Tetrahedron Vol. 40, No. 11, pp. 2083 to 2087, 1984
Printed in Great Britain.

0040-4020/84 $03.00 + .00
Pergamon Press Ltd.

STUDIES DIRECTED AT THE SYNTHESIS OF VERRUCAROL FROM D-GLUCOSE: THE A–B MOIETY

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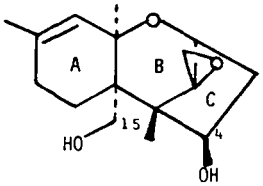
(*Received in the U.S.A.* 16 *June* 1983)

Abstract—The Claisen rearrangement of an ally vinyl ether residue elaborated at C4 of a pyranoside ring, occurs with β-stereoselectivity leading predominantly to the isomer having the ethylene and acetaldehyde groups in equatorial and axial orientations respectively. The acetaldehyde moiety is extended to a butanoate, and the C5 hydroxymethyl of the sugar is oxidized to an aldehyde. Anionic ring closure of the activated methylene to the aldehyde is induced with sodium hydride, and dehydration to the α,β-unsaturated ester is effected with acetic anhydride in pyridine.

A program of research in our laboratories is concerned with the development of synthetic routes to the tricothecanes.[1] This family of natural products is currently the focus of considerable interest in view of the wide range of biological activities displayed by its members.[2] In addition, the intricate structural features, especially in the macrocyclic members, present formidable challenges to which synthetic organic chemists succumb readily.[3] We recently described synthetic routes to the incomplete macrocycle trichoverrin B as well as verrucarin J,[4] in which the macrocyclic components were obtained from D-glucose derivatives,[5] while the tricyclic backbone, verrucarol, **1**, was obtained by deoxygenation of anguidine.[6] D-Glucose is a plausible precursor for verrucarol and its congeners, and efforts towards this objective are underway in our laboratory.



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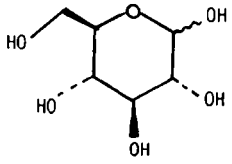

2

Juxtaposition of verrucarol, **1**, with D-glucose, **2**, (Scheme 1) suggests that one synthetic approach might be to construct the A and C rings at the "back" and "front" of the sugar respectively. In this approach, functionalized alkyl groups would have to be placed at all sites on the ring (excepting C5) and twice at C3 and C4. Thus, excellent opportunities exist to take advantage of the attributes of the hexopyranoside ring for effecting stereocontrolled reactions.[7]

The AB moiety indicates the need to furnish C4 of the pyranoside ring with implements that (a) permit the annulation, and (b) provide for the C15 hydroxymethyl group of verrucarol. Thus, different, functionalized geminal alkyl substituents are required at that site. For our model studies we used the 4-uloside, **3**, whose ready preparation from triacetyl glucal has been described.[8] Reaction of **3b** with carbomethoxymethylenetriphenylphosphorane afforded a single ester assigned as the E-isomer **4a** in view of the fact that upon desilylation to the hydroxyester **4b**, cyclization to lactone **5** could not be induced. Our prior experience had shown that Cu(I) induced conjugate additions at C4 proceeded with high β-selectivity.[9] However, Cu(I) mediated addition of vinyl magnesium bromide to **4a** gave a 3 : 2 mixture of isomers **7a** and **8a**, thereby showing poor stereoselectivity.

Configurational assignments of **7a** and **8a** are based on the corresponding lactones **6a** and **9b** which formed spontaneously upon desilylation of the products. The structural assignments for **6a** and **9a** will be discussed below.

As an alternative avenue to geminal substitution, the Claisen Rearrangement of the allyl vinyl ether **4d** seemed appealing, since either of the two possible products, **7b** or **8b**, could be adapted for elaboration of the A ring. Accordingly, the ester **4a** was converted into alcohol **4c** and subsequently **4d** by conventional procedures,[10] the formation of the last being driven to completion by using ethyl vinyl ether itself as a solvent. The rearrangement proceeded smoothly upon refluxing in benzonitrile (190°) for 15–30 min, to give a nearly quantitative mixture of the readily separated epimers **7b** and **8b** in the ratio 9 : 1.

For structural assignments, these products were correlated with the previously obtained lactones **6a** and **9a** in the following manner. Desilylation of each gave a pair of anomeric lactols **6**(b + c) and **9**(b + c), members of each pair being readily separated chromatographically. The most straightforward assignment was for the major anomer **9b** in which H5 contained two couplings of 4.4 Hz (assignable as $J_{5,6}$ and $J_{5,6'}$) and a third one of 2.2 Hz assignable as the *W*-coupling to the anomeric proton H10. The other anomer, **9c**, showed H5 as a doublet of doublets, $J_{5,6} = J_{5,6'} = 4.6$ Hz.

The configurational relationship between **9b** and **9c** was apparent from the fact that oxidation of each gave **9a**, identical with that obtained above.

