Synthesis of a Small Repertoire of Non-Racemic 5a-Carbahexopyranoses and 1-Thio-5a-carbahexopyranoses[‡]

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A short and practical entry to optically pure 5a-carbahexopyranose and 1-thio-5a-carbahexopyranose representatives is described. Besides a few functional group and protecting group manipulations, the synthetic scheme counts on two fundamental carbon–carbon bond-forming reactions, namely (i) a regio- and stereoselective aldol addition between heterocyclic (silyloxy)diene donors (**6** or **13**) and D-glyceraldehyde as the acceptor (**7**) and (ii) a chemo- and stereoselective silylative cycloaldolization involving bifunctional aldehydes (**10**, **16**, and **21**). The ^{1}H NMR based configurational and conformational assignment of target structures **1**–**5** and bicyclic intermediates **11**, **12**, **17**, **18**, and **22** is discussed.

Introduction

Functionally and stereochemically diverse collections of small molecules can be used to explore the basic metabolic pathways in living systems, the alteration of which often lies at the basis of many physiological disorders and pathological conditions.[2] Natural and natural-product-like entities, for example members of the cyclitol and carbasugar families[3] with hydroxy moieties embodied in a ring structure, have attracted our attention for several reasons: (i) Their structures are analogous to those of carbohydrates, which are amongst the most represented and property-rich building blocks used by Nature; (ii) molecules of this family have proven to be potent inhibitors of a variety of glycosidase enzymes that are responsible for post-translational processing of ribosome-synthesized glycopeptides;[4] (iii) the lack of the sugar acetal moiety − here, the ring oxygen atom is replaced by a carbon atom − preserves them from hydrolysis and renders them chemically and biologically resistant; and (iv) these constructions can provide novel scaffolds with which carbocyclic analogues of nucleosides[5] and designed oligomeric entities[6] can be engineered.

Our group has presented[1,7] a synthetic strategy with a high variability potential capable of targeting carbafuranose and carbapyranose structures, as well as carbafuranosyl- and carbapyranosylamines and 1-thio derivatives in diverse stereochemical variants. Basically, the chemistry we employ is founded upon the use of readily available starting materials, namely, the heterocyclic silylketene acetals of type **I**[8] and glyceraldehyde **II** (Figure 1), and features two key carbon−carbon bond-forming reactions, an intermolecular Mukaiyama-type aldol manoeuvre in its vinylogous version (arrow a),[9] followed by an intramolecular silylative aldol junction (arrows b or c).[10] The remaining reactions are simply protecting group and functional group manipulations.

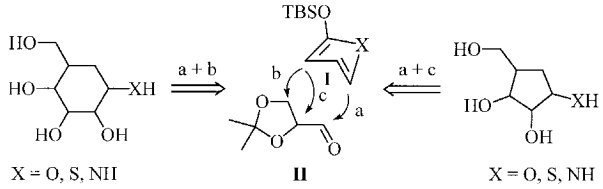

Figure 1. Basic strategy towards carbahexopyranoses and carbapentofuranoses and their analogues

When put into practice, this synthetic tactic proved to be pleasingly efficient, reasonably short, and above all, chemically uniform, which enabled us to obtain a small library of

[‡] Variable Strategy toward Carbasugars and Relatives, 3. Part 2: Ref.[1]

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eleven pseudo-sugar compounds of both the D- and L-series. Our intention was to demonstrate further the general utility and applicability of our original plan and to refine the synthetic protocol for the preparation of enantiopure, richly functionalized cyclohexanoid structures. The outcome of our efforts is presented here by the synthesis of five carbapyranose representatives including the β-D-*gulo*-configured pseudo-sugar **1**, the β-D-allopyranose analogue **2**, the corresponding 1-thio derivatives **3** and **4**, and the L-series *manno*-configured derivative **5** (Figure 2).[11]

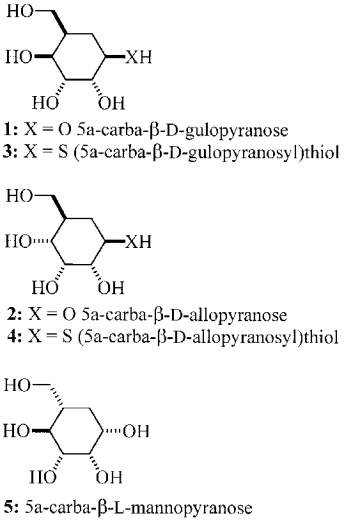
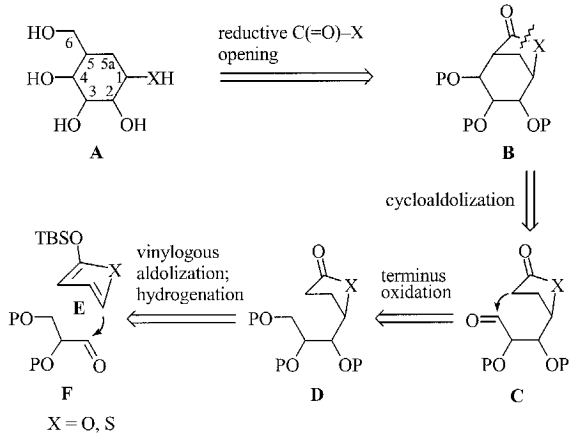


Figure 2. Carbahexopyranoses prepared in this study

Results and Discussion

Planning

In devising the carbapyranose rings of this study (structure **A**, Scheme 1), we imagined them to arise from the reductive opening of the lactone (or thiolactone) function in the bicyclooctane **B**. In turn, **B** was seen to originate by an intramolecular aldol closure from the monocyclic intermediate **C**, whose aldehyde function may be easily implemented onto triol **D**. The structure of **D** mandated a vinylogous aldolization manoeuvre between the heterocyclic (silyloxy)diene **E** and the chiral aldehyde **F**. Basically, **E** and **F** are the building blocks that account for the carbon skeleton and the oxygen (and sulfur) functionalities, with carbon atoms C-2, C-3, and C-4 (target numbering) being furnished by the glyceraldehyde precursor **F**, and carbon atoms C-1, C-5, C-5a, and C-6 coming from the chosen (silyloxy)-diene **E**.

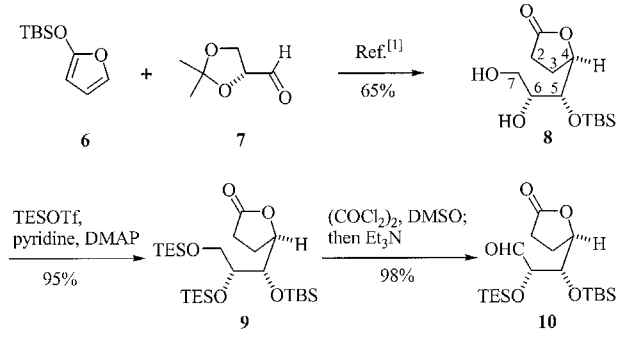


Scheme 1. Retrosynthetic analysis of carbahexopyranoses **A**

The two fundamental carbon−carbon bond-forming reactions (**E** + **F** → **D** and **C** → **B**) − both aldol additions and both of the Mukaiyama type − represent the focal point of the whole strategy, as they orchestrate the construction of the cyclohexane ring and ultimately control four of the five stereocentres present in the targets (absolute configuration at C-3 is that of the initial aldehyde **F**).

Synthesis of 5a-Carba-β-D-gulopyranose (1) and 5a-Carba-β-D-allopyranose (2)

Targeting the title carbapyranoses **1** and **2** entailed the use of the advanced lactone intermediate **8**, whose preparation from 2-[(*tert*-butyldimethyl)silyloxy]furan (**6**) and 2,3-*O*-isopropylidene-D-glyceraldehyde (**7**) has been previously reported (four steps, 65% yield, Scheme 2).[1]

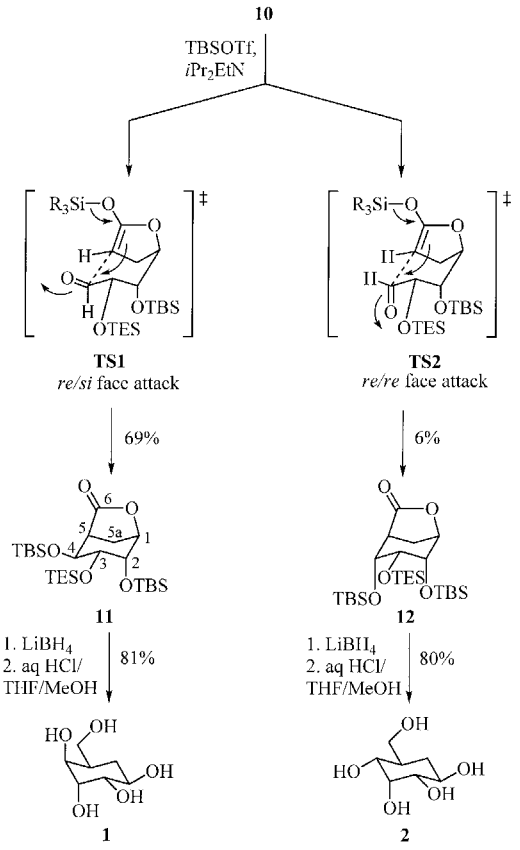


Scheme 2. Preparation of advanced lactone intermediate **10**

Aiming at the crucial cycloaldolization, we had to unmask an aldehyde functionality at the C-7 terminus; to do this, we decided to exploit a slightly modified version of the Swern oxidation,[12] which, fortunately enough, could be directly applied to a protected primary hydroxy group. Thus, **8** was first subjected to complete protection of its free OH groups as triethylsilyl ethers to give lactone **9** (TESOTf, pyridine, DMAP, 95%), which underwent direct oxidation to aldehyde **10** [DMSO, $(COCl_2)_2$; then Et_3N, 98%].

