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Synthesis of chiral, densely functionalized medium-sized rings from carbohydrate precursors via regioselective *exo*/*endo*-primary alkyl radical cyclizations

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Abstract

The first 8-*endo*-*trig* and 7-*exo*-*dig* carbocyclizations of primary alkyl free radicals on acyclic carbohydrate templates derived from D-glucose, leading to chiral and polyfunctionalized medium-sized carbocycles are described.

In spite of some recent developments, the synthesis of medium-sized rings is a challenging goal and remains as a partially unsolved problem.[1] Free radical chemistry[2] has advanced interesting and efficient solutions to this problem.[3] In this context, aryl,[4] α-carbonyl,[5] α-acyl,[6] and acyl[7] radicals, or anion-radicals[8] have been prepared and submitted to regioselective 8-*endo*[9] carbocyclizations to give more or less complex eight-membered ring systems. Very interestingly, 8-*endo*-alkyl radical cyclizations are rare and, to the best of our knowledge, only two examples have been reported.[10] Conversely, 7-*endo*[11] and 7-*exo*[12] radical cyclizations are more common and have been described in several instances.

In our current effort for the synthesis of carbocycles from carbohydrates,[13] very recently we have directed our interest to the preparation of polyfunctionalized cycloheptanes from sugars by using different methodologies.[14] A free radical ring-closure strategy was also sought. In this context, the use of chiral polyoxygenated precursors for the asymmetric synthesis of medium-sized rings is scarcely documented.[15] In this paper, we have systematically analyzed several alternatives for the synthesis of polyhydroxylated medium-sized rings from carbohydrate precursors, and we describe a simple and convenient conversion of D-glucose to highly functionalized chiral medium-sized rings by regioselective 8-*endo*-*trig* and 7-*exo*-dig[15b] primary alkyl radical cyclizations in sugar templates, as we stated previously.

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For the exploratory experiments, and starting from D-mannose, radical precursors **1**–**6** (Fig. 1) have been synthesized.[16] Unfortunately, in the standard experimental conditions for free radical carbocyclizations, using tributyltin or triphenyltin hydrides or tris[(trimethylsilyl)]silane, with or without triethyl borane, in no case the required 7-*exo* ring closure products were detected; depending on the case, only reduced, acyclic, stannylated or recovered starting materials were isolated in variable chemical yields.

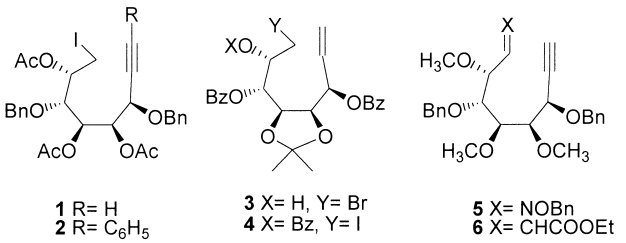
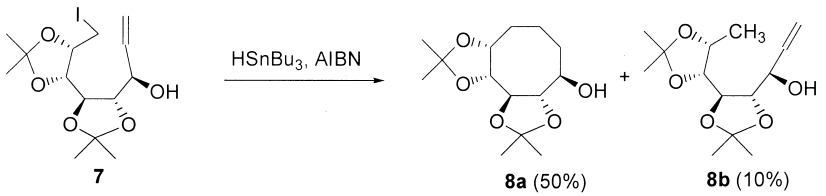


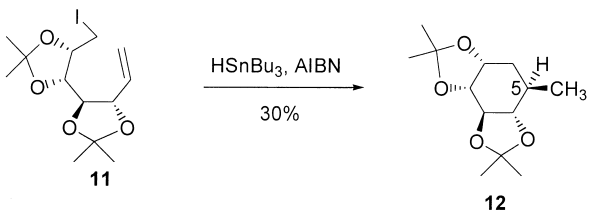
Figure 1.

