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Synthesis and Conformational Study of Chiral Oxepines: The Baylis−Hillman Reaction and RCM Approach with Sugar Aldehyde

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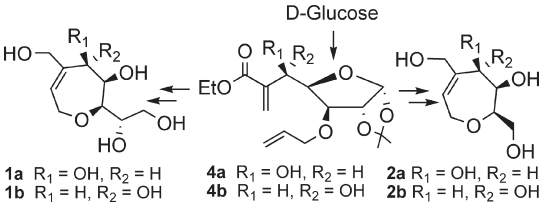

The Baylis−Hillman reaction of 3-*O*-allyl-α-D-*xylo*-pentodialdo-1,4-furanose **3** afforded a diastereomeric mixture of D-gluco- and L-ido-configured α-methylene-β-hydroxy esters **4a** and **4b**, respectively, in a ratio of 2:3. Reduction of the ester functionality in **4a**/**4b** gave alcohols **5a**/**5b**. The diene thus formed in **5a**/**5b** was subjected to ring-closing metathesis (Grubbs' second-generation catalyst) to afford oxa-bicyclic ring system **6a**/**6b** in high yield. Further manipulation of the acetonide functionality in **6a** and **6b** afforded new polyhydroxylated oxepines **1a**/**2a** and **1b/2b**, respectively. The ^{1}H NMR of oxepines **1a** and **1b** in D_2O showed doubling of signals indicating their existence in two different rotamers/conformers. This fact was substantiated by calculating energetics of **1** and **2** conformers using the density functional theory and correlating the calculated ^{1}H NMR chemical shift pattern with that of the experimental spectra.

Introduction

Oxepines are polyhydroxylated seven-membered oxygen heterocyclic compounds with at least one double bond in the ring. The oxepine structural framework is found in a variety of biologically active natural products such as brevetoxin, gambierol, and ciguatoxin, which show promising antiviral and antifungal activities.[1] In addition, the inherent property of seven-membered ring compounds to adopt different conformations coupled with the possibility of hydrogen bonding of the exocyclic hydroxyl groups with the ring oxygen atom, endowed them with protein binding ability.[2] The occurrence of oxepines in natural products and their biological relevance led to the development of various methodologies for their synthesis that include (i) rhodium-catalyzed ene−allene carbocyclization,[3a] (ii) fragmentation of highly strained epoxides,[3b] (iii) intramolecular acyl radical cyclization,[3c] and (iv) base-catalyzed endo mode cyclization of allenyl sulfoxides and sulfones.[3d] Sugars are commonly used in the construction of polyhydroxylated oxepines and oxepanes, and in this direction Peczuh and co-workers reported a cyclization−elimination route utilizing hept-1-enitols,[4a] van Boom and

(1) (a) Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62*, 9301−9320 and references cited therein.

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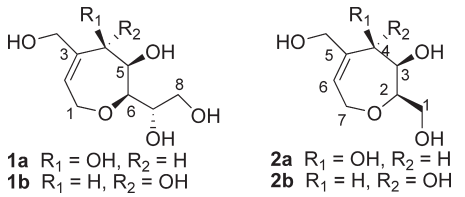
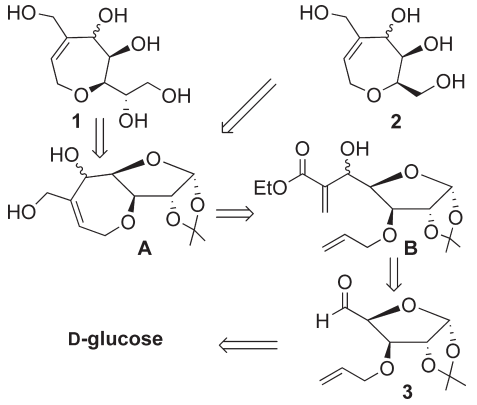


FIGURE 1. Oxepine analogues.

SCHEME 1. Retrosynthetic Analysis of Oxepines



co-workers used the first RCM approach on glycofuranose,[4b] Hoberg[4c] and Jayaram[4d,e] reported ring expansions of cyclopropanated glycols, and McDonald and co-workers developed the *endo*-selective alkynol cycloisomerization strategy with alkynyldiols.[4f] While working in the area of mono- and bicyclic iminosugars,[5] we exploited the Baylis−Hillman reaction with D-glucose-derived 3-*O*-allyl-α-D-*xylo*-pentodialdose followed by RCM, as key reactions, in the synthesis of highly functionalized oxepines **1a**,**b** and **2a**,**b** (Figure 1).

As shown in Scheme 1, we visualized 5−7-fused oxabicyclic ring system **A** as a common intermediate to oxepines **1** and **2** by simple manipulation of the acetonide functionality. The five-membered furan ring in **A** is obtained from the sugar (that will give access to polyhydroxylated carbon framework), and the seven membered oxa-ring could be built by reduction of the ester functionality followed by RCM with intermediate **B**. The required diene functionality with the oxygen atom for RCM could be obtained by utilizing the Baylis−Hillman reaction with the 3-*O*-allyl-α-D-xylo-pentodialdose **3** that will lead to the formation of α-methylene-*β*-hydroxy ester with sugar appendage **B**. Our approach hinges on the RCM strategy that leads to the formation of a trisubstituted double bond in the presence of a hydroxyl functionality which is rarely reported in the literature.[6] At the same time, we envisioned an increase in efficiency of RCM due to the presence of an oxygen atom in the diene system as an additional advantage in the success of the present approach to oxepines.[7] Although carbohydrates are used as substrates in the synthesis of oxepines, their utility exploring a combination of the Baylis−Hillman reaction[8] and RCM strategy,[9] to the best of our knowledge, is not reported so far.[10] Our efforts in the synthesis of hitherto unknown oxepines **1a**,**b** and **2a**,**b** are reported herein.

Result and Discussion

The required 3-*O*-allyl-α-D-xylo-pentodialdo-1,4-furanose **3** was prepared from D-glucose in 58% overall yield, as reported earlier by us.[11] The Baylis−Hillman reaction of **3** with ethyl acrylate, using DABCO as a base in 1,4-dioxane−H_2O (1:1), afforded a diastereomeric mixture of α-methylene-*β*-hydroxy esters **4** in a ratio of 2:3 in 88% yield (Scheme 2), as evident from the ^{1}H NMR spectrum of crude product. The appreciable difference in R_f values allowed us to separate the isomers by column chromatography. On the basis of coupling constant information between the H4−H5 protons in the ^{1}H NMR of C-5 epimeric compounds **4a/b** and comparison of the data with analogous products obtained in the Baylis−Hillman reaction with D-glucose derived sugar aldehyde, the stereochemical assignment at C5 in **4a** and **4b** was found to be ambiguous.[12] Therefore, the absolute configuration at C-5 in **4** was confirmed on the basis of the X-ray crystallographic data of the compound obtained in the subsequent RCM step (vide supra) that confirmed the formation of D-gluco- and L-ido-isomers **4a** and **4b**, respectively, in a ratio of 2:3.

In the next step, treatment of either **4a** or **4b** with the Grubbs first- or second-generation catalyst under a variety of solvent and temperature conditions failed to give the required Seven-membered oxa ring (∼85% starting material was recovered). In order to know if the electron-withdrawing ester group had prevented the RCM reaction from occurring, the major isomer **4b** was reacted with DIBAL-H in THF, which afforded allylic diol **5b**. Treatment of alcohol **5b**

(5) (a) Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667–4670. (b) Karanjule, N. S.; Markad, S. D.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 6273–6276. (c) Bande, O. P.; Jadhav, V. H.; Puranik, V. G.; Dhavale, D. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1176–1182. (d) Bande, O. P.; Jadhav, V. H.; Puranik, V. G.; Dhavale, D. D. *Synlett* **2009**, *12*, 1959−1963 and references cited therein.