To promote the key cycloaldolization, we then had to induce the formation of an enolate of the lactone moiety and subsequently ensure closure on the aldehyde function. Capitalizing on the results of preceding studies,[1] we opted to carry out the reaction of **10** in the presence of equimolar quantities of TBSOTf and diisopropylethylamine (DIPEA, 3.0 equiv.) at room temperature (Scheme 3). Not surprisingly, the reaction proceeded smoothly, furnishing bicyclo-

octane **11** in 69% yield, accompanied by small quantities (6%) of its C-4 epimer **12**.[13]



Scheme 3. Preparation of 5a-carbapyranoses **1** and **2**

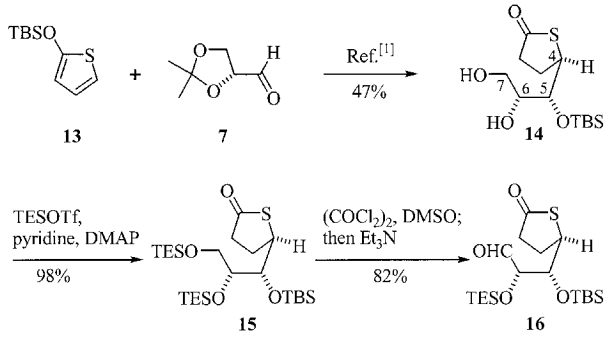
Some points deserve commenting here. Firstly, the chemoselectivity of the process was complete, with the sole lactone moiety being involved in enolization. Secondly, the stereochemical behaviour strongly favours the 3,4-*trans*-configured isomer **11** over the corresponding 3,4-*cis*-disposed counterpart **12**. Thermodynamic control is most probably working here, where the more stable, 3,4-diequatorial product **11** predominates, emerging from the anti-Felkin attack on the *si*-face of the aldehyde function (**TS1**).[14]

Having just crafted the cyclohexane structure of the targets, we next turned to the final stages of the synthesis, namely the reductive opening of the γ-lactone moiety within the bicyclooctanes **11** and **12**. Treatment of the major isomer **11** with $LiBH_4$,[15] followed by removal of the silyl protecting groups (HCl, THF, MeOH), finally yielded the desired 5a-carba-β-D-gulopyranose (**1**) in a 81% yield for the two steps. This corresponds to a nice 34% yield over nine steps from **6** and **7**.[16] According to the same procedure, the minor isomer **12** was converted into the corresponding carbasugar, 5a-carba-β-D-allopyranose (**2**), in a gratifying 80% yield. The configurational and conformational assignments of carbasugars **1** and **2**, as well as those of bicyclic intermediates **11** and **12**, were unequivocally established by 1D and 2D ^1H NMR analyses (vide infra).

Synthesis of 1-Thio-5a-carba-β-D-gulopyranose (3) and 1-Thio-5a-carba-β-D-allopyranose (4)

The experience gained with the above synthetic route, which quickly and efficiently led us to carbapyranoses, as foreseen by the general plan, enticed us to apply this process to the preparation of carbapyranose derivatives containing a thio function at the pseudo-anomeric position. Such monosaccharide analogues, until now completely unheard of, could enrich the library of carbasugars we envisioned.

According to the retrosynthetic plan (Scheme 1), the thio function of the title compounds derives from the sulfur heteroatom within the (silyloxy)diene **E**. Therefore, the synthetic sequence started with the aldol addition between 2-[(*tert*-butyldimethyl)silyloxy]thiophene (**13**) and protected glyceraldehyde **7** (Scheme 4). As previously described,[1] a four-step protocol enabled us to arrive at thiolactone **14** with a 47% overall yield.



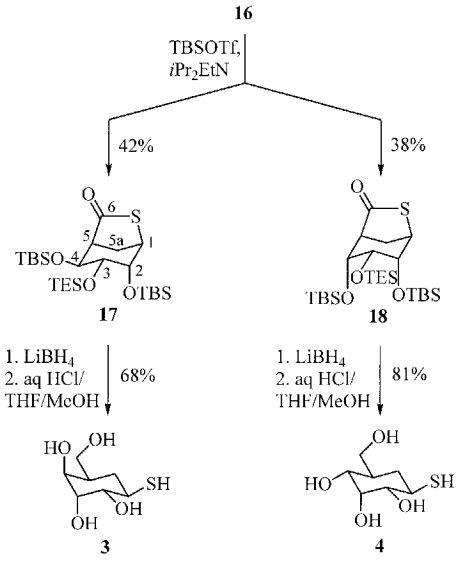
Scheme 4. Preparation of advanced thiolactone intermediate **16**

Protection of the terminal diol function with TESOTf brought us to the fully protected thiolactone **15** (98%), which directly underwent oxidation to aldehyde **16** in 82% isolated yield. With aldehyde **16** in hand, it was assumed that the cycloaldolization event would proceed without problems. Indeed, the TBSOTf/DIPEA reagent system (1:1, 3.0 equiv., room temperature) triggered a cascade of reactions, namely, chemoselective enolsilylation of the thiolactone moiety, Mukaiyama-type cycloaldolization, and silylation of the resulting OH function, which ultimately gave rise to 3,4-*trans*-configured bicycle **17** (42%) along with 38% of its 3,4-*cis*-configured counterpart **18** (Scheme 5).[14]

The cycloadducts **17** and **18** were separately treated with $LiBH_4$, followed by a 1:2:2 mixture of HCl/THF/MeOH. In this way, 1-thio-5a-carba-β-D-gulopyranose (**3**) and epimeric 1-thio-5a-carba-β-D-allopyranose (**4**) were obtained in a 68% and 81% yield, respectively (two steps), corresponding to overall yields of 11% and 12% over nine steps. The stereochemistry of both products, as well as those of the bicyclic intermediates was determined through 1D and 2D ^1H NMR analysis (vide infra).

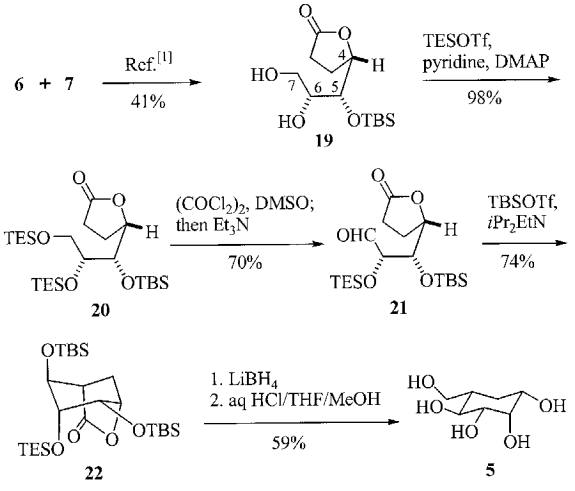
Synthesis of 5a-Carba-β-L-mannopyranose (5)

In engineering the L-series carbasugars, we had to control the configuration of the stereocentres C-1 and C-5 [(1*S*,5*S*), Scheme 1], and ultimately stereocontrol the initial aldol re-



Scheme 5. Preparation of 1-thio-5a-carbapyranoses **3** and **4**

action. For this reason, dienol ether **6** was made to react with aldehyde **7** under the influence of $BF_3{\cdot}OEt_2$ (−80 °C) and the resulting reaction mixture, rich in the 4,5-*syn*-5,6-*anti*-configured butenolide, was allowed to equilibrate under Et_3N. The thermodynamically stable C-4-epimeric butenolide (4,5-*anti*-5,6-*anti*) endowed with the desired (4*S*) absolute configuration was formed. The usual transformations followed,[1] consisting in nickel boride promoted reduction and protecting group manipulation. Butanolide **19** was isolated in 41% yield over five steps from **6** and **7** (Scheme 6).



Scheme 6. Preparation of 5a-carbapyranose **5**

Paralleling the previously disclosed procedure, compound **19** was transformed into aldehyde **21** via the fully protected lactone **20** (69%, two steps). The crucial ring closure − the TBSOTf/DIPEA-promoted silylative cycloaldolization − was performed on aldehyde **21** to give 3,4-*trans*-configured bicycle **22** in a high yield and with complete diastereoselective control.

