A Stereodivergent Approach to 5a-Carba-α-D-gluco-, -α-D-galacto and -β-L-gulopyranose Pentaacetates from D-Mannose, Based on 6-*exo-dig* Radical Cyclization and Barton−McCombie Radical Deoxygenation

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Dedicated to Professor Bert Fraser-Reid on the occasion of his 70th birthday

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The three carbasugars, 5a-carba-α-D-gluco-, -α-D-galacto and -β-L-gulopyranose pentaacetates **42**, **35** and **28** respectively, have been prepared in a stereodivergent manner from D-mannose. Alkynyl derivatives of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose, which are homologated at C-1 by reaction with trimethylsilylacetylide, undergo a 6-*exo-dig* radical cyclization, from a radical located at C-5, to yield a mixture of highly functionalized exo-methylenecyclohexanes. Ozonolysis of the exocyclic double bond in the latter generated cyclohexanones which, upon stereoselective reduction of the carbonyl moiety followed by site-selective deoxygenation either at position C-4 or C-5a (parent carbohydrate numbering), afforded the title carbasugars.

Introduction

The term "pseudo-sugar", nowadays replaced by "carbasugar",[1] was coined by McCasland and co-workers in 1966[2] to describe carbocyclic analogs of monosaccharides in which a methylene group has replaced the endocyclic oxygen. They prepared the first "carbasugars" in racemic forms: 5a-carba-α-DL-talo- (**1**)[1], 5a-carba-β-DL-galacto- (**2**)[3] and 5a-carba-α-DL-gulopyranose (**3**).[4] Carbasugars and some of their derivatives, as anticipated by McCasland,[2−4] display a wide range of biological properties owing to their close resemblance to carbohydrates.[5−7] Interestingly, five years after its synthesis, optically pure 5a-carba-α-D-galactopyranose (**2**) was isolated as a weak antibiotic from the fermentation broth of some *Streptomyces* species.[8] Carbahexopyranoses have been studied extensively during the past three decades, after their derivatives were found to occur naturally. In fact, carbasugar derivatives have been found as components of antibiotic validamycins[9−11] and the α-glucosidase inhibitor acarbose and its homologs[12] (amilostatins, adiposins, oligostatins, trestatins and aminooligosaccharides NS-504).[6,13] As consequence of these findings, an extensive synthetic effort has been devoted to the preparation of carbasugars and their analogs.[1,7,14−18]

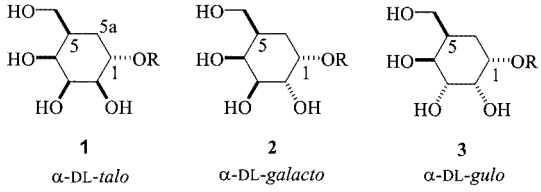
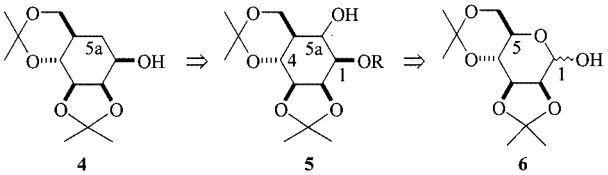


Figure 1. Racemic carbasugars prepared by McCasland and coworkers (shown: D-enantiomers)

In this context, our group, which had been interested in the preparation of carbocycles from carbohydrates,[19,20] has recently paid attention to the synthesis of carbasugars from monosaccharides.[21,22] Our synthetic strategies,[21,22] unlike those of others based on radical cyclization of carbohydrate derivatives,[23,24] were designed to allow the direct transformation of a carbohydrate, **6**, into its corresponding carbasugar, **4** (Scheme 1). We have already shown the usefulness of these approaches by preparing 5a-carba-D-gluco-,[21] 5a-carba-D-galacto-,[21] and 5a-carba-D-mannopyranose[22] pentaacetates from their corresponding monosaccharides.



Scheme 1. Retrosynthesis of 5a-carba-β-D-mannopyranose from D-mannose

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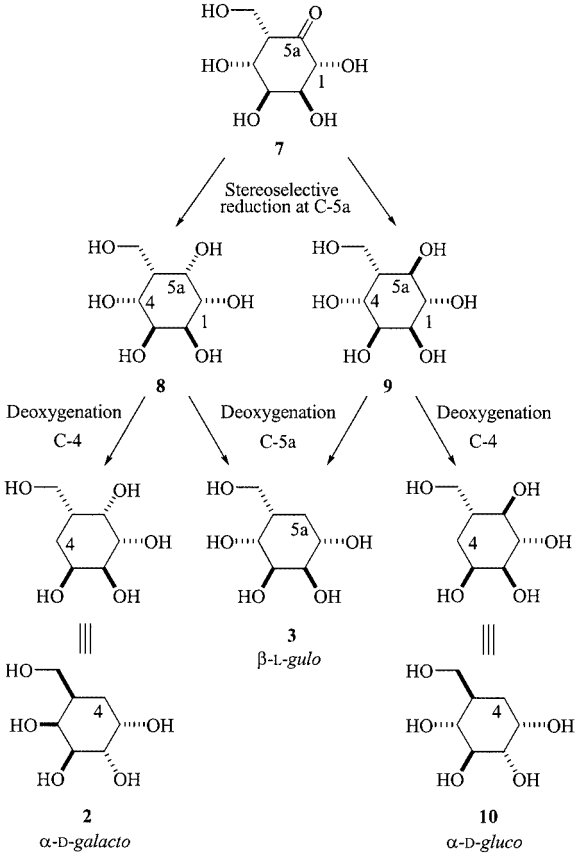
These methods, however, are of limited use for the preparation of carbasugars derived from "rare" sugars, or those corresponding to the L-series, because of the low availability of the starting monosaccharides. Hence, we focused our interest on developing an approach that, starting from a readily available monosaccharide, could allow access to a variety of carbasugars in a stereodivergent manner. In this context, we turned our attention to the hydroxy compound **5** (Scheme 1), an intermediate in our retrosynthesis[22] of the 5a-carba-D-mannopyranose **4**. Compound **5** was prepared by 6-*exo*-*dig* radical cyclization[25] of a carbohydrate-derived alkyne, followed by ozonolysis and reduction.

Stereodivergent Strategy

We have recently shown how a polyoxygenated intermediate, **5**, could be transformed into two different carbasugars by use of the Barton−McCombie radical deoxygenation[26,27] either at C-5a or at C-4.[28] In this paper, we disclose how the stereodivergency in our approach can be enhanced by the use of polyhydroxylated cyclohexanone intermediates (e.g. **7**, Scheme 2) which could be transformed in up to three different carbasugar derivatives as outlined in Scheme 2. Accordingly, stereoselective reduction of the carbonyl group in compound **7** would give rise to a pair of epimeric polyoxygenated intermediates **8**, **9,** which, upon Barton−McCombie deoxygenation either at C-5a or at C-4, would lead to the three different carbasugars **2**, **3**, and **10**. In this work, we illustrate the flexibility of this methodology with the syntheses of 5a-carba-β-L-gulopyranose (**28**), 5a-carba-α-D-galactopyranose (**35**) and 5a-carba-α-D-glucopyranose (**42**) pentaacetates from D-mannose.[29]

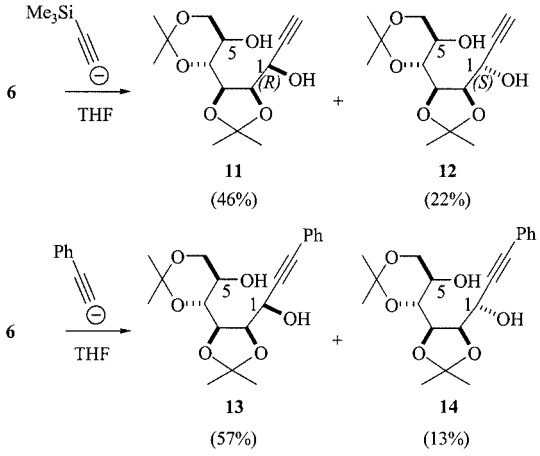


Scheme 2. Stereodivergent access to three carbasugars from a common synthetic intermediate arising from D-mannose

Results and Discussion

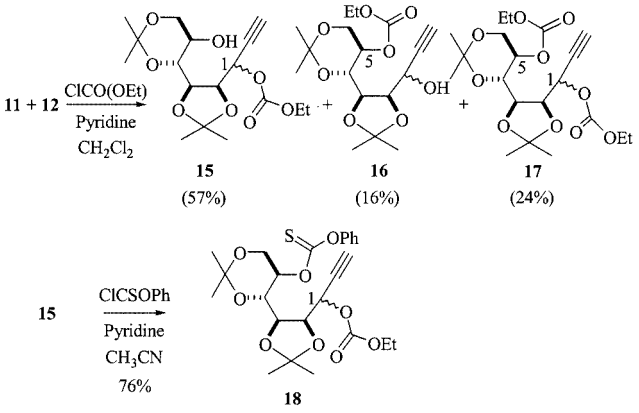
Synthesis of the Precursor for Radical Cyclization

D-Mannose was transformed into 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose (**6**), in a single step, by kinetic acetonation according to Gelas and Horton.[30] Addition of lithium trimethylsilyl acetylide to the latter compound afforded an inseparable (2:1) mixture of epimeric 1*S* and 1*R* isomers, **11** and **12**, respectively,[31] (Scheme 3) in which the trimethylsilyl residues have been lost during workup. The stereochemical outcome of this reaction differs from the stereochemical result of the addition of lithium phenylacetylide to the hemiacetal **6**, which yields a (5:1) mixture of the (1*R*) and (1*S*) isomers **13** and **14**[31].



