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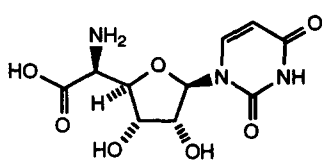
Chemoselectivity in the Manipulation of Polyhydroxylated Compounds Derived from the Diastereoselective Dihydroxylation of Optically Active Allylic Enoate Alcohols.

M. Teresa Barros[a,c], M. Odile Januario-Charmier[a] Christopher D. Maycock[a,b] and Mariana Pires[a]

[a]Instituto de Tecnologia Quimica e Biologica, Universidade Nova de Lisboa, Rua da Quinta Grande 6, 2780 Oeiras [b]Departamento de Química, Universidade de Lisboa, Rua Ernesto de Vasconcelos, 1700 Lisboa, [c]Departamento de Química, FCT, Universidade Nova de Lisboa, Monte de Caparica, Portugal.

Abstract An efficient, practical and stereoselective route for the preparation of several polyols and their corresponding lactols and lactones is described. They are promising precursors for the synthesis of several structurally interesting compounds. Copyright © 1996 Elsevier Science Ltd

The development of strategies for the use of common precursors in the enantioselective synthesis of natural and unnatural compounds of biological interest contributes to a greater efficiency, necessary for economies in the preparation of starting materials. Our interest lies in the synthesis of C_6, C_7 and C_8 polyhydroxylated compounds having an ester group or equivalent in compounds such as sugars and γ- and δ-lactones including those containing amino groups. Such units are present in natural compounds such as Uracil Polyoxin C **1**[1], Goniofurfurone **2**[2] and related compounds, the polyhydroxylated nucleus of the squalene synthase inhibitor Zaragozic acid A **3**[3] and Swainsonine **4**[4]. The chemical manipulation of polyhydroxylated compounds is also of current interest for the synthesis of a wide range of other natural and unnatural products including sugar analogues[5] and mimics[6]. Most of the published syntheses of compounds **1** and **2** start from ribose derivatives and other sugars many of which are not at all readily available cheaply.



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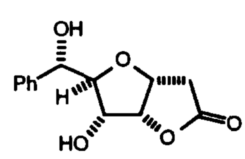

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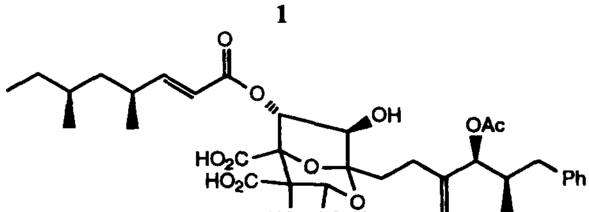

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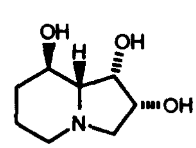

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Our approach to these compounds was envisaged to involve monodihydroxylation (desymmetrisation) of a C_2-symmetrical diendioate system having 8 carbon atoms. Such a system was chosen since the remaining double bond could constitute a protected aldehyde function as in for example Polyoxin C (recovered later by, for example, ozonolysis), or alternatively it could serve as an electrophilic site for the formation of a tetrahydrofuran ring as in goniofurfurone[7]. Selective reactions at the various hydroxyl groups would then permit manipulation of the molecule in such a way that a wide range of configurationally different polyhydroxylated compounds could be obtained. Also, we wished to demonstrate that nitrogen functionality could be selectively introduced into these dihydroxylated products.

The dihydroxylation of allylic alcohols and ethers, using catalytic quantities of osmium tetroxide in the presence of co-oxidants has been studied by several groups[8] either as a means of determining the diastereoselectivity of such reactions or for the purposes of synthesis. Osmium-catalysed dihydroxylation of dienedioate **5** has also been studied[9] and shown to offer high stereoselectivities. Both enantiomers of the diendioate **5** are available[10] from tartaric acid or from mannitol and have been used for the synthesis of a variety of complex molecules[11]. These syntheses usually employed the products of diastereoselective *bis*-dihydroxylation.

Mono- or *bis*-dihydroxylation of the diendioate **5** having the isopropylidene protecting group, using OsO_4/NMO, gave surprisingly low diastereoselectivities[12] (80-90%). The conformation of the molecule having the isopropylidene system must be constrained by the five membered ring in such a manner that both faces of the π-system are sufficiently exposed and hence the undesired diastereomer is also formed. This result was unexpected since it has been possible to carry out *bis* dihydroxylations and to obtain almost exclusively one isomer using unconstrained (non cyclic) diTBS and dibenzyl ethers. The diastereoselectivity of the dihydroxylation was attributed to the conformation of the molecule which involves mutual protection of both carbon-carbon double bonds (figure 1). This conformation is rationalised in terms of the steric interactions between the ether groups causing them to attain a conformation in which these bulky groups are as far apart as possible. We were interested in testing this model using the monoprotected diol **7** where a rigid conformation (such as that in figure 1) and necessary for the diastereoselectivity, was less likely. The monoprotected compound **7** also represents a desymmetrisation of the system at an early stage.

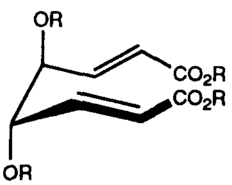
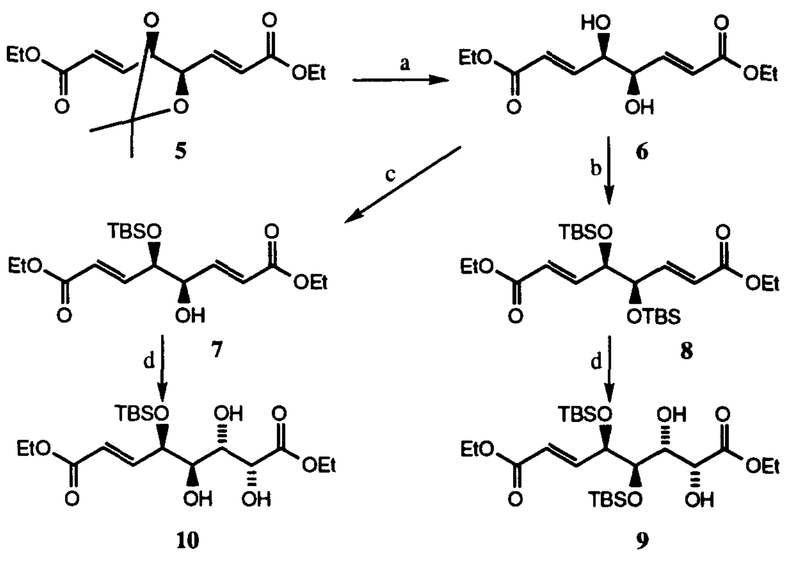


Figure 1 *Postulated preferred conformation for the disilyl ether **8** to explain the high diastereo selectivity of additions to the C-C double bonds.*

The mono and disilyl ethers **7** and **8** respectively are available from the diol **6** by treatment with 1.2 equivalents or 2.4 equivalents of *tert*-butyldimethylsilyl chloride using an excess of imidazole as base and activator (scheme 1). The protection of the second hydroxyl group is much more difficult and good yields (90%) of the monoprotected compound (**7**) are obtained. Catalytic dihydroxylation of the disilyl ether **8** (1 equiv. of NMO) afforded high yields (83%) of the dihydroxylated compound **9** with a little *bis*-dihydroxylated compound (~5%). It was of interest to see if the dihydroxylation reaction on the monoprotected silyl ether **7** was as diastereoselective as for the diprotected compound and also to see if the reaction was regioselective. To be useful, the product, a triol, would need to show a high degree of stability and chemoselectivity in subsequent reactions at the hydroxyl groups. The triol **10** was formed regioselectively and diastereoselectively (>90%) when the monoether **7** was treated with OsO_4 under the same catalytic conditions as **8**. This is in accord with the work of Sharpless[13] who has shown that hydroxyl groups in an allylic position accelerate the dihydroxylation process at the adjacent double bond. The *bis*-dihydroxylation of conjugated dienes is also diastereoselective[14], that is, the second dihydroxylation affords the same diastereoselectivity as observed in the molecules studied. For high diastereoselectivities it is not necessary to have bulky ether groups on both of the hydroxyls of the starting material and the optimum conformation of these compounds is readily achieved. This result, in principle, increased the flexibility of our approach since it was later found that selective monodesilylation of the disilylated compound **11** produced the allylic alcohol **12** (scheme 2).

