Job/Unit: O20898 /KAP1 Date: 24-09-12 17:04:34 Pages: 9

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200898

Stereoselective Synthesis of *cis*-Fused Perhydrofuro[2,3-*b*]furan Derivatives from Sugar-Derived Allyl Vinyl Ethers

Perali Ramu Sridhar,*[a] Gadi Madhusudhan Reddy,[a] and Kalapati Seshadri[a]

Keywords: Oxygen heterocycles / Carbohydrates / Cyclization / Sigmatropic rearrangement / Chiral pool

A stereoselective methodology has been developed for the construction of *cis*-fused perhydrofuro[2,3-*b*]furans, via 3-*C*-branched glycal derivatives, involving Claisen rearrangement of sugar-derived allyl vinyl ethers, followed by a one-pot ozonolysis and acid-mediated acetalization. The methodology was used for the stereoselective synthesis of the P_2 ligand in the recently FDA approved HIV protease inhibitor darunavir (Prezista). The methodology was also successfully used for the synthesis of *cis*-fused perhydro-5-oxofuro[2,3-*b*]-furan derivatives.

Introduction

Carbohydrates, the most naturally abundant molecules in the chiral pool, have played a pivotal role in the enantiospecific synthesis of many intricate biologically active molecular frameworks.[1] Fused-ring systems are an integral part of numerous natural products, and they confer a conformation on the molecules that can have consequences for their biological properties. Many linearly fused molecules, especially of marine origin, show extremely high activity against microorganisms and enzymes. In this context, several bioactive natural products contain a *cis*-fused furo[2,3-*b*]furan ring system as an essential component of their architecture. Such compounds include aflatoxin,[2] sterigmatocystin,[3] rhyacophiline,[4] clerodin,[5] and asteltoxin,[6] etc. (Figure 1).

On the other hand, the *cis*-fused perhydro-5-oxofuro[2,3-*b*]furan system is also an important structural unit present in a number of biologically active spongiane diterpenoids.[7] Such structures include norrisolide[8] (which induces irreversible vesiculation of Golgi membranes),[9] macfarlandin C,[10] spongionellin,[11] dendrillolides A and E,[12] and cheloviolenes A and B,[13] etc. (Figure 2). Surprisingly, to the best of our knowledge, the total syntheses of none of the above-named spongiane diterpenoids was reported, except for norrisolide.[14] More recently, sugar-fused γ-butyrolactones have been shown to be potential $GABA_A$ inhibitors.[15] Despite their wide occurrence, very few methods are available for the stereoselective synthesis of *cis*-fused per-

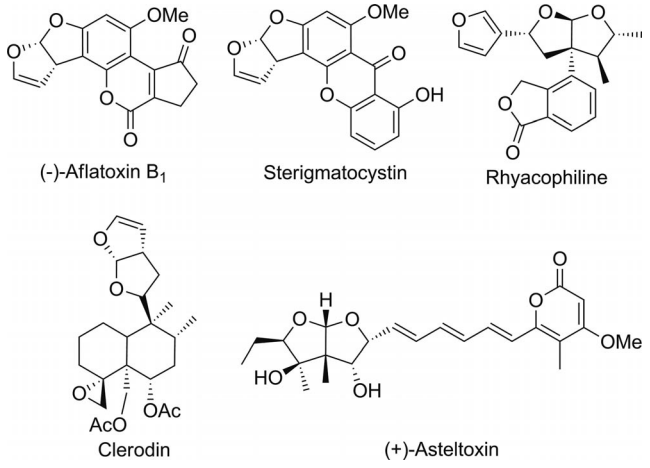


Figure 1. Natural products possessing a *cis*-fused perhydrofuro[2,3-*b*]-furan subunit.

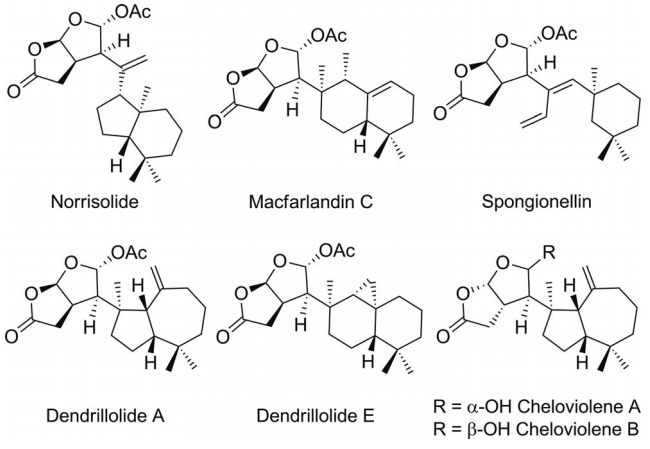


Figure 2. Natural products possessing a *cis*-fused perhydro-5-oxofuro[2,3-*b*]furan subunit.

[a] School of Chemistry, University of Hyderabad, Hyderabad 500046, India
Fax: +91-40-2301-2460
E-mail: prssc@uohyd.ernet.in
Homepage: chemistry.uohyd.ernet.in/~prs/index.htm

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200898.

hydrofuro[2,3-*b*]furan[16] and perhydro-5-oxofuro[2,3-*b*]-furan[17,14b] frameworks. As part of our continuing efforts towards the development of stereoselective methods for the construction of sugar-fused bicycles and spirocycles,[18] we report in this paper a stereoselective synthesis of carbohydrate-derived perhydrofuro[2,3-*b*]furan derivatives, starting from sugar-derived allyl vinyl ethers.

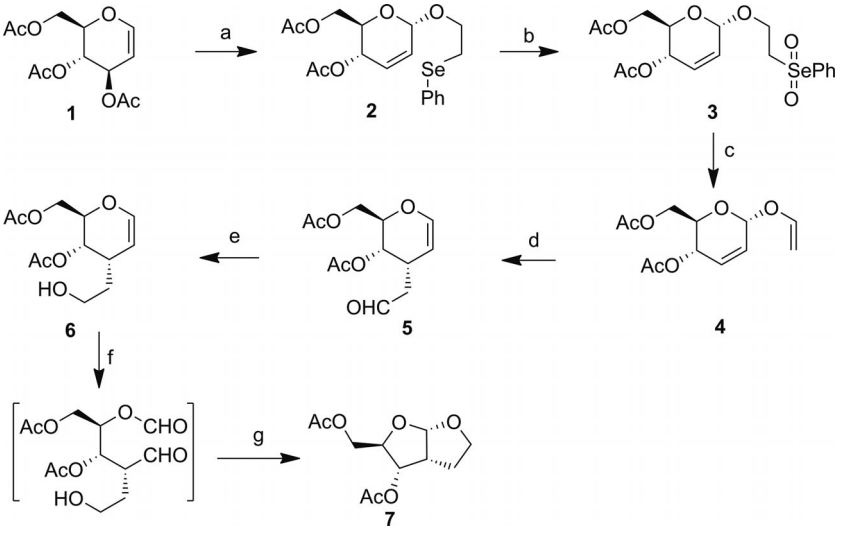
Results and Discussion

Ferrier rearrangement[19] of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with 2-(phenylselenyl)ethanol as a nucleophile provided 2,3-unsaturated glycoside **2**,[20] which, upon oxidation with $NaIO_4$, gave selenone glycoside **3**. Base-mediated thermal fragmentation of **3** provided the required allyl vinyl ether derivative **4** in good yield. Claisen [3,3]-sigmatropic rearrangement of compound **4** effected by heating in nitrobenzene/*N*,*N*-dimethylaniline provided the expected 3-*C*-branched glucal derivative (i.e., **5**). Selective reduction of the aldehyde functional group using $NaBH_4$ in ethanol at 5 °C gave alcohol **6**. Ozonolysis of the olefin in alcohol **6** to give the dialdehyde, followed by subsequent acid-mediated acetalization in one pot, provided perhydrofuro[2,3-*b*]furan derivative **7** in excellent yield, and with very high diastereoselectivity (Scheme 1). The stereochemistry at the bridgehead position was assigned by observing the characteristic coupling constant (^3J = 5.0 Hz) of an acetal hydrogen as a doublet, as well as by a NOESY experiment.

