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CARBOHYDRATE RESEARCH

Note

1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl (TIPS) migration facilitates one-pot formation of enantiomerically pure methyl 2,3-epoxy-D-xylonate

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Abstract

The reaction of 3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*O*-trifluoromethanesulfonyl-D-lyxono-1,4-lactone with K_2CO_3 in dry methanol at −10 °C gave enantiomerically pure methyl 2,3-anhydro-4,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-D-xylonate as the single product, resulting from migration of the TIPS group in an alkoxide intermediate.

Keywords: TIPS; Migration; Methyl 2,3-epoxy-D-xylonate; D-Lyxono-1,4-lactone; epoxyester

Silyl protecting groups are among the most versatile in organic synthesis [1]. In addition, the controlled migration of a silyl group is useful in a range of syntheses [2], though unanticipated rearrangements can cause problems. TIPS [a di-silyl protecting group] can be used to provide either thermodynamically or kinetically controlled di-silyl ether protection; in general, a seven membered TIPS ether is more stable than an eight membered one [3]. This flexibility in the use of TIPS as a protecting group, which in some circumstances is a drawback [4], allows an experimentally convenient one-pot formation of enantiomerically pure methyl 2,3-epoxy-D-xylonate **7**; the epoxyester **7** provides a key intermediate for synthesis of α- and β-amino acids and, as a 2,3-epoxyester, is likely to be an important precursor for syntheses of many synthetic and naturally occurring compounds of biological interest [5].

Alkoxides are the key intermediates in the ring contraction of α-triflate γ-sugar lactones to oxetanes [6]. When TIPS was used to protect the 3- and 5-hydroxyl groups of the α-triflate of γ-lyxonolactone **3**, the initially created anion **4** formed by treatment of **3** with methoxide did not form the oxetane **5** as anticipated. The eight membered silyl ring protecting group in **4** migrated to form the more stable seven membered silyl ether **6** (Scheme 1), which underwent ring closure to the target epoxyester **7**.

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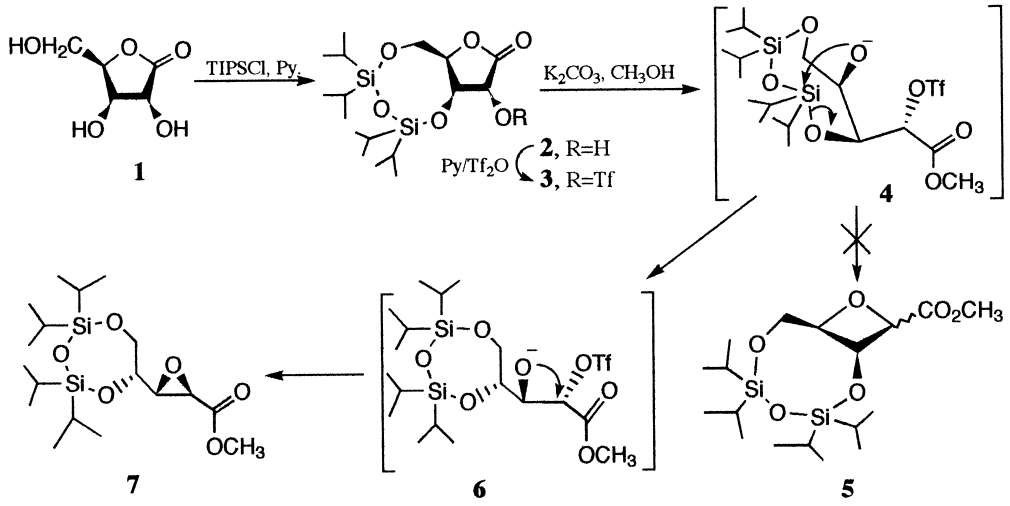


Scheme 1. TIPS migration facilitates formation of enantiomerically pure epoxyester **7** from D-lyxonolactone **1**.

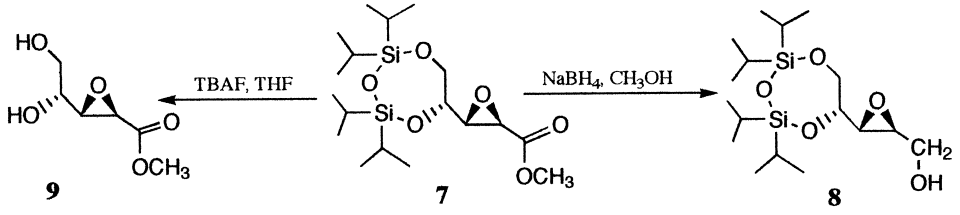
Protection of D-lyxonolactone **1**, readily available from oxidation of galactose [7], with 1,3-dichloro-1,1;3,3-tetraisopropyldisiloxane ($TIPSCl_2$) in dry pyridine under nitrogen gave the 3,5-silyl lactone **2** in 60% yield. The resulting TIPS-D-lyxonolactone **2** was esterified with trifluoromethanesulfonic anhydride and pyridine in dry dichloromethane at −23 °C to give the α-triflate-TIPS-D-lyxonolactone **3** in a 92% yield. The reaction of the α-triflate **3** with K_2CO_3 in dry methanol at −10 °C gave a single product in a good yield of 80%. NMR spectroscopic analyses confirmed the product to be methyl 2,3-epoxy-D-xylonate **7**, enantiomerically pure.

