JOC Article

Differential Use of Anhydropyranosides for Enantiopure Routes to Bis-γ-butyrolactones: A New Approach to the Frameworks of Antibiotic and Anticancer Agents Isoavenaciolide and Ethisolide

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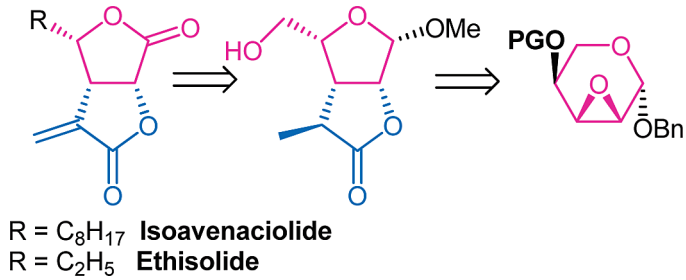
Received January 30, 2009



Regio- and chemoselective syntheses of enantiopure bis-furanoids are described. These compounds are chirons for several families of bioactive natural products, including isoavenaciolide and ethisolide. Reaction of a 3,4-epoxy pyran with β-ketoester dianions delivers substituted pyranosides in high yield. Cyclization then yields fused furan-pyran intermediates. Oxidation, deprotection, and rearrangement lead to bis-furanoids that bear the essential framework and stereochemistry of ethisolide and isoavenaciolide.

Introduction

Modern carbohydrate chemistry is a diverse discipline strongly connected with organic and medicinal chemistry.[1] These polyhydroxylated natural products offer a valuable platform for enantioselective synthesis of stereochemically robust and biologically important molecules. We report herein the synthesis of a set of bis-γ-lactones that utilizes the rich opportunities embodied in the carbohydrates. These synthetic routes yield products with the essential stereochemistry present in many biologically important natural products such as, among others, isoavenaciolide **1** and ethisolide **2** (Figure 1).

Isoavenaciolide **1** and ethisolide **2** are secondary metabolites isolated from *Aspergillus* and *Penicillium* fermentation broths. Both compounds inhibit fungal growth and have antibiotic activity.[1] Recently, it has been found that (−)-isoavenaciolide is a potent irreversible inhibitor of a dual-specificity protein phosphatase (VHR) involved in growth factor signaling, making these targets and their derivatives candidates for cancer chemotherapy.[2] Because of their biological activity and structurally interesting bis-γ-lactone framework, many synthetic methods have been developed to access this family of natural products.[3,4] In this regard, a few enantioselective approaches to this class of natural products have been reported.[3,4e,f] While previous

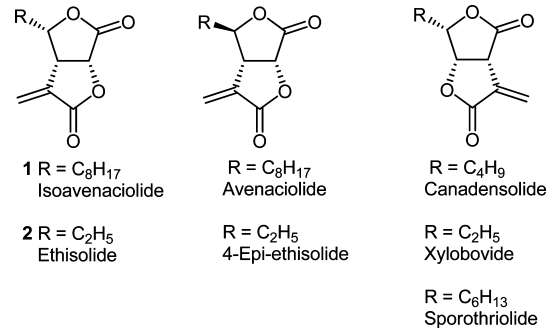


FIGURE 1. Natural products containing the α-methylene-bis-γ-lactone skeleton.

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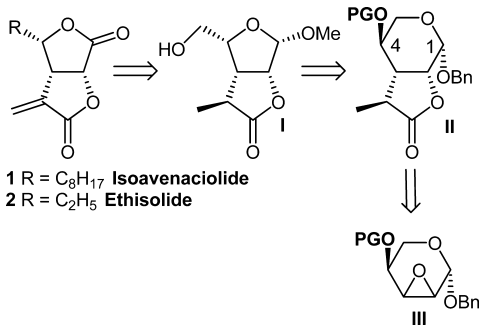
(1) (a) Arjona, O.; Gomez, A. M.; Lopez, J. C; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919. (b) Gruner, A. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491.

(2) Ueda, K.; Usui, T.; Nakayama, H.; Ueki, M.; Takio, K.; Ubukata, M.; Osada, H. *FEBS Lett.* **2002**, *525*, 48.

10.1021/jo900192a CCC: $40.75
Published on Web 05/21/2009

SCHEME 1. Retrosynthetic Analysis

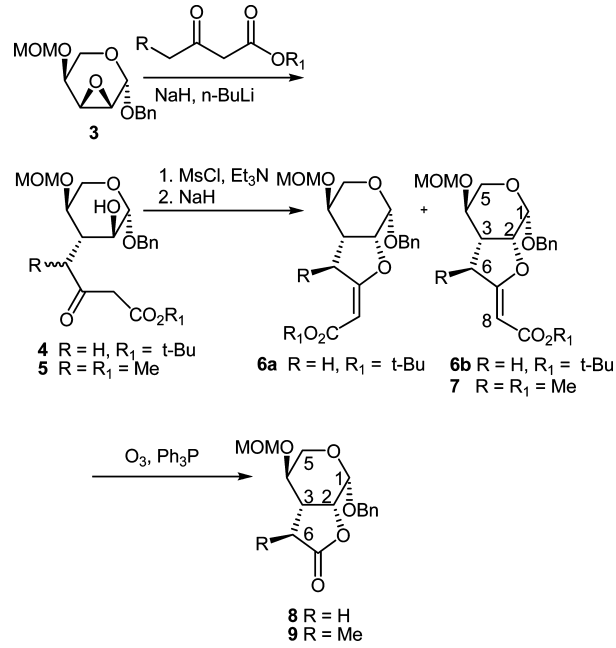


synthetic methods appear to be very selective for one particular core structure and in many cases required chirally pure reagents that are expensive and fairly toxic and difficult to handle reagents (e.g., bromine or stannyl compounds) and did not give perfect selectivity,[4a−d] the route described herein can be used to generate several enantiomerically analogous structures utilizing relatively nontoxic and cheap reagents.

The stereochemistry of these bis-γ-lactone natural product targets seemed to be well-suited for carbohydrate-based routes developed in our laboratories.[5] In this regard, we sought to control all of the stereocenters of the target molecules, taking advantage of the inherent chirality and steric bias of the pyranoside architecture. Previous work has demonstrated that nucleophilic ring opening of epoxypyrans can lead to both chemo- and regioselective annulation of new and enantiopure heterocylic ring systems.[5,6]

Retrosynthetic analysis of isoavenaciolide **1** and ethisolide **2** (Scheme 1) suggested that the oxa-bicyclic furanoid framework **I** would be suitable building block for such natural products, such that all the crucial stereocenters could be stereospecifically derived from the furanoid precursor **II**. Following deprotections at C-4 and C-1, rearrangement of the pyranoside ring would yield the desired bis-furanoid **I**, from which the ultimate targets and analogues could be derived (see Scheme 1).[7,8] In order to arrive at **II**, we would rely upon the demonstrated reactivity of the anhydropyranoside **III** that selectively accepts the β-keto ester dianion, opening the epoxide at C-3 in a *trans*-diaxial manner.[5,6] Cyclization by *O*-alkylation of the β-keto ester substituted sugar followed by oxidative cleavage would then yield the oxa-bicyclic furanoid **II**.

SCHEME 2. Furan Annulation and Control of C-3 Stereochemistry



Results and Discussion

Synthesis of Alkylidene Tetrahydrofurans. As previously reported,[5d] arrival at **4** was achieved through nucleophilic ring opening of the epoxide in **3** by the dianion derived from *tert*-butyl acetoacetate. Subsequent mesylation, followed by the kinetically preferred *O*-alkylation of the β-keto ester anion following NaH deprotonation, delivered the furanoids (*E*)-**6a** and (*Z*)-**6b** in 20% and 75% yields, respectively (Scheme 2). The ketone oxygen anion is presumably able to reach a collinear transition state with the *trans* mesylate leaving group to afford compounds **6a** and **6b**. By inspection of the ^{1}H NMR spectra of **6a** and **6b**, the *Z* and *E* configurations were confirmed by the homoallylic coupling constant between H-6 and the *exo*-alkylidene proton H-8 (**6a**: $J_{6,8}$ = 1.7 Hz and **6b**: $J_{6,8}$ = 0.0 Hz).[9,10] Oxidation of the alkylidene mixture (**6a** and **6b**) by ozonolysis at −78 °C followed by reductive workup with Ph_3P, delivered the γ-lactone **8** in 95% yield. Next, we turned our attention to incorporation of a methyl group on the newly annulated furan ring, as a precursor of the *exo*-methylene moiety in both natural products (vide infra).