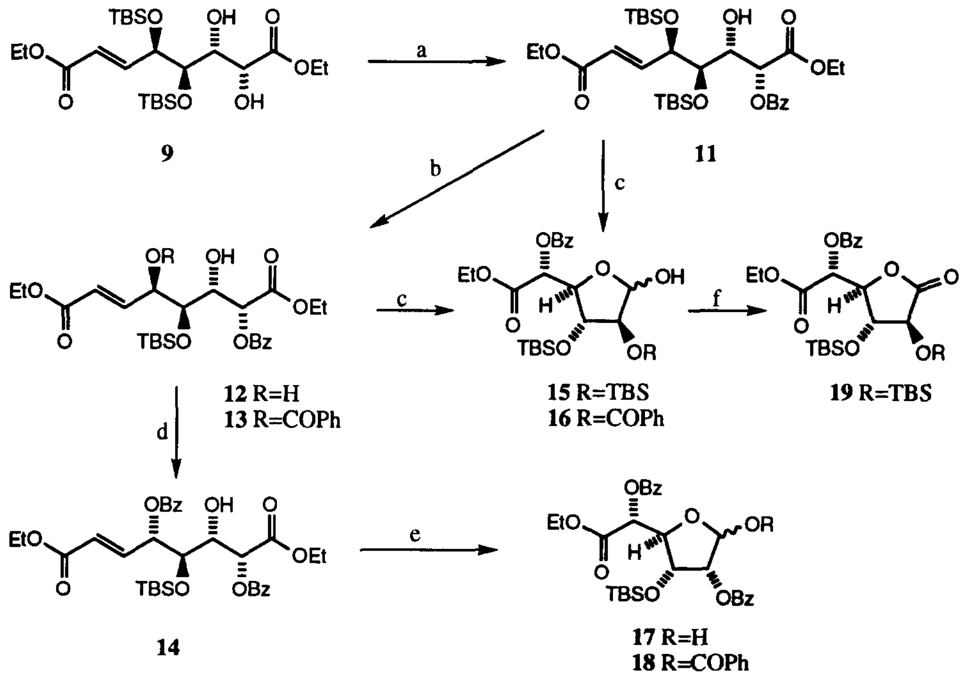
Compound **10** was difficult to isolate because of its polarity and also, because of free rotation about the glycol C-C bond, it lactonised readily. The double silyl protecting groups on compound **8** had the effect of blocking lactonisation after dihydroxylation. Although we have been able to carry out selective chemistry[15] on compound **10** we considered the diol **9** to be of greater utility for our purposes. The rest of this report therefore deals with the chemistry of the diol **9**.



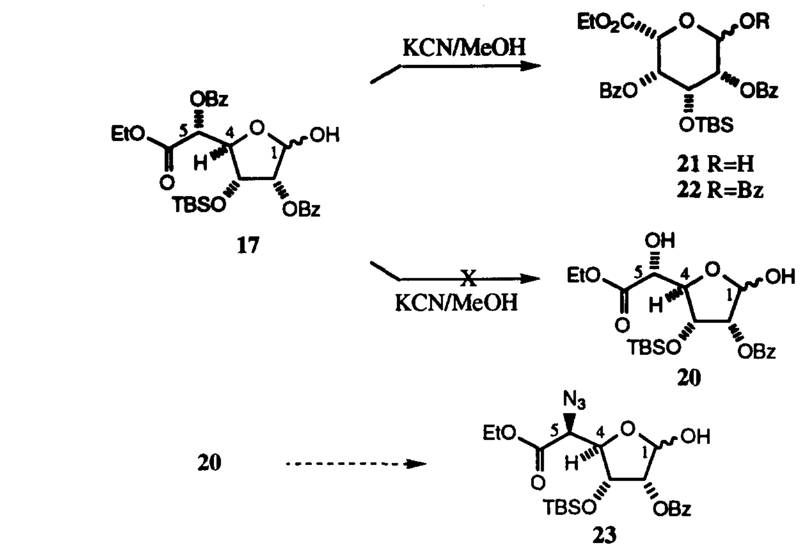
Scheme 1 a) $(CH_2SH)_2$,$BF_3.OEt_2$. b) 2.4 equiv. TBSCl, imidazole. c) 1.2 equiv. TBSCl, imidazole. d)Cat. OsO_4, NMO

Chemoselective protection of the α-hydroxyl group of **9** was possible, by benzoylation, to give **11** in high yield (scheme 2). This α-hydroxyl selectivity has been observed by others[16] and is very useful in polyhydroxylated systems of this type. The β-hydroxyl group is much less reactive particularly when a bulky substituent exists at the γ-position, as is the case here. As mentioned earlier selective monodesilylation was possible using HF under controlled conditions. This afforded the allylic alcohol **12** which proved to be a key and versatile intermediate for the synthesis of polyhydroxylated compounds. Compound **12** could also be selectively benzoylated at the allylic hydroxyl to give **13**. Selective Mitsunobu inversion at the same position using benzoic acid as nucleophile afforded the epimeric dibenzoate **14**.

Ozonolysis of the enoate function of **11** cleanly afforded a lactol **15** which was oxidised with PCC to form the corresponding lactone **19** (scheme 2). Similarly ozonolysis of compound **13** gave a lactol **16** and compound **14** afforded the lactol **17**, characterised as its benzoate **18**. In an attempt to selectively hydrolyse one of the benzoate esters of **17**, preferably to form compound **20**, which we hoped to convert to the azide **23**, a precursor for Polyoxin C, the lactol **17** was heated with a methanolic solution of potassium cyanide (scheme 3). The starting material was consumed but the product was not a monobenzoate. Analysis of the ^{13}C and ^{1}H NMR indicated a 6C dibenzoate **21** which has a pyranose ring structure (characterisation was performed on compound **22** as a mixture of anomers). Kiliani homologation had thus not occurred as had been suspected at first. It seems likely that under the mildly basic conditions the lactol ring-opened form of **17** underwent a benzoate migration from the 5-OH to the 4-OH. The ring then reclosed to form the pyranose structure at the then unprotected 5-OH. Since this must be an equilibrating system the pyranose appears to be the most stable form of these two isomers.

