Synthesis of 2,2-Disubstituted Furanoid Natural Products: Total Synthesis of Sphydrofuran

Romina Di Florio and Mark A. Rizzacasa*

School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia

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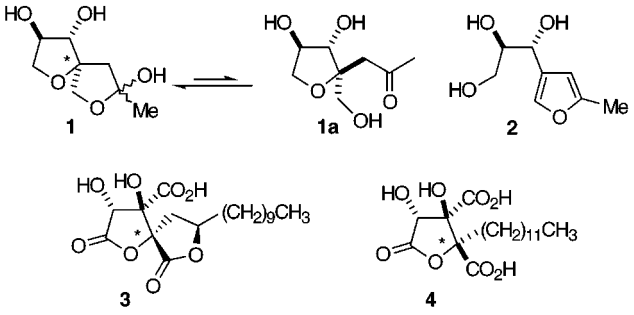
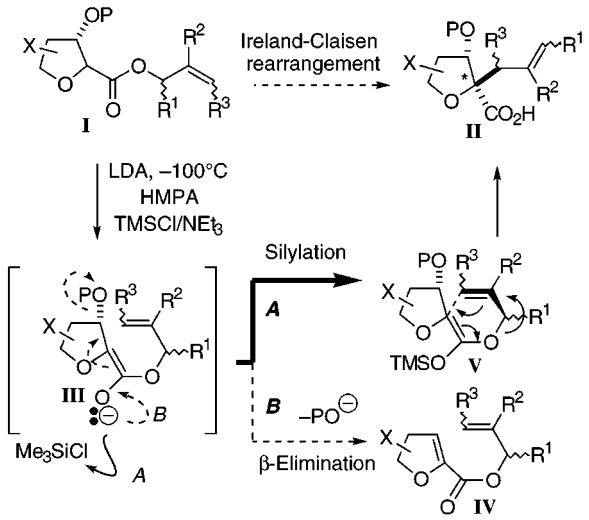
Introduction

Tetrahydrofuran and γ-lactone rings are present in a large number of natural products, which include important biologically active compounds such as carbohydrates and polyether antibiotics.[1] Other examples of furanoid natural products include the microbial metabolite sphydrofuran (**1**)[2−4] and the γ-lactone-containing cinatrins A (**2**) and C_1 (**3**), which are inhibitors of phospholipase A_2 (PLA_2).[5,6] PLA_2 is a lipolytic enzyme that plays a crucial role in the rate-limiting step in the biosynthesis of proinflammatory eicosanoids such as prostaglandins, and inhibition of this enzyme may therefore result in a reduction of inflammatory processes. Compound **1** exists as a complex mixture of two hemiacetals **1** and the open chain form **1a**. Although **1** possesses no significant biological activity itself, the furan derivative (**2**),[2,4] obtained by acid treatment of **1**, exhibits growth promotion for some bacteria and viruses.



It is envisaged that a general route to compounds such as **1**, **3**, and **4** could be developed from simple ester precursors derived from carbohydrates. The stereogenic centers marked by an asterisk in the tetrahydrofuran rings of each of these molecules could be set by an Ireland−Claisen rearrangement[7] of an appropriate allylic ester **I** obtained from a furanose derived acid (Scheme 1). This rearrangement would generate a new asymmetric center in each and provide access to a number of acid derivatives **II** that might not be accessible by simple routes such as alkylation. The detail of this rearrangement sequence is shown in Scheme 1 and is based on work conducted by us in similar systems during our synthetic studies on the zaragozic acids/squalestatins.[8−10]

Scheme 1



Treatment of an ester such as **I** with base in the presence of TMSCl with HMPA as cosolvent generates the enolate **III**, which can undergo either unwanted β-elimination to give a glycal **IV** or silylation to give the silyl ketene acetal **V**. Intermediate **V** can then undergo a facile [3.3]-sigmatropic rearrangement to form the new carbon−carbon bond and asymmetric center. The stereochemistry at the newly formed stereocenter can be controlled to a degree by the configuration β-stereocenter (rearrangement occurs from the β-face in the case shown in Scheme 1), and it has already been demonstrated that β-elimination can be avoided by careful choice of reaction conditions and substrate.[10] To test this proposal, we selected the microbial metabolite sphydrofuran **1** as a target. Compound **1** has been synthesized on two other occasions, one involving a chemoenzymatic protocol[11] while the route reported by Wong utilized a furan oxidation/Michael addition sequence.[12]