Control of Stereochemistry around the Furanoid Ring. Following the same synthetic strategy, we diastereoselectively obtained the *exo*-methyl derivative **7**. Addition of the dianion from methyl propionyl acetate to the epoxy sugar **3** produced the substituted sugar **5** (Scheme 2). Mesylation and sodium hydride mediated ring closure delivered compound **7** in 87%

(3) (a) For a Review, see: Martin, S. V.; Rodriguez, C. M.; Martin, T. *Org. Prep. Proced. Int.* **1998**, *30*, 291. (b) For enantiopure syntheses using carbohydrates, see: Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4781. (c) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4786.

(4) For recent publications, see: (a) Mondal, S.; Ghosh, S. *Tetrahedron* **2008**, *64*, 2359. (b) Hon, Y.-S.; Chen, H.-F. *Tetrahedron Lett.* **2007**, *48*, 8611. (c) Hon, Y.-S.; Hsieh, C.-H. *Tetrahedron* **2007**, *62*, 9713. (d) Hon, Y.-S.; Hsieh, C.-H. *Tetrahedron* **2006**, *62*, 9713. (e) Yu, C.-M.; Youn, J.; Jung, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1553. (f) Liu, H.-M.; Zhang, F.; Zou, D.-P. *J. Chem. Soc., Chem. Commun.* **2003**, 2044. (g) Sharma, G. V. M.; Gopinath, T. *Tetrahedron Lett.* **2001**, *42*, 6183. (h) Alcazar, E.; Kassou, M.; Matheu, I.; Castillon, S. *Eur. J. Org. Chem.* **2000**, *65*, 2285. (i) Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, *64*, 8311. (j) Rodriguez, C. M.; Martin, T.; Martin, V. S. *J. Org. Chem.* **1996**, *61*, 8448.

(5) (a) Naz, N.; Al-Tel, T. H.; Al-Abed, Y.; Voelter, W.; Ficker, R.; Hiller, W. *J. Org. Chem.* **1996**, *61*, 3250. (b) Al-Tel, T. H.; Voelter, W. *J. Chem. Soc. Chem. Commun.* **1995**, 239. (c) Al-Tel, T. H.; Al-Abed, Y.; Voelter, W. *J. Chem. Soc. Chem. Commun.* **1994**, 1735. (d) Al-Tel, T. H.; Voelter, W. *Tetrahedron Lett.* **1995**, *36*, 523.

(6) (a) Al-Tel, T. H.; Meisenbach, M.; Voelter, W. *Liebigs Ann.* **1995**, 689. (b) Al-Qawasmeh, R. A.; Al-Tel, T. H.; Abdel-Jalil, R.; Voelter, W. *Chem. Lett.* **1999**, 541.

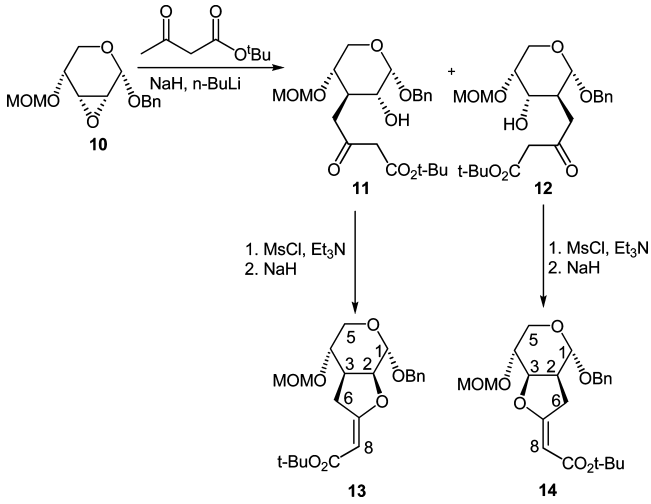
(7) (a) Al-Abed, Y.; Al-Tel, T. H.; Voelter, W. *Tetrahedron* **1993**, *49*, 9295, and references therein. (b) Grieco, P. A. *Synthesis* **1975**, *67*, 564 and relevant references therein.

(8) (a) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 1205. (b) Honda, T.; Kobayoshi, Y.; Tsubuki, M. *Tetrahedron* **1993**, *49*, 1211. (c) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228, and references therein. (d) Nakunan, K.; Liu, R.-S. *J. Chem. Soc. Chem. Commun.* **1998**, 1521 and relevant references therein.

(9) Similar findings in relation to the geometry of the exo-alkylidene tetrahydrofuran derivatives have been reported by Prof. Trost: (a) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550. (b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559.

(10) The adopted numbering scheme is only for the purpose of NMR interpretation (see refs 3b and 3c).

SCHEME 3. Furan Annulation from α-Epoxide 10



overall yield. Notably, only one epimer (HPLC and NMR) was produced at C-6 (*exo*-methyl) of the new furan ring; this outcome is likely due to the thermodynamic equilibrium of the enolate ester formed during the cyclization process, steering the stereochemistry on the furan ring.[5,6]

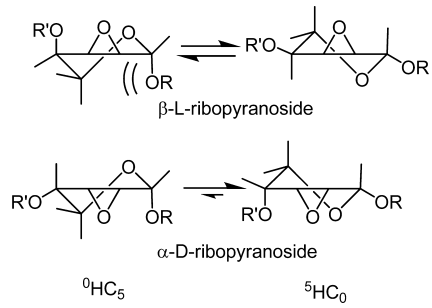
The preferential formation of the *Z*-isomer **7** without the alternative *E*-isomer may be attributable to the steric clash of the ester group with the C-6 methyl group. The *Z* configuration of the *exo*-alkylidene moiety is consistent with the $J_{6,8} = 0.0$ Hz coupling.[9,10] The *cis* ring fusion in **7** was readily identified by the coupling of H-2, a doublet of doublet with $J_{1,2} = 4.8$ Hz and $J_{2,3} = 7.7$ Hz. The *trans* relationship between H-3 and H-6 was also indicated from the coupling constant $J_{3,6} = 12.7$ Hz. Further confirmation of the stereochemistry around **7** was deduced from extensive NOE experiments. Proton H-3 showed a strong reciprocal NOE interaction with both H-2 and H-4, confirming the *cis* relationship. A very weak interaction was observed between H-3 and H-6 consistent with *trans* relationship, while a strong reciprocal NOE was found between H-3 and the furan methyl substituent. Ozonolysis of **7** delivered **9** in 90% yield. The unambiguous confirmation of the stereochemistry in **9** was determined by extensive NOE experiments and from the coupling constant between H-3 and H-6 (12.8 Hz).[10]

Having these results in hand, we directed our efforts toward extending the scope of this strategy to the synthesis of the other isomers of **6**, thereby providing access to other natural products, such as avenaciolide and canadensolide. Thus, the *cis*-alkoxy-epoxide **10** (Scheme 3) was treated with the dianion derived from *tert*-butyl acetoacetate. In contrast to the reaction of **3**, this alkylation delivered two regioisomers, **11** and **12**, in 75% and 20% yield, respectively.

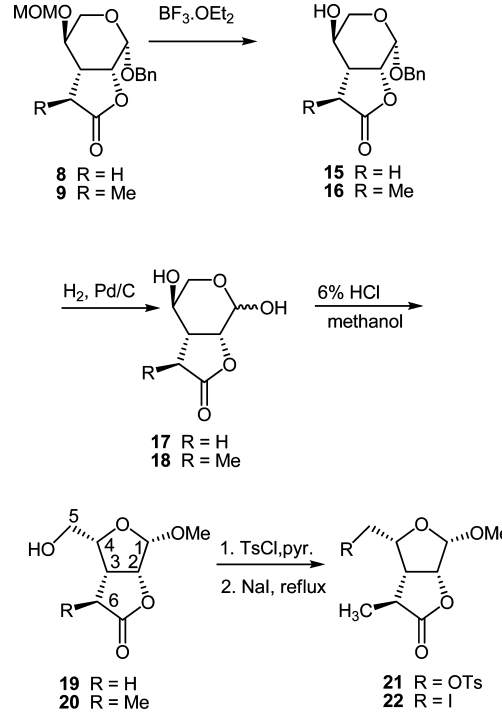
The lower selectivity of the nucleophilic epoxide opening for **10**, in contrast to epoxide **3** that gave a single ring-opening product (Scheme 2), is most readily explained by considering that the relative energies of the two half-chair conformation of α-D-ribopyranoside allowed for nucleophilic attack at C-2 (Scheme 4) of the oxirane ring. This attack was not observed in the case of *β*-L-ribopyranoside, where C-2 is sterically blocked and the thermodynamic equilibrium favors the attack at C-3 of the epoxide ring (Scheme 4). Therefore, one regioisomer is obtained to the complete exclusion of the other.