(6) (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318. (b) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89.

(7) Martin, J. D.; Delgado, M. *J. Org. Chem.* **1999**, *64*, 4798–4816.

(8) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (c) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588. (d) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574. (e) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980–3987. (f) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48. (g) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183–7189.

(9) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (b) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519–529. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056.

(10) For an example of the Baylis−Hillman reaction followed by RCM protocol in the synthesis of azasugars, see: Radha Krishna, P.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426–435.

(11) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323–6332.

(12) In case of the Baylis−Hillman adducts, obtained from 3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose, the compound with the largest coupling constant ($J_{4,5}$ = 8.9 Hz) was assigned the L-ido configuration and the product having the smallest coupling constant ($J_{4,5}$ = 5.9 Hz) was assigned the D-gluco configuration; see: (a) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett*. **2003**, *6*, 888–890. (b) Radha Krishna, P.; Manjuvani, A.; Kannan, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2691–2703. An opposite trend was noticed in the case of **4a** and **4b**. However, we have unambiguously assigned the configurations at C5 by single-crystal X-ray data of the subsequent RCM product. In the case of the Baylis−Hillman adduct **4a** with D-gluco configuration, we observed large coupling constant $J_{4,5}$ = 7.0 Hz, while small coupling constant $J_{4,5}$ = 3.6 Hz was observed for the L-ido-configured product. For more references for the Baylis−Hillman reactions on sugar-derived aldehydes and their applications, see: (c) Radha Krishna, P.; Sharma, G. V. M. *Mini-Rev. Org. Chem.* **2006**, *3*, 137–153. (d) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M. *J. Org. Chem.* **2004**, *69*, 6467–-6469. (e) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031.

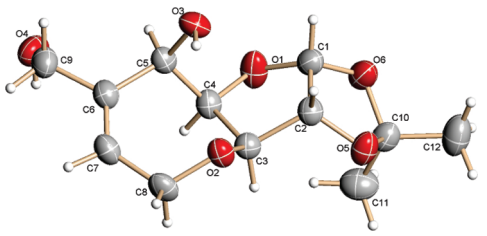
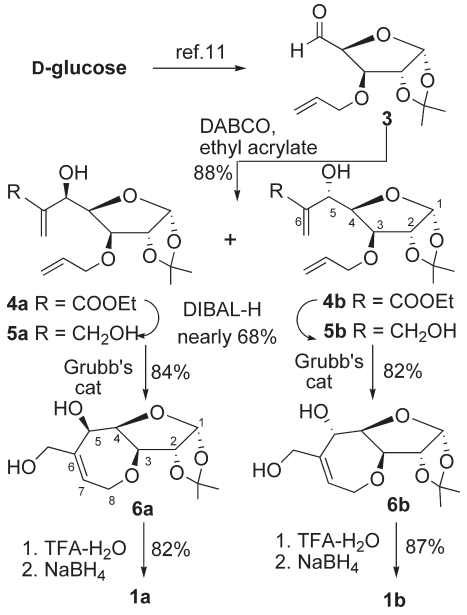


FIGURE 2. ORTEP diagram of **6a**.

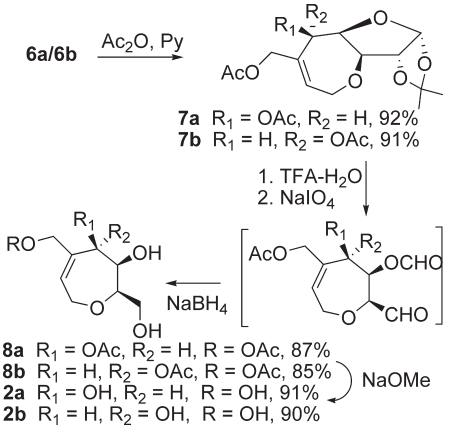
SCHEME 2. Synthesis of Oxepines 1



using Grubbs' first-generation catalyst in dichloromethane at room temperature as well as benzene reflux conditions was unsuccessful. However, to our surprise, the RCM reaction of **5b** with the Grubbs second-generation catalyst (10% mol) in dichloromethane at room temperature afforded 5−7 fused oxa-bicyclic compound **6b** with a trisubstituted double bond in 82% yield. Analogously, reduction of the ester functionality in **4a** (DIBAL-H) afforded alcohol **5a**, which upon RCM gave 5−7 fused oxa-bicyclic compound **6a** in 84% yield. In general, the Grubbs first- and second-generation catalysts are less active with respect to formation of trisubstituted alkenes if the functional groups that can potentially coordinate the metal center (e.g., −OH) are present in the substrate. In spite of this, it is worth noting that RCM of **5a** and **5b** with the Grubbs second-generation catalyst afforded trisubstituted alkenediols **6a** and **6b**, respectively, in high yields. Fortunately, the oxa-bicyclic product **6a** was isolated as a crystalline solid, and single-crystal X-ray analysis (Figure 2) firmly established the "5*R*" absolute configuration; therefore, in **6b** the absolute configuration at the C5 was assigned as 5*S*. As **6a** and **6b** are derived from **4a** and **4b**, respectively, the minor isomer **4a** was assigned the D-gluco (5*R*) and the major isomer **4b** was given the L-ido (5*S*) configuration.

Subsequently, compound **6a** was subjected to hydrolysis of the 1,2-acetonide functionality using TFA−water (3:2), and the hemiacetal thus obtained was reduced with sodium borohydride in MeOH−water to obtain the chiral oxepine **1a**. Similarly, compound **6b** upon reaction with TFA−H_2O followed by $NaBH_4$ reduction gave **1b**.

SCHEME 3. Synthesis of Oxepines 2



Targeting the synthesis of oxepines **2a**,**b**, it was necessary to protect the hydroxyl functionality. Thus, compound **6a** was subjected to acetylation using acetic anhydride in pyridine to afford diacetylated product **7a** in 92% yield (Scheme 3), which was reacted with TFA−water. The hemiacetal thus obtained was subjected to oxidative cleavage using $NaIO_4$ followed by treatment with sodium borohydride in methanol−water to afford diacetylated oxepine **8a.** Finally, deprotection of the acetate groups in **8a** with sodium methoxide (cat.) in methanol afforded oxepine **2a**. Similarly, compound **6b** upon acetylation afforded **7b**, which on hydrolysis (TFA−H_2O), periodate cleavage, and sodium borohydride reduction afforded **8b**. Finally, deacetylation of **8b** gave oxepine **2b**. All of the compounds were characterized by spectral and analytical techniques, and the data were found to be in agreement with the assigned structures.

Conformational Studies

Oxepanes and oxepines are known to exist in different conformations such as chair (C), twist-chair (TC), half-chair (HC), boat (B), and twist-boat (TB) and in various rotamer forms due to the flexibility in the ring and intramolecular hydrogen bonding between exocyclic hydroxyl groups and the ring oxygen atom.[13] During our studies, we have encountered an unusual observation in the case of oxepine **1**. The ^{1}H NMR spectrum of oxepine **1a** and **1b** showed doubling of signals indicating their existence in two different structures in D_2O solution (Figure 3). The proton assignment was made using the decoupling experiments. In case of **1a**, two broad singlets at δ 5.86 and 5.82 as well as two doublets at δ 5.37 (J = 4.2 Hz) and 5.18 (J = 4.5 Hz), appearing in the ratio 85:15 as evident from the integration value, were assigned to the H-2 and H-4 of two different structures, respectively. Similarly, the ^{1}H NMR of oxepine **1b** showed the presence of two different structures in the ratio 60:40 as evident from the appearance of H-2 as the two

(13) (a) DeMatteo, M. P.; Mei, S.; Fenton, R.; Morton, M.; Baldisseri, D. M.; Hadad, C. M.; Peczuh, M. W. *Carbohydr. Res.* **2006**, *341*, 2927–2945. (b) DeMatteo, M. P.; Synder, N. L.; Morton, M.; Baldisseri, D. M.; Hadad, C. M.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 24–38. (c) Driver, G. E.; Stevens, J. D. *Carbohydr. Res.* **2001**, *334*, 81–89.