Scheme 3. Stereoselectivity of the addition of lithium acetylides to **6**

Our synthetic route continued with the selective protection of the 1-hydroxy group (parent carbohydrate number-

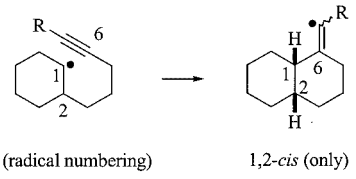


Scheme 4. Synthesis of epimeric carbonates **18**, for radical cyclization

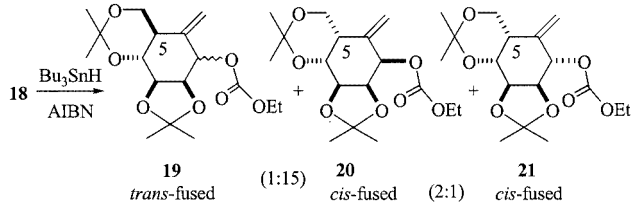
ing) prior to activation of the 5-hydroxy group of diols **11**, **12**. Accordingly, the epimeric mixture (**11** + **12**; Scheme 4) was treated with ethyl chloroformate in CH_2Cl_2 in the presence of pyridine to yield the carbonates **15**, as an epimeric mixture at C-1, in 57% yield, along with mono- **16** and dicarbonates **17**, which could be converted back to diols **11**, **12** by base treatment. To activate the 5-hydroxy group and allow generation of the requisite secondary radical, compounds **15** were treated with an excess of phenyl chlorothionoformate[27] and pyridine in acetonitrile and refluxed for 1 h to provide the desired thionocarbonates **18** in 76% yield.

Radical Cyclization of the Thionocarbonates 18

6-*exo*-*digonal* Radical cyclization was first described by Clive and co-workers[25] for the synthesis of cyclic ketones, and has since found ample use in organic synthesis. In general, radical ring-closure of cyclic radicals onto alkenes[32] and alkynes[25,33,34] is known to afford fused systems with predominantly or exclusively *cis* ring closure (Scheme 5). In keeping with literature references[32−34] then, radical cyclization of **18** yielded a (15:1) mixture of *cis*- and *trans*-fused adducts in which the *cis*-fused isomers prevailed (Scheme 6). The epimeric mixture of *cis*-fused products (**20**/**21**, 2:1 ratio) could be separated by chromatography at this point.



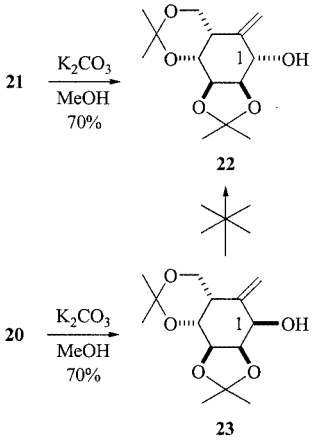
Scheme 5. 6-*exo*-Digonal ring closure of cyclic radicals



Scheme 6. 6-*exo*-Digonal radical cyclization of **18** to afford *cis* or *trans* ring-fused systems

Syntheses of the *exo*-Methylene Precursor 22

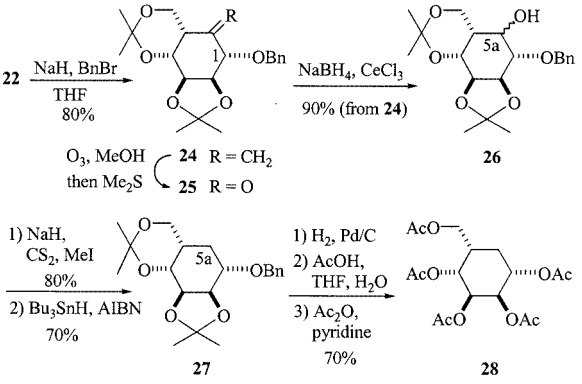
Our synthetic route to carbasugars of the *galacto*, *gluco* and *gulo* series required the use of the *exo*-methylene derivative **22**, with the appropriate stereochemistry at C-1, as the starting material (Scheme 7). Compound **22** could be readily obtained by treatment of minor isomer **21** with K_2CO_3 in MeOH. However, it would be better to devise a synthetic route to **22** from the carbonate **20**, the major isomer of the radical cyclization of **18**. Accordingly, compound **20** was saponified to the hydroxy derivative **23**. First attempts for the transformation **23** → **22** by Mitsunobu inversion,[35] either with acetic acid or *p*-nitrobenzoic acid[36] as nucleophiles, left the starting material unchanged. The corresponding mesylate and triflate were prepared next, and their nucleophilic displacement examined with sodium nitrite in DMF;[37] decomposition of the starting material was observed. The reaction of both derivatives (mesylate and triflate of **23**) with NaOH and Bu_4NHSO_4 [38] resulted in the regeneration of the starting hydroxy compound **23**. The preparation of different derivatives of **23** (activation of 1-OH by reaction with tosylimidazole) and the use of different nucleophiles (sodium acetate) were also unsuccessful. Finally, an oxidation (Swern conditions[39])-reduction ($NaBH_4$, borane−methyl sulfide) sequence served only to regenerate the starting β-hydroxy derivative **23** as the major or only isomer.



Scheme 7. Synthesis of *exo*-methylenecyclohexane derivative **22**

Synthesis of 5a-Carba-β-L-gulopyranose

The preparation of carba-L-gulopyranose required, according to our synthetic strategy, deoxygenation of the 5a-OH. Therefore, a benzyl protecting-group was installed at 1-OH in compound **22** (Scheme 8). The resulting benzylated compound **24** was ozonolyzed (O_3, MeOH, followed by

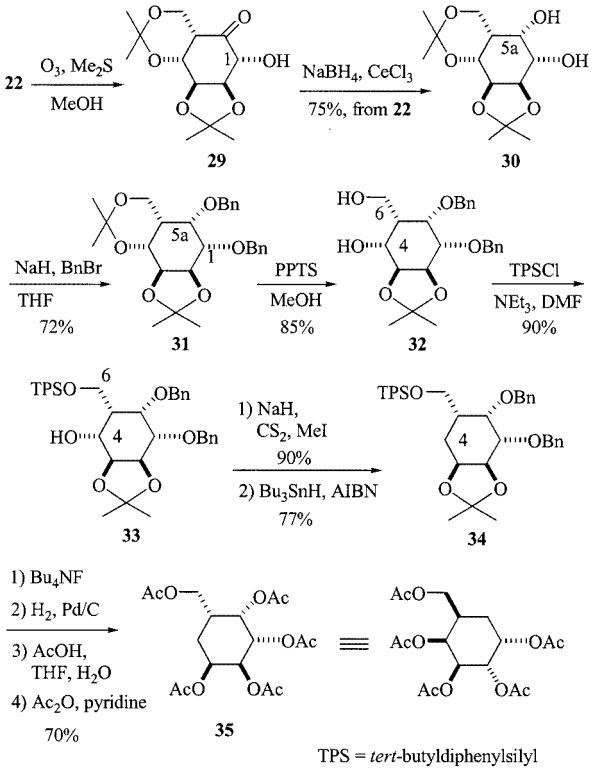


Scheme 8. Synthesis of 5a-carba-β-L-gulopyranose pentaacetate (**28**)

treatment with Me_2S) to yield an unstable ketone **25**, which was not characterized. Accordingly, reduction of **25** ($NaBH_4$, $CeCl_3$) without further purification gave a 3:1 mixture of 5a-OH epimers **26** in 90% yield from **24**. The xanthate of the major isomer was prepared next (NaH, CS_2, MeI, 80% yield) and submitted to deoxygenation with Bu_3SnH and AIBN in toluene at 85 °C to yield the deoxy derivative **27** in 70% yield. Finally, hydrogenolysis of the benzyl group (H_2, Pd/C) followed by acid hydrolysis of the isopropylidene acetals (AcOH/THF/H_2O, 4:2:1, 85 °C) and acetylation (Ac_2O, Pyridine) yielded 5a-carba-β-L-gulopyranose pentaacetate (**28**).[40,41]