Results and Discussion

Our synthesis of **1** began with the alcohol **5**, which is readily synthesized in three steps from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (Scheme 2).[13] Two-step oxidation of **5** provided the acid **6** in excellent yield, which upon treatment with allyl alcohol and DCC/DMAP produced ester **7**. Rearrangement of **7**

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(2) Umezawa, S.; Usui, T.; Umezawa, H.; Tsuchiya, T.; Takeuchi, T.; Hamada, M. *J. Antibiot.* **1971**, *24*, 85.
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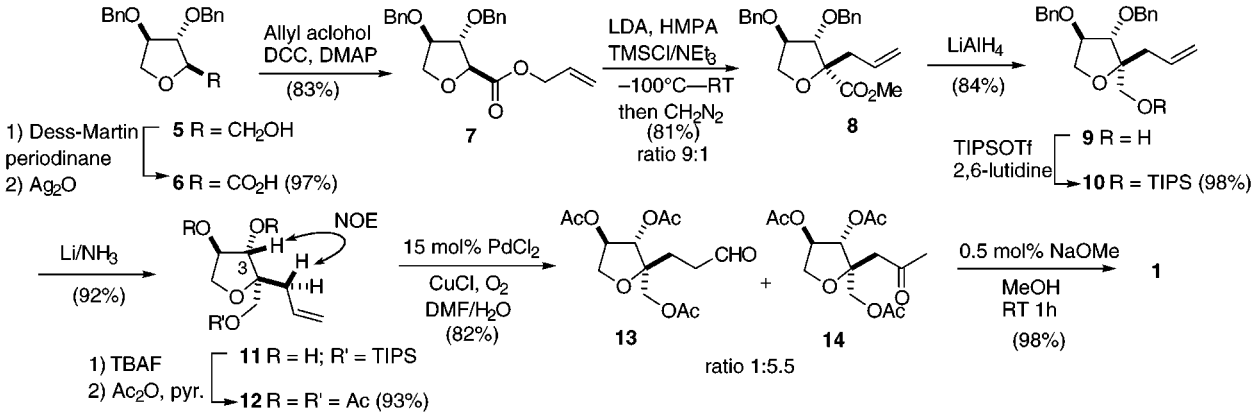
Scheme 2

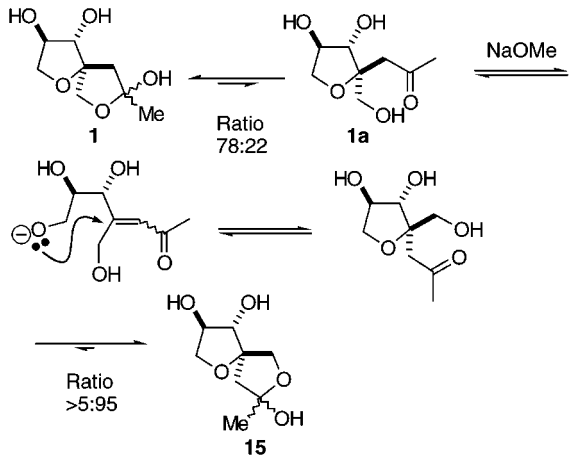


was effected with LDA in the presence of HMPA and TMSCl at −100 °C to give the ester **8** as a 9:1 mixture of diastereoisomers in good yield. Critical to the success of this reaction was the use of the supernatant from a centrifuged mixture (∼1:1 v/v) of TMSCl/NEt_3.[14] Also important to the success of this reaction was the fact that the relative stereochemistry between H2 and the C3 benzyloxy group was cis, which retards β-elimination by an E2 type process. In an earlier study, we observed substantial β-elimination upon attempted rearrangement of a similar substrate that possessed a trans relationship between H2 and a C3 benzyloxy group.[10] The stereochemistry of ester **8** was ultimately confirmed by its conversion to known[11] sphydrofuran intermediate **12**.