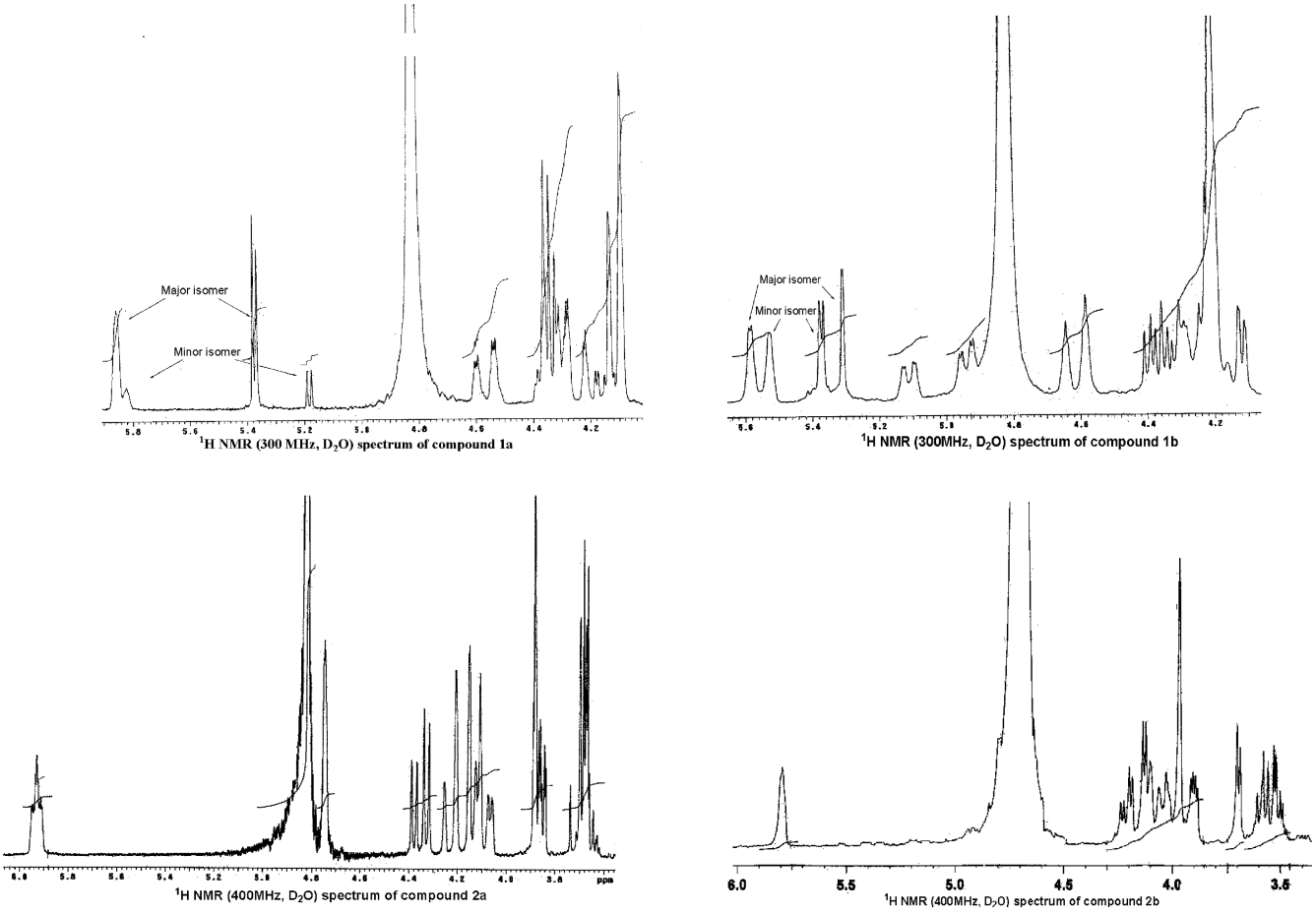


FIGURE 3. ^{1}H NMR spectra of **1a**,**b** and **2a**,**b** in D_2O.

TABLE 1. ΔE_{Rel} **(kJ mol^{-1}) and BC (%) of 1a**

	gas phase		SCRF-PCM				
config	ΔE_{Rel}	BC	ΔE_{Rel}	BC	ring config	C_6-C_7 rotamer	C_7-C_8 rotamer
1a_E10	6.7	6.1	9.8	1.4	$^{2,3}C_6$	gg	gg
1a_F05	0.0	91.7	0.0	71.7	$^{2,3}C_6$	tg	gg
1a_J12	24.8	0.0	16.0	0.1	$^{4}TB_O$	gg	gt
1a_K02	23.1	0.0	11.7	0.6	$^{2,3}C_6$	gt	tg
1a_O12	30.6	0.0	20.7	0.0	$^{5,6}TC_O$	gg	gg
1a_P03	9.3	2.2	2.5	26.2	$^{2,3}C_6$	tg	gg

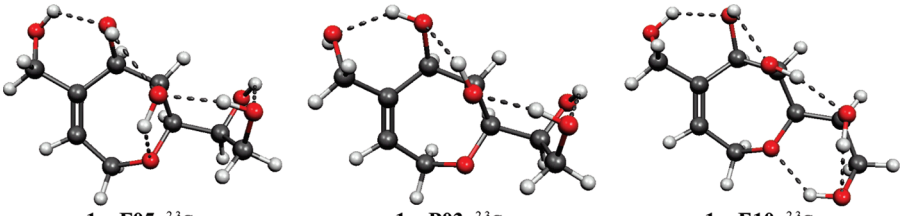
broad singlets at δ 5.59 and 5.53 as well as H-4 as one doublet at δ 5.37 (J = 3.3 Hz) and another broad singlet at δ 5.30, integrating in the ratio 3:2,[14] while the ^{1}H NMR spectrum of oxepines **2a** and **2b** in D_2O showed the presence of only one structure for each compound (Figure 3). This unusual behavior of oxepine **1** in D_2O could be attributed to two conformers or rotamers resulting from intramolecular hydrogen bonding between the hydroxyethyl functionality at the α-carbon of the ring oxygen. This fact was supported by recording the ^{1}H NMR spectrum of compound **1a** in two different solvents, namely D_2O and CD_3OD, wherein conformer population was found to be in the ratio of 85:15 and 75:25, respectively. The change in conformational populations[15] in two different solvents indicates the presence of two conformers in compound **1a** (Figure 44S, Supporting Information).[16] This motivated us to carry out conformational analysis of oxepines **1** and **2** employing density functional theory (DFT).

(14) In order to confirm whether in the ^{1}H NMR spectrum of compounds **1a/1b/2a** and **2b**, any proton signals have merged with the signal of D_2O, we recorded the ^{1}H NMR spectrum of these compounds in CD_3OD but did not observe any signal in the range of δ 4.75−4.90.

(15) Kirschner, K. N.; Woods, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10541–10545.

