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TETRAHEDRON

Oxocarbenium Ion Cyclisations Under Non-Acidic Conditions: Synthesis of Tetrahydropyran Analogues of the Pseudomonic Acids

Noshena Khan, Haiyun Xiao, Bo Zhang, Xuhong Cheng and David R. Mootoo*

Department of Chemistry, Hunter College/CUNY, 695 Park Avenue, New York, NY 10021

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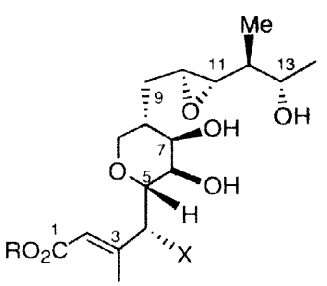
Abstract: Readily available C5 allylated 1,2-O-isopropylidene furanoside precursors are converted with complete stereocontrol, in a single step to derivatives of the tetrahydropyran subunits of the pseudomonic acids.

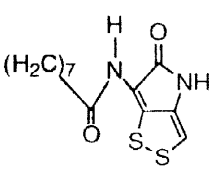
Keywords: Carbohydrates, carbenium ions, cyclisation, ene reaction, oxygen heterocycle

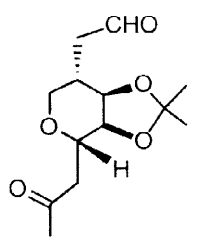
Following the success of the topical antibacterial Bactroban (pseudomonic acid A **1**), there has been ongoing interest in analogs which have high oral absorption and increased metabolic stability. The discovery that the more stable, semisynthetic, derivative ethyl monate C **2** has comparable activity has led to interest in structures which contain a conserved THP core with variable side chains.[1,2] More recently a novel group of related structures (e.g. thiomarinol A, **3**), which may be regarded as side chain analogs, have been found to exhibit more potent and wider spectrum antibacterial activity than pseudomonic acid A.[3] The distinctive features of the thiomarinols are the holothin amide residue and the presence of an additional stereogenic center on the side chain, which is contiguous with those on the THP residue. Several syntheses of the less oxygenated core structures found in pseudomonic acid A and C have been reported, but because of their complexity, are not generally suitable for large scale preparations.[4] Consequently functionalization of the THP **4**, a degradation product of **1** has been the primary method for analog synthesis.[1,2] To the best of our knowledge, no synthetic study has been reported on the higher oxygenated structures found in the thiomarinols.



1 Pseudomonic Acid A: X = H; R = $(CH_2)_8CO_2H$

2 Ethyl Monate C; 10,11 - E alkene : X = H; R = Et

3 Thiomarinol: X = OH; R = 



Semisynthetic Precursor

4

email: dmootoo@shiva.hunter.cuny.edu

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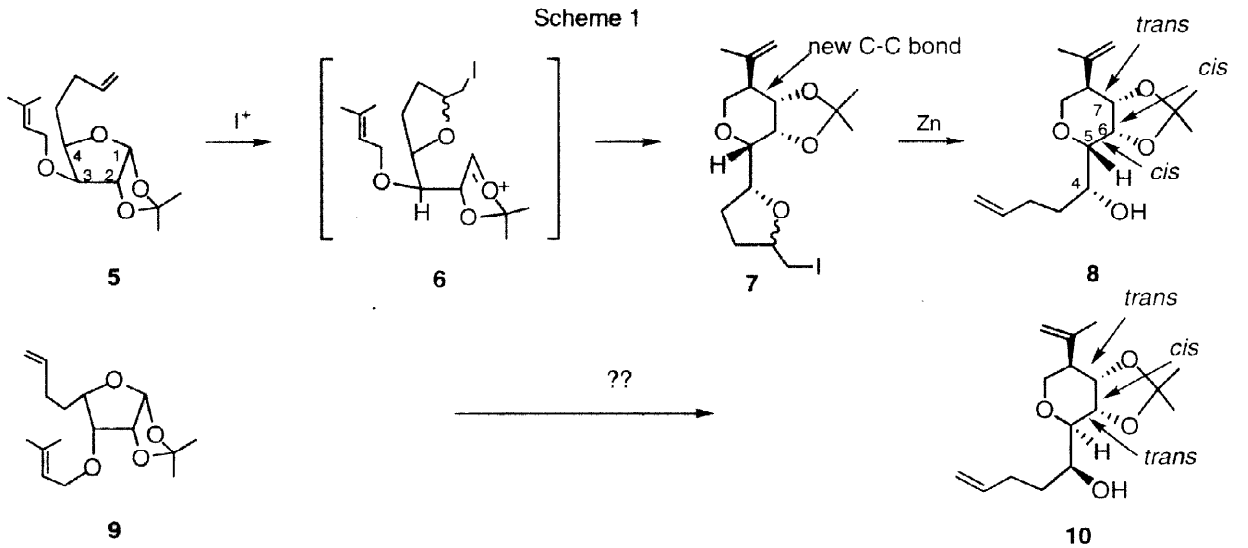
As part of a novel route to adjacently linked polyethers we have shown that treatment of the C5 allylated isopropylidene furanose **5** with iodonium ion led to a mixture of two bis-ethers **7**.[5] The stereochemistry of THP ring in both isomers was identical with the isopropenyl substituent *trans* to a *cis* fused isopropylidenoxy residue. Subsequent treatment of **7** with zinc led to a single THP **8**. The formation of **7** may be explained through the attack of the ring oxygen on an initial formed halonium ion to form a bicyclic oxonium ion which undergoes acetal cleavage to give a THF linked oxocarbenium ion **6**. Cyclisation of **6** leads to the THF-THP **7**. The high yield and stereoselectivity of THP formation presumably stems from the cyclic nature of the cyclic oxocarbenium ion, and the mild reaction conditions.[6] The overall transformation of **5** -> **8** constitutes an expedient to highly oxygenated THP's from readily available monosaccharides. In this paper the stereochemistry of the key THP cyclisation and its application to the synthesis of THP analogs of the pseudomonic acids are investigated.