Following the same strategy as described for the synthesis of **6a, b** and **7**, compounds **13** and **14** were easily produced

SCHEME 4. Half-Chair Conformations of Ribopyranoside Diastereoisomers



SCHEME 5. Formation of Bis-furanoids by Rearrangement of the Pyrans



from **11** and **12** (Scheme 3). Surprisingly, only *E*-isomers are produced. This was evident from the coupling between H-8 and H-6 ($J \approx 1.5$ Hz).[9] It is worthwhile mentioning that the bicyclic furanoids **13** and **14** have the proper stereochemistry for synthesis of the naturally occurring enantiomers of avenaciolide and canadensolide (Figure 1), respectively.

Synthesis of Bis-furanoids. To elaborate our synthons to more advanced building blocks, we pursued the conversion of the pyran ring to the bis-furanoids suitable for the total synthesis of the isoavenaciolide and ethisolide natural products. Standard protocols were used to remove the protecting groups at both C-4 and C-1 to deliver compounds **17** and **18** (Scheme 5). Treatment of **8** and **9** with $BF_3 \cdot OEt_2$ at −78 °C removed the MOM protecting group, furnishing **15** and **16**, respectively. Removal of the benzyl moiety was carried out over Pd/C in EtOAc to deliver compounds **17** and **18** in 90% and 95% yields, respectively. The assignment of methyl group stereochemistry for compound **16** was unambiguously confirmed by the ^{1}H NMR: coupling between H-3 and H-6 was 12.8 Hz, consistent with a *trans* disposition. Having arrived at **17** and **18**, ring contraction of the pyranoside skeleton was carried out using a freshly prepared solution of 6% HCl in MeOH at 0 °C for 30

min to produce **19** and **20**, respectively.[11] The stereochemistry of the anomeric methoxy groups in both **19** and **20** was inferred from the coupling constants of the anomeric protons ($J = 0.0$ Hz),[12] indicating an α-disposition. Furthermore, the ^{13}C NMR spectra of compounds **19** and **20** showed a downfield shift of the anomeric carbons to ca. 105 ppm, indicative of ring contraction to the furanoid framework, whereas the chemical shifts for the anomeric carbon in the pyranoside skeleton are found at ca. 100 ppm.[12] Unambiguous confirmation of the stereochemistry for **19** and **20** utilized extensive NOE analysis.

The protons H-3 and H-2 showed strong reciprocal NOE interactions, indicative of a *cis* relationship between these bridgehead methine protons. Derivatization of **20** by conventional tosylation of the hydroxyl residue led to the bis-furanoid **21**. Substitution of the tosyl group in **21** by iodide, using NaI/acetone, produced compound **22**. A salient feature of the ^1H NMR spectrum of compound **22** was the coupling constant between H-3 and H-6 of 13.3 Hz, indicating a *trans* relationship. This feature further confirmed the stereochemistry around the γ-lactone ring. Extensive NOE experiments unambiguously confirmed the stereochemistry around **22**. Conventional chemistry, using **20**, **21** or **22**, should allow for the total synthesis of isoavenaciolide **1** and ethisolide **2**.[7,8]

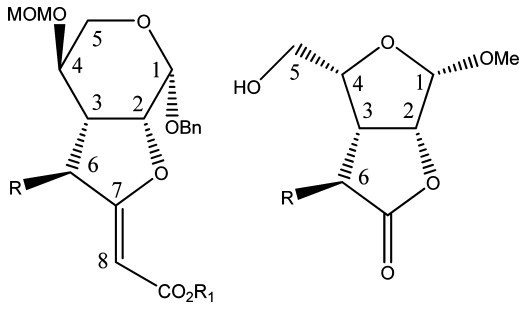
Conclusions

In summary, we have developed a new route from pyranoside **3** to advanced optically active bis-furanoid building blocks **19**−**22**, which should be readily elaborated to the antibiotics isoavenaciolide **1** and ethisolide **2** using chemistry described by other laboratories.[3−8] Further, compounds **21** and/or **22** could serve as important "chirons", replacing the nucleofuge and potentially producing more potent or selective irreversible inhibition of VHR.[2] The scope of this methodology was also tested with the isomeric oxirane **10** to deliver two alkylidene tetrahydrofuran compounds **13** and **14** which are building blocks with clear application to the synthesis of enantiomers of avenaciolide and canadensolide natural products.

Experimental Section

All reactions were performed under argon using anhydrous solvents. Column chromatography was carried out with silica gel (60−120 mesh). ^1H and ^{13}C NMR spectra were recorded on a 500 or 400 MHz spectrometer in $CDCl_3$ with TMS as internal standard in ppm. Elemental analysis was performed on elemental analyzer. The EI, FD, and FAB mass spectra were recorded using a mass spectrometer connected to a PDO 11/34 (DEC) computer system. Optical rotations were obtained with a polarimeter at 546 nm. All chemical used are of commercial grades.

For the purpose of NMR interpretation, the following numbering schemes have been adopted (see refs 3b and 3c):



Benzyl 2,3-Anhydro-4-*O*-methoxymethyl-β-L-ribopyranoside (3). To a suspension of NaH (399 mg, 10.4 mmol, 65% dispersion in mineral oil) in THF (10 mL) at 0 °C was added under argon benzyl 2,3-anhydro-β-L-ribopyranoside (2.22 g, 10 mmol) in 5 mL of THF. The mixture was stirred at 0 °C for 20 min followed by the addition of methoxymethyl chloride (0.78 mL, 10.2 mmol). The mixture was allowed to warm to rt and stirred for an additional 4 h. Workup with saturated NH_4Cl and extraction with EtOAc produced after crystallization from EtOAc/pet ether 2.12 g (80%) of **3** as a white solid: mp 64−66 °C; $[\alpha]^D_{20}$ +220.5 (*c* 0.23, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (5H, m), 5.11 (1H, dd, $J = 2.1$, 4.9 Hz), 4.80 (1H, d, $J = 11.9$ Hz), 4.64 (2H, s), 4.60 (1H, d, $J = 11.9$ Hz), 5.14 (1H, s), 4.00 (1H, dd, $J = 2.4$, 13.0 Hz), 3.67 (1H, d, $J = 13.0$ Hz), 3.43 (2H, br. s), 3.27 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 137.2, 129.1, 128.4, 128.1, 100.0, 92.8, 76.7, 69.5, 62.0, 55.5, 51.8, 49.3; FD-MS $m/z = 267$ ($M^+ + 1$). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C 63.20, H 6.87.

Phenylmethyl 3-Deoxy-3-[4-(1,1-dimethylethoxy)-2,4-dioxobutyl]-4-*O*-(methoxymethyl)-β-L-xylopyranoside (4). A suspension of NaH (174 mg, 4.4 mmol, 65% dispersion in mineral oil) in 10 mL of THF at 0 °C was cautiously treated with *tert*-butyl acetoacetate (0.66 mL, 4 mmol) under argon over a 15 min period. After stirring at this temperature for 30 min, a solution of *n*-BuLi (2.75 mL, 4.4 mmol, 1.6 M in *n*-hexane) was added dropwise over 10 min. The mixture was stirred at 0 °C for 30 min. To the resultant milky solution was added compound **3** (1 mmol, 266 mg in 2 mL of THF). The reaction was then stirred at rt for 5 h, after which the mixture was quenched with a saturated solution of NH_4Cl (5 mL), extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum to give a yellowish crude oil. The crude was purified through a short silica gel column using DCM/ EtOAc (9:1) as eluent to afford compound **4** as a yellowish oil (407 mg, 96% yield): $[\alpha]^D_{20}$ −85.1 (*c* 0.31, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (5H, m, arom. H), 4.83 (1H, d, $J = 11.3$ Hz, OC*H*HPh), 4.68 (2H, dd, $J = 7.0$, 8.3 Hz, OCH_2O), 4.48 (1H, d, $J = 11.3$ Hz, OCH*H*Ph), 4.46 (1H, d, $J = 7.1$ Hz, 1-H), 4.34 (1H, t, $J = 11.3$ Hz, 5-H), 4.13 (1H, dd, $J = 4.9$, 11.3 Hz, 5-H), 3.69 (1H, m, 4-H), 3.31 (1H, m, 2-H), 3.26 (3H, s, OMe), 2.90 (1H, dd, $J = 4.6$, 17.1 Hz, 6-H), 2.80 (2H, br. s, 8-H), 2.73 (1H, dd, $J = 5.2$, 17.1 Hz, 6-H), 2.24 (1H, m, 3-H), 1.39 (9H, s, C$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 200.0 (C-7), 166.5 (*C*O_2C$(CH_3)_3$), 137.5, 128.6, 128.4, 128.3 (Ph), 100.5 (C-1), 97.2 (O*C*H_2O), 81.5 (*C*$(CH_3)_3$), 77.6 (C-4), 74.9 (C-2), 71.0 (O*C*H_2Ph), 67.1 (C-5), 55.8 (OMe), 50.9 (C-8), 39.9 (C-6), 38.7 (C-3), 27.9 (C(*C*$H_3)_3$); FD-MS $m/z = 425$ ($M^+ + 1$). Anal. Calcd for $C_{22}H_{32}O_8$ (424.21): C 62.25, H 7.60. Found: C 62.31, H 7.54.