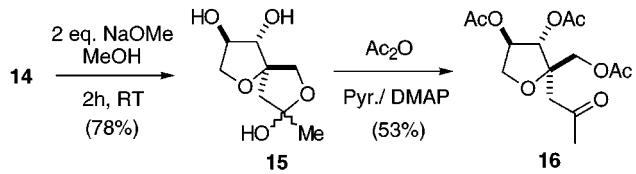
Reductive debenzylation of the alcohol **9** derived from ester **8** proved troublesome; however, debenzylation proceeded smoothly when conducted on the corresponding TIPS ether **10**. Desilylation of **11** followed by acetylation of the resulting triol gave the triacetate **12**, which was identical in all respects to the intermediate obtained by Maliakel and Schmid[11] in their synthesis of **1**, thus confirming the outcome of the rearrangement. In addition, a NOE interaction between the allylic methylene protons and H3 was observed in the NOESY spectrum of triacetate **12**. Wacker oxidation[15] of **12** to provide sphydrofuran triacetate **14** was achieved using a catalytic amount palladium(II) chloride in the presence of CuCl and oxygen. In the previous synthesis of **14**, a stoichiometric amount of palladium(II) chloride was employed, which also gave a substantial amount of the aldehyde **13** (ratio of **14**/**13** is 2.7:1).[11] Using a catalytic amount of Pd(II), the ratio of **14** to **13** was increased to 5.5:1. Treatment of **14** with a catalytic amount (0.5 mol %) of NaOMe in methanol as described previously[3,11] provided sphydrofuran as a complex mixture of anomers and the open chain compound **1a**.

Initially, we employed larger amounts of NaOMe (1−2 equiv) for the deacetylation of **14**, which resulted in the rapid formation of a new compound with a higher R_f than sphydrofuran (**1**). The combustion analysis and mass spectrum of this compound revealed that it was isomeric with **1**, while the ^{1}H and ^{13}C NMR spectra displayed a mixture of only two components in a ratio of ∼5:1. The

Scheme 3



structure was assigned as the spiro epimer of **1**, which we have named "isosphydrofuran" (**15**). Isosphydrofuran (**15**) was more stable than sphydrofuran[16] and exists only in the hemiketal forms with no open chain form detected by NMR. Furthermore, sphydrofuran (**1**) isomerizes quantitatively to spiroisomer **15** on exposure to NaOMe. Compound **15** was further characterized by conversion into its triacetate **16**, which was different from triacetoxy sphydrofuran (**14**).



The formation of **15** under basic conditions can be explained by the sequence shown in Scheme 3 where equilibration of sphydrofuran (**1**) to the thermodynamically more stable isosphydrofuran (**15**) is achieved by a retro-Michael/Michael addition sequence. It is noteworthy that the base-mediated isomerization of **1** has not been observed previously. In the original account, which describes the isolation of **1**, the presence of an impurity of higher R_f during isolation was noted.[2] However, the amount of this impurity increases when the solution becomes acidic during the purification steps, and this material was later identified as the furan **2**.[2,4]

(14) For examples of the use of this silylating mixture in the Ireland−Claisen rearrangement, see: Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288. Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160.

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(16) Sphydrofuran (**1**) is unstable on silica gel but could be purified by rapid chromatography on neutral alumina. Isosphydrofuran (**15**) was stable to silica gel chromatography.

In conclusion, we have achieved a synthesis of sphydrofuran **1** using a highly stereoselective ester−enolate Claisen rearrangement in the presence of a β-leaving group. The application of this methodology to the synthesis of the more complex cinatrins is underway.

Experimental Section

General. Unless otherwise stated, ^{1}H NMR (300 MHz) and proton decoupled ^{13}C NMR spectra (75.5 MHz) were recorded for deuteriochloroform solutions, with residual chloroform as an internal standard. Microanalyses were carried out at the University of Otago, Dunedin, New Zealand. Optical rotations were recorded in a 10 cm microcell. HRMS (electrospray ionization) (ESI) mass spectra were run on a Bruker 4.7T BiOAPEX FTMS mass spectrometer at Monash University, Clayton, Victoria. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from potassium metal under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petroleum ether refers to the fraction boiling between 40 and 60 °C.