Synthesis of 5a-Carba-α-D-galactopyranose

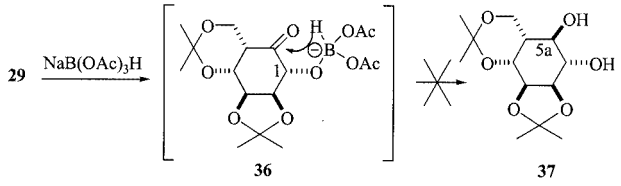
According to our synthetic strategy (Scheme 2), preparation of carba-D-galactopyranose requires (a) reduction of the 5a-keto group to give an α-oriented hydroxy group, and (b) deoxygenation at C-4 (Scheme 2). Thus, alkene **22** was submitted to ozonolysis to give the unstable hydroxy ketone **29** which, without purification, was treated with $NaBH_4$ in the presence of $CeCl_3$ to afford the *syn*-diol **30** with complete stereoselectivity; this was benzylated to the fully protected derivative **31**. Unveiling of the 4-OH group for deoxygenation was carried out in two steps: a) chemoselective deprotection of the six-membered isopropylidene group upon treatment with pyridinium *p*-toluenesulfonate (PPTS) in MeOH to yield the diol **32** (85% yield), and b) selective protection of the 6-OH by treatment with *tert*-butyldiphenylsilyl chloride (TPSCl) and imidazole to furnish **33** (90% yield) (Scheme 9). Barton−McCombie radical deoxygenation of 4-OH in compound **33** paved the way to the protected 5a-carba-D-galactopyranose derivative **34**. Finally, deprotection and peracetylation of **34**, as for **33**, led to 5a-carba-α-D-galactopyranose pentaacetate (**35**)[8,42]



Scheme 9. Synthesis of 5a-carba-α-D-galactopyranose pentaacetate (**35**)

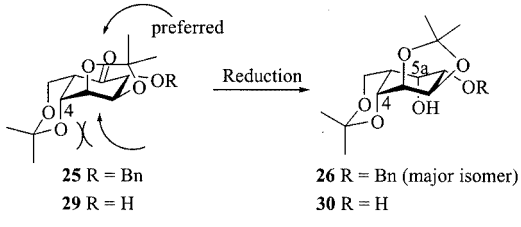
Synthesis of 5a-Carba-α-D-glucopyranose

The synthetic process for the preparation of 5a-carba-D-glucopyranose implied: (a) preparation of a β-oriented 5a-OH rather than an α-isomer (as in **9**, Scheme 2), and (b) deoxygenation at C-4 (Scheme 2). Preliminary results showed us that reduction of the cyclohexanones **25** and **29** was taking place by β-approach of the incoming hydride to give preferentially an α-5a-OH. This tendency was observed for reagents like $NaBH_4$ and $LiAlH_4$. In an attempt to invert the "preferred" stereoselectivity of the reduction we tested sodium triacetoxyborohydride. The latter becomes a reducing species towards a ketone only when complexed with a suitably placed hydroxy group (see Scheme 10), and contrasts with other reducing agents in which competing inter vs. intramolecular hydride transfer might afford mixtures of epimeric alcohols.[43,44] Unfortunately, under the standard reaction conditions the starting material was recovered unchanged, thus reinforcing the hypothesis of the intermolecular hydride transfer for the reduction of the carbonyl group in **29**. Other attempts were carried out with the reagent system Bu_2SnCl_2/Bu_2SnH_2, introduced by Clive et al.[45] for the reduction of highly functionalized cyclohexanones with stereoselectivity opposed to that of conventional reagents. In our case, however, the starting material was recovered unchanged.



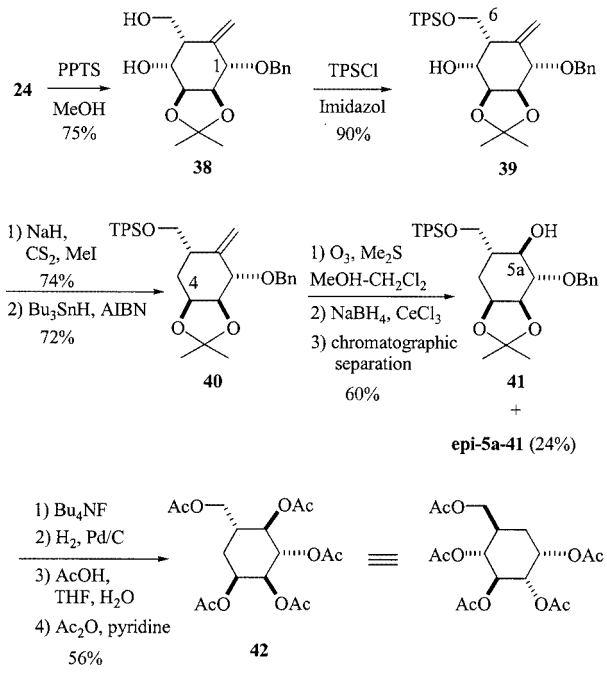
Scheme 10. Attempted reduction of hydroxy ketone **29** with sodium triacetoxyborohydride

These negative results led us to reconsider our strategy. We hypothesized that the strong stereochemical bias for the reduction of the cyclohexanones **25** and **29** was originated by the possible axial orientation of the oxygen substituent at C-4 in the *cis*-dioxadecalin skeleton (Scheme 11).



Scheme 11. Stereochemical outcome of the reduction of **25** and **29**

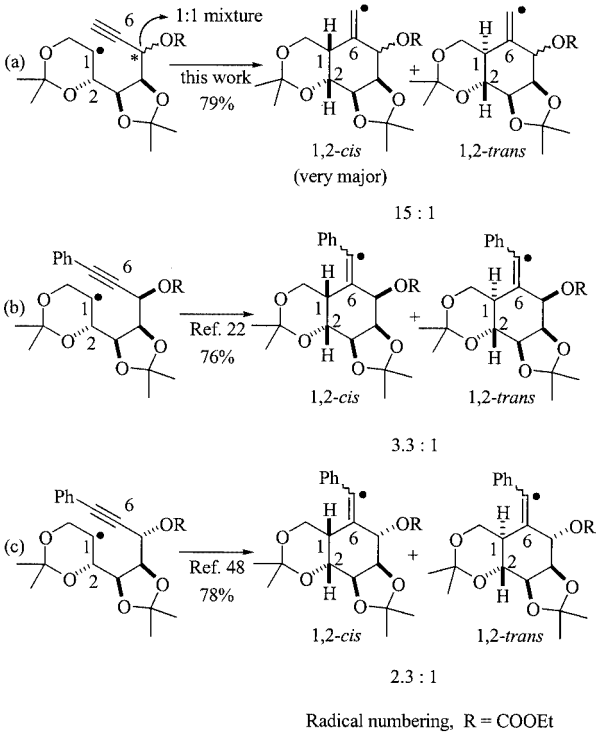
We supposed that deoxygenation at C-4, previous to ketone reduction, could result in a reversal of the observed stereochemical preference since it would eliminate the substituent at O-4. Accordingly, chemoselective deprotection of the primary isopropylidene acetal in **24** afforded diol **38** (Scheme 12). Regioselective silylation at 6-OH in the latter yielded compound **39**, in which the 4-OH was free. Deoxygenation at 4-OH via the corresponding xanthate resulted in the formation of the methylenecyclohexane **40**. Ozonolysis of the latter furnished a ketone, which, without further purification, was submitted to reductive conditions ($NaBH_4$, $CeCl_3$) to yield the desired 5a-OH isomer **41** (60%) as the major isomer of the reaction mixture (2.5:1 ratio), together with its 5a-OH epimer (24%); these were separable by chromatography. Conventional deprotection steps on **41**, followed by acetylation, finally led to 5a-carba-α-D-glucopyranose pentaacetate (**42**).[46]



Scheme 12. Synthesis of 5a-carba-α-D-glucopyranose pentaacetate (**42**)

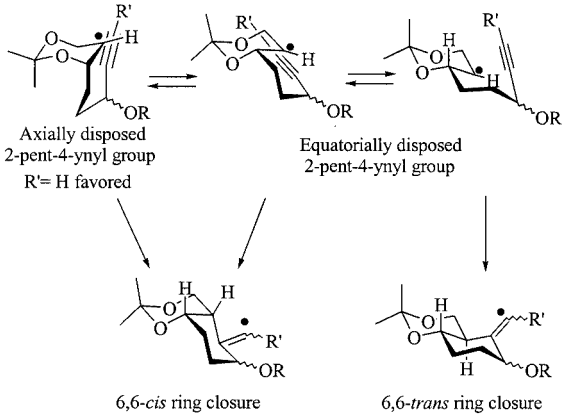
Stereochemical Outcome of the 6-*exo-dig* Radical Cyclization

Radical ring closure of cyclic radicals onto alkenes and alkynes, to afford fused systems, is known to follow a very general guideline: the ring fusion obtained is predominantly or exclusively *cis* (1,2 *cis*, radical numbering) for "small rings" (see Scheme 5).[32,47] The stereochemical outcome of the radical cyclization described in this work takes place, then, according to literature precedents[32–34] [Scheme 13, (a)]. This result, however, is noticeably different from the stereochemical result of the radical cyclization of closely related dioxa-decalin systems recently reported by us,[22,48] in which the only difference is the substitution (H or Ph) of the alkyne [Scheme 13, compare (a), (b), and (c)].



