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Introduction of a Chiral Centre on C-6 of a Carbohydrate Unit: Application to the Synthesis of the C-2 to C-15 Fragment of Ionomycin

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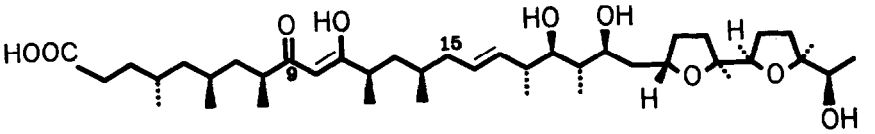
Abstract
Glucose is converted into the $\alpha\beta$-unsaturated urono-8,4-lactone **29** using an intramolecular Wadsworth-Emmons reaction. Higher order cuprates add to the lactone to provide the C-6 substituted carbohydrate derivative with high stereoselectivity. This product can be converted into the dithiane **34b** which when coupled with an appropriate epoxide yields compound **37** which contains the C-2 to C-15 fragment of ionomycin with the correct absolute stereochemistry at each asymmetric centre for conversion into ionomycin.

Ten years ago a group at Squibb reported the isolation of an unusual antibiotic which they named ionomycin from fermentation broths of *Streptomyces conglobatus*.[1] Toeplitz et al. determined the structure of ionomycin (**1**) by X-ray crystallography and spectroscopic analysis.[2] This molecule presents a formidable synthetic challenge. Ionomycin is a unique ionophore because of its ability to form a neutral 1:1 complex with calcium to selectivity transport calcium in biological systems.[3] The molecule comprises a 32-carbon linear backbone containing 14 asymmetric centres. Several groups have reported the synthesis of fragments of ionomycin,[4-9] and recently two total syntheses of ionomycin have been reported.[10,11] We chose to explore the possibility of using a carbohydrate precursor for the synthesis of the "left-hand" portion of ionomycin, namely the C_1 - C_9 fragment. Recently, we have published a model study to join the C_1 - C_9 fragment to a C_{10} - C_{15} fragment, and to generate the β-diketone.[4c] The problem associated with a synthesis of the left-hand portion of ionomycin requires the generation of two pairs of 1,3-dimethyl groups - one pair in an anti relation and the second pair in a syn relation.[12]

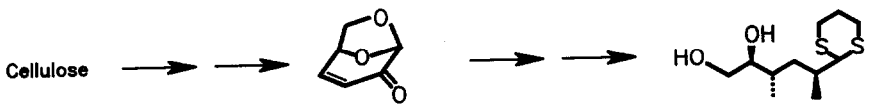


1

For the past twenty years, organic chemists have taken advantage of carbohydrates as starting materials for the synthesis of many natural products.[13] Some of the reasons for using carbohydrates include their enantiomeric purity, their ready availability, and their relatively low cost. In addition, there is a rich background knowledge about the stereo-, regio-, and chemocontrol of functional group interconversions and protecting group manipulations in carbohydrates. Often carbohydrate derivatives exist as five- or six-membered rings, or bicyclic systems that display high conformational rigidity, which controls the stereoselective reactions of these compounds.

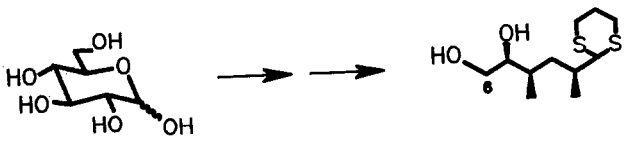
The following two examples illustrate the utility of carbohydrates as templates for the stereoselective construction of syn- or anti-1,3-dimethyl units. In these examples, the carbohydrate ring provided a rigid template on which subsequent stereoselective transformations were carried out. Once the desired stereochemistry had been established, the ring was easily opened to allow conversion into the corresponding natural product. Cellulose on thermolysis gives an

anhydrobicyclic acetal that is readily converted into the enone **2**. Mori et al. used this enone to prepare the dimethyl derivative **3** in five steps enroute to a synthesis of (-)-sericornin.[14a]



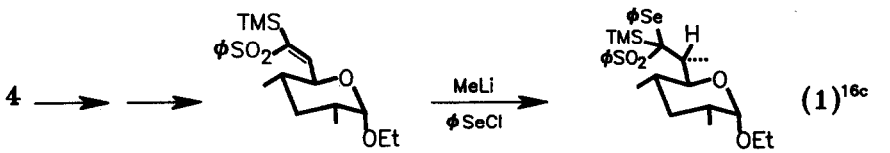
2 **3**

In a synthesis of (-)-α-multistriatin, we reported the synthesis of the dimethyl derivative **5** from D-glucose (**4**).[14b] It would appear that **5** or a related compound might be a useful precursor to the C-4 to C-9 fragment of ionomycin (**1**). However, this approach to the synthesis of ionomycin would require a method to elongate the carbon backbone and introduce a methyl group stereoselectively at C-6 in a glucose derivative.



4 **5**

Normally chiral induction on a side chain exocylic to the pyranose ring of carbohydrates is unpredictable.[15] Isobe and coworkers have taken advantage of the ability of the ether oxygens on a carbohydrate framework to coordinate with the incoming reagent and hence to stereoselectively introduce a methyl group at C-6 in the glucose derivative shown in eq 1.[16] The original reports from this group outlined the procedure to obtain the R stereochemistry at C-6 of **6** (eq 1).[16a-c] This is exactly the opposite to the stereochemistry of C-4 in ionomycin. Recently Isobe and coworkers have extended this methodology to synthesize the S stereochemistry at C-6 in **7** (eq 2).[16d] It is not clear what the salient features are in controlling the stereochemistry of these conjugate additions. Our requirements and possible substituents would seem to be closer to those in eq 1 than those in eq 2. DeNinno et al. have suggested that the stereochemical outcome of reactions of alkenylpyranosides is governed by the ground state conformation of the alkenylpyranoside.[17]



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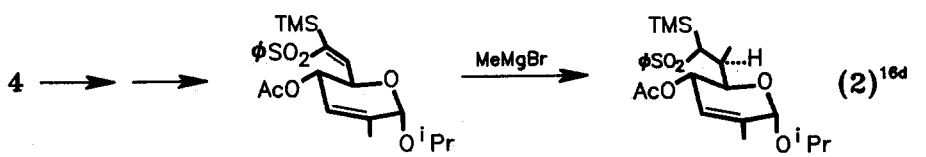
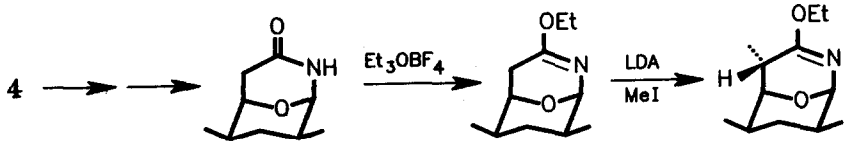


7

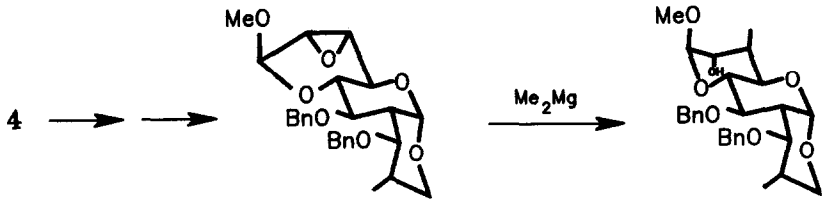
In 1981, Nakahara et al. published a synthesis of a fragment of antibiotic A23187 starting from a carbohydrate precursor (see eq 3).[18] D-Glucose was converted into the lactam **8** which was O-alkylated to give the imino ether **9**. Deprotonation of the active methylene in **9** followed by alkylation with methyl iodide from the less hindered, convex face

gave compound **10**. The stereochemistry at C-6 in **10** is S, as required in ionomycin.



(3) [18]

Subsequently, Fraser-Reid et al. developed the epoxide opening sequence shown in eq 4 to introduce a substituent with the S configuration at C-6 of a glucose derivative.[19] The epoxide **11** was opened with dimethylmagnesium to give the alkylated product **12**. These authors suggested that this intermediate could be used in the synthesis of polymethylated, polyhydroxylated antibiotics.[19]

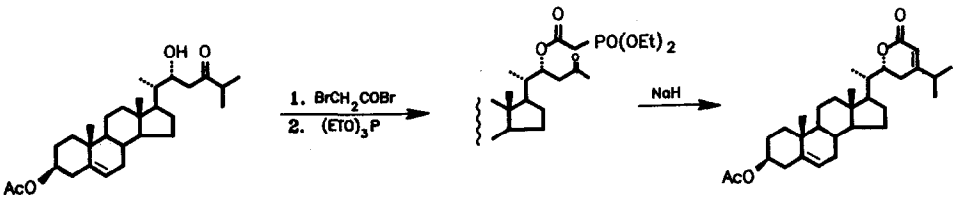


(4) [19]

11 **12**

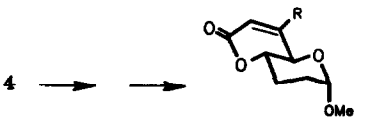
When our plans for a synthesis of the left-hand side of ionomycin were germinating, no method for the stereoselective introduction of alkyl groups at C-6 in a D-glucose derivative had been published. Therefore, we embarked on a study to develop a method for the stereospecific introduction of a methyl group at C-6 of a glucose derivative in a predictable and rational way. Our basic tenet was that a rigid, bicyclic intermediate embodying the D-glucose skeleton would allow us to achieve this goal - see eq 3 and 4. We chose to bridge C-6 and the hydroxyl group at C-4 with an $\alpha\beta$-unsaturated lactone to form a rigid, trans-fused, bicyclic system. We anticipated that reduction or conjugate addition to this bicyclic lactone would exhibit a high degree of stereoselectivity.[20]

In 1978, Welhe and McMorris published a method to prepare an $\alpha\beta$-unsaturated δ-lactone on a steroidal side-chain using the intramolecular Wadsworth-Emmons reaction shown in eq 5.[21]



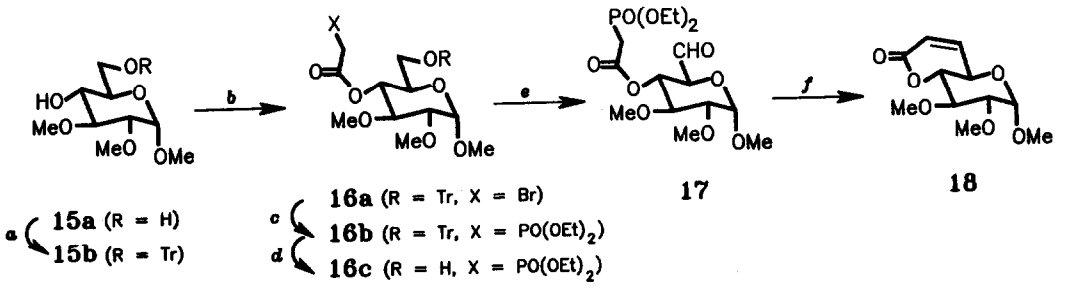
(5) [21]

Modifications to this synthetic scheme should allow us to prepare lactones of the general structures **13** and **14** from the corresponding aldehyde and ketone as shown below. The synthesis and reactivity of these two types of lactones was undertaken as a model study for the eventual approach to the synthesis of ionomycin.



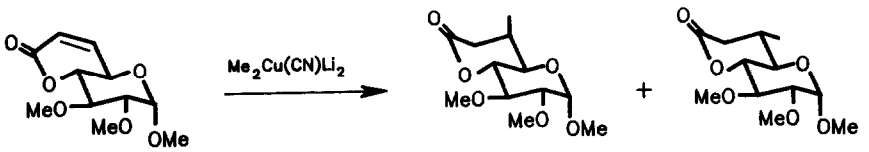
13 (R = H)
14 (R = Me)

For this study, the C-2 and C-3 hydroxyl groups of methyl α-D-glucopyranoside were protected using standard carbohydrate chemistry to give **15a**. The primary hydroxyl group of the diol **15a** was protected as its trityl ether and the free hydroxyl group at C-4 was then acylated with bromoacetyl bromide. Initially, when this reaction was carried out on small scale, ether was used as the solvent for the acylation.[21] However, because of the low solubility of alcohol **15b**, it was impractical to carry out this reaction on large scale using ether as the solvent. Fortunately **15b** is readily soluble in THF and the bromoacetate **16a** could be obtained in excellent yield using THF as solvent. The bromoacetate **16a** was then treated with triethyl phosphite to yield the phosphonoacetate **16b**. Our initial efforts to deprotect the hydroxyl group at C-6 concentrated on the use of acidic ion exchange resins in methanol because of the anticipated ease in work-up of such reactions.[22] The C-6 trityl group could be easily cleaved under these conditions, but invariably there was a significant amount of migration of the acyl group from C-4 to C-6.[23] The desired alcohol **16c** was obtained by catalytic hydrogenolysis of the C-6 trityl. Under these mild conditions no trans-acylation was observed, however, attempts to purify **16c** by chromatography on several different supports did cause varying amounts of trans-acylation. The triphenylmethane was separated from **16c** by continuous extraction of an acetonitrile solution of the reaction mixture with petroleum ether. A Moffatt oxidation[24] of **16c** yielded the aldehyde **17** which was used in the next step without purification. A Wadsworth-Emmons cyclization of the aldehyde **17** gave the α,β-unsaturated urono-8,4-lactone **18** in high crude yield. Analysis of the crude product by ^{1}H NMR indicated that the reaction was quite clean, however, all of the methods used to separate the product from the phosphate ester salts resulted in significantly reduced yields. Martin and Szarek noted the unusual sensitivity of an urono-8,4-lactone[25] and lactone **18** appears to have similar properties.