Scheme 1



5 **6** **7** **8**

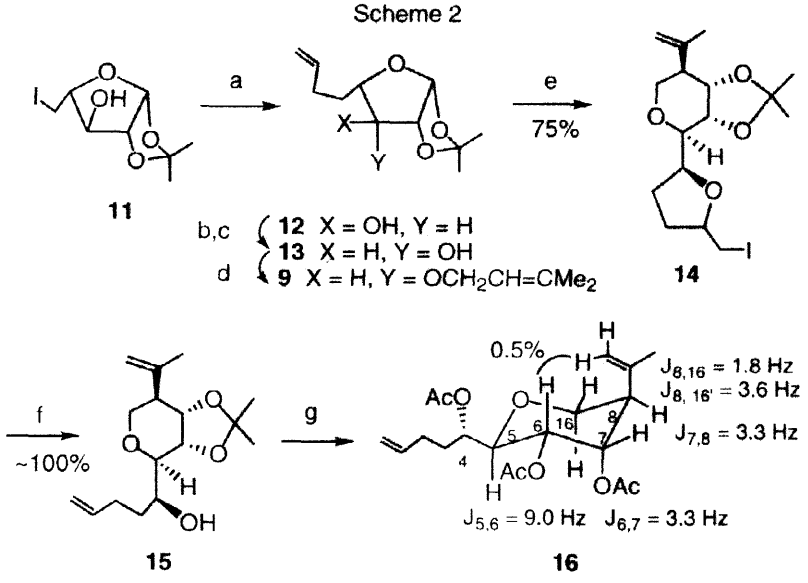
9 **10**

From the foregoing it follows that the antipodal THP core of thiomarinol A **10**, may be correlated with the C5 allylated 1,2-isopropylidene *lyxo* precursor **9**. The THP **10** contains all of the stereogenic centers contained in thiomarinol A, and its branches may be modified to give different side chain analogs. C4, 5 and 6 in **10** (pseudomonic acid numbering) correlates with C4, 3 and 2 respectively, in the starting furanoside (sugar numbering) and C7 and 8 are created in the alkene-oxocarbenium ion reaction. This plan requires that the stereochemical result which was observed for the cyclisation of **5** extends to **9**. Since the stereoselectivity of THP formation was expected to be dependent on the relative stereochemistry of the substituents on the forming ring, and this arrangement is different for these substrates, the outcome of the cyclisation of **9** was not assured.

5-deoxy-5-iodo-1,2-O-isopropylidene-β-L-*arabino*-furanose **11**[7] was converted via the Keck allylation to the C5 allylated derivative **12**.[8,9] Oxidation of the alcohol and reduction of the resulting ketone provided the *lyxo* derivative **13** which was O-alkylated to the desired cyclisation precursor **9**. Treatment of **9** with IDCP in

anhydrous CH_2Cl_2 afforded within 15 min a single THF-THP adduct **14** (75%).[10] Zinc mediated reductive elimination of **14** gave the THP **15** (Scheme 2).