At this point, the final carbasugar target was in our reach. When compound **22** was subjected to reductive treatment ($LiBH_4$), the expected protected carbasugar derivative was obtained, although we had to greatly force the reaction conditions (11 equiv.). The steric hindrance about the C-6 reactive site caused by the silyl protection and by the concavity of the bicycle probably rendered this reduction rather sluggish. Nonetheless, a protected carbasugar derivative was isolated in 59% yield. Acidic deprotection finally provided 5a-carba-β-L-mannopyranose (**5**) in a quantitative yield, corresponding to a nice 12% yield over ten steps from **6** and **7**.

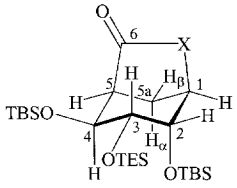
Structural Analysis

By observing the structure of the target carbasugars and the chemical sequence that led to them, it can be seen that of the five stereocentres present, C-1 and C-2 arise from the first aldol reaction, C-3 derives from the configuration of the glyceraldehyde chosen, and C-4 and C-5 are formed during the cycloaldolization. With C-3 fixed as (*R*) [we always started from the (*R*)-configured glyceraldehyde], the remaining C-1, C-2, C-4, and C-5 had to be analysed. The diastereoselective nature of the initial Mukaiyama addition led mainly to the butenolide (or thiobutenolide) adduct with a 4,5-*syn*-5,6-*anti* configuration (**8** or **14** in Schemes 2 and 4). This translates directly into fixing the configurations of the stereocentres C-1 and C-2 within targets **1**−**4** as (1*R*,2*S*), given the stereo-preserving nature of the synthetic sequence followed. On the other hand, when the initial aldol reaction was steered to favour the 4,5-*anti*-5,6-*anti*-configured butenolide (**19**, Scheme 6), the resultant target compound would have the configuration (1*S*,2*S*).

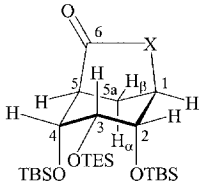
In order to define the configuration of C-4 and C-5, we had to trace the stereochemistry of the cycloaldolization. ^{1}H NMR one- and two-dimensional studies extensively carried out on the bicyclic adducts **11**, **12**, **17**, **18**, and **22**, as well as the final targets, proved fundamental for this determination (Tables 1 and 2).

Certification of the (1*R*,2*S*,3*R*,4*S*,5*S*) configuration and of the $^1C_4$ chair conformation of the hexanoid ring in adducts **11** and **17** (as depicted) was founded on general inspection of the spectra and on the following observations in particular: (i) presence of the coupling constant $^3J_{3,4}$ = 8.8 Hz (for **11**) and 9.1 Hz (for **17**), indicating a *trans*-diaxial positioning of these protons; (ii) presence of long-range coupling constants $^4J_{1,5}$ = 0.7/1.7 Hz and $^4J_{2,5a\beta}$ = 0.6/0.8 Hz for the **11**/**17** couple, pointing to an equatorial coplanar *W* disposition of these protons; and (iii) existence of strong NOE contacts between 4-H and 5a-H_α. On the other hand, diagnosis of the epimeric bicyclic structures **12** and **18**, with a 3,4-*cis* configuration, was solved by piecing together the following evidence: (i) the presence of vicinal coupling constants ranging from 0.0 to 5.2 Hz, indicating only diequatorial and axial/equatorial relationships between protons; (ii) the coupling constants $^4J_{1,5}$ = 0.7 Hz (for **12**) and 1.7 Hz (for **18**), confirming a diequatorial orientation of these protons; and (iii) a strong NOE contact between

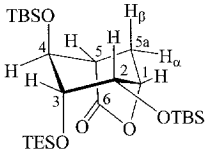
Table 1. Selected ^{1}H NMR resonances (δ, ppm), coupling constants (*J*, Hz), and ^{1}H−^{1}H NOE contacts of bicyclic compounds **11**, **12**, **17**, **18**, and **22**



11: X = O
17: X = S



12: X = O
18: X = S

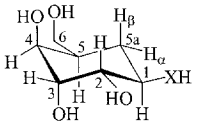


22

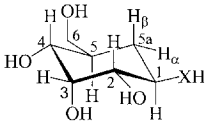
Compd.[a]	5a-H_β	5a-H_α	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,5a\beta}$	$^3J_{5,5a\alpha}$	$^3J_{1,5a\beta}$	$^3J_{1,5a\alpha}$	$^4J_{1,5}$	$^4J_{2,5a\beta}$	$^4J_{1,3}$	$^4J_{3,5}$	NOEs
11	2.08	2.37	5.4	3.9	8.8	2.6	5.4	0.0	5.4	0.0	0.7	0.6	0.0	0.0	4−5aα
17	2.11	2.60	3.9	3.5	9.1	3.6	4.5	0.0	3.9	1.7	1.7	0.8	0.0	0.0	4−5aα
12	1.94	2.97	5.2	4.8	4.3	4.3	5.2	0.0	5.2	0.0	0.7	0.5	0.0	0.0	4−5
18	2.01	3.14	3.9	3.9	3.9	4.7	4.7	0.0	4.8	1.7	1.7	0.5	0.0	0.0	4−5
22	2.23	2.36	0.9	4.3	2.6	4.5	0.0	5.1	0.0	6.3	1.0	0.0	1.4	1.4	2−5aβ

[a] Measured at 300 MHz on 0.1 M solutions in $CDCl_3$ at 300 K.

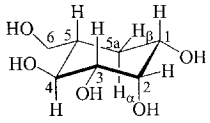
Table 2. Selected ^{1}H NMR resonances (δ, ppm), coupling constants (*J*, Hz), and ^{1}H−^{1}H NOE contacts of target carbasugars **1**−**5**



1: X = O
3: X = S



2: X = O
4: X = S



5

Compd.[a]	5a-H_β	5a-H_α	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,5a\beta}$	$^3J_{5,5a\alpha}$	$^3J_{1,5a\beta}$	$^3J_{1,5a\alpha}$	$^4J_{4,5a\alpha}$	NOEs
1	1.39	1.86	9.9	2.5	3.5	2.8	12.9	4.3	11.7	4.3	0.0	1−5, 2−5aβ
2	1.25	2.07	9.8	3.0	2.9	10.9	12.6	3.9	11.4	4.8	0.0	2−5aβ, 2−4, 4−5aβ, 1−5
3	1.47	1.95	10.9	3.1	3.7	3.0	13.0	3.6	12.5	4.2	1.2	1−5, 2−5aβ
4	1.25	2.11	10.9	2.7	2.8	11.1	12.7	4.1	12.4	4.2	0.0	2−5aβ, 2−4, 4−5aβ, 1−5
5	1.78	1.55	2.7	2.7	9.6	9.7	4.8	10.0	4.8	9.4	0.0	3−5, 4−5aα

[a] Measured at 300 MHz on 0.2 M solutions in D_2O at 300 K.

4-H and 5-H, underlining the *trans* diequatorial disposition for these protons.

In comparing the proton resonances of the 3,4-*trans*-configured compounds (**11** and **17**) and the 3,4-*cis* counterparts (**12** and **18**), an obvious downfield shift for the 5a-H_β resonance and an equally significant upfield shift for the 5a-H_α resonance were observed. The equatorial (**11** and **17**) or the axial (**12** and **18**) positioning of the OTBS group at C-4 most likely induces a significant variation in the electronic environment surrounding the spatially near 5a-H_α and 5a-H_β (see Table 1).

Moving on to consider the bicyclooctane **22**, the general structure, and in particular, the $^4C_1$ conformation of the six-membered ring, together with the *trans* relationship of the substituents at positions 3 and 4, were deciphered by the absence of large couplings (absence of vicinal protons in a *trans*-diaxial disposition) and by the presence of diagnostic ^4J values between 1-H and 3-H, 1-H and 5-H, and 3-H and 5-H.

One- and two-dimensional ^{1}H NMR analysis of compounds **1**−**5** not only served to back up data obtained from analysis of the bicyclic structures, but also revealed the exact conformation of the final targets. Firstly, in cleaving the bicyclic adducts (reductive opening), all these compounds underwent a conformational reversal of their six-membered ring, thus bringing the maximum number of substituents into the equatorial position. In particular, the $^4C_1$ conformation of compounds **1**−**4** is supported by the presence of diagnostic upfield quadruplets (δ = 1.25−1.47 ppm; *J* = 11.4−12.5 Hz) belonging to 5a-H_β and by the existence of coupling constants $^3J_{1,2}$, $^3J_{1,5a\beta}$, and $^3J_{5,5a\beta}$ ranging from 9.8 to 13.0 Hz, which prove that these protons lie in axial positions. Furthermore, medium-to-strong NOE constants 1-H−5-H and 2-H−5a-H_β support the stereo disposition depicted in the structures of Table 2.