After the successful preparation of **7**, the protocol was extended to synthesize a number of perhydrofuro[2,3-*b*]-furan systems. Thus, allyl vinyl ethers **8**, **12**, **16**, and **20**, synthesized from the corresponding glycals 3,4,6-tri-*O*-acetyl-D-galactal, 3,4-di-*O*-acetyl-L-rhamnal, 3,4-di-*O*-acetyl-L-arabinal and 3,4-di-*O*-acetyl-D-arabinal, respectively,[21] upon Claisen rearrangement, provided the 3-*C*-branched aldehyde derivatives **9**, **13**, **17**, and **21**, respectively as single diastereomers in good yields. Reduction of the aldehydes to alcohols gave glycal-derived 3-*C*-branched alcohols **10**, **14**, **18**, and **22**. A one-pot ozonolysis and acid-catalyzed acetalization of these alcohols provided the perhydrofuro[2,3-*b*]furan derivatives, the so-called bis-THF moieties, **11**, **15**, **19**, and **23**, as single diastereomers (Table 1, entries 1–4). Allyl vinyl ether **24**, in which 4-OH was protected with a benzyl group, also underwent Claisen rearrangement smoothly, and provided 3-*C*-branched aldehyde derivative **25**. Reduction of aldehyde **25** to alcohol **26**, followed by ozonolysis and cyclization, provided bis-THF derivative **27** as a single diastereomer (Table 1, entry 5).

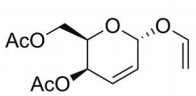
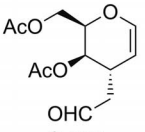
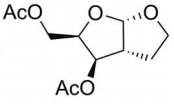
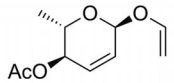
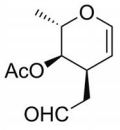
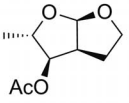
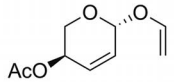
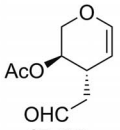
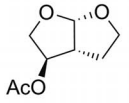
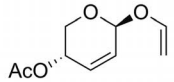
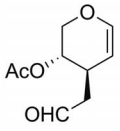
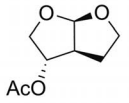
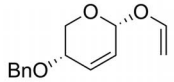
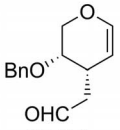
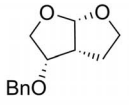
The important role played by the perhydrofuro[2,3-*b*]-furan bicyclic system as an effective P_2 ligand in HIV protease inhibitors is well documented.[22] The significance of the current methodology was further increased by synthesizing (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol **30**,[23] the important bis-THF moiety present in the HIV protease inhibitor darunavir (Prezista)[24] as well as in brecanavir.[25] Very few stereoselective synthetic methods have been reported for the preparation of bis-THF **30**. To this end, deprotection of the acetate in **23** gave alcohol **28**, which, upon Mitsunobu inversion provided compound **29**. Hydrolysis of this ester provided target molecule **30** as a single diastereomer (Scheme 2).

Furthermore, we envisaged that oxidation of aldehyde **5** to the corresponding carboxylic acid, followed by a one-pot ozonolysis and acid-mediated cyclization would provide the *cis*-fused perhydro-5-oxofuro[2,3-*b*]furan framework. Thus, aldehyde **5** was oxidized to acid **31** under Pinnick oxidation[26] conditions. Ozonolysis of compound **31** followed by cyclization in AcOH/MeOH (3:2) provided the expected perhydro-5-oxofuro[2,3-*b*]furan derivative (i.e., **32**), but in very low yield (18%). Optimized reaction conditions of catalytic *p*TsOH in CH_2Cl_2 resulted in an improvement in the yield to 48% over three steps (Scheme 3).

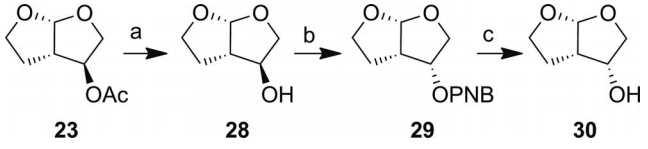


Scheme 1. Synthesis of glucal-derived *cis*-fused perhydrofuro[2,3-*b*]furan. Reagents and conditions: a) $PhSeCH_2CH_2OH$, $BF_3{\cdot}OEt_2$, benzene, 0–25 °C, 5 min, 88%; b) $NaIO_4$, $NaHCO_3$, MeOH/H_2O (6:1), 1 h; c) DIPA, benzene, reflux, 30 min, 55% over two steps; d) *N*,*N*-dimethylaniline, nitrobenzene, 160 °C, 3 h, 85%; e) $NaBH_4$, EtOH, 5 °C, 30 min, 95%; f) O_3, Me_2S, CH_2Cl_2, –78 °C; g) CH_3COOH/MeOH (3:2), reflux, 3 h, 62% over two steps (DIPA = diisopropylamine).

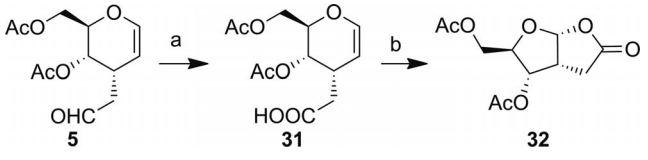
Table 1. Synthesis of *cis*-fused perhydrofuro[2,3-*b*]furan derivatives.

Entry	Vinyl ether (% yield)[a]	3-C-branched aldehyde (% yield)[a]	3-C-branched alcohol (% yield)[a]	Furo-[2,3-*b*]furan (% yield)[a]
1	 **8** (65)	 **9** (65)	**10** (92)	 **11** (65)
2	 **12** (74)	 **13** (72)	**14** (96)	 **15** (64)
3	 **16** (68)	 **17** (82)	**18** (95)	 **19** (55)
4	 **20** (73)	 **21** (80)	**22** (92)	 **23** (67)
5	 **24** (72)	 **25** (81)	**26** (91)	 **27** (58)

[a] Isolated yields after column chromatography.



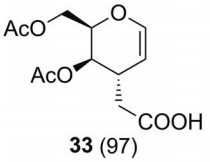
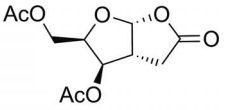
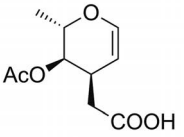
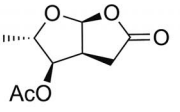
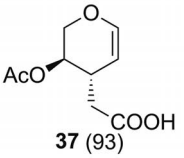
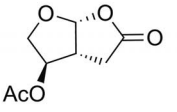
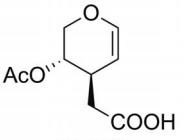
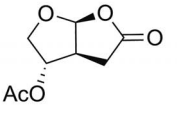
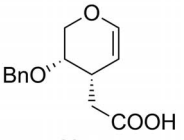
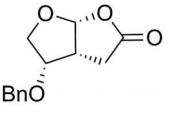
Scheme 2. Stereoselective synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol. a) K_2CO_3, MeOH room temp., 1 h, 97%; b) Ph_3P, DIAD, PNBA, THF, –10 °C to r.t., 99%; c) NaOMe, MeOH, 82%. DIAD = diisopropyl azodicarboxylate, PNBA = *p*-nitrobenzoic acid.



Scheme 3. Synthesis of glucal-derived *cis*-fused perhydro-5-oxofuro[2,3-*b*]furan. a) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, 2-methyl-2-butene, *t*BuOH, room temp., 30 min; b) (i) O_3, Me_2S, CH_2Cl_2, –78 °C. (ii) *p*TsOH, CH_2Cl_2, reflux, 10 h, 48% over three steps.

This methodology could also be used for the synthesis of several 3-*C*-branched carboxylic acids. Thus, aldehydes **9**, **13**, **17**, **21**, and **25** were oxidized to the corresponding carboxylic acids (i.e., **33**, **35**, **37**, **39**, and **41**, respectively). All the acid derivatives were converted into the corresponding *cis*-fused perhydro-5-oxofuro[2,3-*b*]furans (i.e., **34**, **36**, **38**, **40**, and **42**) with high stereoselectivity and in good yields (Table 2).

Table 2. Synthesis of *cis*-fused perhydro-5-oxofuro[2,3-*b*]furan derivatives.