Scheme 2

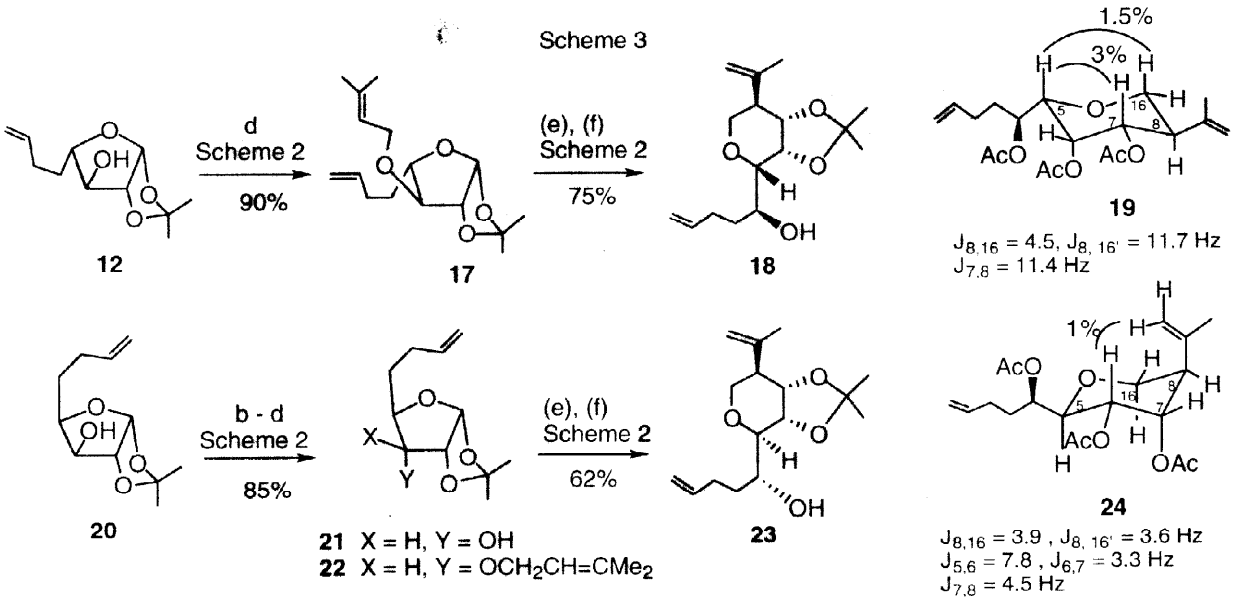


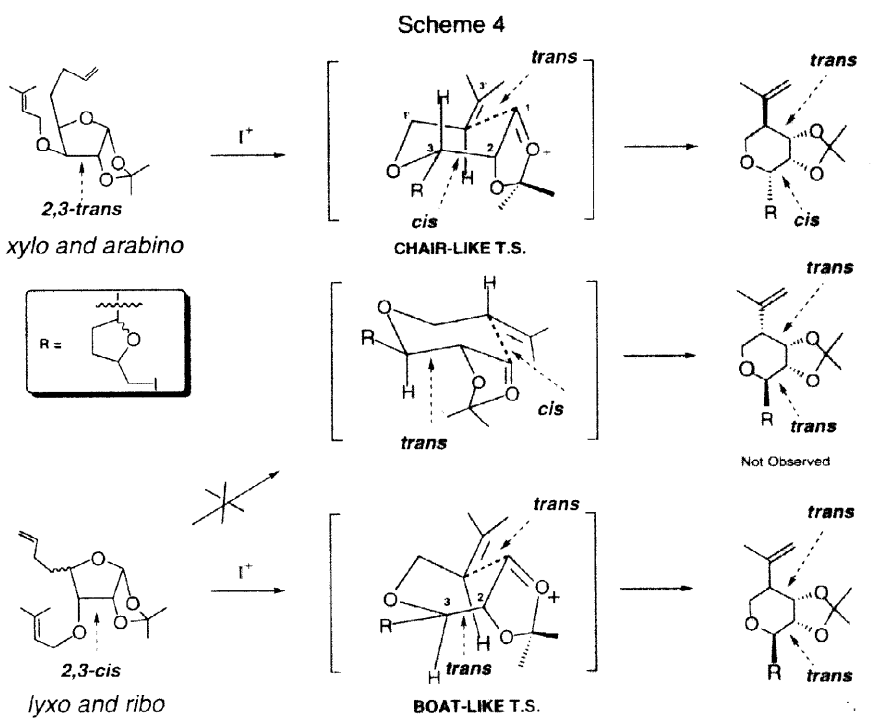
(a) allyltributyltin, AIBN, PhH, 60%; (b) Swern's Oxidn.; (c) $LiAlH_4$, Et_2O 71%, 2 steps; (d) 1-bromo-3-methyl-2-butene, NaH, Bu_4NI, DMF, 93%; (e) IDCP, CH_2Cl_2; (f) Zn, EtOH, Heat; (g) (i) HCl, MeOH; (ii) Ac_2O, DMAP, EtOAc.

Stereochemical assignment was carried out for the triacetate **16**, obtained through acid hydrolysis of **15** and peracetylation of the resulting triol. The $J_{5,6}$ value of 9.0 Hz indicated a *trans* diaxial relationship between these two protons and suggested the chair conformation shown. A small $J_{6,7}$ = 3.3 Hz confirmed that the newly formed alcohol at C7 was *cis* to O6. Values of $J_{8,16}$ and $J_{8,16'}$ of 1.8 and 3.6 Hz suggested that H8, the proton at the other newly formed stereogenic center was equatorial. A nOe (0.5%) between H6 and one of the alkene protons of the isopropenyl residue also supported a 1,3-diaxial arrangement of H6 and the isopropenyl substituent. For better signal resolution, this experiment was performed in CD_3OD at 42 °C.

Thus, even though the relative stereochemistry in the cyclisation precursors **5** and **9** was different, the identical stereochemical result with respect to the newly formed centers on the THP was obtained. Presumably the stereoselectivity of the cyclisation is determined by a preferred conformation of the THP ring that is being formed. Consequently the configuration at C4 of the furanoside precursor which corresponds to an "off-ring" position is not expected to have any significant effect on the stereochemical outcome.