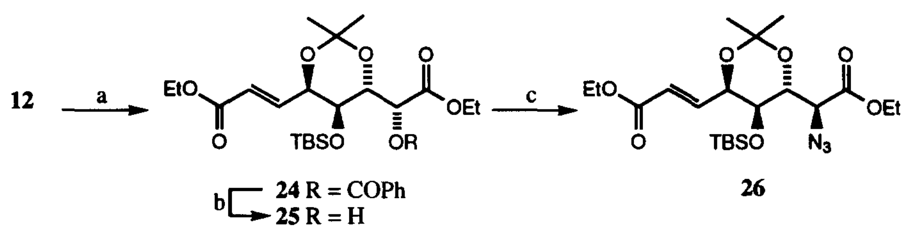


Scheme 2 a) PhCOCl/Pyr, b) HF, c) O_3/DMS, d) PhCOCl/Pyr, e) O_3/DMS, f) PCC



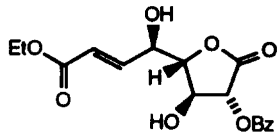
Scheme 3

In order to manipulate the benzoate group α- to the ester function of compound **12** it was necessary to protect the two free hydroxyl groups. This was acheived in good yield by the use of 2,2-dimethoxypropane and acid in DMF. Base (ethoxide) alcoholysis of the resulting benzoate ester **24** afforded the corresponding alcohol **25** which was converted to the azide **26**, with inversion of configuration, using Mitsunobu technology (scheme 4). By this route we were able to introduce the nitrogen function into the system. The conversion of this molecule and analogues into biologically interesting molecules will be reported elsewhere.



Scheme 4 a) $Me_2C(OMe)_2$, pTSA. b) EtO^-. c) DEAD, TPP, HN_3.

Removal of both silyl groups from the benzoate **11** with HF resulted in spontaneous lactonisation to form exclusively the γ-lactone **27**. This compound has a double bond which, in principle, allows elaboration to a wide range of compound types *via* addition reactions and oxidative cleavage.



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We have demonstrated the wide ranging utility of the tetrahydroxy compound **9** as a precursor for the selective synthesis of polyhydroxylated compounds using stereo- and chemoselective reactions. High chemoselectivities are possible in linear polyhydroxylated compounds and a wide range of configurational variations can be achieved. Also we have shown that it is not necessary to have both allylic hydroxyls of the dioldienedioate **6**[17] protected for high diastereoselectivity in the dihydroxylation reaction and this implies that the monoprotected diol **7** is able to attain a conformation where the carbon-carbon double bonds are protected at one of their faces. Having at hand the diol **6** the synthesis of furanose structures with a variety of configurations is possible.

EXPERIMENTAL SECTION

General procedures. Melting points were determined on a Büchi 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 7000 FTIR spectrometer. Optical rotations were recorded on a Perkin Elmer 241 polarimeter using a 0.1 dm cell. Concentrations are given in g/100 ml. NMR spectra were recorded either on a Brüker CXP 300 (300MHz, ^1H, or 75.5MHz, ^{13}C spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ using Me_4Si as an internal reference ; ^{13}C NMR spectra were recorded in the same solvent using the solvent peak at δ 77.0 as an internal reference. Chemical shifts are expressed in parts per million downfield. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Analysis at Vernaison (France).
Column chromatography was performed on silica gel 60H under medium pressure. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F_{254} silica gel plates.

Diethyl 4,5-dihydroxy-2,6-octadienedioate 6.

To a stirred solution of (4R, 5R)-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate **5** (0.2g, 0.67 mmol) in anhydrous CH_2Cl_2 (3 ml), was added $Et_2O.BF_3$ (0.09 ml, 1eq) under argon. To the resultant solution was added dropwise 1,2-ethane dithiol (0.07 ml, 1.2 eq). After 10 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (4 ml) and was allowed to stir for 20 min. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (0.75/0.25 hexane/ethyl acetate) to give the diol **6** (0.2g, 91%) as a white solid: mp 47-48°C; $[\alpha]_D^{20}$+54,7 (c.0.7 in $CHCl_3$); IR (υ, cm^{-1}, KBr) 3441, (OH), 1712 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 6.96-6.90 (dd, 2H, H-3, H-6, J_2=3.8Hz, J_2=15.8Hz), 6.17 (d, 2H, H-2, H-7, J=15.8Hz), 4.28 (sl, 1H, OH), 4.24-4.17 (q, 2H, OCH_2), 3.20 (sl, 1H, OH), 1.32-1.27 (t, 6H, $OCH_2\underline{CH_3}$); ^{13}C NMR δ 0.07, 14.3 (TBSO), 60.7 (OCH_2), 73.4 (CHO), 123.3 (CH=), 145.1 (CH=), 166.1 (CO_2);

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81 ; H, 7.02 Found: C, 55.78, H, 7.00.

Diethyl (4R,5R)-4-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,6-octadienedioate 7.

To a stirred solution of diol **6** (0.52g, 2.00 mmol) in anhydrous DMF, under Argon was added imidazole (0.34g, 5 mmol, 2.5 eq) followed by *tert*-butyldimethylsilylchloride (0.36g, 2.4 mmol, 1.2eq). The reaction mixture was allowed to stir for a further 5h, was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (75/25 hexane/ethylacetate) to afford the compound **7** (0.68g, 90%) as an oil; IR (υ, cm^{-1}) 3468 (OH), 1720 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 6.95–6.85 (m, 2H, H-3, H-6, J_1=4.4Hz, J_2=14.6Hz, J_3=16.0Hz, J_4=5.8Hz), 6.13 (d, 1H, H-2, J=14.6Hz), 6.04 (d, 1H, H-7, J=16.0Hz), 4.27-4.17 (m, 6H, OCH_2, H-4, H-5), 2.57 (sl, 1H, OH), 1.32-1.26 (td, 6H, $OCH_2\underline{CH_3}$), 0.91 (s, 9H, OTBS), 0.06 (d, 6H, OTBS); ^{13}C NMR δ –4.1, 13.8, 14.2, 25.7 (TBSO), 60.6, 62.0 (OCH_2), 70.2, 73.5 ($\underline{C}$HO), 123.6, 128.3, 133.5, 140.9 (H$\underline{C}$=), 164.6, 167.4 (CO_2).

Anal. Calcd. for $C_{18}H_{32}O_6Si_2$: C, 58.03 ; H, 8.66 Found: C, 57.85, H, 8.79.

Diethyl (4R,5R)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-2,6-octadienedioate 8.

To a stirred solution of diol **6** (0.520g, 2.00 mmol) in anhydrous DMF, under an argon atmosphere, was added imidazole (0.68g, 10 mmol, 5eq) followed by *tert*-butyldimethylsilylchloride (0.72g, 4.8 mmol, 2.4eq). After 24 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (85/15 hexane/ethylacetate) to afford the compound **8** (0.88g, 90%) as an oil: $[\alpha]_D^{20}$+67 (c. 0.5 in $CHCl_3$); IR (υ, cm^{-1}) 1724 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 6.94 (dd, 2H, H–3, J_1=2.9Hz, J_2=14.1Hz), 5.95 (d, 2H, H-2, J=14.1Hz), 4.36 (s, 2H, H-4, H-5), 4.27-4.17 (m, 4H, OCH_2), 1.30 (t, 6H, $OCH_2\underline{CH_3}$), 0.91 (s, 18H, OTBS), 0.07 (d, 6H, OTBS); ^{13}C NMR δ -4.9,-4.7, 14.2, 16.1, 25.7 (OTBS), 60.3 (OCH_2), 74.3 (CHO), 121.9 (CH=), 146.1 (CH=), 166.2 (CO_2).