2,5-Anhydro-3,4-di-*O*-benzyl-D-lyxonic acid (6). To a solution of the alcohol **5**[13] (2.95 g, 9.40 mmol) in dry CH_2Cl_2 (31 mL) was added Dess-Martin periodinane (5.98 g, 14.10 mmol), and the reaction mixture was stirred at room temperature for 3 h. Ether, saturated aqueous $NaHCO_3$, and 1.5 M $Na_2S_2O_3$ were added, and stirring was continued until two clear layers resulted. The aqueous layer was then extracted with ether, and the combined organic fractions were washed with brine and dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting oil was dissolved in ethanol (47 mL), and a solution of $AgNO_3$ (3.66 g) in H_2O (5 mL) was added followed by the dropwise addition of a solution of KOH (3.33 g) in H_2O (47 mL). The suspension was stirred for 12 h at room temperature and then filtered through Celite, and the filter cake was washed with aqueous 6% KOH. Most of the ethanol was removed under reduced pressure, and the remaining aqueous solution washed with ether, then acidified with concentrated HCl, and extracted with ether. The combined organic fractions were washed with saturated NaCl and dried, and the solvent was removed under reduced pressure to give the carboxylic acid **6** (2.91 g, 97%) as a clear, viscous oil, which was homogeneous as determined by ^{1}H NMR spectroscopy: $[\alpha]^{18}_D = -2.6$ (*c* 1.28, $CHCl_3$); IR (film) 3850, 3032, 2924, 1738 cm^{-1}; ^{1}H NMR δ 4.01 (d, J = 3.3 Hz, 1H), 4.10 (dd, J = 9.8, 3.3 Hz, 1H), 4.19 (d, J = 9.8 Hz, 1H), 4.24 (s, 1H), 4.58 (s, 1H), 4.46 (ABq, J = 11.7 Hz, 2H), 4.64 (ABq, J = 11.7 Hz, 2H), 7.22−7.37 (m, 10H); ^{13}C NMR δ 71.2, 71.9, 73.1, 80.8, 81.3, 84.8, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 130.2, 136.9, 172.8; MS (CI) *m*/*z* 329 (M^+ + 1, 22%); HRMS (ESI) calcd for $C_{19}H_{20}O_5Na$ ($M + Na^+$) 351.1209, found 351.1195.

Prop-2-enyl 2,5-Anhydro-3,4-di-*O*-benzyl-D-lyxonate (7). To a stirred solution of the acid **6** (3.23 g, 9.85 mmol) in dry CH_2Cl_2 (26 mL) at 0 °C was added allyl alcohol (775 μL, 11.82 mmol), DMAP (120 mg, 0.98 mmol) and DCC (2.24 g, 10.86 mmol). The resulting white suspension was stirred for 1 h, then diluted with petroleum ether, and filtered through a pad of Celite. The filtrate was washed with 10% aqueous HCl, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the crude product by flash chromatography using 30% ethyl acetate/petroleum ether as the eluent gave the allyl ester **7** (3.04, 83%) as a clear oil: $[\alpha]^{21}_D = +7.5$ (*c* 1.78, $CHCl_3$); IR (film) 2874, 1754 cm^{-1};^{1}H NMR δ 4.08−4.14 (m, 3H), 4.38 (t, J = 1.8 Hz, 1H), 4.46 (s, 2H), 4.58−4.63 (m, 3H), 4.64 (ABq, J = 12.0 Hz, 2H), 5.20−5.32 (m, 2H), 5.86 (m, 1H), 7.26−7.37 (m, 10H); ^{13}C NMR δ 65.8, 71.2, 71.8, 72.4, 81.3, 81.7, 85.7, 118.7, 127.6, 127.76, 127.82, 128.0, 128.4, 128.5, 131.6, 137.2, 137.4, 170.3; MS (CI) *m*/*z* 369 (M^+ + 1, 4%). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found C, 71.51; H, 6.31.