(a) TrCl, py (92%); **(b)** $BrCH_2COBr$, DMAP, py, THF (99%); **(c)** $P(OEt)_3$, 150 °C (100%); **(d)** H_2, Pd-C, tr HCl (72%): **(e)** DMSO, DCC, $Cl_2CHCOOH$ (91%); **(f)** NaH, THF, Δ (50-57%).

The Lipshutz higher order mixed organocuprate[26] reacted cleanly with the α,β-unsaturated lactone **18** to give the conjugate addition products **19** and **20** (eq 6). The maximum stereoselectivity was found to be 13:1. Work-up of the reaction was a challenge because of the high acid sensitivity of the products. Eventually a work-up procedure (see Experimental) was developed which resulted in 75-100% yields of the lactone mixture. A pure sample of the major isomer was obtained by preparative GLC. The stereochemistry of the methyl group at C-6 in this isomer was proven by difference nOe experiments. Irradiation of the C-methyl signal resulted in major enhancements of the H-4, H-6 and H-7β signals. In a separate experiment, irradiation of the C-4 methine signal resulted in enhancement of the H-2 and the C-6 methyl signals. Thus H-2, H-4 and the C-6 methyl group are all cis, confirming the axial orientation in the major product **19**.

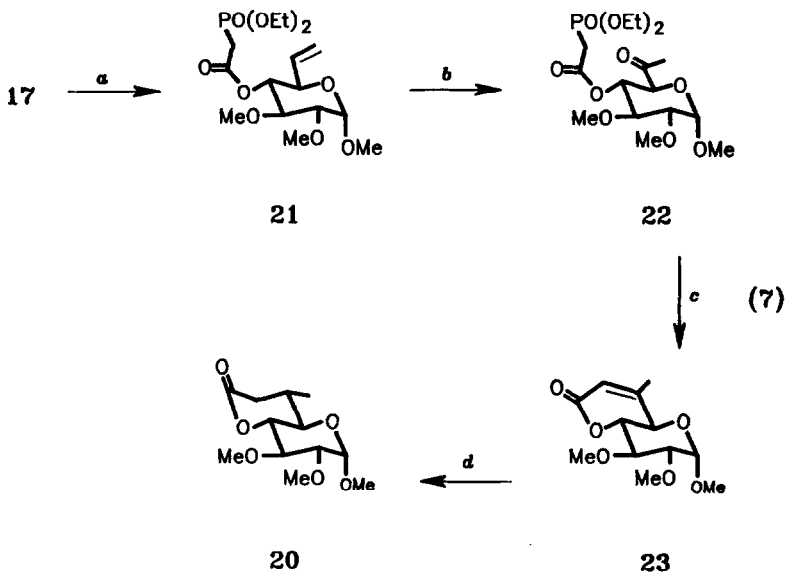


18 **19** **20** (6)

Unfortunately, we were unable to obtain sufficient quantities of the minor product **20** from the above reaction to be able to fully characterize it. Therefore, this isomer was prepared by a separate route shown in eq 7. Although we did try to

find the optimal conditions for the reactions in this sequence, the instability and water solubility of certain intermediates resulted in some low yields. We were unable to isolate any identifiable product following the addition of a methyl Grignard, methillithium or methyltris(2-propoxy)titanium[27] to the aldehyde **17b**. Fortunately treatment of the aldehyde **17b** with the titanium methylene complex[28] using the modified procedure developed by Lombardo[29] afforded the olefin **21** in moderate yield. A one-pot oxymercuration-oxidation[30] of the crude **21** gave a mixture of products in 50% weight balance. The NMR spectrum of this mixture indicated that about one-third of the crude mixture consisted of the desired ketone **22**. All of our attempts to improve this yield failed and other reactions, such as a Wacker oxidation[31] led only to recovered starting material. Cyclization of the crude ketone **22** afforded the α,β-unsaturated lactone **23** in about 10% yield for the last two steps. The ^{1}H NMR spectrum of the lactone **23** is characterized by signals at δ 5.76 and δ 2.00 corresponding to the vinylic proton and methyl group respectively. The saturated lactone **20** was obtained by hydrogenation of **23**. The product from this hydrogenation (eq 7) was shown, by capillary GLC, to be identical to the minor product in the cuprate addition (eq 6). There was no evidence by either ^{1}H NMR or capillary GLC for formation of the axial methyl lactone **19** in the hydrogenation step.

Pirkle and Adams have shown that conjugate additions of cuprates to six-membered α,β-unsaturated lactones involve axial attack of the cuprate.[32] These results and our own are consistent with the minimization of torsional strain[33] or the maximization of staggering[34] proposals for cuprate addition. Corey and Boaz have suggested that cuprate conjugate additions proceed via a reversible d,π^*-complex, followed by copper(III) adduct formation.[35] Their results suggest that if a cuprate conjugate addition to a cyclohexenone with a γ-oxygen is conducted under reversible conditions, the major product will be the one in which the alkyl group transferred from the cuprate is cis to the oxygen functionality. The major product in the above cuprate addition (eq 6) has the methyl group cis to the pyranose oxygen - consistent with the results of Corey and Boaz.



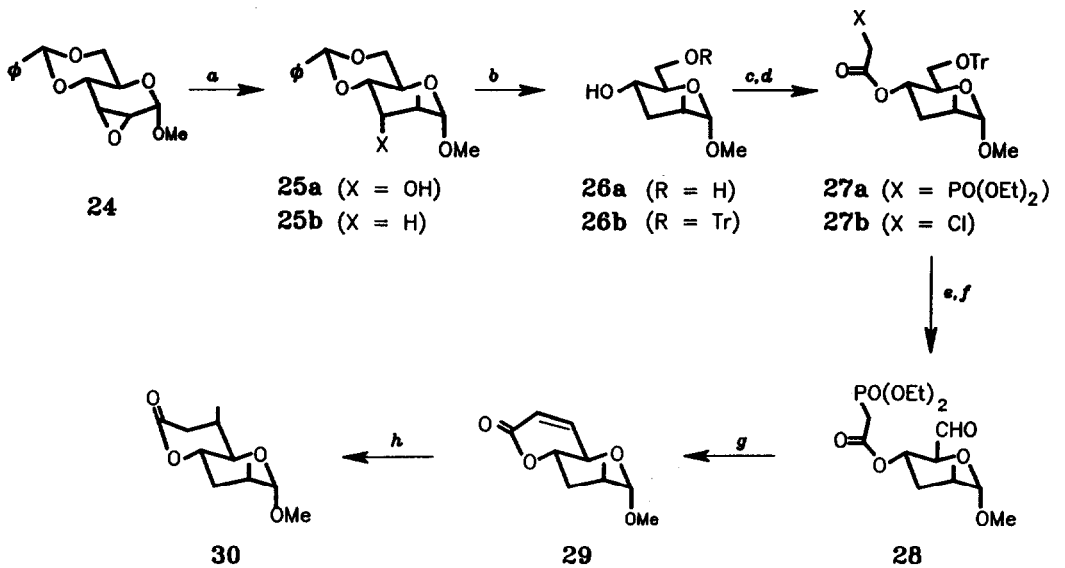
(a) CH_2Br_2-Zn-$TiCl_4$, CH_2Cl_2 (42%); **(b)** $Hg(OAc)_2$, H_2O, acetone; CrO_3, H_2SO_4, H_2O (ca. 20%); **(c)** NaH, THF, Δ (ca. 40%); **(d)** H_2, PtO_2, MeOH (100%).

This sequence of model reactions demonstrated that cuprate addition to carbohydrate uranolactones could be carried to generate the C-6 substituted product with precisely the stereochemistry required in ionomycin. We then embarked on a synthesis of such an ionomycin precursor. The plan for the synthesis of the left-hand segment of ionomycin, involved using the above model reactions to establish the stereochemistry of C-4 in ionomycin, and combining this with our earlier results (cf. **4** to **5** above)[14b] to control the stereochemistry of C-6 and C-8.

D-Glucose(**4**) was converted into the epoxide **24**.[14b,36] In our previous report, the epoxide **24** was treated with lithium dimethylcuprate to give the axial C-2 methyl derivative **25a**. This reaction was capricious and we found that using a

higher order mixed cuprate[37] gave higher and more reproducible yields of **25a**. This compound was deoxygenated and the protecting groups modified according to our earlier protocols[14b] to give the C-4 alcohol **26b**. The alcohol **26b** was acylated as above and treated with triethyl phosphite to give the phosphonate **27a** in good yield. Compound **27a** was contaminated with a trace (ca. 2%) of the chloroester **27b** which we were unable to separate from **27a**. Mass spectroscopic analysis of **27a** showed the presence of **27b** which may arise from traces of phosphorous trichloride in the triethyl phosphite.[38] Hydrogenolysis of the trityl ether in **27a** was quite facile. In fact, the C-4 to C-6 acyl migration which complicated the model studies was not a problem in the synthesis of the "real" compound. The C-6 alcohol was oxidized to give the aldehyde **28**. Wadsworth-Emmons cyclization of **28** afforded the crude α,β-unsaturated lactone **29** in high yield and purity as indicated by capillary GLC. Like the model lactones **18** and **23**, lactone **29** is very acid sensitive. Gel purification on Sephadex permitted separation of most of the sodium phosphate esters, affording **29** in 66% yield. Subsequent chromatography on silica gel reduced the yield to 42%. This second purification was necessary because the next cuprate reaction using partially purified α,β-unsaturated lactone gave poorer yields of the conjugate addition product.

Conjugate addition to the α,β-unsaturated lactone **29** using a higher order mixed organocuprate yielded the axial lactone **30** in 90% yield. The stereochemistry of the C-6 methyl group was assigned by ^{1}H NMR spectroscopy and analogy with the above model study. In particular, all of the proton chemical shifts and couplings for the hydrogens on carbons 4 to 7 could be assigned unambiguously (see Experimental). We could not detect any of the corresponding equatorial methyl epimer in the reaction mixture by capillary GLC or ^{1}H NMR.



24

25a (X = OH)
25b (X = H)

26a (R = H)
26b (R = Tr)

27a (X = $PO(OEt)_2$)
27b (X = Cl)

28

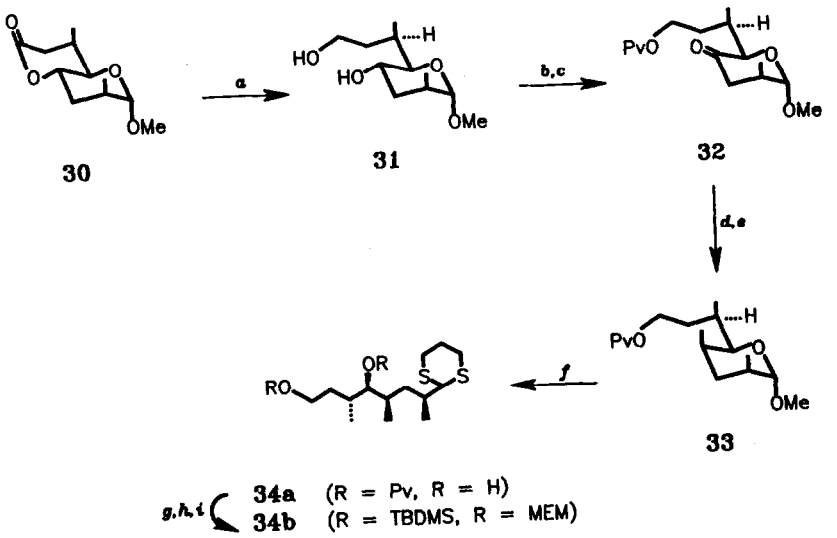
29

30

(a) $Me_2Cu(CN)Li_2$, Et_2O (78%); **(b)** reference 14b: i) NaH, CS_2, MeI, Et_2O; ii) Bu_3SnH, toluene, Δ; iii) TsOH, MeOH; iv) TrCl, py; **(c)** $BrCH_2COBr$, DMAP, py, Et_2O (90%); **(d)** $P(OEt)_3$, Δ (98%); **(e)** H_2, Pd-C, HCl, MeOH (98%): **(f)** DMSO, DCC, $Cl_2CHCOOH$, (81%); **(g)** NaH, THF, Δ (42%); **(h)** $Me_2Cu(CN)Li_2$, Et_2O (91%).