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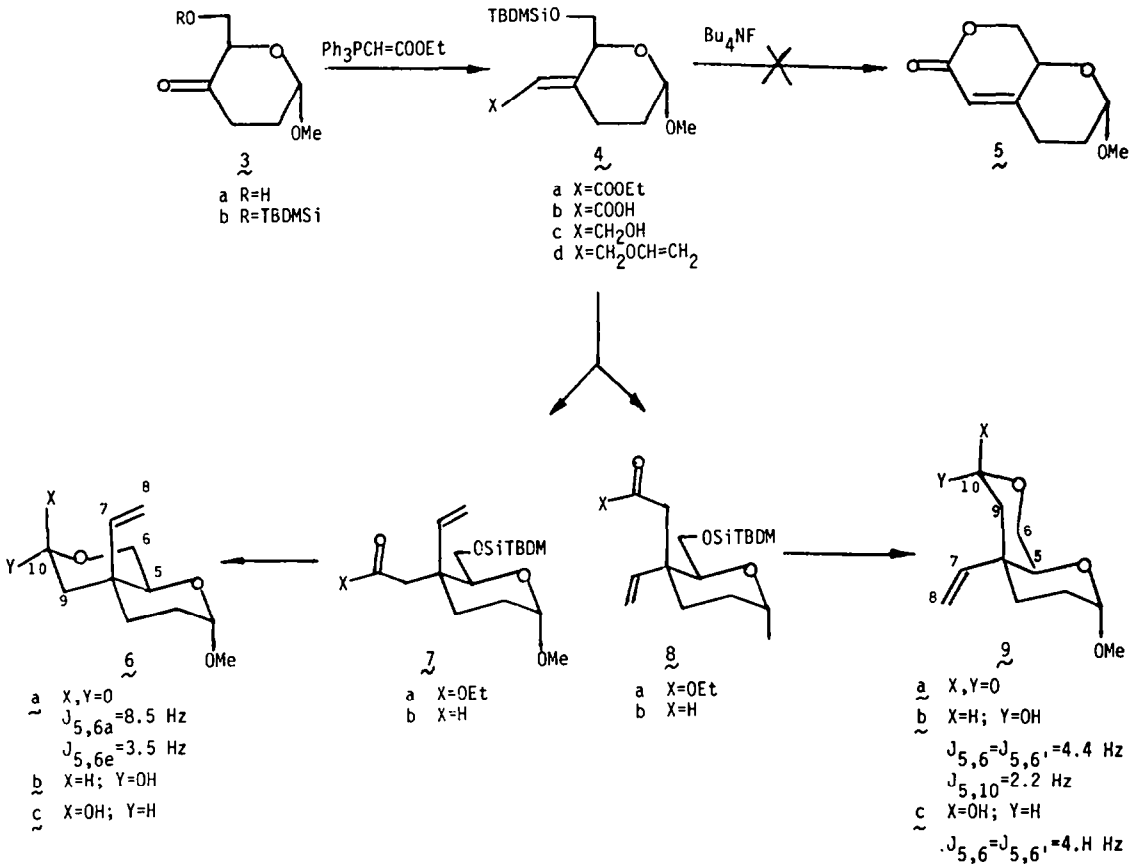
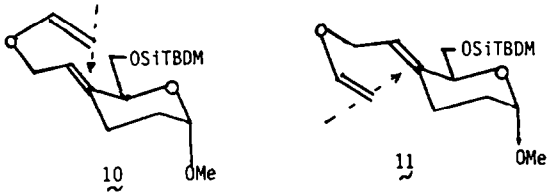


In the case of the hemiacetals **6b** and **6c**, the assignments of H5 were not as readily apparent; however, upon oxidation to the lactone, H5 was readily observable and found to have couplings of 3.5 Hz ($J_{5,6e}$) and 8.5 Hz ($J_{5,6a}$). The latter value, being clearly assignable to the trans-diaxial protons, was enough to make the assignment secure.

These parameters for the lactols and/or lactones (**6** and **9**) then enabled us to make assignments to the corresponding progenitors **7** and **8**.