Methyl 2,5-Anhydro-3,4-di-*O*-benzyl-2-*C*-(prop-2-enyl)-D-xylonate (8). A solution of *n*-BuLi in hexanes (2.2 M, 7.49 mL, 16.48 mmol) was added dropwise to a solution of *i*-Pr_2NH (2.16 mL, 16.48 mmol) in dry THF (36 mL) at 0 °C under an argon atmosphere. The resultant base solution was stirred at 0 °C for 5 min; then it was cooled to −78 °C and added dropwise via cannula to a solution of the ester **7** (3.04 g, 8.25 mmol), HMPA (9.12 mL), and the supernatant from a centrifuged mixture of freshly distilled TMSCl (3.75 mL, 29.15 mmol) and dry NEt_3 (4.02 mL, 28.84 mmol) in dry THF (49 mL) at −100 °C (liquid N_2/MeOH bath). The resulting mixture was stirred at −100 °C for 10 min and then allowed to warm to room temperature and left to stir overnight. The solution was cooled to 0 °C, and aqueous NaOH (1 M, 57 mL) was added followed by ether and water. The aqueous phase was then acidified with concentrated HCl at 0 °C and extracted with ether. The combined organic fractions were washed with water and brine, dried, and then concentrated. A solution of the crude acid in ether (25 mL) was treated with excess CH_2N_2, and the crude product was purified by flash chromatography using 20% ethyl acetate/petroleum ether as the eluent to yield **8** (2.57 g, 81%) as a pale-yellow oil (9:1 mixture of diastereoisomers): $[\alpha]^{19}_D = +10.3$ (*c* 0.80, $CHCl_3$); IR (film) 2947, 2870, 1737 cm^{-1}; ^{1}H NMR δ 2.73 (m, 2H), 3.72 (s, 3H), 4.00−4.08 (m, 3H), 4.29 (dd, J = 9.6, 4.5 Hz, 1H), 4.45 (s, 2H), 4.56 (ABq, J = 12.0 Hz, 2H), 5.07−5.13 (m, 2H), 5.82 (m, 1H), 7.26−7.35 (m, 10H); ^{13}C NMR δ 40.3, 51.9, 71.4, 72.1, 72.8, 82.6, 87.3, 89.7, 118.5, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4, 132.5, 137.3, 137.5, 171.4; MS (CI) *m*/*z* 383 (M^+ + 1, 73%). Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found C, 72.44; H, 6.55.

1,4-Anhydro-2,3-di-*O*-benzyl-4-*C*-(prop-2-enyl)-L-xylitol (9). To a suspension of $LiAlH_4$ (893 mg, 23.52 mmol) in dry ether (70 mL) at 0 °C under an argon atmosphere was added the methyl ester **8** (2.57 g, 6.72 mmol) in dry ether (33 mL) via cannula. The reaction was stirred at 0 °C for 10 min then allowed to warm to room temperature overnight, cooled to 0 °C, and treated with aqueous NaOH (5 M) until a white precipitate had formed. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with 40% ethyl acetate/petroleum spirits as the eluent to give alcohol **9** (2.00 g, 84%) as an oil: $[\alpha]^{18}_D = +16.1$ (*c* 0.50, $CHCl_3$); IR (film) 3448, 2925, 2867 cm^{-1}; ^{1}H NMR δ 2.27 (br s, 1H), 2.40 (br d, J = 7.5 Hz, 2H), 3.68 (ABq, J = 12.0 Hz, 2H), 3.81 (dd, J = 9.3, 4.8 Hz, 1H), 4.06 (d, J = 3.9 Hz, 1H), 4.13 (dd, J = 9.3, 5.4 Hz, 1H), 4.23 (m, 1H), 4.53 (s, 2H), 4.62 (ABq, J = 11.7 Hz, 2H), 5.03−5.11 (m, 2H), 5.81 (m, 1H), 7.20−7.40 (m, 10H); ^{13}C NMR δ 39.9, 65.1, 69.8, 72.0, 72.7, 84.0, 84.8, 87.6, 118.5, 127.7, 127.8, 127.9, 128.0, 128.5, 128.6, 133.2, 137.5, 137.8; MS (CI) *m*/*z* 355 (M^+ + 1, 66%). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.38; H, 7.31.

