Variable Strategy toward Carbasugars and Relatives. 2.[1] Diversity-Based Synthesis of β-D-Xylo, β-D-Ribo, β-L-Arabino, and β-L-Lyxo 4a-Carbafuranoses and (4a-Carbafuranosyl)thiols

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The silyloxy diene-based construction of carbasugars, previously exploited for the synthesis of four carbocyclic furanose and pyranose analogues, has been investigated further. By introducing a novel silylative cycloaldolization protocol and by adjusting a couple of minor transformations, the efficiency of this synthetic sequence was greatly improved. Through a series of lactone/thiolactone aldehyde cyclization precursors, four carbafuranoses (4a-carba-β-D-xylofuranose, 4a-carba-β-D-ribofuranose, 4a-carba-β-L-arabinofuranose, and 4a-carba-β-L-lyxofuranose) and four (carbafuranosyl)thiols [(4a-carba-β-D-xylofuranosyl)thiol, (4a-carba-β-D-ribofuranosyl)thiol, (4a-carba-β-L-arabinofuranosyl)-thiol, and (4a-carba-β-L-lyxofuranosyl)thiol] were assembled. From this study, it was shown that these constructions tolerate a variety of precursors, and in many instances, they are suitable for scaling-up.

Introduction

In the first work of this series,[1] we described the results of a study that demonstrated how varied heterocyclic dienoxy silane synthons can be used to assemble a small collection of chiral nonracemic carbafuranose and carbapyranose compounds,[2] including 5a-carba-β-D-gulopyranose, 5a-carba-β-D-xylofuranose, (5a-carba-β-D-gulopyranosyl)amine, and (5a-carba-β-D-xylofuranosyl)amine. Crucial to the success of these syntheses were two sequential carbon−carbon bond-forming constructions, an intermolecular vinylogous aldolization[3] between a dienoxy silane donor and a suitable aldehyde acceptor, followed by a regio- and diastereoselective cycloaldolization that installs the cyclitol frame (vide infra). Pursuing our efforts to exploit the merits of furan-, pyrrole- and thiophene-based dienoxy silane synthons[4] en route to varied carbasugar repertoires, we now wish to report on the highly efficient synthesis of another set of five-membered ring carbasugars, namely 4a-carba-β-D-xylofuranose (**1**), 4a-carba-β-D-ribofuranose (**2**), 4a-carba-β-L-arabinofuranose (**3**), 4a-carba-β-L-lyxofuranose (**4**), (4a-carba-β-D-xylofuranosyl)thiol (**5**), (4a-carba-β-D-ribofuranosyl)thiol (**6**), (4a-carba-β-L-arabinofuranosyl)thiol (**7**), and (4a-carba-β-L-lyxofuranosyl)thiol (**8**) (Figure 1). An important outcome of this work was the discovery and application of a new, novel, and high-yielding "silylative" cycloaldolization protocol that enabled us to markedly improve the synthetic efficiency of the previous LDA-promoted ring-forming maneuver[1] and thus overcome the major problem encountered in our first syntheses.

Results and Discussion

Planning. To assemble a repertoire of analogues, it is important to have an efficient plan that is not only reasonably short, selective, and scalable but also divergent, so that variations can easily be introduced. To arrive at the target carbasugars, strategic branching points have to be introduced along the length of the main synthetic pathway, where a generic cyclopentane structure **A** (Scheme 1) is envisioned to derive via reductive breakage of a bicyclic heptanoid lactone **B** which, in turn, is constructed from aldehyde **C** through a direct intramolecular aldolization maneuver. Compound **C** can be traced to **D** and **E**, whose construction entails the vinylogous aldol juncture of heterocyclic dienoxy silane **F** with chiral aldehyde **G**. The synthetic options of this scheme—the choice of which ultimately leads to molecular diversity—are the nature of the atom X (oxygen or sulfur) within the heterocycle **F**, the stereochemistry of aldol **E** produced (1,2-threo or 1,2-erythro), and the stereochemistry of the cycloaldol construct **B** (2,3-trans or 2,3-cis). The combination of these three variables renders the synthesis of the eight carbafuranosidic structures in this work feasible.

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(1) Part 1 of this series: Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307−6318.

(2) For review articles on carbasugars, see: (a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (b) Suami, T. *Top. Curr. Chem.* **1990**, *154*, 257. (c) Suami, T. *Pure Appl. Chem.* **1987**, *59*, 1509. (d) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21. (e) Marquez, V. E.; Lim, M. *Med. Res. Rev.* **1986**, *6*, 1. (f) Hudlickly, T.; Cebulak, M. *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993. (g) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Publishers B. V.: Amsterdam, 1992; Vol. 10, p 495.

(3) For a review on vinylogous aldol reaction: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929−1972.

(4) (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−629. (b) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford; 1998; Vol. 3, pp 113−189. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333−1350. (d) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, 109−118.