(16) The change in conformational populations in two different solvents also ruled out the possibility of configurational isomers (C-2 epimers), which is likely during the cleavage of 1,2-acetonide functionality using TFA or under sodium borohydride reduction conditions. In our laboratory, we have followed this type of reaction sequence (TFA−water, $NaBH_4$) on similar types of substrates; however, we did not observe any epimerization. For our recent publications on this type of work, see: (a) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3619–3622. (b) Mane, R. S.; Ajish Kumar, K. S.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3284–3287. (c) Vyavahare, V. P.; Chattopadhyay, S.; Puranik, V. G.; Dhavale, D. D. *Synlett* **2007**, *10*, 559–562.

(17) The structures are displayed in the Supporting Information1.



1a_F05; $^{2,3}C_6$
C_6-C_7 = tg; C_7-C_8 = gg
ΔE_{Rel}=0.0(0.0); BC=91.6(71.7)

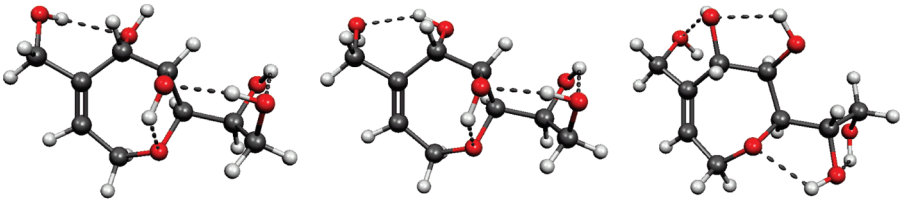
1a_P03; $^{2,3}C_6$
C_6-C_7= tg; C_7-C_8 = gg
ΔE_{Rel}=9.3(0.4); BC=2.5(26.2)

1a_E10; $^{2,3}C_6$
C_6-C_7 = gg; C_7-C_8 = gg
ΔE_{Rel}=6.7(8.0); BC=6.1(2.1)

FIGURE 4. Conformers of **1a** shown with ring conformation, rotamers, ΔE_{Rel}, and BC. Values in parentheses refer to solvent. Hydrogen bonds are shown by dotted lines.

TABLE 2. ΔE_{Rel} (kJ mol^{-1}) and BC (%) of **1b**

	gas phase		SCRF-PCM				
config	ΔE_{Rel}	BC	ΔE_{Rel}	BC	ring config	C_6−C_7 rotamer	C_7−C_8 rotamer
1b_D20	17.8	0.1	14.2	0.2	$^{4}B_O$	gg	gt
1b_E17	0.0	74.7	12.4	0.3	$^{4}B_O$	gg	gg
1b_F01	8.4	2.5	2.3	20.2	$^{2,3}C_6$	tg	gg
1b_F19	24.1	0.0	22.6	0.0	$^{4}B_O$	tg	gg
1b_G01	3.3	19.7	0.0	51.1	$^{2,3}C_6$	tg	gg
1b_H18	13.7	0.3	13.0	0.3	$^{5,6}TC_O$	gg	gg
1b_J20	8.2	2.7	1.5	27.9	$^{4}B_O$	gt	gg



1b_F01; $^{2,3}C_6$
C_6-C_7= tg; C_7-C_8 = gg
ΔE_{Rel}=8.4(2.5); BC=2.5(20.2)

1b_G01; $^{2,3}C_6$
C_6-C_7= tg; C_7-C_8 = gg
ΔE_{Rel}=3.3(0.0); BC=19.7(51.1)

1b_J20; $^{4}B_O$
C_6-C_7= gt; C_7-C_8 = gg
ΔE_{Rel}=8.2(2.7); BC=2.7(27.9)

FIGURE 5. Conformers of **1b** shown with ring conformation, rotamers, ΔE_{Rel}, and BC.

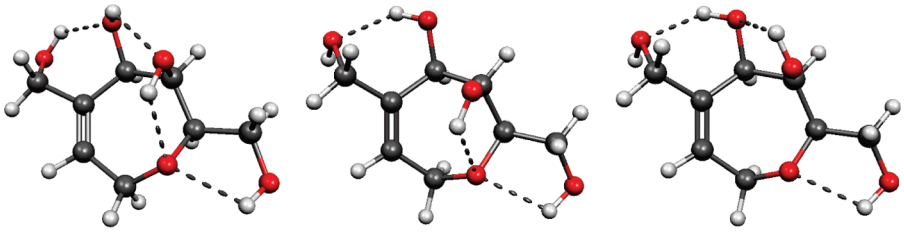
Thus, 16 conformers of **1a**, 11 of **1b**, six of **2a**, and four of **2b** were considered.[17] Ring conformations were analyzed by varying the dihedral angle $C_4C_5C_6O$ from −80° to +80°, and the energy profiles thus obtained are displayed in Figures 35S−38S of the Supporting Information. These scans encompass different ring conformations viz. chair (C), twist-chair (TC), half-chair (HC), twist-boat (TB), and boat (B) (see, for example, Figure 39S, Supporting Information). Local minima along the scans were optimized completely,[18] and the relative stabilization energies (ΔE_{Rel}) thus obtained are given in Table 1S (Supporting Information).[19] Conformers with ΔE_{Rel} less than 30 kJ mol^{-1} were subsequently subjected to further optimization within the framework of B3LYP/6-31G(d) theory, which led to six conformers for **1a** (four of these attain the chair form and one each converged to the twist-chair and twist-boat forms). The gas-phase structures were then reoptimized with water as a solvent employing the SCRF-PCM model. The corresponding energies (ΔE_{Rel}) and the Boltzmann contribution (BC) in the gas phase, and water are reported in Table 1. The low-lying conformers in water are shown in Figure 4. As may be noticed **1a_F05** and **1a_P03** conformers with the "tg" and "gg" rotamers of C_6−C_7 and C_7−C_8, respectively, exhibit relatively large BC values (71.7% and 26.2%) in water. Both these conformers with chair form ($^{2,3}C_6$) are similar albeit possess different hydrogen bonding patterns for the exocyclic hydroxyl groups at C_3, C_4, and C_5 centers. The conformer

TABLE 3. ΔE_{Rel} (kJ mol^{-1}) and BC (%) of **2a**

	gas phase		SCRF-PCM			
config	ΔE_{Rel}	BC	ΔE_{Rel}	BC	ring config	C_6−C_7 rotamer
2a_A01	0.0	64.3	0.0	35.8	$^{2,3}C_6$	gt
2a_B01	4.9	8.9	6.6	2.5	$^{2,3}C_6$	gg
2a_B09	2.3	25.4	4.8	5.2	$^{2,3}C_6$	gg
2a_B14	18.2	0.0	27.0	0.0	$^{2,3}TB_6$	gg
2a_C02	12.8	0.4	0.1	34.4	$^{2,3}C_6$	gt
2a_C13	29.1	0.0	20.4	0.0	$^{2,3}TB_6$	gt
2a_D04	12.5	0.4	1.2	22.1	$^{2,3}C_6$	gt
2a_E18	11.7	0.6	16.4	0.0	$^{2,3}TC_6$	gg

(18) The conformers in which any of the hydroxyl groups are not participating in the hydrogen-bonded interactions are largely destabilized and not dealt with further.

(19) It may be noted that different starting point geometries converged to structures exhibiting similar hydrogen-bonding patterns and the ring conformation as well.



2a_A01; $^{2,3}C_6$; C_6-C_7= gt; ΔE_{Rel}=0.0(0.0); BC=64.3(35.8)

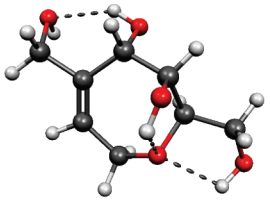
2a_C02; $^{2,3}C_6$; C_6-C_7= gt; ΔE_{Rel}=12.8(0.1); BC=0.4(34.4)

2a_D04; $^{2,3}C_6$; C_6-C_7= gt; ΔE_{Rel}=12.5(1.2); BC=0.4(22.1)

FIGURE 6. Conformers of **2a** are shown with ring conformation, rotamers, ΔE_{Rel}, and BC.

