Synthesis of Optically Active A-Ring Fragments of Taxol via Electrophilic Ring Closure of an Epoxy-Allylsilane

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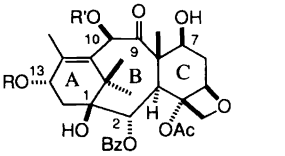
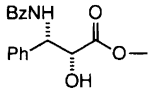
The optically active A-ring fragment **3** (and related derivatives) of taxol (**1**) has been synthesized via electrophilic ring closure of an optically active epoxy-allylsilane, prepared from L-arabinose.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Taxol (**1**) has attracted considerable interest because of its promising anti-cancer properties as well as its complicated structure.[1] Since the isolable amount of taxol is very limited[2] it is highly desirable to make larger quantities available for testing. An important step in this direction was made by Greene and Guéritte-Voegelein *et al.*[3] who solved the problem of synthesizing taxol from 10-deacetylbaccatin III (**2**) and also found that **2** could be



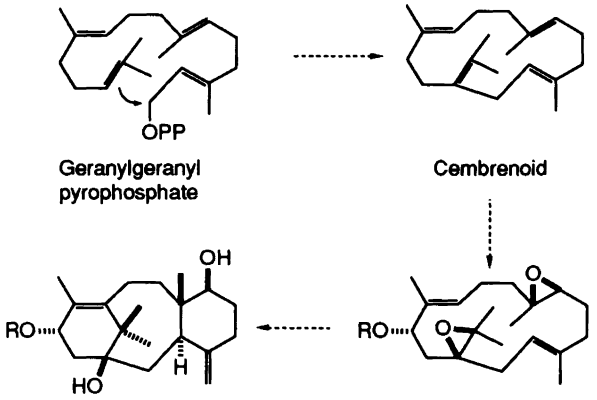
1 Taxol, R = R' = Ac



2 10-Deacetylbaccatin III
R, R' = H

isolated in relatively large amounts from the needles of *Taxus baccata* (1g per kg of needles). Thus an immediate supply of taxol should be readily available. There still remains the challenge of total synthesis of taxol, a task that has been addressed in several laboratories.[4] Syntheses of taxane-related optically active materials of known absolute configuration have been reported in only a few cases.[5–7] Notably, Holton *et al.* reported a remarkably efficient synthesis of (−)-taxusin (opposite stereochemistry to that of taxol) from patchino [(−)-β-patchoulene oxide].[8]

We became intrigued by the possibility of synthesizing taxanes by the use of electrophilic epoxy-olefin cyclizations similar to those involved in the biosynthesis of various polycyclic natural products such as steroids.[9–11] It was previously suggested that geranylgeraniol may be cyclized via its phosphate to give the taxane skeleton.[12,13] In this cyclization it is possible that a 14-membered ring system (cembranoid) is formed, which may undergo epoxidation, followed by ring closure, to give the taxane ring system as outlined in Scheme 1. These aspects have



Scheme 1.

lately been discussed by several authors.[14–17] In order to test the idea of epoxy-olefin ring-clusure we focused on the A-ring fragment **3** (Scheme 2) to find out whether it could be synthesized in optically active form from an open chain derivative carrying the necessary epoxy-olefin arrangement such as **4**. The A-ring fragment **3** carries reactive groups which may be used for further transformations into the taxane system.[18] The present report gives full details of our synthesis of **3** and related derivatives, some of which have been summarized previously.[19]

L-Arabinose was chosen as the optically active starting material for the synthesis of **3**. By this choice the

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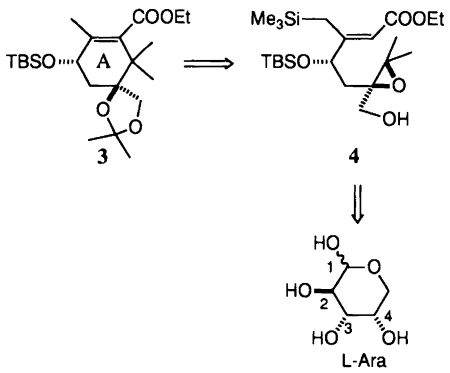


Scheme 2.

other enantiomer of all compounds involved would also become available by the same methodology, since arabinose is commercially available in both enantiomeric forms. Some important points of our plan were to invert the C-2 stereogenic center of arabinose, to deoxygenate the 3-position and to make chain extensions at C-4 and C-1 as outlined in Scheme 2.

Results and discussion

The epoxy alcohol **5** (Scheme 3) was obtained routinely in 50–60% overall yield from L-arabinose[20–22] and then oxidized under Swern conditions to the ketone **6**.[23] The reductive opening of the epoxide ring of **6** with NaI–HOAc was remarkably regioselective and provided **7** (70%) exclusively after silylation with *tert*-butyldimethylsilyl chloride (TBSCl). An alternative route from the dibenzyl derivative **8** (obtained by partial benzylation of benzyl 3-deoxy-β-L-arabinopyranoside followed by oxidation[20]) was not useful since the 2-*O*-benzyl group could not be removed selectively.[24]

The isopropylidene moiety at C-4 of **13** was introduced via the β-lactone route, using the dianion of isobutyric acid.[25] This technique has the advantage that the olefin may stay protected as the β-lactone during several reaction steps; for example hydrogenolytic removal of a benzyl group could be achieved without concomitant saturation of the double bond. The hydroxy acid **9a,b** was obtained as a diastereomeric mixture (which did not cause a problem since both diastereomers will eventually give the same olefin) and was subsequently converted into the β-lactone **10a,b** by benzenesulfonyl chloride treatment. It was important rigorously to purify **10a,b** prior to hydrogenolysis of the benzyl group otherwise the formation of **11a,b** was extremely slow. Sulfur impurities from the Swern oxidation may poison the catalyst. Oxidation of lactol **11a,b** with pyridinium dichromate activated by acetic anhydride,[26] provided the spiro-bislactone **12a,b**, which was cleanly decarboxylated to give the unsaturated lactone **13** (93%) by heating to 170°C. The thermal decarboxylation at the acetal stage (**10a,b**), on the other hand, gave a mixture of products. Swern oxidation[27,28] was also tried on **11a**, but resulted in the formation of the 1-chloro sugar derivatives **14a,b**, which became the main product if the reaction was performed in the absence of base (triethylamine) (see the Experimental part).[29] The formation of **14a,b** was observed (NMR experiment) even at −50°C.