Reduction of the lactone **30** with diisobutylaluminum hydride yielded the water soluble diol **31** which could be isolated in excellent yield following careful work-up.[39] Diol **31** was converted into the monopivalate and oxidized[40] to yield the ketone **32**. Ketone **32** was then treated with the active methylene titanium complex[28,29] to yield the corresponding exocyclic alkene which was hydrogenated[14b] using Wilkinson's catalyst to give the trimethyl compound **33**. The stereochemistry of the hydrogenated product **33**, which was expected on mechanistic grounds,[14b] is supported by the spectroscopic data. In the ^{1}H NMR spectrum, the one-proton doublet at δ 4.26 with a coupling constant of 4 Hz is assigned to H-1, indicating that **33** retains the $^4C_1$ chair conformation. The ^{13}C NMR spectrum of **33** showed only three signals upfield from δ 25 and two of these, the peaks at δ 15.22 and 15.56, are attributed to the axial methyl groups at C-2 and C-4. Axial methyl groups on a cyclohexane ring normally have ^{13}C NMR signals at δ 15 - 18, whereas the

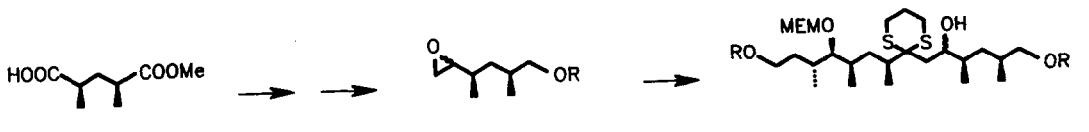
corresponding equatorial methyl groups are usually found at δ 18 - 25.[41] The calculated chemical shift for the C-6 methyl group in **33** is δ 21.63,[42] and the third signal at δ 19.14 is attributed to this methyl group. At this stage the carbon chain with the three pendent methyl groups on the left-hand fragment of ionomycin have been introduced with the correct relative and absolute stereochemistry.



(a) DIBAL, Et_2O (94%); **(b)** PvCl, py, 0 °C (74%); **(c)** $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -60 °C→ room temp (78%); **(d)** CH_2Br_2-Zn-$TiCl_4$, CH_2Cl_2 (83%); **(e)** $(\phi_3P)_3RhCl_3$, H_2, ϕH (75%); **(f)** $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (84%); **(g)** MEMCl, i-Pr_2NEt, CH_2Cl_2 (61%); **(h)** LAH, Et_2O, 0 °C (86%); **(i)** TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (87%).

The pyranose ring had served its final function in the synthesis and now could be opened to yield the acyclic chain. Thus treatment of **33** with 1,3-propanedithiol afforded the dithiane **34a**. Consistent with our earlier results,[14b] no epimerization of the C-2 methyl group was detected. A number of reactions to deoxygenate C-5 were investigated without success. For example, reduction[43] of the corresponding mesylate was complicated by the presence of the dithane. We therefore decided that it would be best to postpone this deoxygenation until the two left-hand fragments had been coupled and the resulting dithioketal was hydrolyzed. With this plan in mind, the alcohol **34a** was protected and the pivaloate protecting group at C-1 was interchanged for the tert-butyldimethylsilyl ether to give **34b**.

Methyl (R^*,S^*)-2,4-dimethylglutaric acid (**35**) was resolved via its (+)-α-methylbenzylamonium salts[44] and converted[4c] into a mixture of epoxides **36** which are epimeric at C-5. Both epimers could be used, since this centre would subsequently be oxidized to a ketone group. The two fragments were coupled via metallation of the dithiane[4c] to give compound **37** in 40% yield. This completed a synthesis of the C-2 to C-15 fragment of ionomycin with the five pendant methyl groups having the correct absolute stereochemistry.



35 **36** (R = TBDMS) **37** (R = TBDMS)

Experimental

For all moisture sensitive reactions, dry solvents were used and the glassware was oven-dried and cooled under a stream of nitrogen before use. Nitrogen was dried by passing it through a column of indicating Drierite. Petroleum ether was of boiling range ca. 30-60 °C. Methyllithium (in ether) and n-butyllithium (in hexanes) were obtained from Aldrich Chemical Co. The alkyllithiums were standardized by titration against 1,3-diphenyl-2-propanone p-tosylhydrazone in THF.[45] Reactions were stirred at room temperature unless specific temperature conditions are mentioned. Cold temperature baths were prepared as follows: -78 °C (dry ice-acetone), -60 °C (dry ice-chloroform), -40 °C (dry ice-acetonitrile), -25 °C and -10 °C (dry ice-aqueous $CaCl_2$).[46] Solvents were evaporated under reduced pressure using a Buchi rotary evaporator followed by vacuum evaporation (0.05 - 0.1 Torr) for at least 20 min.

Analytical thin layer chromatography (TLC) was carried out using commercial, pre-coated, aluminum-backed silica gel plates (silica gel 60 F_{254}) supplied by E. Merck Co. Visualization was effected by ultraviolet fluorescence (UV), iodine vapour (I_2), 2,4-dinitrophenylhydrazine spray (2,4-DNP-hydrazine) or 10% aqueous sulfuric acid spray followed by heating (H_2SO_4). Analytical GLC was performed on a Hewlett Packard model 5880A gas chromatograph using a 0.2 mm x 12 m column of 3% OV-101 or 10% Carbowax 20M and a flame ionization detector.

Flash chromatography[47] was performed using silica gel 230-400 mesh ASTM supplied by E. Merck Co. Gel filtration was performed on Sephadex LH-20 supplied by Pharmacia. Preparative gas liquid chromatography (GLC) was carried out on a Varian Aerograph model 90-P equipped with a 0.25 in x 10 ft stainless steel column packed with 5% OV-17 on Supelco WHP (100-120 mesh).

Melting points were determined on a Kofler hot stage apparatus. Boiling points are given as the air-bath temperatures required for Kugelrohr distillation. Melting points and boiling points are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter at 20-25 °C using sodium D light (589 nm). The solution concentrations (c) for specific rotations, $[\alpha]_D$, are given in grams of solute per 100 mL of solution. Infrared spectra were recorded on a Perkin-Elmer model 710B spectrophotometer. Solution spectra were obtained using sodium chloride solution cells of 0.2 mm thickness and are calibrated by means of the 1601 cm^{-1} band of polystyrene.

Nuclear magnetic resonance spectra were taken in deuterochloroform solution. Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Varian EM 360L (60 MHz), a Bruker WP-80 (80 MHz), HXS-270 (270 MHz) or WH-400 (400 MHz) instrument. Signal positions are given in parts per million downfield from internal tetramethylsilane (TMS) on the δ scale for all compounds except those containing the tert-butyldimethylsilyl group. In these cases the chemical shifts are measured relative to chloroform (δ 7.27). Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-400 (100 MHz) and chemical shifts are reported on the δ scale relative to internal TMS.

Low resolution mass spectra were determined on a Varian MAT CH4B or a Kratos-AEI MS 50 mass spectrometer. High resolution mass measurements were made using a Kratos-AEI MS 50 mass spectrometer. All instruments were operated at an ionizing potential of 70 eV. Microanalyses were performed at the Microanalytical Laboratory, University of British Columbia or the Canadian Microanalytical Service Ltd., 5704 University Boulevard, Vancouver.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside

This compound was prepared from methyl α-D-glucopyranoside in 68% yield following the procedure of Richtmyer;[36] mp 163.5-165.5 °C (lit. mp 163-164 °C).[36]

Methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside

To a solution of the above diol (23.4 g, 83.0 mmol) in dry DMSO (500 mL) under nitrogen was added a solution of sodium methyl sulfinate anion in DMSO (80.1 mL, 2.81 M, 225 mmol). After stirring for 1 h, the solution was cooled to 20 °C and iodomethane (26.0 mL, 417 mmol) was added slowly so that the temperature did not rise above 25 °C. After 45 min, the reaction was quenched with water (600 mL). The aqueous layer was extracted with ether and the combined extracts were washed with 1 M hydrochloric acid, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded the desired benzylidene (24.9 g, 97%) as white crystals; mp 121-123 °C (lit. mp 121-123 °C).[48]

Methyl 2,3-di-O-methyl-α-D-glucopyranoside (15a)

To a solution of the above benzylidene acetal (24.9 g, 80.3 mmol) in methanol (450 mL) was added p-toluenesulfonic acid monohydrate (0.95 g, 5.0 mmol). The reaction mixture was stirred for 3 h, and then solid sodium carbonate (ca. 1 g) was added to neutralize the acid. After stirring for 10 min, the reaction mixture was filtered and concentrated. The resulting residue was diluted with water (200 mL) and ether (200 mL). The ether layer was extracted with distilled water (2 x 100 mL) and the combined aqueous extracts were concentrated. The residue was dissolved in dichloromethane (900 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded white crystals (17.1 g). Recrystallization of the crude product from benzene - petroleum ether yielded diol **15a** (16.5 g, 92%) as white crystals; mp 83.5-85.0 °C (lit. mp 81-84 °C).[48]

Methyl 2,3-di-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (15b)

To a solution of diol **15a** (3.00 g, 13.5 mmol) in dry pyridine (30 mL) under nitrogen in the fume hood was added triphenylmethyl chloride (5.65 g, 20.3 mmol) and the resulting mixture was stirred for 42 h. The reaction mixture was poured into an ice-cold mixture of water (25 mL) and dichloromethane (20 mL) and then was acidified with ice-cold 1 M

hydrochloric acid (15 mL). The aqueous layer was extracted with dichloromethane and the combined extracts were washed with saturated aqueous sodium bicarbonate, brine, and water, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded the crude product (8.32 g) as a solid. Purification by flash chromatography on silica gel using the sequence of solvents: petroleum ether-ethyl acetate 2:1, 1:1, and then neat ethyl acetate as eluant yielded trityl ether **15b** (5.73 g, 92%) as white crystals, which were pure enough for the next reaction. A small sample was recrystallized from ethanol for characterization; mp 172.0-174.5 °C (lit. mp 172-174 °C).[48]

Methyl 4-O-bromoacetyl-2,3-di-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (16a)

To a solution of alcohol **15b** (50.5 g, 110 mmol), dry pyridine (17.5 mL, 218 mmol), and DMAP (1.3 g, 11 mmol) in dry THF (600 mL) at 0 °C under nitrogen in the fume hood was added over 0.5 h a solution of bromoacetyl bromide (14.2 mL, 160 mmol) in dry THF (300 mL). The ice bath was removed and the reaction mixture was stirred for 3 h, while warming to room temperature. The reaction mixture was diluted with ether (350 mL), filtered through a sintered glass filter, and the precipitate was rinsed with ether. The combined filtrate was washed with saturated aqueous sodium bicarbonate, 1 M hydrochloric acid, brine, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded the crude product (63.8 g) as yellow crystals which were then dissolved in ethyl acetate. Filtration of the resulting solution through a short column of silica gel and evaporation of the solvent yielded bromoacetate **16a** (62.9 g, 99%) as off-white needles which were pure enough to use in the next reaction. A small sample was recrystallized from ethanol to yield analytically pure, off-white needles for characterization; R_f 0.55 (petroleum ether-ethyl acetate 1:1, UV and H_2SO_4); mp 161.5-163.5 °C; $[\alpha]_D$ +72.7 (c 0.400, $CHCl_3$); IR ($CHCl_3$): 1750, 1100, 1030 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 3.05-3.20 (m, 2H), 3.22-3.45 (dd, J=10, 4 Hz, 1H), 3.45-4.10 (m, 3H), 3.51 (s, 6H), 3.55 (s, 3H), 4.77-5.10 (m, 3H), 7.10-7.60 (m, 15H); MS **m/z**: 586(^{81}Br: M^+, 0.1), 584(^{79}Br: M^+, 0.1), 554(0.4), 552(0.4), 244(30), 243(100), 165(47), 88(65), 77(95); Exact mass: calcd. for $C_{30}H_{33}BrO_7$: 584.1410; found: 584.1404. Anal. calcd. for $C_{30}H_{33}BrO_7$: C 61.54, H 5.68, Br 13.65; found: C 61.39, H 5.76, Br 13.51.