The equatorial orientation of 4-H in the 3,4-*trans* products **1** and **3** was demonstrated, as expected, by the vicinal coupling constants and, in the case of compound **3**, also by

a diagnostic long-range *W* coupling constant $^4J_{4,5a\alpha}$ = 1.2 Hz. In the 3,4-*cis*-configured counterparts **2** and **4**, 4-H was determined to lie in the axial position by the large $^3J_{4,5}$ constants (10.9 and 11.1 Hz) and by the considerable NOE correlations 2-H−4-H and 4-H−5a-H$_\beta$. Once more, the 5a-H$_\beta$ and 5a-H$_\alpha$ resonances are markedly influenced by the configuration of C-4; in the (4*S*)-configured products **1** and **3** the 5a-H$_\beta$ resonances fall downfield, whilst the protons 5a-H$_\alpha$ resonate upfield with respect to the corresponding protons in the (4*R*)-disposed compounds **2** and **4** (δ = 1.39 vs. 1.25 ppm; δ = 1.47 vs. 1.25 ppm; δ = 1.86 vs. 2.07 ppm; δ = 1.95 vs. 2.11 ppm). Finally, for the L-series pseudosugar **5**, the presence of two large vicinal constants ($^3J_{1,5a\alpha}$ = 9.4 Hz and $^3J_{5,5a\alpha}$ = 10.0 Hz), together with the general analysis of the vicinal and long-range coupling constants, as well as strong NOE correlations for 3-H−5-H and 4-H−5a-H$_\alpha$, all but validate the $^1C_4$ structure thus shown in Table 2.

Conclusion

With the synthesis of five diverse carbapyranoses successfully executed, a further element has been woven into the design of carbasugars and analogues. The defining step in this approach is a direct silylative cycloaldolization that assembles the densely oxygenated cyclohexane frame from diverse and readily obtainable aldehyde intermediates (e.g. **10**, **16**, and **21**). The final carbocyclic construct is formed by reductive fragmentation of a lactone/thiolactone unit that delivers both the pseudo-anomeric function and the hydroxymethyl terminal in one step.

The viability of this synthetic avenue was verified by the efficient preparation of 5a-carba-β-D-gulopyranose (**1**), 5a-carba-β-D-allopyranose (**2**), and 5a-carba-β-L-mannopyranose (**5**). The syntheses of 1-thio-5a-carba-β-D-gulopyranose (**3**) and 1-thio-5a-carba-β-D-allopyranose (**4**) were realized with a similar overall efficiency from **13** and **7**.

Experimental Section

General Remarks: Moisture- and air-sensitive reactions were carried out under nitrogen or argon. Reaction flasks were flame-dried and reactants were introduced by means of syringes. All solvents were dried by distillation from the appropriate drying agents immediately prior to use. All reagents obtained from commercial sources were used without further purification. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (0.20 mm layer thickness, Merck). Flash chromatography was performed on 40−63 μm silica gel (Merck) using the indicated solvent mixtures. The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate or in an ethanolic solution of ninhydrin, followed by charring with a heat gun. Proton and carbon NMR spectra were recorded with Bruker AC-300, Avance 300, and with Varian XL-300 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. Connectivity was determined by ^{1}H−^{1}H COSY experiments. ^{13}C NMR assignments were obtained from HETCOR experiments. Optical rotations were measured with a Perkin−Elmer 341 polarimeter at ambient temperature using a 100-mm cell with a 1-mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari. Melting points were determined with an optical thermomicroscope Optiphot2-Pol Nikon.

Materials: 2-[(*tert*-Butyldimethylsilyl)oxy]furan (**6**) and 2-[(*tert*-butyldimethylsilyl)oxy]thiophene (**13**) were prepared from 2-furaldehyde and thiophene, respectively, according to reported methods.[17] 2,3-*O*-Isopropylidene-D-glyceraldehyde (**7**) was prepared from D-mannitol according to a recently optimized protocol.[18]

Lactone 8: The title compound was prepared from (silyloxy)furan **6** (5.00 g, 25.2 mmol) and glyceraldehyde **7** (3.93 g, 30.2 mmol) according to a recently reported four-step procedure.[1] Lactone **8** (4.76 g) was isolated in 65% yield as white crystals. M.p. 81−83 °C. $[\alpha]_D^{20}$ = −14.2 (*c* = 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.13 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 2.14 (m, 1 H), 2.27 (m, 1 H), 2.55 (m, 2 H), 3.32 (br. s, 2 H), 3.66 (m, 1 H), 3.79 (m, 3 H), 4.76 (td, *J* = 7.2, 3.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.5, −4.4, 18.0, 23.5, 25.7 (3 C), 28.4, 63.1, 72.3, 74.3, 80.8, 177.6 ppm. $C_{13}H_{26}O_5Si$ (290.4): calcd. C 53.76, H 9.02; found C 53.69, H 8.81.

Lactone 9. Typical Procedure: To a solution of lactone **8** (4.50 g, 15.5 mmol) in dry pyridine (50 mL) under argon at room temperature, were added triethylsilyl triflate (TESOTf, 10.5 mL, 46.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.28 g, 2.3 mmol). After stirring at room temperature for 2 h, the reaction was quenched by addition of distilled water and 5% aqueous citric acid solution until neutral. The mixture was diluted with CH_2Cl_2 (30 mL), the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure, and the residue was subjected to flash-chromatographic purification (hexanes/EtOAc, 80:20), to give 7.60 g (95% yield) of **9** as a colourless oil. $[\alpha]_D^{20}$ = −23.2 (*c* = 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 3 H), 0.10 (s, 3 H), 0.54 (m, 12 H), 0.89 (s, 9 H), 0.94 (br. t, *J* = 7.9 Hz, 18 H), 1.87 (dq, *J* = 12.4, 9.4 Hz, 1 H), 2.23 (dq, *J* = 12.2, 5.7 Hz, 1 H), 2.46 (m, 2 H), 3.39 (dd, *J* = 9.1, 4.8 Hz, 1 H), 3.72 (m, 2 H), 3.79 (m, 1 H), 4.62 (dt, *J* = 8.9, 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.7, −4.5, 4.2 (3 C), 4.8 (3 C), 6.7 (6 C), 18.3, 25.0, 25.9 (3 C), 29.2, 62.9, 73.5, 78.3, 82.3, 177.2 ppm. $C_{25}H_{54}O_5Si_3$ (519.0): calcd. C 57.86, H 10.49; found C 57.78, H 10.58.

Aldehyde 10. Typical Procedure: To a solution of oxalyl chloride (6.3 mL, 72.3 mmol) in CH_2Cl_2 (50 mL) at −80 °C under argon was added dropwise a solution of dimethyl sulfoxide (DMSO, 10.3 mL, 144.5 mmol) in CH_2Cl_2 (50 mL). After 10 min, a solution of protected lactone **9** (7.50 g, 14.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After 20 min at −80 °C, the mixture was allowed to rise to −40 °C and was stirred at this temperature for an additional 20 min, after which time it was again placed at −80 °C and Et_3N (36.2 mL, 260.1 mmol) was added dropwise. The reaction mixture was stirred at −80 °C for 10 min and then warmed to 25 °C over a period of 2 h. Toluene (100 mL) was added to the mixture, and the solution was filtered and concentrated under vacuum. The residue was dissolved in hexanes (100 mL), filtered again, and concentrated under reduced pressure to give aldehyde **10** (5.70 g, 98%) as a colourless oil, which was used as such without further purification. $[\alpha]_D^{20}$ = −7.8 (*c* = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.60 (q, *J* = 7.5 Hz, 6

H), 0.85 (s, 9 H), 0.93 (t, J = 7.9 Hz, 9 H), 1.96 (dq, J = 12.6, 9.6 Hz, 1 H), 2.23 (dq, J = 12.9, 7.0 Hz, 1 H), 2.50 (m, 2 H), 3.92 (dd, J = 6.3, 2.7 Hz, 1 H), 3.98 (dd, J = 2.8, 1.5 Hz, 1 H), 4.55 (q, J = 7.2 Hz, 1 H), 9.59 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.8, −4.7, 4.5 (3 C), 6.5 (3 C), 18.1, 23.7, 25.6 (3 C), 28.4, 77.6, 78.9, 80.2, 176.2, 202.8 ppm. $C_{19}H_{38}O_5Si_2$ (402.7): calcd. C 56.67, H 9.51; found C 56.75, H 9.68.

Bicycles 11 and 12. Typical Procedure: To a solution of diisopropylethylamine (DIPEA, 7.4 mL, 42.5 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 °C under argon, was added TBSOTf (9.8 mL, 42.5 mmol), and the resulting mixture was stirred at the same temperature for 10 min before adding aldehyde **10** (5.70 g, 14.2 mmol), dissolved in anhydrous CH_2Cl_2 (70 mL). After 15 min, the mixture was allowed to come to room temperature and was stirred at room temperature for 2 h. The reaction was then quenched with distilled water and saturated NH_4Cl solution until pH = 5, and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography (hexanes/EtOAc, 95:5) to give 5.10 g (69%) of **11** accompanied by 0.44 g (6%) of **12**.