Although not necessary for the synthesis the diastereomeric hydroxy acids **9a** and **9b** could be separated by chromatography. These compounds were then separately converted into the crystalline β-lactones **10a** and **10b**, respectively, and an X-ray investigation of **10b** confirmed the relative configuration as shown in Fig. 1. This also means that the absolute stereochemistry is known since the compounds are optically active; *complete* inversion at the sterogenic centers at C-1 and C-2 is a highly improbable event.

Having made the chain extension at C-4 of the original pyranoside, we then turned to the chain extension at C-1. The lactone ring of compound **13** was opened by the use of titanium tetraisopropoxide,[30–32] which gave the isopropyl ester **15**. In order to attach the two-carbon fragment of ethyl acetate, **15** was protected[33] as its THP-ether (**16**) and then treated with the lithium enolate of ethyl acetate.[34] This procedure gave a high yield of the β-keto ester **17**. One extra equivalent of lithium hexamethyldisilazide (LiHMDS) was used in order to prevent protonation of the enolate by the relatively acidic β-keto ester formed in the reaction. In contrast with LDA, LiHMDS has been reported to deprotonate α-substituted esters very slowly[35,36] and consequently the racemization of **16** or **17** by deprotonation at the respective sterogenic centers was not expected. (Indeed the high diastereomeric excess in the Sharpless epoxidation of **21** indicated that no racemization had occurred). Compound **17** existed as a

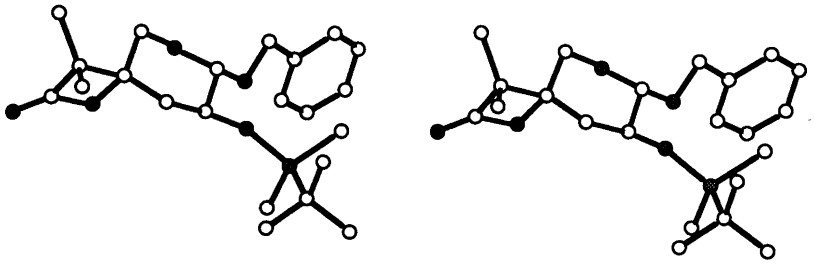
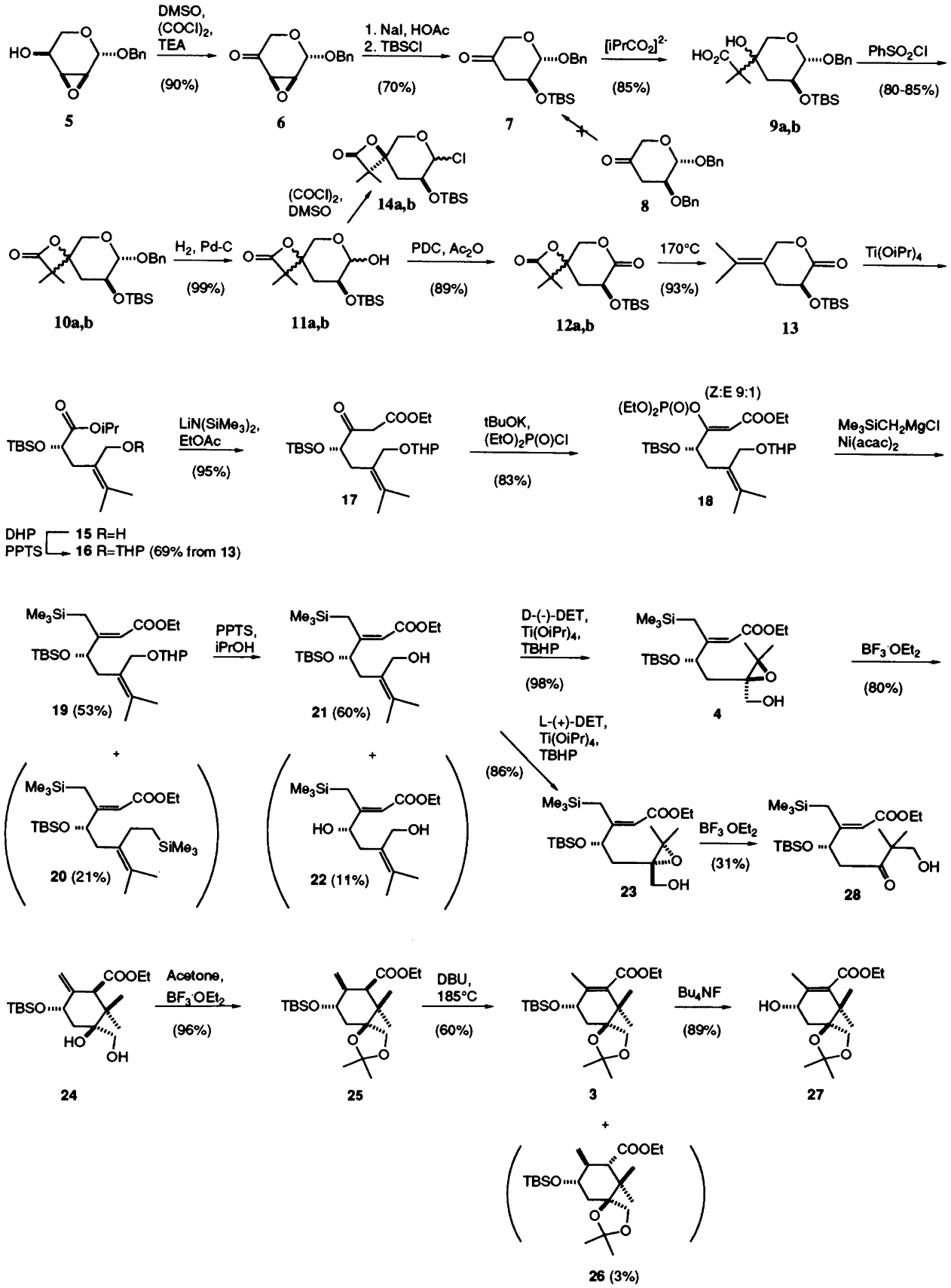


Fig. 1. Stereoview of the spirolactone **10b**. The X-ray coordinates were converted for presentation by the MacMIMIC[57] computer program. Hydrogen atoms are omitted.