Methyl 4-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (16b)

To neat bromoacetate **16a** (9.20 g, 15.7 mmol) under a stream of nitrogen in the fume hood was added dry triethyl phosphite (5.38 mL, 31.4 mmol). After approximately one-eighth of the triethyl phosphite had been added, the reaction mixture was heated to 150 °C.[21] The remaining triethyl phosphite was added dropwise at a rate sufficient to keep the reaction mixture under reflux. The bromoethane produced was distilled out of the reaction mixture. After all of the triethyl phosphite had been added, the reaction mixture was stirred at 150 °C for 1 h and then was allowed to cool to room temperature. The excess triethyl phosphite and ethyl bromide were removed under vacuum to yield a pale amber gum. Purification by flash chromatography on silica gel in the fume hood using the sequence of solvents: petroleum ether-ethyl acetate 1:1 and then ethyl acetate-methanol 9:1 as eluant yielded diethyl phosphonate **16b** (10.5 g, 100%) as a pale amber gum; R_f 0.80 (ethyl acetate-1-propanol-water 65:23:12, UV and H_2SO_4); IR ($CHCl_3$): 1750, 1300-1200, 1035, cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.30 (t, J=7 Hz, 6H), 2.62 (d, $J_{P,CH}$=22 Hz, 2H), 2.80-3.20 (m, 2H), 3.33 (dd, J=10, 3 Hz, 1H), 3.45-3.80 (m, 2H), 3.48 (s, 3H), 3.53 (s, 6H), 3.80-4.35 (m, 4H), 4.77-5.10 (m, 2H), 7.00-7.55 (m, 15H); MS **m/z**: 642(M^+, 0.1), 565(1), 399(29), 244(29), 243(100), 179(55), 165(58), 139(33), 88(88), 75(45); Exact mass: calcd. for $C_{28}H_{38}O_{10}P$ (M^+-C_6H_5): 565.2202; found: 565.2195.

Methyl 6-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-α-D-glucopyranoside

To a solution of trityl ether **16b** (0.76 g, 1.2 mmol) in methanol (20 mL) was added a spatula tip full of Amberlite IR-120. After stirring for 44 h, the reaction mixture was filtered and concentrated. The gummy residue was purified by flash chromatography on silica gel using ethyl acetate to elute methyl triphenylmethyl ether and then methanol to elute the product. Evaporation of methanol, with heating, yielded the rearranged C-6 acetate (0.44 g, 91%) as a pale amber gum; R_f 0.56 (ethyl acetate-1-propanol-water 65:23:12, H_2SO_4); IR ($CHCl_3$): 3600, 3575-3275, 1740, 1300-1200, 1020 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.35 (t, J=7 Hz, 6H), 3.04 (d, J=22 Hz, 2H), 3.10-3.90 (m, 5H), 3.43 (s, 3H), 3.51 (s, 3H), 3.64 (s, 3H), 3.90-4.70 (m, 6H), 4.82 (d, J=3 Hz, 1H); MS **m/z**: 369(M^+-OMe, 1), 368(1), 101(42), 83(100), 75(55), 73(20), 45(25); Exact mass: calcd. for $C_{14}H_{25}O_9P$ (M^+-MeOH): 368.1235; found: 368.1213.

Methyl 4-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-α-D-gluco pyranoside (16c)

To a solution of trityl ether **16b** (1.22 g, 1.90 mmol) in dry methanol (15 mL) was added 5% palladium-on-charcoal (0.240 g) and 2 drops of 12 M hydrochloric acid. The reaction mixture was stirred overnight under hydrogen at atmospheric pressure. The catalyst was recovered by filtration and washed with methanol. Concentration of the filtrate, without heating, yielded a mixture of alcohol **16c** and triphenylmethane as a white semi-solid which was subsequently purified by continuous liquid-liquid extraction. The crude product mixture was dissolved in acetonitrile and the resulting solution was extracted continuously with petroleum ether. After 8 h, TLC of the acetonitrile layer showed no triphenylmethane. The acetonitrile layer was filtered through a pad of Celite to remove traces of palladium catalyst. Evaporation of the solvent, without heating, yielded alcohol **16c** (0.546 g, 72%) as a pale amber gum. After six weeks the product crystallized to yield the analytically pure monohydrate of alcohol **16c** as white crystals; R_f 0.45 (ethyl acetate-1-propanol-water 3:1:0.2, H_2SO_4); mp 34-38.5 °C; $[\alpha]_D$ +79.9 (c 0.568, $CHCl_3$); IR ($CHCl_3$): 3670, 3625-3200, 1740, 1200-1300, 1025 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.35 (t, J=7 Hz, 6H), 2.70 (bs, 1H, D_2O exchangeable), 3.02 (d, $J_{P,CH}$=22 Hz, 2H), 3.29 (dd, J=10, 3 Hz, 1H), 3.40-3.85 (m, 4H), 3.43 (s, 3H), 3.52 (s, 3H), 3.54 (s, 3H), 3.93-4.50 (m, J=7

Hz, 4H), 4.70-5.10 (m, 2H); MS m/z: 400(M^+, 0.5), 369(4), 368(4), 179(37), 103(23), 88(100), 75(26); Exact mass: calcd. for $C_{15}H_{29}O_{10}P$: 400.1496; found: 400.1487; Anal. calcd. for $C_{15}H_{29}O_{10}P \cdot H_2O$: C 43.06, H 7.47, O 42.06; found: C 43.05, H 7.31, O 42.0.

Methyl 4-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-α-D-gluco-hexodialdo-1,5-pyranoside(17)

To a solution of alcohol **16c** (2.22 g, 5.55 mmol) and freshly distilled DCC (3.40 g, 16.5 mmol) in dry DMSO (20 mL) under nitrogen in the fume hood was added dry dichloroacetic acid (0.23 mL, 2.8 mmol).[24] After stirring for 1 h, the cloudy white reaction mixture was filtered through a sintered glass filter, and the precipitate was rinsed with distilled water. The combined aqueous filtrate was extracted repeatedly with ether and then frozen using a dry ice-acetone bath. Freeze-drying under vacuum for 2 days yielded aldehyde **17** (2.00 g, 91%) as a colourless semi-solid; R_f 0.54 (ethyl acetate-1-propanol-water 3:1:0.2, H_2SO_4 and 2,4-DNP-hydrazine); IR ($CHCl_3$): 3575, 3550-3150, 1750, 1200-1300, 1030 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.35 (t, J=7 Hz, 6H), 3.02 (d, $J_{P,CH}$=22 Hz, 2H), 3.28 (dd, J=9, 3 Hz, 1H), 3.40-3.85 (m, 1H), 3.45 (s, 3H), 3.53 (s, 3H), 3.55 (s, 3H), 3.90-4.40 (m, 5H), 4.93 (d, J=3 Hz, 1H), 4.98 (dd, J=10, 9 Hz, 1H), 9.57 (d, J=2 Hz, 1H); MS m/z: 398(M^+, 0.1), 367(1), 179(43), 101(20), 88(100), 75(33), 45(24); Exact mass: calcd. for $C_{15}H_{27}O_{10}P$: 398.1342; found: 398.1339.

Methyl 6,7-dideoxy-2,3-di-O-methyl-α-D-gluco-oct-6-eno-1,5-pyranosid)-urono-8,4-lactone (18)

Sodium hydride (0.275 g, 60% dispersion in mineral oil, 6.86 mmol) was washed free of oil with dry ether (3 x 5 mL) under nitrogen and then dry THF (10 mL) was added to the sodium hydride. The resulting slurry was added via pipette to a solution of aldehyde **17** (2.75 g, 6.86 mmol) in dry THF (250 mL) under nitrogen which resulted in immediate evolution of hydrogen. The reaction mixture was stirred for 5 min, heated under reflux for 1 h and then was allowed to cool to room temperature.[21] Amberlite IR-120 (several spatula tips full) was added to neutralize any excess base. After stirring for 10 min, the reaction mixture was filtered and concentrated to yield a dark amber oil. Purification by gel filtration on Sephadex LH-20 using methanol-chloroform 1:1 as eluant, followed by partially dissolving the resulting residue in ether, decanting and concentrating the solution, yielded a 9:1 mixture of α,β-unsaturated lactone **18** and the isomeric 8,6-lactone (0.910 g, 54%) as a pale amber oil. Kugelrohr distillation yielded a 9:1 mixture of the α,β-unsaturated lactones as a white semi-solid; bp 195 °C/0.25 Torr; R_f 0.29 (petroleum ether-ethyl acetate 1:1, UV and H_2SO_4); IR ($CHCl_3$): 3020, 1745, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 3.25 (dd, $J_{2,3}$=9 Hz, $J_{1,2}$=3.5 Hz, 1H, H-2), 3.47 (s, 3H), 3.55 (s, 3H), 3.66 (s, 3H), 3.70 (t, $J_{2,3}$=$J_{3,4}$=9 Hz, 1H, H-3), 3.98 (dd, $J_{4,5}$=10 Hz, $J_{3,4}$=9 Hz, 1H, H-4), 4.48 (ddd, $J_{4,5}$=10 Hz, $J_{5,7}$=3 Hz, $J_{5,6}$=2 Hz, 1H, H-5), 4.87 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 5.96 (dd, $J_{6,7}$=10 Hz, $J_{5,7}$=3 Hz, 1H, H-7), 6.87 (dd, $J_{6,7}$=10 Hz, $J_{5,6}$ =2 Hz, 1H, H-6); MS m/z: 244(M^+, 0.3), 213(1), 88(100), 73(22), 55(21), 45(23); Exact mass: calcd. for $C_{11}H_{16}O_6$: 244.0947; found: 244.0972; calcd. for $C_{10}H_{13}O_5$ (M^+-OMe): 213.0762; found: 213.0764.

Methyl 6,7-dideoxy-6-C-methyl-2,3-di-O-methyl-D-glycero-α-D-gluco-octo-1,5-pyranosid)urono-8,4-lactone (19)

To a suspension of copper(I) cyanide (32 mg, 0.36 mmol) in dry ether (5 mL, distilled from sodium) at -78 °C under nitrogen in the fume hood was added a solution of methyllithium in ether (0.42 mL, 1.7 M, 0.72 mmol). After stirring for 5 min at -78 °C, the mixture was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 10 min by which time the copper(I) cyanide had all reacted to give a cloudy tan solution of the cuprate $Me_2Cu(CN)Li_2$.[26a] The cuprate solution was cooled to -78 °C and a solution of α,β-unsaturated lactone **18** from above (77 mg, 0.30 mmol) in dry ether (distilled from sodium) (2 mL) was added dropwise. The resulting bright yellow reaction mixture was stirred at -78 °C for 30 min and at -25 °C for 1 h. The reaction was quenched by adding glacial acetic acid (0.04 mL, 0.72 mmol) and was diluted with ethyl acetate. The mixture became a clear, pale green solution containing a small amount of a fine white precipitate. The cold bath was removed and the mixture was allowed to warm to room temperature. Disodium ethylenediamine-tetraacetic acid dihydrate (0.13 g, 0.36 mmol) was added and the resulting mixture was stirred for 10 min. Brine (6 drops) and water (6 drops) were added and immediately a flocculant, white precipitate formed. The aqueous layer containing the precipitate was extracted with ethyl acetate and the combined organic solvents were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent yielded a pale green oil (78 mg, 100%). Purification of a small sample by preparative glc yielded lactone **19** as a colourless oil; R_f 0.28 (petroleum ether-ethyl acetate 1:1, H_2SO_4); IR ($CHCl_3$): 1730, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.07 (d, $J_{6,9}$=7 Hz, 3H, Me), 2.31-2.40 (A part of ABX system plus additional couplings, 1H, H-6), 2.42 (B part of ABX system, $J_{7\alpha,7\beta}$ =17 Hz, $J_{6,7\beta}$ =4 Hz, 1H, H-7β), 2.78 (X part of ABX system, $J_{7\alpha,7\beta}$ =17 Hz, $J_{6,7\alpha}$ =7 Hz, 1H, H-7α), 3.20 (dd, $J_{2,3}$=9 Hz, $J_{1,2}$=3.5 Hz, 1H, H-2), 3.43 (s, 3H), 3.53 (s, 3H), 3.61 (t, $J_{2,3}$=$J_{3,4}$=9 Hz, 1H, H-3), 3.63 (s, 3H), 3.87 (dd, $J_{4,5}$=10.5 Hz, $J_{5,6}$=6 Hz, 1H, H-5), 4.05 (dd, $J_{4,5}$=10.5 Hz, $J_{3,4}$=9 Hz, 1H, H-4), 4.83 (d, $J_{1,2}$=3.5 Hz, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 14.29 (Me), 27.63 (C-6), 36.93 (C-7), 55.52 59.26 61.10 (OMe), 65.64 76.27 80.78 81.24 (CH), 98.31 (C-1), 169.54 (C=O); MS m/z: 260(M^+, 0.3), 229(1), 88(100), 73(12); Exact mass: calcd. for $C_{12}H_{20}O_6$: 260.1260; found: 260.1245.