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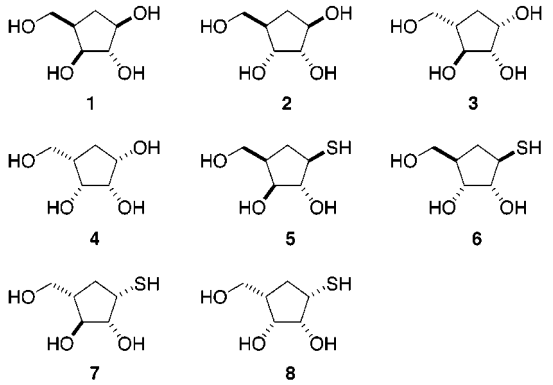
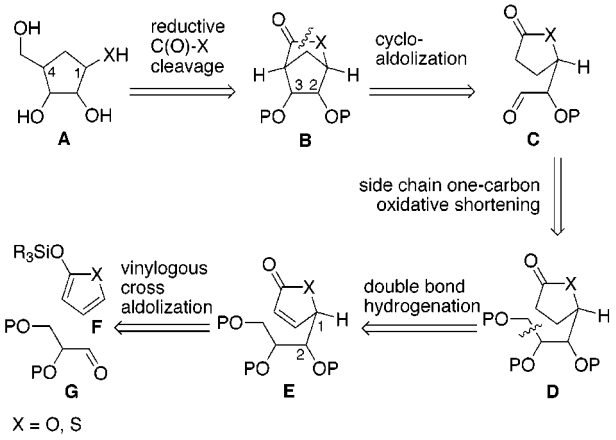
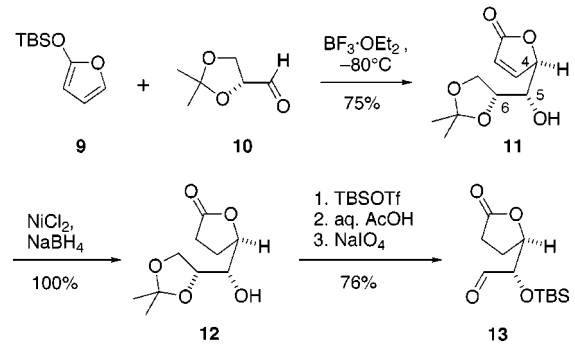


Figure 1.

Scheme 1

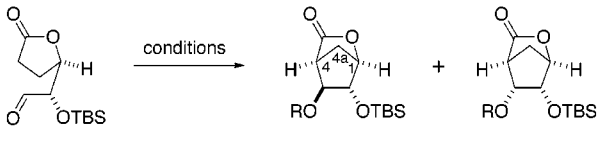


Scheme 2



4a-Carba-β-D-xylofuranose (1) and 4a-Carba-β-D-ribofuranose (2). The assemblage of the title carbafuranoses called for threo-configured aldehyde **13** as the common precursor. Its preparation began with the boron trifluoride-assisted vinylogous aldolization between furan-based dienoxy silane **9** and 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**) (Scheme 2). Working on a 10 g scale, 4,5-*threo*-5,6-*erythro*-butenolide **11** was obtained in 75% yield by simple crystallization of the crude reaction product. Saturation of the double bond in **11** ($NiCl_2$, $NaBH_4$)[5] provided lactone **12** quantitatively, which was transformed into aldehyde **13** through a three-step sequence consisting of (i) silylation of the free secondary hydroxyl (TBSOTf, 2,6-lutidine), (ii) deacetonidation (aqueous AcOH, 50 °C), and (iii) oxidative breakage of the terminal diol moiety (aqueous $NaIO_4$, SiO_2). The six-carbon aldehyde **13** was obtained as a crystalline compound in an overall yield of 76% for the three steps. At this point, we were ready to forge the cyclopentane motif of the carbasugar targets via a cycloaldolization maneuver.

Scheme 3[a]



run	conditions[a]	isolated compounds (% yield) 14	15	16	17	trans/cis ratio
1	DIPEA (1.0 eq), TBSOTf (1.0 eq), -90°C	2	0	40	4	5:95
2	DIPEA (1.0 eq), TBSOTf (1.0 eq), 25°C	62	0	0	0	100:0
3	DIPEA (2.0 eq), TBSOTf (2.0 eq), -90°C	5	21	4	40	37:63
4	DIPEA (2.0 eq), TBSOTf (2.0 eq), 25°C	0	56	0	19	75:25
5	**DIPEA (3.0 eq), TBSOTf (3.0 eq), -90°C**	**0**	**24**	**0**	**71**	**25:75**
6	**DIPEA (3.0 eq), TBSOTf (3.0 eq), 25°C**	**0**	**78**	**0**	**20**	**80:20**
7	DIPEA (0.1 eq), TBSOTf (0.1 eq), 25°C	no reaction				

[a] All reactions were carried out in anhydrous CH_2Cl_2 at 0.6×10^{-2} M substrate concentration.

We are pleased to report here a significant improvement in conjoining the carbon adjacent to the lactone carbonyl of **13** (C2) to its aldehyde terminal (C6), thereby permitting installation of the carbafuranose ring. During our earlier studies,[1] this ring-forming event was conducted by briefly exposing **13** to LDA and led to the cycloaldolization product in, at best, a modest 30−50% yield, albeit with excellent diastereoselectivity. We considered improvement in the construction of the cyclitol ring a prime task if a truly efficient and scalable synthesis was to be pursued.

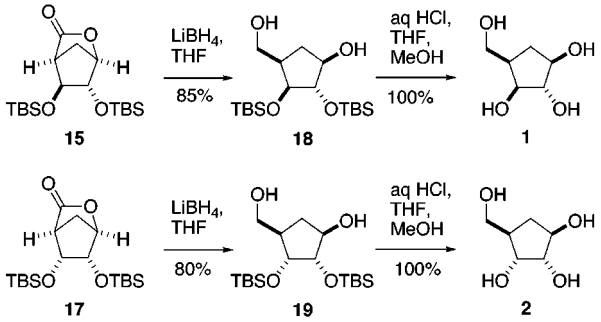
Fortunately, after a thorough and frustrating period of experimentation employing the most disparate metal-based enolization/aldolization protocols,[6] a promising technique was discovered, based simply on the use of the TBSOTf/DIPEA couple. Scheme 3 lists the selected cycloaldolization experiments that ultimately brought us to the optimization of this crucial step.