Scheme 3. The designation **a** and **b** refers to the orientation of the oxygen atom at C-4 as above the plane and below the plane, respectively.

keto–enol mixture (85 : 15, $CDCl_3$) according to NMR spectroscopy and was trapped as the enol phosphate **18** (*Z* : *E* 9 : 1) by the action of *t*-BuOK/THF followed by $(EtO)_2P(O)Cl$. These conditions are supposedly not basic enough to generate the enolate di-anion of **17**.[37] However, we did not check at this point whether partial inversion at the stereogenic center had occurred.

It is interesting to note that the bulky TBS group influenced the *Z* : *E* ratio of **18** in a favorable way. When the C-4 hydroxy group of **17** was protected by the less bulky benzyl group a *Z* : *E* ratio of ca. 7 : 3 was obtained, while the corresponding methyl ether gave a 45 : 55 ratio. The enol phosphate **18** was then cross-coupled with trimethylsilylmethylmagnesium chloride using nickel catalysis[38,39] to give the allylic silane **19**. Both $Ni(acac)_2$ and $NiCl_2(PPh_3)_2$ could be used as catalysts, whereas $Pd(P_3)_4$ was ineffective. In order to obtain high yields of **19** an excess of the Grignard reagent was required, although substantial amounts of **20** were produced (via a Felkin-type reaction[40,41]) in addition to the desired **19**. Products formed by exclusive coupling to the allylic carbon were not found and it is possible that the amount of the Grignard reagent can be adjusted further to give a higher yeild of **19**. Fortunately, compounds **19** and **20** could be easily separated by column chromatography.

Deprotection of **19** to provide the allylic alcohol **21**, i.e., a selective deblocking of a THP-protected allylic alcohol in the presence of a TBS-protected secondary alcohol, was more difficult than expected. The ordinary, rather mild conditions for THP deprotection [pyridinium tosylate (PPTS) in methanol or ethanol] resulted in concurrent solvolysis of the TBS ester. Although the reaction was slower in ethanol compared with methanol the selectivity was very poor. The selectivity was improved, however, by performing the reaction in 2-propanol which allowed the isolation of **21** in 60 % yield together with 11 % of the diol **22** and 23 % of the starting material. We also tested other reagents reported to cleave THP ethers selectively in the presence of TBS ethers. Thus, anhydrous $MgBr_2$ in ether[42] resulted in a slow reaction with the formation of by-products, while $(SnBu_2NCS)_2O$ in ethanol[43] was comparable to PPTS in propanol. However, a small amount of an unknown by-product was formed.

Asymmetric epoxidation[44–48] of **21** gave the epoxy alcohol **4** in an excellent yield (98 %, 92 % d.e.). For comparison compound **23** (a diastereomer of **4**) was also prepared from **21** using the enantiomeric tartrate in the epoxidation reaction. This epoxidation resulted in an 86 % yield of the epoxide but with only 67 % d.e. The low stereoselectivity may be explained by a mismatched combination of substrate and catalyst.[49] The diastereomeric excess was determined by integration of ^1H NMR signals at 2.85 and 2.93 ppm (CH_2–TMS) and at 2.06 and 2.31 ppm (H-4) respectively. We also tried GLC analysis of the silylated derivatives for determination of the d.e. but the method failed owing to decomposition of the compounds.

To our satisfaction the ring closure of **4** by $BF_3 \cdot OEt_2$ at 0°C was a high-yield process;[50] **24** was isolated in 80 % yield. The structural proof of **24** was based on ^1H and ^{13}C NMR spectral data. Thus, the appearance of the *exo* methylene double bond, the tertiary CH in the α position to the carboxylate group, two quaternary carbons and NOE enhancement from the α hydrogen to one of the geminal methyl groups all strongly support the structure of **24**. A diaxial coupling constant $J_{H4,H5}$ of 11.7 Hz indicated a chair conformation, which was enforced by the observation that the chemical shift of the ester carbonyl carbon in **24** was 4.5 ppm to lower field compared with the acetonide **25** (175.89 ppm compared with 171.34 ppm). This effect may be ascribed to the presence of an intramolecular hydrogen bond between the axial tertiary hydroxy group and the ester carbonyl oxygen of the axial carboxylate group in **24**. No such possibility exists for **25**, which was obtained by $BF_3 \cdot OEt_2$ treatment of **24** in acetone. This protection was done in order to prevent intramolecular ether formation (via conjugate addition to the α,β-unsaturated ester moiety of **3**) during the attempts to move the *exo*-methylene double bond of **25** into conjugation with the ester function. Several methods were tried until we found that heating **25** in neat DBU at 185°C was a reproducible method of conjugation, which gave **3** in 60 % yield.

Epimerization at the α-carbon of **25** took place to some extent as evidenced by the isolation of a minor amount of **26**.

The TBS group of **3** was removed by treatment with Bu_4NF to give the alcohol **27**, suitable for ester formation with various carboxylic acid derivatives in conformity with the left-hand part of taxol.[51]

In contrast with **4**, its epimer **23** did not give any ring-closed product on treatment with $BF_3 \cdot OEt_2$. Instead, the hydroxymethyl group migrated to give the keto alcohol **28**. An investigation of the Lewis acid induced reactions of various epoxy olefins similar to **4** will be reported shortly.[52]

In conclusion we have synthesized optically active cyclohexane derivatives, which may be used as A-ring precursors in the synthesis of taxanes and perhaps taxol. Our synthesis seems to be the first preparation of fully substituted taxol A-ring derivatives (**3** and **27**), and the epoxy allylsilane **4** is the first example of a tetra-substituted epoxide used in an electrophilic epoxy olefin ring-closure reaction.