Scheme 13. 6-*exo*-Digonal ring closure of cyclic radicals onto alkynes to afford tricyclic systems

Our rationale for this opposite behavior lies in the work of RajanBabu,[49] who has shown for cyclohexyl radicals that transition states having an equatorial and an axial butenyl side chain may compete. Axial orientation of the chain in the transition state of the radical cyclization of 2-pent-4-ynyl radicals (Scheme 14), because of geometrical restrictions, would lead to *cis*-decalin-type systems (6,6-*cis* ring fusion). On the other hand, an equatorial disposition of the side chain could give rise to either *cis*- or *trans*-dioxadecalins depending on the facial approach of the side chain to the radical (see Scheme 14). We believe that in our case, although tricyclic structures rather than bicyclic ones are originated, the radical cyclization of the unsubstituted al-



Scheme 14. Possible dispositions of the side chain in the radical cyclization of 2-pent-4-ynylcyclohexyl radicals

kyne takes place via an axial disposition of the side chain (R′ = H, Scheme 14), whereas the phenyl-substituted alkyne (R′ = Ph, Scheme 14) might cyclize through an axial or an equatorial orientation of the side chain.

Conclusion

We have reported a stereodivergent strategy for the preparation of carbasugars from monosaccharides. The strategy features a 6-*exo*-*dig* radical cyclization and a Barton−McCombie radical deoxygenation as the key steps. The approach is based on the preparation and synthetic manipulation of polyhydroxycyclohexanones readily accessible by ozonolysis of methylenecyclohexane derivatives arising from D-mannose. We have illustrated how a single cyclohexanone derivative can give rise to three different carbasugar derivatives by stereoselective reduction of the carbonyl group at C-5a followed by a site-selective deoxygenation either at C-4 or at C-5a (parent carbohydrate numbering). During the course of this work, we have applied this strategy to the preparation of pentaacetylated carbasugars **28**, **35** and **42**. The scope of this methodology is yet to be extended either by stereoselective transformations (alkyne addition to the reducing monosaccharide, radical cyclization, and ketone reduction) leading to different polyoxygenated cyclohexanones, or by the use of different monosaccharide starting materials.

Experimental Section

General Remarks: All reactions were performed in dry flasks fitted with a glass stopper or rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred by syringe or stainless-steel cannula. Flash column chromatography was performed with 230−400 mesh silica gel. Thin-layer chromatography was conducted with Kieselgel 60 F_{254} (Merck). Detection was first by UV (254 nm) then charring with a solution of 20% aqueous sulfuric acid (200 mL) in acetic acid (800 mL). Anhydrous $MgSO_4$ or $NaSO_4$ was used to dry the organic solutions during work-up, and the removal of the solvents was done under vacuum with a rotary evaporator. Solvents were dried and purified using standard methods.^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 400 or 500 and 75 or 50 MHz respectively. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual protonated NMR solvent ($CHCl_3$: δ = 7.25 ppm).

General Procedure for Xanthate Formation: A solution of the alcohol in dry THF (5 mL/mmol) was treated with NaH (2 equiv.) at 0 °C for 30 min. Then, the mixture was treated with CS_2 (2 equiv.) at room temperature for 60 min after which MeI was added (6 equiv.). Stirring was maintained for an additional 30 min and then the reaction was diluted with CH_2Cl_2, washed with water, dried and concentrated to give a residue which was purified by flash chromatography.

General Procedure for Radical Deoxygenation of Thionocarbonates or Xanthates: A thoroughly degassed (argon) solution of the substrate in toluene (0.02 M) was heated to 85 °C. A solution of HS*n*Bu_3 (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 for 30 min. After cooling, the organic solvent was evaporated and the residue purified by flash chromatography.

General Method for Sequential Isopropylidene Group Hydrolysis-Peracetylation: The compound containing the isopropylidene group was dissolved in a previously prepared mixture of AcOH/THF/H_2O (4:2:1, 10 mL/mmol). The resulting solution was warmed to 85 °C, and stirred at that temperature until consumption of the starting material was observed (TLC, usually between 40 and 60 min). The solvent was then evaporated from the reaction mixture. The crude polyols were subjected to standard acetylation conditions by treatment with pyridine and an excess of acetic anhydride. After stirring overnight, the mixture was concentrated to yield a crude material, which was purified by flash chromatography.

Diols 11−12: BuLi (86.4 mmol, 54 mL solution 1.6 M in *n*-hexane) was added to a solution of trimethylsilylacetylene (16.4 mL, 115.3 mmol) in dry THF (100 mL) under argon at −78 °C. A solution of **6**[30] (7.5 g, 28.8 mmol) in dry THF (80 mL) was added dropwise and the reaction mixture was allowed to reach room temperature, after which time stirring was continued for 10 h. The reaction mixture was then diluted with Et_2O (250 mL) and washed with water. The organic layer was dried and concentrated and the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give the diols **11** and **12** as a 2:1 inseparable mixture of diastereomers (5.6 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.67 (m, 2 H), 4.60 (dd, *J* = 1.5, 6.7 Hz, 1 H), 4.54 (d, *J* = 6.8 Hz, 1 H), 4.33 (m, 2 H), 4.22 (dd, *J* = 1.4, 9.1 Hz, 1 H), 4.11 (dd, *J* = 8.3 Hz, 1 H), 4.02−4.11 (m, 4 H), 3.69 (m, 2 H), 2.54 (d, *J* = 2.2 Hz, 1 H), 2.49 (d, *J* = 2.3 Hz, 1 H,), 1.57 (s, 3 H), 1.54 (s, 6 H), 1.51(s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.7, 108.9, 99.1, 98.6, 82.5, 80.9, 80.0, 78.3 (× 2), 77.2, 74.3, 74.1, 73.8, 72.0, 71.5, 64.4, 64.3, 62.3, 62.2, 61.0, 28.1, 26.1 (× 2), 25.7, 24.4 (× 2), 18.5 (× 2) ppm.

Carbonates 15: Pyridine (3 mL, 37 mmol) and ethyl chloroformate (3.5 mL, 37 mmol) were added to a solution of the diol **11** (5.3 g, 18.5 mmol) in dry CH_2Cl_2 (110 mL) under argon at 0 °C. The solution was stirred for 2 h. The mixture was then diluted with CH_2Cl_2 and successively washed with 10% HCl, aqueous sodium hydrogencarbonate, water and brine. The organic layer was dried (Na_2SO_4) and concentrated, giving a residue that was purified by flash chromatography (hexane/EtOAc, 8:2) to give the monocarbonates **15** (3.77 g, 57%) and **16** (1.1 g, 16%) and the dicarbonate **17** (1.9 g, 24%). **15:** (Two diastereomers at C-1). MS: *m*/*z* = 343.1 [M^+ −15]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67 (dd, *J* = 2.2, 7.1 Hz, 1 H), 5.50 (dd, *J* = 2.2, 9.3 Hz, 1 H), 4.56−4.31 (m, 2 H), 4.43 (dd, *J* = 6.6, 9.3 Hz, 1 H), 4.29−4.20 (m, 4 H), 4.01−3.87 (m, 5 H), 3.74−3.61 (m, 4 H), 2.62 (d, *J* = 2.2 Hz, 1 H), 2.59 (d, *J* = 2.2 Hz, 1 H), 1.56 (s, 3 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 6 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.6, 153.1, 110.1, 109.3, 98.3, 98.2, 78.9, 76.8, 76.7, 76.1, 75.9, 74.9, 73.8, 73.7, 72.1, 71.7, 65.9, 65.7, 64.3, 64.2 (× 2), 64.1, 61.9, 61.7, 28.1, 27.9, 26.1, 25.9, 25.5, 25.3, 18.6, 18.2, 13.7 (× 2) ppm. **16:** (Only one diastereomer was observed). $[\alpha]_D^{21}$ = −57.0 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.84 (dt, *J* = 5.5, 13.2 Hz, 1 H), 4.59 (m, 1 H), 4.23−3.99 (m, 6 H), 3.70−3.62 (m, 2 H), 2.47 (d, *J* = 2.2 Hz, 1 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.30 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.8, 109.1, 99.6, 82.7, 78.3, 74.5, 73.9, 69.0, 68.5, 64.2, 61.3, 60.9, 27.1, 26.1, 25.3, 19.9, 13.9 ppm. **17:**