Anal. Calcd. for $C_{24}H_{46}O_6Si$: C, 59.22 ; H, 9.52 Found: C, 59.02, H, 9.52.

Diethyl (2R,3S,4R,5R)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxy-6-octenedioate 9.

To the disilyl ether **8** (1.28g, 2.60 mmol) in acetone (5.2 ml) was added a catalytic amount of OsO_4 in MeCN (1 drop of a 0.39M solution), followed by an aqueous solution of *N*-methylmorpholine *N*-oxide (NMO 60%, 1.17 ml, 2eq.). The reaction mixture was allowed to stir for 4h, then quenched with potassium metabisulfite and allowed to stir for 20 min.The residue was dissolved in ethyl acetate, filtered andthe organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (80/20 hexane/ethylacetate) to give the diol **9** as an oil (1.13g, 83%); $[\alpha]_D^{20}$+39 (c. 1.5 in $CHCl_3$); IR (υ, cm^{-1}) 3493 (OH), 1726 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 7.05–7.04 (dd, 1H, H–3, J_1=2.9Hz, J_2=16.1Hz), 6.00 (d, 1H, H-2, J=16.0Hz), 4.45 (m, 1H, H-4), 4.14-4.06 (m, 5H, OCH_2, H-5), 3.61 (s, 1H, H-7), 2.85 (d, 1H, H-6), 1.22-1.15 (m, 6H, $OCH_2\underline{CH_3}$), 0.81 (d, 18H, OTBS), 0.04 (d, 12H, OTBS); ^{13}C NMR δ –5.0, –4.4, 14.2, 18.1, 25.7 (OTBS), 60.5, 61,6 (OCH_2), 70.2, 70.9, 74.4, 75.4 (CHO), 122.5 (CH=), 145.1 (CH=), 165.9, 173.4 (CO_2).

Anal. Calcd. for $C_{24}H_{48}O_8Si_2$: C, 55.35 ; H, 9.29 Found: C, 55.40, H, 8.93.

Diethyl (2R,3S,4R,5R)-4-((*tert*-butyldimethylsilyl)oxy)-2,3,4-trihydroxy-6-octenedioate 10.

Compound **10** was synthesised from **7** (1.1g, 2.95 mmol) using the same procedure as that outlined above to afford a triol (0.95g, 90%) as a white solid, m.p.40-41°C; $[\alpha]_D^{20}$ -21.7 (c. 1.24 in $CHCl_3$); IR (υ, cm^{-1}, KBr) 3520 (OH), 1716 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 7.01–6.94 (dd, 1H, H-3, J_1=4.4Hz, J_2=14.9Hz), 5.95 (d, 1H, H-2, J=14.8Hz), 4.65 (d, 1H, H-4, *J*=4.3Hz), 4.50 (d, 1H, H-7, *J*=4.4Hz), 4.25-4.10 (m, 4H, OCH_2), 3.82-3.76 (t, 1H, H-5, *J*=9.6Hz, *J*=9.1Hz), 3.62-3.51 (m, 1H, H-6, *J*=9.9Hz, *J*=8.9Hz, *J*=4.5Hz), 2.95 (d, 1H, OH, *J*=9.0Hz), 2.80 (d, 1H, OH, *J*=8.9Hz), 1.25-1.21 (t, 6H, $OCH_2\underline{CH_3}$), 0.88 (s, 9H, OTBS), 0.05 (d, 6H, OTBS); ^1H NMR ($CDCl_3$, D_2O) δ 6.97–6.91 (dd, 1H, HC=, J_1=4.4Hz, J_2=15.9Hz), 5.95 (d, 1H, HC=, *J*=14.6Hz), 4.64 (d, 1H, C$\underline{H}$OTBS, *J*=4.3Hz), 4.46 (s, 1H, CHOH), 4.23-4.06 (m, 4H, OCH_2), 3.75 (d,1H), 3.51 (d, 1H), 1.22-1.17 (t, 6H, $OCH_2\underline{CH_3}$), 0.85 (s, 9H, OTBS), 0.03 (d, 6H, OTBS); ^{13}C NMR δ –4.2, –3.3, 14.1, 14.2, 18.2, 25.8 (OTBS), 60.5, 61.9 (OCH_2), 70.1, 71.0, 72.3, 72.5 (CHO), 121.9, 147.8 (CH=), 166.3, 173.8 (CO_2).

Anal. Calcd. for $C_{18}H_{34}O_8Si$: C, 53.18 ; H, 8.43 Found: C, 53.21, H, 8.72.

Diethyl (2R,3S,4R,5R)-2-benzoyloxy-4,5-bis(*tert*-butyldimethylsilyloxy)-3-hydroxy-6-octenedioate 11.

To a stirred solution of diol **9** (2.28g, 4.38 mmol) in pyridine (10 ml) was added BzCl (0.51 ml, 1eq.) under argon atmosphere at 0°C and a catalytic amount of DMAP. After 2h at room temperature the reaction was quenched with $NaHCO_3$ and allowed to stir for 15 mn. The mixture was extracted with CH_2Cl_2, the organic phase dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica (85/15 hexane/ethyl acetate) to yield compound **11** as an oil (2.7g, 99%); $[\alpha]_D^{20}$+23°(c. 2.25 in $CHCl_3$); IR (υ, cm^{-1}) 3489 (OH), 1764 (ester), 1660 (C=C); ^1H NMR ($CDCl_3$) δ 8.07 (d, 2H, ortho-C$\underline{H}$, Ph), 7.55-7.39 (m, 3H, meta,para-C$\underline{H}$, Ph), 7.21-7.15 (dd, 1H, H-3, J_1=2.8Hz, J_2=16.2Hz), 6.12 (d, 1H, H-2, *J*=16.2Hz), 5.23 (s, 1H, H-7), 4.59 (m, 1H, H-4), 4.26-4.16 (m, 4H, OCH_2), 4.00-3.97 (m, 1H, H-5), 3.84 (s, 1H, OH), 1.31-1.21 (m, 6H, $OCH_2\underline{CH_3}$), 0.96 (s, 9H, TBSO), 0.64 (s, 9H, TBSO), 0.00-0.15 (m, 12H, TBSO); ^{13}C NMR δ –5.37, –4.07, 14.1, 19.1, 25.7 (OTBS), 60.5, 61.6 (OCH_2), 70.6, 72.7, 73.5, 75.2 (CHO), 122.8 (HC=), 129.3, 129.7, 133.2, 144.3 (Ph), 145.6 (HC=), 165.7, 169.2 (CO_2).

Anal. Calcd. for $C_{31}H_{52}O_9Si_2$: C, 59.58 ; H, 8.39 Found: C, 59.80, H, 8.41.