Experimental

Column chromatography separations were performed using Merck SiO_2 60 (0.040–0.063 mm) silica gel. TLC analyses were done on Merck SiO_2 60 F254 precoated aluminium sheets and the spots were visualized by charring with 10 % aqueous H_2SO_4 or by Merck molybdophosphoric acid spray reagent. The chromatographic eluents were heptane–EtOAc mixtures throughout and the ratios are given in parentheses in this order. Melting points were determined with a Reichert microscope and are uncorrected. Optical rotations were measured with

a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a Finnigan 4021 spectrometer (electron impact mode at 70 eV). The high resolution mass spectrum (of compound **5**) was recorded on a ZAB-HF, VG Analytical 11-250 spectrometer. X-Ray analysis was performed with an Enraf-Nonius CAD 4 diffractometer. NMR spectra were recorded at 23°C with a Varian XL-300 spectrometer using $CDCl_3$ as the solvent and $CHCl_3$ as an internal standard if not otherwise stated ($\delta_{^1H}$ 7.26 ppm and $\delta_{^{13}C}$ 77.00 ppm). The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet or complex signal). ^{13}C NMR spectra were recorded for all substances and copies may be obtained on request from the authors. Heptane and EtOAc were distilled before use. Dry CH_2Cl_2 and *N,N*-dimethylformamide (DMF) were prepared by distillation and stored over molecular sieves (4 Å). Dry toluene, Et_2O (diethyl ether), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were prepared by drying the commercial solvents (*p.a.* grade) over molecular sieves (4 Å).

X-Ray crystal structure determination of **10b**. Colorless crystal needles were obtained from the evaporation of the eluent (ethyl acetate–heptane 1 : 10) after chromatographic purification. A crystal with the dimensions $0.52 \times 0.17 \times 0.03$ mm was used for data collection on an Enraf-Nonius CAD4F-11 diffractometrer using monochromatized Cu Kα. The angular settings of 25 reflections ($23 < \theta < 35°$) were measured to calculate the lattice parameters. The $\omega/2\theta$ scan method was employed with a scan width of 1.6° and a scan speed of 3.2 deg min^{-1}. Three standard reflections measured every hour showed a decay of 3% which was corrected for. 2032 independent reflections within the range $1 < \theta < 60°$ were measured. 1323 reflections with $I > 3\sigma(I)$ were considered observed. The intensities were corrected for Lorentz polarization effects.

Crystal data. Molecular formula $C_{22}H_{34}O_5Si$; space group $P2_12_12_1$, unit cell $a = 8.231(2)$, $b = 12.603(2)$, and $c = 22.850(3)$ Å, $V = 2370.3(8)$ Å^3, $Z = 4$, $M = 406.595$; $D_c = 1.139$ g cm^{-3}, μ(Cu Kα) = 10.6 cm^{-1}.

The structure was solved by direct methods using the program MITHRIL.[53] The non-hydrogen atom parameters were refined by the full-matrix least-squares method using anisotropic temperature factors. Hydrogen atoms connected to methyl carbon atoms were found from a Fourier difference synthesis map (C–H distances normalized to 1.0 Å) and remaining hydrogen atoms were included at calculated positions. An isotropic temperature factor $U = 0.05$ was assigned for all hydrogens. The hydrogen atom parameters were kept fixed during the subsequent refinement. The final residuals were $R = 0.045$ and $R_w = 0.041$ and the weighting scheme used was $w = \sigma^2(F)^{-1}$. The maximum shift/sigma ratio was less than 0.001 and the final residual electron density was +0.17 (−0.19) e Å^{-3}. All calculations were performed on a μVAX3400 computer using the NRCVAX[54] program system.[55]

*Benzyl 2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-*β*-*L*-glycero-pentopyranosid-4-ulose* (**7**). A solution of **6**[23] (31.5 g, 0.143 mol) in acetone (500 ml) was added to a solution of NaI (80.0 g, 0.534 mol), acetic acid (160 ml) and $NaOAc \cdot 3H_2O$ (5.6 g) in acetone (500 ml). The reaction mixture immediately darkened owing to formation of I_2. The mixture was stirred for 2.5 h after which the acetone and the acetic acid were removed at reduced pressure and replaced with CH_2Cl_2 (300 ml) and the solution was decolorized by being washed with portions of $Na_2S_2O_3$ (aq.). The organic phase was washed with $NaHCO_3$ (sat.) and water and dried (Na_2SO_4) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc, 4:1 then 1:1) gave benzyl 3-deoxy-β-L-*glycero*-pentopyranosid-4-ulose (oil, 29.6 g, 93%): R_f (1 : 1) 0.34; $[\alpha]_D^{20}$ + 131° (*c* 1.90, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 2.56 (dddd, 1 H, $J_{AB} = 16.7$ Hz, $J = 4.3$, 1.5, 1.0 Hz, H-3), 2.80 (s, 1 H, br, OH), 2.88 (dd, 1 H, $J_{AB} = 16.7$ Hz, $J = 4.5$ Hz, H-3), 3.98 (dd, 1 H, $J_{AB} = 16.5$ Hz, $J = 1.5$ Hz, H-5), 4.13 (ddd, 1 H, $J = 4.3$, 4.5, 2.9 Hz, H-2), 4.14 (dd, 1 H, $J_{AB} = 16.5$, $J = 1.0$ Hz, H-5), 4.63, 4.83 (2 d, 2 H, $J_{AB} = 12.0$ Hz, benzyl), 4.86 (d, 1 H, $J = 2.9$ Hz, H-1), 7.30–7.40 (m, 5 H, Ph). Anal. $C_{12}H_{14}O_4$: C, H, O.

This compound (27.6 g, 0.124 mol) was added to a solution of *tert*-butyldimethylsilyl chloride (TBS-Cl, 22.4 g, 0.149 mol) and imidazole (21.1 g, 0.310 mol) in DMF (60 ml). The reaction mixture was stirred at room temperature for 6 h and then CH_2Cl_2 (300 ml) was added. The solution was washed with water, 1.0 M HCl, $NaHCO_3$ (sat.), again with water and dried ($MgSO_4$). The solvent was evaporated off at reduced pressure to give crude **7** (41.5 g, 99%) as a pale oil (pure by TLC, heptane–EtOAc 1 : 1). Column chromatography (heptane–EtOAc 9 : 1) gave **7** (oil, 31.5 g, 76%): R_f (1 : 1) 0.6; $[\alpha]_D^{20}$ + 94° (*c* 2.64, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.04 [2 s, 6 H, $-Si(CH_3)_2-$], 0.86 (s, 9 H, *t*-Bu), 2.50 (ddd, 1 H, $J_{AB} = 15.9$ Hz, $J = 5.1$, 1.5 Hz, H-3), 2.83 (dd, 1 H, $J_{AB} = 15.9$ Hz, $J = 4.2$ Hz, H-3), 3.97 (dd, 1 H, $J_{AB} = 16.6$ Hz, $J = 1.5$ Hz, H-5), 4.09 (d, 1 H, $J_{AB} = 16.6$ Hz, H-5), 4.16 (ddd, 1 H, $J = 5.1$, 4.2, 2.7 Hz, H-2), 4.62 (d, 1 H, $J_{AB} = 11.7$ Hz, benzyl), 4.79 (d, 1 H, $J = 2.7$ Hz, H-1), 4.83 (d, 1 H, $J_{AB} = 11.7$ Hz, benzyl), 7.31–7.40 (m, 5 H, Ph). Anal. $C_{18}H_{28}O_4Si$: C, H.