Active Methylene Complex

To a stirred slurry of zinc dust (11.5 g, 176 mmol), dibromomethane (4.04 mL, 56 mmol) and dry THF (100 mL) at -40 °C under nitrogen in the fume hood was added dropwise, over 0.5 h, titanium(IV) chloride (4.6 mL, 42 mmol).[29] The reaction was extremely vigorous and a copious amount of green gas was produced. After the addition of titanium(IV) chloride, the reaction mixture became a grey slurry and was stirred at -40 °C for 2 h, at 2 °C for a least 24 h and then was stored between 0 °C and 5 °C until use. The complex could be stored for up to two weeks without deterioration.

Methyl 6,7-dideoxy-4-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-α-D-gluco-hept-6-eno-1,5-pyranoside (21)

To a stirred solution of aldehyde **17** (0.80 g, 2.0 mmol) in dry dichloromethane (20 mL) at 0 °C under nitrogen was added in portions, via pipette, the active methylene complex prepared above (20 x ca. 1.5 mL), until TLC analysis of the reaction mixture (2,4-DNP-hydrazine) indicated that all of the aldehyde had been consumed. The black reaction mixture was poured into a slurry of sodium bicarbonate in saturated aqueous sodium bicarbonate (100 mL) and the resulting slurry was diluted with ethyl acetate (200 mL). The mixture was stirred for 1 h giving a clear, colourless organic layer and a pale grey-green aqueous layer. The aqueous layer was extracted with ethyl acetate and the combined organic solvents were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent yielded olefin **21** (0.34 g, 42%) as an amber gum; R_f 0.50 (ethyl acetate-1-propanol-water 3:1:0.2, I_2); IR ($CHCl_3$): 1740, 1660-1640, 1300-1200, 1035 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.35 (t, J=7 Hz, 6H), 2.75-3.85 (m, 3H), 2.95 (d, J_{P,CH_2}=22 Hz, 2H), 3.43 (s, 3H), 3.52 (s, 3H), 3.53 (s, 3H), 3.90-4.50 (m, 4H), 4.60-5.20 (m, 5H); MS **m/z**: 396(M, 1), 365(4), 179(100), 151(30), 123(37), 110(23), 109(35), 101(51), 97(20), 88(31), 75(73), 73(27), 45(50), 41(20); Exact mass: calcd. for $C_{15}H_{26}O_8P$ (M^+-OMe): 365.1365; found: 365.1363.

Methyl 7-deoxy-4-O-(diethyl phosphonoacetyl)-2,3-di-O-methyl-α-D-glcuo-hepto-1,5-pyranosid-6-ulose (22)

To a solution of mercuric acetate (96 mg, 0.30 mmol) in acetone (5 mL) and water (10 drops) was added a solution of alkene **21** from above (86 mg, 0.21 mmol) in acetone (2 mL) and the resulting solution was stirred for 40 min. To the clear yellow solution was added Jones reagent (0.21 mL, 1.4 M, 0.30 mmol) and the resulting red mixture was stirred for 4.5 h.[30] The brown reaction mixture was filtered and the green chromium salts were washed with ethyl acetate. The combined organic solvents were evaporated and the resulting residue was redissolved in ethyl acetate. The organic solution was washed with saturated aqueous sodium bicarbonate (6 x 10 drops), dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated to yield crude methyl ketone **22** (45 mg, 50%) as an amber gum. All traces of acetone and ethyl acetate were then removed by coevaporation with carbon tetrachloride. The yield of methyl ketone **22** is approximately 17% based on integration of the methyl ketone signal at δ 2.23 in the ^1H NMR spectrum. The crude mixture was characterized by the following: R_f 0.55 (ethyl acetate-1-propanol-water 3:1:0.2, H_2SO_4 and 2,4-DNP-hydrazine); IR ($CHCl_3$): 1740, 1375, 1300-1200, 1030 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.35 (t, J=7 Hz, 6H), 2.23 (s, 1H, methyl ketone), 2.75-3.18 (m, 2H), 3.18-3.80 (m, 11H), 3.80-4.50 (m, 5H), 4.50-5.05 (m, 2H), 5.05-6.05 (m, residual olefin); MS **m/z**: 412(M^+, 0.8), 179(53), 101(21), 88(100), 75(29); Exact mass: calcd. for $C_{16}H_{29}O_{10}P$: 412.1498; found: 412.1489.

(Methyl 6,7-dideoxy-6-C-methyl-2,3-di-O-methyl-α-D-gluco-oct-6-eno-1,5-pyranosid)urono-8,4-lactone (23)

Sodium hydride (16 mg, 60% dispersion in mineral oil, 0.4 mmol) was washed free of oil with dry ether (3 x 1 mL) under nitrogen and then dry THF (2 mL) was added to the sodium hydride. The resulting slurry was added via pipette to a solution of methyl ketone **22** from above (0.171 g, 33% pure, 0.133 mmol) in dry THF (20 mL) under nitrogen. The reaction mixture was stirred for 5 min, heated under reflux for 2 h and then was allowed to cool to room temperature. Amberlite IR-120 (several spatula tips full) was added to neutralize any excess base. After stirring for 10 min, the reaction mixture was filtered and concentrated to yield a brown gum. Purification by flash chromatography on silica gel using petroleum ether - ethyl acetate 1:1 as eluant yielded a 4:1 mixture of α,β-unsaturated lactone **23** and the same 8,6-lactone which was obtained in the synthesis of **18** above. The mixture (13 mg, 39%) was a white semi-solid; mp 70-108 °C; R_f 0.25 (petroleum ether-ethyl acetate 1:1, UV and H_2SO_4); IR ($CHCl_3$): 1730, 1650, 1070 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 2.00 (t, J=1 Hz, 3H), 3.25 (dd, J=9, 3 Hz, 1H), 3.40-4.70 (m, 3H), 3.47 (s, 3H), 3.60 (s, 3H), 3.67 (s, 3H), 4.90 (d, J=3 Hz, 1H), 5.76 (m, 1H); MS **m/z**: 258(M^+, 0.2), 227(0.5), 88(100), 73(14); Exact mass: calcd. for $C_{11}H_{15}O_5$ (M^+-OMe): 227.0920; found: 227.0926.

(Methyl 6,7-dideoxy-6-C-methyl-2,3-di-O-methyl-L-glycero-α-D-gluco-octo-1,5-pyranosid)urono-8,4-lactone (20)

A suspension of platinum oxide (2 mg) in methanol (1 mL) was pre-hydrogenated at atmospheric pressure for 1 h to give elemental platinum as black granules. To this mixture was added a solution of α,β-unsaturated lactone **23** from above (4 mg, 0.01 mmol) in methanol (0.25 mL). After stirring under hydrogen at atmospheric pressure for 3.5 h, the reaction mixture was filtered and the catalyst was rinsed with methanol. Evaporation of the solvent yielded a 72:17:11 mixture of lactones **20**, the reduced 8,6-lactone, and an unidentified product (4 mg, 100%) as a colourless oil; R_f 0.26 (petroleum ether-ethyl acetate 1:1, H_2SO_4); IR ($CHCl_3$): 1740, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.10 (d, $J_{6,9}$=7 Hz, 3H, Me), 2.04-2.17 (A part of ABX system plus additional couplings, 1H, H-6), 2.26 (B part of ABX system, $J_{7\alpha,7\beta}$=18 Hz, $J_{6,7\beta}$=9 Hz, 1H, H-7β), 2.90 (X part of ABX system, $J_{7\alpha,7\beta}$=18 Hz, $J_{6,7\alpha}$=8 Hz, 1H, H-7α), 3.25 (dd, $J_{2,3}$=9 Hz, $J_{1,2}$=3.5 Hz, 1H, H-2), 3.33-3.52 (m, 1H), 3.44 (s, 3H), 3.54 (s, 3H), 3.60 (t, J=9 Hz, 1H), 3.64 (s, 3H), 3.88 (t, J=9 Hz, 1H), 4.84 (d, $J_{1,2}$=3.5 Hz, 1H, H-1); MS **m/z**: 260(M^+, 0.1), 229(3), 168(78), 88(100), 75(49), 73(13); Exact mass: calcd. for $C_{11}H_{17}O_5$ (M^+-OMe): 229.1076; found: 229.1078.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (24)

This compound was prepared in 86% yield following the procedure of Sum and Weiler;[14b] mp 199-201 °C (lit. mp 198-200 °C).[14b]

Methyl 4,6-O-benzylidene-2-deoxy-2-C-methyl-α-D-altro-pyranoside (25a)

To a slurry of copper(I) cyanide (20.1 g, 224 mmol) in dry ether (525 mL, distilled from sodium) at -78 °C under

nitrogen in the fume hood was added a solution of methyllithium in ether (320 mL, 1.4 M, 448 mmol). After stirring for 5 min at -78 °C, the mixture was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 25 min at which time the copper(I) cyanide had all reacted to give a cloudy pale green solution of the cuprate, $Me_2Cu(CN)Li_2$.[37] The cuprate solution was cooled to -78 °C and epoxide **24** (49.2 g, 186 mmol) was added. The resulting slurry was stirred at -78 °C for 15 min and at 0 °C for 4 h. The reaction was quenched carefully with a solution of saturated aqueous ammonium chloride - 16 M ammonium hydroxide 9:1 (100 mL). The mixture was transferred to a separatory funnel and diluted with ether (1100 mL) and NH_4Cl-NH_4OH 9:1 (50 mL). The ether layer was washed with NH_4Cl-NH_4OH 9:1 (4 x 50 mL), brine (3 x 100 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded alcohol **25a** (51.1 g, 98%) as white crystals which could be used in the next reaction without purification. Recrystallization of the crude product from ether-petroleum ether yielded pure alcohol **25a** (39.8 g, 76%) in two crops; mp 112-114 °C (lit. mp 111-113 °C).[49]

Methyl 4,6-O-benzylidene-2-deoxy-2-C-methyl-3-O-[(thiomethyl)-thiocarbonyl]-α-D-altro-pyranoside

This compound was prepared from alcohol **25a** in 99% crude yield following the procedure of Hicks and Fraser-Reid[46] and could be used directly in the next reaction.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-α-D-arabino-hexo pyranoside (25b)

To a solution of tri-n-butylstannane (27.9 g, 106 mmol) in dry toluene (150 mL) at reflux under nitrogen in the fume hood was added a solution of the above crude xanthate (19.6 g, 53.0 mmol) in dry toluene (200 mL). The yellow solution was heated under reflux overnight to afford a very pale mixture. The reaction mixture was allowed to cool to room temperature and then was concentrated. The residue was partially purified by flash chromatography on silica gel in the fume hood using the sequence of solvents: neat petroleum ether, petroleum ether-ether 19:1, 7:1 and then 1:1 as eluant. Evaporation of solvent from the purest fractions yielded a semi-solid which was then recrystallized from petroleum ether to yield the pure deoxygenated compound **25b** (4.4 g) as large white crystals. The other chromatography fractions and the mother liquor were combined and concentrated. The ^1H nmr of this material indicated the presence of starting material. The entire experimental procedure was repeated on this crude material to yield additional product (4.1 g), bringing the total yield of deoxygenated compound **25b** to 8.5 g (62%) as white crystals; mp 71.0-72.5 °C; R_f 0.34 (petroleum ether-ether 7:1, UV, H_2SO_4 and I_2); IR ($CHCl_3$): 1100, 1055 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.16 (d, J=7 Hz, 3H), 1.50-2.35 (m, 3H), 3.38 (s, 3H), 3.60-4.10 (m, 3H), 4.13-4.30 (m, 1H), 4.38 (s, 1H), 5.56 (s, 1H), 7.25-7.65 (m, 5H); MS **m/z**: 264(M^+, 15), 233(7), 115(100), 105(21), 82(32), 73(25), 55(29).

Methyl 2,3-dideoxy-2-C-methyl-α-D-arabino-hexopyranoside (26a)

This compound was prepared from benzylidene acetal **25b** in 98% yield following the procedure of Sum and Weiler;[14b] R_f 0.10 (petroleum ether-ether 1:1, H_2SO_4); IR ($CHCl_3$): 3600, 3570-3100, 1055 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.07 (d, J=7 Hz, 3H), 1.50-2.20 (m, 3H), 2.80-3.15 (bs, 2H, D_2O exchangeable), 3.35 (s, 3H), 3.25-4.00 (m, 4H), 4.35 (s, 1H); MS **m/z**: 145(M^+-OMe, 19), 86(28), 84(44), 83(23), 74(65), 72(100), 71(21), 61(23), 57(31), 56(36), 55(36), 43(34), 41(26).