A few points deserve comment. First, maximum efficiency is reached when an excess of the DIPEA/TBSOTf mix is used (3.0 equiv), and under these conditions almost complete conversion of aldehyde **13** into the expected cycloadducts occurs at both −90 °C and room temperature (runs 5 and 6). Second, the temperature-dependent diastereocontrol switch is worthy of note, allowing either the 2,3-trans adduct **15** or its 2,3-cis counterpart **17** to be prepared in synthetically useful yields. Third, the reaction can basically be compared to a one-pot (tandem) aldolization−silylation process, which gives rise directly to stable silylated cycloaldols. Although a complete rationale for this transformation is hard to construct, we can postulate a mechanism where a preliminary regi-

(5) Caggiano, T. J. In *Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; Wiley: Chichester; 1999; pp 246−250.

(6) Experienced protocols included Na, Li, and KHMDS in THF; Et_2-BOTf, DIPEA, CH_2Cl_2; $Bu_2{}^nBOTf$ and Cy_2BOTf, Et_3N, THF; LDA, THF, DMPU; $Sn(OTf)_2$, Et_3N, CH_2Cl_2; 9-BBNOTf, DIPEA, THF; $TiCl_4$, DIPEA, CH_2Cl_2.

Scheme 4



oselective enolsilylation stage is followed by a Mukaiyama-type intramolecular aldolization (TBSOTf-promoted) with subsequent silylation of the aldol formed. At low temperatures and in silylating conditions (Scheme 3, entry 5), the cycloaldolization is reversible for the trans isomer **14** while the same transformation is irreversible (or at least slower to equilibrate) for the cis counterpart **16**. A situation thus arises in which the reaction is dragged toward the formation of the cis compound **16** (at the expense of the trans aldol **14**), which is then silylated to produce **17**. At higher temperatures (entry 6), there is a more comparable thermodynamic equilibration of both **14** and **16** resulting in the preferential formation of the more stable trans isomer **14**, which is promptly silylated into **15**.[7,8]

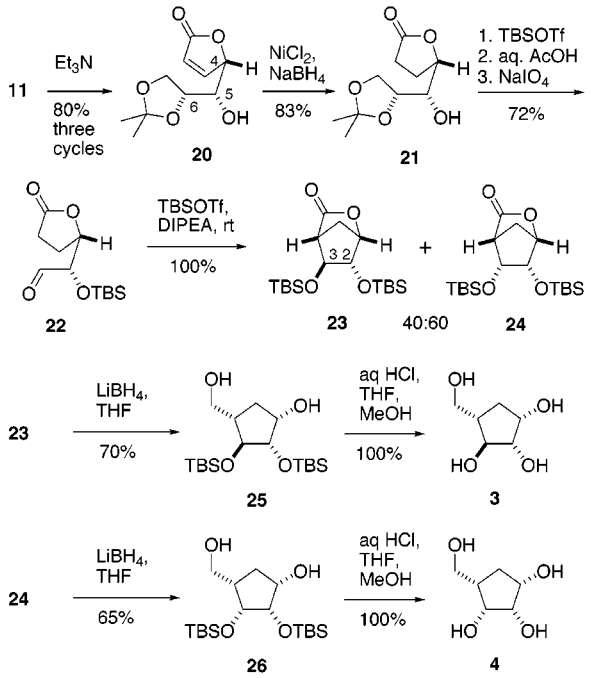
Our ability to easily install the cyclitol ring and simultaneously protect the aldol hydroxyl was welcomed and proved to be a valid contribution to the efficiency and step economy of the synthesis as a whole. With an advantageous silylative aldol protocol secured, the completion of the cyclitol constructs was close at hand. Our point of departure for carbaxylofuranose **1** was the trans-configured bicycle **15**, whereas cis-disposed **17** served as the precursor for carbaribofuranose **2** (Scheme 4).

In parallel, bicycloheptanoids **15** and **17** were subjected to reductive opening of the γ-lactone framework ($LiBH_4$, THF)[9] followed by acidic removal of the silyl protective groups (6 N HCl, THF, MeOH). This resulted in completion of our syntheses, with 4a-carba-β-D-xylofuranose (**1**) being formed in 85% isolated yield (two steps) and 4a-carba-β-D-ribofuranose (**2**) formed in 80% yield.

Overall, the two carbasugars **1**[10] and **2**[11] were thus available in eight individual steps (from **10**) and 38% and 32% yields, respectively, compared to our previous route to **1** of eight steps and 20% overall yield.[1]

4a-Carba-β-L-arabinofuranose (3) and 4a-Carba-β-L-lyxofuranose (4). We next turned to the construction of L-series carbasugars **3** and **4**, beginning with crystalline 4,5-erythro-configured butenolide **20**, readily prepared in 80% yield (3 cycles) via Et_3N-promoted C4 epimerization of threo derivative **11** (Scheme 5).

Scheme 5



Nickel boride reduction of the carbon−carbon double bond within **20** led to lactone **21**, which was used as such in the subsequent reaction sequence. By paralleling the previously disclosed chemistry (Scheme 2), silylation of the secondary hydroxyl, followed by acidic removal of the isopropylidene protection and sodium periodate oxidation of the resultant diol, produced six-carbon aldehyde **22** (72%, three steps), the key intermediate in this transformation.

Capitalizing on the results of the above-discussed cycloaldolization (Scheme 3), epimeric protected bicycloheptanoids **23** and **24** were implemented, via DIPEA/TBSOTf-assisted intramolecular aldolization of aldehyde **22**. At this point, it should be noted that, unlike the *threo*-aldehyde congener **13**, *erythro*-aldehyde **22** was reluctant to react at low temperatures, and the cycloaldolization could only be performed at room temperature. In the event, a well-separable 40:60 mixture of *trans*-**23** and *cis*-**24** was recovered in a 100% combined yield. It is at this point that the desired 4a-carba-β-L-arabinofuranose (**3**) and 4a-carba-β-L-lyxofuranose (**4**) could be synthesized from the corresponding intermediates **23** and **24**. Treatment of **23** and **24** in parallel with $LiBH_4$ followed by hydrochloric acid quickly ensured preparation of **3**[12] and **4**[13] in 70% and 65% yields, respectively.