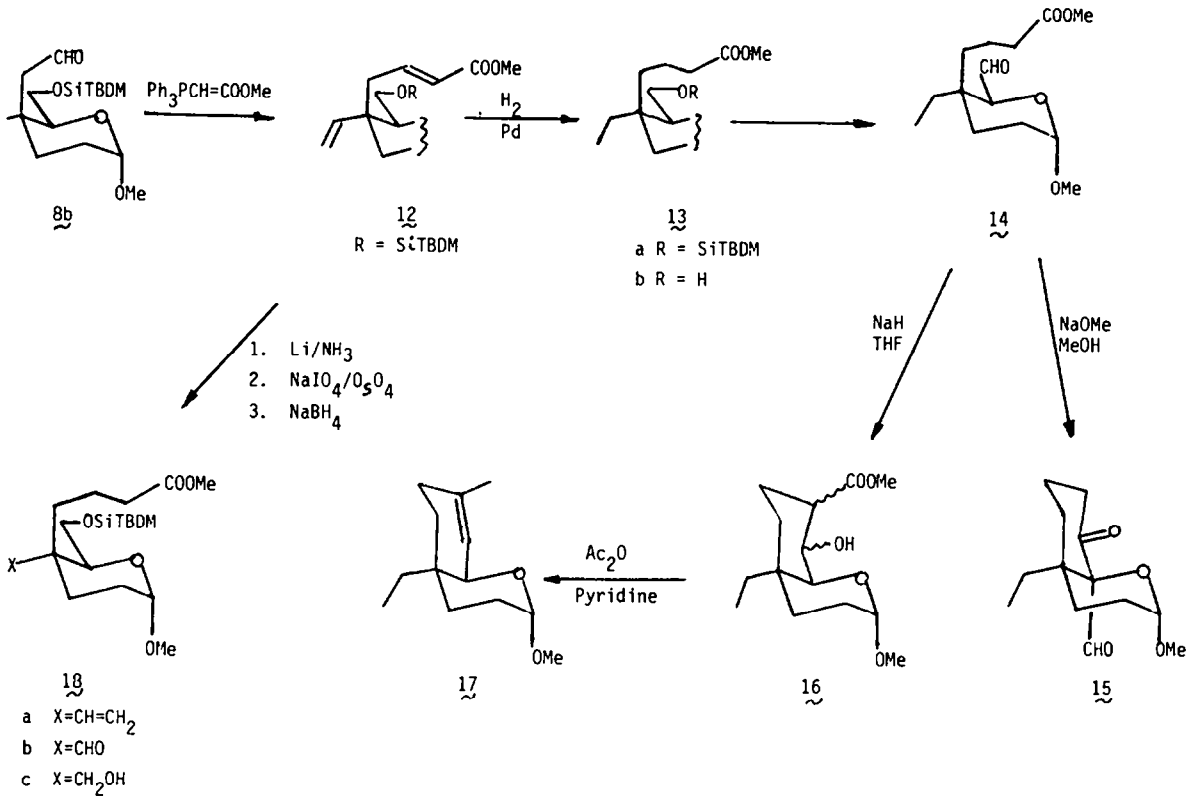


Thus, the predominant isomer from the rearrangement of **4d** was **8b**, implying that the β-folding pattern, **10**, was preferred to the α-alternative **11**. This result might seem surprising since in the β-folding pattern, the terminal methylene approaches cis to the siloxymethyl group and should therefore experience greater steric interactions than with the α-folding pattern, **11**. This phenomenon is currently being examined as part of a general study on application of Claisen rearrangements at various sites of pyranoside ring and will receive further comment in due course.

Aldehyde **8b** was converted into the unsaturated and saturated esters, **12** and **13a** respectively, and then desilylated and oxidized to the aldehydo ester **14** in 80% overall yield from **8b**. Treatment of **14** with potassium tertiary butoxide in either tertiary butanol or benzene as solvent led to decomposition. With sodium methoxide in methanol a product was formed; but the disappearance of the ester methoxyl (which is distinguishable from the glycosidic methoxyl in the NMR—see Experimental) combined with the presence of an aldehyde proton suggested that the product was **15**. However, the desired material **16**, was obtained by use of sodium hydride in tetrahydrofuran, and dehydration for **17** was effected by stirring with acetic anhydride in pyridine at room temperature.

Compound **12** had thus been shown to be plausible precursor for the AB ring model **17**; however, for verrucarol, the C4 substituent should be hydroxymethyl instead of ethyl. Provision for this would be made (a) if the vinyl group of **12** could be oxidized selectively, or (b) if the conjugated double bond could be hydrogenated selectively. In pursuing option (a), ozonolysis of **12** was attempted; but cleavage of the vinyl group was only partial successful. With respect to option (b) attempted reductions with copper hydride[11] or triethyl silane[12] were unsuccessful; however, success was had with lithium in ammonia and the product, **18a** was oxidized with the Lemieux–Johnson reagents,[13] the resulting aldehyde, **18b**, being reduced directly to give alcohol **18c**.

In summary, the Claisen rearrangement proceeds with great stereoselectivity to give the gem-dialkyl derivative **12**. The C4 substituents of this material can be manipulated selectively to provide implements for the elaboration of the AB component of verrucarol.



EXPERIMENTAL

General. M.p.s were determined in capillary tubes in a Büchi Model 510 and are uncorrected. Elemental analyses were performed by Dr. F. Kasler, Department of Chemistry, University of Maryland. ^{1}H NMR spectra were determined in deuteriochloroform with internal tetramethylsilane as the standard, unless otherwise stated, on one of the following spectrometers: Varian T-60, Varian EM-360, Perkin–Elmer R-12B, Bruker WP-80, Varian XL-100, Varian XL-200, Varian HR-220, Varian XL-360 or Bruker WH-400. (For numbering patterns, see Scheme 2.) Coupling constants were measured directly from the spectra or calculated from the peak listings. IR spectra were determined on either a Beckman IR-10 or a Perkin–Elmer 298 spectrometer. Neat samples were smeared on sodium chloride plates and solutions were placed in sodium chloride cells. Low resolution MS were run on a Hitachi/Perkin–Elmer RMH-2 and HRMS were determined with a VG 7070F. Optical rotations were determined on a Perkin–Elmer 231 polarimeter. GLC was performed on a Hewlett–Packard 5730A gas chromatograph using a stainless steel column 6 ft × 1/8in.) packed with 3% OV-170n on Chromasorb WHP. The detector and injector temperatures were 260° and 230° respectively. The helium flow rate was 25 mL/min. Ratios were determined by measuring peak areas. TLC was performed using aluminum plates precoated with silica gel (HF-254, 0.2 mm thickness) containing a fluorescent indicator (Merck, No, 5539). The following solvent systems were used: (A) ethyl acetate–petroleum ether (30°–60°), (10:90); (B) ethyl acetate–petroleum ether (30°–60°), (20 : 80); (C) ethyl acetate; (E) methanol—methylene chloride (90 : 10). The chromatograms were viewed under a UV light (254 nm), sprayed with concentrated sulfuric acid and heated until charring occurred. PTLC was done using glass plates (20 cm × 20 cm) coated with silica gel (PR-254, Merck) and the above-mentioned solvent systems. Column chromatography was carried out using silica gel (Merck 70-230 mesh ASTM or 230–500 mesh ASTM).