In view of these deceiving results, and assuming that more conformationally constrained radical precursors were needed to promote effective cyclization reactions,[13c] we prepared intermediates which have two isopropylidene moieties at carbons C2/C3 and C4/C5 (sugar numbering). Then, starting from D-glucose we synthesized radical precursor **7**.[16] In the usual free radical conditions,[17] instead of the expected 7-*exo* compound, we isolated compound **8a** in 50% yield and the reduced, acyclic derivative **8b** in 10% yield (Eq. (1)). The structure for **8a**[16,17] was assigned based on the spectroscopic (compound **8a** showed in the ^{13}C NMR spectrum three methylene carbons for CH_2 at high field, confirming the structure and excluding then the *exo* product) and analytical data.[16] Although predicted by MO calculations and experimentally corroborated by Beckwith,[18] the exclusive formation of the 8-*endo* product (**8a**) in this radical cyclization is noteworthy. In fact, we think that the presence of two isopropylidene groups in precursor **7** has also deeply affected the regioselective and exclusive 8-*endo* mode for this cyclization, as Redlich and our own results have demonstrated in 7-*endo*-*trig* (see the ring closure of **9** to **10**)[15] and in the 6-*endo*-dig[13c] cyclizations, in related substrates.

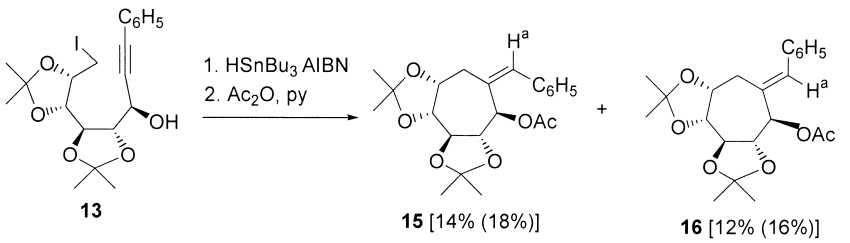
In order to confirm and extend these results, we have prepared and submitted to free radical cyclization precursor **11**.[16] Very surprisingly, this compound afforded the 6-*exo*-*trig* product **12**[16] in 30% (40%)[19] yield (Eq. (2)) (compound **12** showed in the ^1H NMR spectrum a doublet for the methyl group at 1.13 ppm with $J = 6.5$ Hz, confirming this structure and excluding then the *endo* product), as the only detected and isolated regio- (no 7-*endo* product) and diastereoisomer (absolute configuration *R* at C5, in agreement with the asymmetric diastereoselection observed in related precursors in our laboratory).[13] The formation of the exclusive 6-*exo*-*trig* product was surprising in this case taking into account Redlich's report.[15]



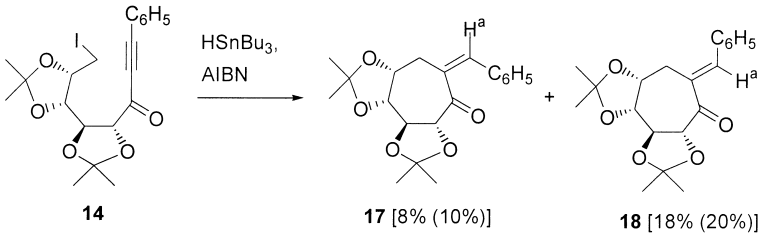
7 **8a** (50%) **8b** (10%) (1)



(2)



(3)



(4)

Apparently, this result proves that not only is the presence of the isopropylidene protecting groups for defining the course of the radical cyclization important, but so is the the relationship between the stereogenic sequence of the asymmetric carbons and the location of the carbon centered radical and the radical trap. In compound **11** the primary radical is vicinal to a *syn*-isopropylidene group, while in Redlich's example[15] the primary radical is vicinal to an *anti*-isopropylidene group.

