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Synthesis of Branched Chain Cyclitols: Preparation of some Useful Chiral Building Blocks

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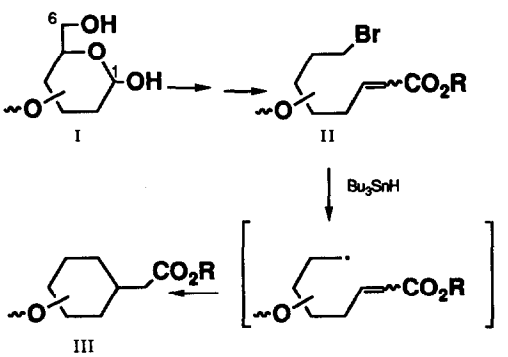
Abstract: The conveniently functionalized carbohydrate intermediates **1-4** and **9** undergo 6-exo free radical intramolecular cyclization giving branched chain cyclitols in good yield and low to good diastereoselectivity. These compounds are useful chiral building blocks for further manipulation.

Since polyoxygenated carbocycles are present in a variety of natural products, development of a general method for the stereoselective synthesis of these oxygenated compounds is of importance.[1] The free radical[2] strategy in the carbohydrate area is highly promising.[3]

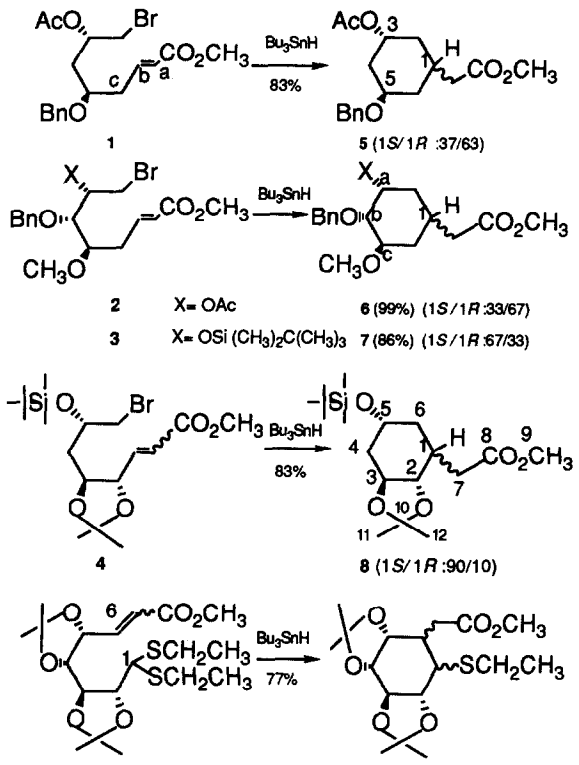
In the context of a program directed to the asymmetric synthesis of the cyclohexyl fragment of some natural products, we report here a new synthetic route to branched chain cyclitols [4] III via 6-exo free radical ring closure of acyclic chiral intermediates II derived from carbohydrates I (Scheme 1). In order to obtain versatile chiral building blocks, substrates functionalized at the side chain were selected for a preliminary study.

Scheme 1



The radical precursors **1-4**[5] have been easily synthesized from 2,3:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal.[6] Compounds **1-3** have been isolated as pure E isomers (**1**: δ H_b 6.96, dt, $J_{a,b}$=15.7 Hz, $J_{b,c}$=7.5 Hz); on the contrary, compound **4** has been obtained and cyclized as mixture of E and Z (67:33) isomers, that we could not separate.In the typical free radical cyclization conditions[7] compounds **1-4** gave the expected carbocycles as mixtures of diastereomers, that we could separate by flash chromatography, in the yields and ratios shown in Scheme 2.The absolute configuration at the new stereocenter (C1) in the major isomers of compounds **5-8** has been established by ^{1}H NMR analysis. For compound **5** [C1 (*R*)] we could observe δ H_3 5.11, tt, J=11.2 Hz, J=4.3 Hz, and H_5 3.87, qt, J=3.0 Hz, which is consistent for a cyclohexane in a chair conformation with the acetoxy (C3) and the benzyloxy (C5) group in equatorial and axial position, respectively. The same conclusion were obtained from compound **6** [C1 (*R*)] (d H_a 5.05, ddd

Scheme 2

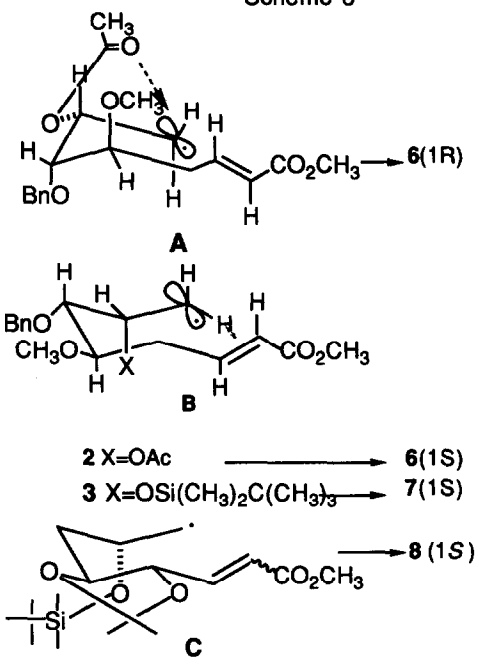


$J_{a,b}$=3.1 Hz, J=4.6 Hz, J=11.8 Hz; H_b 3.81 Hz, t, $J_{a,b}$=$J_{b,c}$=3.1 Hz; H_c 3.54, q, J=3.2 Hz) : the acetoxy, benzyloxy and methoxy groups are in equatorial, axial and axial position, respectively, in a chair conformation. Very surprisingly, the cyclization of compound **3** gave **7** [C1 (*S*)] as major isomer: (δ H_a 4.12, ddd,$J_{a,b}$=2.6 Hz,.J=2.2 Hz, J=2.0 Hz; H_b 3.09, dd, $J_{a,b}$=2.6 Hz, $J_{b,c}$=9.2 Hz; H_c 3.56, ddd, $J_{b,c}$=9.3 Hz, J=9.1 Hz, J=4.7 Hz), which implies that the *t*-butyldimethylsilyloxy group is in an axial, and the substituents at C3 and C4, in equatorial position of the favoured chair conformation.