Diethyl (2R,3S,4R,5R)-2-benzoyloxy-4-(*tert*-butyldimethylsilyloxy)-3,5-dihydroxy-6-octenedioate 12

To a stirred solution of **11** (0.5 g, 0.8 mmol) in CH_3CN (18 ml) was added aqeous HF (0.60 ml, 13.78 mmol, 16 eq.), and the mixture was allowed to stand 3h at room temperature. After this time the reaction was judged complete by TLC and the solution was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude residue was separated by column chromatography (70/30 hexane/ethyl acetate) to afford **8** (0.28g, 68%) as an oil; $[\alpha]_D^{20}$+24,7°(c. 0.3 in $CHCl_3$); IR (υ, cm^{-1}) 3454 (OH), 1759, 1726 (esters), 1658 (C=C); ^1H NMR ($CDCl_3$) δ 8.24 (d, 2H, ortho-Ph), 7.72-7.56 (m, 3H, meta, para-Ph), 7.32-7.26 (dd, 1H, H-3, J_1=16.1Hz, J_2=2.9Hz), 6.35 (d, 1H, H-2, *J*=16.1Hz), 5.42 (d, 1H, H-7, *J*=6.6Hz), 4.71 (s, 1H, OH), 4.37-4.30 (m, 4H, OCH_2), 4.22-4.18 (dd, 1H, H-4, J=2.9Hz, J=8.7Hz), 3.98 (d, 1H, H-6, J=6.6Hz), 3.86 (d, 1H, H-5, J=8.7Hz), 1.44-1.35 (td, 6H, $OCH_2\underline{CH_3}$), 0.99 (s, 9H, OTBS), 0.07 (d, 6H, OTBS); ^{13}C NMR ($CDCl_3$) δ −3.9, 14.3, 25.8, 60.5, 62.1 (OCH_2), 72.1, 72.7, 72.9, 73.3 (CHO), 122.5 (HC=), 128.6, 129.8, 133.6 (Ph), 146.8 (HC=), 165.6, 166.1, 168.4 (CO_2).

Anal. Calcd. for $C_{25}H_{38}O_9Si$: C, 58.80 ; H, 7.50 Found: C, 58.97, H, 7.43.

Diethyl (2R,3S,4R,5R)-2,5-dibenzoyloxy-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-6-octenedioate 13

Diol **12** (0.5g, 0.97 mmol) was converted almost quantitative yield into the corresponding dibenzoate **13** with benzoyl chloride in pyridine as previously described for **9**. The oily residue was chromatographed on silica (70/30 hexane/ethylacetate) to yield compound **13** (0.54g, 90%); $[\alpha]_D^{20}$-6 (c. 0.3 in $CHCl_3$); IR (υ, cm^{-1}) 3474 (OH), 1761, 1726 (esters), 1662 (C=C); ^1H NMR ($CDCl_3$) δ 8.13 (d, 2H, Ph), 8.08 (d, 2H, Ph), 7.63-7.41 (m, 6H, Ph), 7.17-7.10 (dd, 1H, H-3, J_1=16.1Hz, J_2=4.3.Hz), 6.18 (d, 1H, H-2, J=16.1Hz), 6.07 (d, 1H, H-4, J=4.3Hz), 5.38 (s, 1H, H-7), 4.28-4.17 (m, 6H, OCH_2, H-5, H-6), 3.05 (d, 1H, OH), 1.30-1.21 (t, 6H, $OCH_2\underline{CH_3}$), 0.91 (s, 9H, OTBS), 0.09 (s, 3H, OTBS), -0.08 (s, 3H, OTBS); ^{13}C NMR ($CDCl_3$) δ −5.0,−4.05, 13.8, 14.1, 18.1, 25.8 (CH_3), 60.6, 61.9 (OCH_2), 70.4, 71.5, 71.7, 73.6 (CHO), 123.7 (HC=), 128.2, 128.5, 129.8, 133.0, 133.4 (Ph), 140.9 (HC=), 164.6, 165.3, 165.5, 167.3 (CO_2).

Diethyl (2R,3S,4R,5S)-2,5-dibenzoyloxy-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-6-octenedioate 14

To the diol **12** (0.392g, 0.78 mmol) in anhydrous THF (15.6 ml) was added succesively PPh_3 (0.409g, 1.56 mmol, 2 eq.), followed by benzoic acid (0.19g, 1.56 mmol, 2 eq.) and by the dropwise addition of DEAD (0.271g, 1.56 mmol, 2 eq.) in THF (0.8 ml) over about 2 min. The reaction mixture was left to stir at room temperature. After 4h the residue was washed with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (50/50 hexane/ethyl acetate) to yield the compound **14** (0.43g, 90%) as an oil; $[\alpha]_D^{20}$ -14.7 (c 0.15 in $CHCl_3$); IR (υ, cm^{-1}) 3475 (OH), 1759, 1726 (CO_2Et), 1662 (C=C); ^1H NMR ($CDCl_3$) δ 8.18 (d, 4H, Ph), 7.69-7.53 (m, 6H, Ph), 7.30-7.23 (dd, 1H, H-3, J_1=16.1Hz, J_2=6.0Hz), 6.30-6.22 (m, 2H, H-2, H-4, J_1=6.0Hz, J=16.1Hz), 5.53 (s, 1H, H-7), 4.42-4.29 (m, 6H, OCH_2, H-5, H-6), 1.41-1.35 (t, 6H, $OCH_2\underline{CH_3}$), 0.95 (s, 9H, OTBS), 0.17 (s, 3H, OTBS), -0.39 (s, 3H, OTBS); ^{13}C NMR ($CDCl_3$) δ −5.2,−3.9, 14.1, 18.1, 22.0, 25.8 (CH_3), 60.6, 62.1 (OCH_2), 72.4, 72.5, 74.0, 75.1 (CHO), 123.8 (HC=), 128.5, 129.8, 133.4 (Ph), 141.0 (HC=), 165.5, 165.6, 168.3 (CO_2).

Ethyl 5-O-benzoyl-2,3-di-O-(*tert*-butyldimethylsilyl)-L-galactarate-1,4-lactone 19

Ozone was bubbled into a stirred solution of compound **11** (0.119g, 0.19 mmol) in anhydrous CH_2Cl_2 (50 ml) at -78°C until a blue endpoint was reached. The reaction mixture was allowed to stir a further 10 min. then excess DMS (2 ml) was added and the solution was allowed to warm up to room temperature. The solvent was removed to give 0.093g (91%) of the corresponding lactol **15** as an oil which was dissolved in anhydrous pyridine (3 ml) under argon atmosphere at room temperature. To this solution was added PCC (0.11g, 0.51mmol, 3eq.) and was allowed to stir 20h. The mixture was washed with ether, filtered through Celite and evaporated. Purification of the resulting oil by column chromatography (hexane/ethyl acetate 70/30) yielded lactone **19** (0.047g, 50%); $[\alpha]_D^{20}$+24 (c. 1.5 in $CHCl_3$); IR (υ, cm^{-1}) 1768, 1736 (ester, C=O); ^1H

NMR ($CDCl_3$) δ 8.08 (d, 2H, ortho-Ph), 7.62-7.45 (m, 3H, meta, para-Ph), 5.50 (d, 1H, H-5, J=2.6Hz), 4.74.-4.71 (dd, 1H, H-4, J=2.6Hz, J=7.3Hz), 4.44 (d, 1H, H-2, J=7.2Hz), 4.36-4.31 (m, 1H, H-3, J=7.2Hz), 4.28-4.25 (m, 4H, OCH_2), 1.29-1.25 (t, 3H, $OCH_2\underline{CH_3}$), 0.90 (d, 18H, TBSO), 0.19 (d, 6H, TBSO), 0.04 (d, 6H, TBSO); ^{13}C NMR ($CDCl_3$) δ -5.1, -4.9, 14.1 (Me), 25.6, 25.7 (TBSO), 62.4 (OCH_2), 69.6, 75.1, 76.1, 80.1 (CHO), 128.6, 130.1, 133.8 (Ph), 164.5 (CO_2).

