

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

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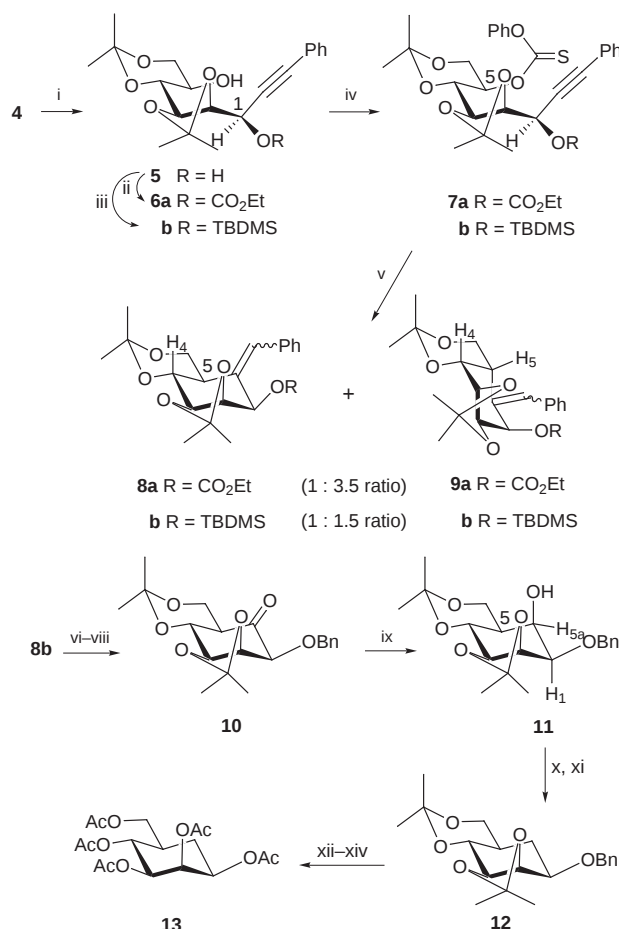
Carbohydrate-derived 2,3:4,6-diacetonides which are homologated at C-1 by reaction with phenyl acetylide undergo a 6-*exo-dig* radical cyclization, from a radical located at C-5, to yield highly functionalized cyclohexanes that are correlated with carba-sugars.

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

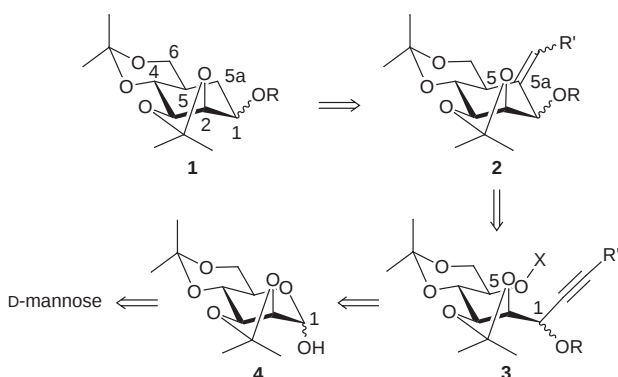
As a continuation of our interest in the synthesis of highly functionalized carbocycles<sup>10</sup> from carbohydrates,<sup>11</sup> we turned our attention to the preparation of 5a-carba-hexopyranosides by radical ring closure of carbohydrate derived alkynes. Here we report some preliminary results which have resulted on the synthesis of 5a-carba- $\beta$ -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,<sup>12</sup> was treated with lithium phenylacetylide to yield, as a very major

isomer, diol **5** in 65% isolated yield.<sup>†</sup> Chemoselective protection of the prop-2-ynyl hydroxy group could be accomplished by the use of either ethyl chloroformate (**6a**, 60%)<sup>13</sup> or TBDMSCl (**6b**, 65%).<sup>‡</sup> The hydroxy group at C-5 in **6a**, or **6b**, was next treated with phenyl chlorothioformate<sup>14</sup> to furnish derivatives **7a** (85%) and **7b** (80%), respectively, which upon reaction with Bu<sub>3</sub>SnH and AIBN<sup>15</sup> (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:  $\delta$  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 2** Reagents and conditions: i, PhC≡CLi, THF, −78 °C; ii, ClCO<sub>2</sub>Et, Py, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; iii, TBDMSCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; iv, ClC(S)OPh, Py, MeCN, 85 °C, 1 h; v, Bu<sub>3</sub>SnH, AIBN, toluene (0.02 M), 90 °C; vi, TBAF, THF; vii, HN<sub>3</sub>, Bu<sub>4</sub>NI, BnBr; viii, O<sub>3</sub>, MeOH–CH<sub>2</sub>Cl<sub>2</sub> (1:1), −78 °C, then Me<sub>2</sub>S; ix, BH<sub>3</sub>·SMe<sub>2</sub>, THF; x, HN<sub>3</sub>, CS<sub>2</sub>, MeI; xi, Bu<sub>3</sub>SnH, AIBN, toluene, 90 °C; xii, H<sub>2</sub>, Pd/C, MeOH; xiii, AcOH–THF–H<sub>2</sub>O (4:2:1), 60 °C; xiv, Ac<sub>2</sub>O, Py.



**Scheme 1**

C-1 in **8b** (OTBDMS→OBn), ozonolysis was carried out to yield ketone **10**, which upon reduction (BH<sub>3</sub>·SMe<sub>2</sub>) 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,<sup>14,15</sup> 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**<sup>16¶</sup> (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 phenylacetylde as the radical acceptor was made on the basis of the beneficial effects of the phenyl group in alkyne cyclizations;<sup>17,18</sup> (iii) unlike other approaches to carba-sugars from carbohydrates,<sup>8,9</sup> 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;<sup>4</sup> (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<sup>19</sup> (**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.*<sup>9</sup> 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 (<sup>13</sup>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 (<sup>1</sup>H NMR, C<sub>6</sub>D<sub>6</sub>, 400 MHz) were in accord with those reported in the literature (ref. 16): [ $\alpha$ ]<sub>D</sub> +2.0 (*c* 0.6, CHCl<sub>3</sub>), lit.,<sup>16a</sup>

+2.9 (*c* 1.1, CHCl<sub>3</sub>); lit.,<sup>16b</sup> +2.53 (*c* 1.67, CHCl<sub>3</sub>); lit.,<sup>16c</sup> +2.9 (*c* 1.28, CHCl<sub>3</sub>).

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