Methyl 6 - *O* - *t* - *butyldimethylsilyl* - 2,3 - *dideoxy* - α - D - *glycero* - *hexopyranoside* - 4 - *ulose* (**3b**). A soln of methyl 2,3 - dideoxy - α - D - *glycero* - hexopyranosid - 4 - ulose **3a**,[8] (3.0 g, 18.75 mmol) in dry DMF (50 mL) was stirred at room temperature for 3 hr with tertbutyldimethylsilyl chloride (3.15 g, 21 mmol) and imidazole (1.45 g, 21.0 mmol). The reaction mixture was then diluted with diethyl ether (300 mL), washed with water (2 × 100 mL), and dried (Na_2SO_4). Evaporation of the solvent gave **3b** as a syrup (4.85 g, 95%): TLC R_f 0.40 (A); IR ($CHCl_3$) 1729 (C=O) cm^{-1}; ^{1}H NMR δ 0.06 (s, 6, $Si(CH_3)_2$), 0.90 (s, 9, $(CH_3)_3CSi$), 1.9–2.3 (m, 2, H-2a, H-2e), 2.4–s.7 (m, 2, H-3a, H-3e), 3.40 (s, 3, OCH_3), 3.85–4.20 (m, 3, H-6a, H-6e, H-5), 4.95 (t, 1, $J_{1,2'} = 3.9$ Hz, $J_{1,2} = 4.3$ Hz, H1) (Found: C, 56.86; H, 9.52. Calc. for $C_{13}H_{26}O_4Si$: C, 56.93; H, 9.49%.)

Methyl 6 - *O* - *t* - *butyldimethylsilyl* - 2,3,4 - *trideoxy* - 4- *C* (*E-carboethoxy* - *methylene*) - α - D - *glycero* - *hexopyranoside*-(**4a**). The keto sugar **3b** (4.0 g, 14.6 mmol) and carboethoxymethylenetriphenylphosphorane (24.4 g 70 mmol) were dissolved in dry acetonitrile (200 mL) and the solution was refluxed for 2 days. The product, compound **4a**, (3.50 g, 70%) was obtained as a syrup: TLC R_f 0.60 (B); IR ($CHCl_3$) 1725, 1658 (α,β-unsaturated ester) cm^{-1}; $[\alpha]_D^{20}$ + 78.0° (C, 1.36, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6, $(CH_3)_2Si$), 0.94 (s, 9, $(CH_3)_3CSi$), 1.25 (t, 3, J = 7.0 Hz, $OCOCH_2CH_3$), 1.75–2.10 (m, 3, H-2a, H-2e), 2.8–3.0 (m, 2, H-3a, H-3e), 3.25 (s, 3, OCH_3), 3.85–4.22 (m, 5, H-5, H-6a, H-6e, $OCOCH_2$), 4.8 (t, 1, $J_{1,2} = 3.9$ Hz, $J_{1,2'} = 4.20$, H-1), 5.75 (m, 2, H-7) (Found: C, 59.19; H, 9.24. Calc. for $C_{17}H_{32}O_5Si$: C, 59.30; H, 9.30%.)

Methyl 6 - *O* - *t* - *butyldimethylsilyl* - 2,3,4 - *trideoxy* - 4- *C* - (*Hydroxymethyl methylene*) - α - D - glycero - *hexopyranoside* (**4c**). The ester **4a** (3.5 g, 10.1 mmol) was dissolved in dry diethyl ether (150 mL) and lithium aluminum hydride (0.45 g, 12 mmol) added. The reduction was completed after refluxing for 1 hr and $Na_2SO_4 \cdot 10H_2O$ was added to the cooled reaction mixture to destroy the excess reagent. The mixture was filtered through a pad of Celite and evaporation gave **4c** (2.75 g 90%) as a syrup. TLC R_f 0.18 (C); $[\alpha]_D^{20}$ + 94.40° (c, 1.6, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6 $(CH_3)Si$), 0.90 (s, 9, $(CH_3)_3CSi$), 1.6–2.5 (m, 4, H-2a, H-2e, H-3a, H-3e), 3.4-3.9 (m, 3, H-5, H-6a, H-6e), 4.1–4.3

(m, 2, H-8, H-8′), 5.5–5.7 (m, 1, H-7). (Found: C, 59.52; H, 9.98. Calc. for $C_{15}H_{30}O_4Si$: C, 59.61; H, 9.93%.)