Anal. Calcd. for $C_{27}H_{44}O_8Si_2$: C, 58.66 ; H, 8.02 Found: C, 58.46, H, 8.03.

Ethyl 2,5-di-O-benzoyl-3-O-(*tert*-butyldimethylsilyl)-L-galactofuranuronate 16

Lactol **16** was synthesised from **13** (0.115g, 0.187 mmol) using the same procedure as that outlined for compound **12.** The lactol was not converted into the corresponding lactone with PCC. The crude residue was separated by column chromatography (70/30 hexane/ethyl acetate) to afford **16** (0.09g, 88%) as an oil and a mixture of α,β-anomers; IR (υ, cm^{-1}) 3479 (OH), 1728 (ester); ^1H NMR ($CDCl_3$) anomer 1: δ 8.19–7.33 (m, 10H, Ph), 5.70 (sl, 1H, OH), 5.53 (d, 1H, H-1, J=7.0Hz), 5.10 (d, 1H, H-5, J=4.5Hz), 4.84 (d, 1H, H-2, J=7.0Hz), 4.56 (d, 1H, H-4, J=4.5Hz), 4.27-4.17 (m, 2H, OCH_2), 3.90 (d, 1H, H-3, J=4.5Hz), 1.26-1.16 (td, 3H, $OCH_2\underline{CH_3}$), 0.89 (s, 9H, OTBS), 0.10 (d, 3H, OTBS), -0.03 (d, 3H, OTBS); anomer 2: δ 5.45 (d, 1H, H-1, J=3.9Hz), 5.19 (s, 1H, H-5), 4.77 (dd, 1H, H-2, J=7.2Hz, J=3.9Hz), 4.46 (dd, 1H, H-4, J=4.5Hz, J=7.2Hz), 4.27-4.17 (m, 2H, OCH_2), 3.80 (d, 1H, H-3, J=7.2Hz), 1.26-1.16 (td, 3H, $OCH_2\underline{CH_3}$), 0.89 (s, 9H, OTBS), 0.10 (d, 3H, OTBS), -0.03 (d, 3H, OTBS); ^{13}C NMR ($CDCl_3$) of mixture δ –4.7, –4.8, 13.9, 17.8, 25.6 (OTBS), 61.9 (OCH_2), 71.0, 71.9, 72.9, 75.8, 79.4, 80.8, 83.6, 84.1, 94.7, 101.4 (CHO), 129.1, 128.4, 129.9, 133.43 (Ph), 165.8, 167.5 (CO_2);

Ethyl 2,5-di-O-benzoyl-3-O-(*tert*-butyldimethylsilyl)-L-talofuranuronate 17

Compound **17** was synthetised from **14** (0.3g, 0.48 mmol) using ozone as outlined above. The crude residue was separated by column chromatography (70/30 hexane/ethyl acetate) to afford lactol **17** (0.21g, 80%) as an oil and a mixture of anomers; IR (υ, cm^{-1}) 3462 (OH), 1737 (ester); ^1H NMR ($CDCl_3$) β-anomer δ 8.17–7.39 (m, 10H, Ph), 5.49 (s, 1H, H-1), 5.39 (d, 2H, H-2, H-5), 4.82-4.80 (dd, 1H, H-4, J=2.7Hz, J=7.9Hz,), 4.66-4.64 (dd, 1H, H-3, J=1.7Hz, J=7.9Hz), 4.37-4.26 (m, 2H, OCH_2), 3.70 (sl, 1H, OH), 1.34-1.30 (td, 3H, $OCH_2\underline{CH_3}$), 0.75 (s, 9H, OTBS), -0.02 (d, 3H, OTBS); α-anomer δ 5.64 (d, 1H, H-1, J=4.3Hz), 5.42 (d, 1H, H-5, J=2.9Hz), 5.32 (t, 1H, H-2, J=4.5Hz, J=4.6Hz), 4.86-4.85 (dd, 1H, H-4, J=1.7Hz, J=2.9Hz,), 4.63-4.60 (dd, 1H, H-3, J=1.7Hz, J=4.6Hz), 0.84 (s, 9H, OTBS); ^{13}C NMR ($CDCl_3$) δ –3.3, 14.1, 17.6, 25.5 (OTBS), 62.1 (OCH_2), 64.6, 69.2, 69.3, 70.2, 93.6 (CHO), 128.1, 128.4, 130.0, 132.89 (Ph), 165.7, 166,7, 168.6 (CO_2).

Ethyl 1,2,5-tri-O-benzoyl-3-O-(*tert*-butyldimethylsilyloxy)-L-talofuranuronate 18

Lactol **17** (0.08g, 0.15 mmol), pyridine (1 ml), BzCl (0.043 ml, 0.38 mmol, 2.5 eq.) and cat.DMAP were stirred for 1h. The crude residue was separated by column chromatography (75/25 hexane/ethyl acetate) to give the tribenzoate compound **18** (0.06g, 62%) as a white solid; m.p 34-35°C; $[\alpha]_D^{20}$ +18 (c. 0.25 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.19–7.14 (m, 15H, Ph), 6.59 (s, 1H, H-1), 5.68 (d, 1H, H-2, J=4.3Hz), 5.56 (s, 1H, H-5), 4.90 (d, 1H, H-4, J=4.6Hz), 4.85-4.81 (dd, 1H, H-3, J=4.3Hz, J=4.6Hz), 4.36-4.32 (m, 2H, OCH_2), 1.37-1.32 (t, 3H, $OCH_2\underline{CH_3}$), 0.85 (s, 9H, OTBS), 0.11 (d, 6H, OTBS); ^{13}C NMR ($CDCl_3$) δ –5.1, –4.9, 14.1, 17.9, 25.5 (CH_3), 62.1 (OCH_2), 70.1, 70.2, 76.2, 82.9, 98.8 (CHO), 128.3, 128.5, 129.9, 133.4 (Ph), 164.5, 165.3, 165.7, 167.2 (CO_2).

Anal. Calcd. for $C_{35}H_{40}O_{10}$: C, 64.80 ; H, 6.21 Found: C, 65.01, H, 6.41.

Ethyl 2,4-di-O-benzoyl-3-O-(*tert*-butyldimethylsilyloxy)-L-talopyranuronate 21

To a stirred solution of KCN (0.5 mmol) in methanol (4 ml) was added in one portion the lactol **17** (0.55g, 1 mmol). The resulting mixture was stirred at room temperature until complete conversion to the product had taken place. After 24h, t.l.c (hexane/ethyl acetate 50/50) showed no starting material and the solution was quenched by addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (70/30 hexane/ethyl acetate) to give the mixture of α,β-anomers of lactol **21** as an oil (0.24g, 45%); IR (υ, cm^{-1}) 3331 (OH), 1732 (ester); ^1H NMR ($CDCl_3$) δ 8.10-7.05 (m, 10H, Ph), 5.94-5.92 (dd, 1H, J=2.0Hz, J=3.9Hz), 5.66 (d, 1H), 5.26 (d, 1H, J=4.8Hz), 5.01 (d, 1H, J=2.0Hz), 4.60 (sl, 1H, OH), 4.49-4.47 (t, 1H, J=4.08Hz, J=4.05Hz), 4.28-4.06 (m, 2H, OCH_2), 1.13-1.09 (t, 3H, $OCH_2\underline{CH_3}$), 0.70 (s, 9H, OTBS), 0.17 (s, 3H, OTBS), 0.08 (s, 3H, OTBS); ^{13}C NMR ($CDCl_3$) of mixture δ −3.6, −3.5, −3.4, −3.2, 14.1, 14.2, 17.7, 25.5, 25.7 (OTBS), 62.3 (OCH_2), 70.1, 70.3, 71.9, 72.2, 76.9, 72.7, 81.8, 83.9, 96.9, 100.1 (CHO), 128.4, 128.5, 128.6, 128.7, 128.8, 129.8, 130.0, 133.3, 133.5, 133.8 (Ph), 165.5, 165.6, 165.8, 165.9, 166.8, 168.2 (CO_2);