Phenylmethyl 3-Deoxy-4-*O*-(methoxymethyl)-3-(4-methoxy-1-methyl-2,4-dioxobutyl)-β-L-xylopyranoside (5). Following procedure similar to the conversion of oxirane **3** to **4**, a suspension of NaH (4.4 mmol, 174 mg, 65% dispersion in mineral oil) in 10 mL of THF at 0 °C was cautiously treated with methyl propionyl acetate (0.5 mL, 4 mmol) under argon over a 15 min period. After stirring at this temperature for 30 min, a solution of *n*-BuLi (2.75 mL, 4.4 mmol of 1.6 M in *n*-hexane) was added dropwise over 10 min. Stirring at 0 °C was continued for an additional 30 min, after which oxirane **3** (1 mmol, 266 mg) was added. Following workup/ purification procedure as employed for **4**, a diastereomeric mixture (1:1 as indicated from the ^{13}C and ^1H NMR spectra) of the long chain pyranoside **5** (376 mg, 95% yield) was obtained as a yellowish oil: $[\alpha]^D_{20}$ −63.2 (*c* 0.43, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (10H, m, arom. H), 4.81 (1H, d, $J = 7.8$ Hz, 1-H), 4.77 (1H, d, $J = 8.0$ Hz, 1-H), 4.61 (5H, m), 4.34−4.27 (3H, m), 4.10−4.02 (2H, m), 3.64−3.60 (5H, m), 3.52−3.20 (9H, m),

(11) Motawia, M. S.; Pedersen, E. B. *Liebigs Ann.* **1990**, 599.

(12) (a) Thibaudeau, C.; Foldesi, A.; Chattopadhyaya, J. *Tetrahedron* **1998**, *54*, 1867. (b) Plavec, J.; Tong, W.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1993**, *115*, 9734.

2.97−2.91 (3H, m), 2.30−2.21 (2H, m), 1.08−0.97 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 205.1, 204.5 (*C*O), 168.3 (*C*O_2C(CH_3)$_3$), 137.2, 137.1, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6 (Ph), 103.4, 103.1 (C-1), 97.2, 96.4 (O*C*H_2O), 72.5, 72.2 (C-4), 70.7, 70.0 (O*C*H_2Ph), 69.1, 68.2 (C-2), 66.9, 66.0 (C-5), 55.8, 55.7 (OMe), 52.2, 52.1 (OMe), 46.9, 46.8 (2C-8), 44.1, 43.8 (C-3), 47.5, 46.7 (C-6), 9.6, 8.9 (Me); FD-MS m/z = 397 (M^+ + 1). Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12. Found: C, 60.23; H, 6.98.

[3a*R*-(2*E*,3aα,4α,7*β*,7aα)]-Acetic Acid-[hexahydro-4-(methoxymethoxy)-7-(phenylmethoxy)-2*H*-furo[2,3-*c*]pyran-2-ylidene]-1,1-dimethylethyl Ester (6a). Semisolid, (81 mg, 20%); $[\alpha]^D_{20}$ +112.6 (*c* 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.19 (5H, m, arom. H), 5.30 (1H, t, *J* = 1.7 Hz, 8-H), 4.82 (1H, d, *J* = 4.0 Hz, 1-H), 4.73 (1H, d, *J* = 12.5 Hz, OC*H*HPh), 4.62 (2H, dd, *J* = 7.1, 9.8 Hz, OC*H*$_2$O), 4.50 (1H, d, *J* = 12.5 Hz, OCH*H*Ph), 4.43 (1H, dd, *J* = 4.0, 7.0 Hz, 2-H), 4.34 (1H, dd, *J* = 2.7, 12.3 Hz, 5-H), 3.67 (1H, dd, *J* = 3.9, 6.8 Hz, 4-H), 3.47 (1H, dd, *J* = 3.8, 12.3 Hz, 5-H), 3.31 (3H, s, OMe), 3.16 (1H, ddd, *J* = 1.7, 8.5, 17.5 Hz, 6-H), 2.97 (1H, ddd, *J* = 1.8, 9.8, 17.5 Hz, 6′-H), 2.53 (1H, m, 3-H), 1.38 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 174.3, 166.5 (*C*O_2C(CH_3)$_3$, C-7), 137.5, 128.4, 127.6, 127.2 (Ph), 95.9 (C-1), 95.6 (O*C*H_2O), 92.9 (C-8), 79.1 (*C*(CH_3)$_3$), 76.4 (C-2), 69.7 (O*C*H_2Ph), 71.9 (C-4), 59.5 (C-5), 55.6 (OMe), 39.6 (C-3), 33.8 (C-6), 28.4 (C(*C*H_3)$_3$); FD-MS m/z = 407 (M^+ + 1). Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.16; H, 7.39.

[3a*R*-(2*Z*,3aα,4α,7*β*,7aα)]-Acetic Acid-[hexahydro-4-(methoxymethoxy) (phenylmethoxy)-2*H*-furo[2,3-*c*]pyran-2-ylidene]-1,1-dimethylethyl Ester (6b). To a solution of the branched chain sugar **2** (1 mmol, 424 mg) in 10 mL of DCM at 0 °C was added Et_3N (0.17 mL, 1.2 mmol) and DMAP (0.1 mmol, 12 mg) followed by the dropwise addition of MsCl (0.1 mL in 10 DCM, 1.2 mmol). The resulting mixture was stirred at 0 °C for 2 h, after which TLC analysis showed no starting material. The mixture was diluted with 10 mL of DCM and 5 mL of saturated $NaHCO_3$, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude mesylate product was used in the next step without further purification. The mesylated derivative of compound **4** (424 mg, 1 mmol) was dissolved in 10 mL of THF and added dropwise to a cooled suspension of NaH (47.5 mg, 1.2 mmol, 65% dispersion in mineral oil) in 10 mL of THF. The mixture was warmed to rt and stirred overnight. It was then diluted with 5 mL of saturated NH_4Cl, extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4 and concentrated under high vacuum to give compounds **6a** and **6b** as a yellowish oil. The crude was purified via column chromatography using EtOAc/DCM (1:9) as eluent to produce compound **6b** (303 mg, 75%): $[\alpha]^D_{20}$ +98.1 (*c* 0.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.15 (5H, m, arom. H), 5.02 (1H, d, *J* = 4.6 Hz, 1-H), 4.78 (1H, s, 8-H), 4.74 (1H, dd, *J* = 4.6, 7.0 Hz, 2-H), 4.67 (1H, d, *J* = 12.4 Hz, OC*H*HPh), 4.64 (2H, dd, *J* = 7.0, 8.3 Hz, OC*H*$_2$O), 4.50 (1H, d, *J* = 12.4 Hz, OCH*H*Ph), 4.34 (1H, dd, *J* = 2.0, 12.6 Hz, 5-H), 3.73 (1H, bd, *J* = 2.1 Hz, 4-H), 3.55 (1H, dd, *J* = 1.8, 12.6 Hz, 5-H), 3.33 (3H, s, OMe), 2.82 (3H, m, 3-H, 6-H), 1.42 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 170.4, 165.2 (*C*O_2C(CH_3)$_3$, C-7), 137.5, 128.3, 127.5, 127.1 (Ph), 96.1 (C-1), 95.4 (O*C*H_2O), 90.7 (C-8), 78.9 (*C*(CH_3)$_3$), 77.9 (C-2), 70.1 (O*C*H_2Ph), 71.7 (C-4), 57.8 (C-5), 55.8 (OMe), 38.3 (C-3), 34.8 (C-6), 28.4 (C(*C*H_3)$_3$); FD-MS m/z = 407 (M^+ + 1). Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.22; H, *7.32*.

