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A novel entry to 5a-carba-hexopyranoses from carbohydrates based on a 6-*exo-dig* radical cyclization: synthesis of 5a-carba-β-D-mannopyranose pentaacetate

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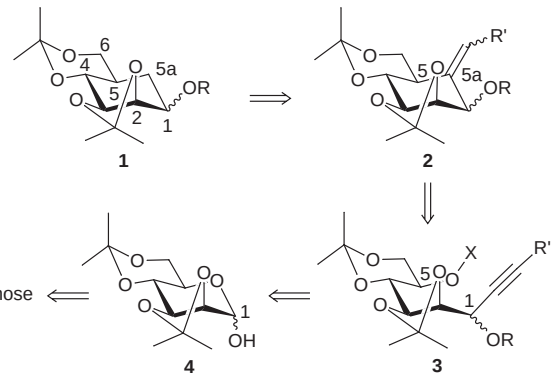
Carbohydrate-derived 2,3:4,6-diacetonides which are homologated at C-1 by reaction with phenyl acetylide undergo a 6-*exo-dig* radical cyclization, from a radical located at C-5, to yield highly functionalized cyclohexanes that are correlated with carba-sugars.

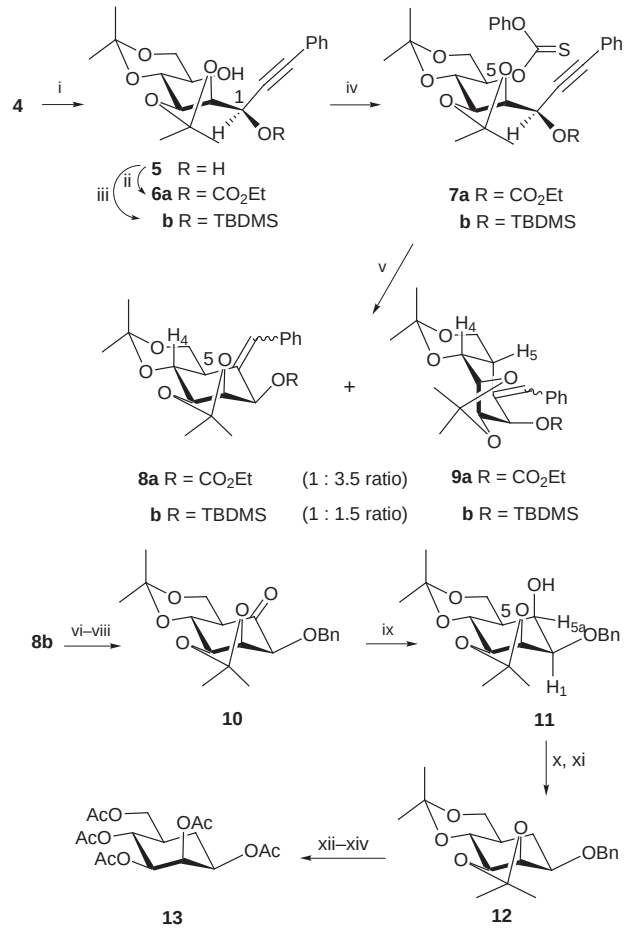
The term 'carba-sugar' is currently used to describe monosaccharide analogs having a methylene group instead of the ring oxygen atom.[1] Carba-sugars derived from hexopyranoses, 'carba-pyranoses' (*e.g.* **1**), were first prepared more than three decades ago by McCasland and co-workers[2] prior to their isolation from natural sources as components of important antibiotics.[3] Many of these substances, owing to their close structural resemblance to carbohydrates, are endowed with an interesting range of biological activities[4] which has triggered the development of different synthetic approaches for their preparation.[1,5,6] However, to the best of our knowledge only one synthetic approach involving radical ring closure[7] leading to 6-deoxy-5a-carba-pyranosides has been reported.[8] A very recent report by Maudru, Singh and Wightman[9] on the synthesis of carba-pyranoses by 6-*exo-dig* radical cyclization of carbohydrate derived alkynes prompts us to disclose our own results in this area.

As a continuation of our interest in the synthesis of highly functionalized carbocycles[10] from carbohydrates,[11] we turned our attention to the preparation of 5a-carba-hexopyranosides by radical ring closure of carbohydrate derived alkynes. Here we report some preliminary results which have resulted on the synthesis of 5a-carba-β-D-mannose pentaacetate **13**. Our general approach, outlined in Scheme 1 for D-mannose, correlates retrosynthetically the methylene group of the carba-pyranoside (*e.g.* **1**) with an exocyclic double bond in a highly functionalized cyclohexane (*e.g.* **2**). The latter could thus be obtained by a 6-*exo-dig* radical cyclization of a carbohydrate derived alkyne (*e.g.* **3**) easily derived from a pyranose 2,3:4,6-diacetonide derivative (*e.g.* **4**).