(Two diastereomers at C-1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.65 (dd, *J* = 2.0, 9.4 Hz, 1 H), 5.44 (dd, *J* = 1.9, 9.3 Hz, 1 H), 4.94−4.89 (m, 2 H), 4.52 (dd, *J* = 6.8, 9.4 Hz, 1 H), 4.44−4.17 (m, 12 H), 4.12 (dd, *J* = 3.3, 4.9 Hz, 1 H), 4.08 (dd, *J* = 2.9, 4.9 Hz, 1 H), 3.89 (d, *J* = 9.0 Hz, 1 H), 3.77−3.68 (m, 2 H), 2.63 (d, *J* = 2.0 Hz, 1 H,), 2.59 (d, *J* = 1.9 Hz, 1 H), 1.57 (s, 3 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.42 (s, 3 H), 1.41(s, 3 H), 1.40 (s, 6 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.1, 153.9 (× 2), 153.4, 110.6, 109.9, 99.6, 99.2, 79.3, 77.9, 77.5, 77.3, 76.9, 76.2, 75.3, 74.4, 69.6, 69.2, 69.1, 68.7, 66.1, 66.0, 64.6, 64.4, 64.3, 64.2, 61.8, 61.3, 27.4, 26.6, 26.4, 26.3, 25.9, 25.6, 20.5, 19.6, 14.1 (× 4) ppm.

Thionocarbonate 18: A solution of the alcohols **15** (3.0 g, 8.37 mmol) in acetonitrile (160 mL) was treated with pyridine (2 mL, 25.1 mmol) and phenyl chlorothionoformate (3.5 mL, 25.1 mmol). The reaction mixture was heated at 85 °C for 1 h after which time it was cooled to room temperature and then quenched with water. The solution was diluted with CH_2Cl_2 and washed successively with HCl (10%), saturated $NaHCO_3$, and brine. The organic phase was dried, filtered and concentrated under vacuum giving a residue which was purified by flash chromatography (hexane/EtOAc, 95:5) to give thionocarbonate **18** (3.18 g, 76%) (two diastereomers at C-1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49−7.37 (m, 3 H), 7.34−7.19 (m, 2 H), 7.12−7.07 (m, 3 H), 6.97−6.79 (m, 2 H), 5.67 (dd, *J* = 2.2, 9.3 Hz, 1 H), 5.53 (m, 2 H), 5.47 (dd, *J* = 2.1, 8.7 Hz, 1 H), 4.57 (dd, *J* = 6.6, 9.3 Hz, 1 H), 4.46−4.34 (m, 4 H), 4.32−4.19 (m, 6 H), 4.07 (dd, *J* = 1.3, 8.4 Hz, 1 H), 3.95 (dd, *J* = 4.9, 12.6 Hz, 1 H), 3.89 (dd, *J* = 6.2, 12.3 Hz, 1 H), 2.64 (d, *J* = 2.2 Hz, 1 H,), 2.60 (d, *J* = 2.1 Hz, 1 H), 1.60 (s, 3 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 9 H), 1.38 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.5 (× 2), 153.5, 153.3, 128.4 (× 3), 125.7 (× 2), 121.7 (× 3), 120.6, 115.3, 110.8, 109.0, 100.3, 99.9, 78.9, 77.6, 76.7, 76.2, 76.1, 75.9, 75.3, 75.1, 74.5, 74.4, 68.3 (× 2), 65.9, 65.7, 64.4, 64.2, 61.0, 60.4, 26.4, 26.1, 26.0, 25.6, 25.4, 25.3, 21.2, 20.2, 13.8 (× 2) ppm.

Radical Cyclization of Thionocarbonates 18: A thoroughly degassed (argon) solution of the thionocarbonate **18** (3.18 g, 6.27 mmol) in toluene (0.02 M) was heated to 85 °C under argon. A solution of HBu_3Sn (2.8 mL, 10.3 mmol) and AIBN (130 mg, 0.6 mmol) in toluene (3 mL) was then added and the reaction mixture was kept at that temperature for 12 h. After cooling, the organic solvent was evaporated and the residue purified by flash chromatography (hexane/EtOAc, 95:5) to give the methylenecyclohexanes **19** (107 mg, 5%), **20** (1.09 g, 51%) and **21** (494 mg, 23%). **20:** M.p. 68−70 °C. $[\alpha]_D^{21}$ = +153.7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 5.35 (s, 1 H), 5.14 (s, 1 H), 4.62 (dd, *J* = 3.3, 7.4 Hz, 1 H), 4.37 (dd, *J* = 2.7, 7.4 Hz, 1 H), 4.27−4.19 (m, 3 H), 4.15 (dd, *J* = 3.8, 11.7 Hz, 1 H), 3.91 (dd, *J* = 2.8, 11.7 Hz, 1 H), 2.60 (m, 1 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 140.2, 111.2, 109.6, 99.0, 75.5, 74.6, 73.9, 66.9, 65.3, 64.1, 35.4, 28.8, 25.9, 24.0, 19.1, 14.1 ppm. $C_{17}H_{26}O_7$ (342.4): calcd. C 59.64, H 7.65; found C 59.88, H 7.41. **21:** $[\alpha]_D^{21}$ = +75.85 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.34 (t, *J* = 1.5 Hz, 1 H), 5.27 (s, 1 H), 5.11 (d, *J* = 6.6 Hz, 1 H), 4.53 (d, *J* = 3.1 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 4.18−4.12 (m, 4 H), 2.33 (m, 1 H), 1.58 (s, 3 H), 1.54 (s, 3 H), 1.46 (s, 3 H), 1.33 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.7, 138.8, 111.0, 108.9, 99.2, 79.2, 78.2, 77.6, 68.7, 64.1, 60.5, 36.4, 29.2, 27.9, 26.1, 18.7, 14.2 ppm. $C_{17}H_{26}O_7$ (342.4): calcd. C 59.64, H 7.65; found C 59.79, H 7.38.

Alcohol 22: A solution of the carbonate **21** (490 mg, 1.43 mmol) in methanol (50 mL) was treated with K_2CO_3 (395 mg, 2.86 mmol). The reaction mixture was stirred overnight and then the solution was diluted with CH_2Cl_2 and washed successively with water and brine. The organic phase was dried, filtered and concentrated under vacuum giving a residue which was purified by flash chromatography (hexane/EtOAc, 8:2) to give the alcohol **22** (271 mg, 70%). M.p. 97−99 °C. $[\alpha]_D^{21}$ = +94.4 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (s, 1 H), 5.26 (d, *J* = 2.0 Hz, 1 H), 4.33 (dd, *J* = 4.2, 6.6 Hz, 1 H), 4.29 (t, *J* = 2.3 Hz, 1 H), 4.25 (dd, *J* = 2.3, 6.6 Hz, 1 H), 4.15 (dd, *J* = 3.6, 12.0 Hz, 1 H), 4.12 (dd, *J* = 4.2, 9.6 Hz, 1 H), 4.02 (dd, *J* = 2.0, 12.0 Hz, 1 H), 3.78 (d, *J* = 9.6 Hz, 1 H), 2.40 (m, 1 H, H-5), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 116.2, 108.5, 99.6, 78.1, 75.1, 73.2, 68.7, 63.7, 34.1, 29.0, 26.8, 24.5, 18.9 ppm. $C_{14}H_{22}O_5$ (270.3): calcd. C 62.20, H 8.20; found C 62.24, H 7.98.