Methyl 6 - *O* - *t* - *butyldimethylsilyl* - 2,3,4 - *trideoxy* - 4 - *C* - (*vinyloxymethyl* - *methylene*) - α - D - *glycero* - *hexopyranoside* (**4d**). A solution of the alcohol **4c** 2.0 g, 6.5 mmol) in ethyl vinyl ether (400 mL) was stirred with a catalytic amount of mercuric acetate until TLC indicated that the reaction was complete (12 h). The soln was then washed with saturated sodium bicarbonate, water, dried (Na_2SO_4) and evaporated to give **4d** (1.95 g, 90%) as a syrup: TLC R_f 0.65 (A); $[\alpha]_D^{20} + 73.35°$ (c, 2.75 $CHCl_3$); ^1H NMR δ 0.05 (s, 6, CH_3)Si), 0.95 (s, 9, $(CH_3)_3CSi$), 3.35 (s, 3, OCH_3), 3.6–4.3 (m, 7, H-5, H-6a, H-6e, H-8, H-8′, H-10, H-10′), 4.75 (t, 3, $J_{1,2} = J_{1,2'} = 4.0$ Hz, H1), 5.45 (bt, 1, $J_{7,8} = 6.0$ Hz, H-7), 6.45 (dd, 1, $J_{9,10} = 7.0$ Hz, $J_{9,10} = 14.0$ Hz, H-9) (Found: C, 62.05; H, 9.69. Calc. for $C_{17}H_{32}O_4Si$: C, 62.19; H, 9.75%.)

Methyl - 6 - *O* - *t* - *butyldimethylsilyl* - 2,3,4 - *trideoxy* - 4 - *C* - (*formylmethyl*) - 4 - *C* - *vinyl* - α - D - *threo* - *hexopyranoside* (**7b**) *and* α - D - *erythro* - *hexopyranoside* (**8b**). The ally vinyl ether **4d** (1.50 g, 4.57 mmol) dissolved in dry benzonitrile (50 mL) was boiled under reflux for 1 hr. Evaporation of the solvent under high vacuum gave a 1 : 9 mixture **7b** and **8b** (1.35 g, 90%) which was chromatographed on a silica gel column using solvent A. For the major compound **8b**: TLC R_f 0.58 (A); $[\alpha]_D^{20} + 61.90°$ (c, 1.3, $CHCl_3$); IR ($CHCl_3$); 1725 cm^{-1}; ^1H NMR 0.05 (s, 6, $(CH_3)_2Si$), 0.90 (s, 9,($CH_{33}CSi$), 1.60–2.40 (m, 4, H-2a, H-2e, H-3e, H-3a), 2.45–2.6 (m, 2, H-9, H-9′), 3.30 (s, 3, $OC2_3$), 3.35–3.8 (m, 3, H-5, H-6, H-6′), 4.5–4.65 (m, 1, H-1), 4.85–5.3 (m, 2, H-8, H-8′), 6.25 (dd, 1, $J_{7,8} = 11.0$ Hz, $J_{7,8'} = 18.0$ Hz, H-7), 9.75 t, 1, $J_{9,10} = J_{9,10'} = 2.8$ Hz, H-10). (Found: C, 62.15; H, 9.62. Calc. for $C_{17}H_{32}O_4Si$: C, 62.19; H, 9.75%.) For the minor product **7b**: TLC R_f 0.55 (A); $[\alpha]_D^{20} + 30.1°$ (c, 0.55 $CHCl_3$); ^1H NMR δ 2.38 (dd, 1, $J_{9,9'} = 1.60$ Hz, $J_{9,10} = 3.0$ Hz, H-9), 2.90 (dd, 1, $J_{9',10} = 3.2$ Hz, H-9′), 6.00 (dd, 1, $J_{7,8} = 18.0$ Hz, $J_{7,8} = 11.0$ Hz, H-7), 9.75 (bt, 1, H-10).

Methyl 2,3,4 - *trideoxy* - 4 - *C* - (*formylmethyl*) - 4 - *C* - *vinyl* - α - D - *erythro* - *hexopyranoside* - 6,10 - *lactone* (**9b**). A soln of **8b** (1.0 g, 3.0 mmol) in THF was stirred with nBu_4NF at room temp until the silyl ether was removed (TLC). The solvent was then evaporated, and the residue dissolved in diethyl ether and washed with water. The recovered material was a mixture of **9b** and **9c** (0.61 g, 95%) which was chromatographed on a silica gel column using solvent D. The major product **9b** exhibited the following characteristics: TLC R_f 0.40 (D); ^1H NMR δ 3.38 (s, 3, OCH_3), 3.90 (ddd, 1, $J_{5,6} = J_{5,6'}$ 4.4 Hz, $J_{5,10} = 2.2$ Hz, H-5), 4.75 (bd, 1, H-1), 5.00 (ddd, 1, $J_{9,10} = J_{9',10}$ 6.6 Hz, H-10), 5.30 (dd, 1, $J_{7,8'} = 18.0$ Hz, $J_{8',9} = 1.5$ Hz, H-8′), 5.45 (dd, 1, $J_{7,8} = 11.0$ Hz, H-8), 6.32 (dd, 1, H-7). For the minor product **9c**: ^1H NMR δ 3.85 (dd, 1, $J_{5,6} = J_{5,6'} = 4.1$ Hz, H-5).