In order to evaluate this hypothesis, the cyclisation of **17** and **22**, the C4 epimers of **5** and **9** were examined. These substrates were prepared from the C5 allylated furanosides **12** and **20**[5] via procedures similar to those described for **9**. Iodocyclisation of **17** and **22** under standard conditions, followed by treatment of the cyclisation products with zinc dust gave THP's **18** and **23** respectively as single products. The stereochemistry was determined on the basis of J values and nOe's which were obtained in $CDCl_3$ and C_6D_6 solutions respectively, for the tri-O-acetates **19** and **24**. For **19**, nOe's of 1.5 and 3% between H5 and H16-ax, and H5 and H7 respectively pointed to a *syn*-axial relationship for these three protons. The $J_{7,8}$ value of 11.4 Hz suggested that H7 and H8 were *trans* diaxial. As for its C4 epimer **16**, tri-O-acetate **24**, showed a nOe (1%) between H6 and one of the vinyl protons of the isopropenyl group, indicating a 1,3-diaxial arrangement of H6 and the isopropenyl group. The small $J_{6,7}$ value of 3.3 Hz supported the equatorial positioning of H7.





While the *cis*-6,7 selectivity in the products for both sets of furanoside precursors (i.e. *trans*- and *cis*- 2,3 in the furanosides, corresponding to *cis*- and *trans*-C5,6 in the final THP), is reasonable because of the preferred formation of a *cis*-fused isopropylidenoxy residue, the basis for the 7,8-*trans* selectivity is not clear. In the case of the 5,6-*cis* substituted systems, the observed result is in line with a chair or half-chair like transition state C1 in which the isopropenyl and R substituents are in low energy equatorial positions. However, application of this model to the 5,6-*trans* substrates suggests a preferred chair C2 which would lead to 7,8-*trans* arrangement of isopropenyl and acetonide residues, and not the observed 7,8-*cis* pattern. This result appears to be more consistent with a boat like geometry B. Thus it appears that the preservation of the 7,8 *trans* product irrespective of the relative stereochemistry of the cyclisation precursors, is connected to a change in transition state geometry of the oxocarbenium ion cyclisation.

Mechanistic speculations withstanding, the cyclisation of the readily accessible *lyxo*- and *ribo*- 1,2-O-isopropylidene furanosides **9** and **23** provides rapid entry to the THP nucleus of the pseudomonic acids. The

substrates used in this study lead to the unnatural enantiomers of pseudomonic acids. Following identical procedures the natural series could be prepared form D-arabinose, which is as easily available as the L-enantiomer. A variety of side chain analogs would be available through alteration of the substitution on the C5 and O3 alkenyl branches in the furanoside precursor.

Experimental

General. TLC was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck) and employed a stepwise solvent polarity gradient, correlated with TLC mobility. ^1H and ^{13}C NMR spectra were recorded on a GE QE 300 instrument at 300 and 75.5 MHz respectively, in $CDCl_3$ or C_6D_6 solutions, with residual $CHCl_3$ and C_6H_6 as internal standards. Unless noted otherwise data is reported for solutions in $CDCl_3$. Melting points are reported uncorrected.

5,6,7,8,-Tetradeoxy-1,2-*O*-isopropylidene-β-L-*arabino*-oct-7-enofuranose (12). A solution of the 5-deoxy-5-iodo-1,2-O-isopropylidene-β-L-*arabino*-furanose **11** (2.30 g, 7.67 mmol), allyltributyltin (8.54 g, 25.4 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.20 g, 1.22 mmol) in dry benzene (15 mL) was degassed, then heated at reflux for 18 h. The solvent was then concentrated under reduced pressure, the residue was dissolved in ether (80 mL) and stirred with saturated, aqueous potassium fluoride (20 mL) for 0.5 h. The resulting suspension was filtered, the organic layer was separated, and the aqueous phase was extracted with ether. The combined organic fraction was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography provided **12** (0.95 g, 58%). R_f 0.20 (20% ethyl acetate:petroleum ether); needles (petroleum ether-ethyl acetate), mp 52-54 °C; $[\alpha]_D^{26}$ -24° (*c* 0.52, $CHCl_3$); IR (neat) 3396, 1641 cm^{-1}; ^1H NMR: 1.32, 1.52 (both s, 3H each), 1.70 (m, 1H), 1.90 (m, 1 H), 2.20 (m, 2H), 3.94 (m, 1H), 4.11 (m, 1H), 4.51 (d, J = 3.9 Hz, 1H) 5.00 (dd, J = 1.2, 10.2 Hz, 1H), 5.07 (dd, J = 1.5, 17.1 Hz, 1H), 5.84 (m, 1H), 5.89 (d, J = 4.2 Hz, 1H). ^{13}CNMR: 27.4, 28.0, 31.2, 34.0, 80.0, 88.2, 88.5, 106.5, 113.7, 116.2, 138.9. FAB HRMS calcd for $C_{11}H_{19}O_4$ (M+H) 215.1283, found 215.1283.

5,6,7,8,-Tetradeoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-oct-7-enofuranose (13). DMSO (1.50 mL, 21.1 mmol) was slowly added at -78 °C, to a mixture of oxalyl chloride (0.91 mL, 10.4 mmol) and anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred at this temperature for 20 min, at which time a solution of **12** (0.74 g, 3.46 mmol) in CH_2Cl_2 (15 mL) was slowly introduced. Stirring was continued at this temperature for an additional 20 min, then Et_3N (3.10 mL, 22.3 mmol) added to the solution. The reaction mixture was warmed to rt, then diluted with ether (50 mL). The resulting suspension was washed with saturated $NaHCO_3$ (25 mL), and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residual syrup was

dissolved in ether and filtered through a short column of celite. The filtrate was evaporated under reduced pressure, the residue was dried under high vacuum and used directly in the next step.

