Stereodivergent Synthesis of Carbasugars from D-Mannose. Syntheses of 5a-Carba-α-D-allose, β-L-Talose, and α-L-Gulose Pentaacetates

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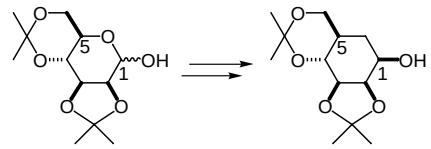
Abstract: A stereodivergent entry to 5a-carba-D- and L-pyranoses from a single precursor is described. The approach is based on the selective deoxygenation of polyoxygenated methylcyclohexane intermediates, readily available from radical cyclization of D-mannose derivatives. This strategy has been applied to the preparation of 5a-carba-α-D-allo-, 5a-carba-β-L-talo-, and 5a-carba-α-L-gulopyranose pentaacetates.

Key words: stereodivergent synthesis, carbasugars, radical cyclization, stereoselective synthesis

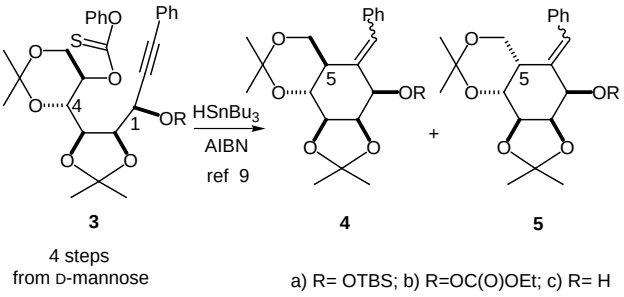
The term 'carbasugar' is used to describe monosaccharide analogues in which the oxygen ring has been replaced by a methylene group.[1] Many of these substances, owing to their close resemblance to carbohydrates,[2] are endowed with an interesting range of biological activities[3] which has triggered the development of different synthetic approaches for their preparation.[1,4,5] As part of an ongoing program in our laboratory aimed at the preparation of carbocycles from carbohydrates[6,7] we have recently reported two synthetic strategies for such an approach.[8,9] These methods, based on radical cyclizations of monosaccharide derivatives, were designed to directly correlate a given carbohydrate, **1**, with its corresponding 5a-carba-D-pyranose analogue, **2** (Scheme 1).[8,9] However a direct correlation method for the preparation of 'rare' carbasugars, or those corresponding to the L-series, would present problems related with the availability of the starting monosaccharides.



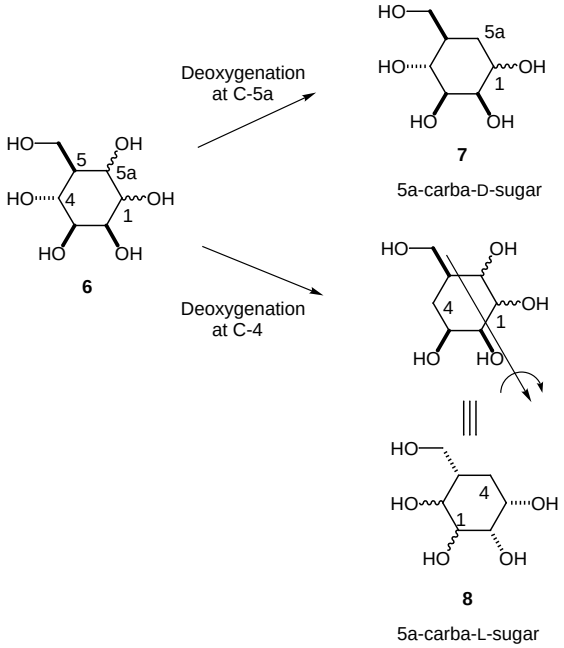
Scheme 1 Direct correlation of carbohydrates with carbasugars

In this communication we disclose a novel, stereodivergent, approach for the synthesis of D- and L-carbasugars from a single precursor which has been illustrated with the syntheses of 5a-carba-α-L-gulo, **13**, 5a-carba-α-D-allo, **19**, and 5a-carba-β-L-talopyranose, **23**, pentaacetates from intermediates **4** and **5** (Scheme 2) readily obtained by radical cyclization of a D-mannose derivative precursor, **3**. Our strategy, outlined in Scheme 3, is based on the selective deoxygenation of a polyoxygenated intermediate[10] (e.g. **6**, Scheme 3) at C-4 or at C-5a to afford either a 5a-carba-L-sugar derivative, **7**, or a 5a-carba-D-sugar derivative **8**, respectively.