TABLE 4. ΔE_{Rel} (kJ mol^{-1}) and BC (%) of 2b

	gas phase		SCRF-PCM			
config	ΔE_{Rel}	BC	ΔE_{Rel}	BC	ring config	C_6-C_7 rotamer
2b_B10	10.4	1.3	7.5	4.6	$^{2,3}C_6$	gg
2b_B19	4.4	14.2	13.3	0.4	$^{O}TC_{5,6}$	tg
2b_C01	0.0	83.9	0.0	94.8	$^{2,3}C_6$	gt
2b_D20	12.1	0.6	15.9	0.2	$^{2,3}C_6$	gg



2b_C01; $^{2,3}C_6$; C_6-C_7= gt; ΔE_{Rel}=0.0(0.0); BC=83.9(94.8)

FIGURE 7. Conformers of **2b** shown with ring conformation, rotamers, ΔE_{Rel}, and BC.

1a_E10 in the chair form ($^{2,3}C_6$) with the "gg" rotamer of C_6-C_7 and C_7-C_8 contributes significantly toward the Boltzmann distribution in the gas phase. In other words, **1a** in solution exists in the chair form with two rotamers around the C_6-C_7 bond, one of which is **1a_F05** and/or **1a_P03** and the other is **1a_E10**.

The relative stabilization energies and BC values of **1b** conformers are given in Table 2. Here four boat, two chair, and one twist-chair conformers were located. Furthermore, three low energy **1b_F01**, **1b_G01** (both $^{2,3}C_6$) and **1b_J20** (^4B_O) conformers (BC > 5%) in water are shown in Figure 5. It may be remarked here that the energy rank order of **1b** conformers has been influenced significantly by solvation.[20] The conformers **1b_F01** and **1b_G01** in the $^{2,3}C_6$ chair conformation with "tg" and "gg" rotamers of C_6-C_7 and C_7-C_8, respectively, exhibited differently only in the intramolecular hydrogen-bonded interactions of hydroxyl groups at C_3 and C_4, turn out to be of lower energy. Both the hydroxyl groups of exocyclic dihydroxyethyl functionality do not participate in the hydrogen bonding with ring oxygen. In addition, the boat form **1b_J20** (^4B_O) contributes 27.9% toward BC. Thus, the present calculations reveal that oxepine **1b** in solution exists in two ring conformations viz. chair ($^{2,3}C_6$) and one boat form (^4B_O).[21]

The relative stabilization energies of oxepine **2a** in the gas phase and water possessing different ring conformations and C_6-C_7 rotamers are given along with corresponding BC values in Table 3. Interestingly, the chair conformation ($^{2,3}C_6$) is common to five lower energy conformers in solution; out of these, three conformers with BC greater than 5% are shown in Figure 6. In solution, the conformers with the hydrogen bonding between the ring oxygen and the hydroxyl group at C_7 (hydroxymethyl) led to the lowering of energy and facilitate three chair conformations **2a_A01**, **2a_C02**, and **2a_D04** with a "gt" configuration around C_6-C_7 bond. These conformers possess the $^{2,3}C_6$ ring conformation and exhibit different intramolecular hydrogen-bonding patterns between the hydroxyl groups at C_3, C_4, and C_5.

For **2b**, the ΔE_{Rel} values and BC values are given in Table 4. A low energy conformer of **2b** is displayed in Figure 7. Furthermore, **2b_C01** in chair form ($^{2,3}C_6$) with "gt" rotamer configuration of C_6-C_7 is the lowest energy (BC = 98.4%) conformer.

Optimized conformers of **1** and **2** (SCRF-PCM model) were further subjected to ^{1}H NMR chemical shift calculations in water. The spectra thus obtained are given in Figure 40S (**1a**), Figure 41S (**1b**), Figure 42S (**2a**), and Figure 43S (**2b**) (Supporting Information). Calculated H2 and H4 chemical shifts were compared with those observed in the recorded ^{1}H NMR spectra. In the recorded ^{1}H NMR of **1a**, the minor conformer reveals shielding of the H2 and H4 protons as compared to the major conformer (Figure 3). In the calculated spectra, the upfield signals were observed for the **1a_E10** conformer compared to those in **1a_P03** (Figure 40S, Supporting Information). Thus it may be concluded that the recorded spectrum of **1a** is a mixture of two rotamers in chair conformation ($^{2,3}C_6$), namely **1a_P03** (major) with the "gg" rotamer around the C6−C7 bond and **1a_E10** with the "tg" rotamer (minor).[22] The existence of **1a_F05** is ruled out as it shows a largely shielded H2 signal. In the case of **1b**, the experimental NMR showed shielding of H2 and

(20) The lowest energy **1b_E17** (boat form) conformer in the gas phase turned out to be 12.2 kJ mol^{-1} higher in energy in water compared to **1b_G01** (chair conformer). The stability of **1b_E17** with the "gg" rotamer of C_7-C_8 in the gas phase can be attributed to the extended hydrogen-bonded network within the exocyclic hydroxyl groups.

(21) Compounds **1a** and **1b** differ only in the position of hydroxyl group at C4. An extended hydrogen-bonding pattern(s) bridged by this −OH group is possible in the chair conformer of **1a**. On the other hand, in the chair conformer of **1b**, the C4-OH in the α-position forms the hydrogen bond with $-C3-CH_2OH$ only. The hydrogen bond with C5-OH (β- oriented) is not possible (as both the −OH groups at the C4 and C5 positions are axial). However, in the boat form of **1b** (Figure 5, **1b_J20**), the extended hydrogen bonding of C4-OH with $C3-CH_2OH$ as well as C5-OH is possible, which in turn stabilizes this conformer.

(22) Rotamers resulting from the intramolecular hydrogen bonding are known to give different ^{1}H NMR spectra; see: Mustafa, K. A.; Kjaergaard, H. G.; Perry, N. B.; Weavers, R. T. *Tetrahedron* **2003**, *59*, 6113–6120.

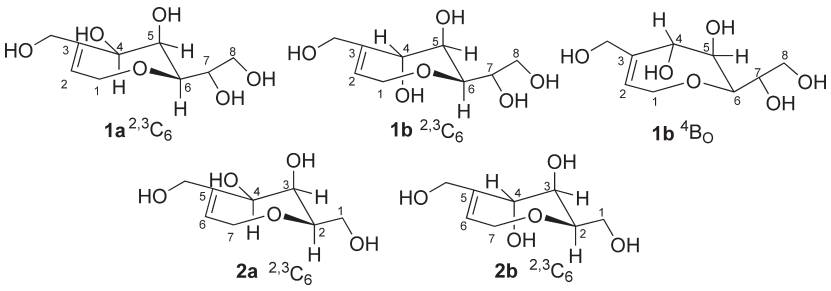


FIGURE 8. Stable ring conformers of **1a**,**b** and **2a**,**b** in water.

deshielding of H4 in minor conformer. Thus, the NMR pattern is consistent with that predicted from the B3LYP calculations (Figure 41S, Supporting Information) indicating that **1b** comprises two different ring conformers, namely the chair ($^{2,3}C_6$) conformer **1b_G01** as the major conformer and the boat ($^{O}B_4$) conformer **1b_J20** in a minor amount. These chair and boat conformations of **1** are shown in Figure 8.