1,4-Anhydro-2,3-di-*O*-benzyl-4-*C*-(prop-2-enyl)-5-*O*-triisopropylsilyl-L-xylitol (10). To a solution of the alcohol **9** (875 mg, 2.47 mmol) and 2,6-lutidine (489 μL, 4.20 mmol) in dry CH_2Cl_2 (37 mL) was added triisopropylsilyl trifluoromethanesulfonate (863 μL, 3.21 mmol) at 0 °C under argon, and the reaction was stirred at 0 °C for 1.5 h and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ether, and the combined organic fractions were washed with cold 5% aqueous HCl (10 mL), water, saturated $NaHCO_3$, and saturated NaCl and dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash chromatography using 5% ethyl acetate/petroleum ether as the eluent afforded the ether **10** (1.23 g, 98%) as a pale-yellow oil: $[\alpha]^{19}_D = -10.8$ (*c* 0.4, $CHCl_3$); IR (film) 3029, 1462 cm^{-1}; ^{1}H NMR δ 1.03−1.08 (m, 21H), 2.41 (m, 2H), 3.75 (dd, J = 9.3, 4.5 Hz, 1H), 3.76 (ABq, J = 10.2 Hz, 2H), 3.96 (d, J = 3.9 Hz, 1H), 4.17 (dd, J = 9.3, 6.3 Hz, 1H), 4.32 (m, 1H), 4.46 (s, 2H), 4.62 (ABq, J = 12.0 Hz, 2H), 5.00−5.08 (m, 2H), 5.84 (m, 1H), 7.29−7.35 (m, 10H); ^{13}C NMR δ 12.0, 18.0, 38.8, 64.9, 70.4, 71.9, 72.4, 84.0, 85.6, 86.1, 117.9, 127.5, 127.6, 127.7, 128.2, 128.4, 133.9, 138.1, 138.4; MS (CI) *m*/*z* 511 (M^+ + 1, 6%). Anal. Calcd for $C_{31}H_{46}O_4Si$: C, 72.90; H, 9.08. Found C, 72.60; H, 8.66.

1,4-Anhydro-4-*C*-(prop-2-enyl)-5-*O*-triisopropylsilyl-L-xylitol (11). To a blue solution of Li metal (65 mg, 9.32 mmol) in anhydrous liquid NH_3 (~10 mL) at −78 °C was added a solution of the dibenzyl ether **10** (476 mg, 0.93 mmol) in dry THF (6.5 mL) via a cannula. The reaction mixture was stirred at −78 °C for 10 min, then ether was added, and the reaction was quenched by the slow addition of solid NH_4Cl until the blue color had dissipated. The NH_3 was allowed to evaporate, and the salts were removed by filtration through Celite. Concentration of the filtrate gave the crude product, which was purified by silica gel chromatography with 40% ethyl acetate/petroleum ether as the eluent to give diol **11** (282 mg, 92%) as a viscous

oil: $[\alpha]^{18}_D = +3.4$ (*c* 0.26, $CHCl_3$); IR (film) 3420, 2940 cm^{-1}; ^1H NMR δ 1.07−1.12 (m, 21H), 2.37 (m, 2H), 3.65 (dd, $J = 9.3, 5.1$ Hz, 1H), 3.80 (ABq, $J = 10.5$ Hz, 2H), 4.02 (d, $J = 4.2$ Hz, 1H), 4.11 (dd, $J = 9.3, 5.7$ Hz, 1H), 4.32 (m, 1H), 5.10−5.17 (m, 2H), 5.87 (m, 1H); ^{13}C NMR δ 11.8, 17.8, 40.5, 67.4, 71.3, 79.0, 84.1, 84.8, 118.8, 132.9; MS (CI) *m/z* 331 ($M^+ + 1$, 24%). Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found C, 61.46; H, 10.51.