Compound 11: Colourless crystals. M.p. 32−33 °C. $[\alpha]_D^{20}$ = +54.8 (c = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.04 (s, 3 H, Me), 0.08 (s, 3 H, Me), 0.09 (s, 3 H, Me), 0.10 (s, 3 H, Me), 0.63 (q, J = 8.0 Hz, 6 H, Si−CH_2CH$_3$), 0.87 (s, 9 H, tBu), 0.93 (s, 9 H, tBu), 0.94 (t, J = 8.2 Hz, 9 H, Si−CH$_2$$CH_3$), 2.08 (dtd, J = 11.9, 5.4, 0.6 Hz, 1 H, 5a-H$_β$), 2.37 (d, J = 11.9 Hz, 1 H, 5a-H$_α$), 2.53 (ddd, J = 5.4, 2.5, 0.7 Hz, 1 H, 5-H), 3.63 (dd, J = 8.8, 3.9 Hz, 1 H, 3-H), 3.77 (dd, J = 8.8, 2.6 Hz, 1 H, 4-H), 4.07 (td, J = 4.8, 0.7 Hz, 1 H, 2-H), 4.47 (td, J = 5.4, 0.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.9 (Si−CH$_3$), −4.6 (Si−CH$_3$), −4.5 (Si−CH$_3$), −3.9 (Si−CH$_3$), 5.3 (3 C, Si−CH_2CH$_3$), 7.0 (3 C, Si−CH$_2$$CH_3$), 18.0 [Si−$C$(CH$_3$)$_3$], 18.1 [Si−$C$(CH$_3$)$_3$], 25.7 [3 C, Si−C($CH_3$)$_3$], 26.0 [3 C, Si−C($CH_3$)$_3$], 29.9 (C-5a), 44.7 (C-5), 70.8 (C-3), 72.3 (C-4), 74.1 (C-2), 78.9 (C-1), 175.1 (C-6) ppm. $C_{25}H_{52}O_5Si_3$ (517.0): calcd. C 58.09, H 10.14; found C 57.96, H 10.20.

Compound 12: Colourless oil. $[\alpha]_D^{20}$ = −4.2 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.04 (s, 3 H, Me), 0.05 (s, 3 H, Me), 0.08 (s, 3 H, Me), 0.09 (s, 3 H, Me), 0.62 (q, J = 7.9 Hz, 6 H, Si−CH_2CH$_3$), 0.87 (s, 18 H, tBu), 0.95 (t, J = 7.9 Hz, 9 H, Si−CH$_2$$CH_3$), 1.94 (broad dt, J = 11.8, 5.2 Hz, 1 H, 5a-H$_β$), 2.65 (td, J = 5.1, 0.8 Hz, 1 H, 5-H), 2.97 (d, J = 11.8 Hz, 1 H, 5a-H$_α$), 3.61 (t, J = 4.2 Hz, 1 H, 3-H), 4.03 (br. t, J = 4.8 Hz, 1 H, 2-H), 4.08 (br. t, J = 4.3 Hz, 1 H, 4-H), 4.55 (td, J = 5.2, 0.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.2 (2 C, Si−CH$_3$), −4.4 (2 C, Si−CH$_3$), 5.0 (3 C, Si−CH_2CH$_3$), 7.0 (3 C, Si−CH$_2$$CH_3$), 18.1 [2 C, Si-$C$(CH$_3$)$_3$], 24.8 (C-5a), 25.7 [6 C, Si−C(CH_3)$_3$], 45.2 (C-5), 68.5 (C-3), 69.9 (C-4), 70.3 (C-2), 80.1 (C-1), 177.0 (C-6) ppm. $C_{25}H_{52}O_5Si_3$ (517.0): calcd. C 58.09, H 10.14; found C 58.00, H 10.06.

5a-Carba-β-D-gulopyranose (1). Typical Procedure: To a solution of bicyclic adduct **11** (5.10 g, 9.8 mmol) in anhydrous THF (100 mL) under argon at room temperature was added dropwise $LiBH_4$ (4.9 mL of a 2.0 M solution in THF, 9.8 mmol). After 4 h, the reaction was quenched with saturated NH_4Cl solution and with 5% aqueous citric acid solution. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solutions were dried, filtered, and concentrated to leave a residue that was purified by flash chromatography (hexanes/EtOAc, 70:30) to give a partially protected carbasugar (4.12 g, 81%) as a colourless oil. $[\alpha]_D^{20}$ = −38.5 (c = 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.10 (s, 3 H), 0.58 (q, J = 7.9 Hz, 6 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.93 (t, J = 7.9 Hz, 9 H), 1.37 (q, J = 12.3 Hz, 1 H), 1.69 (dt, J = 12.3, 3.9 Hz, 1 H), 1.95 (br. s, 2 H), 2.10 (m, 1 H), 3.49 (dd, J = 10.3, 6.9 Hz, 1 H), 3.55 (dd, J = 10.3, 7.9 Hz, 1 H), 3.71 (dd, J = 9.1, 2.3 Hz, 1 H), 3.80 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, −4.6, −4.2, −3.6, 5.1 (3 C), 6.9 (3 C), 17.9, 18.3, 25.8 (3 C), 26.0 (3 C), 29.0, 37.8, 64.0, 69.4, 72.3, 75.3, 75.5 ppm. $C_{25}H_{56}O_5Si_3$ (521.0): calcd. C 57.64, H 10.83; found C 57.79, H 10.75. This carbasugar intermediate (4.12 g, 7.9 mmol) was treated with a solution of 6 N aqueous HCl/THF/MeOH (1:2:2) (50 mL) at room temperature. The reaction mixture was stirred for 3 h and then concentrated to dryness under vacuum. The oily crude residue was purified by flash chromatography (EtOAc/MeOH, 80:20) to afford fully deprotected carbasugar **1** (1.40 g, 100%) as a glassy solid.[7] $[\alpha]_D^{20}$ = −47.0 (c = 1.15, MeOH). ^{1}H NMR (D_2O, 300 MHz): δ = 1.39 (td, J = 12.9, 11.7 Hz, 1 H, 5a-H$_β$), 1.86 (dt, J = 12.9, 4.3 Hz, 1 H, 5a-H$_α$), 2.10 (m, 1 H, 5-H),), 3.61 (dd, J = 10.9, 6.5 Hz, 1 H, 6b-H), 3.71 (dd, J = 9.6, 2.5 Hz, 1 H, 2-H), 3.72 (dd, J = 10.9, 7.4 Hz, 1 H, 6a-H), 3.84 (ddd, J = 11.3, 9.9, 4.8 Hz, 1 H, 1-H), 4.05 (m, 2 H, 3-H, 4-H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 29.4 (C-5a), 36.6 (C-5), 62.6 (C-6), 69.2 (C-1), 69.9 (C-4), 72.8 (C-2), 73.1 (C-3) ppm. $C_7H_{14}O_5$ (178.2): calcd. C 47.19, H 7.92; found C 47.13, H 8.02.

5a-Carba-β-D-allopyranose (2): The title compound was prepared from bicycle **12** (0.44 g, 0.9 mmol) according to the two-step procedure described for compound **1**. After the reductive treatment and flash-chromatographic purification (hexanes/EtOAc, 70:30), a partially protected carbasugar intermediate was isolated as a colourless solid. $[\alpha]_D^{20}$ = +4.9 (c = 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.12 (s, 3 H), 0.13 (s, 3 H), 0.65 (q, J = 7.5 Hz, 6 H), 0.93 (s, 9 H), 0.94 (s, 9 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.04 (q, J = 12.9 Hz, 1 H), 1.55 (br. s, 1 H), 1.87 (br. s, 1 H), 1.91 (ddd, J = 13.0, 5.1, 4.2 Hz, 1 H), 2.26 (m, 1 H), 3.21 (dd, J = 9.1, 1.9 Hz, 1 H), 3.44 (dd, J = 10.4, 1.7 Hz, 1 H), 3.56 (dd, J = 10.5, 4.4 Hz, 1 H), 3.66 (dd, J = 10.5, 5.8 Hz, 1 H), 3.90 (t, J = 1.8 Hz, 1 H), 3.93 (ddd, J = 11.3, 9.1, 5.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.9, −4.6, −4.0, −3.9, 5.5 (3 C), 7.0 (3 C), 18.0, 18.3, 26.1 (6 C), 31.4, 38.1, 65.2, 69.3, 75.8, 77.1, 78.0 ppm. $C_{25}H_{56}O_5Si_3$ (521.0): calcd. C 57.64, H 10.83; found C 57.58, H 10.77. After the deprotection and flash-chromatographic purification (EtOAc/MeOH, 80:20), pure carbasugar **2** was isolated (122 mg) in 80% yield (two steps) as a colourless glassy solid.[19] $[\alpha]_D^{20}$ = +3.1 (c = 0.32, MeOH). ^{1}H NMR (D_2O, 300 MHz): δ = 1.25 (q, J = 12.6 Hz, 1 H, 5a-H$_β$), 1.98 (m, 1 H, 5-H), 2.07 (ddd, J = 12.6, 4.9, 3.9 Hz, 1 H, 5a-H$_α$), 3.49 (dd, J = 9.8, 3.0 Hz, 1 H, 2-H), 3.63 (dd, J = 10.9, 2.9 Hz, 1 H, 4-H), 3.71 (dd, J = 11.1, 5.9 Hz, 1 H, 6b-H), 3.84 (dd, J = 11.3, 3.6 Hz, 1 H, 6a-H), 3.88 (ddd, J = 11.4, 9.7, 4.8 Hz, 1 H, 1-H), 4.14 (t, J = 2.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 27.0 (C-5a), 35.1 (C-5), 63.4 (C-6), 70.0 (C-1), 71.2 (C-4), 74.1 (C-3), 75.0 (C-2) ppm. $C_7H_{14}O_5$ (178.2): calcd. C 47.19, H 7.92; found C 47.26, H 7.84.