Reduction of the epoxyester **7** with sodium borohydride in methanol gave a quantitative yield of epoxy alcohol **8**; the TIPS group in **7** is readily removed with tetrabutylammonium fluoride to give a quantitative yield of **9** (Scheme 2). Both **8** and **9** are versatile precursors for syntheses of many interesting compounds [8]. Further investigation of the scope of TIPS-facilitated epoxyester formation from sugar lactones, and the behaviour of the oxiran ring of **7** under nucleophilic attack, is being undertaken.

1. Experimental

General methods.—Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 instrument at 200 MHz and 50 MHz, respectively. All chemical shifts are quoted on the δ-scale using residual solvent as an internal standard. IR spectra were recorded on a Perkin–Elmer 1750 spectrophotometer. Low resolution mass spectra were recorded on a VG Micromass 30F ZAB 1F spectrometer using chemical ionization (CIMS) in positive mode. Microanalyses were determined by the microanalysis service of the Dyson-Perrins laboratory and Butterworth Laboratories Ltd.

3,5-O-1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl-D-lyxono-1,4-lactone (**2**).—A mixture of lactone **1** (360 mg, 2.4 mmol), TIPSCI (790 mg, 2.5 mmol) and dry pyridine (10 mL) was stirred at room temperature for 12 h under N_2. The solvent was removed and the residue extracted with EtOAc (10–20 mL); the resulting solution was washed with



Scheme 2. Reduction of ester group and removing TIPS group of **7**.

H_2O (2×15 mL), dried over $MgSO_4$, and purified by flash chromatography (This working procedure is referred to as standard work-up in the following.) to give the trifate **2** (800 mg, 60%), a colourless oil; ν 3446 (OH), 1786 (C=O) cm^{-1}; NMR ($CDCl_3$): ^1H, δ 4.65 (dd, 1 H, $J_{3,2}$ 4.6, $J_{3,4}$ 2.6 Hz, H-3), 4.46 (dd, 1 H, $J_{2,OH}$ 10.5 Hz, H-2), 4.41 (m, 1 H, H-5), 4.12 (m, 1 H, H-4), 3.95 (m, 1 H, H-5′), 1.11–1.02 (m, 28 H, H-4 x isopropyl); ^{13}C, δ 175.0 (s, *C*O), 77.8 (d, C-2), 70.8 (d, C-3), 69.5 (d, C-4), 57.5 (t, C-5), 17.2, 17.0, and 16.7 (3 q, 4 CH(*C*H_3)$_2$), 12.8, 12.8, 12.3, and 12.2 (4 d, 4 *C*H(CH_3)$_2$); CIMS: *m*/*z* 408 $(M + NH_4)^+$. Anal. Calcd for $C_{17}H_{34}O_6Si_2$: C, 52.29; H, 9.01. Found: C, 52.27; H, 8.77.

*3,5-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-O-trifluoromethanesulfonyl-*D*-lyxono-1,4-lactone* (**3**).—To a solution of **2** (230 mg, 0.51 mmol) in dry CH_2Cl_2 (30 mL) with dry pyridine (0.5 mL, 6 mmol) was added dropwise trifluoromethanesulfonic anhydride (1.0 mL, 6 mmol) at −23 °C, then stirred for further 30 min. When TLC showed no starting material remained and one major product, standard work-up afforded **3** (245 mg, 92%) as syrup; ν 1816 (C=O) cm^{-1}; NMR ($CDCl_3$): ^1H, δ 5.43 (d, 1 H, $J_{2,3}$ 4.2 Hz, H-2), 4.88 (dd, 1 H, $J_{3,4}$ 2.3 Hz, H-3), 4.51 (m, 1 H, H-4), 4.11–3.92 (m, 2 H, H-5), 1.03 (m, 28 H, H-4 x isopropyl); ^{13}C, δ 167.3 (s, *C*O), 79.1 (d, C-2), 78.1 (d, C-3), 69.0 (d, C-4), 57.1 (t, C-5), 17.0 and 16.6 (2 q, 4 CH(*C*H_3)$_2$), 13.0, 12.6, 12.3, and 12.2 (4 d, 4 *C*H(CH_3)$_2$); CIMS: *m*/*z* 540 $(M + NH_4)^+$. Anal. Calcd for $C_{18}H_{33}O_8Si_2SF_3$: C, 41.50; H, 6.73. Found: C, 41.36; H, 6.36.