1,4-Anhydro-2,3,5-tri-*O*-acetyl-4-*C*-(prop-2-enyl)-L-xylitol (12). To a solution of the diol **11** (500 mg, 1.51 mmol) in dry THF (54 mL) was added TBAF·$3H_2O$ (955 mg, 3.03 mmol) at 0 °C. After the mixture was stirred at 0 °C for 45 min, the solvent was evaporated under reduced pressure and the crude product was flash filtered through a plug of TLC grade silica with 1:8 MeOH/CH_2Cl_2 as the eluent. The triol was then dissolved in a mixture of dry pyridine (15.1 mL) and acetic anhydride (7.6 mL), and DMAP (38 mg) was added. The mixture was stirred at room temperature overnight, and the solvents were removed under reduced pressure to give a brown residue, which was purified by silica gel chromatography using 40% ethyl acetate/petroleum ether as the eluent to provide the triacetate **12** (434 mg, 93%) as an oil: $[\alpha]^{20}_D = -24.0$ (*c* 0.36, $CHCl_3$); IR (film) 2980, 1750, 1436 cm^{-1}; ^1H NMR δ 2.06 (s, 3H), 2.08 (s, 6H), 2.45 (m, 2H), 3.77 (dd, $J = 10.5, 3.9$ Hz, 1H), 4.08 (ABq, $J = 11.7$ Hz, 2H), 4.28 (dd, $J = 10.5, 6.0$ Hz, 1H), 5.14−5.22 (m, 3H), 5.33 (d, $J = 3.3$ Hz, 1H), 5.79 (m, 1H); ^{13}C NMR δ 20.7, 20.8, 20.9, 39.1, 64.0, 70.3, 78.4, 79.3, 83.7, 119.7, 131.7, 169.5, 170.2, 170.3; MS (EI) *m/z* 300 (M^+, 89%). Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found C, 55.75; H, 6.83.

1,4-Anhydro-2,3,5-tri-*O*-acetyl-4-*C*-(2-oxoprop-1-yl)-L-xylitol, Sphydrofuran Triacetate (14). A mixture of palladium chloride (20 mg, 0.11 mmol), copper chloride (75 mg, 0.76 mmol) in DMF (2.1 mL), and water (314 μL) was stirred under an oxygen atmosphere (balloon) for 1 h (black suspension turned green-brown), after which time a solution of the alkene (229 mg, 0.76 mmol) in DMF (2.2 mL) and water (306 μL) was added. The reaction was left to stir at room temperature overnight and then heated to 45 °C for 4 h, cooled, diluted with ether, and filtered through a pad of Celite. The solvents were evaporated under reduced pressure to give the crude product (^1H NMR showed the presence of aldehyde **13**; ratio of ketone to aldehyde, 5.5:1), which was purified by flash chromatography using 30% acetone/petroleum ether as the eluent to provide **14** (198 mg, 82%) as a yellow oil. The spectroscopic data of this compound were identical to that reported previously:[3,11] $[\alpha]^{19}_D = -29.8$ (*c* 0.29, $CHCl_3$), lit.[3] $[\alpha]^{20}_D = -30$ (*c* 1.0, MeOH); IR (film) 1745 cm^{-1}; ^1H NMR δ 2.05 (s, 6H), 2.07 (s, 3H), 2.17 (s, 3H), 2.88 (ABq, $J = 16.5$ Hz, 2H), 3.80 (dd, $J = 10.2, 3.3$ Hz, 1H), 4.20 (ABq, $J = 12.0$ Hz, 2H), 4.21 (dd, $J = 10.5, 5.7$ Hz, 1H), 5.16 (m, 1H), 5.48 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR δ 20.6, 20.7, 31.5, 47.2, 63.7, 70.1, 78.0, 79.5, 82.3, 169.5, 169.9, 170.1, 205.2; MS (EI) *m/z* 316 (M^+, 34%); HRMS (ESI) calcd for $C_{14}H_{20}O_8Na$ ($M+Na^+$) 339.1056, found 339.1029.

(3*R*,4*S*,5*S*)-8-Methyl-1,7-dioxospiro[4,4]nonane-3,4,8-triol, Sphydrofuran (1). To a solution of the ketone **14** (98 mg, 0.310 mmol) in dry methanol (10 mL) under argon was added a solution of NaOMe in methanol (0.05 M, 31.0 μL, 1.55 μmol). After the solution was stirred at room temperature for 30 min, the methanol was removed under reduced pressure and the residue was chromatographed on neutral alumina (activity I) with 6:1:1 methanol/acetone/water as the eluent to give sphydrofuran (**1**) (58 mg, 98%). The spectroscopic data of this compound were identical to that reported previously:[3] $[\alpha]^{20}_D = +15.9$ (*c* 0.66, H_2O), lit.[2] $[\alpha]^{22}_D = +18.0$ (*c* 1.0, H_2O), lit.[4] $[\alpha]^{20}_D = +16.0$ (*c* 0.5, H_2O); ^1H NMR (300 MHz, DMSO-d_6, DMSO internal standard) δ 1.28 (s, 3H, α- or β-anomer), 1.33 (s, 3H, α- or β-anomer), 1.94 (br s, 1H), 1.95 (ABq, $J = 13.2$ Hz, 2H, α- or β-anomer), 2.07 (s, 3H, open chain form), 2.72 (ABq, $J = 14.4$ Hz, 2H, open chain form), 3.38−4.10 (m, 6H); HRMS (ESI) calcd for $C_8H_{14}O_5Na$ ($M+Na^+$) 213.0739, found 213.0728.