*Benzyl 2-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(2-carboxypropan-2-yl)-3-deoxy-*β*-*L*-erythro-pentopyranoside* (**9a**) *and benzyl 2-*O*-(*tert*-butyldimethylsilyl)-4-*C*-(2-carboxypropan-2-yl)-3-deoxy-*α*-*D*-threo-pentopyranoside* (**9b**). BuLi (31.7 ml, 46.0 mmol, 1.45 M in hexane) was added to a stirred solution of diisopropylamine (4.65 g, 46.0 mmol) in dry THF (46 ml) under nitrogen at 0°C. The cooling bath was removed and after 10 min a solution of isobutyric acid (2.02 g, 23.0 mmol) in dry THF (23 ml) was added. Stirring was continued for 1 h and then a solution of **7** (5.82 g, 17.3 mmol) in dry THF (8 ml) was

added. The reaction mixture was stirred overnight and then poured into ice–water (ca. 150 ml). Most of the THF was evaporated off at reduced pressure and the remaining aqueous solution was washed with ether (20 ml). The aqueous phase was acidified and the product was extracted with ether (2 × 200 ml). The combined organic phases were washed with water and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure followed by column chromatography of the residue (heptane–EtOAc 2 : 1 then 1 : 1) gave crystalline **9a** (2.10 g, 29%) and **9b** (oil, 4.09 g, 56%).

9a: R_f (3 : 1) 0.22; m.p. 61–69°C; $[\alpha]_D^{20} + 75°$ (*c* 1.60, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.04, 0.07 [2 s, 6 H, $-Si(CH_3)_2-$], 0.89 (s, 9 H, *t*-Bu), 1.22, 1.25 [2 s, 6 H, $-C(CH_3)_2-$], 1.69 (dddd, 1 H, $J_{AB} = 14.2$ Hz, $J = 2.9$, 2.7, 1.0 Hz, H-3), 2.15 (dd, 1 H, $J_{AB} = 14.2$ Hz, $J = 2.9$ Hz, H-3), 3.58 (dd, 1 H, $J_{AB} = 11.5$ Hz, $J = 2.9$ Hz, H-5), 3.94 (m, 1 H, br, H-2), 3.95 (d, 1 H, $J_{AB} = 11.5$ Hz, H-5), 4.54 (d, 1 H, $J_{AB} = 12.0$ Hz, benzyl), 4.65 (s, 1 H, br, H-1), 4.77 (d, 1 H, $J_{AB} = 12.0$ Hz, benzyl), 7.28–7.40 (m, 5 H, Ph). Anal. $C_{22}H_{36}O_6Si$: C, H.

9b: R_f (3 : 1) 0.13; $[\alpha]_D^{20} + 52°$ (*c* 1.00, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.04, 0.06 [2 s,. 6 H, $-Si(CH_3)_2-$], 0.86 (s, 9 H, *t*-Bu), 1.26, 1.29 [2 s, 6 H, $-C(CH_3)_2-$], 1.63 (dd, 1 H, $J_{AB} = 13.2$ Hz, $J = 10.7$ Hz, H-3), 2.03 (ddd, 1 H, $J_{AB} = 13.2$ Hz, $J = 5.4$, 2.8 Hz, H-3), 3.68 (d, 1 H, $J_{AB} =$ 12.0 Hz, H-5), 3.80 (dd, 1 H, $J_{AB} = 12.0$ Hz, $J = 2.8$ Hz, H-5), 3.83 (ddd, 1 H, $J = 10.7$, 5.4, 7.8 Hz, H-2), 4.27 (d, 1 H, $J = 7.8$ Hz, H-1), 4.62, 4.87 (2 d, 2 H, $J_{AB} = 11.8$ Hz, benzyl), 7.28–7.39 (m, 5 H, Ph). Anal. $C_{22}H_{36}O_6Si$: C, H.

*Benzyl 2-O-(*tert*-butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*β*-*L*-*erythro*-pentopyranoside β-lactone* (**10a**) *and benzyl 2-O-(*tert*-butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*α*-*D*-*threo*-pentopyranoside β-lactone* (**10b**). Benzenesulfonyl chloride (1.31 g, 7.40 mmol) was added to a solution of **9a** (1.56 g, 3.68 mmol) in pyridine (25 ml). After being stirred overnight at 40–50°C the reaction mixture was diluted with ether (50 ml) and washed with water (3 × 10 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc 10 : 1) of the remaining dark oil gave **10a** (1.24 g, 83%) which crystallized on standing. Compound **9b** was treated similarly to give **10b** (80–85%).

10a: R_f (3 : 1) 0.45; m.p. 68–73°C; $[\alpha]_D^{20} + 76°$ (*c* 1.30, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.03, 0.06 [2 s, 6 H, $-Si(CH_3)_2-$], 0.88 (s, 9 H, *t*-Bu), 1.33, 1.35 [2 s, 6 H, $-C(CH_3)_2-$], 1.98 (ddd, 1 H, $J_{AB} = 14.3$ Hz, $J = 6.6$, 1.2 Hz, H-3), 2.24 (ddd, 1 H, $J_{AB} = 14.3$ Hz, $J = 4.1$, 1.2 Hz, H-3), 3.70 (ddd, 1 H, $J = 6.6$, 4.1, 3.9 Hz, H-2), 3.77, 4.02 (2 dd, 2 H, $J_{AB} = 12.5$ Hz, $J = 1.2$ Hz, H-5), 4.52 (d, 1 H, $J = 3.9$ Hz, H-1), 4.59, 4.80 (2 d, 2 H, $J_{AB} = 12.0$ Hz, benzyl), 7.29–7.40 (m, 5 H, Ph). Anal. $C_{22}H_{34}O_5Si$: C, H.