Thiolactone 14: The title compound was prepared from (silyloxy)-thiophene **13** (3.75 g, 17.5 mmol) and glyceraldehyde **7** (2.96 g, 22.8 mmol) according to a recently reported four-step procedure.[1] Thiolactone **14** (2.52 g) was isolated in 47% yield as white crystals. M.p. 77−79 °C. $[\alpha]_D^{20}$ = −86.6 (c = 1.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.85 (s, 9 H), 1.99 (tdd, J = 12.4, 10.8, 8.3 Hz, 1 H), 2.20 (dtd, J = 12.4, 6.3, 3.4 Hz, 1 H), 2.54 (m, 2 H), 2.82 (br. s, 1 H), 3.03 (br. s, 1 H), 3.67 (m, 3 H), 3.90 (dd, J = 5.1, 3.7 Hz, 1 H), 4.13 (dt, J = 10.2, 5.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5, −3.9, 18.2, 25.8

(3 C), 28.7, 42.1, 53.7, 62.8, 73.5, 76.0, 208.8 ppm. $C_{13}H_{26}O_4SSi$ (306.5): calcd. C 50.94, H 8.55; found C 50.89, H 8.50.

Thiolactone 15: The title compound was prepared from thiolactone **14** (2.52 g, 8.2 mmol) according to the procedure described for compound **9**. After flash-chromatographic purification (hexanes/EtOAc, 90:10), pure thiolactone **15** was recovered (4.32 g) in 98% yield as a yellow oil. $[\alpha]_D^{20} = -50.8$ (c = 10.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.51 (q, J = 7.9 Hz, 4 H), 0.63 (q, J = 7.7 Hz, 8 H), 0.89 (s, 9 H), 0.93 (t, J = 8.0 Hz, 6 H), 0.97 (t, J = 7.9 Hz, 12 H), 1.90 (tdd, J = 11.6, 11.1, 8.8 Hz, 1 H), 2.31 (dtd, J = 9.1, 5.8, 3.4 Hz, 1 H), 2.56 (m, 2 H), 3.45 (dd, J = 9.5, 4.8 Hz, 1 H), 3.73 (dd, J = 9.6, 8.0 Hz, 1 H), 3.82 (ddd, J = 8.0, 4.7, 1.2 Hz, 1 H), 3.95 (dd, J = 7.6, 1.1 Hz, 1 H), 4.28 (ddd, J = 10.7, 7.5, 5.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.1, −3.6, 4.3 (3 C), 4.9 (3 C), 6.4, 6.7 (4 C), 6.8, 18.4, 26.0 (3 C), 29.1, 42.6, 54.4, 63.3, 74.5, 79.1, 209.0 ppm. $C_{25}H_{54}O_4SSi_3$ (535.0): calcd. C 56.12, H 10.17; found C 56.01, H 10.24.

Aldehyde 16: The title compound was prepared from thiolactone **15** (4.00 g, 7.5 mmol) according to the procedure described for compound **10**. After flash-chromatographic purification (hexanes/EtOAc, 85:15), pure aldehyde **16** was isolated (2.57 g) in 82% yield as a yellow oil. $[\alpha]_D^{20} = -51.0$ (c = 9.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.56 (q, J = 7.9 Hz, 2 H), 0.63 (q, J = 7.5 Hz, 4 H), 0.85 (s, 9 H), 0.94 (t, J = 8.1 Hz, 3 H), 0.95 (t, J = 7.8 Hz, 6 H), 1.75 (dq, J = 12.3, 9.9 Hz, 1 H), 2.27 (dtd, J = 12.3, 5.5, 4.5 Hz, 1 H), 2.58 (m, 2 H), 3.99 (t, J = 1.5 Hz, 1 H), 4.01 (dt, J = 10.2, 1.2 Hz, 1 H), 4.15 (ddd, J = 10.1, 8.2, 5.6 Hz, 1 H), 9.61 (t, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.9, −3.9, 4.7 (2 C), 5.8, 6.5, 6.6 (2 C), 18.2, 25.8 (3 C), 28.2, 42.4, 53.6, 79.1, 80.2, 203.7, 207.5 ppm. $C_{19}H_{38}O_4SSi_2$ (418.7): calcd. C 54.50, H 9.15, found C 54.38, H 9.27.

Bicycles 17 and 18: The title compounds were obtained from aldehyde **16** (2.57 g, 6.1 mmol) according to the procedure described for compounds **11** and **12** (reaction time, 4 h). After flash-chromatographic purification (hexanes/EtOAc, 97:3), pure bicycle **17** (1.37 g) and bicycle **18** (1.24 g) were recovered in 42% and 38% yields, respectively.

Compound 17: White crystals. M.p. 43−47 °C. $[\alpha]_D^{20} = +91.8$ (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.08 (s, 6 H, Me), 0.09 (s, 3 H, Me), 0.13 (s, 3 H, Me), 0.64 (q, J = 7.9 Hz, 3 H, S−CH_2CH$_3$), 0.65 (q, J = 7.6 Hz, 3 H, Si−CH_2CH$_3$), 0.92 (s, 9 H, tBu), 0.93 (s, 9 H, tBu), 0.96 (t, J = 8.0 Hz, 9 H, Si−CH$_2$$CH_3$), 2.11 (dddd, J = 12.2, 5.0, 4.0, 0.8 Hz, 1 H, 5a-H$_\beta$), 2.60 (dd, J = 12.2, 1.5 Hz, 1 H, 5a-H$_\alpha$), 2.66 (td, J = 4.5, 1.5 Hz, 1 H, 5-H), 3.67 (tt, J = 3.9, 1.7 Hz, 1 H, 1-H), 3.80 (dd, J = 9.1, 3.6 Hz, 1 H, 4-H), 4.09 (td, J = 4.2, 0.8 Hz, 1 H, 2-H), 4.30 (dd, J = 9.2, 3.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.9 (Si−CH$_3$), −4.4 (2 C, Si−CH$_3$), −3.9 (Si−CH$_3$), 5.4 (3 C, Si−CH_2CH$_3$), 7.1 (3 C, Si−CH$_2$$CH_3$), 18.1 [Si−$C$(CH$_3$)$_3$], 18.2 [Si−$C$(CH$_3$)$_3$], 25.8 [3 C, Si−C($CH_3$)$_3$], 26.0 [3 C, Si−C($CH_3$)$_3$], 32.2 (C-5a), 50.3 (C-1), 54.7 (C-5), 72.3 (C-3), 72.7 (C-4), 74.0 (C-2), 204.4 (C-6) ppm. $C_{25}H_{52}O_4SSi_3$ (533.0): calcd. C 56.34, H 9.83; found C 56.46, H 9.91.

Compound 18: White crystals. M.p. 85−86 °C. $[\alpha]_D^{20} = +20.2$ (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 3 H, Me), 0.10 (s, 3 H, Me), 0.11 (s, 3 H, Me), 0.13 (s, 3 H, Me), 0.65 (q, J = 8.0 Hz, 6 H, Si−CH_2CH$_3$), 0.90 (s, 9 H, tBu), 0.93 (s, 9 H, tBu), 0.99 (t, J = 8.1 Hz, 9 H, Si−CH$_2$$CH_3$), 2.01 (br. dt, J = 11.4, 4.8 Hz, 1 H, 5a-H$_\beta$), 2.76 (td, J = 4.7, 1.7 Hz, 1 H, 5-H), 3.14 (dd, J = 12.1, 1.7 Hz, 1 H, 5a-H$_\alpha$), 3.75 (tt, J = 3.9, 1.7 Hz, 1 H, 1-H), 4.04 (br. t, J = 4.7 Hz, 1 H, 4-H), 4.06 (br. t, J = 3.9 Hz, 1 H, 2-H), 4.24 (t, J = 3.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.2 (2 C, Si−CH$_3$), −4.1 (2 C, Si−CH$_3$), 5.1 (3 C, Si−CH_2CH$_3$), 7.1 (3 C, Si−CH$_2$$CH_3$), 18.1 [2 C, Si−$C$(CH$_3$)$_3$], 25.9 [6 C, Si−C($CH_3$)$_3$], 27.5 (C5a), 51.2 (C-1), 56.6 (C-5), 67.2 (C-3), 71.8 (C-4), 73.8 (C-2), 208.1 (C-6) ppm. $C_{25}H_{52}O_4SSi_3$ (533.0): calcd. C 56.34, H 9.83; found C 56.22, H 9.90.