(3*R*,4*S*,5*R*)-8-Methyl-1,7-dioxospiro[4,4]nonane-3,4,8-triol, Isosphydrofuran (15). To a solution of the ketone **14** (96 mg, 0.303 mmol) in dry methanol (9.6 mL) under argon was added a solution of $NaOCH_3$ in MeOH (25 wt %, 139 μL, 0.607 mmol). The solution stirred at room temperature for 1.5 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 1:4 MeOH/CH_2Cl_2 as the eluent to afford compound **15** (45 mg, 78%) as a solid, which was recrystallized from acetone to give needles: mp 136−137 °C; $[\alpha]^{18}_D = -22.6$ (*c* 0.26, H_2O); IR (KBr disk) 3346, 2974 cm^{-1}; ^1H NMR (D_2O, HDO set to δ 4.80, 5:1 mixture of α- and β-anomers) δ 1.49 (s, 3H, α- or β-anomer), 1.53 (s, 3H, α- or β-anomer), 2.18 (ABq, $J = 14.4$ Hz, α- or β-anomer), 2.21 (ABq, $J = 14.7$ Hz, α- or β-anomer), 3.71 (s, 2H), 3.81 (s, 2H), 3.88 (m, 2H), 3.93 (d, $J = 10.5$ Hz), 3.98 (dd, $J = 10.5, 2.7$ Hz), 4.23 (d, $J = 2.7$ Hz), 4.33−4.40 (m, 2H), 4.36 (br s, 1H); ^{13}C NMR (100 MHz, D_2O, 1,4-dioxane external standard) δ 26.1, 27.5, 47.2, 65.0, 65.3, 73.6, 74.8, 75.5, 77.1, 88.9, 90.8, 95.1, 95.2, 107.5, 108.0; MS (EI) *m/z* 172 ($M^+ - H_2O$, 80%), 140 (47%), 95 (100%). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found C, 50.64; H, 7.67.

1,4-Anhydro-2,3,5-tri-*O*-acetyl-4-*C*-(2-oxo-prop-1-yl)-D-arabinitol, Isosphydrofuran Triacetate (16). To isosphydrofuran (**15**) (69 mg, 0.363 mmol) was added dry pyridine (3.63 mL), acetic anhydride (1.82 mL), and DMAP (9.0 mg), and the resultant solution was stirred at room temperature for 2 days then quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic fractions were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Removal of the solvent afforded the crude triacetate, which was purified by flash chromatography with 40% ethyl acetate/petroleum ether as the eluent to give the triacetate **16** (60 mg, 53%) as a pale-yellow oil: $[\alpha]^{18}_D = -8.6$ (*c* 1.45, $CHCl_3$); IR (film) 1746 cm^{-1}; ^1H NMR δ 2.03 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.17 (s, 3H), 2.88 (ABq, $J = 17.1$ Hz, 2H), 3.80 (dd, $J = 10.8, 3.6$ Hz, 1H), 4.22 (dd, $J = 10.8, 5.7$ Hz, 1H), 4.34 (ABq, $J = 11.7$ Hz, 2H), 5.10 (m, 1H), 5.29 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR δ 20.5, 20.8, 20.8, 30.9, 44.4, 64.0, 70.6, 78.01, 78.04, 83.6, 168.8, 169.9, 170.4, 205.2; MS (EI) *m/z* 316 (M^+, 11.3%); HRMS (ESI) calcd for $C_{14}H_{20}O_8Na$ ($M + Na^+$) 339.1056, found 339.1033.

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