Chromium trioxide (0.3 g, 2.9 mmol) was added to a mixture of pyridine (0.50 mL, 5.8 mmol) and dry methylene chloride (10 mL) and the resulting solution was stirred for 5 min. To this was added **9b** or **9c** (0.05 g, 0.24 mmol) and the solution was stirred for an additional 5 min. Diethyl ether (50 mL) was then added and the solution was filtered through a pad of Florisil. Evaporation of solvent gave **9a** (0.26 g, 90%) as a syrup: TLC R_f 0.58 (C); ^1H NMR δ 0.9–1.3 and 1.5–1.9 (m, 4, H-2a, H-2e, H-3a, H-3e), 2.28 (dd, 1, $J_{99'} = 17.0$ Hz, $J_{95} = 1.0$ Hz, H-9), 2.88 (d, 1, H-9′), 3.40, (s, 3, OCH_3), 4.10 (dd, 1, $J_{5,6e} = 6.2$ Hz, $J_{6a,6e} = 13.5$ Hz, H-6e), 4.25 (d, 1, H-6a), 4.18 (dd, 1, H-5), 4.80 (m, 1, H-1), 5.25 (dd, 1, $J_{7,8'} = 17.0$ Hz, H-8′), 5.40 (dd, 1, $J_{7,8} = 11.0$ Hz, H-8), 6.35 (dd, 1, H-7); HRMS (Found: 213.1124. Calc. for $C_{11}H_{16}O_4$: 213.1127 (M^+ 1)%.)

Methyl 2,3,4 - *trideoxy* - 4 - *C* - (*formylmethyl*) - 4 - *C* - *vinyl* - α - D - *thereo* - *hexopyranoside* - 6,10 - *lactone* (**6a**). Compound **7b** (0.60 g, 2.0 mmol) was desilylated as described above for **8b** and the mixture of hemiacetals obtained, **6b** and **6c**, was oxidized as described for **9b** to give lactone **6a** (0.18 g, 90%): TLC R_f 0.32 (C); ^1H NMR 4.20 (dd, 1, $J_{5,6a} = 8.5$ Hz, $J_{5,6e} = 3.5$ Hz, H-5), 4.82 (m, 1, H-1), 6.10 (dd, 1, $J_{7,8} = 11.0$ Hz, $J_{7,8'} = 17.0$ Hz, H-7); HRMS (Found: 213-1123. Calc. for $C_{11}H_{16}O_4$: 213.1127 ($M^+ + 1$)%.)

Methyl 4 - *C* - (*E* - *carboethoxymethylene*) - 2,3,4 - *trideoxy* - α - D - *glycero* - *hexopyranoside* (**4b**). The unsaturated ester **4a** (0.1 g, 0.29 mmol) was desilylated as described above for **8b** (1 hr) to give **4b** (0.055 g, 85%) as a syrup: TLC R_f 0.05 (D); ^1H NMR δ 1.32 (t, 3, J = 7.5 Hz, $OCOCH_2CH_3$), 1.75–2.10 (m, 2, H-2a, H-2e), 2.8–3.0 (m, 2, H-3a, H-3e), 3.28 (s, 3, OCH_3), 4.2 (q, 2, $OCHOCH_2CH_3$), 5.00 (5, 1, $J_{1,2} = J_{1,2'} = 4.0$ Hz, H-1), 5.66 (5, 1, $J_{7,3} = 1.2$ Hz, H-7). (Found: C, 57.36; H, 7.81. Calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.85%.)

Methyl 2,3,4 - *trideoxy* - 4 - *C* - (*formylmethyl*) - 4 - *C* - *vinyl* - α - D - *threo* (**6a**) *and erythro* (**9a**) *hexopyranoside* - 6,10 *lactone*. Magnesium (0.06 g, 1.2 mmol), vinyl bromide (0.90 mL) and a crystal of iodine were refluxed in dry diethyl ether (20 mL) under argon for 0.5 hr. This soln was then cooled to −78° and a soln of tri-n-butylphosphine copper iodide complex[14] (0.01 g) in dry diethyl ether (5 mL) was added. The resulting yellow suspension was stirred at −78° for 0.5 hr. The ester **4a** (0.1 g, 0.29 mmol) was then added, the reaction mixture was stirred for 1 hr and then poured in aqueous ammonium chloride soln. The blue aqueous layer was then extracted with chloroform (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated to give a 3 : 2 mixture of **7a** and **8a** respectively. A soln of this crude mixture in dry THF (50 mL) was then desilylated as described above for **8b** (1 hr). The ^1H NMR spectrum showed that the product was a mixture of **6a** and **9b** in the ratio of 3 : 2.