(4a-Carba-β-D-xylofuranosyl)thiol (5) and (4a-Carba-β-D-ribofuranosyl)thiol (6). According to our retrosynthetic perspective (Scheme 1), to obtain thiol derivatives **5** and **6**, the obvious choice was to begin with 2-silyloxythiophene **27** and to follow exactly the same reaction panel previously portrayed for the oxygen series. As illustrated in Scheme 6, vinylogous aldolization between **27** and aldehyde **10** under BF_3 etherate guidance afforded 4,5-*threo*-thiobutenolide **28** almost exclusively (≥98% de by ^1H NMR analysis), whose isolation proved troublesome owing to its exceedingly facile C4 epimerization.

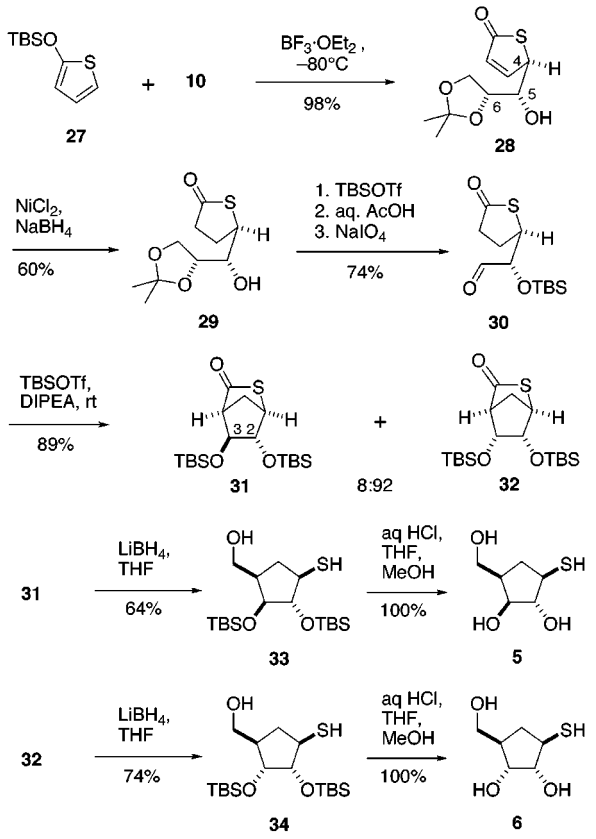
Therefore, to prevent epimerization and to accumulate a substantial quantity of the requisite threo-configured thiolactone **28**, we opted to directly saturate the C−C

(7) To support this hypothesis, ad hoc experiments were accomplished with the following results: (a) exposure of **14** to 3.0 equiv of DIPEA/TBSOTf at −90 °C resulted in formation of transient aldehyde **13** with production of a 25: 75 mixture of **15** and **17**; (b) exposure of **14** to the above promoter system at 25 °C resulted in exclusive formation of **15**; (c) exposure of **16** to the above promoter system at −90 °C resulted in exclusive formation of **17**; and (d) exposure of **16** to the above promoter system at 25 °C resulted in formation of a 40: 60 mixture of **17** and **15**.

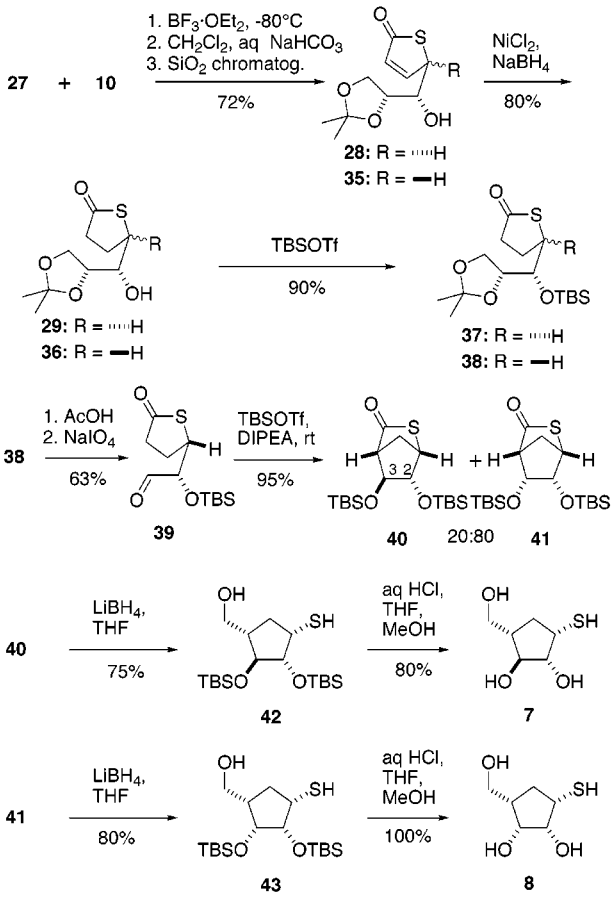
(8) The authors are indebted to a reviewer for his enlightening suggestions about this matter.

(9) Reductive ring opening could be easily effected using $LiAlH_4$ (1 M THF solution). However, during reduction, partial desilylation could occur.

