated with trichloroacetonitrile (TCA) with a catalytic amount of sodium hydride in dichloromethane to give a trichloroacetimidate 7. A signal due to the imino proton of 7 was observed at 8.30 ppm as a singlet in NMR. The imidate 7 was heated in refluxing toluene overnight to give a rearranged 3-enoside 8 bearing a trichloroacetamido group at the allylic position (89%). NMR showed a signal due to the amido proton at 6.65 ppm (d). Oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) of the 3-enoside 8 at ambient temperature furnished an epoxide 9 as a single product in good yield (91%). Treatment of epoxide 9 with acetic anhydride in acetic acid with a catalytic amount of $BF_3 \cdot OEt_2$ for 24 hr at room temperature gave ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-mannopyranoside 10 and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-idopyranoside 11 (88%, 10:11= 8.5:1)[10]. When the reaction was carried out for 5 min under the same acidic

Scheme I



a) EtOH(2.0 equiv.), BF_3 OEt_2(cat.), benzene, r.t., 80%;
b) NaOMe(cat.), MeOH, r.t., 86%;
c) TBSCl(1.1 equiv.), imidazole(1.1equiv.), DMF-CH_2Cl_2, r.t., 95%
d) PhCOOH(4.0 equiv.), Ph_3P(4.0 equiv.), EtOOCN=NCOOEt(4.0 equiv.), THF, r.t., 85%;
e) NaOMe(cat.), MeOH, r.t., quant.;
f) $NCCCl_3$(1.5 equiv.), NaH(cat.), CH_2Cl_2, r.t., 90%;
g) xylene, reflux, 89%;
h) *m*-CPBA(4.0 equiv.), $CHCl_3$, r.t., 91%;
i) Ac_2O, AcOH, BF_3·OEt_2(cat.), r.t., 88%;
j) 1) OsO_4(1.1 equiv.), pyridine, r.t., 2) $NaHSO_3$, pyridine, 3) TBAF, THF, r.t., 4) Ac_2O, pyridine, r.t., 84%;

conditions as above, a small amount of ethyl 4,6-di-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-mannopyranoside 14 was obtained together with the starting epoxide 9 and a trace of mannopyranoside 10. It therefore seemed likely that the configuration of epoxide 9 would be D-talo type. However, since we failed to confirm the above tentative structure by NMR data, the configuration of the definite epoxide will be determined by other means. The predominant conformation of 11 would adopt half chair form by the coupling constants ($J_{1,2}=J_{2,3}=1.5$, $J_{3,4}=J_{4,5}=2.0$ Hz). On the other hand, an oxidation of 8 by osmium tetroxide in pyridine followed by hydrolysis of the resulting osmium ester by sodium bisulfite and peracetylation afforded ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-altropyranoside 12 and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-talopyranoside 13 (84%, 12:13=3.8:1)[11]. A skew conformation of compound 12 was suggested based on the coupling constants of the pyranose ring protons in pyridine-d_6. Treatment of 10 with 1N-HCl at 95°C for 3.5 hr furnished the corresponding D-mannosamine hydrochloride in good yield after azeotropic removal of volatile material from the reaction mixture under reduced pressure (81%, after purification)[12].

In the [3,3]-sigmatropic rearrangement, the imino group of compound 7 may attacks 2-position from the upper side of the pyranose ring by way of cyclic transition state. It is worthy of note that the thermal rearrangement of 4-epimer(15) of 7 did not take place. This may come from the steric hindrance of α-oriented the anomeric ethoxy group, namely the configuration of the anomeric position may be crucial for the feasibility of rearrangement. The nucleophilic reactions of epoxide 9 with several nucleophiles such as azide, nitrile, and carbanion were also studied and reported in a subsequent paper.

The application of [3,3]-sigmatropic rearrangement to the synthesis of 2-amino-2-deoxy sugars has been achieved and further extention to synthesis of other amino sugars are in progress.

References and notes

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3) D-Mannosamine and its derivatives were synthesized by several methods. For example: Chemical construction from D-arabinose derivatives; (a) Kuhn, R.; Kirschenlohr, W.; Bister, W. *Justus Liebigs Ann. Chem.* 1956, *600,* 115. (b) Kuhn, R.; Bister, W. *ibid,* 1957, *602,* 217. (c) O'Neill, A. N. *Can. J. Chem.* 1959, *37,* 1747. (d) Sowden, J. C.; Oftedahl, M. L. *J. Am. Chem. Soc.* 1960, *82,* 2303., and earlier references. Isomerization of D-glucosamine; (e) Spivak, C. T.; Roseman, S. *J. Am. Chem. Soc.* 1959, *81,* 2403. Azidonitration of D-glucal; (f) Paulsen, H.; Lorentzen, J. P.; Kutschker, W. *Carbohydr Res.* 1985, *136,* 153., and references cited therein.
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6) (a) Overman, L. E. *J. Am. Chem. Soc.* 1974, *96,* 597. (b) Overman, L. E.

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8) Although the use of 3, 4, 6-tri-*O*-acetyl-D-galactal whose 4-OH group is "up" is reasonable as starting material in this synthesis of D-manno type, the Ferrier rearrangement of D-galactal with ethanol was quite sluggish and in addition yields was not satisfactory (~ 40 %). Therefore, we used D-glucal as starting material.

9) (a) Mitsunobu, O. *Synthesis,* 1981, 1. (b) Grynkiewicz, G. ; Burzynska, H. *Tetrahedron,* 1976, *32,* 2109.