Methyl 6 - *O* - *t* - *butyldimethylsilyl* - 2,3,4 - *trideoxy* - 4- *C* - (*methyl* - 4 - *but* - 2 - *enoate*) - 4 - *C* - *vinyl* - α - D - *erythro* - *hexopyranoside* (**12**). The aldehyde **8b** (1.0 g, 0.3 mmol) was refluxed in acetonitrile with carbomethoxymethylene triphenylphosphorane (3.0 g, 1.0 mmol) for 1 hr and worked up according to procedure described above for **4a**. The product **12** (1.05 g, 90%) was a syrup: TLC R_f 0.70 (C); IR ($CHCl_3$) 1725 (C–O) cm^{-1}; ^1H NMR δ 0.05 (s, 6, $(CH_3)_2Si$), 0.95 (s, 9, $(CH_3)_3CSi$), 1.5–1.8 (m, 4, H-2a, H-2e, H-3a, H-3e), 2.2–2.6 (m, 2, H-9, H-9′), 3.4 (s, 3, (OCH_3), 3.75 (s, 3, $COOCH_3$), 3.68–3.8 (m, 3, H-5, H-6, H-6′), 4.6–4.7 (m, 1, H-1), 4.85–5.3 (m, 2, H-8, H-8′), 6.20 (dd, $J_{7,8} = 11.0$ Hz, $J_{7,8'} = 18.0$ Hz, H-7), 7.0 (dd, 1, $J_{9,10} = 8.0$ Hz, $J_{10,11} = 16.0$ Hz, H-10). (Found: C, 62.54; H, 9.36. Calc. for $C_{20}H_{36}O_5Si$: C, 62.5; H, 9.38%.)

Methyl 4 - *C* - (*carbomethoxy* - *n* - *propyl*) 2,3,4 - *trideoxy* - 4 - *C* - *ethyl* - α - D - *threo* - *hexopyranoside* (**13b**). The ester **12** (0.5 g, 1.3 mmol) was reduced in 95% ethanol with a catalytic amount of palladium on charcoal at 16 psi in 1 hr. The solution was filtered and evaporated to give **13a** (0.45 g, 90%) as an oil: TLC R_f 0.7 (C); ^1H NMR δ (0.05 (s, 6, $(CH_3)_2Si$), 0.92 (s, 9, $CH_3)_3CSi$), 0.6–0.9 (m, 3, CH_2CH_3), 1.25–2.0 (m, 10, H-2a, H-2e, H-3a, H-3e, H-7, H-7′, H-8, H-8′, H-10, H-10′), 2.2–2.5 (m, 2, H-9, H-9′), 3.28 (s, 3, OCH_3), 3.70 (s, 3, $COOCH_3$), 4.68 (m, 1, H-1). A portion of product **13a** (0.30 g) was desilylated as described above for **8b** in 2 hr to give the hydroxy ester **13b**: TLC R_f 0.50 (C); ^1H NMR 0.6–0.9 (m, 3, CH_3CH_3), 1.25–2.0 (m, 10, H-2a, H-2e, H-3a, H-3e, H-7, H-7′, H-8, H-8′, H-10, H-10′), 2.2–2.5 (m, 2, H-9, H-9′), 3.30 (s, 3, OCH_3), 3.65 (s, 3, $COOCH_3$), 3.5–3.8 (m, 3, H-5, H-6, H-6′), 4.65 (m, 1, H-1); (Found: C, 61.26; H, 9.39. Calc. for $C_{14}H_{26}O_5$: C, 61.32; H, 9.49%.)

Methyl 4 - *C* - (*carbomethoxy* - *n* - *propyl*) - 2,3,4, - *trideoxy* - 4 - *C* - *ethyl* - α - D - *threo* - *hexodialdo* - 1,5 - *pyranoside* (**14**). Chromium trioxide (0.3 g, 2.9 mmol) was added to pyridine (0.5 mL, 5.8 mmol) in dry methylene chloride (10 mL). After stirring for 3 to 5 min, **13b** (0.055 g, 0.2 mmol) was added and resulting soln was stirred for an additional 5 min. Dry diethyl ether (50 mL) was then added and the solution was filtered through a pad of Florisil. Evaporation of the solvent gave **14** (0.049 g, 90%) as a

syrup: TLC R_f 0.75 (C); IR ($CHCl_2$) 1700 (H–C=O), 1740 (O–C=O) cm^{-1}; ^1H NMR δ 0.85 (q, 3, J = 7.0 Hz, CH_2CH_3), 1.3–1.9 (m, 10, H-2a, H-2e, H-3a, H-3e, H-7, H-7′, H-8, H-8′, H-10, H-10′), 2.2-2.5 (m, 2, H-9, H-9′), 3.3 (s, 3, OCH_3), 3.65 (s, 3, $COOCH_3$), 4.15 (d, 1, $J_{5,6}$ = 1.0 Hz, H-5), 4.85 (m, 1, H-1), 9.70 (d, 1, H-6). (Found: C, 61.69; H, 8.72. Calc. for $C_{14}H_{24}O_5$: C, 61.76; H, 8.82%.)

Cyclization for A–B ring moiety

Method A. Compound **14** (0.05 g) was dissolved in dry benzene (10 mL) and was first stirred at room temp with a catalytic amount of potassium t-butoxide and a drop of t-butanol under argon. when no reaction was observed for several hours, it was then refluxed. Compound **14** decomposed under these conditions.