10b: R_f (3 : 1) 0.39; m.p. 91–92°C; $[\alpha]_D^{20} + 75°$ (*c* 0.67, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.02, 0.05 [2 s, 6 H, $-Si(CH_3)_2-$], 0.86 (s, 9 H, *t*-Bu), 1.34, 1.39 [2 s, 6 H, $-C(CH_3)_2-$], 1.99 (ddd, 1 H, $J_{AB} = 14.1$ Hz, $J = 7.5$, 1.2 Hz, H-3), 2.27 (ddd, 1 H, $J_{AB} = 14.1$ Hz, $J = 4.3$, 1.8 Hz, H-3), 3.72 (dd, 1 H, $J_{AB} = 12.5$ Hz, $J = 1$-2 Hz, H-5), 3.88 (ddd, 1 H, $J = 7.5$, 4.3, 4.6 Hz, H-2), 4.07 (dd, 1 H, $J_{AB} = 12.5$ Hz, $J = 1$-2 Hz, H-5), 4.37 (d, 1 H, $J = 4.6$ Hz, H-1), 4.56, 4.83 (2 d, 2 H, $J_{AB} = 11.6$ Hz, benzyl), 7.27–7.38 (m, 5 H, Ph). Anal. $C_{22}H_{34}O_5Si$: C, H.

*2-O-(*tert*-Butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*β*-*L*-erythro-pentopyranose β-lactone* (**11a**) *and 2-O-(*tert*-butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*α*-*D*-threo-pentopyranose β-lactone* (**11b**). Compound **10a** (5.40 g, 13.3 mmol) was dissolved in acetic acid (50 ml) and hydrogenated for 5 days at 1 atm using Pd–C (5%, 500 mg) as the catalyst. The rate of the reaction was highly dependent on the purity of the starting material as well as on the amount of catalyst. The reaction was monitored by TLC (heptane–EtOAc 3 : 1), and when judged complete, the slurry was filtered and the catalyst washed with EtOAc. The filtrate was co-evaporated with toluene several times to give **11a** (oil, 4.16 g, 99%) as an anomeric mixture (ca. 1 : 1 in $CDCl_3$): R_f (3 : 1) 0.13; $[\alpha]_D^{20} + 10°$ (*c* 1.00, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.10 [s, 3 H, $-Si(CH_3)_2-$], 0.12, 0.13 [2 s, 3 H, $-Si(CH_3)_2-$], 0.90, 0.92 (2 s, 9 H, *t*-Bu), 1.38, 1.40, 1.41, 1.43 [4 s, 6 H, $-C(CH_3)_2-$], 2.00, 2.17 (2 ddd, 1 H, $J_{AB} = 13.9$ Hz, $J = 8.1$, 1.0 Hz, $J_{AB} = 13.4$ Hz, $J = 5.1$, 2.0 Hz, H-3), 2.31, 2.25 (ddd, dd, 1 H, $J_{AB} = 13.9$ Hz, $J = 4.4$, 2.0 Hz, $J_{AB} = 13.4$ Hz, $J = 9.2$ Hz, H-3), 3.59, 3.73–3.81 (ddd, m, 2 H, $J = 8.1$, 4.4, 4.4 Hz, H-2, H-5), 4.15, 4.15 (dd, d, 1 H, $J_{AB} = 12.3$ Hz, $J = 2.0$ Hz, $J_{AB} = 12.3$ Hz, H-5), 4.75, 4.91 (2 d, 1 H, $J = 4.4$ Hz, $J = 3.2$ Hz, H-1). Anal. $C_{15}H_{28}O_5Si$: C, H.

Compound **10b** was treated as above to give **11b** (99%) as an anomeric mixture (ca. 2 : 1 in $CDCl_3$): R_f (3 : 1) 0.10; m.p. 129–134°C; $[\alpha]_D^{20} - 13°$ (*c* 1.29, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.11, 0.12 [2 s, 6 H, $-Si(CH_3)_2-$], 0.90, 0.90 (2 s, 9 H, *t*-Bu), 1.29, 1.31, 1.34, 1.37 [4 s, 6 H, $-C(CH_3)_2-$], 1.87, 1.99–2.03, 2.26 (ddd, m, ddd, 2 H, $J_{AB} = 14.1$ Hz, $J = 9.4$, 0.7 Hz, $J_{AB} = 14.1$ Hz, $J = 4.6$, 2.6 Hz, H-3), 2.79, 2.84 (2 d, 1 H, $J = 5.5$ Hz, $J = 1.9$ Hz, OH), 3.70–3.79, 4.03 (m, ddd, 2 H, $J = 3.4$, 8.1, 8.1 Hz, H-5, H-2), 4.08, 4.12 (d, dd, 1 H, $J_{AB} = 12.8$ Hz, $J_{AB} =$ 12 Hz, $J = 2.6$ Hz, H-5), 4.54, 5.08 (2 dd, 1 H, $J = 5.5$, 6.0 Hz, $J = 1.9$ Hz, 3.4 Hz, H-1). Anal. $C_{15}H_{28}O_5Si$: C, H.

*(3S,5S)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-3-hydroxymethyl-2,2-dimethylhexanedioic acid (1β,6δ)-bis-spirolactone* (**12a**) *and (3R,5S)-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-3-hydroxymethyl-2,2-dimethylhexanedioic acid (1β,6δ)-bis-spirolactone* (**12b**). A solution of **11a** (158 mg, 0.500 mmol) in dry CH_2Cl_2 (0.5 ml) was added to a mixture of freshly prepared pyridinium dichromate[56] (PDC, 129 mg, 0.500 mmol) and Ac_2O (142 µl, 0.500 mmol) in dry CH_2Cl_2 (2.0 ml). The reaction mixture was refluxed for 5 h, a further portion of PDC (129 mg) was added and reflux was continued for 1 h. After cooling, column chromatography (heptane–EtOAc 1 : 1) of the reaction mixture gave **12a** (140 mg,

89%) as white amorphous crystals. In large-scale operations (10–50 mmol) diastereomeric mixtures of **11a,b** together with 1.0 molar equivalent of PDC were used and the reaction mixtures were refluxed overnight. Prior to column chromatography (heptane–EtOAc 3 : 1), the reaction mixtures were filtered through silica gel followed by evaporation of the solvent at reduced pressure. Yields of 75–85% were obtained. Pure fractions of **12a** and **12b** were collected for analytical purposes.