[3*S*-(2*Z*,3α,3aα,4α,7*β*,7aα)]-Acetic Acid-[hexahydro-4-(methoxymethoxy)-3-methyl-7-(phenylmethoxy)-2*H*-furo[2,3-*c*]pyran-2-ylidene]-methyl Ester (7). Following the procedure for the conversion of long chain pyranoside **4** to **6a, b**, compound **7** was synthesized accordingly. Compound **5** (1 mmol, 396 mg, 10 mL of DCM), Et_3N (0.17 mL, 1.2 mmol), DMAP (12 mg, 0.1 mmol) and MsCl (0.1 mL, 1.2 mmol) then NaH (47.5 mg, 1.2 mmol, 65% dispersion in mineral oil) gave one epimer of the alkylidene tetrahydrofuran **7** (346 mg, 92%) as a yellowish oil: $[\alpha]^D_{20}$ +150.0 (*c* 0.50, CH_2Cl_2); significant NMR NOEs are 2-H to 3-H, 32%; 3-H to 6-CH_3, 37%; 3-H to 6-CH_3, 28%; 8-H to 6-CH_3, 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (5H, m, arom. H), 5.06 (1H, d, *J* = 4.8 Hz, 1-H), 4.84 (1H, s, 8-H), 4.80 (1H, dd, *J* = 4.8, 7.7 Hz, 2-H), 4.69 (1H, d, *J* = 12.4 Hz, OC*H*HPh), 4.68 (2H, br. s, OCH_2O), 4.52 (1H, d, *J* = 12.4 Hz, OCH*H*Ph), 3.86 (1H, dd, *J* = 1.6, 13.0 Hz, 5-H), 3.71 (1H, bs, 4-H), 3.68 (3H, s, OMe), 3.65 (1H, dt, *J* = 1.5, 13.0 Hz, 5-H), 3.36 (3H, s, OMe), 2.93 (1H, dd, *J* = 6.7, 12.7 Hz, 6-H), 2.20 (1H, dd, *J* = 7.7, 12.7 Hz, 3-H), 1.15 (3H, d, *J* = 6.7 Hz, 6-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 175.9, 166.4 (*C*$O_2$$CH_3$), C-7), 137.4, 128.4, 127.6, 127.1 (Ph), 95.8 (C-1), 95.1 (O*C*H_2O), 88.1 (C-8), 76.7 (C-2), 70.8 (C-4), 70.2 (O*C*H_2Ph), 57.3 (C-5), 55.6 (OMe), 50.8 (OMe), 45.7 (C-6), 39.8 (C-3), 16.5 (6-*C*H_3); FD-MS m/z = 379 (M^+ + 1). Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.50; H 6.90.

(3a*R*,4*R*,7a*R*)-7-(Benzyloxy)-4-(methoxymethoxy)hexahydro-2*H*-furo[2,3-*c*]pyran-2-one (8). A solution of **6a,b** (1 mmol, 404 mg) in 20 mL of DCM was cooled to −78 °C. A stream of O_3/O_2 was then bubbled through this mixture until the blue color of the excess O_3 appeared (ca. 10−15 min). Reductive workup with PPh_3 (1.4 mmol, 371 mg) led (after 30 min stirring at rt) to the corresponding lactone. The mixture was concentrated under vacuum and purified via column chromatography (50% v/v pet ether/DCM eluent) to produce **8** (293 mg, 95%) as colorless oil: $[\alpha]^D_{20}$ +85.1 (*c* 0.198, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (5H, m, arom. H), 5.00 (1H, d, *J* = 4.5 Hz, 1-H), 4.85 (1H, d, *J* = 12.1 Hz, OC*H*HPh), 4.70 (1H, d, *J* = 7.2 Hz, OCH_2O), 4.65 (1H, d, *J* = 7.2 Hz, OCH_2O), 4.64 (1H, dd, *J* = 4.5, 7.6 Hz, 2-H), 4.56 (1H, d, *J* = 12.1 Hz, OCH*H*Ph), 3.94 (1H, dd, *J* = 2.3, 12.6 Hz, 5-H), 3.781 (1H, dd, *J* = 2.3, 6.0 Hz, 4-H), 3.62 (1H, dd, *J* = 3.7, 12.6 Hz, 5-H), 3.36 (3H, s, OMe), 2.84 (1H, m, 3-H), 2.55 (1H, dd, *J* = 12.1, 17.1 Hz, 6-H), 2.48 (1H, dd, *J* = 7.5, 17.1 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 175.9 (C-7), 136.7, 128.4, 127.8, 127.4 (Ph), 95.2 (C-1), 95.3 (O*C*H_2O), 71.2 (C-2), 72.9 (C-4), 69.7 (O*C*H_2Ph), 57.8 (C-5), 55.6 (OMe), 31.6 (C-6), 38.0 (C-3); FD-MS m/z = 309 (M^+ + 1). Anal. Calcd for $C_{16}H_{20}O_6$ (308.33): C, 63.33; H, 6.54. Found: C, 62.48; H, 6.43.

(3*S*,3a*R*,4*R*,7a*R*)-7-(Benzyloxy)-4-(methoxymethoxy)-3-methylhexahydro-2*H*-furo[2,3-*c*]pyran-2-one (9). Following procedure for preparation of compound **8**, a solution of **7** (1 mmol, 376 mg, 20 mL of DCM) was cooled to −78 °C, after which a stream of O_3/O_2 was bubbled through this mixture until the blue color of the excess O_3 appeared (about 10−15 min). Reductive workup with PPh_3 (1.4 mmol, 371 mg) led after 30 min of stirring at rt to the corresponding lactone **9** in 87% (280 mg) as colorless oil: $[\alpha]^D_{20}$ +156.6 (*c* 0.144, CH_2Cl_2); significant NMR NOEs are 2-H to 3-H, 29%; 3-H to 6-CH_3, 34%; 3-H to 6-CH_3, 35%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.19 (5H, m, arom. H), 4.98 (1H, d, *J* = 4.7 Hz, 1-H), 4.67 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.66 (1H, d, *J* = 11.9 Hz, OC*H*HPh), 4.63 (1H, d, *J* = 7.0 Hz, OCH_2O), 4.55 (1H, dd, *J* = 4.7, 7.2 Hz, 2-H), 4.47 (1H, d, *J* = 11.9 Hz, OCH*H*Ph), 3.88 (1H, dd, *J* = 3.9, 12.8 Hz, 5-H), 3.69 (1H, m, 4-H), 3.67 (1H, dd, *J* = 1.8, 12.8 Hz, 5-H), 3.33 (3H, s, OMe), 2.63 (1H, m, 3-H), 2.40 (1H, dq, *J* = 7.7, 12.8 Hz, 6-H), 1.14 (3H, d, *J* = 7.7 Hz, 6-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 178.8 (C-7), 136.7, 128.5, 128.0, 127.4 (Ph), 95.0 (C-1), 94.9 (O*C*H_2O), 70.9 (C-2), 70.4 (C-4), 70.1 (O*C*H_2Ph), 57.1 (C-5), 55.6 (OMe), 45.6 (C-6), 36.3 (C-3), 14.5 (6-*C*H_3); FD-MS m/z = 323 (M^+ + 1). Anal. Calcd for $C_{17}H_{22}O_6$ (322.35): C, 63.34; H, 6.88. Found: C, 63.30; H, 6.29.

Benzyl 2,3-Anhydro-4-*O*-methoxymethyl-α-D-ribopyranoside (10). To a suspension of NaH (399 mg, 10.4 mmol, 65% dispersion in mineral oil) in THF (10 mL) at 0 °C was added under argon benzyl 2,3-anhydro-α-D-ribopyranoside (2.22 g, 10 mmol) in 5 mL of THF. The mixture was stirred at 0 °C for 20 min followed by the addition of methoxymethyl chloride (0.78 mL, 10.2 mmol). The mixture was allowed to warm to rt and stirred for an additional 4 h. Workup with saturated NH_4Cl and extraction with EtOAc produced after crystallization from EtOAc/pet ether 2.00 g (75%) of **10** as a white

solid: mp 84−85 °C; $[\alpha]^{D}_{20}$ +104.1 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (5H, m), 5.11 (1H, dd, J = 1.7, 5.4 Hz), 4.80 (1H, d, J = 12.2 Hz), 4.68 (2H, s), 4.60 (1H, d, J = 12.2 Hz), 4.49 (1H, s), 4.00 (1H, dd, J = 1.7, 13.0 Hz), 3.66 (1H, d, J = 13.0 Hz), 3.41 (2H, br. s), 3.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 137.0, 128.6, 128.1, 128.0, 97.1, 93.6, 76.2, 69.3, 61.7, 55.4, 51.9, 48.8; FD-MS *m*/*z* = 267 (M^+ + 1). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C 63.12, H 6.86.