Scheme 6



Scheme 7



double bond within the crude butenolide product. We thus arrived at threo-configured saturated thiolactone **29**, which was obtained as a crystalline compound by chromatography on silica (59% yield, two steps). With **29** in hand, we turned to elaborate the triol side chain via silylation of the free secondary hydroxyl, followed by acidic removal of the acetonide blockage and oxidative breakage of the diol terminus. Aldehyde **30** was thus obtained in 74% yield for the three steps. Subjection of **30** to optimized silylative cycloaldolization protocol (1:1 DIPEA/TBSOTf, 3.0 equiv) at room temperature produced 2,3-cis-disposed bicyclic compound **32** almost exclusively (82% yield), accompanied by only 7% of its epimeric trans counterpart **31**.

Completion of our syntheses entailed the reductive breakage of the C(O)−S bond within **31** and **32** ($LiBH_4$) followed by acidic deprotection. In the event, D-ribo- and D-xylocarbafuranoses **5** and **6** were constructed in 64% and 74% yields (two steps).

(4a-Carba-β-L-arabinofuranosyl)thiol (7) and (4a-Carba-β-L-lyxofuranosyl)thiol (8). To arrive at the title β-L-mercaptoderivatives, we opted to start from the erythro-configured intermediate **38**. To have an appreciable quantity of this substance, the previously disclosed aldol maneuver between dienoxy silane **27** and aldehyde **10** was carried out, delivering a crude mixture that was directly subjected to aqueous $NaHCO_3$ equilibration and silica gel chromatography to give an unseparable 60:40 threo/erythro butenolide mixture **28**/**35** (Scheme 7). Saturation of the double bond following the usual procedure afforded a mixture of thiobutanolide compounds **29**/**36** whose separation proved yet again to be problematic. At this point, we decided to proceed by silylating the free secondary hydroxyl function present. It was then possible to easily separate the two completely protected isomers **37** and **38**. Chromatographic separation on silica gel finally permitted us to isolate the erythro-configured compound **38** as a pure oily substance in 20% yield (three steps) with a 27% recovery of threo isomer **37**.

Conversion of **38** to the key aldehyde **39** was easily attained again, by acetic acid-promoted deacetonidation and oxidative cleavage of the terminal carbon (63%, two steps). The crucial intramolecular silylative aldolization was then performed by treating aldehyde **39** with the usual DIPEA/TBSOTf reagent system at room temperature. A 20:80 mixture of separable bicyclic 2,3-trans and 2,3-cis diastereoisomers **40** and **41** was recovered in a 95% combined yield. The reductive opening of the thiolactone moiety within **40** and **41** ($LiBH_4$)[14] and subsequent acidic removal of the protective groups were executed in parallel, leading to the targeted sulfur-

(10) (a) β-D-Enantiomer, see ref 1. (b) β-L-Enantiomer, Yoshikawa, M.; Cha, B. C.; Okaichi, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1988**, *36*, 3718−3721. (c) racemic compound, Marschner, C.; Baumgartner, J.; Griengl, H. *J. Org. Chem.* **1995**, *60*, 5224−5235.

(11) (a) β-D-Enantiomer: Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron Lett.* **1990**, *31*, 2873−2874. (b) β-D-Enantiomer: Tadano, K.; Hakuba, K.; Kimura, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 276−279. (c) β-L-Enantiomer: Shoberu, K. A.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2419−2425.

(12) (a) β-L-Enantiomer: Tadano, K.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *Chem. Lett.* **1986**, 1081−1084. (b) β-L-Enantiomer: Tadano, K.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946−1956. (c) β-D-Enantiomer: see ref 10b. (d) β-D-Enantiomer: Tadano, K.; Kimura, H.; Hoshino, M.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3673−3678. (e) Racemic compound: see ref 10c.

(13) (a) β-L-Enantiomer: Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1427−1432. (b) β-D-Enantiomer: see ref 10c. (c) β-D-Enantiomer: Horneman, A. M.; Lundt, I. *J. Org. Chem.* **1998**, *63*, 3, 1919−1928.

containing pseudosugars **7** and **8** in yields of 60% and 80%, respectively (two steps).

Structural Analysis. The structural analysis of the carbasugars of this study, and of numerous intermediates of the various syntheses, relied mainly on the ^{1}H NMR spectral results of the key bicyclic derivatives **15**, **17**, **23**, **24**, **31**, **32**, **40**, and **41**. The rigid nature of these scaffolds strongly favored this diagnosis rendering all the spectra easily decipherable. As a rule, 2,3-cis-disposed compounds (**17**, **32**, **24**, and **41**) display H2−H3 vicinal constants noticeably higher (5.5−8.0 Hz) with respect to the corresponding 2,3-trans isomers (**15**, **31**, **23**, and **40**) (0.0−1.8 Hz) in accordance with the dihedral angles $\theta_{H2-C2-C3-H3}$ of 0−10° for the cis compounds and about 90° for the trans compounds. Furthermore, the 1,2-threo-configured compounds, where protons H1 and H2 are orientated in trans, usually show values of $^3J_{1,2}$ smaller than those of the corresponding 1,2-erythro isomers, where the same protons are in cis. This is reflected even more evidently in the values for the $^3J_{3,4}$ constants, which appear to be higher for the 3,4-cis derivatives (**15**, **31**, **24**, and **41**) than for the corresponding 3,4-trans derivatives (**17**, **32**, **23**, and **40**). A convincing piece of evidence confirming this structural analysis is also given by the presence of the *W* long-range couplings which involve certain pseudoequatorial protons. Thus, for example, the compound pair **17**/**32** possesses two long-range couplings, H2−H4aβ and H3−H4aβ, which prove the β-location of the three protons involved (H2, H3, and H4aβ). On the other hand, for the **24**/**41** pair, the absence of these couplings corroborates the β pseudoaxial arrangement for H2 and H3. A final decisive piece of diagnostic evidence comes from the presence of several strong NOE interproton contacts involving spatially near protons (see Table S1 in the Supporting Information).