For oxepine **2a**, the calculated ^{1}H NMR spectra of **2a_A01** (out of three conformers **2a_A01**, **2a_C02**, and **2a_D04**) only agrees with the experimentally observed ^{1}H NMR signals, while in the case of **2b**, only the **2b_C01** conformer prevailed energetically and the splitting pattern of its calculated ^{1}H NMR spectrum was in consonance with the recorded spectrum. Thus, the **2a_A01** and **2b_C01** conformers of **2a** and **2b**, respectively, exist in the chair ($^{2,3}C_6$) conformation in water (Figure 8).

Computational Method

The chair conformations of oxepines of **1** and **2** possessing different intramolecular hydrogen-bonded networks were optimized at the Hartree−Fock (HF/3-21G) level of theory using the Gaussian03 package.[23] These conformers possessing unique hydrogen-bonding patterns were labeled with notations A, B, C... (cf. Figure 30S−33S in the Supporting Information). Other ring conformations, viz. chair, twist-chair, half-chair, twist-boat, and boat forms, were generated by scanning the $C_4C_5C_6O$ dihedral angle from −80.0° to 80.0°. TC conformation is assigned by considering the plane formed by three atoms in the case of septanosides; however, the double bond in the seven-membered ring renders coplanar C_1, C_2, C_3, and C_4, and therefore, the rigid plane formed by these atoms was considered here. Minima on the scanned potential energy surface of $C_4C_5C_6O$ dihedral angle were identified and further optimized by relaxing all the constraints. The conformers with relative stabilization energy less than 30 kJ mol^{-1} were subjected to B3LYP optimization incorporating the 6-31G(d) basis set.[24,25] Self-consistent reaction field theory was utilized to investigate the influence of solvent on the conformational energies of **1** and **2**. The gas phase structures were further optimized employing the polarizable continuum model (PCM)[26−28] for this purpose. Boltzmann contributions (BC) (cf. the Supporting Information for details) of these conformers were estimated from the relative stabilization energy values in the gas phase and water. BC values are directly derived from the stabilization energies of different conformers. The calculated BC values therefore provide valuable information regarding the relative population of different conformers. NMR chemical shifts were calculated from the gauge invariant atomic orbital (GIAO) method by subtracting the nuclear magnetic shielding tensors of protons in conformers of **1** and **2** from that of the protons in TMS.[29]

Conclusions

In summary, we have adroitly exploited the combination of the Baylis−Hillman and RCM protocol with 3-*O*-allyl-α-D-*xylo*-pentodialdose **3** in the synthesis of new polyhydroxylated oxepines **1** and **2**. An attractive feature of our strategy lies in the RCM reaction in the presence of hydroxyl functionality leading to the formation of trisubstituted double bond. The ^{1}H NMR of oxepines **1a** and **1b** in D_2O showed doubling of signals. The B3LYP calculations in solution engender different low energy conformers of **1** and **2**. The calculated ^{1}H NMR spectral data was correlated with experimentally observed chemical shifts, which showed that **1a** exists in chair form with two rotamers (**1a_P03** and **1a_E10**) around the C6−C7 bond, whereas **1b** exists in two ring conformers, namely the chair ($^{2,3}C_6$) conformer **1b_G01** and the boat ($^{O}B_4$) conformer **1b_J20**. Similarly, **2a** and **2b** were noticed to be in a chair form ($^{2,3}C_6$), namely **2a_A01** and **2b_C01**, respectively.

Experimental Section

Ethyl 3-*O*-Allyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-α-D-gluco-1,4-heptofuranoate (4a) and Ethyl 3-*O*-Allyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-β-L-ido-1,4-heptofuranoate (4b). To a solution of sugar aldehyde **3** (3.0 g, 13.15 mmol) in 1,4-dioxane−H_2O (1:1, 50 mL) was added DABCO (1.47 g, 13.15 mmol) and ethyl acrylate (3.94 mL, 39.47 mmol) at 30 °C. Reaction mixture was stirred for 48 h and quenched by adding saturated NH_4Cl solution. The solution was extracted with ethyl acetate (3 × 20 mL), and ethyl acetate was evaporated to give crude product. Purification by column chromatography and

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elution first with (n-hexane/ethyl acetate = 9/1) gave **4a** (1.55 g, 35%): R_f = 0.5 (*n*-hexane/ethyl acetate = 6/3); $[\alpha]_D$ −35.5 (*c* 1.40, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.30 (s, 3H), 1.42 (s, 3H), 2.18 (bs, 1H, exchangeable with D_2O), 4.02 (d, *J* = 3.0 Hz, 1H), 4.04 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.15 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.38 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.55 (d, *J* = 3.6 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 5.18−5.37 (m, 2H), 5.80−5.98 (m, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 5.94 (bs, 1H), 6.37 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.4, 26.9, 61.0, 70.0, 71.4, 79.8, 82.1, 82.2, 105.0, 111.7, 118.0, 127.6, 133.5, 139.2, 166.2. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.77; H, 7.52. Further elution with (*n*-hexane/ethyl acetate = 8.5/1.5) afforded **4b** as a thick liquid (2.55 g, 53%): R_f = 0.45 (*n*-hexane/ethyl acetate = 6/3); $[\alpha]_D$ −18.0 (*c* 1.4, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H) 1.30 (s, 3H), 1.42 (s, 3H), 2.18 (bs, 1H, exchangeable with D_2O, 1H), 3.92−4.06 (m, 2H), 4.12−4.28 (m, 3H), 4.46 (t, *J* = 3.6 Hz, 1H), 4.57 (d, *J* = 3.9 Hz, 1H), 4.87 (d, *J* = 3.6 Hz, 1H), 5.23 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.29 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.78−5.98 (m, 1H), 5.97 (d, *J* = 3.9 Hz, 1H), 6.10 (bs, 1H), 6.40 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.5, 26.9, 60.8, 69.0, 71.1, 80.0, 82.3, 83.8, 104.9, 111.9, 118.3, 127.5, 133.0, 138.5, 165.9. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.80; H, 7.52.

3-*O*-Allyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose (5a). To a solution of **4a** (1.5 g, 4.60 mmol) in THF (20 mL) under N_2 atmosphere was added DIBAL-H (9.6 mL, 9.60 mmol) in THF at −78 °C, and the resulting reaction mixture was stirred for 2 h. The reaction mixture was quenched by adding saturated NH_4Cl (5 mL). The reaction mixture was filtered through Celite, and the filtrate was dried over sodium sulfate and evaporated to give a thick oil. Purification by column chromatography (*n*-hexane/ethyl acetate = 7/3) afforded **5a** as a thick liquid (0.9 g, 69%): R_f = 0.5 (*n*-hexane/ethyl acetate = 5/5); $[\alpha]_D$ −34.4 (*c* 1.6, $CHCl_3$); IR (neat) 3200−3600 (broadband) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 3H), 2.89 (bs, exchangeable with D_2O, 2H), 3.98−4.10 (m, 2H), 4.11−4.32 (m, 4H), 4.52 (d, *J* = 7.8 Hz, 1H), 4.55 (d, *J* = 3.9 Hz, 1H), 5.18−5.38 (m, 4H), 5.80−5.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.9, 64.4, 70.9, 71.2, 81.1, 81.9, 82.0, 105.0, 111.7, 114.4, 118.1, 133.5, 147.7. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.73. Found: C, 59.00; H, 7.89.