Phenylmethyl 3-Deoxy-3-[4-(1,1-dimethylethoxy)-2,4-dioxobutyl]-4-*O*-(methoxymethyl)-α,D-xylopyranoside (11). Following the procedure used for **4**, compounds **11** (318 mg, 75%) and **12** (85 mg, 20%) were produced from **10** utilizing NaH (174 mg, 4.4 mmol, 65% dispersion in mineral oil) in 10 mL of THF, *tert*-butyl acetoacetate (0.66 mL, 4 mmol), and *n*-BuLi (2.75 mL, 4.4 mmol, 1.6 M in *n*-hexane). The mixture was stirred at 0 °C for 30 min. Next, compound **10** (1 mmol, 266 mg in 2 mL of THF) was added and the reaction stirred at rt for 5 h: $[\alpha]^{D}_{20}$ +77.2 (*c* 0.320, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (5H, m, arom. H), 4.73 (1H, d, J = 3.5 Hz, 1-H), 4.70 (1H, d, J = 11.8 Hz, OC*H*HPh), 4.68 (2H, s, OCH_2O), 4.43 (1H, d, J = 11.8 Hz, OCH*H*Ph), 3.70 (1H, dd, J = 5.0, 10.6 Hz, 5-H), 3.47 (1H, t, J = 5.3 Hz, 4-H), 3.27 (4H, m, 2-H, 5-H, H-8,8′), 3.24 (3H, s, OMe), 2.68 (1H, dd, J = 6.3, 16.3 Hz, 6-H), 2.63 (1H, dd, J = 5.4, 16.3 Hz, 6-H), 2.37 (1H, m, 3-H), 1.38 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 203.3 (C-7), 166.6 (*C*O_2C(CH_3)$_3$), 137.2, 128.5, 128.0, 127.9 (Ph), 96.4 (C-1), 97.1 (O*C*H_2O), 81.7 (*C*(CH_3)$_3$), 76.0 (C-4), 69.3 (C-2), 69.1 (O*C*H_2Ph), 61.8 (C-5), 55.7 (OMe), 50.9 (C-8), 42.4 (C-6), 41.2 (C-3), 28.0 (C(*C*H_3)$_3$); FD-MS *m*/*z* = 425 (M^+ + 1). Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 62.34; H, 7.51.

Phenylmethyl 2-Deoxy-2-[4-(1,1-dimethylethoxy)-2,4-dioxobutyl]-4-*O*-(methoxymethyl)-α-D-arabinopyranoside (12). $[\alpha]^{D}_{20}$ +98.1 (*c* 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.20 (5H, m, arom. H), 4.75 (1H, d, J = 11.7 Hz, OC*H*HPh), 4.68 (2H, s, OCH_2O), 4.43 (1H, d, J = 11.7 Hz, OCH*H*Ph), 4.25 (1H, d, J = 7.3 Hz, 1-H), 4.00 (1H, dd, J = 3.6, 12.4 Hz, 5-H), 3.60 (1H, dd, J = 3.0, 5.8 Hz, 4-H), 3.42 (1H, dd, J = 2.0, 12.4 Hz, 5-H), 3.37 (3H, s, OMe), 3.35 (1H, dd, J = 2.0, 5.8 Hz, 3-H), 3.25 (2H, d, J = 15.7 Hz, 8,8-H), 2.58 (1H, dd, J = 5.4, 17.3 Hz, 6-H), 2.65 (1H, dd, J = 6.6, 17.3 Hz, 6-H), 2.43 (1H, m, 2-H), 1.38 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 202.4 (C-7), 166.5 (*C*O_2C(CH_3)$_3$), 137.1, 128.5, 128.1, 127.9 (Ph), 101.2 (C-1), 96.6 (O*C*H_2O), 81.8 (*C*(CH_3)$_3$), 74.7 (C-4), 71.4 (C-3), 70.3 (O*C*H_2Ph), 63.9 (C-5), 55.8 (OMe), 50.9 (C-8), 40.8 (C-6), 41.5 (C-2), 27.9 (C(*C*H_3)$_3$); FD-MS *m*/*z* = 425 (M^+ + 1). Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H 7.60. Found: C, 62.21; H, 7.57.

(2*E*)-Acetic Acid-[(3a*S*,4*S*,7*S*,7a*S*)-hexahydro-4-(methoxymethoxy)-7-(phenylmethoxy)-2*H*-furo[2,3-*c*]pyran-2-ylidene]-1,1-dimethylethyl Ester (13). Mesylation of compound **11** (424 mg, 1 mmol, 10 mL of DCM), Et_3N (0.17 mL, 1.2 mmol), DMAP (12 mg, 0.1 mmol), MsCl (0.1 mL, 1.2 mmol in 10 mL of DCM). The mesylated derivative of compound **9** (1 mmol) was dissolved in 10 mL of THF and added dropwise to a cooled suspension of NaH (47.5 mg, 1.2 mmol, 65% dispersion in mineral oil) in 10 mL of THF. The mixture was allowed to reach rt and stirred overnight. Following the procedure described for synthesis of **6a, b**, α-methylene-furanyl annelated **13** was produced from **11** in 84% yield (339 mg) as a colorless oil following column chromatography using EtOAc/DCM (25%) as eluent: $[\alpha]^{D}_{20}$ +153.7 (*c* 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (5H, m, arom. H), 4.92 (1H, d, J = 3.6 Hz, 1-H), 5.12 (1H, d, J = 1.4 Hz, 8-H), 4.34 (1H, dd, J = 3.6, 7.3 Hz, 2-H), 4.57 (1H, d, J = 12.6 Hz, OC*H*HPh), 4.67 (1H, d, J = 7.0 Hz, OCH*H*O), 4.59 (1H, d, J = 7.0 Hz, OC*H*HO), 4.50 (1H, d, J = 12.6 Hz, OCH*H*Ph), 4.44 (1H, dd, J = 5.6, 11.6 Hz, 5-H), 3.53 (1H, m, 4-H), 3.65 (1H, dd, J = 3.8, 11.6 Hz, 5-H), 3.27 (3H, s, OMe), 2.82 (1H, dd, J = 4.5, 15.3 Hz, 6-H), 2.81 (1H, m, 3-H), 2.73 (1H, dd, J = 3.2, 15.3 Hz, 6-H), 1.15 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 172.4 (C-7), 165.1 (*C*O_2C(CH_3)$_3$), 137.8, 128.5, 127.7, 127.3 (Ph), 93.5 (C-1), 95.8 (O*C*H_2O), 93.5 (C-8), 79.7 (*C*(CH_3)$_3$), 78.3 (C-2), 71.2 (O*C*H_2Ph), 70.7 (C-4), 60.5 (C-5), 54.6 (OMe), 38.0 (C-3), 29.8 (C-6), 28.1 (C(*C*H_3)$_3$); FD-MS *m*/*z* = 407 (M^+ + 1). Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H 7.44. Found: C, 65.31; H, 7.11.