12a: R_f (1 : 1) 0.43; m.p. 126–141°C (decomp.); $[\alpha]_D^{20}+25°$ (*c* 0.40, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.12, 0.18 [2 s, 6 H, $-Si(CH_3)_2-$], 0.91 (s, 9 H, *t*-Bu), 1.37, 1.43 [2 s, 6 H, $-C(CH_3)_2-$], 2.37 (ddd, 1 H, $J_{AB}=15.6$ Hz, $J=8.8$, 1.2 Hz, H-4), 2.68 (dd, 1 H, $J_{AB}=15.6$, $J=7.1$ Hz, H-4), 4.33 (dd, 1 H, $J=8.8$, 7.1 Hz, H-5), 4.44 (d, 1 H, $J_{AB}=12.7$ Hz, $-CH_2O-$), 4.65 (dd, 1 H, $J_{AB}=12.7$ Hz, $J=1.2$ Hz, $-CH_2O-$). Anal. $C_{15}H_{26}O_5Si$: C, H.

12b: R_f (1 : 1) 0.54; m.p. 123–143°C (decomp); $[\alpha]_D^{20}-47°$ (*c* 0.60, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.15, 0.18 [2 s, 6 H, $-Si(CH_3)_2-$], 0.91 (s, 9 H, *t*-Bu), 1.35, 1.41 [2 s, 6 H, $-C(CH_3)_2-$], 2.37–2.48 (m, 2 H, H-4), 4.47 (dd, 1 H, $J=8.0$, 6.4 Hz, H-5), 4.52 (d, 1 H, $J_{AB}=13.3$ Hz, br, $-CH_2O-$), 4.66 (d, 1 H, $J_{AB}=13.3$ H2, $-CH_2O-$). Anal. $C_{15}H_{26}O_5Si$: C, H.

*(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxymethyl-5-methyl-4-hexenoic acid δ-lactone* (**13**). A diastereomeric mixture of **12a,b** (340 mg, 1.26 mmol) was heated under nitrogen at 170°C for 20 min. After cooling, the crude product was purified by column chromatography (heptane–EtOAc, 10 : 1) to give **13** (272 mg, 93%) as an oil which crystallized on standing. Large-scale operations (10–50 mmol) require longer periods of heating and vigorous stirring. The reaction can also be performed on a TLC-plate by heating a spot of **12** at elevated temperatures for a few seconds before elution with heptane–EtOAc (3 : 1).

13: R_f (1 : 1) 0.65; m.p. 48–53°C; $[\alpha]_D^{20}+49°$ (*c* 1.70, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.12, 0.18 [2 s, 6 H, $-Si(CH_3)_2-$], 0.92 (s, 9 H, *t*-Bu), 1.67–1.70 [m, 6 H, $=C(CH_3)_2$], 2.52 (ddd, 1 H, $J_{AB}=16.5$ Hz, $J=9.5$, 0–1 Hz, H-3), 2.80 (ddd, 1 H, $J_{AB}=16.5$ Hz, $J=6.6$, 0–1 Hz, H-3), 4.44 (dd, 1 H, $J=9.5$, 6.6 Hz, H-2), 4.73, 5.00 (2 d, 2 H, $J_{AB}=13.3$ Hz, $-CH_2O-$). Anal. $C_{14}H_{26}O_3Si$: C, H.

*2-O-(*tert*-Butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*α-L-erythro-*pentopyranosyl chloride β-lactone* (**14a**) *and 2-O-(*tert*-butyldimethylsilyl)-4-C-(2-carboxypropan-2-yl)-3-deoxy-*β-L-erythro-*pentopyranosyl chloride β-lactone* (**14b**). A solution of oxalyl chloride (430 µl, 5.0 mmol) in dry CH_2Cl_2 (1.0 ml) was added to a solution of **11a** (500 mg, 1.6 mmol) and DMSO (500 µl, 7.0 mmol) in dry CH_2Cl_2 (5.0 ml) under nitrogen at −60°C. The cooling bath was removed after 30 min and then ether (5.0 ml) was added followed by $NaHCO_3$ (10 ml, sat.). The organic phase was washed with brine, dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc, 5 : 1) gave **14a** (oil, 21 mg, 4%) and **14b** (oil, 164 mg, 31%). These compounds are unstable on silica gel (completely converted into the starting material after less than 2 h on TLC plates) and thus the yields after chromatography are poor.

14a: R_f (3 : 1) 0.46; $[\alpha]_D^{20}-103°$ (*c* 0.51, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.10 [s, 6 H, $-Si(CH_3)_2-$], 0.90 (s, 9 H, *t*-Bu), 1.44, 1.47 [2 s, 6 H, $-C(CH_3)_2-$], 2.23 (dddd, 1 H, $J_{AB}=12.9$ Hz, $J=4.4$, 2.7, 1.1 Hz, H-3), 2.38 (dd, 1 H, $J_{AB}=12.9$ Hz, $J=11.8$ Hz, H-3), 3.81 (ddd, 1 H, $J=11.8$, 4.4, 3.8 Hz H-2), 3.93 (dd, 1 H, $J_{AB}=12.2$ Hz, $J=2.7$ Hz, H-5), 4.14 (d, 1 H, $J_{AB}=12.2$ Hz, H-5), 5.89 (d, 1 H, $J=3.8$ Hz, br, H-1). Anal. $C_{15}H_{27}ClO_4Si$: C, H.