3-*O*-Allyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose (5b). Reaction of **4b** (2.2 g, 6.70 mmol) with DIBAL-H (14.1 mL, 14.0 mmol) in THF was carried out as described in **5a** and purified by column chromatography (*n*-hexane/ethyl acetate = 6.5/3.5) to give **5b** as a thick liquid (1.3 g, 68%): R_f = 0.5 (*n*-hexane/ethyl acetate 4/6); $[\alpha]_D$ −24.43 (*c* 1.6, $CHCl_3$); IR (neat) 3200−3600 (broadband) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 2.59 (bs, exchangeable with D_2O, 2H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.95 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.18 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.20−4.30 (ABq, *J* = 12.5, 4.8 Hz, 2H), 4.29 (dd, *J* = 4.8, 3.6 Hz, 1H), 4.57 (d, *J* = 3.9 Hz, 1H), 4.65 (d, *J* = 4.8 Hz, 1H), 5.18−5.38 (m, 4H), 5.77−5.96 (m, 1H), 5.98 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.5, 64.4, 71.7, 72.9, 82.2, 82.6, 83.6, 105.6, 112.5, 115.4, 118.8, 133.8, 147.1. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.73. Found: C, 58.89; H, 7.90.

1,2-*O*-Isopropylidene-3,8-anhydro-6,7,8-trideoxy-6-hydroxymethyl-α-D-*gluco*-oct-6-ene-1,4-furanose (6a). To a solution of compound **5a** (0.8 g, 3.10 mmol) in dry dichloromethane (10 mL) was added Grubbs' second-generation catalyst (10 mol %) and the reaction mixture stirred at 30°C for 12 h. Dichloromethane was evaporated, and the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 3.5/7) to give **6a** as a crystalline solid (0.6 g, 84%): R_f = 0.20 (*n*-hexane/ethyl acetate = 2/8); $[\alpha]_D$ −20.7 (*c* 2.4, $CHCl_3$); mp = 145−147 °C; IR (KBr) 3200−3600 (broadband) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.39 (s, 3H), 2.12 (bs, 2H, exchangeable with D_2O), 3.95 (ABq, *J* = 12 Hz, 2H), 4.20−4.31 (m, 3H), 4.46−4.60 (m, 2H), 4.66 (d, *J* = 4.2 Hz, 1H) 5.62−5.76 (m, 1H), 6.08 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ 26.3, 26.7, 64.6, 69.0, 69.2, 82.5, 85.0, 85.5, 104.1, 111.3, 124.8, 139.3. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.80; H, 7.05.

1,2-*O*-Isopropylidene-3,8-anhydro-6,7,8-trideoxy-6-hydroxymethyl-β-L-*ido*-oct-6-ene-1,4-furanose (6b). Reaction of **5b** (1.1 g, 3.84 mmol) with Grubbs' second-generation catalyst (10 mol %) in dry DCM (10 mL) was carried out as described in **6a** and purified by column chromatography (*n*-hexane/ethyl acetate = 6.5/3.5) to give **6b** as a colorless solid (0.81 g, 82%): R_f = 0.45 (*n*-hexane/ethyl acetate = 4/6); $[\alpha]_D$ −5.8 (*c* 2.0, $CHCl_3$); mp = 84−85 °C; IR (KBr) 3200−3600 (broadband) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.49 (s, 3H), 2.78 (bs, 2H, exchangeable with D_2O), 4.07 (d, *J* = 4.5 Hz, 1H), 4.10 (d, *J* = 12.3 Hz, 1H), 4.17 (dd, *J* = 12.3, 1.5 Hz, 2H), 4.45 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.54 (d, *J* = 1.5 Hz, 1H), 4.57 (d, *J* = 3.6 Hz, 1H), 5.04 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.33 (m, 1H), 5.95 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 27.3, 65.8, 70.9, 72.1, 82.5, 85.5, 87.8, 105.1, 112.1, 122.7, 138.0. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 56.02; H, 7.30.

1,6-Anhydro-3-hydroxymethyl-4,5,7,8-tetrahydroxy-1,2,3-trideoxy-L-threose-L-*allo*-oct-2-enitol (1a). TFA−water (2 mL, 3:1) was added to **6a** (0.10 g, 0.38 mmol), and the reaction mixture was stirred for 3 h at 0 °C. TFA was coevaporated with toluene to furnish a thick liquid. To an ice-cooled solution of hemiacetal in MeOH−water (4 mL, 4:1) was added sodium borohydride (0.021 g, 0.58 mmol) in two portions and the mixture stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated aq NH_4Cl solution. MeOH and water were evaporated under reduced pressure, and the residue thus obtained was purified by column chromatography (chloroform/methanol = 9/1) to give **1a** as a thick liquid (0.07 g, 82% over two steps): R_f = 0.5 (chloroform/methanol = 8/2); $[\alpha]_D$ −35.0 (*c* 0.7, MeOH); IR (neat) 3200−3600 (broadband) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.16−4.20 (m, 3H), 4.20−4.42 (m, 5H), 4.50−4.62 (bdd, 1H), 5.37 (d, *J* = 4.2 Hz, 1H), 5.80−5.90 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 63.3, 66.5, 67.9, 74.1, 77.1, 82.4, 92.6, 128.4, 132.9. Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.21; H, 7.20. The ^1H NMR spectrum of this compound showed doubling of signals (Cal: 15%) due to the presence of different conformations in the solution (D_2O). The ^{13}C NMR values are given for only the major isomer.

1,6-Anhydro-3-hydroxymethyl-4,5,7,8-tetrahydroxy-1,2,3-trideoxy-L-threose-L-*galacto*-oct-2-enitol (1b). Reaction of **6b** (0.10 g, 0.38 mmol) in TFA−water (2 mL, 3:1) followed by sodium borohydride (0.021 g, 0.58 mmol) in MeOH−water was carried out as described in **1a** and purified by column chromatography (chloroform/methanol = 8.8/1.2) to give **1b** as a thick liquid (0.074 g, 87% over two steps): R_f = 0.5 (chloroform/methanol = 7.5/2.5); $[\alpha]_D$ −24.9 (*c* 0.50, MeOH); IR (neat) 3200−3600 (broadband) cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.06−4.42 (m, 7H), 4.62 (bd, *J* = 17.7 Hz, 1H), 4.95 (dd, *J* = 9.9, 2.7 Hz, 1H), 5.38 (d, *J* = 3.9 Hz, 1H), 5.50−5.70 (m, 1 H); ^{13}C NMR (100 MHz, D_2O) δ. 62.9, 70.7, 71.2, 76.2, 83.5, 86.2, 94.5, 123.8, 136.6. Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.20; H, 7.00. The ^1H NMR spectrum of this compound showed doubling of signals (Cal: 40%) due to the presence of different conformations in the solution (D_2O). The ^{13}C NMR values are given for only the major isomer.

1,2-*O*-Isopropylidene-3,8-anhydro-6,7,8-trideoxy-5-acetoxy-6-methylacetoxy-α-D-*gluco*-oct-6-ene-1,4-furanose (7a). To an ice-cooled solution of **6a** (0.45 g, 1.74 mmol) in dry pyridine (2.6 mL) were added acetic anhydride (5.7 mL, 55.8 mmol) and catalytic DMAP. After the reaction mixture was stirred for 6 h at 30 °C, water was added and the mixture extracted with chloroform

(3 × 15 mL). Usual workup and chromatographic purification (*n*-hexane/ethyl acetate = 8/2) afforded diacetate **7a** as a thick liquid (0.54 g, 92%): R_f = 0.5 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D$ −58.7 (*c* 1.3, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.49 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 4.19 (dd, *J* = 17.6, 3.2 Hz, 1H), 4.26 (d, *J* = 5.2 Hz, 1H), 4.39 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.52 (dd, *J* = 5.2, 3.2 Hz, 1H), 4.55−4.72 (m, 3H), 5.66 (d, *J* = 3.2 Hz, 1H), 5.85 (bs, 1H), 5.93 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.2, 26.7, 27.3, 67.2, 68.3, 69.9, 81.5, 84.1, 85.6, 105.2, 112.4, 132.3,132.5, 170.4, 170.5. Anal. Calcd for $C_{16}H_{22}O_8$: C, 56.13; H, 6.48. Found: C, 56.30; H, 6.23.