Method B. Compound **14** (0.02 g) was stirred at room temp in dry methanol (10 mL) with a catalytic amount of sodium methoxide overnight. The soln was neutralized with Dowex® 50 × 2–100 acid resin (H^+) and filtered and the filtrate was evaporated to give **15** (0.012 g, 60%) as a syrup: TLC R_f 0.62 (C); IR ($CHCl_3$) 1740 (H–C=O), 1710 (O–C=O) cm^{-1}; ^1H NMR 0.88 (q, 3, J = 7.2 Hz, CH_2CH_3), 1.2–2.0 (m, 10, H-2a, H-2e, H-3a, H-3e, H-7, H-7′, H-8, H-8′, H-10, H-10′), 2.3 t, 2, J = 6.2 Hz, H-9, H-9′), 3.35 (s, 3, OCH_3), 4.80 (m, 1, H-1), 9.70 (s, 1, H-6).

Method C. Methyl 4,5 - *C* - (2 - *carbomethoxy* - 1 - *hydroxy* - 1,4 - *diyl*) - 2,3,4 - *trideoxy* - 4 - *C* - *ethyl* - α - D - *threo* - *pentopyranoside* (**16**). Compound **14** (0.02 g, 0.07 mmol) was dissolved in dry THF (30 mL) sodium hydride (0.005 g) added, and the suspension was stirred for 10 hr at room temp. The reaction mixture was then cooled, and methanol (5.0 mL) was added. After neutralization with toluene-p-sulfonic acid, the solution was filtered and evaporated to dryness. The residue was extracted with methylene chloride (2 × 20 mL), dried and evaporated to give **16** (0.012 g, 60%) as a syrup: TLC R_f 0.40 (C); ^1H NMR 0.9;1.1 (m, 3, CH_2CH_3, 1.2–2.0 (m, 10, H-2, H-2′, H-3, H-3′, H-8, H-8′, H-9, H-9′, H-10, H-10′), 2.3-2.4 (m, 1,-H-7), 3.40 (s, 3, OCH_3), 3.7 (s, 3, $COOCH_3$), 3.8–3.95 (m, 1, H-5), 4.8 (m, 1, H-6), 4.0 (m, 1, H-1). (Found C, 61.16; H, 8.75. Calc for $C_{14}H_{24}O_5$: C, 61.26; H, 8.82%.)

Methyl 4,5 - *C* - (*carbomethoxy* - 1 - *butene* - 1,4 - *diyl*)-2,3,4 - *trideoxy* - 4 - *C* - *ethyl* - α - D - *threo* - *pentopyranoside* (**17**). The hydroxy ester **16** (0.1 g, 0.37 mmol) was stirred in dry pyridine (5 mL) with acetic anhydride (2 ml) at room temp for 4 hr. The soln was then cooled to 0°, methanol (5 mL) was added, and the soln was warmed up to room temp. The residue from evaporation of the solvent was azeotroped with toluene to give **17** (0.09 g, 80%) as a syrup: TLC R_f 0.80 (C); ^1H NMR δ 0.95 (t, e, J = 7.0 Hz, CH_3CH_2), 1.2–2.0 (m, 8, H-2, H-2′ H-3, H-3′, H-9, H-9′, H-10, H-10′), 2.3–2.5 (m, 2, H-8, H-8′), 3.4 (s, 3, OCH_3), 3.78 3, $COOCH_3$), 4.05 (d, 1, $J_{5,6}$ = 4.5 Hz, H-5), 4.80 (m, 1, H-1), 6.50 (d, 1, H-6) (Found: C, 66.06; H, 8.72. Calc. for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66%.)

Methyl 6 - *O* - *t-butyldimethylsilyl* - 4 - *C* - (*carbomethoxy-n - butyl*) - 2,3,4 - *trideoxy* - 4 - *C* - *vinyl* - α - D - *erythro-hexopyranoside* (**18a**). A soln of compound **12** (0.05 g) in dry THF (15 mL) was saturated with ammonia. Lithium (very small pieces) was then added until a blue colour persisted for 10 min. The soln was then neutralized with ammonium chloride, warmed up to room temp, filtered and evaporated to give **18a** (0.04 g 80%) as a syrup: TLC R_f 0.78 (C); $[\alpha]_D^{20}$ + 26.5° (c, 1.23 $CHCl_3$); ^1H NMR δ 0.05 (s, 6, $(CH_3)_2Si$), 0.95 (s, 9, $(CH_3)_3CSi$), 1.5–1.9 (m, 6, H-2a, H-2e, H-3a, H.3e, H-9, H-9′, H.10, H-10′), 2.2 (t, 2, J = 6.2 Hz, H-11, H-11′), 3.45 (s, 3, OCH_3), 3.7 (s, 3, $COOCH_3$), 3.65–3.80 (m, 3, H-5, H-6, H-6′), 4.6-4.75 (m, 1, H-1), 4.85–5.35 (m, 2, H-8, H-8′), 6.15 (dd, 1, $J_{7,8}$ = 11.0 Hz, $J_{7,8'}$ = 18.0 Hz, H-7). (Found: C, 62.08; H, 9.82. Calc. for $C_{20}H_{38}O_5Si$: C, 62.18; H, 9.84%.)

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