Entry	3-C-branched aldehyde	3-*C*-branched acid (% yield)[a]	Furo[2,3-*b*]furan-5-one (% yield)[b]
1	**9**	 **33** (97)	 **34** (52)
2	**13**	 **35** (89)	 **36** (48)
3	**17**	 **37** (93)	 **38** (50)
4	**21**	 **39** (92)	 **40** (48)
5	**25**	 **41** (95)	 **42** (49)

[a] Yield represents crude product obtained after oxidation. [b] Yield represents pure compound isolated by column chromatography after three steps.

Conclusions

In conclusion, an efficient and stereoselective protocol for the synthesis of *cis*-fused perhydrofuro[2,3-*b*]furan derivatives was developed by implementing a Claisen rearrangement of 2,3-unsaturated vinyl glycosides and a one-pot oxidative acetalization as key steps. The generality of the reaction was investigated by synthesizing a number of bis-THF derivatives. The methodology was also successfully extended to construct several *cis*-fused perhydro-5-oxo-

furo[2,3-*b*]furan derivatives. The application of this method to the stereoselective total synthesis of natural products is in progress.

Experimental Section

General Methods: All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dichloromethane, methanol, and benzene were intially dried and stored over molecular sieves (4 Å). TLC was run on silica gel 60 F254 (Merck) plates, and the spots were detected by staining with H_2SO_4 in methanol (5%, v/v) or phosphomolybdic acid in ethanol (5%, w/v) and heating. Silica gel (100–200 mesh) was used as the stationary phase for column chromatography. NMR spectra were recorded at 25 °C with Bruker Avance III 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) or 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) instruments in $CDCl_3$, using residual $CHCl_3$ (δ_H = 7.26 ppm) as internal standard for ^{1}H, and $CDCl_3$ (δ_C = 77.0 ppm) as internal standard for ^{13}C. Chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. IR spectra were recorded with a JASCO FTIR-5300 instrument. High resolution mass spectra were recorded with a Bruker maXis ESI-TOF spectrometer. A Welsbach Ozonizer was used for all ozonolysis reactions.

General Procedure for the Oxidation and Thermal Fragmentation of 2-(Phenylselenenyl)ethyl Glycosides To Obtain Vinyl Glycosides 4, 8, 12, 16, 20 and 24: Sodium periodate (1.5 equiv.) and sodium hydrogen carbonate (1.1 equiv.) were added to a solution of a 2-(phenylselenenyl)ethyl glycoside **2** (2 mmol) in methanol/water (6:1). After complete trasformation of the starting material (1 h), the suspension was filtered through a plug of Celite 545, and the filtrate was concentrated in vacuo. The crude material was dissolved in ethyl acetate and washed with water, and the organic phase was concentrated in vacuo. The crude selenoxide thus obtained was dissolved in benzene (20 mL), diisopropylamine (5 equiv.) was added, and the mixture was heated at reflux for 30 min. After the reaction was complete, the solvent was evaporated, and the crude product was purified by column chromatography eluting with hexanes and ethyl acetate to obtain pure vinyl glycoside in good yield.

[(2*R*,3*R*,6*S*)-3-Acetoxy-6-(vinyloxy)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (8): Yield 65%. R_f = 0.70 (silica gel, 30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (dd, J = 6.8, 14.0 Hz, 1 H), 6.22 (dd, J = 5.6, 10.0 Hz, 1 H) 6.08 (dd, J = 3.2, 10.0 Hz, 1 H), 5.38 (d, J = 3.2 Hz, 1 H), 5.07 (dd, J = 2.4, 5.6 Hz, 1 H), 4.59 (dd, J = 1.2, 14.0 Hz, 1 H), 4.36–4.32 (m, 1 H), 4.23 (s, 1 H), 4.22 (dd, J = 1.6, 5.6 Hz, 1 H), 2.08 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.2, 148.8, 129.2, 126.1, 92.9, 92.2, 67.3, 62.3, 62.3, 20.7, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 3366, 2924, 1736, 1645, 1510, 1458, 1371, 1230, 1049, 829, 756 cm^{-1}. $[\alpha]_D^{25}$ = –140.8 (c = 0.5, $CHCl_3$). HRMS (ESI): calcd. for $C_{12}H_{16}O_6Na$ [M + Na]$^+$ 279.0845; found 279.0845.

(2*S*,3*R*,6*R*)-2-Methyl-6-(vinyloxy)-3,6-dihydro-2*H*-pyran-3-yl Acetate (12): Yield 74%. R_f = 0.30 (silica gel, 10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (dd, J = 6.4, 14.0 Hz, 1 H), 5.92 (d, J = 10.0 Hz, 1 H), 5.83 (td, J = 2.4, 10.4 Hz, 1 H), 5.24 (s, 1 H), 5.06 (dd, J = 1.6, 9.2 Hz, 1 H), 4.54 (dd, J = 1.6, 14.0 Hz, 1 H), 4.17 (dd, J = 1.2, 6.4 Hz, 1 H), 3.97–3.90 (m, 1 H), 2.06 (s, 3 H), 1.20 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 149.1, 130.6, 126.3, 93.4, 91.6, 70.4, 65.4, 20.9, 17.7 ppm. IR (neat): $\tilde{\nu}$ = 2982, 2934, 1743, 1641, 1375, 1236, 1101, 1033, 916, 842 cm^{-1}. $[\alpha]_D^{25}$ = –98.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{10}H_{14}O_4Na$ [M + Na]$^+$ 221.0790; found 221.0790.

(3*R*,6*R*)-6-(Vinyloxy)-3,6-dihydro-2*H*-pyran-3-yl Acetate (16) and (3*S*,6*S*)-6-(Vinyloxy)-3,6-dihydro-2*H*-pyran-3-yl Acetate (20): Yield 68% for **16** and 73% for **20**. R_f = 0.70 (silica gel, 20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (dd, J = 6.4, 14.0 Hz, 1 H), 6.15 (dd, J = 5.2, 10.0 Hz, 1 H), 6.06 (dd, J = 3.2, 10.4 Hz, 1 H), 5.30 (d, J = 3.2 Hz, 1 H), 4.96 (dd, J = 2.8, 5.2 Hz, 1 H), 4.55 (dd, J = 1.6, 14.0 Hz, 1 H), 4.19 (dd, J = 2.6, 6.8 Hz, 1 H), 4.13 (dd, J = 2.8, 13.2 Hz, 1 H), 3.87 (dd, J = 1.2, 13.2 Hz, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 149.0, 129.3, 125.7, 92.0, 91.7, 62.7, 61.6, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 3445, 2920, 1726, 1364, 1232, 1078, 739 cm^{-1}. $[\alpha]_D^{25}$ = –128.6 (c = 0.60, $CHCl_3$) for **16** and +130.4 (c = 0.67, $CHCl_3$) for **20**. HRMS (ESI): calcd. for $C_9H_{12}O_4Na$ [M + Na]$^+$ 207.0364; found 207.0364.

(3*S*,6*R*)-3-(Benzyloxy)-6-(vinyloxy)-3,6-dihydro-2*H*-pyran (24): Yield. 72%. R_f = 0.70 (silica gel, 15% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H), 6.49 (dd, J = 6.4, 14.0 Hz, 1 H), 6.18 (qd, J = 1.2, 2.8, 10.4 Hz, 1 H), 5.83 (td, J = 2.0, 10.4 Hz, 1 H), 5.23 (d, J = 0.8 Hz, 1 H), 4.66–4.54 (m, 3 H), 4.20 (dd, J = 1.2, 6.4 Hz, 1 H), 4.17–4.13 (m, 1 H), 3.87 (ddd, J = 1.2, 5.6, 10.8 Hz, 1 H), 3.79 (d, J = 9.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 137.9, 132.4, 128.4, 127.8, 127.6, 125.5, 93.2, 91.5, 71.0, 69.3, 60.9 ppm. IR (neat): $\tilde{\nu}$ = 3032, 2922, 2885, 1639, 1454, 1392, 1317, 1168, 1099, 1024, 912, 839, 734, 698 cm^{-1}. $[\alpha]_D^{25}$ = +53.0 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{16}O_3Na$ [M + Na]$^+$ 255.0997; found 255.0997.

General Procedure for the Claisen Rearrangement of Vinyl Glycosides To Obtain 3-*C*-Branched Aldehydes 5, 9, 13, 17, 21, and 25: *N*,*N*-Dimethylaniline (0.2 mL) was added to the vinyl glycoside **4**, **8**, **12**, **16**, **20** or **24** (2.4 mmol, 1 equiv.) in nitrobenzene (10 mL), and the mixture was heated at 150–170 °C until the complete consumption of starting material was observed (5–6 h). The resulting solution was directly loaded onto a silica gel column, and the product was purified eluting with hexanes and ethyl acetate to obtain the 3-*C*-branched glycal derivative in good yield.