Benzyl Ether 24: The alcohol **22** (270 mg, 1.0 mmol) was dissolved in dry THF (45 mL) and treated with NaH (79 mg 60%, 1.97 mmol) at 0 °C under argon for 30 min. Then, benzyl bromide (170 μL, 1.43 mmol) and Bu_4NI (405 mg, 1.1 mmol) were added. After 3 h the reaction was diluted with Et_2O and washed with water. The organic phase was dried, concentrated and the residue purified by flash chromatography (hexane/EtOAc, 95:5) to yield **24** (288 mg, 80%) as an colourless oil. $[\alpha]_D^{21}$ = +115.3 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42−7.29 (m, 5 H), 5.49 (s, 1 H), 5.41 (s, 1 H), 4.78 (d, *J* = 12.3 Hz, 1 H), 4.62 (d, *J* = 12.3 Hz, 1 H), 4.48 (d, *J* = 2.3 Hz, 1 H), 4.13−4.06 (m, 4 H), 3.82 (d, *J* = 7.1 Hz, 1 H), 2.19 (m, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 138.7, 128.5 (× 2), 128.0 (× 2), 127.7, 111.6, 108.4, 99.3, 81.1, 80.6, 77.5, 71.8, 69.3, 61.0, 36.8, 29.5, 28.2, 26.3, 19.1 ppm. $C_{21}H_{28}O_5$ (360.4): calcd. C 69.98, H 7.83; found C 69.74, H 7.93.

Alcohol 26: Ozone was bubbled through a solution of the methylenecyclohexane **24** (280 mg, 0.78 mmol) in MeOH/CH_2Cl_2 (1:1 mixture, 6 mL) at −78 °C until TLC showed complete consumption of the starting compound. Oxygen was then bubbled through the solution for 5 min. Next, the mixture was treated with dimethyl sulfide (1 mL) and the solution was warmed to room temperature over 2 h. After stirring for an additional hour, the solvent was removed to yield the ketone **25**. **25:** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.20 (m, 5 H), 4.89 (d, *J* = 12.2 Hz, 1 H, benzyl-H), 4.72 (dd, $J_{4,5}$ = 3.7, $J_{3,4}$ = 2.2 Hz, 1 H, H-4), 4.60 (d, *J* = 12.3 Hz, 1 H, benzyl-H), 4.45 (dd, $J_{1,2}$ = 6.2, $J_{2,3}$ = 5.4 Hz, 1 H, H-2), 4.43 (dd, $J_{6,6'}$ = 11.5, $J_{5,6}$ = 1.5 Hz, 1 H, H-6), 4.23 (dd, $J_{3,4}$ = 2.2, $J_{2,3}$ = 5.4 Hz, 1 H, H-3), 3.95 (d, $J_{1,2}$ = 6.2 Hz, 1 H, H-1), 3.90 (dd, $J_{6,6'}$ = 11.9, $J_{6',5}$ = 3.5 Hz, 1 H, H-6′), 2.48 (m, 1 H, H-5), 1.46 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H) ppm.

The residue, containing ketone **25**, was then dissolved in MeOH (15 mL) and treated with $CeCl_3 \cdot H_2O$ (581 mg, 1.56 mmol). The mixture was cooled to 0 °C, treated with $NaBH_4$ (118 mg, 3.12 mmol) and then warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc and washed with water and brine. The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography (hexane/EtOAc, 8:2) to give the alcohol **26** (255 mg, 90%). **26:** $[\alpha]_D^{21}$ = +72.9 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44−7.26 (m, 5 H), 4.80 (s, 2 H), 4.55 (dd, *J* = 5.5, 8.0 Hz, 1 H, H-2), 4.48 (d, *J* = 3.2 Hz, 1 H, H-4), 4.31−4.24 (m, 3 H), 4.06 (d, *J* = 12.2 Hz, 1 H, H-6), 3.28 (dd, *J* = 2.2, 8.0 Hz, 1 H, H-1), 3.21 (d, *J* = 2.4 Hz, 1 H, OH), 1.58 (m, 1 H, H-5), 1.52 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (50 MHz,

$CDCl_3$): δ = 138.4, 128.3 (× 2), 127.9 (× 2), 127.5, 108.1, 99.5, 79.4, 77.8, 72.4, 71.0, 67.6 (× 2), 63.4, 33.4, 29.3, 28.0, 26.2, 18.4 ppm. $C_{20}H_{28}O_6$ (364.2): calcd. C 65.91, H 7.74; found C 66.10, H 7.88.

Benzyl Carbagulopyranose 27: Alcohol **26** (130 mg, 0.36 mmol) was converted into the corresponding xanthate and this material deoxygenated according to the general procedure. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to yield the carbagulose derivative **27** (70 mg, 70%). $[\alpha]_D^{21}$ = +53.3 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40−7.29 (m, 5 H), 4.76 (d, *J* = 12.2 Hz, 1 H), 4.69 (d, *J* = 12.2 Hz, 1 H), 4.35 (s, 1 H), 4.16 (dd, *J* = 5.5, 7.7 Hz, 1 H), 4.10−4.07 (m, 2 H), 3.63 (d, *J* = 11.8 Hz, 1 H), 3.49 (ddd, *J* = 4.5, 7.7, 12.3 Hz, 1 H), 2.14 (q, *J* = 12.3 Hz, 1 H), 1.65 (m, 2 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 128.3 (× 2), 127.7 (× 2), 127.4, 108.3, 99.0, 79.2, 78.8, 78.0, 71.2, 67.6, 63.8, 31.4, 29.6, 28.1, 27.1, 26.3, 18.5 ppm. $C_{20}H_{28}O_5$ (348.4): calcd. C 68.94, H 8.10; found C 69.10, H 8.08.

5a-Carba-β-L-gulopyranose Pentaacetate (28): A solution of the benzyl ether **27** (70 mg, 0.20 mmol) in MeOH (25 mL) was hydrogenolyzed in the presence of 10% Pd/C (10 mg) at 35 psi at room temperature for 60 min. The reaction mixture was filtered through a short pad of Celite and concentrated to give a residue which was subjected to the general procedure for the cleavage of the isopropylidene moiety and acetylation. Purification of the residue was carried out by flash chromatography (hexane/EtOAc, 7:3) to yield carba-β-L-gulopyranose pentaacetate (**28**, 54 mg, 70% overall). $[\alpha]_D^{21}$ = −18.7 (*c* = 0.4, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38 (m, 1 H), 5.16 (m, 2 H), 5.10 (m, 1 H), 4.01 (dd, *J* = 8.2, 11.2 Hz, 1 H), 3.84 (dd, *J* = 6.4, 11.2 Hz, 1 H), 2.43 (m, 1 H, H-5), 2.13 (s, 6 H), 2.05 (m, 1 H, H-5a), 2.04 (s, 6 H), 1.99 (s, 3 H), 1.58 (m, 1 H) ppm. $C_{17}H_{24}O_{10}$ (414.5): calcd. C 52.57, H 6.23; found C 52.28, H 6.45.

Diol 30: Ozone was bubbled through a solution of the methylenecyclohexane **22 (**270 mg, 1.0 mmol) in MeOH/CH_2Cl_2 (1:1 mixture, 8 mL) at −78 °C until TLC showed complete consumption of the starting compound. Oxygen was then bubbled through the solution for 5 min. Next, the mixture was treated with dimethyl sulfide (1 mL) and the solution was warmed to room temperature over 2 h. After stirring for an additional hour, the solvent was removed. The residue containing ketone **29** was not purified but was then dissolved in MeOH (15 mL) and treated with $CeCl_3{\cdot}H_2O$ (581 mg, 1.56 mmol). The mixture was cooled to 0 °C, treated with $NaBH_4$ (118 mg, 3.12 mmol) and then warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc and washed with water and brine. The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography (hexane/EtOAc, 6:4) to give the diol **30** (205 mg (75%). $[\alpha]_D^{21}$ = +56.9 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.49 (m, 1 H), 4.34 (dd, *J* = 5.8, *J* = 7.0 Hz, 1 H), 4.29−4.21 (m, 2 H), 4.18−4.12 (m, 2 H), 3.58 (ddd, *J* = 3.3, 7.0, 9.7 Hz, 1 H), 3.18 (d, *J* = 5.2 Hz, 1 H), 2.84 (d, *J* = 9.7 Hz, 1 H), 1.77 (m, 1 H, H-5), 1.52 (s, 3 H), 1.48 (s, 3 H), 1.39 (s, 3 H), 1.37(s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 128.3 (× 2), 127.9 (× 2), 127.5, 108.1, 99.5, 79.4, 77.8, 72.4, 71.0, 67.6 (× 2), 63.4, 33.4, 29.3, 28.0, 26.2, 18.4 ppm. $C_{13}H_{22}O_6$ (274.1): calcd. C 56.92, H 8.08; found C 56.77, H 7.78.