*Methyl 2,3-anhydro-4,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*D*-xylonate* (**7**).—To a stirred solution of **3** (670 mg, 1.3 mmol) in dry MeOH (30 mL) was added K_2CO_3 (220 mg, 1.5 mmol) at −10 °C. The resulting suspension was stirred for 10–20 min, then TLC showed no starting material remained and one major product. After standard work-up, **7** was obtained (414 mg, 80%) as a colourless oil; $[\alpha]_D^{20}$ −75.8° (*c* 0.9, $CHCl_3$); ν 1758 (C=O) cm^{-1}; NMR ($CDCl_3$): ^1H, δ 4.08 (m, 1 H, H-4), 4.00 (m, 1 H, H-5), 3.79 (m, 1 H, H-5′), 3.75 (s, 3 H, H-CH_3), 3.49 (d, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 3.22 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 1.05 (m, 28 H, H-4 x isopropyl); ^{13}C, δ 169.6 (s, *C*O), 73.1 (d, C-4), 67.3 (t, C-5), 58.1 (d, C-2), 52.3 (q, O*C*H_3), 49.1 (d, C-3), 17.0 and 16.7 (2 q, 4 CH(*C*H_3)$_2$), 13.1, 13.0, 12.8, and 12.7 (4 d, 4 *C*H(CH_3)$_2$); CIMS: *m*/*z* 422 $(M + NH_4)^+$, 405 $(M + H)^+$. Anal. Calcd for $C_{18}H_{36}O_6Si_2$: C, 53.32; H, 8.66. Found: C, 53.42; H, 8.97.

*2,3-Anhydro-4,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*D*-xylitol* (**8**).—To a solution of **7** (40 mg, 0.1 mmol) in MeOH (10 mL) was added $NaBH_4$ (4.0 mg, 0.1 mmol) at 0 °C, and the mixture was stirred for 30 min at room temperature. When TLC showed no starting material and only one product, excess NH_4Cl (5 mg) was added and the solvent was removed under reduced pressure. After standard work-up, **8** (37 mg, 100%) was obtained as a colourless oil; $[\alpha]_D^{20}$ −10.9° (*c* 2.8, $CHCl_3$); ν 3402 (OH) cm^{-1}; NMR ($CDCl_3$): ^1H, δ 4.01–3.93 (m, 3 H, H-1,4,5), 3.83 (dd, 1 H, $J_{5',4}$ 8.6, $J_{5',5}$ 17.2 Hz, H-5′), 3.65 (dd, 1 H, $J_{1',2}$ 4.1, $J_{1,1'}$ 12.8 Hz, H-1′), 3.19 (m, 1 H, H-2), 3.05 (dd, 1 H, $J_{3,4}$ 4.1, $J_{3,2}$ 2.3 Hz, H-3), 1.06 (m, 28 H, H-4 x isopropyl); ^{13}C, δ 74.4 (d, C-4), 67.6 (t, C-5), 61.0 (t, C-1), 55.9 (d, C-3), 54.8 (d, C-2), 17.1 and 17.0 (2 q, 4 CH(*C*H_3)$_2$), 12.9, 12.5, 12.3, and 12.1 (4 d, 4 *C*H(CH_3)$_2$); CIMS: *m*/*z* 394 $(M + NH_4)^+$, 377 $(M + H)^+$. Anal. Calcd for $C_{17}H_{36}O_5Si_2$: C, 53.99; H, 9.76. Found: C, 54.16; H, 9.57.

*Methyl 2,3-anhydro-*D*-xylonate* (**9**).—*tetra*-Butylammonium fluoride in THF (1 mL, 1 M, 1.0 mmol) was added dropwise to a stirred solution of **7** (80 mg, 0.2 mmol) in THF (10 mL). After 20 min, TLC showed no starting material remained and one major product; standard work-up afforded the epoxyester **9** (33 mg, 100%) as a colourless oil; $[\alpha]_D^{20}$ −37.4° (*c* 1.3, H_2O); ν 3402 (OH), 1741 (C=O) cm^{-1}; NMR ($CDCl_3$): ^1H, δ 4.21 (s, 1 H, OH), 4.01 (s, 1 H, OH), 3.70 (s, 3H, Me), 3.61 (s, 3 H, H-5,5′,4), 3.47 (d, 1 H, $J_{2,3}$ 1.9 Hz, H-2), 3.25 (dd, $J_{3,4}$ 4.1 Hz, H-3); ^{13}C, δ 170.4 (s, *C*O), 71.3 (d, C-4), 64.4 (t, C-5), 59.8 (d, C-3), 52.5 (q, CH_3), 50.6 (d, C-2); CIMS: *m*/*z* 180 $(M + NH_4)^+$. Anal. Calcd for $C_6H_{10}O_5$: C, 44.08; H, 6.54. Found: C, 44.44; H, 6.17.

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