[(2*R*,3*R*,4*S*)-3-Acetoxy-4-(2-oxoethyl)-3,4-dihydro-2*H*-pyran-2-yl]-methyl Acetate (9): Yield 65%. R_f = 0.40 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 6.41 (dd, J = 1.2, 6.0 Hz, 1 H), 4.83 (s, 1 H), 4.76–4.73 (m, 1 H), 4.21 (d, J = 6.0 Hz, 2 H), 4.08–4.05 (m, 1 H), 2.73–2.70 (m, 1 H), 2.61 (ddd, J = 1.6, 6, 17.2 Hz, 1 H), 2.51 (ddd, J = 1.2, 8.8, 17.2 Hz, 1 H), 2.08 (s, 3 H), 2.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 170.6, 170.1, 142.9, 101.1, 70.3, 68.9, 62.5, 48.8, 29.9, 20.8, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 3368, 2918, 1741, 1651, 1373, 1232, 1043 cm^{-1}. $[\alpha]_D^{25}$ = +84.6 (c = 0.3, $CHCl_3$). HRMS (ESI): calcd. for $C_{12}H_{16}O_6Na$ [M + Na]$^+$ 279.0845; found 279.0845.

(2*S*,3*R*,4*R*)-2-Methyl-4-(2-oxoethyl)-3,4-dihydro-2*H*-pyran-3-yl Acetate (13): Yield 72%. R_f = 0.40 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, J = 1.2 Hz, 1 H), 6.29 (dd, J = 2.0, 6.4 Hz, 1 H), 4.93 (t, J = 5.6 Hz, 1 H), 4.57 (dd, J = 3.6, 6.4 Hz, 1 H), 4.06 (t, J = 6.4 Hz, 1 H), 3.10–3.04 (m, 1 H), 2.62 (ddd, J = 1.6, 7.2, 17.6 Hz, 1 H), 2.44 (ddd, J = 1.6, 6.4, 17.6 Hz, 1 H), 2.03 (s, 3 H), 1.25 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 169.9, 142.5, 100.1, 70.9, 69.8, 45.2, 26.9, 20.7, 16.8 ppm. IR (neat): $\tilde{\nu}$ = 3468, 2982, 2939, 1732, 1649, 1377, 1238, 1051, 750 cm^{-1}. $[\alpha]_D^{25}$ = –130.8 (c = 2.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{10}H_{14}O_4Na$ [M + Na]$^+$ 221.0790; found 221.0790.

(3*R*,4*S*)-4-(2-Oxoethyl)-3,4-dihydro-2*H*-pyran-3-yl Acetate (17) and (3*S*,4*R*)-4-(2-Oxoethyl)-3,4-dihydro-2*H*-pyran-3-yl Acetate (21): Yield 82% for **17** and 80% for **21**. R_f = 0.50 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 6.39 (dd, J = 1.6, 6.0 Hz, 1 H), 4.80 (dd, J = 5.6, 8.0 Hz, 1 H), 4.65 (dd, J = 3.6, 6.0 Hz, 1 H), 3.96 (dd, J = 2.8, 11.2 Hz, 1 H) 3.88 (dd, J =

6.6, 11.2 Hz, 1 H), 2.80 (d, J = 2.8 Hz, 1 H), 2.60 (dd, J = 1.2, 6.0 Hz, 1 H), 2.56 (dd, J = 1.2, 6.0 Hz, 1 H), 2.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 170.1, 143.7, 100.8, 69.2, 64.0, 48.2, 30.4, 20.8 ppm. IR (neat): $\tilde{\nu}$ = 3430, 2876, 2728, 1736, 1643, 1364, 1250, 1090, 1046, 964, 926 cm^{-1}. $[\alpha]_D^{25}$ = +120 (c = 0.55, $CHCl_3$) for **17** and –116.5 (c = 0.52, $CHCl_3$) for **21**. HRMS (ESI): calcd. for $C_9H_{12}O_4Na$ [M + Na]$^+$ 207.0634; found 207.0634.

2-[(3*S*,4*S*)-3-(Benzyloxy)-3,4-Dihydro-2*H*-pyran-4-yl]acetaldehyde (25): Yield 81%. R_f = 0.60 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (t, J = 1.6 Hz, 1 H), 7.36–7.29 (m, 5 H), 6.35 (dd, J = 2.0, 6.0 Hz, 1 H), 4.63 (d, J = 12.0 Hz, 1 H), 4.59 (dd, J = 3.6, 6.0 Hz, 1 H), 4.52 (d, J = 11.6 Hz, 1 H), 3.91 (d, J = 5.2 Hz, 2 H), 3.84 (dd, J = 4.8, 10.0 Hz, 1 H), 3.09–3.04 (m, 1 H), 2.79 (ddd, J = 1.2, 7.6, 17.6 Hz, 1 H), 2.42 (ddd, J = 1.2, 6.0, 17.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 143.7, 137.7, 128.4, 127.8, 127.7, 101.56, 71.3, 71.1, 63.7, 45.2, 30.0 ppm. IR (neat): $\tilde{\nu}$ = 3481, 3414, 2926, 2883, 1720, 1647, 1454, 1242, 1091, 916, 738, 698 cm^{-1}. $[\alpha]_D^{25}$ = +53.0 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{16}O_3Na$ [M + Na]$^+$ 255.0997; found 255.0997.

General Procedure for the Reduction of the Aldehyde Functionality To Obtain Alcohols 6, 10, 14, 18, 22 and 26: $NaBH_4$ (1.45 mmol, 1.2 equiv.) was added to a solution of aldehyde **5**, **9**, **13**, **17**, **21** or **25** (1.20 mmol, 1 equiv.) in absolute ethanol (5 mL) at 0–5 °C, and the mixture was stirred for 15 min. After complete disappearance of the starting material, the reaction was quenched by adding aqueous NH_4Cl (1 mL), and the mixure was filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography over silica gel eluting with hexanes and ethyl acetate to obtain the alcohol in excellent yield.

[(2*R*,3*S*,4*S*)-3-Acetoxy-4-(2-hydroxyethyl)-3,4-dihydro-2*H*-pyran-2-yl]methyl Acetate (6): Yield 95%. R_f = 0.25 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (dd, J = 2.0, 6.0 Hz, 1 H), 5.07 (t, J = 6.0 Hz, 1 H), 4.66 (dd, J = 4.0, 6.0 Hz, 1 H), 4.26–4.22 (m, 1 H), 4.17–4.11 (m, 2 H), 3.69–3.62 (m, 2 H), 2.61–2.58 (m, 1 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.75–1.66 (m, 1 H), 1.51–1.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.1, 141.5, 101.5, 71.7, 67.5, 62.4, 59.8, 33.3, 28.8, 20.7, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 3449, 2947, 1743, 1649, 1437, 1373, 1234, 1045, 738 cm^{-1}. $[\alpha]_D^{25}$ = +137.3 (c = 0.67, $CHCl_3$). HRMS (ESI): calcd. for $C_{12}H_{18}O_6Na$ [M + Na]$^+$ 281.1001; found 281.1001.

[(2*R*,3*R*,4*S*)-3-Acetoxy-4-(2-hydroxyethyl)-3,4-dihydro-2*H*-pyran-2-yl]methyl Acetate (10): Yield 92%. R_f = 0.25 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (d, J = 6.0 Hz, 1 H), 4.88 (s, 1 H), 4.72 (t, J = 6.0 Hz, 1 H), 4.20 (d, J = 2.0 Hz, 1 H), 4.18, (s, 1 H), 4.02 (t, J = 6.0 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.72–3.67 (m, 1 H), 2.60 (s, 1 H), 2.27 (br. d, J = 5.2 Hz, 1 H), 2.06 (s, 6 H), 1.61 (q, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.6, 142.4, 102.4, 69.9, 69.5, 63.1, 59.4, 37.7' 32.6, 20.9, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 3447, 2926, 1739, 1651, 1373, 1232, 1041, 754 cm^{-1}. $[\alpha]_D^{25}$ = +60.0 (c = 0.31, $CHCl_3$). HRMS (ESI): calcd. for $C_{12}H_{18}O_6Na$ [M + Na]$^+$ 281.1001; found 281.1001.