The synthetic route takes further advantage from the fact that the relative ratio of compounds **4** and **5** can be modulated upon changes in the nature of the substituent at C-1



Scheme 2 6-*Exo-dig* radical cyclization of a D-mannose derivative[9]



Scheme 3 Stereodivergent synthesis of carbasugars from polyoxygenated intermediates

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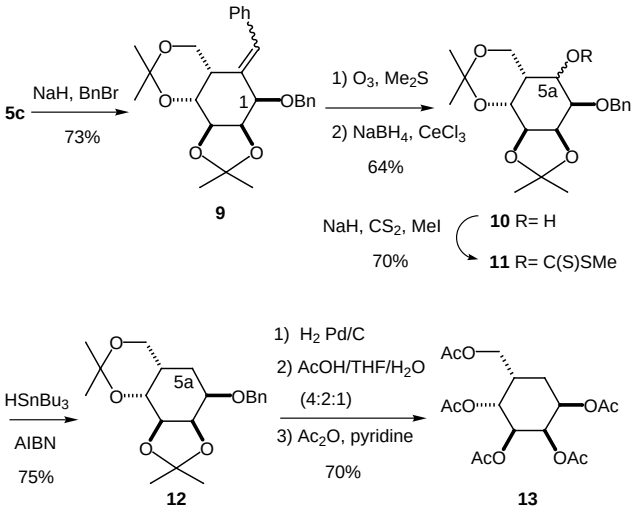
(Table). Cyclization of **3c** yields a 1:4.2 mixture of *trans*- and *cis*-dioxa-decalines **4c** and **5c**, compared to a 1:1.5 ratio when the protecting group at C-1 is a *tert*-butyldimethylsilyl group.

Table Influence of the Nature of the Substituent at C-1 in the Stereochemical Outcome of the Radical Cyclization

3 $\xrightarrow[\text{AIBN}]{\text{HSnBu}_3}$ **4** + **5**

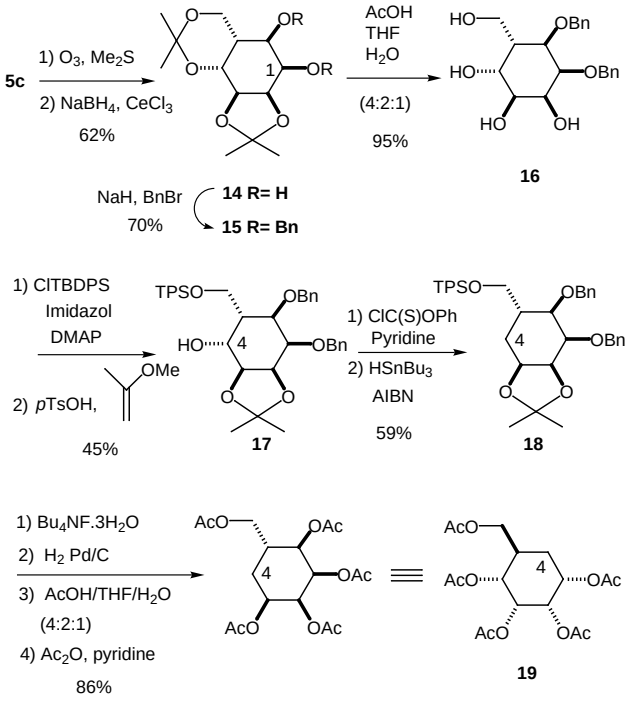
Entry	Substrate	Ratio (**4**:**5**)	Yield (%)
i	**3a**	1:1.5	95
ii	**3b**	1:3.3	75
iii	**3c**	1:4.2	51

Accordingly, compound **5c** was transformed into carbasugars of the L-gulo- and D-allo-series by deoxygenation at C-5a and C-4 respectively. Protection of the 1-OH group in **5c** led to **9** (Scheme 4), which upon ozonolysis and reduction of the resulting carbonyl group afforded compounds **10**, as a 1:1 epimeric mixture. Deoxygenation at C-5a in the latter, via the corresponding epimeric xanthates, **11**, furnished L-gulo derivative **12**. Routine transformations in **12**, then led to 5a-carba-α-L-gulose pentaacetate **13**[11,12]. {$[\alpha]_D^{21}$ –34.0 (*c* 0.32, $CHCl_3$). Lit. ref.[11] $[\alpha]_D^{21}$ –29.5 (*c* 1.5, $CHCl_3$}.