Methyl 2,3-dideoxy-2-C-methyl-6-O-triphenylmethyl-α-D-arabino-hexopyranoside (26b)

This compound was prepared from diol **26a** in 76% yield following the procedure of Sum and Weiler;[14b] mp 146-147 °C (lit. 147-149 °C).[14b]

Methyl 4-O-bromoacetyl-2,3-dideoxy-2-C-methyl-6-O-triphenylmethyl-α-D-arabino-hexopyranoside

To a solution of alcohol **26b** (17.1 g, 41 mmol), dry pyridine (13.2 mL, 164 mmol), and DMAP (0.50 g, 4.1 mmol) in dry ether (250 mL) at 0 °C under nitrogen in the fume hood was added bromoacetyl bromide (7.1 mL, 82 mmol) over 5 min.[21] The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 17 h. The orange reaction mixture was filtered through a sintered glass filter and the precipitate was washed with ether (50 mL). The filtrate was washed with 1 M hydrochloric acid (3 x 50 mL), saturated aqueous sodium bicarbonate (3 x 50 mL), brine (3 x 50 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded crude bromoacetate (19.7 g, 90%) as a yellow semi-solid which could be used directly in the next reaction. Purification of a small sample by flash chromatography on silica gel using petroleum ether-ethyl acetate 8:1 as eluant yielded pure bromoacetate as a colourless gum which crystallized on standing. Recrystallization from ethanol afforded an analytically pure sample of off-white crystals; mp 90-92 °C; R_f 0.34 (petroleum ether-ethyl acetate 8:1, UV and H_2SO_4); $[\alpha]_D$ +66.2 (c 1.20, $CHCl_3$); IR ($CHCl_3$): 1740, 1075, 965 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.13 (d, J=7 Hz, 3H), 1.70-2.20 (m, 3H), 3.00-3.28 (m, 2H), 3.28-3.67 (m, 2H), 3.44 (s, 3H), 3.67-4.00 (m, 1H), 4.43 (d, J=2 Hz, 1H), 4.80-5.20 (m, 1H), 7.15-7.60 (m, 15H); MS **m/z**: 540(^{81}Br: M^+, 1), 538(^{79}Br: M^+, 1), 258(24), 244(29), 243(100), 165(30); Exact mass: calcd. for $C_{29}H_{31}{}^{81}BrO_5$: 540.1335; found: 540.1338. Anal. calcd. for $C_{29}H_{31}BrO_5$: C 64.57, H 5.79, Br 14.81, O 14.83; found C 64.71, H 5.83, Br 14.69, O 14.71.

Methyl 2,3-dideoxy-4-O-(diethyl phosphonoacetyl)-2-C-methyl-6-O-triphenylmethyl-α-D-arabino-hexo-pyranoside (27a)

To the neat bromoacetate prepared above (3.0 g, 5.6 mmol) under a stream of nitrogen in the fume hood was added dry triethyl phosphite (9.5 mL, 56 mmol). The reaction mixture was heated to 135-140 °C and the bromoethane produced was distilled out of the reaction mixture. After 4 h, the reaction mixture was allowed to cool to room temperature and was

purified by flash chromatography on silica gel in the fume hood using the sequence of solvents: petroleum ether-ethyl acetate 1:1 and neat ethyl acetate as eluant. Evaporation of solvent from the appropriate fractions yielded two compounds.

a) Chloroacetate **27b** (0.07 g, 2%) was isolated from the petroleum ether-ethyl acetate solvent as white crystals which were then recrystallized; mp 104-106 °C; R_f 0.88 (petroleum ether-ethyl acetate 1:1, UV and H_2SO_4); IR ($CHCl_3$): 1760, 1740, 1075, 960 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.15 (d, J=7 Hz, 3H), 1.50-2.25 (m, 3H), 3.00-3.30 (m, 2H), 3.43 (s, 3H), 3.60-4.05 (m, 3H), 4.43 (d, J=2 Hz, 1H), 4.85-5.27 (m, 1H), 7.10-7.65 (m, 15H); MS **m/z**: 496(^{37}Cl: M^+, 0.2), 494 (^{35}Cl: M^+, 0.2), 258(23), 244(26), 243(100), 165(22); Exact mass: calcd. for $C_{29}H_{31}{}^{37}ClO_5$: 496.1830; found: 496.1789; calcd. for $C_{29}H_{31}{}^{35}ClO_5$: 494.1860; found: 494.1857.

b) Phosphonoacetate **27a** (3.5 g, 104%) was isolated from the ethyl acetate fractions as a gum which crystallized on standing. A small sample was recrystallized repeatedly from ether-petroleum ether to yield analytically pure fine white needles; mp 85-86 °C; R_f 0.15 (petroleum ether-ethyl acetate 1:1, UV and H_2SO_4); $[\alpha]_D$ +50.2 (c 0.804, $CHCl_3$); IR ($CHCl_3$): 1740, 1320-1200, 1020 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.10 (d, J=7 Hz, 3H), 1.28 (t, J=7 Hz, 6H), 1.55-2.20 (m, 3H), 2.70 (d, $J_{P,CH}$=22 Hz, 2H), 2.95-3.35 (m, 2H), 3.45 (s, 3H), 3.70-4.35 (m, 5H), 4.43 (d, J=2 Hz, 1H), 4.80-5.25 (m, 1H), 7.05-7.65 (m, 15H); MS **m/z**: 596(M^+, 0.1), 321(70), 244(29), 243(100), 197(27), 179(32), 165(31), 127(36); Exact mass: calcd. for $C_{27}H_{36}O_8P$ (M^+-C_6H_5): 519.2148; found: 519.2143. Anal. calcd. for $C_{33}H_{41}O_8P$: C 66.43, H 6.93, O 21.45; found: C 66.22, H 6.93, O 21.25.

Methyl 2,3-dideoxy-4-O-(diethyl phosphonoacetyl)-2-C-methyl-α-D-arabino-hexopyranoside

To a solution of trityl ether **27a** (0.50 g, 0.84 mmol) in methanol (10 mL) was added 5% palladium-on-charcoal (0.1 g) and a trace of 12 M hydrochloric acid. The reaction mixture was stirred under hydrogen at atmospheric pressure for 8 h, filtered through a pad of Celite, and concentrated, without heating, to give a white semi-solid residue which consisted of triphenylmethane and the desired C-6 alcohol. Although the crude material could be used directly in the next reaction, this sample was purified by continuous liquid-liquid extraction. The crude product mixture was dissolved in acetonitrile and the resulting solution was extracted continuously with petroleum ether. After 2.5 h, TLC of the acetonitrile layer showed no triphenylmethane. The acetonitrile layer was filtered and concentrated, without heating, to yield the alcohol (0.29 g, 98%) as a pale amber oil; R_f 0.12 (ethyl acetate, H_2SO_4); IR ($CHCl_3$): 3650-3250, 1740, 1320-1200, 1050, 1025 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.10 (d, J=7 Hz, 3H), 1.35 (t, J=7 Hz, 6H), 1.70-2.25 (m, 3H), 2.83 (bs, 1H, D_2O exchangeable), 2.95 (d, $J_{P,CH}$=22 Hz, 2H), 3.38 (s, 3H), 3.50-3.95 (m, 3H), 3.95-4.31 (m, 4H), 4.40 (bs, 1H), 4.80-5.25 (m, 1H); MS **m/z**: 323(M^+-OMe, 9), 223(20), 197(100), 179(83), 151(29), 127(22), 123(25), 115(27), 72(41); Exact mass: calcd. for $C_{13}H_{24}O_7P$ (M^+-OMe): 323.1259; found: 323.1256.

Methyl 2,3-dideoxy-4-O-(diethyl phosphonoacetyl)-2-C-methyl-α-D-arabino-hexodialdo-1,5-pyranoside (28)

To a solution of the above C-6 alcohol (0.29 g, 0.8 mmol) and freshly distilled DCC (0.51 g, 2.4 mmol) in dry DMSO (3.5 mL) under nitrogen in the fume hood was added dry dichloroacetic acid (0.03 mL, 0.4 mmol).[24] After stirring for 1.75 h, the cloudy white reaction mixture was filtered through a sintered glass filter and the precipitate was rinsed with distilled water. The combined aqueous filtrate was extracted with ether (6 x 10 mL) and then frozen using a dry ice-acetone bath. Freeze-drying under vacuum overnight yielded aldehyde **28** (0.24 g, 81%) as a pale amber oil; R_f 0.70 (ethyl acetate-1-propanol 3:1, H_2SO_4 and 2,4-DNP-hydrazine); IR ($CHCl_3$): 1740, 1320-1200, 1045, 1025 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.05 (d, J=7 Hz, 3H), 1.35 (t, J=7 Hz, 6H), 1.50-2.25 (m, 3H), 2.98 (d, $J_{P,CH}$=22 Hz, 2H), 3.45 (s, 3H), 3.90-4.39 (m, 5H), 4.42 (d, J=3 Hz, 1H), 5.00-5.40 (m, 1H), 9.71 (s, 1H); MS **m/z**: 323(M^+-CHO, 20), 197(39), 179(100), 151(50), 128(20), 127(86), 125(28), 123(54), 115(39), 109(27), 97(23), 95(36), 85(32), 83(31), 81(25), 73(26), 72(72), 59(33); Exact mass: calcd. for $C_{13}H_{24}O_7P$ (M^+-CHO): 323.1260; found: 323.1265.

(Methyl 2,3,6,7-tetradeoxy-2-C-methyl-α-D-arabino-oct-6-eno-1,5-pyranosid)-urono-8,4-lactone (29)

Sodium hydride (0.13 g, 60% dispersion in oil, 3.3 mmol) was washed free of oil with dry THF under nitrogen and then dry THF (5 mL) was added to the sodium hydride. The resulting slurry was added via pipette to a solution of aldehyde **28** (0.99 g, 2.8 mmol) in dry THF (120 mL) under nitrogen. The reaction mixture was stirred for 5 min, heated under reflux for 1 h and then was allowed to cool to room temperature. Amberlyst-15 (several spatula tips full) was added to neutralize any excess base. After stirring for 10 min, the reaction mixture was filtered and concentrated to yield an amber gum (1.1 g). Partial purification by gel filtration on Sephadex LH-20 using chloroform-methanol 1:1 as eluant yielded a pale amber gum (0.36 g). Purification by flash chromatography on silica gel using petroleum ether-ethyl acetate 3.5:1 as eluant yielded $\alpha\beta$-unsaturated lactone **29** (0.23 g, 42%) as a clear, colourless oil which crystallized overnight, mp 56.5-58 °C. A small amount was Kugelrohr distilled, bp 61-63 °C/0.01 Torr, to yield an analytically pure sample; R_f 0.25 (petroleum ether-ethyl acetate 3.5:1, UV and H_2SO_4); $[\alpha]_D$ +135 (c 0.088, $CHCl_3$); IR ($CHCl_3$): 1745, 1730, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.12 (d, J=7 Hz, 3H), 2.80-2.88 (m, 1H), 3.13-3.25 (m, 2H), 3.39 (s, 3H), 4.29 (dt, J=11, 5 Hz, 1H), 4.40-4.48 (m, 2H), 5.97 (dd, J=10, 3 Hz, 1H), 6.88 (d, J=10 Hz, 1H); MS **m/z**: 198(M^+, 1), 167(11), 96(100), 83(56), 73(32), 68(49), 55(90), 45(32), 41(30), 39(50); Exact mass: calcd. for $C_9H_{11}O_3$ (M^+-OMe): 167.0708; found: 167.0704. Anal. calcd. for $C_{10}H_{14}O_4$: C 60.59, H 7.12; found: C 60.33, H 7.29.