Anal. Calcd. for $C_{28}H_{36}O_9Si$: C, 61.75 ; H, 6.66 Found: C, 61.75, H, 6.72

Ethyl 1,2,4-tri-O-benzoyl-3-O-(*tert*-butyldimethylsilyloxy)-L-talopyranuronate 22

Benzoylation of the product; **21** (0.2g, 0.367 mmol), pyridine (1 ml), BzCl (0.1 ml, 0.91 mmol, 2.5 eq.) and cat.DMAP for 1h. The crude residue was separated by column chromatography (75/25 hexane/ethyl acetate) to give the tribenzoate compound **22** (0.17g, 75%). ^1H NMR ($CDCl_3$) δ 8.13-7.13 (m, 15H, Ph), 6.78 (d, 1H, H-1, $J_{4,5}$=1.9Hz), 5.99 (dd, 1H, H-4, $J_{4,3}$=3.8Hz, $J_{4,5}$=1.9Hz), 5.38 (dd, 1H, H-2, $J_{1,2}$=1.4Hz, $J_{2,3}$=4.0Hz), 4.89 (d, 1H, H-5, $J_{4,5}$=1.9Hz), 4.57-4.54 (m, 1H, H-3, $J_{4,3}$=3.8Hz, $J_{2,3}$=4.0Hz), 4.20-4.10 (m, 2H, OCH_2), 1.15-1.10 (t, 3H, $OCH_2\underline{CH_3}$), 0.74 (s, 9H, OTBS), 0.20 (s, 3H, OTBS), 0.11 (s, 3H, OTBS);

^{13}C NMR ($CDCl_3$) −3.4, −3.1, 14.1, 17.9, 25.45, 25.6, 29.8, (OTBS), 61.6 (OCH_2), 68.3, 68.4, 70.6, 73.6, 94.9 (CHO), 128.0, 128.2, 130.0, 130.7, 132.5, 132.8 (Ph), 165.9, 165.9, 166.7 (CO_2).

Diethyl-(2R,3S,4R,5R)-2-benzoyloxy-4-(*tert*-butyldimethylsilyloxy)-3,5-O-isopropylidene-3,5-dihydroxy-6-octenodioate 24

To a solution of **12** (0.542g, 1.06 mmol) in DMF (1 ml) was added 2,2-dimethoxypropane (1.95 ml, 15.9 mmol, 15 eq) followed by 2 drops of concentrated sulfuric acid. The reaction mixture was stirred 24 h. A saturated aqueous $NaHCO_3$ was then added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (($MgSO_4$) and evaporated. The residue was purified by column chromatography (75/25 hexane/ethyl acetate) to give the compound **24** (0.43g, 90%) as an oil; ^1H NMR ($CDCl_3$) δ 8.13–7.46 (m, 5H, Ph), 6.91-6.89 (dd, 1H, H-3, J=5.3Hz, J=15.5Hz), 6.12 (d, 1H, H-2, J=15.5Hz), 5.48 (d, 1H, H-7, J=2.1Hz), 4.59 (t, 1H, H-4, J= 5.3Hz), 4.29-4.15 (m, 6H, OCH_2, H-5, H-6), 1.41 (d, 6H, CH_3), 1.31-1.24 (td, 6H, $OCH_2\underline{CH_3}$), 0.87 (s, 9H, TBS), 0.07 (d, 6H, TBS); ^{13}C NMR ($CDCl_3$) δ −3.2, −3.0, 14.2, 23.8, 24.7, 25.7, 39.5 (CH_3), 60.3, 61.8 (OCH_2), 70.2, 71.5, 72.1, 73.6 (CHOR), 101.6, 122.9 (HC=), 128.5, 129.9, 133.5 (Ph), 143.2 (HC=), 165.7, 165.8, 167.3 (CO_2).

Diethyl-(2R,3S,4R,5R)-2-hydroxy-4-(*tert*-butyldimethylsilyloxy)-3,5-O-isopropylidene-3,5-dihydroxy-6-octenedioate 25

To a solution of **24** (0.347g, 0.63 mmol) dissolved in ethanol (4 ml) was added slowly under argon atmosphere, sodium ethoxide (0.03g, 0.315 mmol, 0.5 eq.). The reaction mixture was stirred for 10 mn, before a solution of saturated aqueous ammonium chloride was added when TLC showed no starting material remained. The solution was extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (75/25 hexane/ethyl acetate) to give **25** (0.25g, 0.56 mmol, 88%) as an oil; $[\alpha]_D^{20}$-4.6 (c. 0.35 in $CHCl_3$); IR (υ, cm^{-1}) 3495 (OH), 1745, 1724 (CO_2Et), 1666 (C=C); ^1H NMR ($CDCl_3$) δ 6.96–6.90 (dd, 1H, H–3, *J*=5.5Hz, *J*=15.5Hz), 6.09 (d, 1H, H-2, *J*=15.5Hz), 4.49-4.47 (t, 1H, H-4, *J*= 5.5Hz), 4.35-4.16 (m, 6H, OCH_2, H-5, H-6), 3.90 (d, 1H, H-7, *J*=7.5Hz), 2.95 (d, 1H, OH, *J*=7.5Hz), 1.34-1.25 (td, 6H, $OCH_2\underline{CH_3}$), 0.88 (s, 9H, TBS), 0.06 (d, 6H, OTBS); ^{13}C NMR ($CDCl_3$) δ –4.6, –4.3, 14.3, 24.1, 24.5, 25.8, 60.3, 61.9 (OCH_2), 69.7, 72.2, 74.7 (CHO), 101.1, 122.6 (HC=), 143.6 (HC=), 165.9, 172.5 (CO_2).

Anal. Calcd. for $C_{21}H_{38}O_8Si$: C, 56.48 ; H, 8.58 Found: C, 56.67, H, 8.90.