Scheme 4 Synthesis of **5a**-carba-α-L-gulose pentaacetate **13**

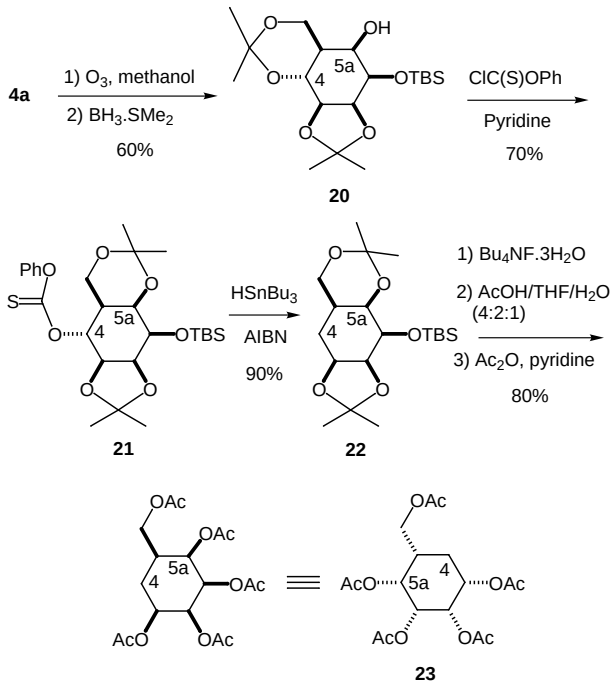
The synthetic process for the deoxygenation at C-4 of compound **5c** (Scheme 5), involved ozonolysis of the latter followed by reduction of the resulting carbonyl group to yield diol **14**, which upon benzylation afforded diacetonide **15**. Deprotection of the acid labile isopropylidene groups in **15** resulted in the formation of tetraol **16**. Compound **17**, in which the 4-OH group was now differentiated, was prepared from **16** through a reactions sequence which involved regioselective silylation at the primary hydroxyl group followed by selective protection of the *cis* diol moiety as *O*-isopropylidene acetal. Deoxygenation at C-4, then in **17**, via the corresponding phenyl thionocarbonate, paved the way to D-allo-derivative **18**, which upon conventional deprotection steps and acetylation led to 5a-carba-α-D-allose **19**[11–13]. {$[\alpha]_D^{21}$ +36.0 (*c* 1.0, $CHCl_3$, mp 95–98 °C). Lit. ref.[12] $[\alpha]_D^{21}$ +78.7 (*c* 1.5, $CHCl_3$, mp 96–97 °C}.



Scheme 5 Synthesis of **5a**-carba-β-L-talose pentaacetate **19**

Compound **20**, obtained by ozonolysis and reduction of **4a** (Scheme 6), was treated with phenylchlorothionoformate in the presence of pyridine to afford thiocarbonate **21**, in which an unexpected rearrangement of the *trans* 4,6-*O*-isopropylidene group to a *cis*-5a,6-*O*-isopropylidene ring had taken place prior to activation of the hydroxyl group at C-4. Compound **22**, which was obtained by treatment of **21** with tri-*n*-butyltin hydride in toluene, was then transformed into 5a-carba-β-L-talose pentaacetate **23**[14] {$[\alpha]_D^{21}$ +5.2 (*c* 0.4, $CHCl_3$), mp 135–138 °C}.

In summary, we have reported a stereodivergent strategy for the preparation of carbasugars based on the selective deoxygenation of polyoxygenated intermediates readily available from D-mannose upon radical cyclization. We have illustrated the synthetic potential of this approach with the preparation of carbasugars **13**, **19**, and **23** from synthetic intermediates **4** and **5**. The scope of this strategy can still be greatly enhanced by modifying the stereocenters at C-5, C-5a and C-1 in the latter compounds, while maintaining the stereochemical integrity, at positions C-2, C-3 and C-4, arising from D-mannose, or by utilizing a different monosaccharide starting material. Use of the above strategy for the preparation of additional carbasugars and derivatives thereof is underway in our laboratory and will be described in due course.