(2*E*)-Acetic Acid-2-[(3a*R*,4*R*,7*S*,7a*S*)-Tetrahydro-7-(methoxymethoxy)-4-(phenylmethoxy)-4*H*-furo[3,2-*c*]pyran-2(3*H*)-ylidene]-1,1-dimethylethyl Ester (14). β-Keto ester derivative **12** (424 mg, 1 mmol, 10 mL of DCM), Et_3N (0.17 mL, 1.2 mmol), DMAP (12 mg, 0.1 mmol), MsCl (1.2 mmol, in 10 DCM). The mesylated derivative of compound **12** (1 mmol) was dissolved in 10 mL of THF and added dropwise to a cooled suspension of NaH (47.5 mg, 1.2 mmol, 65% dispersion in mineral oil) in 10 mL of THF. The mixture was warmed up to rt and stirred overnight. Following the same procedure described for the synthesis of compounds **6a, b**, compound **11** was prepared from **9a** in 88% (355 mg) yield as colorless oil after column chromatography (EtOAc/DCM, 25%): $[\alpha]^{D}_{20}$ +78.7 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (5H, m, arom. H), 4.62 (1H, d, J = 1.8 Hz, 1-H), 5.33 (1H, d, J = 1.6 Hz, 8-H), 4.19 (1H, dd, J = 7.8, 10.9 Hz, 3-H), 4.67 (1H, d, J = 11.7 Hz, OC*H*HPh), 4.68 (1H, d, J = 7.2 Hz, OCH*H*O), 4.61 (1H, d, J = 7.8 Hz, OC*H*HO), 4.50 (1H, d, J = 11.7 Hz, OCH*H*Ph), 4.63 (1H, dd, J = 4.4, 11.6 Hz, 5-H), 3.65 (1H, m, 4-H), 3.75 (1H, dd, J = 3.8, 11.6 Hz, 5-H), 3.38 (3H, s, OMe), 2.91 (1H, dd, J = 4.7, 14.6 Hz, 6-H), 2.91 (1H, m, 2-H), 2.73 (1H, dd, J = 3.2, 14.6 Hz, 6-H), 1.25 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 171.4 (C-7), 166.3 (*C*O_2C(CH_3)$_3$), 137.5, 128.1, 127.3, 127.1 (Ph), 99.2 (C-1), 95.3 (O*C*H_2O), 92.3 (C-8), 80.3 (*C*(CH_3)$_3$), 77.6 (C-3), 70.1 (O*C*H_2Ph), 70.4 (C-4), 61.2 (C-5), 53.8 (OMe), 38.5 (C-2), 29.6 (C-6), 28.3 (C(*C*H_3)$_3$); FD-MS *m*/*z* = 407 (M^+ + 1). Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.11; H 7.23.

(3a*R*,4*R*,7a*R*)-7-(Benzyloxy)-4-hydroxyhexahydro-2*H*-furo[2,3-*c*]pyran-2-one (15). To a − 78 °C solution of MOM derivative **8** (1 mmol, 308 mg) in 10 mL of DCM and thiophenol (1.1 mmol, 121 mg) was added under argon BF_3·OEt_2 (2 mL, 2 mmol, 1 M solution). The temperature was maintained with stirring (10 min); the solution was then warmed to 0 °C and stirred for additional 1 h. Workup was effected by extraction of the organic layer (3 × 10 mL of EtOAc) resulting from addition of 10 mL of saturated NH_4Cl to the extraction mixture. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude oil was loaded on a short column (25% EtOAc/DCM) delivering alcohol **15** as a colorless oil (251 mg, 95% yield): $[\alpha]^{D}_{20}$ +114.9 (*c* 0.100, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.08 (5H, m, arom. H), 4.75 (1H, d, J = 4.7 Hz, 1-H), 4.55 (1H, d, J = 12.2 Hz, OC*H*HPh), 4.42 (1H, dd, J = 4.7, 7.2 Hz, 2-H), 4.35 (1H, d, J = 12.2 Hz, OCH*H*Ph), 3.73 (1H, br. d, J = 12.5 Hz, 5-H), 3.63 (1H, bd, J = 1.5 Hz, 4-H), 3.29 (1H, dd, J = 1.5, 12.5 Hz, 5-H), 2.54 (1H, m, 3-H), 2.30 (1H, dd, J = 11.2, 16.8 Hz, 6-H), 2.20 (1H, dd, J = 9.4, 16.8 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 176.7 (C-7), 136.8, 129.1, 128.6, 127.8 (Ph), 95.3 (C-1), 73.1 (C-2), 65.7 (C-4), 69.9 (O*C*H_2Ph), 60.2 (C-5), 31.7 (C-6), 40.0 (C-3); FD-MS *m*/*z* = 265 (M^+ + 1). Anal. Calcd for $C_{14}H_{16}O_5$ (264.27): C, 63.62; H 6.10. Found: C, 63.69; H, 6.25.

(3*S*,3a*R*,4*R*,7a*R*)-7-(Benzyloxy)-4-hydroxy-3-methylhexahydro-2*H*-furo[2,3-*c*]pyran-2-one (16). Preparation of **16** is analogous to MOM-cleavage procedure for**15**; MOM-protected **9** (1 mmol, 322 mg, 10 mL of DCM), thiophenol (1.1 mmol, 121 mg) and BF_3·OEt_2 (2 mL, 2 mmol, 1 M solution). The resulting mixture was stirred at −78 °C for 10 min before warming to 0 °C with continued stirring for an additional 1 h. Deprotected alcohol **16** was produced in 95% (264 mg) as a white solid: mp 151−153 °C; $[\alpha]^{D}_{20}$ +97.6 (*c* 0.0171, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (5H, m, Ph), 5.40 (1H, d, J = 4.8 Hz, 1-*H*), 4.65 (1H, dd, J = 4.8, 7.6 Hz, 2-*H*), 4.45 (1H, d, J = 12.1 Hz, OC*H*HPh), 4.21 (1H, d, J = 12.1 Hz, OCH*H*Ph), 3.90 (1H, bd, J = 1.7 Hz, 4-*H*), 4.05 (1H, dd, J = 1.7, 12.8 Hz, 5-*H*), 3.57 (1H, dt, J = 1.7, 12.8 Hz, 5-*H*), 2.46 (1H, ddd, J = 1.7, 7.6, 12.8 Hz, 3-*H*), 2.66 (1H, dq, J = 7.0, 12.8

Hz, 6-*H*), 1.24 (3H, d, $J = 7.0$ Hz, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, GASPE) δ 177.0 (*C*-7), 95.1 (*C*-1), 70.6 (*C*-2), 70.3 (O*C*H_2Ph), 66.0 (*C*-4), 59.4 (*C*-5), 47.7 (*C*-3), 36.5 (*C*-6), 14.7 (6-*C*H_3).); FD-Ms *m*/*z* 278 (M^+). Anal. Calcd for $C_{14}H_{16}O_5$ (278.30): C, 64.74; H, 6.52. Found: C, 64.53; H, 6.29.

(3*S*,3a*R*,4*R*,7a*R*)-4,7-Dihydroxy-3-methylhexahydro-2*H*-furo[2,3-*c*]pyran-2-one (17). A solution of **15** (1 mmol, 264 mg) in 15 mL of EtOAc and 10% w/w of Pd/C (26.5 mg, 25% w/w) was shaken under positive pressure of H_2 at rt for overnight. Mixture was filtered over Celite and concentrated to afford 157 mg (90%) of the lactol **17** as colorless oil: $[\alpha]^D_{20}$ −78.8 (*c* 0.054, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (1H, s, 1-*H*), 4.72 (1H, d, $J = 4.4$ Hz, 2-*H*), 4.13 (1H, dd, $J = 7.3$, 13.2 Hz, 4-*H*), 4.34 (1H, dd, $J = 7.3$, 11.5 Hz, 5-*H*), 3.82 (1H, dd, $J = 6.2$, 11.5 Hz, 5-*H*), 3.75 (1H, dd, $J = 4.4$, 6.2, 11.8 Hz, 3-*H*), 2.75 (2H, m, 6-*H*); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 179.2, 100.6, 81.0, 66.8, 61.9, 40.5, 29.7; FD-MS *m*/*z* = 175 ($M^+ + 1$). Anal. Calcd for $C_7H_{10}O_5$ (174.15): C, 48.28; H, 5.79. Found: C, 48.43; H, 5.92.

(3*S*,3a*R*,4*R*,7a*R*)-4,7-Dihydroxy-3-methylhexahydro-2*H*-furo[2,3-*c*]pyran-2-one (18). Following procedure for synthesis of compound **17**, a solution of **16** (1 mmol, 277 mg) in 15 mL of EtOAc and 10% w/w of Pd/C (27.7 mg, 25% w/w) was shaken under positive pressure of H_2 at rt overnight. Compound **10** was formed in 95% yield (178.6 mg) as a colorless oil: $[\alpha]^D_{20}$ −42.6 (*c* 0.101, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, s, 1-*H*), 4.83 (1H, d, $J = 6.7$ Hz, 2-*H*), 4.05 (1H, dd, $J = 7.1$, 14.3 Hz, 4-*H*), 4.40 (1H, dd, $J = 4.6$, 11.2 Hz, 5-*H*), 3.82 (1H, dd, $J = 4.2$, 11.2 Hz, 5-*H*), 3.71 (1H, dd, $J = 4.4$, 6.7, 12.8 Hz, 3-*H*), 2.75 (1H, m, 6-*H*), 1.26 (3H, d, $J = 7.4$ Hz, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, GASPE) δ 181.0 (*C*-7), 100.1 (*C*-1), 85.6 (*C*-2), 78.6 (*C*-4), 61.3 (*C*-5), 34.4 (*C*-3), 37.4 (*C*-6), 17.3 (6-*C*H_3).); FD-Ms *m*/*z* 189 ($M^+ + 1$). Anal. Calcd for $C_8H_{12}O_5$ (188.18): C, 51.06; H, 6.43. Found: C, 50.92; H, 6.50.