Continuing with our project, and in view of these results, we decided to prepare the radical precursors **13**[16] and **14**,[16] which have acetylenic radical traps vicinal to hydroxyl or keto groups, respectively. Under the standard conditions, and starting from precursor **13**, after cyclization and acetylation, we obtained, separated and analyzed the 7-*exo*-*dig* products **15**[16] and **16**,[16] in the yields shown in Eq. (3); moreover, acyclic materials, apparently resulting from the reduction of the precursor **13**, without cyclization, were isolated, but their structure could not be assigned. Analogously, precursor **14** gave alkylidene-cycloheptanones **17**[16] and **18**[16,17] in 8% (10%)[19] and 18% (20%)[19] yields, respectively. Extensive and full spectroscopic analysis (^{1}H, ^{13}C, ^{13}C–DEPT, ^{1}H–^{1}H COSY, HMQC, HMBC) clearly confirmed the '*exo*' structure of these carbocyclization derivatives. In fact, and as we expected, the vinylic protons appear (H^a) in all the cases as singlets; similarly, the *E* or *Z* stereochemistry has been unequivocally assigned by NOE experiments. In the cyclization of precursor **14** we also detected other more polar products, none of which were isolated or characterized. Apparently, and by comparing the reactivity of precursors **7** with **13**/**14**, the substituted acetylenic moiety drives the cyclization to the *exo* mode by a steric effect.

In summary, we have reported a series of experiments which show that the 7-*exo*/8-*endo* cyclization protocols in carbohydrate templates are possible and can be modulated to give polydroxylated carbocycles in enantiomerically pure form. Studies are now in progress to extend these

results to other substrates and analyze the synthetic scope of this protocol; in addition, complementary molecular orbital calculations will be attempted to ascertain the transition state for these cyclizations, in order to give a more adequate explanation to these results.

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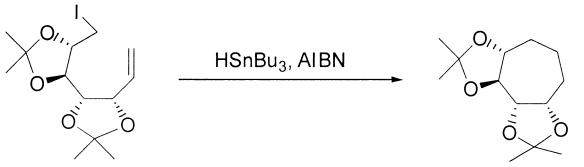

9 **10**

16. All new compounds showed good analytical and spectroscopic data. The synthesis of radical precursors **1**–**6** (from D-mannose) and **7**, **11**, **13** and **14** (from D-glucose) will be described elsewhere.
17. General protocol for the free radical ring-closing reaction: A degassed solution of the radical precursor, dissolved in toluene (0.02 M), under argon, was slowly (10 h) treated with a solution of tributyltin hydride (1.5 equiv.) plus AIBN (10% mol) in toluene via syringe pump. After complete reaction (TLC analysis), the solvent was removed and the residue treated with an aqueous solution (15%) of potassium fluoride and stirred overnight. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated. The residue was submitted to flash chromatography (eluting with hexane/ethyl acetate mixtures) to isolate the pure corresponding carbocycles. *Selected spectroscopic data*: compound **8a**: oil; $[\alpha]_D^{25}$ +5 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.30 (t, J = 8.4 Hz, 1H), 4.19–4.12 (m, 3H), 3.71 (dd, J = 8.4, 2.3 Hz, 1H), 2.32 (t, J = 7.4 Hz, 1H), 2.03–1.82 (m, 4H), 1.68–1.50 (m, 2H), 1.47, 1.46, 1.44, 1.36 (s, s, s, s, 4×CH_3, 12H); ^{13}C NMR ($CDCl_3$) δ 108.4, 108.3, 81.4, 79.8, 76.1, 73.9, 70.0, 28.9, 28.5, 28.0, 27.2, 26.9, 25.4, 17.7. Compound **18**: oil; $[\alpha]_D^{25}$ +145 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.63–7.24 (m, 5H), 4.72 (d, J = 10.3 Hz, 1H), 4.60 (dt, J = 6.0, 2.0 Hz, 1H), 4.38 (dd, J = 6.0, 8.4 Hz, 1H), 4.12 (dd, J = 10.3, 8.4 Hz, 1H), 3.40 (dd, J = 16.0, 6.1 Hz, 1H), 2.73 (dd, J = 16.0, 2.0 Hz, 1H), 1.55 (s, 2×CH_3, 6H), 1.49, 1.48 (s, s, 2×CH_3, 6H); ^{13}C NMR ($CDCl_3$) δ 194.9, 142.6, 134.4, 130.0–128.5 (C_6H_5), 111.9, 109.9, 86.4, 80.0, 78.1, 74.9, 28.4, 26.9 (2×C), 25.9 (2×C).
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