Once the relative stereochemistry of these intermediates had been ascertained, the chemistry that linked these adducts through the various synthetic steps to their respective precursors and to the final targets was simple and straightforward. In fact, given that the absolute configuration of the first butenolide adducts **11**, **20**, **28**, and **35** had already been ascertained in previous works by this group,[4] the actual stereostructures of all the compounds shown in the synthetic schemes are proven.

Conclusions

The original goal of our research was to implement a diversity-based plan directed toward the synthesis of carbasugar constructs and to demonstrate its genuine effectiveness, variability, and applicability. Having completed the synthesis of four representatives of the 4a-carbafuranose family (**1**−**4**) and of four sulfur-containing congeners (**5**−**8**), we have certified that the synthetic plan does indeed meet these important requisites.[15,16] Central to the success of this endeavor was the discovery of a novel, high-yielding silylative cycloaldolization, whose application allowed us to remedy the major problem of the previous synthesis,[1] which lay in the low efficiency and reproducibility of the LDA-promoted aldol annulation.

Experimental Section

(1′*S*,4′′*R*,5*R*)-5-[(2,2-Dimethyl-1,3-dioxolan-4-yl)hydroxymethyl]-5*H*-furan-2-one (11). Typical Procedure. To a solution of **9** (10.0 g, 50.4 mmol) in anhydrous CH_2Cl_2 (90 mL), under argon atmosphere, was added 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**) (7.86 g, 60.4 mmol), and the resulting mixture was cooled to −80 °C. BF_3·etherate (6.39 mL, 50.4 mmol), cooled to the same temperature, was added dropwise to the stirring solution, and the reaction was allowed to proceed for 4 h at −80 °C. The reaction was then quenched at −80 °C by the addition of saturated aqueous $NaHCO_3$, and after ambient temperature was reached, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a solid crude residue, which was recrystallized from a 7:3 EtOAc/hexanes mixture. Pure **11** (8.10 g, 75%) was obtained as white crystals: mp 125 °C; $[\alpha]^{20}_D$ +69.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.8, 1.7 Hz, 1H), 6.17 (dd, J = 5.8, 1.9 Hz, 1H), 5.27 (dt, J = 3.8, 1.8 Hz, 1H), 4.18 (m, 2H), 4.05 (m, 1H), 3.67 (td, J = 7.2, 4.0 Hz, 1H), 2.94 (d, J = 6.6 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 154.3, 122.1, 109.8, 84.2, 75.5, 72.9, 67.1, 26.7, 25.1. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.71.

(1′*S*,4′′*R*,5*R*)-5-[(2,2-Dimethyl-1,3-dioxolan-4-yl)hydroxymethyl]dihydrofuran-2-one (12). Typical Procedure. A solution of **11** (8.10 g, 37.8 mmol) in 320 mL of absolute MeOH was cooled to 0 °C and treated with 2.25 g (9.46 mmol) of $NiCl_2$·$6H_2O$. The resulting mixture was stirred at the same temperature for 15 min before the addition of 1.43 g (37.8 mmol) of $NaBH_4$. After 30 min, further portions of $NiCl_2$·$6H_2O$ (1.13 g, 4.73 mmol) and $NaBH_4$ (714 mg, 18.9 mmol) were added, and the reaction was allowed to stirr for an additional 10 min. The reaction was then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. Flash chromatographic purification (6:4 EtOAc/hexanes) afforded **12** (8.20 g, 100%) as a colorless oil: $[\alpha]^{20}_D$ −13.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (td, J = 7.5, 2.1 Hz, 1H), 4.14 (m, 2H), 4.01 (m, 1H), 3.53 (dd, J = 6.0, 2.3 Hz, 1H), 3.35 (d, J = 7.4 Hz, 1H), 2.64 (ddd, J = 17.7, 8.5, 7.2 Hz, 1H), 2.51 (ddd, J = 17.7, 9.7, 7.6 Hz, 1H), 2.31 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 109.3, 79.9, 75.6, 73.7, 66.8, 28.5, 26.6, 25.1, 23.6. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.33; H, 7.60.

(2*S*,2′*R*)-2-(*tert*-Butyldimethylsilanyloxy)-2-(5-oxotetrahydrofuran-2-yl)acetadehyde (13). Typical Procedure. 2,6-Lutidine (14.57 mL, 125.1 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (9.57 mL, 41.7 mmol) were sequentially added to a stirred solution of the saturated lactone **12** (8.20 g, 37.9 mmol) in anhydrous CH_2Cl_2 (90 mL) under argon atmosphere at room temperature. After 5 h, the reaction was quenched with 5% aqueous citric acid solution. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic solutions were dried ($MgSO_4$), filtered, and concentrated to afford a crude residue which was purified by flash chromatography (6:4 hexanes/EtOAc). A protected lactone intermediate was obtained (11.27 g, 90%) as a colorless oil: $[\alpha]^{20}_D$ −9.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (ddd, J = 7.5, 6.8, 3.7 Hz, 1H), 4.13 (m, 1H), 4.06 (dd, J = 8.1, 6.3 Hz, 1H), 3.87 (dd, J = 8.1, 6.9

(14) The kinetics of the $LiBH_4$-promoted reductive opening of the bicyclic intermediates of this work are heavily dependent upon their stereochemistry. The observed reaction rates are as follows: **17**, **32** and **23**, **40**, fast; **15**, **31**, slow; **24**, **41**, very slow. This behavior can be ascribed to the steric congestion around the carbonyl function, as can be evinced from the stereostructures displayed in Table S1 (see the Supporting Information).

(15) Basically, without altering the chemical set up of this synthesis, all the remaining members of the 4a-carbafuranose β-anomer family could be in our reach by simply varying the stereochemistry of the initial aldehyde **10** (*S* in lieu of *R*).