(3a*R*,4*R*,6*S*,6a*R*)-4-(Hydroxymethyl)-6-methoxytetrahydrofuro[3,4-*b*]furan-2(3*H*)-one (19). The lactol **17** (1 mmol, 174 mg) was dissolved in 10 mL of dry MeOH to which was also added a freshly prepared solution of 6% HCl (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h until TLC indicated no starting material. Workup involved neutralization with solid $NaHCO_3$, gravity filtration and evaporation under reduced pressure to yield a yellowish oily material which was purified over a short silica gel column (25% EtOAc/DCM). Colorless oil, 169 mg (90% yield): $[\alpha]^D_{20}$ −46.12 (*c* 0.600, EtOH); significant NMR NOEs are 1-H to 2-H, 42%; 2-H to 3-H, 32%; 3-H to 4-H, 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, s, 1-H), 4.82 (1H, d, $J = 6.2$ Hz, 2-H), 4.23 (1H, dd, $J = 3.5$, 7.7 Hz, 4-H), 3.86 (1H, dd, $J = 4.0$, 12.2 Hz, 5-H), 3.74 (1H, dd, $J = 4.0$, 12.2 Hz, 5-H), 3.35 (3H, s, OMe), 3.18 (1H, m, Hz, 3-H), 2.74 (1H, dd, $J = 3.1$, 18.4 Hz, 6-H), 2.56 (1H, dd, $J = 10.3$, 18.4 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$, GASPE) δ 176.2 (C-7), 105.4 (C-1), 86.4 (C-2), 78.5 (C-4), 61.2 (C-5), 54.7 (OMe), 38.5 (C-3), 29.1 (C-6); FD-MS *m*/*z* = 189 ($M^+ + 1$). Anal. Calcd for $C_8H_{12}O_5$ (188.18): C, 51.06; H, 6.43. Found: C, 51.12; H, 6.40.

(3*S*,3a*R*,4*R*,6*S*,6a*R*)-4-(Hydroxymethyl)-6-methoxy-3-methyltetrahydrofuro[3,4-*b*]furan-2(3*H*)-one (20). Methyl ketal **20** was prepared as per the procedure for **19** using lactol **18** (1 mmol, 188 mg, 10 mL of MeOH) and 6% HCl (10 mL) at 0 °C. Compound **20** was isolated in 90% yield (172 mg) as a colorless oil: $[\alpha]^D_{20}$ −35.88 (*c* 0.0171, DCM); significant NMR NOEs are 1-H to 2-H, 39%; 2-H to 3-H, 36%; 3-H to 4-H, 33%; 3-H to 6-CH_3, 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, s, 1-H), 4.75 (1H, d, $J = 6.6$ Hz, 2-H), 4.21 (1H, dd, $J = 4.7$, 10.9 Hz, 4-H), 3.83 (1H, dd, $J = 4.4$, 13.7 Hz, 5-H), 3.65 (1H, dd, $J = 4.3$, 13.7 Hz, 5-H), 3.31 (3H, s, OMe), 3.65 (1H, m, 3-H), 2.78 (1H, m, 6-H), 1.25 (3H, d, $J = 7.4$ Hz, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, GASPE) δ 179.3 (C-7), 105.8 (C-1), 85.6 (C-2), 78.9 (C-4), 61.1 (C-5), 54.8 (OMe), 47.3 (C-6), 34.7 (C-3), 17.2 (Me-6); FD-MS *m*/*z* = 203 ($M^+ + 1$). Anal. Calcd for $C_9H_{14}O_5$ (202.20): C, 53.46; H, 6.98. Found: C, 53.55; H, 6.75.

((3*S*,3a*R*,4*R*,6*S*,6a*R*)-6-Methoxy-3-methyl-2-oxohexahydrofuro[3,4-*b*]furan-4-yl)methyl-4-methylbenzenesulfonate (21). To a solution of bifuranoid **20** (1 mmol, 202 mg) in 15 mL of DCM containing 1 mL of pyridine at 0 °C was added *p*-toluenesulfonyl chloride (5 mmol, 935 mg). The mixture was maintained at 0 °C for 2 h and, then at rt for another 12 h. Ice water was added, followed by 5 mL of a saturated solution of $NaHCO_3$. The mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, and evaporated to dryness to afford a white solid. Crystallization from EtOAc/petroleum ether gave 338 mg (95%) of compound **21**: mp 83−85 °C; $[\alpha]^D_{20}$ −80.60 (*c* 0.0475, DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, d, $J = 8.3$ Hz, Ts), 7.31 (2H, d, $J = 8.3$ Hz, Ts), 4.86 (1H, s, 1-H), 4.73 (1H, d, $J = 7.4$ Hz, 2-H), 4.32 (1H, dd, $J = 6.1$, 12.2 Hz, 4-H), 4.16 (1H, dd, $J = 6.0$, 10.5 Hz, 5-H), 4.05 (1H, dd, $J = 6.6$, 10.4 Hz, 5-H), 3.25 (3H, s, OMe), 2.44(1H, ddd, $J = 7.4$, 8.3, 13.0 Hz, 3-H), 2.75 (1H, dd, $J = 7.4$, 13.0 Hz, 6-H), 2.43 (3H, s, Ts-Me), 1.21 (3H, d, $J = 7.4$ Hz, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, GASPE) δ 178.3 (C-7), 145.4, 132.1, 130.0, 127.9 (Ts), 106.6 (C-1), 84.8 (C-2), 75.2 (C-4), 67.0 (C-5), 54.9 (OMe), 47.3 (C-6), 33.7 (C-3), 21.6 (Ts-Me), 19.9 (Me-6); FD-MS *m*/*z* = 357 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{20}O_7S$ (356.39): C, 53.92; H, 5.65. Found: C, 54.13; H, 5.55.

(3*S*,3a*S*,4*R*,6*S*,6a*R*)-4-(Iodomethyl)-6-methoxy-3-methyltetrahydrofuro[3,4-*b*]furan-2(3*H*)-one (22). To a solution of tosylate **21** (1 mmol, 356 mg) in 20 mL of dry acetone was added NaI (3 mmol, 447 mg). The mixture was refluxed under argon for 5 h, allowed to reach rt, concentrated to 3 mL, and partitioned between H_2O (5 mL) and DCM (3 × 5 mL). Combined organic layers were dried over Na_2SO_4, evaporated and purified on a short silica gel column eluting with DCM. Product appeared as a yellowish oil (249.6 mg, 80% yield): $[\alpha]^D_{20}$ −44.30 (*c* 0.2113, DCM); significant NMR NOEs are 1-H to 2-H, 38%; 2-H to 3-H, 38%; 3-H to 4-H, 34%; 3-H to 6-CH_3, 39%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (1H, d, $J = 7.4$ Hz, 2-H), 4.75 (1H, s, 1-H), 4.38 (1H, ddd, $J = 5.7$, 8.9, 11.5 Hz, 4-H), 3.32 (1H, dd, $J = 6.1$, 13.3 Hz, 5-H), 3.31 (3H, s, OMe), 3.01 (1H, dd, $J = 8.9$, 13.3 Hz, 5-H), 2.86 (1H, ddd, $J = 5.7$, 7.4, 13.3 Hz, 3-H), 2.53 (1H, dd, $J = 7.4$, 13.3 Hz, 6-H), 1.35 (3H, d, $J = 7.4$ Hz, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, GASPE) δ 178.5 (C-7), 107.0 (C-1), 85.5 (C-2), 79.0 (C-4), 67.6 (C-5), 55.0 (OMe), 48.2 (C-6), 33.6 (C-3), 17.7 (Me-6); FD-MS *m*/*z* = 312 ($M^+ + 1$). Anal. Calcd for $C_9H_{13}IO_4$ (312.10): C, 34.64; H, 4.66; I, 40.66. Found: C, 34.73; H, 4.43; I, 40.32.

Acknowledgment. We thank Professor Scott McN Sieburth (Temple University) and Professor Gary Hiel (Ferris University) for their valuable comments and suggestions. We are also grateful to the College of Research and Graduate Studies at the University of Sharjah-UAE for their generous financial assistance (research grant number 52219).

Supporting Information Available: Experimental procedures and spectral data of compounds **3**−**22**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **4**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900192A