(Methyl 2,3,6,7-tetradeoxy-2,6-di-C-methyl-α-D-altro-octo-1,5-pyranosid)-urono-8,4-lactone (30)

To a suspension of copper(I) cyanide (0.178 g, 1.99 mmol) in dry ether (20 mL, distilled from sodium) at -78 °1C under nitrogen in the fume hood was added a solution of methyllithium in ether (2.65 mL, 1.5 M, 3.98 mmol). After stirring

for 5 min at -78 °C, the reaction mixture was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 20 min by which time the copper(I) cyanide had all reacted to give a cloudy solution of $Me_2Cu(CN)Li_2$.[26a] The cuprate solution was cooled to -78 °C and a solution of α,β-unsaturated lactone **29** (0.328 g, 1.66 mmol) in dry ether (12 mL, distilled from sodium) was added dropwise. The resulting bright yellow reaction mixture was stirred at -78 °C for 15 min, at -40 °C for 30 min and then was allowed to warm to 0 °C. The reaction was diluted with ether and quenched with glacial acetic acid (6 mL) to give a clear pale turquoise solution containing a small amount of a fine white precipitate. Tetrasodium ethylenediaminetetra-acetate trihydrate (0.86 g, 2.0 mmol) was added and the resulting mixture was stirred for 15 min while warming to room temperature. Brine (5 mL) was added and a flocculant white precipitate formed. The mixture was stirred for an additional 5 min and then was filtered on a sintered glass filter. The filtrate was washed with a solution of saturated aqueous sodium carbonate-brine 1:1 (5 x 4 mL), brine (2 x 4 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded lactone **30** (0.32 g, 91%) as a very pale amber oil which was pure enough to use in the next reaction. A small amount was Kugelrohr distilled, bp 70-73 °C/0.01 Torr, to yield an analytically pure sample as a colourless oil; R_f 0.45 (petroleum ether-ethyl acetate 2:1, H_2SO_4); $[\alpha]_D$ +37 (c 0.070, $CHCl_3$); IR ($CHCl_3$): 1735, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.10 (d, J=7 Hz, 3H), 1.13 (d, J=7 Hz, 3H), 1.83-1.92 (m, 1H), 2.01-2.18 (m, 2H), 2.24-2.36 (m, 1H), 2.48 (dd, $J_{7\alpha,7\beta}$ =18 Hz, $J_{6,7\beta}$ =3.5 Hz, 1H, H-7β), 2.82 (dd, $J_{7\alpha,7\beta}$ =18 Hz, $J_{6,7\alpha}$ =7 Hz, 1H, H-7α), 3.38 (s, 3H), 3.84 (dd, $J_{4,5}$=10 Hz, $J_{5,6}$=5 Hz, 1H, H-5), 4.34-4.44 (m, 2H); MS m/z: 214(M^+, 1), 183(10), 112(100), 84(42), 72(58), 69(33), 56(46), 43(26), 41(28); Exact mass: calcd. for $C_{11}H_{18}O_4$: 214.1205; found: 214.1204. Anal. calcd. for $C_{11}H_{18}O_4$: C 61.66, H 8.47; found: C 61.52, H 8.55.

Methyl 2,3,6,7-tetradeoxy-2,6-di-C-methyl-α-D-altro-octo-1,5-pyranoside (31)

To a solution of lactone **30** (0.323 g, 1.51 mmol) in dry ether (10 mL) under nitrogen was added a solution of diisobutylaluminum hydride in hexanes (9.3 mL, 1.0 M, 9.3 mmol). After stirring overnight, the reaction mixture was cooled to 0 °C, diluted with ethyl acetate (30 mL) and quenched with saturated aqueous sodium sulfate (5 mL). The gelatinous aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic solvents were washed with 10% aqueous sodium bisulfate (1 x 25 mL, 1 x 5 mL), 10% aqueous potassium carbonate (1 x 5 mL), brine (2 x 5 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded diol **31** (0.308 g, 94%) as a colourless oil which could be used in the next reaction. Purification of a small sample by flash chromatography on silica gel using neat ethyl acetate as eluant, followed by Kugelrohr distillation, bp 105-110 °C/0.01 Torr, yielded analytically pure diol **31** as a white semi-solid; R_f 0.29 (ethyl acetate, H_2SO_4); $[\alpha]_D$ +112 (c 0.460, $CHCl_3$); IR ($CHCl_3$): 3640, 3600-3100, 1055 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.04 (d, J=7 Hz, 3H), 1.07 (d, J=7 Hz, 3H), 1.15-2.40 (m, 6H), 3.20-4.00 (m, 6H, 2H are D_2O exchangeable), 3.35 (s, 3H), 4.33 (bs, 1H); MS m/z: 187(M^+-OMe, 1), 169(5), 72(100), 55(20); Exact mass: calcd. for $C_{10}H_{19}O_3$ (M^+-OMe): 187.1334; found: 187.1319. Anal. calcd. for $C_{11}H_{22}O_4$: C 60.52, H 10.16; found: C 60.72, H 10.24.

Methyl 2,3,6,7-tetradeoxy-2,6-di-C-methyl-8-O-pivaloyl-α-D-altro-octo-1,5-pyranoside

To a solution of diol **31** (0.216 g, 1.00 mmol) and dry pyridine (2 mL) at 0 °C under nitrogen was added pivaloyl chloride (0.123 mL, 1.00 mmol) over 5 min and the resulting mixture was stirred at 0 °C for 3 h. Ice was added to quench the reaction, the mixture was stirred for 1 h and then was diluted with dichloromethane (10 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic solvents were washed with 1 M hydrochloric acid (4 x 10 mL), saturated aqueous sodium bicarbonate (2 x 10 mL), brine (2 x 10 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded the C-8 pivaloate ester (0.222 g, 74%) as a colourless oil which could be used in the next reaction. Purification of a small amount by flash chromatography on silica gel using petroleum ether-ethyl acetate 3:1 as eluant, followed by Kugelrohr distillation, bp 105-110 °C/0.1 Torr, yielded an analytically pure sample; R_f 0.70 (petroleum ether-ethyl acetate 1:1, H_2SO_4); $[\alpha]_D$ +88.1 (c 0.520, $CHCl_3$); IR ($CHCl_3$): 3625, 3600-3300, 1720, 1160 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.03 (d, J=7 Hz, 3H), 1.06 (d, J=7 Hz, 3H), 1.20 (s, 9H), 1.40-2.25 (m, 7H, 1H is D_2O exchangeable), 3.25-3.50 (m, 1H), 3.35 (s, 3H), 3.55-3.95 (m, 1H), 3.95-4.25 (m, 2H), 4.30 (d, J=2 Hz, 1H); MS m/z: 302(M^+, 0.1), 271(3), 98(25), 85(75), 83(56), 73(40), 72(97), 71(44), 69(41), 57(100), 56(23), 55(64), 43(40); Exact mass: calcd. for $C_{15}H_{27}O_4$ (M^+-OMe): 271.1909; found: 271.1912. Anal. calcd. for $C_{16}H_{30}O_5$: C 63.55, H 10.00; found: C 63.36, H 10.00.

When excess pivaloyl chloride was used in this reaction, the dipivaloate ester was also produced. Separation of the two products by flash chromatography on silica gel using the sequence of solvents: petroleum ether-ethyl acetate 20:1, 15:1 and then 3:1 as eluant yielded dipivaloate ester as a clear, colourless oil. A small amount was Kugelrohr distilled, bp 100-110 °C/0.05 Torr, to yield an analytically pure sample; R_f 0.93 (petroleum ether-ethyl acetate 3:1, H_2SO_4); $[\alpha]_D$ +87.7 (c 0.618, $CHCl_3$); IR ($CHCl_3$): 1720, 1160 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.02 (d, J=7 Hz, 3H), 1.07 (d, J=7 Hz, 3H), 1.18 (s, 9H), 1.20 (s, 9H), 1.55-2.15 (m, 6H), 3.38 (s, 3H), 3.63 (dd, J=9, 3 Hz, 1H), 4.02-4.22 (m, 2H), 4.32 (d, J =2 Hz, 1H), 4.75-5.25 (m, 1H); MS m/z: 355(M^+-OMe, 1), 95(20), 85(29), 72(100), 57(73), 55(21). Anal. calcd. for $C_{21}H_{38}O_6$: C 65.26, H 9.91; found: C 65.17, H 10.01.

Methyl 2,3,6,7-tetradeoxy-2,6-di-C-methyl-8-O-pivaloyl-α-D-arabino-octo-1,5-pyranosid-4-ulose (32)

To a solution of oxalyl chloride (34 μL, 0.40 mmol) in dry dichloromethane (2 mL) at -60 °C under nitrogen was added DMSO (55 μL, 0.80 mmol) and the resulting solution was stirred at -60 °C for 5 min. To this mixture was added a

solution of alcohol 114 (98 mg, 0.32 mmol) in dry dichloromethane (3 mL) and the resulting solution was stirred at -60 °C for 20 min. Triethylamine (225 μL, 1.6 mmol) was added slowly and the reaction mixture was stirred at -60 °C for 5 min and then at room temperature for 5 h. Ice was added to quench the reaction and the mixture was stirred for 20 min. The resulting solution was diluted with dichloromethane (20 mL) and the organic layer was washed with 1 M hydrochloric acid (1 x 2 mL, 2 x 1 mL), saturated aqueous sodium bicarbonate (1 x 2 mL), brine (2 x 2 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded an amber oil (89 mg) which was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate 12:1 as eluant to yield ketone **32** (76 mg, 78%) as a clear, colourless oil. A small amount was Kugelrohr distilled, bp 100-105 °C/0.09 Torr, to yield an analytically pure sample; R_f 0.32 (petroleum ether-ethyl acetate 8:1, H_2SO_4); $[\alpha]_D$ +208 (c 0.884, $CHCl_3$); IR ($CHCl_3$): 1720, 1160 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 1.07 (d, J=7 Hz, 3H), 1.10 (d, J=7 Hz, 3H), 1.20 (s, 9H), 1.45-1.85 (m, 2H), 1.85-2.55 (m, 4H), 3.44 (s, 3H), 3.88-4.18 (m, 3H), 4.53 (d, J=4 Hz, 1H); MS **m/z**: 300(M^+, 1), 269(2), 72(100), 57(34), 41(26); Exact mass: calcd. for $C_{16}H_{28}O_5$: 300.1937; found: 300.1942. Anal. calcd. for $C_{16}H_{28}O_5$: C 63.97, H 9.40; found: 64.10, H 9.40.

Methyl 2,3,4,6,7-pentadeoxy-2,6-di-C-methyl-4-C-methylene-8-O-pivaloyl-α-D-arabino-octo-1,5-pyranoside

To a solution of ketone **32** (66 mg, 0.22 mmol) in dry dichloromethane (5 mL) was added in portions, via pipette, the active methylene complex (see above) (9 x ca. 1.5 mL) until TLC analysis indicated that the reaction was complete. The black reaction mixture was poured into a slurry of sodium bicarbonate in saturated aqueous sodium bicarbonate (15 mL) and the resulting slurry was diluted with ethyl acetate (25 mL). The mixture was stirred for 40 min giving a clear, colourless organic layer and a pale grey aqueous layer. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic solvents were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent yielded an oil (84 mg) which was purified by flash chromatography using petroleum ether-ethyl acetate 8:1 as eluant to yield the C-4 alkene (55 mg, 83%) as a clear, colourless oil. A small amount was Kugelrohr distilled, bp 85-90 °C/0.1 Torr, to yield an analytically pure sample; R_f 0.48 (petroleum ether-ethyl acetate 8:1, H_2SO_4); $[\alpha]_D$ +122 (c 0.560, $CHCl_3$); IR ($CHCl_3$): 1720, 1650, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 0.98 (d, J=7 Hz, 3H), 1.02 (d, J=7 Hz, 3H), 1.20 (s, 9H), 1.41-1.52 (m, 1H), 1.73-1.82 (m, 1H), 1.95 (dd, J=13, 8 Hz, 1H), 2.02-2.13 (m, 2H), 2.42 (dd, J= 13, 5 Hz, 1H), 3.40 (s, 3H), 4.02 (bd, J=4 Hz, 1H), 4.08-4.20 (m, 2H), 4.36 (d, J=4 Hz, 1H), 4.77 (bs, 1H), 4.85 (bs, 1H); MS **m/z**: 298(M^+, 0.2), 269(3), 141(99), 121(24), 109(100), 107(23), 85(43), 81(44), 72(59), 71(22), 57(50); Exact mass: calcd. for $C_{17}H_{30}O_4$: 298.2144; found: 298.2159. Anal. calcd. for $C_{17}H_{30}O_4$: C 68.42, H 10.13; found: C 68.64, H 10.16.

Methyl 2,3,4,6,7-pentadeoxy-2,4,6-tri-C-methyl-8-O-pivaloyl-α-D-manno-octo-1,5-pyranoside (33)

A solution of freshly prepared Wilkinson's catalyst[50] (0.310 g, 0.33 mmol) in dry benzene (25 mL) was prehydrogenated by bubbling hydrogen through the stirred solution for 1.5 h. To the resulting pale orange-red mixture was added a solution of the above alkene (0.100 g, 0.336 mmol) in dry benzene (10 mL).[14b] Hydrogen was continuously bubbled through the stirred mixture and the reaction was monitored by capillary GLC. Complete hydrogenation is effected providing the solution is either yellow or pale orange-red during the entire course of the reaction. After 6.5 h, the reaction mixture was diluted with petroleum ether-ethyl acetate 4:1 and the resulting suspension was filtered through a pad of silica gel. Evaporation of the solvent yielded compound **33** (75 mg, 75%) as a pale amber oil; R_f 0.70 (petroleum ether-ethyl acetate 6:1, H_2SO_4); IR ($CHCl_3$): 1720, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 0.86 (d, J=7 Hz, 3H), 0.93 (d, J=7 Hz, 3H), 1.02 (d, J=7 Hz, 3H), 1.19 (s, 9H), 1.31-1.42 (m, 1H), 1.61-1.79 (m, 3H), 1.81-1.98 (m, 2H), 2.12-2.23 (m, 1H), 3.37 (s, 3H), 3.40 (dd, J=11, 4 Hz, 1H), 4.15 (dd, J=8, 6 Hz, 2H), 4.26 (d, J=4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 15.22 15.56 19.14 (CH_3), 27.23 (tert-butyl), 28.86 31.38 31.79 (CH), 32.52 34.36 (CH_2), 38.69 (C), 55.08 (OCH_3), 63.19 (CH), 73.75 (CH), 105.91 (CH), 178.53 (C=O); MS **m/z**: 269(M^+-OMe, 6), 268(10), 109(29), 96(80), 95(57), 85(36), 81(56), 72(75), 69(29), 57(100), 55(48); Exact mass: calcd. for $C_{16}H_{29}O_3$ (M-OMe): 269.2116; found: 269.2104.