(16) Widening further the synthetic horizons of the chemistry outlined herein, one can expect that, by inverting the configuration of the pseudo-anomeric C1 center within suitable all-oxygen cyclopentanoid structures, a door will open out onto the synthesis of all the representatives of the 4a-α-carbafuranose family.

Hz, 1H), 3.78 (dd, J = 6.0, 3.6 Hz, 1H), 2.51 (m, 2H), 2.21 (m, 2H), 1.41 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 109.0, 81.2, 76.3, 74.3, 66.6, 28.4, 26.5, 25.8 (3C), 25.2, 23.6, 18.1, −4.0 (2C). Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.15. Found: C, 58.30; H, 9.09.

This lactone intermediate (11.2 g, 33.9 mmol) was dissolved in 130 mL of 80% aqueous acetic acid, and the resulting solution was allowed to react at 50 °C. The reaction was monitored by TLC and was judged complete after 8 h. The solution was then concentrated under vacuum to leave a crude residue that was flash chromatographed (8:2 EtOAc/hexanes) utilizing silica gel and a small amount of solid $NaHCO_3$ (1.0 g) charged on the top of the column. A pure terminal diol was obtained (9.45 g, 96%) as white crystals: mp 81−83 °C; $[\alpha]^{20}_D$ −14.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (td, J = 7.2, 3.0 Hz, 1H), 3.79 (m, 3H), 3.66 (m, 1H), 3.32 (bs, 2H), 2.55 (m, 2H), 2.27 (m, 1H), 2.14 (m, 1H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 80.8, 74.3, 72.3, 63.1, 28.4, 25.7 (3C), 23.5, 18.0, −4.4, −4.5. Anal. Calcd for $C_{13}H_{26}O_5Si$: C, 53.76; H, 9.02. Found: C, 53.69; H, 8.81.

This diol intermediate (9.45 g, 32.5 mmol) was dissolved in CH_2Cl_2 (600 mL) and treated with a 0.65 M aqueous $NaIO_4$ solution (65 mL) and chromatography grade SiO_2 (65 g). The resulting heterogeneous mixture was vigorously stirred at room temperature until complete consumption of the starting material (about 30 min, monitoring by TLC). The slurry was filtered under suction and the silica thoroughly washed with CH_2Cl_2 and EtOAc. The filtrates were evaporated to afford aldehyde **13** (7.39 g, 88%) as colorless crystals: mp 60−61 °C; $[\alpha]^{20}_D$ −97.8 (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 1.3 Hz, 1H), 4.88 (ddd, J = 8.1, 5.4, 2.6 Hz, 1H), 4.04 (dd, J = 2.6, 1.3 Hz, 1H), 2.63 (ddd, J = 17.7, 10.6, 7.3 Hz, 1H), 2.52 (ddd, J = 17.7, 7.4, 6.2 Hz, 1H), 2.37 (m, 1H), 2.19 (m, 1H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 176.5, 79.6, 79.2, 27.7, 25.5 (3 C), 23.2, 18.0, −4.7, −5.2. Anal. Calcd for $C_{12}H_{22}O_4Si$: C, 55.78; H, 8.58. Found: C, 55.58; H, 8.63.

(1*R*,4*S*,5*S*,6*S*)-5,6-Bis(*tert*-butyldimethylsilanyloxy)-2-oxabicyclo[2.2.1]heptan-3-one (15) and (1*R*,4*S*,5*R*,6*S*)-5,6-Bis(*tert*-butyldimethylsilanyloxy)-2-oxabicyclo[2.2.1]-heptan-3-one (17). Typical Procedure. Optimized Protocol to 15. To a solution of diisopropylethylamine (DIPEA) (14.16 mL, 81.3 mmol) in anhydrous CH_2Cl_2 (300 mL) at 25 °C, under argon atmosphere, was added TBSOTf (18.67 mL, 81.3 mmol), and the resulting mixture was stirred at the same temperature for 10 min before aldehyde **13** (7.0 g, 27.1 mmol) dissolved in anhydrous CH_2Cl_2 (150 mL) was added. The reaction was monitored by TLC and was judged complete after 30 min. The solution was then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography (95:5 hexanes/EtOAc) to give 7.88 g (78%) of **15** accompained by 2.02 g (20%) of **17**.

Optimized Protocol to 17. The above procedure to **15** was followed by carrying the reaction at −90 °C and starting with 705 μL of DIPEA (4.05 mmol), 930 μL of TBSOTf (4.05 mmol) in anhydrous CH_2Cl_2 (15 mL), and 350 mg of aldehyde **13** (1.35 mmol) dissolved in anhydrous CH_2Cl_2 (7.5 mL) and precooled at −90 °C. After 3 h, the reaction mixture was quenched with saturated NH_4Cl solution and processed in the predescribed manner to give 360 mg (71%) of **17** accompanied by 120 mg (24%) of **15**.

Compound 15: a colorless oil; $[\alpha]^{20}_D$ +8.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (dquint, J = 2.5, 1.4 Hz, 1H, H1), 4.06 (dt, J = 4.3, 1.3 Hz, 1H, H3), 3.83 (dt, J = 2.5, 1.3 Hz, 1H, H2), 2.79 (dq, J = 4.3, 1.4 Hz, 1H, H4), 2.21 (dq, J = 11.1, 1.4 Hz, 1H, H4aβ), 2.11 (dt, J = 11.1, 1.1 Hz, 1H, H4aα), 0.89 (s, 9H, Bu^t), 0.87 (s, 9H, Bu^t), 0.12 (s, 6H, Me), 0.09 (s, 6H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (C5), 81.5 (C1), 79.3 (C3), 79.0 (C2), 47.2 (C4), 35.5 (C4a), 25.6 (3C, SiC(CH_3)$_3$), 25.5 (3C, SiC(CH_3)$_3$), 17.8 (Si*C*(CH$_3$)$_3$), 17.7 (Si*C*(CH$_3$)$_3$), −4.6 (SiCH_3), −4.7 (SiCH_3), −4.9 (SiCH_3), −5.1 (SiCH_3). Anal.Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.02; H, 9.74. Found: C, 58.08; H, 9.71.