1,2-*O*-Isopropylidene-3,8-anhydro-6,7,8-trideoxy-5-acetoxy-6-methylacetoxy-*β*-L-*ido*-oct-6-ene-1,4-furanose (7b). Reaction of **6b** (0.6 g, 2.30 mmol) in dry pyridine (3.4 mL) with acetic anhydride (7.6 mL, 74.4 mmol) and catalytic DMAP was carried out as described in **7a** and purified by column chromatography (*n*-hexane/ethyl acetate = 8.5/1.5) to give diacetate **7b** as a thick liquid (0.72 g, 91%): R_f = 0.5 (*n*-hexane/ethyl acetate = 7/3); $[\alpha]_D$ −16.8 (*c* 0.7, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.50 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 4.08 (d, *J* = 4.2 Hz, 1H), 4.23 (bd, *J* = 21.0 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 4.50−4.70 (m, 4H), 5.54−5.61 (narrow, 1H), 5.95 (d, *J* = 3.9 Hz, 1H), 6.11 (dd, *J* = 9.1, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.1, 26.6, 27.3, 64.8, 70.5, 71.9, 82.7, 84.0, 85.1, 105.3, 111.9, 127.6, 132.0, 170.2 (s). Anal. Calcd for $C_{16}H_{22}O_8$: C, 56.13; H, 6.48. Found: C, 56.10; H, 6.52.

(2*R*,3*R*,4*R*)-2-Hydroxymethyl-3-hydroxy-4-acetoxy-5-(acetoxymethyl)oxep-5-ene (8a). TFA−water (2 mL, 3:1) was added to **7a** (0.5 g, 1.46 mmol), and the reaction mixture was stirred for 3 h at 0 °C. TFA was coevaporated with toluene to furnish a thick liquid. To an ice-cooled solution of hemiacetal in acetone−water (10 mL, 5:1) was added sodium metaperiodate (0.47 g, 2.19 mmol). After the reaction was stirred at 30 °C for 1.5 h, ethylene glycol (1 mL) was added, the reaction mixture was concentrated, and the residue was extracted with dichloromethane (2 × 30 mL). The aldehyde thus obtained was directly subjected for reduction by using $NaBH_4$ (0.08 g, 2.19 mmol) in MeOH−H_2O (10 mL, 4:1) at 0 °C for 30 min and quenched by addition of saturated NH_4Cl. The reaction mixture was extracted with ethyl acetate (1 × 30 mL). Usual workup and purification by column chromatography (*n*-hexane/ethyl acetate = 4/6) gave **8a** as a thick liquid (0.35 g, 87%): R_f = 0.6 (*n*-hexane/ethyl acetate = 0/10); $[\alpha]_D$ +3.0 (*c* 0.5, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.10 (s, 3H), 3.57−3.79 (m, 3H), 4.15 (bd, *J* = 15.9 Hz, 1H), 4.16 (bs, 1H), 4.34 (dd, *J* = 15.6, 6.9 Hz, 1H), 4.54 (d, *J* = 12.6 Hz, 2H), 5.74 (bs, 1H), 6.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 20.9, 63.7, 65.2, 66.6, 70.3, 75.4, 82.7, 127.5, 129.5, 170.4 (s). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.72; H, 6.90.

(2*R*,3*R*,4*S*)-2-Hydroxymethyl-3-hydroxy-4-acetoxy-5-(acetoxymethyl)oxep-5-ene (8b). Reaction of **7b** (0.50 g, 1.46 mmol) with TFA−water (2 mL, 3:1) followed by sodium metaperiodate (0.47 g, 2.19 mmol) cleavage in acetone−water and subsequent $NaBH_4$ (0.08 g, 2.19 mmol) reduction in MeOH−water was carried out as described in **8a** and purified by column chromatography (*n*-hexane/ethyl acetate = 3/7) to give **8b** as a thick liquid (0.34 g, 85%): R_f = 0.4 (*n*-hexane/ethyl acetate = 0/10); $[\alpha]_D$ +35.0 (*c* 0.5, $CHCl_3$); IR (neat) 3200−3600 (broadband), 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.10 (s, 3H), 3.67 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.83 (m, 2H), 4.0 (dd, *J* = 6.9, 4.2 Hz, 1H), 4.26 (bd, *J* = 15.9 Hz, 1H), 4.39 (dd, *J* = 15.9, 6.0 Hz, 1H), 4.59 (q, *J* = 20.4, 12.9 Hz, 2H), 5.45 (d, *J* = 6 Hz, 1H), 6.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (s), 63.6, 67.5, 68.6, 71.8, 77.2, 80.3, 132.9, 134.4, 169.7, 170.4. Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.31; H, 6.35.

(2*R*,3*R*,4*R*)-2-Hydroxymethyl-3,4-dihydroxy-5-(hydroxymethyl)-oxep-5-ene (2a). To a solution of **8a** (0.15 g, 0.54 mmol) in dry MeOH (4 mL) was added NaOMe (0.062 g, 1.14 mmol) and the mixture stirred for 3 h at 0 °C to rt. The reaction mixture was neutralized using Amberlite IR-400 acidic resin and filtered through Celite. MeOH was removed under reduced pressure, and purification by column chromatography (chloroform/methanol = 9/1) gave **2a** as a liquid (0.091 g, 91%): R_f = 0.5 (chloroform/methanol = 8/2); $[\alpha]_D$ −80.0 (*c* 0.8, MeOH); IR (neat) 3600 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.60−3.77 (m, 2H), 3.81−3.92 (m, 2H), 4.08 (dd, *J* = 15.3, 5.4 Hz, 1H), 4.13 (d, *J* = 13.2 Hz, 1H), 4.23 (d, *J* = 13.2 Hz, 1H), 4.36 (dd, *J* = 15.3, 6.3 Hz, 1H), 4.74 (bs, 1H), 5.88−5.96 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 62.2, 63.6, 66.5, 72.0, 73.1, 83.0, 123.7, 142.5. Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.70; H, 7.17.

(2*R*,3*R*,4*S*)-2-Hydroxymethyl-3,4-dihydroxy-5-(hydroxymethyl)-oxep-5-ene (2b). Reaction of **8b** (0.15 g, 0.54 mmol) with NaOMe (0.062 g, 1.14 mmol) in dry MeOH (4 mL) was carried out as described in **2a** and purified by column chromatography (chloroform/methanol = 9/1) to give **2b** as a liquid (0.09 g, 90%): R_f = 0.5 (chloroform/methanol = 8:2); $[\alpha]_D$ +18.5 (*c* 0.2, MeOH); IR (neat) 3600 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.46−3.75 (m, 3H), 3.85−4.30 (m, 6H), 5.75−5.85 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 62.4, 65.2, 67.4, 70.4, 70.6, 79.6, 127.4, 140.0. Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.30; H, 7.61.

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Supporting Information Available: General experimental methods, copies of ^1H and ^{13}C NMR spectra of compounds **2a**, **b**, **1a**,**b**, **4a**,**b**, **5a**,**b**, **6a**,**b**, **7a**,**b**, **8a**,**b** and hydrogen-bonding pattern in exocyclic hydroxyls, ^1H NMR spectra of **1** and **2**, as well as crystallographic data of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.