(2*S*,3*R*,4*R*)-4-(2-Hydroxyethyl)-2-methyl-3,4-dihydro-2*H*-pyran-3-yl Acetate (14): Yield 96%. R_f = 0.30 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (dd, J = 1.6, 6.4 Hz, 1 H), 4.84 (t, J = 4.8 Hz, 1 H), 4.54–4.51 (m, 1 H), 4.10–4.04 (m, 1 H), 3.65–3.60 (m, 2 H), 2.75 (s, 1 H), 2.83 (dd, J = 2.8, 4.8 Hz, 1 H), 2.03 (s, 3 H), 1.69–1.61 (m, 1 H), 1.50–1.43 (m, 1 H), 1.20 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 141.3, 100.6, 71.3, 70.3, 59.8, 33.2, 27.8, 20.8, 16.9 ppm. IR (neat): $\tilde{\nu}$ = 3449, 2939, 2885, 1734, 1649, 1439, 1377, 1238, 1138, 1049, 815, 736 cm^{-1}. $[\alpha]_D^{25}$ = –98.7 (c = 2.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{10}H_{16}O_4Na$ [M + Na]$^+$ 223.0947; found 223.0947.

(3*R*,4*S*)-4-(2-Hydroxyethyl)-3,4-dihydro-2*H*-pyran-3-yl Acetate (18) and (3*S*,4*R*)-4-(2-Hydroxyethyl)-3,4-dihydro-2*H*-pyran-3-yl Acetate (22): Yield 95% for **18** and 92% for **22**. R_f = 0.5 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, J = 6.4 Hz, 1 H), 4.79 (s, 1 H), 4.65 (t, J = 4.8 Hz, 1 H), 3.90 (dd, J = 4.0, 11.6 Hz, 1 H), 3.84 (d, J = 11.2 Hz, 1 H), 3.73–3.61 (m, 2 H), 2.76 (s, 1 H), 2.23 (s, 1 H), 2.02 (s, 3 H), 1.61–1.46 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 142.9, 102.0, 69.9, 63.5, 59.3, 37.5, 32.0, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 3398, 2924, 1736, 1649, 1373, 1240, 1043 cm^{-1}. $[\alpha]_D^{25}$ = +113.2 (c = 0.68, $CHCl_3$) for **18** and –111.5 (c = 0.65, $CHCl_3$) for **22**. HRMS (ESI): calcd. for $C_9H_{14}O_4Na$ [M + Na]$^+$ 209.0790; found 209.0790.

2-[(3*S*,4*S*)-3-(Benzyloxy)-3,4-dihydro-2*H*-pyran-4-yl]ethanol (26): Yield 91%. R_f = 0.40 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 6.32 (dd, J = 2.0, 6.0 Hz, 1 H), 4.70 (d, J = 11.6 Hz, 1 H), 4.62 (dd, J = 4.0, 6.0 Hz, 1 H), 4.58 (d, J = 12.0 Hz, 1 H), 4.00 (dd, J = 6.8, 11.2 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.80–3.76 (m, 1 H), 3.72–3.62 (m, 2 H), 2.61–2.58 (m, 1 H), 1.99 (s, 1 H), 1.95–1.86 (m, 1 H), 1.62–1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 137.8, 128.4, 127.7, 102.2, 72.0, 70.9, 63.8, 60.6, 33.9, 32.1 ppm. IR (neat): $\tilde{\nu}$ = 3408, 2928, 2878, 1647, 1454, 1240, 1089, 1028, 738, 698 cm^{-1}. $[\alpha]_D^{25}$ = +41.0 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{18}O_3Na$ [M + Na]$^+$ 257.1154; found 257.1154.

General Procedure for the One-Pot Ozonolysis and Acid-Mediated Acetalization of Alcohols To Obtain *cis*-Fused Perhydrofuro[2,3,*b*]furan Derivatives 7, 11, 15, 19, 23 and 27: CH_2Cl_2 (20 mL) was added to the alcohol **6**, **10**, **14**, **18**, **22** or **26** (0.46 mmol) in a two-necked round-bottomed flask with a gas outlet on one neck and a gas inlet on the other neck. The solution was cooled to –78 °C using an EtOAc/liquid nitrogen bath. Ozone was bubbled through the gas inlet into the solution until the pale blue color persisted. Then, oxygen followed by nitrogen were passed through the inlet until the pale blue color disappeared. Dimethyl sulfide (0.5 mL) was added to the reaction mixture at –78 °C, which was then allowed to warm to 25 °C. The solvent was evaporated in vacuo to obtain the crude formate ester, which was used in the next step without purification.

The crude formate ester was dissolved in AcOH/MeOH (3:2, 5 mL) and heated at reflux for 3 h. After complete consumption of the starting material, the solvent was evaporated in vacuo and the crude residue was partitioned between diethyl ether and aqueous $NaHCO_3$. The organic phase was washed with H_2O and dried with anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography wluting with hexanes and ethyl acetate gave the *cis*-fused perhydrofuro[2,3-*b*]furan derivative in good yield over two steps.

[(2*R*,3*S*,3a*R*,6a*S*)-3-Acetoxyperhydrofuro[2,3-*b*]furan-2-yl]methyl Acetate (7): Yield 62%. R_f = 0.70 (50% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (d, J = 5.0 Hz, 1 H), 4.98 (t, J = 8.0 Hz, 1 H), 4.29 (dd, J = 3.0, 12.0 Hz, 1 H), 4.16–4.12 (m, 1 H), 4.07 (dd, J = 5.5, 12.0 Hz, 1 H), 3.99 (dt, J = 3.5, 8.5 Hz, 1 H), 3.93 (dt, J = 6.5, 9.5 Hz, 1 H), 3.21–3.16 (m, 1 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 1.98–1.93 (m, 1 H), 1.91–1.83 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.0, 108.6, 78.9, 73.3, 69.2, 63.5, 44.8, 25.5, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 2957, 2924, 1739, 1452, 1371, 1228, 1039, 927 cm^{-1}. $[\alpha]_D^{25}$ = +78.0 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{11}H_{16}O_6Na$ [M + Na]$^+$ 267.0845; found 267.0845.

[(2*R*,3*R*,3a*R*,6a*S*)-3-Acetoxyperhydrofuro[2,3-*b*]furan-2-yl]methyl Acetate (11): Yield 65%. R_f = 0.70 (50% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (d, J = 5.0 Hz, 1 H), 5.11 (d, J = 3.5 Hz, 1 H), 4.32–4.29 (m, 1 H) 4.21 (dd, J = 4.5, 11.5 Hz, 1 H), 4.12 (dd, J = 7.5, 12.0 Hz, 1 H), 3.90–3.81 (m, 2 H) 2.81–2.77

(m, 1 H), 2.21–2.13 (m, 1 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.85–1.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.0, 108.3, 78.7, 78.3, 67.7, 62.2, 50.0, 28.6, 20.7, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 2968, 2885, 1741, 1452, 1373, 1232, 1045, 931 cm^{-1}. $[\alpha]_D^{25}$ = +11.1 (c = 2.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{11}H_{16}O_6Na$ [M + Na]$^+$ 267.0845; found 267.0845.

(2*S*,3*R*,3a*S*,6a*R*)-2-Methyl-perhydrofuro[2,3-*b*]furan-3-yl Acetate (15): Yield 64%. R_f = 0.50 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69 (d, J = 5.2 Hz, 1 H), 4.67 (t, J = 8.4 Hz, 1 H), 4.00–3.86 (m, 3 H), 3.19–3.13 (m, 1 H), 2.09 (s, 3 H), 1.95–1.88 (m, 1 H), 1.86–1.78 (m, 1 H), 1.25 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 107.8, 78.3, 76.5, 69.3, 44.8, 25.4, 20.7, 18.3 ppm. IR (neat): $\tilde{\nu}$ = 3414, 2978, 1741, 1616, 1375, 1236, 1043, 937 cm^{-1}. $[\alpha]_D^{25}$ = –94.7 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_9H_{14}O_4Na$ [M + Na]$^+$ 209.0790; found 209.0790.