The product from above was dissolved in anhydrous ether (20 mL) and cooled to 0 °C. Lithium aluminium hydride (0.33 g, 8.68 mmol) was added in small portions to the solution, and the reaction warmed to rt, and stirred for an additional 1 h. The resulting suspension was recooled to 0 °C, and a mixture of ice and water (20 mL) was cautiously added. The organic layer was separated, and the aqueous extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue afforded **13** (0.51, 71% from **12**); colorless oil; R_f 0.30 (20% ethyl acetate:petroleum ether); $[\alpha]_D^{26}$ +0.39° (*c* 2.9, $CHCl_3$); IR (neat) 3423, 1640 cm^{-1}; ^1H NMR: 1.39, 1.59 (both s, 3H each), 1.84 (m, 2H), 2.22 (m, 2H), 2.56 (d, J = 7.5 Hz, 1H), 3.90 (m, 1H), 4.15 (t, J = 6.0 Hz, 1H), 4.63 (dd, J = 4.2, 6.0 Hz, 1H) 4.97 (dd, J = 1.0, 12 Hz, 1H), 5.07 (d, J = 1.0, 18.0 Hz, 1H), 5.70 (d, J = 4.5 Hz, 1H), 5.84 (m, 1H). ^{13}CNMR: 27.1, 28.6, 30.3, 70.4, 80.4, 81.9, 88.5, 104.8, 114.6, 115.1, 138.4. FAB HRMS calcd for $C_{11}H_{17}O_4$ (M-H) 213.1127, found 213.1126.

5,6,7,8,-Tetradeoxy-3-*O*-(2'-methyl-2'-buten-4'-yl)-1,2-*O*-isopropylidene-β-L-*lyxo*-oct-7-enofuranose (9). NaH (800 mg, 20 mmol, 60% suspension in mineral oil) and n-Bu_4NI (100 mg, 0.27 mmol) was added to a solution of **13** (415 mg, 1.94 mmol) in anhydrous THF (20 mL) at 0 °C. The suspension was stirred at this temperature for 15 min, at which time 1-bromo-2-methyl-2-butene (1.5 mL, 13.0 mmol) was added. The reaction was warmed to rt and stirred for an additional 1 h. MeOH (0.1 mL) was then added and stirring continued for 15 min. The reaction mixture was poured into water (25 mL), and extracted with ether (3 x 20 mL). The organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a brown syrup. Flash column chromatography afforded **9** (507 mg, 93%). R_f 0.55 (20% EtOAc:PE); clear oil; $[\alpha]_D^{26}$ +11° (*c* 1.5, $CHCl_3$); ^{1}HNMR: 1.32, 1.57 (both s, 3H ea.), 1.68, 1.75 (both s, 3H ea.), 1.75 (m, buried under singlet, 1H), 2.08 (m, 2H), 2.30 (m, 1H), 3.94 (dd, J = 4.0, 5.0 Hz, 1H), 4.10 (m, 3H), 4.61 (t, J = 3.0 Hz, 1H), 4.96 (dd, J = 1.0, 12.0 Hz, 1H), 5.04 (dd, J = 1.0, 18.0 Hz, 1H), 5.36 (br t, J = 6.0 Hz, 1H), 5.72 (d, J = 3.0 Hz, 1H), 5.83 (m, 1H). ^{13}CNMR (C_6D_6): 18.5, 26.1, 27.2, 27.5, 30.4, 31.3, 67.5, 78.7, 79.9, 80.9, 105.8, 113.8, 115.0, 122.5, 136.7, 139.3. FAB HRMS calcd for $C_{15}H_{23}O_4$ ($M-CH_3$) 267.1596, found 267.1596.

THF-THP bis-ether 14. I(coll)$_2$ClO$_4$ (704 mg, 1.5 mmol) was added to a solution of **9** (300 mg, 1.06 mmol), in dry CH_2Cl_2 (100 mL) containing freshly activated, powdered, 4Å molecular sieves (1 g). After stirring at room temperature for 10 min, the solution was filtered, diluted with ether (100 mL), and washed with 10% aqueous $Na_2S_2O_3$ (75 mL) and brine (75 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the residue afforded **14** as a mixture of THF isomers (323 mg, 75%): R_f 0.60 (20% ethyl acetate:petroleum ether); clear oil; $[\alpha]_D^{26}$ -8.9° (*c* 2.0, $CHCl_3$); IR (neat) 1645

cm^{-1}; ^{1}HNMR: 1.36, 1.49 (both s, 3H ea.), 1.68 (m, 1H), 1.82 (s, 3H), 2.05 (m, 2H), 2.25 (m, 1H), 2.55 (m, 1H), 3.14 (m, 1H), 3.28 (m, 2H), 3.80 (m, 2H), 4.12 (m, 3H), 4.30 (m, 1H), 4.91 (m, 2H). FAB HRMS calcd for $C_{16}H_{26}IO_4$ (M+H) 409.0876, found 409.0876.