Compound 17: a white solid; mp 38.2−39.7 °C; $[\alpha]^{20}_D$ −52.0 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (tdd, J = 1.5, 1.2, 1.0 Hz, 1H, H1), 4.02 (ddd, J = 5.7, 1.5, 0.8 Hz, 1H, H3), 3.92 (dt, J = 5.7, 1.5 Hz, 1H, H2), 2.55 (quint, J = 1.2 Hz, 1H, H4), 2.29 (dt, J = 10.7, 1.0 Hz, 1H, H4aα), 2.04 (dquint, J = 10.7, 1.5 Hz, 1H, H4aβ), 0.91 (s, 9H, Bu^t), 0.81 (s, 9H, Bu^t), 0.13 (s, 3H, Me), 0.12 (s, 3H, Me), 0.08 (s, 6H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7 (C5), 82.8 (C1), 72.4 (C2), 69.1 (C3), 49.4 (C4), 34.5 (C4a), 25.8 (6C, SiC(CH_3)$_3$), 18.2 (2C, Si*C*(CH$_3$)$_3$), −4.5 (2C, SiCH_3), −4.9 (SiCH_3), −5.1 (SiCH_3). Anal. Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.02; H, 9.74. Found: C, 58.10; H, 9.65.

(1*R*,2*S*,3*S*,4*R*)-2,3-Di-*O*-(*tert*-butyldimethylsilanyl)-4-hydroxymethylcyclopentane-1,2,3-triol (18). Typical Procedure. A solution of bicyclic adduct **15** (7.88 g, 21.15 mmol) in anhydrous THF (40 mL), under argon atmosphere, was cooled to 0 °C and treated dropwise with $LiBH_4$ (10.58 mL of 2.0 M solution in THF, 21.15 mmol). After 15 min, the ice bath was removed and the temperature of the reaction mixture was allowed to reach 25 °C, while further portions of $LiBH_4$ (4 × 10.58 mL, 4 × 21.15 mmol) were added over 6 h. The reaction mixture was then quenched with saturated NH_4Cl solution and with 5% aqueous citric acid solution. The separated aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and EtOAc (10 mL). The combined organic solutions were dried, filtered and concentrated to leave a residue which was purified by flash chromatography (6:4 hexanes/EtOAc) to give partially protected carbasugar **18** (6.77 g, 85%) as white crystals: mp 94.2−98.6 °C; $[\alpha]^{20}_D$ −6.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (m, 1H), 3.87 (m, 2H), 3.79 (dd, J = 10.7, 4.6 Hz, 1H), 3.71 (dd, J = 10.7, 6.1 Hz, 1H), 2.68 (bs, 1H), 2.40 (m, 1H), 2.32 (ddd, J = 13.5, 9.9, 6.6 Hz, 1H), 1.90 (bs, 1H), 1.53 (ddd, J = 13.4, 6.6, 2.5 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.6, 80.3, 77.1, 62.5, 43.5, 35.1, 25.7 (3C), 25.6 (3C), 18.0, 17.9, −4.6, −4.7, −4.9, −5.1. Anal. Calcd for $C_{18}H_{40}O_4Si_2$: C, 57.40; H, 10.70. Found: C, 57.47; H, 10.61.

(1*R*,2*S*,3*S*,4*R*)-4-Hydroxymethylcyclopentane-1,2,3-triol [4a-Carba-β-D-xylofuranose] (1). Typical Procedure. Compound **18** (6.77 g, 17.98 mmol) was treated with a solution mixture of 6 N HCl−THF−MeOH (1:2:2) (100 mL) at room temperature. The reaction was stirred for 4 h and then concentrated to dryness under vacuum. The oily crude residue was flash chromatographed (1:1 EtOAc/MeOH) to afford fully deprotected carbasugar **1** (2.66 g, 100%) as a glassy solid: $[\alpha]^{20}_D$ −7.6 (*c* 0.8, MeOH) [lit.[10b] for the β-L-enantiomer $[\alpha]^{20}_D$ +5 (MeOH)]; ^{1}H NMR (400 MHz, D_2O) δ 3.95 (dd, J = 7.5, 5.4 Hz, 1H, H3), 3.88 (ddd, J = 8.4, 7.2, 6.6 Hz, 1H, H1), 3.73 (bt, J = 6.0 Hz, 1H, H2), 3.72 (dd, J = 11.1, 6.6 Hz, 1H, H5a), 3.53 (dd, J = 11.1, 6.9 Hz, 1H, H5b), 2.24 (dquint, J = 9.3, 6.9 Hz, 1H, H4), 2.12 (dt, J = 12.9, 7.8 Hz, 1H, H4aα), 1.38 (dt, J = 12.9, 9.0 Hz, 1H, H4aβ); ^{13}C NMR (75 MHz, D_2O) δ 83.7 (C1), 75.9 (C2), 75.1 (C3), 61.7 (C5), 39.7 (C4), 32.6 (C4a). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.51; H, 8.26.

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Supporting Information Available: Complete experimental procedures and product characterization data, ^{1}H and ^{13}C NMR spectra of **1**−**8**, and a table of diagnostic coupling constants and ^{1}H−^{1}H NOE contacts for bicycloheptanoid compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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