(3*R*,3a*R*,6a*S*)-Perhydrofuro[2,3-*b*]furan-3-yl Acetate (19) and (3*S*,3a*S*,6a*R*)-Perhydrofuro[2,3-*b*]furan-3-yl Acetate (23): Yield 55% for **19** and 67% for **23**. R_f: 0.45 (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80 (d, J = 5.0 Hz, 1 H), 5.01 (d, J = 3.5 Hz, 1 H), 4.01 (dd, J = 4.0, 11.0 Hz, 1 H), 3.91 (dd, J = 11.0, 15.0 Hz, 1 H), 3.87 (dd, J = 5.0, 8.5 Hz, 1 H), 3.82–3.77 (m, 1 H), 2.83 (q, J = 4.0, 9.5 Hz, 1 H), 2.20–2.11 (m, 1 H), 2.02 (s, 3 H), 1.83–1.77 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 108.7, 79.6, 72.5, 67.7, 49.0, 28.9, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 3449, 2926, 1739, 1371, 1240, 1018, 979 cm^{-1}. $[\alpha]_D^{25}$ = +44.5 (c = 1.0, $CHCl_3$) for **19** and –45.3 (c = 1.0, $CHCl_3$) for **23**. HRMS (ESI): calcd. for $C_8H_{12}O_4Na$ [M + Na]$^+$ 195.0634; found 195.0634.

(3*S*,3a*R*,6a*S*)-3-(Benzyloxy)-perhydrofuro[2,3-*b*]furan (27): Yield 58%. R_f = 0.60 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5 H), 5.71 (d, J = 5.2 Hz, 1 H), 4.57 (q, J = 11.6 Hz, 2 H), 4.21 (dd, J = 8.0, 15.2 Hz, 1 H), 4.00–3.89 (m, 3 H), 3.66 (t, J = 8.4 Hz, 1 H), 2.95–2.89 (m, 1 H), 2.36–2.30 (m, 1 H), 1.91–1.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 128.4, 127.8, 127.5, 109.2, 77.8, 72.1, 70.5, 69.6, 44.6, 24.8 ppm. IR (neat): $\tilde{\nu}$ = 3449, 2955, 2879, 1722, 1454, 1099, 1024, 923, 698 cm^{-1}. $[\alpha]_D^{25}$ = +40.2 (c = 2.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{13}H_{16}O_3Na$ [M + Na]$^+$ 243.0997; found 243.0997.

General Procedure for the One-Pot Oxidation to Obtain 31, 33, 35, 37, 39 and 41, Ozonolysis and Acid-Mediated Cyclization of Aldehydes To Obtain Perhydro-5-oxofuro[2,3-*b*]furan Derivatives 32, 34, 36, 38, 40 and 42: Aqueous NaH_2PO_4 (3.4 mL, 2.7 mmol, 5 equiv.) and aqueous $NaClO_2$ (3.4 mL, 1.65 mmol, 3 equiv.) were added to a vigorously stirred solution of aldehyde **5**, **9**, **13**, **17**, **21** or **25** (0.55 mmol, 1 equiv.) and 2-methyl-2-butene (6.15 mmol, 11 equiv.) in *t*BuOH (7.16 mL) at 30 °C, and the mixture was stirred for 30 min at room temp. After complete consumption of starting material was observed, aqueous NaCl (10 mL) was added, and the solvent was removed by freeze drying. The resulting solid residue was dissolved in MeOH (25 mL) and filtered through Celite 545. The filtrate was concentrated in vacuo. Thus crude residue was dissolved in EtOAc (25 mL) and filtered through Celite 545. The filtrate was concentrated in vacuo to obtain the pure acid derivative, which was used without further treatment in the next step.

CH_2Cl_2 (20 mL) was added to the acid derivative (0.50 mmol) in a two-necked round-bottomed flask with a gas outlet on one neck and a gas inlet on the other neck. The solution was cooled to –78 °C using a EtOAc/liquid nitrogen bath. Ozone was bubbled through the gas inlet into the solution until the pale blue color persisted. Then, oxygen followed by nitrogen were passed through the inlet until the pale blue color disappeared. Dimethyl sulfide (0.5 mL) was added to the reaction mixture at –78 °C, and the mixture was allowed to warm to 25 °C. The solvent was evaporated in vacuo to obtain the crude formate ester, which was used in the next step without purification.

p-Toluenesulfonic acid (0.3 equiv.) was added to the crude formate ester in dry CH_2Cl_2 (10 mL), and the mixture was heated at reflux for 10 h. After complete consumption of the starting material was observed, the solvent was evaporated in vacuo and the residue was dissolved in diethyl ether. The solution was washed with aqueous $NaHCO_3$ and H_2O, and then dried with anhydrous Na_2SO_4. The solvent was removed using a rotary evaporator, and the residue was purified by column chromatography eluting with hexanes and ethyl acetate to give the fused perhydro-5-oxofuro[2,3-*b*]furan derivative in good yield over three steps.

2-[(2*R*,3*S*,4*S*)-3-Acetoxy-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (31): Yield 97% (crude). R_f = 0.40 (1% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (s, 1 H), 6.32 (d, J = 6.0 Hz, 1 H), 5.18 (t, J = 5.6 Hz, 1 H), 4.68 (t, J = 4.4 Hz, 1 H), 4.68 (t, J = 4.4 Hz, 1 H), 4.31 (dd, J = 5.6, 11.6 Hz, 1 H), 4.17–4.07 (m, 2 H), 2.9 (s, 1 H), 2.5 (dd, J = 7.6, 16.4 Hz, 1 H), 2.05 (s, 3 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 170.8, 169.7, 142.6, 100.8, 71.1, 66.6, 62.1, 35.7, 29.3, 20.6, 20.5 ppm. IR (neat): $\tilde{\nu}$ = 3292, 2926, 1741, 1651, 1375, 1099, 1099, 1039, 760 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}O_7Na$ [M + Na]$^+$ 295.0794; found 295.0794.

2-[(2*R*,3*R*,4*S*)-3-Acetoxy-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (33): Yield 97% (crude). R_f = 0.40 (1% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 6.40 (d, J = 6.0 Hz, 1 H), 4.91 (s, 1 H), 4.77 (t, J = 4.4 Hz, 1 H), 4.18 (d, J = 6.0 Hz, 2 H), 4.10–4.03 (m, 1 H), 2.56 (s, 1 H), 2.48 (dd, J = 6.8, 15.6 Hz, 1 H), 2.34 (dd, J = 8.4, 15.6 Hz, 1 H), 2.05 (s, 3 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 170.8, 169.8, 142.6, 100.9, 71.1, 66.7, 62.1, 35.7, 29.3, 20.6, 20.5 ppm. IR (neat): $\tilde{\nu}$ = 3553, 2926, 1742, 1375, 1227, 1095, 1041, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}O_7Na$ [M + Na]$^+$ 295.0794; found 295.0794.

2-[(2*S*,3*R*,4*R*)-3-Acetoxy-2-methyl-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (35): Yield 89% (crude). R_f = 0.35 (1% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1 H), 6.29 (dd, J = 2.0, 6.0 Hz, 1 H), 4.97 (t, J = 5.6 Hz, 1 H), 4.59 (dd, J = 3.2, 6.0 Hz, 1 H), 4.12–4.04 (m, 1 H), 2.98–2.93 (m, 1 H), 2.50 (dd, J = 7.6, 16.4 Hz, 1 H), 2.37 (dd, J = 7.2, 16.4 Hz, 1 H), 2.05 (s, 3 H), 1.25 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 170.4, 142.4, 100.1, 70.8, 69.9, 35.6, 28.6, 20.7, 16.8 ppm. IR (neat): $\tilde{\nu}$ = 3470, 2924, 1732, 1376, 1230, 1041, 980, 735 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}O_5Na$ [M + Na]$^+$ 237.0739; found 237.0739.

2-[(3*R*,4*S*)-3-Acetoxy-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (37) and 2-[(3*S*,4*R*)-3-Acetoxy-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (39): Yield 93% (crude). R_f = 0.40 (1% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 6.39 (d, J = 6.0 Hz, 1 H), 4.85 (s, 1 H), 4.71 (dd, J = 3.6, 5.2 Hz, 1 H), 3.94–3.87 (m, 2 H), 2.65 (s, 1 H), 2.50 (dd, J = 6.4, 15.6 Hz, 1 H), 2.35 (dd, J = 8.0, 15.6 Hz, 1 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 170.6, 143.9, 100.8, 69.25, 63.9, 38.9, 32.4, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 2924, 1734, 1707, 1648, 1375, 1231, 1043, 928, 874 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{12}O_5Na$ [M + Na]$^+$ 223.0583; found 223.0583.