1-Thio-5a-carba-β-D-gulopyranose (3): The title compound was prepared from bicycle **17** (1.37 g, 2.6 mmol) according to the two-step procedure described for compound **1**. During the reduction stage, further portions of $LiBH_4$ (4 × 1.3 mL of a 2.0 M solution in THF, 4 × 2.6 mmol) were added over a period of 5 h. After flash-chromatographic purification (hexanes/EtOAc,90:10), a partially protected carbasugar intermediate was isolated as a colourless oil. $[\alpha]_D^{20} = -25.3$ (c = 1.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 6 H), 0.18 (s, 3 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.92 (s, 9 H), 0.94 (s, 9 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.40 (br. s, 1 H), 1.47 (q, J = 12.7 Hz, 1 H), 1.59 (d, J = 5.0 Hz, 1 H), 1.75 (br. dt, J = 12.7, 3.7 Hz, 1 H), 2.13 (m, 1 H), 3.27 (ddt, J = 12.7, 9.3, 4.4 Hz, 1 H), 3.48 (dd, J = 10.4, 6.1 Hz, 1 H), 3.53 (dd, J = 10.4, 7.7 Hz, 1 H), 3.73 (dd, J = 10.1, 2.3 Hz, 1 H), 3.77 (dd, J = 3.8, 2.3 Hz, 1 H), 3.88 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, −4.2 (2 C), −3.0, 5.2 (3 C), 7.0 (3 C), 17.9, 18.4, 25.8 (3 C), 26.3 (3 C), 31.9, 38.9, 39.2, 64.0, 72.7, 75.0, 75.4 ppm. $C_{25}H_{56}O_4SSi_3$ (537.0): calcd. C 55.91, H 10.51; found C 56.02, H 10.64. After the deprotection step, a crude residue was obtained, which was purified by flash chromatography (EtOAc/MeOH, 95:5) utilizing silica gel and a small amount of solid $NaHCO_3$ (30 mg) charged on the top of the column. Pure carbasugar **3** was isolated (0.34 g) in 68% yield (two steps) as a white solid. $[\alpha]_D^{20} = -28.4$ (c = 0.8, MeOH). ^1H NMR (D_2O, 300 MHz): δ = 1.47 (q, J = 12.8 Hz, 1 H, 5a-H$_\beta$), 1.95 (dtd, J = 13.1, 4.1, 1.2 Hz, 1 H, 5a-H$_\alpha$), 2.07 (dtdd, J = 13.0, 7.0, 3.6, 2.7 Hz, 1 H, 5-H), 3.07 (ddd, J = 12.5, 10.9, 4.2 Hz, 1 H, 1-H), 3.55 (dd, J = 11.0, 6.7 Hz, 1 H, 6b-H), 3.64 (dd, J = 10.9, 3.4 Hz, 1 H, 2-H), 3.65 (dd, J = 11.0, 7.4 Hz, 1 H, 6a-H), 4.00 (t, J = 3.3 Hz, 1 H, 3-H), 4.05 (m, 1 H, 4-H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 32.6 (C-5a), 38.2 (C-5), 39.0 (C-1), 62.8 (C-6), 70.5 (C-4), 72.9 (C-3), 74.2 (C-2) ppm. $C_7H_{14}O_4S$ (194.2): calcd. C 43.28, H 7.26; found C 43.21, H 7.30.

1-Thio-5a-carba-β-D-allopyranose (4): The title compound was prepared from bicycle **18** (1.24 g, 2.3 mmol) according to the two-step procedure described for compound **1**. After the reductive step (reaction time, 2 h), a partially protected carbasugar intermediate was obtained as white crystals. M.p. 91−95 °C. $[\alpha]_D^{20} = +2.1$ (c = 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.11 (s, 3 H), 0.17 (s, 3 H), 0.65 (q, J = 7.9 Hz, 6 H), 0.92 (s, 9 H), 0.94 (s, 9 H), 0.95 (t, J = 7.9 Hz, 9 H), 1.09 (q, J = 12.6 Hz, 1 H), 1.56 (d, J = 4.9 Hz, 1 H), 1.85 (br. s, 1 H), 1.96 (dt, J = 13.5, 4.2 Hz, 1 H), 2.22 (m, 1 H), 3.19 (dd, J = 10.1, 1.6 Hz, 1 H), 3.31 (ddt, J = 12.2, 9.3, 4.5 Hz, 1 H), 3.41 (dd, J = 10.4, 1.6 Hz, 1 H), 3.52 (dd, J = 10.5, 4.7 Hz, 1 H), 3.63 (dd, J = 10.5, 5.5 Hz, 1 H), 3.89 (t, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.2, −4.3, −4.1, −3.7, 5.3 (3 C), 6.8 (3 C), 17.8, 18.1, 25.9 (3 C), 26.0 (3 C), 33.9, 38.4, 39.3, 64.5, 75.4, 76.4, 78.2 ppm. $C_{25}H_{56}O_4SSi_3$ (537.0): calcd. C 55.91, H 10.51; found C 55.88, H 10.44. After the deprotection step, a crude residue was obtained, which was purified by flash chromatography (EtOAc/MeOH, 70:30) utilizing silica gel and a small amount of solid $NaHCO_3$ (30 mg) charged on the top of the column. Pure carbasugar **4** was isolated (0.37 g) in 81% yield (two steps) as a colourless glassy solid. $[\alpha]_D^{20} = -34.2$ (c = 1.1, MeOH). ^1H NMR (D_2O, 300 MHz): δ = 1.25 (q, J = 12.7 Hz, 1 H, 5a-H$_\beta$), 1.91 (m, 1 H, 5-H), 2.11 (dt, J = 13.5, 4.1 Hz, 1 H, 5a-H$_\alpha$), 3.01 (ddd, J = 12.4, 11.0, 4.2 Hz,

1 H, 1-H), 3.36 (dd, J = 10.9, 2.7 Hz, 1 H, 2-H), 3.54 (dd, J = 11.1, 2.8 Hz, 1 H, 4-H), 3.61 (dd, J = 11.2, 6.2 Hz, 1 H, 6b-H), 3.75 (dd, J = 11.2, 3.7 Hz, 1 H, 6a-H), 4.06 (t, J = 2.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 35.1 (C-5a), 38.5 (C-1), 39.5 (C-5), 62.8 (C-6), 70.8 (C-4), 73.8 (C-3), 76.0 (C-2) ppm. $C_7H_{14}O_4S$ (194.2): C 43.28, H 7.26; found C 43.35, H 7.32.

Lactone 19: The title compound was prepared from (silyloxy)furan **6** (2.50 g, 12.6 mmol) and glyceraldehyde **7** (1.97 g, 15.1 mmol) according to a recently reported five-step procedure.[1] Lactone **19** (1.5 g) was isolated in 41% yield as a colourless oil. $[\alpha]_D^{20}$ = +7.0 (c = 9.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 3 H), 0.01 (s, 3 H), 0.79 (s, 9 H), 2.08 (m, 1 H), 2.25 (m, 1 H), 2.42 (m, 2 H), 3.50 (m, 4 H), 3.68 (m, 1 H), 3.91 (dd, J = 6.8, 2.5 Hz, 1 H), 4.75 (td, J = 7.6, 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.9, −4.4, 17.9, 20.8, 25.7 (3 C), 28.7, 63.1, 72.0, 72.3, 81.2, 178.0 ppm. $C_{13}H_{26}O_5Si$ (290.4) calcd. C 53.76, H 9.02; found C 53.69, H 9.09.