Dibenzyl Ether 31: The diol **30** (205 mg, 0.75 mmol) was dissolved in dry THF (45 mL) and treated with NaH (120 mg 60%, 2.25 mmol) at 0 °C under argon for 30 min. Then, benzyl bromide (260 μL, 2.25 mmol) and Bu_4NI (810 mg, 2.2 mmol) were added. After 3 h the reaction was diluted with Et_2O and washed with water. The organic phase was dried, concentrated and the residue purified by flash chromatography (hexane/EtOAc, 9:1) to yield **31** (245 mg, 72%) as a colourless oil. $[\alpha]_D^{21}$ = −2.0 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.27 (m, 10 H), 4.85 (d, *J* = 11.9 Hz, 1 H), 4.77 (d, *J* = 11.9 Hz, 1 H), 4.65 (d, *J* = 11.9 Hz, 2 H), 4.57 (t, *J* = 6.6 Hz, 1 H), 4.46 (dd, *J* = 4.5, 6.6 Hz, 1 H), 4.14 (dd, *J* = 4.5, 7.6 Hz, 1 H), 3.98 (t, *J* = 9.8 Hz, 1 H), 3.83 (m, 1 H, H-4), 3.71 (dd, *J* = 6.0, 9.8 Hz, 1 H), 3.49 (d, *J* = 6.6 Hz, 1 H), 2.11 (m, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 138.7, 128.5 (× 2), 128.0 (× 2), 127.7, 111.6, 108.4, 99.3, 81.1, 80.6, 77.5, 71.8, 69.3, 61.0, 36.8, 29.5, 28.2, 26.3, 19.1 ppm. $C_{27}H_{34}O_6$ (454.5): calcd. C 71.34, H 7.54; found C 71.09, H 7.63.

Diol 32: A solution of **31** (245 mg, 0.54 mmol) in MeOH (12 mL) was treated with PPTS (23 mg, 0.05 mmol) and the solution was stirred for 24 h. The mixture was concentrated and the residue purified by flash chromatography (hexane/EtOAc, 6:4) to yield **32** (190 mg, 85%) as white crystals. m.p. 87−88 °C. $[\alpha]_D^{21}$ = +42.8 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44−7.29 (m, 10 H), 4.98 (d, *J* = 11.3 Hz, 1 H), 4.86 (d, *J* = 12.3 Hz, 1 H), 4.75 (d, *J* = 12.3 Hz, 1 H), 4.61 (d, *J* = 11.3 Hz, 1 H), 4.54 (dd, *J* = 5.4, 7.7 Hz, 1 H), 4.39 (dd, *J* = 2.2, 5.4 Hz, 1 H), 4.18 (s, 1 H), 4.09 (m, 1 H), 3.87−3.81 (m, 3 H), 3.49 (dd, *J* = 2.3, 7.7 Hz, 1 H), 1.95 (ddt, *J* = 1.5, 3.5, 8.0 Hz, 1 H), 1.59 (s, 1 H), 1.38 (s, 3 H),1.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 137.6, 128.4 (× 2), 128.2 (× 2), 128.1 (× 2), 128.0, 127.5 (× 3), 108.6, 81.6, 79.2, 77.3, 76.8, 74.9, 71.9, 68.8, 60.3, 41.4, 28.1, 26.2 ppm. $C_{24}H_{3o}O_6$ (414.5): calcd. C 69.54, H 7.30; found C 69.83, H 7.58.

Silyl Ether 33: Imidazole (56 mg, 0.83 mmol) and *tert*-butylchlorodiphenylsilane (TPSCl) (194 mg, 0.70 mmol) was added to a solution of diol **32** (190 mg, 0.46 mmol) in DMF (5 mL) and the reaction mixture was stirred at room temperature for 12 h. It was then diluted with Et_2O and washed with water. The organic layer was dried and concentrated, giving a residue which was purified by flash chromatography (hexane/EtOAc, 9:1) to yield the silyl ether **33** (269 mg, 90%). $[\alpha]_D^{21}$ = +55.1 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68−7.61 (m, 4 H), 7.43−7.17 (m, 16 H), 4.97 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 12.5 Hz, 1 H), 4.74 (d, *J* = 12.5 Hz, 1 H), 4.50 (dd, *J* = 5.3, 8.0 Hz, 1 H), 4.43 (d, *J* = 11.0 Hz, 1 H), 4.34−4.30 (m, 2 H), 4.00 (d, *J* = 10.2 Hz, 1 H), 3.99 (m, 1 H), 3.79 (dd, *J* = 6.6, *J* = 10.2 Hz, 1 H, H-6), 3.41 (dd, *J* = 2.2, *J* = 8 Hz, 1 H, H-1), 1.90 (m, 1 H, H-5), 1.57 (s, 1 H, OH de C-4), 1.36 (s, 6 H), 1.07 (s, 9 H) ppm. ^{13}C NMR(50 MHz, $CDCl_3$): δ = 138.3, 137.8, 135.4 (× 4), 133.3, 133.2, 129.6 (× 2), 128.4 (× 2), 128.3 (× 2), 127.8 (× 3), 127.7 (× 2), 127.6 (× 2), 127.5 (× 3), 108.6, 81.5, 79.5, 77.4, 77.3, 75.2, 71.7, 68.7, 61.5, 41.7, 28.2, 26.9 (× 3), 26.3, 19.1 ppm.

Silyl Ether 34: Alcohol **33** (265 mg, 0.4 mmol) was converted into the corresponding xanthate and this material deoxygenated according to the general procedure. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to yield the carbagalactose derivative **34** (201 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65−7.61 (m, 4 H), 7.42−7.27 (m, 16 H), 5.01 (d, *J* = 11.2 Hz, 1 H), 4.85 (d, *J* = 12.5 Hz, 1 H), 4.76 (d, *J* = 12.5 Hz, 1 H), 4.45 (d, *J* = 11.2 Hz, 1 H), 4.32 (m, 2 H), 4.21 (d, *J* = 1.5 Hz, 1 H), 3.65 (t, *J* = 9.5 Hz, 1 H), 3.52 (dd, *J* = 5.6, 9.5 Hz, 1 H), 3.43 (d, *J* = 7.7 Hz, 1 H), 2.15 (m, 1 H), 1.78−1.60 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 138.8, 135.5 (× 3), 133.5, 129.6 (× 2), 128.3 (× 2), 128.1 (× 2), 127.7 (× 3), 127.6 (× 2), 127.5 (× 2), 127.4 (× 2), 127.3 (× 2),

127.2, 108.0, 82.0, 79.0, 74.7, 74.2, 74.1, 71.5, 64.1, 38.3, 28.3, 26.9 (× 3), 26.8, 26.4, 19.2 ppm.

5a-Carba-α-D-galactopyranose Pentaacetate (35): Bu_4NF (1.4 g, 3.1 mmol) was added to a solution of the silyl ether **34** (170 mg, 0.27 mmol) in THF (15 mL) and the reaction mixture was stirred overnight. The reaction was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried, filtered and concentrated to give a residue which was purified by flash chromatography (hexane/EtOAc, 7:3). The pure material was dissolved in MeOH (25 mL) and hydrogenolyzed in the presence of 10% Pd/C (10 mg) at 35 psi at room temperature for 60 min. The reaction mixture was then filtered through a short pad of Celite and concentrated to give a residue which was subjected to the general procedure for the cleavage of the isopropylidene moiety and acetylation. The crude material was purified by flash chromatography (hexane/EtOAc, 7:3) to yield carba-α-D-galactopyranose pentaacetate (**35**, 78 mg, 70%). $[\alpha]_D^{21}$ = +35.8 (*c* = 0.4, $CHCl_3$). {Ref.[42a] $[\alpha]_D^{20}$ = +35.16 (*c* = 1.77, $CHCl_3$), ref.[42b][42d] $[\alpha]_D^{20}$ = +43.2 (*c* = 1.1, $CHCl_3$), ref.[42c] $[\alpha]_D^{20}$ = +43.2 (*c* = 1.06, $CHCl_3$), ref.[42e] $[\alpha]_D^{25}$ = +30.6 (*c* = 1, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.57 (t, *J* = 2.3 Hz, 1 H), 5.51 (m, 1 H), 5.23 (dd, *J* = 2.3, 10.8 Hz, 1 H), 5.17 (dd, *J* = 2.7, 10.8 Hz, 1 H), 3.96 (t, *J* = 10.4 Hz, 1 H), 3.88 (dd, *J* = 6.1, 10.4 Hz, 1 H), 2.47 (m, 1 H), 2.11 (s, 6 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.99 (s, 3 H), 1.79−1.75 (m, 2 H) ppm. $C_{17}H_{24}O_{10}$ (414.5): calcd. C 52.57, H 6.23; found C 52.34, H 6.48.