Diastereomeric excesses obtained in the cyclization of compounds **1-3** are relatively low showing also that the substituent at C4 is not critical for the stereochemical result. These results could be rationalized assuming that of the two chair-like conformations[8] corresponding to the transition states **A** and **B** (Scheme 3) that derived from **A** is of lower energy than the relatively less stable conformer **B**, due to the superior stabilizing effect of the electron-attracting acetoxy group located in a pseudoequatorial position as in **A**, than in a pseudoaxial position as in **B**.This is a powerful stereoelectronic effect that overcompensates the steric repulsion due to the presence of substituents at C4 and C5 in axial position.[9] For compound **3** ,the less efficient stereoelectronic directing property of the *t*-butyldimethylsilyloxy group compared with the acetoxy,

does not suffice to compensate for the increase of the steric repulsion and major isomer **7** [C1 (*R*)] is obtained.

Scheme 3



The radical precursor **4** gave major isomer **8** (d.e.: 80%) (Scheme 2) with C1 (*S*) as absolute configuration at the new stereocenter; this, has been established by ^{1}H NMR (δ H2 3.03, dd, $J_{1,2}$=10.8 Hz, $J_{2,3}$=8.5 Hz),which determines axial-axial vicinal coupling constants between H2 and H1, H3. In the formation of **8** (1*S*) (Scheme 3, see C) the conformational equilibrium is restricted and the major product arises via a conformer where the substituents occupy quasiequatorial positions.[10]

Finally,in the cyclization of the radical precursor **5**,[5] easily available from 2,3:4,5-di-*O*-isopropylidene-D-glucose diethyl dithioacetal[11] we inverted the direction of the ring closure by putting the initiator at C1 (sugar numbering) and the acceptor at C6. In fact, the use of dithioketals as source of carbon centered radicals is known,[12] but this is the first time that has been used in a carbohydrate type precursor. In the typical free radical cyclization conditions,[7] we could isolate in good yield a mixture of diastereomers **10**, in 22:13:65 ratio, as determined by glc. Unfortunately, we were not able to obtain pure each isomer by chromatography and analyze relative configurations at the new stereocenters. The residual thioethyl group at C2 could not be removed using excess of tributyltin hydride or prolonged reaction times.

In summary, we have shown that the 6-exo free radical cyclization of conveniently functionalized carbohydrate intermediates is a new and powerful method for the synthesis of branched chain cyclitols. Applications of these valuable building blocks in total synthesis, especially in the field of pseudosugars and vitamin D, are under current investigation.

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References and Notes

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(5) All new compounds gave satisfactory analytical and spectroscopic data. The synthesis of the radical precursors **1-4**, **9** will be detailed elsewhere.

(6) Munro, J.; Percival, E.G.U. *J. Chem. Soc.* **1936**, *640*, 873.

(7) In a typical experiment, a solution of tributyltin hydride (3.4 ml, 0.013 mol, 2 equiv) and AIBN (cat.) in toluene (12 ml) was added dropwise (syringe pump), under argon, to a stirred solution of compound **4** (3.0 g, 6.8 mmol) in refluxing toluene (453 ml, 0.015 M) over 6h. After completion of the reaction, the solvent was evaporated and ether was added. The resulting solution was treated with 20% aqueous potassium fluoride and submitted to chromatography (hexane:AcOEt, 95/5) giving compound **8** [C1 (*R*)] (1.84 g, 75%) and its epimer at C1 (192 mg, 8%). **8** [C1 (*R*)]: Oil; $[\alpha]^{25}_{D}$ +4.0 (*c* 3.7, $CHCl_3$); ^1H NMR (300 MHz,$CDCl_3$) δ 4.19 (qt, $J_{5eq,4ax}=J_{5eq,4eq}=J_{5eq,6ax}=J_{5eq,6eq}$= 2.8 Hz 1H, H5, 3.84 (ddd, $J_{3ax,4eq}$=3.9 Hz, $J_{3ax,2ax}$=8.5 Hz, $J_{3ax,4ax}$=12 Hz, 1H, H3), 3.06 (s, 3H), 3.03 (dd, $J_{1ax,2ax}$= 10.8 Hz, 1H, H2), 2.72 (dd, $J_{7,7'}$=4.0 Hz, 1H, H7) 2.44 (m, H1), 2.16 (dd, $J_{7',1ax}$= 9.7 Hz, 1H, H7'; m, 1H, $H4_{eq}$), 1.89 (ddd, $J_{6eq,1ax}$=5.37, $J_{6eq,6ax}$= 13.7 Hz, 1H, $H6_{eq}$), 1.52 (dt, $J_{4ax,4eq}$= 12.0 Hz,1H, $H4_{ax}$), 1.43, 1.41 (s, s, H1, 3H), 1.17 (ddd, $J_{6ax,1ax}$= 11.7 Hz, 1H, $H6_{ax}$), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 172.32 (C8), 108.81 (C 10), 83.16, 75.43, 67.11 (C2, 3, 5), 51.29 (C9), 38.18, 37.01, 36.60 (C4, 6,7), 32.74 (C1), 26.81, 26.95 (C11, C2), 25.60, 17.13-5.11 [OSi $(CH_3)_2C(CH_3)_3$].

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