2-[(3*S*,4*S*)-3-(Benzyloxy)-3,4-dihydro-2*H*-pyran-4-yl]acetic Acid (41): Yield 95% (crude). R_f = 0.70 (1% MeOH in EtOAc): IR (neat): $\tilde{\nu}$ = 3412, 2928, 1732, 1454, 1051, 740, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{16}O_4Na$ [M + Na]$^+$ 271.0947; found 271.0947.

[(2*R*,3*S*,3a*R*,6a*R*)-3-Acetoxy-5-oxo-perhydrofuro[2,3-*b*]furan-2-yl]-methyl Acetate (32): Yield 48%. R_f = 0.60 (50% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.1 (d, J = 5.2 Hz, 1 H), 5.09 (dd, J = 6.4, 8.4 Hz, 1 H), 4.37 (dd, J = 3.2, 12.0 Hz, 1 H), 4.30–4.27 (m, 1 H), 4.19 (dd, J = 4.4, 12 Hz, 1 H), 3.47–3.40 (m, 1 H), 2.65 (s, 1 H), 2.63 (d, J = 0.8 Hz, 1 H), 2.13 (s, 3 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 170.4, 69.9, 106.8, 80.0, 72.0, 62.5, 41.3, 28.7, 20.7, 20.5 ppm. IR (neat): $\tilde{\nu}$ = 3470, 2961, 2928, 1786, 1739, 1425, 1371, 1228, 1024, 798 cm^{-1}. $[\alpha]_D^{25}$ = +41.4 (c = 0.84, $CHCl_3$). HRMS (ESI): calcd. for $C_{11}H_{14}O_7Na$ [M + Na]$^+$ 281.0368; found 281.0368.

[(2*R*,3*R*,3a*R*,6a*R*)-3-Acetoxy-5-oxo-perhydrofuro[2,3-*b*]furan-2-yl]-methyl Acetate (34): Yield 52%. R_f = 0.60 (50% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.20 (d, J = 4.8 Hz, 1 H), 5.09 (d, J = 2.4 Hz, 1 H), 4.40 (dd, J = 3.2, 6.4 Hz, 1 H), 4.36 (dd, J = 4.0, 12.0 Hz, 1 H), 4.26 (dd, J = 7.2, 11.6 Hz, 1 H), 3.15 (t, J = 6.0 Hz, 1 H), 2.99 (dd, J = 11.6, 19.2 Hz, 1 H), 2.61 (dd, J = 3.6, 18.8 Hz, 1 H), 2.10 (s, 3 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 170.5, 169.9, 106.4, 77.9, 77.4, 61.1, 46.3, 31.4, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 3439, 2926, 1788, 1741, 1236, 1043 cm^{-1}. $[\alpha]_D^{25}$ = +1.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{11}H_{14}O_7Na$ [M + Na]$^+$ 281.0368; found 281.0368.

(2*S*,3*R*,3a*S*,6a*S*)-2-Methyl-5-oxo-perhydrofuro[2,3-*b*]furan-3-yl Acetate (36): Yield 48%. R_f = 0.45 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (d, J = 5.6 Hz, 1 H), 4.74 (t, J = 8.4 Hz, 1 H), 4.12 (dd, J = 6.4, 7.6 Hz, 1 H), 3.49–3.42 (m, 1 H), 2.61 (dd, J = 3.6, 4.8 Hz, 2 H), 2.13 (s, 3 H), 1.36 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.0, 106.2, 76.4, 40.7, 28.2, 20.5, 17.4 ppm. IR (neat): $\tilde{\nu}$ = 2982, 2935, 1786, 1743, 1379, 1238, 1126, 1087, 974 cm^{-1}. $[\alpha]_D^{25}$ = –80.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_9H_{12}O_5Na$ [M + Na]$^+$ 223.0583; found 223.0583.

(3*R*,3a*R*,6a*R*)-5-Oxohexahydrofuro[2,3-*b*]furan-3-yl Acetate (38) and (3*S*,3a*S*,6a*S*)-5-Oxo-perhydrofuro[2,3-*b*]furan-3-yl Acetate (40): Yield 50%. R_f = 0.55 (50% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.20 (d, J = 5.5 Hz, 1 H), 5.01 (d, J = 3.0 Hz, 1 H), 4.13 (dd, J = 0.5, 12.0 Hz, 1 H), 4.07 (dd, J = 3.5, 11.5 Hz, 1 H), 3.17–3.12 (m, 1 H), 2.97 (dd, J = 11.5, 19.0 Hz, 1 H), 2.57 (dd, J = 4.5, 19.5 Hz, 1 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 170.3, 107.3, 78.7, 71.0, 45.5, 31.6, 20.8 ppm. IR (neat): $\tilde{\nu}$ = 3456, 2922, 1784, 1736, 1365, 1242, 1176, 1093, 974 cm^{-1}. $[\alpha]_D^{25}$ = + and –21.1 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_8H_{10}O_5Na$ [M + Na]$^+$ 209.0426; found 209.0426.

(3a*R*,4*S*,6a*R*)-4-(Benzyloxy)-perhydrofuro[2,3-*b*]furan-2(6aH)-one (42): Yield 49%. R_f = 0.50 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 6.00 (d, J = 5.6 Hz, 1 H), 4.55 (q, J = 12.0 Hz, 2 H), 4.22 (dd, J = 8.0, 14.4 Hz, 1 H), 4.10 (dd, J = 6.4, 9.2 Hz, 1 H), 3.73 (t, J = 9.2 Hz, 1 H), 3.17–3.12 (m, 1 H), 3.05 (dd, J = 3.6, 18.4 Hz, 1 H), 2.54 (dd, J = 10.4, 18.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 136.9, 128.6, 128.2, 127.7, 107.3, 76.2, 69.4, 40.8, 27.7 ppm. IR (neat): $\tilde{\nu}$ = 3479, 3414, 2924, 1784, 1616, 1456, 1116, 738 cm^{-1}. $[\alpha]_D^{25}$ = +13.5 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd. for $C_{13}H_{14}O_4Na$ [M + Na]$^+$ 257.0790; found 257.0790.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H, ^{13}C, and DEPT NMR spectra of all compounds, and 2D ^{1}H–^{1}H COSY ^{1}H–^{1}H NOESY spectra of all bicyclic compounds.

Acknowledgments

This work was supported by Council of Scientific and Industrial Research (CSIR), New Delhi (grant number 01(2408)/10/EMR-II). G. M. R. and K. S. gratefully acknowledge the CSIR for senior research fellowships.