Diethyl-(2S,3S,4R,5R)-2-azido-4-(*tert*-butyldimethylsilyloxy)-3,5-O-isopropylidene-3,5-dihydroxy-6-octenedioate 26

To a stirred solution of **25** (0.114, 0.25 mmol) in THF, was added succesively Ph_3P (0.099g, 0.38 mmol, 1.5 eq.) and HN_3 1.4M (0.3 ml, 0.38 mmol, 1.5 eq.) under argon atmosphere, followed by the dropwise addition of DEAD (0.066g, 0.38 mmol) dissolved in 0.5 ml of THF. After 3h the solvent was evaporated and the crude product was purified by chromatography column (75/25 hexane/ethyl acetate) to afford **26** (0.25g, 0.56 mmol, 75%) as an oil; ^1H NMR ($CDCl_3$) δ 6.91–6.84 (dd, 1H, H–3, *J*=5.2Hz, *J*=15.7Hz), 6.10 (d, 1H, H-2, *J*=15.7Hz), 4.49-4.47 (t, 1H, H-4, *J*= 5.2Hz, *J*= 3.8Hz), 4.45-4.36 (m, 1H, H-5, *J*= 6.5Hz, *J*= 3.8Hz),), 4.35-4.16 (m, 4H, OCH_2), 4.08-4.05 (dd, 1H, H-6, *J*= 2.1Hz, *J*= 6.5Hz), 3.76 (d, 1H, H-7, *J*=2.1Hz), 1.49 (s, 6H, CH_3), 1.32-1.25 (td, 6H, $OCH_2\underline{CH_3}$), 0.85 (s, 9H, TBS), 0.07 (d, 6H, TBS); ^{13}C NMR ($CDCl_3$) δ –3.8, 1.0, 14.3, 17.9, 23.6, 24.5, 25.7, 30.3, 60.4 (OCH_2), 61.5 (CHN_3), 62.1 (OCH_2), 69.8, 70.9, 72.0, 77.5 (CHO), 101.8, 122.9 (HC=), 143.7 (HC=), 166.0, 167.9 (CO_2).

Anal. Calcd. for $C_{21}H_{37}NO_7Si$: C, 56.86 ; H, 8.41 Found: C, 56.72, H, 8.09.

Ethyl 2-O-benzoyl-D-*galacto*-oct-6-enarate-1,4-lactone 27

To a stirred solution of **11** (0.747 g, 1.19 mmol) in CH_3CN (25.5 ml) was added 40% aqeous HF (0.84 ml, 19.07 mmol, 16 eq.) and the mixture was allowed to stand 24h at room temperature. After the reaction was judged complete by TLC the solution was quenched by addition of excess saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (50/50 hexane/ethyl acetate) to give the lactone **27** as white crystals (0.17g, 43%); m.p 174-175°C; $[\alpha]_D^{20}$-26.3 (c. 0.8 in acetone); IR (υ, cm^{-1}, KBr) 3493, 3429, 1743, 1722 (ester, C=O), 1670 (C=C); ^1H NMR (CD_3OCD_3) δ 8.08 (d, 2H, ortho-Ph), 7.72-7.53 (m, 3H, meta, para-Ph), 7.13-7.07 (dd, 1H, H-6, J_1=14.9Hz, J_2=4.3Hz), 6.23 (d, 1H, H-7, *J*=14.9Hz), 5.98 (d, 1H, H-2, *J*=8.5Hz), 4.94-4.89 (t, 1H, H-3, *J*=8.5Hz), 4.66 (s, 1H, H-5), 4.52-4.49 (dd, 1H, H-4, *J*=8.5Hz), 4.21-4.14 (q, 2H, OCH_2), 2.93 (sl,1H, OH), 1.28-1.23 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (CD_3OCD_3) δ 12.7 (Me), 58.9 (OCH_2), 67.2, 70.0, 74.4 (CHO), 81.2 (CHOBz), 121.1 (HC=), 127.5, 128.6, 132.6 (Ph), 145.1 (HC=), 164.9, 165.9, 166.5 (CO_2).

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.29 ; H, 5.18 Found: C, 58.26, H, 5.18.

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References and Notes.

1. Barrett, A.G.M.; Lebold, S.A. *J.Org.Chem.*, 1990, **55**, 3853 and references therein. Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265. Garner, P.; Park, J.M. *J. Org. Chem.* **1990**, *55*, 3772. Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019. Chen, A.; Savage, I.; Thomas, E.J.; Wilson, P.D. *Tetrahedron Lett.***1993**, *34*, 6769. Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc. Chem. Commun.* **1994**, 111.
2. For recent approaches see: Shing, T.K.M.; Tsui, H-C, *Tetrahedron Asymm.* **1994**, *5*, 1269.
3. Bergstrom, J.D.; Liech, J.M.; Hensens, O.D.; Onishi, J.C.; Huang, L.; VanMiddlesworth, F.; Diez, M.T.; Bartizal, K.F.; Nallin Omstead, M.; Rozdilsky, W.; Perez, F.P., Patent Appl. EP 450812. Dawson, M.J.; Farthing, J.E.; Marshall, P.S.; Middleton, R.F.; O'Neill, M.J.; Shuttleworth, A.; Stylli, C.; Tait, R.M.; Taylor, P.M.; Wildman, H.G.; Buss, A.D.; Langley, D.; Hayes, M.V., *J. Antibiotics*,**1992**, *45*, 639. Kraus, G.A.; Maeda, H., *J. Org. Chem.* **1995**, *60*, 2.
4. Jirousek, M.R.; Cheung, A.W-H.; Babine, R.E.; Sass, P.M.; Schow, S.R.;Wick, M.M. for leading references. Although it may not appear obvious initially the conversion of the terminal carboxylic groups provide a route to a possible precursor of **4** since selective reactions at these terminii can produce a primary hydroxyl suitable for activation for cyclisation and the rearrangement of the Curtius type at the other thus reducing the chain length by one carbon atom and introducing the amino group. Subsequent bicyclisation could afford the required product.
5 For an extensive review on the synthesis of carbohydrate derivatives from acyclic precursors see: Ager, D.J.; East, M.B. *Tetrahedron* **1993**, *49*, 5683.
6. Bichard, C.J.F.; Wheatley, J.R.; Fleet, G.W.J., *Tetrahedron Asymm.* **1994**, *5*, 431. and references therein.
7 Saito, S.; Morikawa, Y.; Moriwake, T. *Synlett* **1990**, 523.
8. Cha, J.K.; Christ, W.J.; Kishi, Y., *Tetrahedron.* **1984**, *40*, 2247. Houk, K.N.; Duh, H-Y.; Wu, Y-D.; Moses, S.R., *J. Am. Chem. Soc.*, **1986**, *108*, 2754. Vedejs, E.; Dent, W.H. III, *J. Am. Chem. Soc.*,**1989**, *111*, 6861. Evans, D.A.; Kaldor, S.W., *J. Org. Chem.*, **1990**, *55*, 1698. Hale, K.J.; Manaviazar, S.; Peak, S.A. *Tetrahedron Lett.* **1994**, *35*, 425. Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483.
9. Saito, S.; Morikawa, Y.; Moriwake, T. *J.Org. Chem.* **1990**, *55*, 5424.
10. From D-Mannitol and D-tartaric acid by multistep processes.
11. For example: Schreiber, S.L.; Goulet, M.T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. Krief, A.;Dumont, W.; Pasav, P. *Tetrahedron Lett.* **1988**, *29*, 1079.

12. Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T.; Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292. We have independently carried out the dihydroxylation reaction on the acetonide and found unsatisfactory diastereoselectivities. Our diastereomer ratio was around 4:1.
13. Xu, D.; Park, C.Y.; Sharpless, K.B. *Tetrahedron Lett.* **1994**, *35*, 2495.
14. Park,C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* **1991**, *32*, 1003.
15. Selective reactions at the α-hydroxyl are possible and we have been able to produce cyclic carbonates which prevent lactonisation.
16. Fleming, P.R.; Sharpless, K.B. *J. Org. Chem.* **1991**, *56*, 2869.
17. The C_2-symmetric diol diendioate **6** is prepared from inexpensive D-mannitol by a lengthy process. This causes a bottleneck but we are working on a method of preparing this compound by a simpler route having less steps, from symmetric starting materials.

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