10) Compounds 10 and 11 were obtained as a mixture (17.6 mg, 88%). The mixture ratios of 10 and 11 were confirmed with integral values of 4-H signal in NMR spectrum (10:11=8.5:1). 10 and 11 were separated by preparative TLC (AcOEt:hexane=1:3) to give 10 as crystals (15.5 mg) and 11 as colorless syrup (1.8 mg). 10: mp 105-107°C; $[\alpha]_D^{24}$ +46.5° (*c* 0.46, $CHCl_3$); IR (neat) 3420, 3320 (NH), 2950 (CH), 1750, 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $OCH_2\underline{CH_3}$,), 1.99, 2.05, 2.10 (s x 3, 9H, $OCOCH_3$), 3.58 (m, 1H, $OCHH'CH_3$), 3.77 (m, 1H, $OCHH'CH_3$), 4.01 (ddd, $J_{5,6'}$=2.5, $J_{5,6}$=4.5, $J_{5,4}$=10.5 Hz, 1H, 5-H), 4.12 (dd, $J_{6',5}$=2.5, $J_{6',6}$=12.5 Hz, 1H, 6'-H), 4.22 (dd, $J_{6,5}$=4.5, $J_{6,6'}$=12.5 Hz, 1H, 6-H), 4.57 (ddd, $J_{2,1}$=1.5, $J_{2,3}$=4.0, $J_{2,NH}$=9.5 Hz, 1H, 2-H), 4.87 (d, $J_{1,2}$=1.5 Hz, 1H, 1-H), 5.18 (dd, $J_{4,3}$=10.0, $J_{4,5}$=10.5 Hz, 1H, 4-H), 5.39 (dd, $J_{3,2}$=4.0, $J_{3,4}$=10.0 Hz, 1H, 3-H), 6.85 (d, $J_{NH,2}$=9.5 Hz, 1H, NH); ^{13}C NMR δ 14.83 ($OCH_2\underline{CH_3}$), 20.64 ($OCO\underline{CH_3}$ x 3), 52.17 (2-C), 62.06 (6-C), 64.33 ($O\underline{CH_2}CH_3$), 65.45 (4-C), 68.08 (5-C), 69.35 (3-C), 92.29 (CCl_3), 97.88 (1-C), 161.98 (NHCO), 169.58, 169.99, 170.42 ($O\underline{C}OCH_3$ x 3); HRFABMS *m/z* (calcd for $C_{16}H_{22}O_9N^{35}Cl_3$+H 478.0438) 478.0448 $[M+H]^+$.

11) Compounds 12 and 13 were isolated by preparative TLC (AcOEt:hexane=1:3). 12; colorless syrup (72 mg, 67.0 %). 13; mp 84-87°C (19.0 mg, 17.0%). 12; $[\alpha]_D^{23}$ +53.2° (*c* 0.47, $CHCl_3$) ; IR (neat) 3325 (NH), 2950 (CH), 1750, 1720 cm^{-1} (CO); ^1H NMR (pyridine-d_6) δ 1.09 (t, 3H, $OCH_2\underline{CH_3}$,), 1.82, 1.87, 1.96 (s x 3, 9H, $OCOCH_3$), 3.52 (m, 1H, $OCHH'CH_3$), 3.78 (m, 1H, $OCHH'CH_3$), 4.17 (dd, $J_{6,6}$=2.0, $J_{6,6'}$=11.0 Hz, 1H, 6-H), 4.40 (dd, $J_{6',5}$=7.0, $J_{6',6}$=11.0 Hz, 1H, 6-H'), 4.42 (ddd, $J_{5,6}$=2.0, $J_{5,4}$=4.5, $J_{5,6'}$=7.0 Hz, 1H, 5-H), 4.76 (ddd, $J_{2,1}$=5.5, $J_{2,NH}$=9.0, $J_{2,3}$=9.5 Hz, 1H, 2-H), 5.33 (d, $J_{1,2}$=5.5 Hz, 1H, 1-H), 5.62 (dd, $J_{4,3}$=4.0, $J_{4,5}$=4.5 Hz, 1H, 4-H), 5.83 (dd, $J_{3,4}$=4.0, $J_{3,2}$=9.5 Hz, 1H, 3-H), 10.32 (d, $J_{NH,2}$=9.0 Hz, 1H, NH): ^{13}C NMR (pyridine-d_6) δ 15.44 ($OCH_2\underline{CH_3}$), 20.58, 20.65, 20.73 ($OCO\underline{CH_3}$ x 3), 53.62 (2-C), 63.16 (6-C), 64.60 ($O\underline{CH_2}CH_3$), 68.06 (4-C), 68.41 (3-C), 71.13 (5-C), 93.26 (CCl_3), 99.60 (1-C), 163.35 (CONH), 170.39, 170.42, 170.49 ($O\underline{C}OCH_3$ x 3); HRFABMS *m/z* (calcd for $C_{16}H_{22}O_9N^{35}Cl_3$+H 478.0438) 478.0417 $[M+H]^+$.

12) D-Mannosamine hydrochloride was identical with an authentic sample on the base of TLC on cellulose and of mass spectroscopy; further, its penta-acetate was confirmed by ^1H NMR spectrum to be identical with penta-*O*-acetylmannosamine was prepared by peracetylation of *N*-acetylmannosamine.

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