THP-Acetonide 15. The THF-THP **14** (40 mg, 0.10 mmol) in 95% EtOH (5 mL) and freshly activated zinc dust (300 mg), was heated at reflux for 1h. The reaction mixture was then diluted with ether (100 mL), filtered through florisil and the filtrate was evaporated *in vacuo*. Flash chromatography of the residual brown syrup gave **15** (29 mg, 100%). R_f 0.50 (20% ethyl acetate:petroleum ether); oil; $[\alpha]_D^{26}$ +17° (*c* 1.0, $CHCl_3$); IR (neat) 3489, 1641 cm^{-1}; ^{1}HNMR: 1.37, 1.49 (both s, 3H ea.), 1.70 (m, 2H), 1.82 (s, 3H), 2.20 (m, 3H, contains OH, D_2O ex), 2.58 (m, 1H), 3.18 (dd, J = 4.2, 8.7 Hz, 1H), 3.61 (m, 1H), 3.81 (m, 2H), 4.15 (dd, J = 5.1, 8.4 Hz, 1H), 4.85-5.15 (m, 4H), 5.85 (m, 1H). ^{13}CNMR: 22.8, 26.4, 28.4, 30.2, 32.7, 44.2, 66.3, 71.3, 71.6, 74.6, 79.6, 108.4, 113.3, 115.0, 138.7, 144.3. FAB HRMS calcd for $C_{16}H_{27}O_4$ (M+H) 283.1909, found 283.1908.

THP-tri-O-acetate 16. A solution of THP-acetonide **15** (29 mg, 0.10 mmol) in methanolic HCl (5 mL, pH ~2) was stirred at rt for 2h, then neutralized by the addition of solid $NaHCO_3$ and filtered. The filtrate was evaporated in vacuo, and the oily residue triturated with EtOAc. The suspension was filtered through a short column of silica gel, and the filtrate evaporated *in vacuo*. The residue was dissolved in ethyl acetate (2 mL) and treated with acetic anhydride (0.1 mL, 1.1 mmol) and DMAP (10 mg, 0.08 mmol). After stirring at rt for 30 min, MeOH (0.1 mL) was added to the reaction mixture and the volatiles removed *in vacuo*. Flash chromatography of the residue provided **16** (33 mg, 87%): R_f 0.40 (20% ethyl acetate:petroleum ether); oil; $[\alpha]_D^{26}$ -45° (*c* 1.7, $CHCl_3$); IR (neat) 1733, 1643 cm^{-1}; ^{1}HNMR: 1.72 (m, 1H), 1.85 (s, 3H), 1.88 (m, buried under singlet at 1.85, 1H), 1.98, 2.02, 2.10 (all s, 3H ea.), 2.16 (m, buried under singlets, 2H), 2.37 (bs, 1H), 3.77 (dd, J = 2.1, 9.0 Hz, 1H), 3.85 (dd, J = 3.6, 12.0 Hz, 1H), 4.05 (dd, J = 1.8, 12.0 Hz, 1H), 5.02 (m, 4H), 5.10 (m, 1H), 5.21 (s, 1H), 5.44 (t, J = 3.3 Hz, 1H), 5.80 (m, 1H). ^{13}CNMR: 20.9, 21.0, 21.2, 22.8, 29.8, 29.9, 46.0, 65.9, 66.1, 69.3, 70.4, 75.1, 114.6, 115.3, 137.8, 142.2, 170.1, 170.2, 170.7. FAB HRMS calcd for $C_{19}H_{29}O_7$ (M+H) 369.1913, found 369.1908.

5,6,7,8,-Tetradeoxy-3-*O*-(2'-methyl-2'-buten-4'-yl)-1,2-*O*-isopropylidene -β-L-*arabino*- -oct-7-enofuranose (17). Compound **17** was obtained in 90 % yield from alcohol **12** by application of the identical O-alkylation procedure used for the preparation of **9**. For **17**: R_f 0.60 (20% EtOAc:PE); clear oil; $[\alpha]_D^{26}$ -30° (*c* 0.51, $CHCl_3$); ^{1}HNMR: 1.32, 1.51 (both s, 3H ea.), 1.68, 1.74 (both s, 3H ea.), 1.72 (m, buried under singlet at δ 1.74, 1H), 1.84 (m, 1H), 2.18 (m, 2H), 3.70 (d, J = 3.0, 1H), 4.02 (m, 3H), 4.55 (d, J = 3.9 Hz, 1H), 4.96 (dd, J = 1.0, 10.0 Hz, 1H), 5.04 (dd, J = 1.2, 17.1 Hz, 1H), 5.32 (br t, J = 6.6 Hz, 1H), 5.82 (m, 2H). ^{13}CNMR: 17.3, 25.0, 25.7, 26.4, 29.4, 32.6, 65.5, 83.1, 84.6, 84.9, 104.5, 111.9, 114.1, 119.4, 137.1. FAB HRMS calcd for $C_{16}H_{27}O_4$ (M+H) 283.1909, found 283.1908.