Diol 38: A solution of **24** (592 mg, 1.66 mmol) in MeOH (20 mL) was treated with PPTS (73 mg, 0.16 mmol) and the solution was stirred for 24 h. The mixture was concentrated and the residue purified by flash chromatography (hexane/EtOAc, 6:4) to yield **38** (400 mg, 75%) as a colourless oil. $[\alpha]_D^{21}$ = +87.7 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.41 (s, 1 H), 5.34 (s, 1 H), 4.69 (d, *J* = 11.7 Hz, 1 H), 4.49 (m, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.13−3.95 (m, 4 H), 2.86 (m, 1 H, H-5), 2.53 (s, 1 H, OH), 1.65 (s, 1 H, OH), 1.36 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 136.7, 128.6 (× 2), 128.0 (× 2), 119.3 (× 2), 108.8, 80.2, 76.3 (× 2), 70.6, 69.3, 64.0, 41.5, 26.5, 24.4 ppm. $C_{18}H_{24}O_5$ (320.4): calcd. C 67.48, H 7.55; found C 67.24, H 7.67.

Alcohol 39: Imidazole (56 mg, 0.83 mmol) and *tert*-butyldiphenylchlorosilane (TPSCl) (194 mg, 0.70 mmol) were added to a solution of the diol **38** (150 mg, 0.47 mmol) in DMF (5 mL) and the reaction mixture was stirred at room temperature for 12 h. It was then diluted with Et_2O and washed with water. The organic layer was dried and concentrated, giving a residue which was purified by flash chromatography (hexane/EtOAc, 9:1) to yield the alcohol **39** (235 mg, 90%). $[\alpha]_D^{21}$ = +52.0 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75−7.69 (m, 4 H), 7.41−7.29 (m, 11 H), 5.26 (s, 1 H), 5.23 (s, 1 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 4.48 (dd, *J* = 3.1, 6.6 Hz, 1 H), 4.39 (m, 2 H), 4.27 (dt, *J* = 3.1, 10.5 Hz, 1 H), 4.05 (dd, *J* = 8.4, 9.7 Hz, 1 H), 3.85 (m, 2 H), 3.67 (d, *J* = 10.5 Hz, 1 H), 2.86 (m, 1 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.2, 135.8 (× 3), 135.7 (× 3), 133.7, 133.6, 129.7 (× 2), 128.5 (× 2), 127.9 (× 2), 127.7 (× 4), 118.1, 108.9, 80.8, 77.5, 76.8, 70.8, 66.0, 64.4, 42.4, 26.9 (× 4), 24.9, 19.2 ppm.

Silyl Ether 40: Alcohol **39** (230 mg, 0.41 mmol) was converted into the corresponding xanthate and this material deoxygenated according to the general procedure. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to yield the carba-D-glucose derivative **40** (160 mg, 72%). $[\alpha]_D^{21}$ = +62.6 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65−7.61 (m, 4 H), 7.42−7.27 (m, 16 H), 5.14 (s, 1 H, H_{sp^2}), 5.13 (s, 1 H, H_{sp^2}), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.48 (m, 1 H, H-1), 4.30 (d, *J* = 12.1 Hz, 1 H), 4.21 (dd, *J* = 3.5, 6.6 Hz, 1 H, H-2), 3.74−3.62 8m, 3 H, H-3, H-6, H-6′), 2.74 (m, 1 H, H-5), 2.25 (ddd, *J* = 3.2, 5.9, 14.9 Hz, 1 H, H-5_{eq}), 1.80 (ddd, *J* = 2.8, 11.5, 14.9 Hz, 1 H, H-5_{ax}), 1.37 (s, 3 H), 1.32 (s, 3 H), 1.05 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.1, 138.2, 134.8, 133.7, 129.6, 128.3, 127.6, 127.5, 115.8, 108.3, 81.4, 78.4, 72.8, 70.2, 68.0, 37.2, 27.7, 26.9 (× 3), 24.9, 19.3 ppm.

Alcohols 41 and epi-5a-41: Ozone was bubbled through a solution of the methylenecyclohexane **46** (115 mg, 0.21 mmol) in MeOH/CH_2Cl_2 (1:1 mixture, 5 mL) at −78 °C until TLC showed complete consumption of the starting compound. Oxygen was then bubbled through the solution for 5 min. Next, the mixture was treated with dimethyl sulfide (0.5 mL) and the solution was warmed to room temperature over 2 h. After stirring for an additional hour, the solvent was removed. The residue was then dissolved in MeOH (10 mL) and treated with $CeCl_3 \cdot H_2O$ (156 mg, 0.42 mmol). The mixture was cooled to 0 °C, treated with $NaBH_4$ (32 mg, 0.84 mmol) and then warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc and washed with water and brine. The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography (hexane/EtOAc, 95:5) to give the alcohol **41** (70 mg, 60%) along with its epimer **epi-5a-41** (28 mg, 24%). **epi-5a-41:** $[\alpha]_D^{21}$ = +34.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.69−7.63 (m, 5 H), 7.46−7.28 (m, 6 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 4.73 (d, *J* = 12.4 Hz, 1 H), 4.35 (m, 1 H), 4.26 (m, 2 H), 3.71 (m, 2 H), 3.34 (dd, *J* = 2.6, 7.5 Hz, 1 H), 2.00−1.78 (m, 3 H, H-5 and 2H-5a), 1.36 (s, 6 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 138.4, 135.6 (× 3), 135.5 (× 3), 133.2, 129.2 (× 2), 128.3 (× 2), 127.9 (× 2), 127.7 (× 3), 127.6, 108.2, 80.7, 78.5, 74.1, 71.2, 68.4, 65.3, 36.7, 28.2, 26.8 (× 3), 26.4, 23.3, 19.2 ppm. **41:** $[\alpha]_D^{21}$ = +22.6 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.82−7.73 (m, 4 H), 7.31−7.05 (m, 11 H), 5.05 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.01 (dd, *J* = 4.6, 9.9 Hz, 1 H), 3.94 (m, 1 H), 3.86 (t, *J* = 5.8 Hz, 1 H), 3.74 (dd, *J* = 3.1, 9.9 Hz, 1 H), 3.50 (m, 2 H), 2.70 (s, 1 H), 2.40 (m, 2 H), 2.10 (td, *J* = 3.4, *J* = 14.4 Hz, 1 H, H_{ax}-CH_2), 1.37 (s, 3 H), 1.25 (s, 3 H), 1.14 (s, 9 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 140.0, 136.7 (× 3), 136.6 (× 3), 134.7, 134.6, 130.6 (× 2), 129.3 (× 2), 128.9 (× 3), 109.4, 86.2, 81.7, 75.0, 74.0, 72.1, 65.2, 39.5, 29.1, 28.4, 27.8 (× 3), 27.1, 20.3 ppm.

5a-Carba-α-D-glucopyranose Pentaacetate (42): Bu_4NF (700 mg, 1.6 mmol) was added to a solution of silyl ether **41** (70 mg, 0.13 mmol) in THF (7 mL) and the reaction mixture was stirred overnight. The reaction was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried, filtered and concentrated to give a residue which was purified by flash chromatography (hexane/EtOAc, 1:1). The pure material was dissolved in MeOH (7 mL) and hydrogenolyzed in the presence of 10% Pd/C (5 mg) at 35 psi at room temperature for 60 min. The reaction mixture was then filtered through a short pad of Celite and concentrated to give a residue which was subjected to the general procedure for the cleavage of the isopropylidene moiety and acetylation. The crude material was purified by flash chromatography (hexane/EtOAc, 6:4) to yield carba-α-D-glucopyranose pentaacetate (**42**, 30 mg, 56%). $[\alpha]_D^{21}$ = +32.1 (*c* = 0.4, $CHCl_3$). {Ref.[46a] $[\alpha]_D^{22}$ = +37 (*c* = 0.79, $CHCl_3$), ref.[46b] $[\alpha]_D^{22}$ = +57 (*c* = 0.90, $CHCl_3$), ref.[46c] $[\alpha]_D^{20}$ = +63 (*c* = 1.0, $CHCl_3$), ref.[46d] $[\alpha]_D^{20}$ = +36.7 (*c* = 0.791, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.45 (m, 1 H), 5.40 (t, *J* = 10.2 Hz, 1 H), 5.03 (t, *J* = 10.2 Hz, 1 H), 4.93 (dd, *J* = 3.2, 10.4 Hz, 1 H), 4.15 (dd, *J* = 4.6, 11.6 Hz, 1 H),

3.90 (dd, J = 3.2, 11.6 Hz, 1 H), 2.34 (m, 1 H), 2.14 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.99 (s, 3 H), 1.96 (m, 1 H), 1.72 (dt, J = 2.2, 15.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 171.9, 170.0, 169.9 (× 2), 71.7, 71.3, 67.9, 67.8, 62.8, 34.9, 28.6, 25.6, 21.0, 20.7, 20.6 (× 2) ppm. $C_{17}H_{24}O_{10}$ (414.5): calcd. C 52.57, H 6.23; found C 52.46, H 6.35.

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