(2S,4R,5S,6R)-5-Hydroxy-2,4,6-trimethyl-8-[(pivaloyl)oxy]-1,1-(propane-1',3'-dithio)octane (34a)

To a solution of acetal **33** (70 mg, 0.23 mmol) in dry dichloromethane (4 mL) at 0 °C under nitrogen in the fume hood was added 1,3-propanedithiol (6 drops, ca. 0.7 mmol) and boron trifluoride etherate (56 μL, 0.47 mmol). After stirring for 2.5 h at 0 °C, the reaction mixture was diluted with ethyl acetate (30 mL). The organic layer was washed with 3 M sodium hydroxide (3 x 4 mL), brine (3 x 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give an oil (93 mg). Purification by flash chromatography on silica gel using petroleum ether-ethyl acetate 6:1 as eluant yielded hydroxy dithiane **34a** (74 mg, 84%) as a clear, colourless gum; R_f 0.16 (petroleum ether-ethyl acetate 6:1, UV and H_2SO_4); IR ($CHCl_3$): 3650, 3600-3300, 2980, 1720, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 0.88 (d, J=7 Hz, 3H), 0.91 (d, J=7 Hz, 3H), 1.10 (d, J=7 Hz, 3H), 1.20 (s, 9H), 1.42-1.53 (m, 1H), 1.59 (bs, 1H, D_2O exchangeable), 1.65-1.91 (m, 5H), 1.93-2.16 (m, 3H), 2.82-2.97 (m, 4H), 3.21 (b d, J=7 Hz, 1H), 4.08-4.23 (m, 3H); MS **m/z**: 376(M^+, 3), 358(2), 159(26), 146(26), 119(100), 85(29), 57(72), 55(28); Exact mass: calcd. for $C_{19}H_{36}O_3S_2$: 376.2106; found: 376.2114.

(2S,4R,5S,6R)-5-[(2'-Methoxyethoxymethyl)oxy]-2,4,6-trimethyl-8-[(pivaloyl)-oxy]-1,1-(propane-1",3"-dithio)octane

To a solution of alcohol **34a** (12 mg, 0.032 mmol) in dry dichloromethane (1 mL) at 0 °C under nitrogen was added 2-methoxyethoxymethyl chloride (11 μL, 0.096 mmol) and N-ethyldiisopropylamine (25 μL, 0.144 mmol). The reaction mixture was stirred at 0 °C for 30 min and at room temperature overnight. After 18 h, TLC analysis indicated that the reaction was about 30% complete. The reaction mixture was cooled to 0 °C, additional 2-methoxyethoxymethyl chloride (54 μL, 0.48 mmol) and N-ethyldiisopropylamine (83 μL, 0.48 mmol) were added and the reaction mixture was stirred

overnight at room temperature. After a total of 42 h, TLC analysis indicated that the reaction was complete. The reaction mixture was diluted with ether (25 mL) and the combined organic solvents were washed with 0.5 M hydrochloric acid (3 x 3 mL), saturated aqueous sodium bicarbonate (2 x 5 mL), brine (2 x 5 mL), dried over anhydrous magnesium sulfate, and filtered. Evaporation of the solvent yielded 2-methoxy ethoxymethyl ether (15 mg, 100%) as an amber oil which could be used in the next reaction. Purification by flash chromatography on silica gel using petroleum ether-ethyl acetate 6:1 as eluant yielded the desired C-5 MEM ether (9 mg, 61%) as a clear, colourless oil; R_f 0.22 (petroleum ether-ethyl acetate 6:1, UV and H_2SO_4); IR ($CHCl_3$): 1710, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ : 0.93 (d, J=7 Hz, 3H), 0.96 (d, J=7 Hz, 3H), 1.09 (d, J=7 Hz, 3H), 1.20 (s, 9H), 1.22-2.18 (m, 9H), 2.80-2.95 (m, 4H), 3.12 (dd, J=6, 4 Hz, 1H), 3.40 (s, 3H), 3.53-3.60 (AA' part of AA'BB' system, 2H), 3.72-3.79 (BB' part of AA'BB' system, 2H), 4.07-4.19 (m, 3H), 4.77 (s, 2H); MS **m/z**: 464(M^+, 0.6), 388(52), 307(21), 273(22), 231(20), 161(31), 159(56), 149(20), 148(22), 147(29), 146(31), 125(35), 121(21), 119(100), 89(88), 59(82), 57(39); Exact mass: calcd. for $C_{23}H_{44}O_5S_2$: 464.2630; found: 464.2634.

(2S,4R,5S,6R)-8-Hydroxy-5-[(2'-methoxyethoxy-methyl)oxy]-2,4,6-trimethyl-1,1-(propane-1',3'-dithio)octane

To a slurry of lithium aluminum hydride (8.5 mg, 0.22 mmol) in dry ether (5 mL) at 0 °C under nitrogen was added a solution of crude pivaloate ester from above (71 mg, 0.15 mmol) in ether (5 mL) and the resulting mixture was stirred at 0 °C. After 1 h, TLC indicated that the reaction was not complete so additional lithium aluminum hydride (12 mg, 0.32 mmol) was added. After a further 30 min, the reaction was complete and was quenched with 0.5 M hydrochloric acid (10 mL). The aqueous layer was extracted with ether (1 x 25 mL, 2 x 25 mL) and the combined organic extract was washed with 0.5 M hydrochloric acid (2 x 5 mL), saturated aqueous sodium bicarbonate (1 x 5 mL), brine (2 x 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to yield a colourless oil (62 mg). Purification by flash chromatography on silica gel using ether as eluant yielded an alcohol (50 mg, 86%) as a clear, colourless oil. A small amount was Kugelrohr distilled, bp 130-140 °C/0.1 Torr, to yield an analytically pure sample; R_f 0.50 (ether, UV and H_2SO_4); $[\alpha]_D$ +15 (c 0.020, $CHCl_3$); IR ($CHCl_3$): 3675, 3625-3300, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ : 0.92 (d, J=7 Hz, 3H), 0.94 (d, J=7 Hz, 3H), 1.08 (d, J=7 Hz, 3H), 1.10-2.25 (m, 10H), 2.80-3.00 (m, 4H), 3.15 (d, J=6, 4 Hz, 1H), 3.38 (s, 3H), 3.50-3.90 (m, 6H), 4.15 (d, J=3 Hz, 1H), 4.78 (s, 2H); MS **m/z**: 380(0.2), 159(33), 146(29), 125(21), 119(100), 89(51), 85(27), 59(67); Exact mass: calcd. for $C_{18}H_{36}O_4S_2$: 380.2055; found: 380.2054. Anal. calcd. for $C_{18}H_{36}O_4S_2$: C 56.80, H 9.53; found: C 57.00, H 9.60.

(2S,4R,5S,6R)-8-[(tert-Butyldimethylsilyl)oxy]-5-[(2'-methoxy-ethoxymethyl)oxy]-2,4,6-trimethyl-1,1-(propane-1',3'-dithio)octane (34b)

To a solution of the above C-8 alcohol (15 mg, 0.039 mmol) in dry dichloromethane (1 mL) at 0 °C under nitrogen was added tert-butyldimethylsilyl triflate (30 μL, 0.13 mmol) and dry 2,6-dimethylpyridine (20 μL, 0.16 mmol).[51] After stirring at 0 °C for 15 min, the reaction mixture was allowed to warm to room temperature for 15 min. The reaction mixture was diluted with ether (15 mL) and the combined organic solvents were washed with brine (3 x 3 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to yield an oil (21 mg). Purification by flash chromatography on silica gel using petroleum ether-ether 3:1 as eluant yielded silyl ether **34b** (17 mg, 87%) as a pale amber oil; R_f 0.30 (petroleum ether-ether 3:1, UV and H_2SO_4); IR ($CHCl_3$): 2945, 1095, 1040 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 0.02 (s, 6H), 0.75-0.98 (m, 6H), 0.87 (s, 9H), 0.98-1.15 (m, 3H), 1.45-2.30 (m, 9H), 2.72-3.02 (m, 4H), 3.12 (dd, J=6, 3 Hz, 1H), 3.38 (s, 3H), 3.44-3.84 (m, 6H), 4.15 (d, J=3 Hz, 1H), 4.76 (s, 2H); MS **m/z**: 494(M^+, 0.1), 437(1), 159(24), 133(59), 119(51), 89(100), 75(28), 73(26), 59(75); Exact mass: calcd. for $C_{24}H_{50}O_4S_2Si$: 494.2920; found: 494.2892.

(2S,4R)-1-[(tert-Butyldimethylsilyl)oxy]-5,6-epoxy-2,4-dimethylhexane (36)

This compound was prepared from methyl (R,S)-2,4-dimethylglutaric acid (**35**) according to the method of Shelly[52] with minor modifications to yield the epimeric epoxides **36** as a clear, colourless oil; R_f 0.43 (petroleum ether-ether 19:1, H_2SO_4); IR ($CHCl_3$): 1260, 1095, 835 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ : 0.02 (s, 6H), 0.86 (s, 9H), 0.75-1.95 (m, 10H), 2.35-2.85 (m, 3H), 3.15-3.50 (m, 2H).

(3R,4S,5R,7S,11R,13S)-1,14-Di[(tert-butyldimethylsilyl)oxy]-10-hydroxy-4-[(2'-methoxyethoxymethyl)oxy]-3,5,7,11,13-pentamethyl -8,8-(propane-1',3'-dithio)tetradecane (37)

To neat dithiane **34b** (10 mg, 0.020 mmol) at -40 °C under nitrogen was added a solution of n-butyllithium in hexanes (0.270 mL, 1.5 M, 0.40 mmol) and TMEDA (61 μL, 0.40 mmol) and the resulting amber mixture was stirred at -40 °C for 1 h. Then HMPA (70 μL, 0.40 mmol) was added and the resulting deep amber suspension was stirred at -40 °C for 15 min and then was cooled to -78 °C. To the reaction suspension was added neat epoxide **36** mixture (68 μL, 0.24 mmol), in portions, via syringe. The reaction mixture was stirred at -78 °C for 30 min, at -40 °C for 30 min and at -10 °C for 2 h and then the pale yellow solution was stored at 2 °C for 40 h.[52] The solution was quenched with water (20 drops) and the colour disappeared. The mixture was diluted with ether (5 mL) and the aqueous layer was extracted with ether (2 x 5 mL). The combined ether extract was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent yielded a pale amber oil which was purified by flash chromatography on silica gel using the sequence of solvents: petroleum ether-ether 19:1, 10:1, 6:1 and then neat ether as eluant. Evaporation of solvent from the appropriate fractions yielded two compounds.

a) Recovered epoxide **36** (43 mg, 80% recovery) was isolated as a colourless oil.

b) The desired alcohol **37** (6 mg, 40%) was isolated as a pale amber oil; R_f 0.27 (petroleum ether-ether 3:1, UV and H_2SO_4); IR ($CHCl_3$): 3675, 3600-3350, 2945, 1095, 1040, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 0.05 (s, 12H), 0.80-1.10

(m, 12H), 0.89 (s, 9H), 0.90 (s, 9H), 1.16 (d, J=7 Hz, 3H), 1.20-2.25 (m, 15H), 2.75-2.92 (m, 4H), 3.18-3.22 (m, 1H), 3.31-3.42 (m, 1H), 3.38 (s, 3H), 3.45-3.82 (m, 8H), 4.05 (b d, J=8 Hz, 1H), 4.75-4.83 (m, 2H); MS m/z: 752(M^+, 1), 734(1), 695(1), 377(24), 246(20), 245(100), 187(30), 133(35), 113(63), 95(26), 89(67), 75(50), 73(42), 59(51); Exact mass: calcd. for $C_{38}H_{80}O_6S_2Si_2$: 752.4935; found: 752.4946.

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