THP-Acetonide 18. Compound **17** (200 mg, 0.71 mmol) was treated with $I(coll)_2ClO_4$ following the procedure used for the preparation of **14**. Flash chromatography of the reaction product afforded a single THF-THP product (260 mg, 90%): R_f 0.55 (20% ethyl acetate:petroleum ether); oil; ^{1}HNMR: 1.26, 1.43 (both s, 3H ea.), 1.58 (m, 1H), 1.67 (s, 3H), 1.93 (m, 1H), 2.08 (m, 2H), 2.34 (ddd, J = 4.5, 9.6, 11.7 Hz, 1H), 3.06 (m, 2H), 3.19 (dd, J = 4.5, 9.6 Hz, 1H), 3.43 (dd, J = 2.1, 6.3 Hz, 1H), 3.76 (dd, J = 4.5, 11.4 Hz, 1H), 4.04 (m, 3H), 4.24 (apparent q, J = 6.6 Hz, 1H) 1H), 4.69, 4.82 (both br s, 1H ea). A portion of the THF-THP product from the previous step (150 mg, 0.37 mmol) was treated with zinc dust following the procedure used for the preparation of **15**. Flash chromatography of the reaction product provided **18** (100 mg, 96%). R_f 0.30 (20% ethyl acetate:petroleum ether); oil; IR (neat) 3476, 1642 cm^{-1}; ^{1}HNMR: 1.36, 1.54 (both s, 3H ea.), 1.58 (m, 1H), 1.78 (s, 3H), 1.80 (m, 1H), 2.18 (m, 1H), 2.40 (m, 2H), 3.13 (t, J = 7.2 Hz, 1H), 3.46 (dd, J = 2.4, 6.9 Hz, 1H), 3.86 (dd, J = 4.5, 11.7 Hz, 1H), 3.90 (m, 1H), 4.14 (dd, J = 5.1, 9.9 Hz, 1H), 4.28 (dd, J = 2.4, 5.1 Hz, 1H), 4.78, 4.92 (both br s, 1H ea), 4.97 (br d, J = 11.1 Hz, 1H), 5.06 (br d, J = 17.1 Hz, 1H), 5.86 (m, 1H). ^{13}CNMR: 22.3, 26.9, 28.8, 30.2, 33.7, 47.3, 68.8, 71.7, 72.3, 76.7, 79.0, 109.6, 112.7, 115.0, 138.6, 144.0. FAB HRMS calcd for $C_{16}H_{27}O_4$ (M+H) 283.1909, found 283.1908.

THP-tri-O-acetate 19. THP-acetonide **18** was converted to the tri-O-acetate **19** following the procedure used for the preparation of **16**. For **19** : R_f 0.40 (20% EtOAc:PE); $[\alpha]_D^{26}$ -85^0 (*c* 4.0, $CHCl_3$); oil; IR (neat) 1730, 1644 cm^{-1}; ^{1}HNMR: 1.62 (m, 1H), 1.68 (s, 3H), 1.94, 2.00, 2.12 (all s, 3H ea.), 1.60-2.15 (m buried under singlets, 3H), 2.78 (dt, J = 4.5, 1.4 Hz, 1H), 3.33 (t, J = 11.4 Hz, 1H), 3.48 (d, J = 9.0 Hz, 1H), 3.99 (dd, J = 4.5, 11.7 Hz, 1H), 4.80 (br s, 1H), 4.88-5.10 (m, 5H), 5.32 (br d, J = 2.1 Hz, 1H), 5.78 (m, 1H). ^{13}CNMR: 21.0, 21.2, 21.3, 29.2, 31.3, 43.6, 65.9, 69.6, 70.8, 71.5, 78.4, 114.2, 115.1, 137.9, 140.5, 170.1, 170.4, 170.7. FAB HRMS calcd for $C_{19}H_{29}O_7$ (M+H) 369.1913, found 369.1909.

5,6,7,8,-Tetradeoxy-1,2-*O*-isopropylidene-α-D-*ribo*-oct-7-enofuranose (21). The Swern's oxidation procedure that was described for the preparation of **13** was applied to alcohol **20** (0.500 g, 2.30 mmol). DMSO (0.80 mL, 11.0 mmol), oxalyl chloride (0.83 mL, 9.50 mmol) and Et_3N (2.62 mL, 19.0 mmol) were used. The crude product was dissolved in ethyl acetate and filtered through a short colum of silica gel. The filtrate was evaporated under reduced pressure and used directly in the next step.

The product from above was dissolved in ethanol (5 mL) and treated with sodium borohydride (83 mg, 2.21 mmol). The mixture was stirred at rt for 15 min, then cooled to 0 ^{0}C and the pH was adjusted to 8 by careful addition of methanolic HCl. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography to give **21** (390 mg, 80% from **20**); R_f 0.30 (20% ethyl acetate:petroleum ether); oil; $[\alpha]_D^{26}$ +49^0 (*c* 0.73, $CHCl_3$); IR (neat) 3482, 1641 cm^{-1}; ^{1}H NMR: 1.36, 1.55 (both s, 3H each), 1.65 (m, 1H), 1.82 (m, 1H), 2.22 (m, 3H), 3.61 (m, 1H), 3.70 (dt, J = 4.0, 8.0 Hz, 1H), 4.53 (t, J = 4.8 Hz, 1H), 4.97 (dd, J =

1.0, 10.2 Hz, 1H), 5.04 (d, J = 1.0, 17.2 Hz, 1H), 5.78 (d, J = 4.8 Hz, 1H), 5.84 (m, 1H). ^{13}CNMR: 27.2, 27.4, 30.5, 32.1, 76.5, 79.3, 80.2, 104.5, 113.0, 115.5, 138.7.