[1] a) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624–1672; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576–1624; b) G.-J. Boons, K. J. Hale, *Organic Synthesis with Carbohydrates*, Sheffield Academic Press Ltd., England, **2000**, part B, p. 175–333.
[2] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.
[3] E. Bullock, J. C. Roberts, J. G. Underwood, *J. Chem. Soc.* **1962**, 4179–4183.
[4] M. C. Fernandez, B. Esquivel, J. Cardenas, A. A. Sanchez, R. A. Toscano, L. Rodriguez-Hahn, *Tetrahedron* **1991**, *47*, 7199–7208.
[5] A. T. Merritt, S. V. Ley, *Nat. Prod. Rep. Lett.* **1992**, 243–287.
[6] a) S. L. Schreiber, K. Satake, *J. Am. Chem. Soc.* **1984**, *106*, 4186–4188; b) S. L. Schreiber, K. Satake, *Tetrahedron Lett.* **1986**, *27*, 2575–2578.
[7] M. A. González, *Curr. Bioact. Compd.* **2007**, *3*, 1–36.
[8] J. E. Hochlowski, D. J. Faulkner, G. K. Matsumoto, J. Clardy, *J. Org. Chem.* **1983**, *48*, 1141–1142.
[9] T. P. Brady, E. K. Wallace, S. H. Kim, G. Guizzunti, V. Malhotra, E. A. Theodorakis, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5035–5039.
[10] a) T. F. Molinski, D. J. Faulkner, *J. Org. Chem.* **1986**, *51*, 2601–2603; b) T. F. Molinski, D. J. Faulkner, H. Cun-Heng, G. D. Van Duyne, J. Clardy, *J. Org. Chem.* **1986**, *51*, 4564–4567.
[11] L. Mayol, V. Piccialli, D. Sica, *Tetrahedron* **1986**, *42*, 5369–5376.
[12] a) B. Sullivan, D. J. Faulkner, *J. Org. Chem.* **1984**, *49*, 3204–3206; b) S. C. Bobzin, D. J. Faulkner, *J. Org. Chem.* **1989**, *54*, 3902–3907.
[13] P. R. Bergquist, B. F. Bowden, R. C. Cambie, P. A. Craw, P. Karuso, A. Poiner, W. C. Taylor, *Aust. J. Chem.* **1993**, *46*, 623–632.
[14] a) T. P. Brady, S. H. Kim, K. Wen, C. Kim, E. A. Theodorakis, *Chem. Eur. J.* **2005**, *11*, 7175–7190; b) K. Granger, M. L. Snapper, *Eur. J. Org. Chem.* **2012**, 2308–2311.
[15] A. C. Araújo, F. Nicotra, B. Costa, G. Giagnoni, L. Cipolla, *Carbohydr. Res.* **2008**, *343*, 1840–1848.
[16] For the use of radical cyclization, see: a) S. Mayer, J. Prandi, T. Bamhaoud, S. Bakkas, O. Guillou, *Tetrahedron* **1998**, *54*, 8753–8770; b) T. Harrison, G. Pattenden, P. L. Myers, *Tetrahedron Lett.* **1988**, *29*, 3869–3872; c) M.-C. Lamas, S. E. Vaillard, B. Wibbeling, A. Studer, *Org. Lett.* **2010**, *12*, 2072–2075; Cycloaddition: d) D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem.* **1998**, *110*, 3553–3557; *Angew. Chem. Int. Ed.* **1998**, *37*, 3372–3375; e) W. Zhuang, J. Thorhauge, K. A. Jørgensen, *Chem. Commun.* **2000**, 459–460; f) Y. Sugita, K. Kawai, I. Yokoe, *Heterocycles* **2001**, *55*, 135–144; for acid-catalyzed cyclization, see: g) Y. Suzuki, R. Nishimaki, M. Ishikawa, T. Murata, K.-I. Takao, K.-I. Tadano, *J. Org. Chem.* **2000**, *65*, 8595–8607; h) P. J. L. M. Quaedflieg, B. R. R. Kesteleyn, P. B. T. P. Wigerinck, N. M. F. Goyvaerts, R. J. Vijn, C. S. M. Liebregts, J. H. M. H. Kooistra, C. Cusan, *Org. Lett.* **2005**, *7*, 5917–5920; i) F. Alonso, E. Lorenzo, J. Meléndez, M. Yus, *Tetrahedron* **2003**, *59*, 5199–5208; for donor-acceptor cyclopropanes, see: j) T. F. Schneider, J. Kaschel, B. Dittrich, D. B. Werz, *Org. Lett.* **2009**, *11*, 2317–2320; k) S. D. Haveli, P. R. Sridhar, P. Suguna, S. Chandrasekaran, *Org. Lett.* **2007**, *9*, 1331–1334; l) C. Su, X. Huang, *Adv. Synth. Catal.* **2009**, *351*, 135–140; for a Walker-type reaction, see: m) F. Alonso, D. Sánchez, M. Yus, *Adv. Synth. Catal.* **2008**, *350*, 2118–2126.
[17] a) E. J. Corey, W. G. Su, *J. Am. Chem. Soc.* **1987**, *109*, 7534–7536; b) R. Petit, R. Furstoss, *Synthesis* **1995**, 1517–1520; c) E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617; d) R. Weisser, W. Yue, O. Reiser, *Org. Lett.* **2005**, *7*, 5353–5356; e) C. Kim, R. Hoang, E. A. Theodorakis, *Org. Lett.* **1999**, *1*, 1295–1297; f) C. Kim, T. Brady, S. H. Kim, E. A. The-

odorakis, *Synth. Commun.* **2004**, *34*, 1951–1965; g) T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis, *Angew. Chem.* **2004**, *116*, 757–760; *Angew. Chem. Int. Ed.* **2004**, *43*, 739–742; h) M. J. Schnermann, C. M. Beaudry, N. E. Genung, S. M. Canham, N. L. Untiedt, B. D. W. Karanikolas, C. Sütterlin, L. E. Overman, *J. Am. Chem. Soc.* **2011**, *133*, 17494–17503; i) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.

[18] a) P. R. Sridhar, K. Seshadri, G. M. Reddy, *Chem. Commun.* **2012**, *48*, 756–758; b) S. D. Haveli, P. R. Sridhar, P. Suguna, S. Chandrasekaran, *Org. Lett.* **2007**, *9*, 1331–1334.

[19] a) A. de Raadt, R. J. Ferrier, *Carbohydr. Res.* **1991**, *216*, 93–107; b) R. J. Ferrier, *Top. Curr. Chem.* **2001**, *215*, 153–175.

[20] P. Rollin, V. V. Bencomo, P. Sinaÿ, *Synthesis* **1984**, 134–135.

[21] The major diastereomer obtained after Ferrier rearrangement was converted further into the allyl vinyl ether.

[22] A. K. Ghosh, P. R. Sridhar, N. Kumaragurubaran, Y. Koh, I. T. Weber, H. Mitsuya, *ChemMedChem* **2006**, *1*, 939–950.

[23] a) M. Pezechk, A. P. Brunetiere, J. Y. Lallemand, *Tetrahedron Lett.* **1986**, *27*, 3715–3718; b) A. K. Ghosh, Y. Chen, *Tetrahedron Lett.* **1995**, *36*, 505–508; c) M. Uchiyama, M. Hirai, M. Nagata, R. Kotoh, R. Ogawa, A. Ohta, *Tetrahedron Lett.* **2001**, *42*, 4653–4656; d) A. K. Ghosh, S. Leshchenko, M. Noetzel, *J. Org. Chem.* **2004**, *69*, 7822–7829; e) A. K. Ghosh, J. Li, P. R. Sridhar, *Synthesis* **2006**, *18*, 3015–3018; f) R. H. Yu, P. R. Polniaszek, M. W. Becker, C. M. Cook, L. H. L. Yu, *Org. Process Res. Dev.* **2007**, *11*, 972–980; g) M. G. Kulkarni, Y. B. Shaikh, A. S. Borhade, A. P. Dhondge, S. W. Chauhan, M. P. Desai, D. R. Birhade, N. R. Dhatrak, R. Gannimani, *Tetrahedron: Asymmetry* **2010**, *21*, 2394–2398; h) D. M. Black, R. Davis, B. D. Doan, T. C. Lovelace, A. Millar, J. F. Toczko, S. Xie, *Tetrahedron: Asymmetry* **2008**, *19*, 2015–2019; i) W. L. Canoy, B. E. Cooley, J. A. Corona, T. C. Lovelace, A. Millar, A. M. Weber, S. Xie, Y. Zhang, *Org. Lett.* **2008**, *10*, 1103–1106.

[24] R. Pauwels, *Antiviral Res.* **2006**, *71*, 77–89.

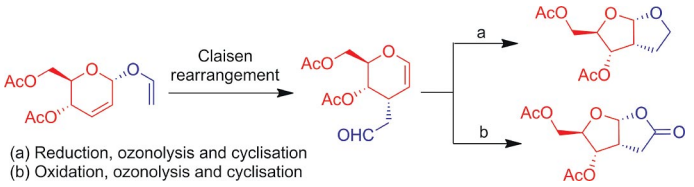
[25] J. F. Miller, C. W. Andrews, M. Brieger, E. S. Furfine, M. R. Hale, M. H. Hanlon, R. J. Hazen, I. Kaldor, E. W. McLean, D. Reynolds, D. M. Sammond, A. Spaltenstein, R. Tung, E. H. M. Turner, R. X. Xua, R. G. Sherrill, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1788–1794.

[26] P. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.

Received: July 7, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry

Oxygen Heterocycles



A general protocol for the stereoselective synthesis of *cis*-fused perhydrofuro[2,3-*b*]-
676 furans has been developed using carbohydrates as chiral-pool starting materials. Depending on the precursor sugar, this procedure can provide any stereoisomer of the bis-THF system in a stereoselective fashion. The extension of the methodology for the synthesis of perhydro-5-oxofuro[2,3-*b*]furans is also reported.

Keywords: Oxygen heterocycles / Carbohydrates / Cyclization / Sigmatropic rearrangement / Chiral pool