Lactone 20: The title compound was prepared from lactone **19** (1.50 g, 5.2 mmol) according to the procedure described for compound **9**. After flash-chromatographic purification (hexanes/EtOAc, 95:5), pure lactone **20** was recovered (2.60 g) in 98% yield as a colourless oil. $[\alpha]_D^{20}$ = −15.1 (c = 5.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.58 (q, J = 7.9 Hz, 6 H), 0.59 (q, J = 7.8 Hz, 6 H), 0.87 (s, 9 H), 0.93 (t, J = 7.9 Hz, 9 H), 0.94 (t, J = 7.8 Hz, 9 H), 2.10 (m, 1 H), 2.40 (m, 1 H), 2.50 (m, 2 H), 3.46 (dd, J = 10.1, 6.0 Hz, 1 H), 3.58 (dd, J = 10.1, 6.8 Hz, 1 H), 3.74 (td, J = 6.3, 3.3 Hz, 1 H), 4.09 (t, J = 2.8 Hz, 1 H), 4.72 (td, J = 7.0, 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.1, −4.8, 4.0 (3 C), 4.7 (3 C), 6.4 (3 C), 6.5 (3 C), 17.8, 21.9, 25.6 (3 C), 28.3, 64.2, 73.6, 75.8, 80.2, 176.4 ppm. $C_{25}H_{54}O_5Si_3$ (519.0): calcd. C 57.86, H 10.49; found C 57.93, H 10.40.

Aldehyde 21: To a solution of oxalyl chloride (3.3 mL, 38.0 mmol) in CH_2Cl_2 (40 mL) at −80 °C under argon, was added dropwise a solution of DMSO (5.4 mL, 76.0 mmol) in CH_2Cl_2 (40 mL). After 20 min, a solution of protected lactone **20** (2.60 g, 5.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was allowed to come to −40 °C and, after being stirred for 20 min at this temperature, the reaction mixture was stirred at −15 °C for 30 min. The mixture was cooled again at −40 °C and Et_3N (19.0 mL, 136.9 mmol) was added dropwise. The reaction mixture was stirred at −40 °C for 5 min, and then warmed to 25 °C. After 1 h, toluene (100 mL) was added to the mixture, and the solution was filtered and concentrated under vacuum. The residue was dissolved in hexanes (50 mL), filtered again, and concentrated under reduced pressure to give, after flash-chromatographic purification (hexanes/EtOAc, 80:20), aldehyde **21** (1.27 g, 70%) as a yellow oil. $[\alpha]_D^{20}$ = −5.3 (c = 2.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.05 (s, 3 H), 0.08 (s, 3 H), 0.58 (q, J = 8.0 Hz, 6 H), 0.82 (s, 9 H), 0.91 (t, J = 8.0 Hz, 9 H), 2.18 (m, 2 H), 2.46 (m, 2 H), 3.97 (dd, J = 3.2, 1.8 Hz, 1 H), 4.02 (dd, J = 4.8, 3.3 Hz, 1 H), 4.57 (td, J = 7.5, 5.2 Hz, 1 H), 9.56 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.0, −4.5, 4.5 (3 C), 6.5 (3 C), 17.9, 23.0, 25.6 (3 C), 28.3, 75.9, 78.9, 79.2, 176.5, 202.6 ppm. $C_{19}H_{38}O_5Si_2$ (402.7): calcd. C 56.67, H 9.51; found C 56.63, H 9.64.

Bicycle 22: The title compound was obtained from aldehyde **21** (1.27 g, 3.1 mmol) according to the procedure described for compounds **11** and **12**. After flash-chromatographic purification (hexanes/EtOAc, 90:10), pure bicycle **22** (1.20 g) was recovered in 74% as a colourless oil. $[\alpha]_D^{20}$ = +29.2 (c = 2.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 3 H, Me), 0.09 (s, 9 H, Me), 0.58 (q, J = 7.9 Hz, 6 H, Si-CH_2CH_3), 0.87 (s, 9 H, tBu), 0.92 (s, 9 H, tBu), 0.94 (t, J = 7.9 Hz, 9 H, Si−CH_2CH_3), 2.23 (dddd, J = 11.4, 6.3, 5.1, 1.5 Hz, 1 H, 5a-H_α), 2.36 (d, J = 11.5 Hz, 1 H, 5a-H_β), 2.57 (tt, J = 4.8, 1.0 Hz, 1 H, 5-H), 3.83 (dd, J = 4.3, 0.9 Hz, 1 H, 2-H), 3.90 (ddt, J = 4.1, 2.6, 1.4 Hz, 1 H, 3-H), 4.01 (ddd, J = 4.5, 2.3, 1.5 Hz, 1 H, 4-H), 4.55 (bd, J = 6.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.0 (Si−CH_3), −4.9 (Si−CH_3), −4.8 (Si−CH_3), −4.3 (Si−CH_3), 4.9 (3 C, Si−CH_2CH_3), 6.7 (3 C, Si−CH_2CH_3), 17.8 [Si−$C(CH_3)_3$], 18.5 [Si−$C(CH_3)_3$], 25.5 [3 C, Si−$C(CH_3)_3$], 26.1 [3 C, Si−$C(CH_3)_3$], 31.0 (C-5a), 43.6 (C-5), 69.5 (C-2), 71.5 (C-4), 76.0 (C-3), 82.9 (C-1), 175.2 (C-6) ppm. $C_{25}H_{52}O_5Si_3$ (516.9): calcd. C 58.09, H 10.14; found C 58.16, H 10.27.

5a-Carba-β-L-mannopyranose (5): The title compound was prepared from bicycle **22** (1.20 g, 2.3 mmol) according to the two-step procedure described for compound **1**. During the reductive step, further portions of $LiBH_4$ (10 × 1.2 mL of a 2.0 M solution in THF, 10 × 2.3 mmol) were added over a period of 24 h. After flash-chromatographic purification (hexanes/EtOAc, 60:40), a partially protected carbasugar intermediate was isolated a colourless oil. $[\alpha]_D^{20}$ = −1.27 (c = 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.10 (s, 3 H), 0.13 (s, 3 H), 0.67 (q, J = 8.0 Hz, 6 H), 0.89 (s, 9 H), 0.93 (s, 9 H), 1.98 (t, J = 8.0 Hz, 9 H), 1.70 (m, 1 H), 1.84 (m, 4 H), 3.64 (m, 1 H), 3.76 (m, 2 H), 3.83 (dd, J = 10.7, 6.3 Hz, 1 H), 3.89 (dd, J = 10.9, 5.5 Hz, 1 H), 3.94 (t, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −4.9, −4.7, −4.1, −3.9, 5.1 (3 C), 7.0 (3 C), 18.0, 18.5, 25.9 (3 C), 26.1 (3 C), 29.7, 42.5, 64.5, 71.0, 72.2, 76.8 (2 C) ppm. $C_{25}H_{56}O_5Si_3$ (521.0): calcd. C 57.64, H 10.83; found C 57.55, H 10.91. The deprotection step lasted 6 h at 40 °C. After flash-chromatographic purification (EtOAc/MeOH/28% aq NH_4OH, 49:49:2), pure carbasugar **5** was isolated (0.24 g) in 59% yield (two steps) as colourless needles. M.p. 218−219 °C. $[\alpha]_D^{20}$ = −10.7 (c = 0.6, H_2O) {ref.[20] for the β-D-enantiomer: M.p. 223 °C, $[\alpha]_D$ +10.4 (c = 0.24, H_2O)}. ^{1}H NMR (D_2O, 300 MHz): δ = 1.55 (m, 2 H, 5-H and 5a-H_α), 1.78 (dtd, J 12.3, 4.8, 1.4 Hz, 1 H, 5a-H_β), 3.45 (dd, J = 9.6, 2.7 Hz, 1 H, 3-H), 3.50 (t, J = 9.7 Hz, 1 H, 4-H), 3.60 (dd, J = 11.2, 6.0 Hz, 1 H, 6b-H), 3.77 (dd, J = 11.2, 3.3 Hz, 1 H, 6a-H), 3.80 (ddd, J = 9.4, 4.8, 2.7 Hz, 1 H, 1-H), 4.02 (td, J = 2.6, 1.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (D_2O, 75 MHz): δ = 29.2 (C-5a), 40.8 (C-5), 63.0 (C-6), 69.2 (C-1), 70.4 (C-4), 73.6 (C-2), 74.7 (C-3) ppm. $C_7H_{14}O_5$ (178.2): calcd. C 47.19, H 7.92; found C 47.21, H 7.88.

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[13] Worthy of note is the use of LDA in a similar cycloaldolization reaction (THF, −90 °C) that gave rise exclusively to the corresponding 3,4-*trans*-configured aldol adduct, but with a low conversion of the starting aldehyde.[7] In the present silylative cycloaldolization, a complete conversion of the starting aldehyde was observed. The slightly lower diastereoselectivity (*dr* = 92:8) is largely compensated for by the greater efficiency of this improved manoeuvre.

[14] At the moment, we cannot completely explain the mechanism of this transformation, which most probably proceeds through a cascade of events (enolsilylation, aldolization, silylation). One could argue that such subtle kinetic and thermodynamic factors dictate the diastereocontrol of this and other cycloaldolization reactions mentioned in this study.

[15] The same transformation could be conveniently effected by exposure of **11** to $LiAlH_4$ (1.0 M solution in THF). The loss of the TES group, however, was observed.

[16] Compare this result to the 14% overall yield (11steps) of the previously reported synthesis of compound **1**.[7]

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