5,6,7,8,-Tetradeoxy-3-*O*-(2'-methyl-2'-buten-4'-yl)-1,2-*O*-isopropylidene-α-D-*ribo*-oct-7-enofuranose (22). Compound **22** was obtained in 84 % yield from alcohol **21** by application of the identical O-alkylation procedure used for the preparation of **9**. For **22**: R_f 0.55 (20% EtOAc:PE); clear oil; IR (neat) 1641 cm^{-1} ^{1}HNMR: 1.33, 1.55 (both s, 3H ea.), 1.68, 1.75 (both s, 3H ea.), 1.76 (m, buried under singlet at δ 1.75, 2H), 1.84 (m, 1H), 2.16 (m, 2H), 3.36 (dd, J = 4.5, 9.0 1H), 3.95 (m, 2H), 4.18 (dd, J = 6.6, 8.7 Hz, 1H), 4.57 (t, J = 3.9 Hz, 1H), 4.94 (dd, J = 10.0 Hz, 1H), 5.02 (dd, J = 1.5, 17.1 Hz, 1H), 5.36 (br t, J = 5.7 Hz, 1H), 5.71 (d, J = 3.9 Hz, 2H), 5.83 (m, 1H). ^{13}CNMR: 18.3, 26.0, 26.8, 26.9, 30.2, 32.0, 66.9, 77.7, 77.8, 82.2, 104.0, 112.8, 114.8, 121.1, 138.0, 138.5. FAB HRMS calcd for $C_{15}H_{23}O_4$ (M-CH_3) 267.1596, found 267.1596.

THP-Acetonide 23. Compound **22** (275 mg, 0.98 mmol) was treated with I(coll)$_2$ClO$_4$ following the procedure used for the preparation of **14**. Flash chromatography of the reaction product afforded a mixture of THF-THP products (270 mg, 68%): R_f 0.60 (20% ethyl acetate:petroleum ether); oil; ^{1}HNMR: 1.36, 1.51 (both s, 3H ea.), 1.72 (m, 1H), 1.81 (s, 3H), 1.97-2.27 (m, 3H), 2.53 (m, 1H), 3.20 (m, 2H), 3.56 (dd, J = 2.7, 9.3 Hz, 1H), 3.77 (m, 2H), 3.90-4.40 (m, 4H), 4.85, 4.88, 4.92 (all br s, 2H).

A portion of the THF-THP mixture from the previous step (73 mg, 0.18 mmol) was treated with zinc dust following the procedure used for the preparation of **15**. Flash chromatography of the reaction product provided **23** (49 mg, 97%). R_f 0.50 (20% ethyl acetate:petroleum ether); oil; $[\alpha]_D^{26}$ 21^0 (*c* 2.0, $CHCl_3$); IR (neat) 3494, 1642 cm^{-1}; ^{1}HNMR: 1.36, 1.50 (both s, 3H ea.), 1.62 (m, 2H), 1.80 (s, 3H), 2.20 (m, 3H, contains OH, D_2O ex), 2.55 (apparent q, J = 3.0 Hz, 1H), 3.28 (dd, J = 3.9, 8.4 Hz, 1H), 3.78 (m, 3H), 4.25 (m, 2H), 4.86, 4.91 (both br s, 1H ea), 4.94 (br d, J = 12 Hz, 1H), 5.04 (br d, J = 18 Hz, 1H), 5.83 (m, 1H). ^{13}CNMR: 22.9, 27.5, 28.4, 30.3, 31.3, 44.1, 66.3, 70.8, 72.6, 75.1, 79.7, 108.7, 113.4, 115.0, 138.8, 144.4. FAB HRMS calcd for $C_{16}H_{27}O_4$ (M+H) 283.1909, found 283.1908.

THP-tri-O-acetate 24. THP-acetonide **23** was converted to the tri-O-acetate **24** following the procedure used for the preparation of **16**. For **24** : R_f 0.30 (20% ethyl acetate:petroleum ether); $[\alpha]_D^{26}$ -3.1^0 (*c* 1.6, $CHCl_3$); oil; IR (neat) 1746, 1643 cm^{-1}; ^{1}HNMR (C_6D_6/$CDCl_3$:1/1, 500 MHz): 1.70 (s, 3H), 1.79, 1.82, 1.88 (all s, 3H ea), 1.75-1.90 (m, 2H buried under singlets), 2.07 (m, 2H), 2.32 (apparent q, J = 4.2 Hz, 1H), 3.73 (dd, J = 4.0, 12.0 Hz, 1H), 3.82 (dd, J = 4.0, 12.0 Hz, 1H), 4.08 (dd, J = 4.0, 7.5 Hz, 1H), 4.94 (br s, 1H), 4.94 (br d, J = 10.0 Hz, 1H), 5.02 (dd, J = 1.8, 17.0 Hz, 1H), 5.17 (br s, 1H), 5.31 (dd, J = 3.5, 7.5 Hz, 1H), 5.34 (m, 1H), 5.60 (dd, J = 3.0, 5.5 Hz, 1H), 5.73 (m, 1H). ^{13}CNMR: 21.0, 21.1, 21.3, 22.3, 28.4,

29.7, 43.3, 65.4, 66.5, 68.7, 71.5, 76.1, 114.5, 115.4, 137.6, 141.8, 170.0, 170.2, 170.6. HRMS(CI) calcd for $C_{19}H_{29}O_7$ (M+H) 369.1913, found 369.1912.

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