Accordingly mannose diacetonide **4** (Scheme 2), prepared in one single step from D-mannose by kinetic acetonation,[12] was treated with lithium phenylacetylide to yield, as a very major isomer, diol **5** in 65% isolated yield.† Chemoselective protection of the prop-2-ynylic hydroxy group could be accomplished by the use of either ethyl chloroformate (**6a**, 60%)[13] or TBDMSCl (**6b**, 65%).‡ The hydroxy group at C-5 in **6a**, or **6b**, was next treated with phenyl chlorothioformate[14] to furnish derivatives **7a** (85%) and **7b** (80%), respectively, which upon reaction with Bu_3SnH and AIBN[15] (toluene, 90 °C, 0.02 M) afforded tricyclic derivatives **8**§ and **9**§ in 95% combined yield. The synthetic scheme was next continued with compound **8b**§ [two isomers: δ 2.89 (ddt, $J_{4,5}$ = $J_{5,6ax}$ = 10.8 Hz, $J_{5,6eq}$ = 4.5 Hz, $J_{5,Holef}$ = 2.8 Hz, H-5 one isomer), 2.48 (ddt, $J_{4,5}$ = $J_{5,6ax}$ = 11.1 Hz, $J_{5,6eq}$ = 5.1 Hz, $J_{5,Holef}$ = 2.3 Hz, H-5 other isomer)]. Accordingly, after a change in the protecting group at



Scheme 1



Scheme 2 *Reagents and conditions*: i, PhC≡CLi, THF, −78 °C; ii, $ClCO_2Et$, Py, CH_2Cl_2, 0 °C; iii, TBDMSCl, Et_3N, DMAP, CH_2Cl_2; iv, ClC(S)OPh, Py, MeCN, 85 °C, 1 h; v, Bu_3SnH, AIBN, toluene (0.02 M), 90 °C; vi, TBAF, THF; vii, HNa, Bu_4NI, BnBr; viii, O_3, MeOH–CH_2Cl_2 (1:1), −78 °C, then Me_2S; ix, BH_3·SMe_2, THF; x, HNa, CS_2, MeI; xi, Bu_3SnH, AIBN, toluene, 90 °C; xii, H_2, Pd/C, MeOH; xiii, AcOH–THF–H_2O (4:2:1), 60 °C; xiv, Ac_2O, Py.

C-1 in **8b** (OTBDMS→OBn), ozonolysis was carried out to yield ketone **10**, which upon reduction ($BH_3 \cdot SMe_2$) gave, in a stereoselective manner, the highly functionalized cyclohexane **11** ($J_{5a,1}$ = 3.8 Hz) (75%, three steps). The hydroxy function at C-5a was deoxygenated under radical conditions, *via* its xanthate,[14,15] to afford 5a-carba-D-mannopyranoside derivative **12** (85%, two steps). Hydrolysis of the acetals followed by hydrogenation and acetylation gave 5a-carba-β-D-mannose pentaacetate **13**[16]¶ (87%, three steps).

In our opinion, several aspects of the synthetic scheme deserve further comment: (i) the choice of a 2,3:4,6-diacetonide derivative has reduced the protecting group manipulations in the synthetic scheme to a minimum; (ii) the selection of a phenylacetylide as the radical acceptor was made on the basis of the beneficial effects of the phenyl group in alkyne cyclizations;[17,18] (iii) unlike other approaches to carba-sugars from carbohydrates,[8,9] in this synthetic scheme an hexose is correlated with its corresponding carba-pyranoside; (iv) the present method permits access to fully functionalized cyclohexanes (*e.g.* **11**) of potential interest in the synthesis of biologically active compounds;[4] (v) by changing the protecting group of the hydroxy function α to the radical acceptor some stereocontrol has been attained in the cyclization reaction in favor of the isomer with *trans* 6,6-ring fusion[19] (**8**, Scheme 2); (vi) similar chemistry carried out on **9a** or **9b** would allow access to 5a-carba-α-L-gulopyranose.

In conclusion we have disclosed a novel entry into functionalized cyclohexane derivatives and carba-sugars from monosaccharides by 6-*exo-dig* cyclization of alk-6-ynyl radicals. Our approach complements the one recently described by Maudru *et al*.[9] in the sense that it allows for functionalization at all positions of the cyclohexane ring. The application of this synthetic scheme to other pyranose derived diacetonides is currently under study.

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Notes and references

† Compound **5** was the major isomer observed in the crude reaction mixture and could be easily separated by chromatography. The stereochemistry at C-1 was probed at a later stage on the synthesis. The corresponding epimer at C-1 was also observed (> 4:1 ratio) together with some isomeric 2,3:5,6-diacetonides (^{13}C NMR).

‡ Compounds resulting from the reaction of both hydroxy groups were always present, in yields ranging from 10–15%, and could be easily separated by chromatography.

§ Compounds **8a** and **8b** existed as two isomers (*ca.* 1:1 ratio), corresponding to the orientation of the phenyl group in the exocyclic double bond. Conversely, only one isomer at the phenyl group was observed for the *cis*-fused products **9a** and **9b**.

¶ The spectral properties (^1H NMR, C_6D_6, 400 MHz) were in accord with those reported in the literature (ref. 16): $[\alpha]_D$ +2.0 (*c* 0.6, $CHCl_3$), lit.,[16a] +2.9 (*c* 1.1, $CHCl_3$); lit.,[16b] +2.53 (*c* 1.67, $CHCl_3$); lit.,[16c] +2.9 (*c* 1.28, $CHCl_3$).

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