Scheme 6 Synthesis of **5a**-carba-β-L-talose pentaacetate **23**

General Procedure for Radical Cyclization

A thoroughly degassed (argon) solution of thiocarbonate in toluene (0.02 M) was heated to 85 °C under argon. A solution of Bu_3SnH (1.6 equiv) and AIBN (0.1 equiv) in toluene (5 mL/mmol) was then added and the reaction mixture was kept at that temperature over 12 h. After cooling, the organic solvent was evaporated and the residue was purified by flash chromatography.

Data for selected compounds:

1,2,3,4,6-penta-*O*-Acetyl-5a-carba-α-l-gulopyranose 13. (39 mg, 70% overall): $[\alpha]_D^{21}$ –34.1 (*c* 0.3, $CHCl_3$) ^{1}H NMR (300 MHz, C_6D_6): δ (ppm) = 5.83 (dd, *J* = 3.2, 6.5 Hz, 1 H, H3), 5.72 (m, 2 H, H2 y H4), 5.61 (dt, *J* = 3.0, 6.7 Hz, 1 H, H1), 4.24 (dd, *J* = 7.0, 10.8 Hz, 1 H, H6), 4.02 (dd, *J* = 6.7, 10.8 Hz, 1 H, H6), 2.76 (m, 1 H, H5), 1.96 (m, 2 H, 2H5a), 1.97 (s, 3 H), 1.91(s, 3 H), 1.90 (s, 3 H); 1.89 (s, 3 H), 1.80 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.8, 169.7, 169.5, 169.4, 169.3, 69.1, 68.3, 67.5, 62.9, 53.3, 30.2, 26.9, 20.5, 20.3, 20.2, 20.0, 18.5. MS: *m/z* = 411.2 [M + Na^+]. Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.81; H, 6.51.

1,2,3,4,6-penta-*O*-Acetyl-5a-carba-α-d-allopyranose 19. (43 mg, 86% overall): mp 95–98 °C, $[\alpha]_D^{21}$ +36.0 (*c* 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, C_6D_6): δ (ppm) = 5.54 (t, *J* = 3.1 Hz, 1 H, H3), 5.38 (m, 1 H, H1), 4.96 (t, *J* = 3.1 Hz, 1 H, H2), 4.89 (dd *J* = 3.1, 11.3 Hz, 1 H, H4), 4.18 (dd, *J* = 4.7, 11.3 Hz, 1 H, H6), 4.00 (dd, *J* = 2.9, 11.3 Hz, 1 H, H6), 2.56 (m, 1 H, H5), 2.14 (s, 3 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 2.02 (s, 3 H), 2.01 (m, 1 H, H5a_{ax}), 2.00 (s, 3 H), 1.71 (dt, *J* = 3, 14 Hz, 1 H, H5a_{eq}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.8, 170.1, 170.0, 169.7, 169.6, 69.3, 68.9, 68.5, 67.1, 63.0, 30.7, 29.3, 20.9, 20.8, 20.7, 20.6, 20.5. Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.76; H, 6.51.

1,2,3,4,6-penta-*O*-Acetyl-5a-carba-β-l-talopyranose 23. (84 mg, 80%): mp 135–138 °C, $[\alpha]_D^{21}$ +5.2 (*c* 0.4, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.49 (t, *J* = 3.1 Hz, 1 H, H2), 5.38 (t, *J* = 2.9 Hz, 1 H, H4), 4.39 (m, 2 H, H1, H3), 4.05 (dd, *J* = 8.8, 11.1 Hz, 1 H, H6$_{ax}$), 3.91 (dd, *J* = 6.3, 11.1 Hz, 1 H, H6$_{eq}$), 2.20–2.10 (m, 1 H, H5), 2.11 (s, 3 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H), 1.88 (q, *J* = 12.5 Hz, 1 H, H5a_{ax}), 1.69 (dt, *J* = 4, 12.5 Hz, 1 H, H5a_{eq}). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.8, 170.1, 170.0, 169.8, 169.6, 69.0, 68.9, 68.7, 66.1, 63.0, 29.7, 23.5, 26.8 (× 2), 20.7, 20.6, 20.5. Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.71; H, 6.43.

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