14b: R_f (3 : 1) 0.40; $[\alpha]_D^{20}+93°$ (*c* 1.82, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.10 [s, 6 H, $-Si(CH_3)_2-$], 0.91 (s, 9 H, *t*-Bu), 1.29, 1.34 [2 s, 6 H, $-C(CH_3)_2-$], 2.03 (dddd, 1 H, $J_{AB}=14.9$ Hz, $J=3$, 2.6, 1.5 Hz, H-3), 2.36 (dd, 1 H, $J_{AB}=14.9$ Hz, $J=3.4$ Hz, H-3), 4.00–4.04 (m, 1 H, H-2), 4.03 (dd, 1 H, $J_{AB}=13.0$ Hz, $J=2.6$ Hz, H-5), 4.14 (d, 1 H, $J_{AB}=13.0$ Hz, H-5), 5.87 (m, 1 H, H-1). Anal. $C_{15}H_{27}ClO_4Si$: C, H, Cl.

*(2S)-Isopropyl-2-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-4-[(2-tetrahydropyran-2-yloxy)methyl]-4-hexenoate* (**16**). Compound **13** (5.15 g, 19.0 mmol) was dissolved in $Ti(OiPr)_4$ (20 ml) and the solution was stirred at room temperature overnight. The reaction mixture was diluted with ether (200 ml) and then water (6 ml) was added. The solution turned milky and after 5 min of vigorous stirring, Celite was added. Stirring was continued for 10 min and the slurry was then filtered through Celite (addition of larger amounts of water rendered the filtration difficult). Washing the Celite pad several times with ether was necessary to extract the product. Co-evaporation with toluene at reduced pressure and column chromatography (heptane–EtOAc 5 : 1) gave (2*S*)-isopropyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxymethyl-5-methyl-4-hexenoate (**15**) (4.95 g, 79%) as an oil, which crystallized in the freezer.

15: R_f (1 : 1) 0.55; m.p. 8°C; $[\alpha]_D^{20}-21°$ (*c* 0.75, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.03, 0.08 [2 s, 6 H, $-Si(CH_3)_2-$], 0.90 (s, 9 H, *t*-Bu), 1.25 [d, 6 H, $J=5.9$ Hz, $-CH(CH_3)_2$], 1.72, 1.74 [2 s, 6 H, $=C(CH_3)_2$], 2.58 (dd, 1 H, $J_{AB}=14.2$ Hz, $J=5.0$ Hz, H-3), 2.67 (dd, 1 H, $J_{AB}=14.2$ Hz, $J=7.5$ Hz, H-3), 4.09 (dd, 1 H, $J_{AB}=12.0$ Hz, $J=6.1$ Hz, $-CH_2OH$), 4.16 (dd, 1 H, $J_{AB}=12.0$ Hz, $J=4.5$ Hz, $-CH_2OH$), 4.30 (dd, 1 H, $J=5.0$, 7.5 Hz, H-2), 5.02 [septet, 1 H, $J=5.9$ Hz, $-CH(CH_3)_2$]. Anal. $C_{17}H_{34}O_4Si$: C, H.

Pyridinium tosylate (150 mg, 0.67 mmol) was added to a solution of **15** (1.91 g, 5.78 mmol) and 2,3-dihydropyran (2.7 ml, 30 mmol) in dry CH_2Cl_2 (3.0 ml) and the solution was stirred for 3 h at room temperature. After dilution with ether (50 ml), the solution was washed with $NaHCO_3$ (sat.) and water, and dried (Na_2SO_4) and the solvent was evaporated off at reduced pressure to give crude **16** (2.40 g, 100%) as an oil which could be used directly in the next step. Purification by column

chromatography (heptane–EtOAc 25 : 1) gave **16** (oil, 2.09 g, 87%) as a diastereomeric mixture (1 : 1): R_f (10 : 1) 0.48; $[\alpha]_D^{20} - 19°$ (*c* 0.67, $CDCl_3$); ^1H NMR ($CDCl_3$): δ − 0.02, 0.03 [2 s, 6 H, $-Si(CH_3)_2-$], 0.87, 0.87 (2 s, 9 H, *t*-Bu), 1.22, 1.24 [2 d, 6 H, $J = 6.4$ Hz, $-CH(CH_3)_2$], 1.48–1.88 (m, 6 H, THP), 1.76 [s, 6 H, $=C(CH_3)_2$], 2.51–2.64 (m, 2 H, H-3), 3.48–3.56 (m, 1 H, THP), 3.85–3.94 (m, 1 H, THP), 4.02, 4.03 (2 d, 1 H, $J_{AB} = 11.0$ Hz, $J_{AB} = 11.2$ Hz, $-CH_2-$OTHP), 4.26–4.31 (m, 2 H, $-CH_2-$OTHP, H-2), 4.59–4.63 (m, 1 H, acetal), 5.02, 5.03 [2 septets, 1 H, $J = 6.4$ Hz, $-CH(CH_3)_2$]. Anal. $C_{22}H_{42}O_5Si$: C, H.

*(4S)-Ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-7-methyl-3-oxo-6-[(2-tetrahydropyran-2-yloxy)methyl]-6-octenoate* (**17**). *n*-BuLi (21.2 ml, 30.9 mmol, 1.46 M inhexane) was added to a solution of hexamethyldisilazane (7.09 ml, 34.0 mmol) in dry THF (25 ml) under nitrogen at 0°C. The temperature was then lowered to −70°C and dry EtOAc (1.51 ml, 15.4 mmol) was added slowly. After 10 min of stirring at this temperature a solution of **16** (4.27 g, 10.3 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 4.60 ml, 30.9 mmol) in dry THF (5 ml) was added. The cooling bath was removed and after ca. 40 min ether (300 ml) was added. The solution was washed with 1.0 M HCl (150 ml) and brine (2 × 50 ml), dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc, 12 : 1) gave **17** (oil, 4.32 g, 95%) as a keto–enol mixture (85 : 15 in $CDCl_3$), [^1H NMR δ (enol-form) 5.28 (vinylic), 11.96 (–OH)].

17: R_f (10 : 1) 0.17; $[\alpha]_D^{20} - 43°$ (*c* 1.40, $CDCl_3$); ^1H NMR ($CDCl_3$): δ (keto-form) −0.01, 0.00, 0.02 [3 s, 6 H, $-Si(CH_3)_2-$], 0.89 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, $J = 7.3$ Hz, CH_2CH_3), 1.48–1.88 (m, 6 H, THP), 1.74, 1.76 [2 s, 6 H, $=C(CH_3)_2$], 2.40–2.60 (m, 2 H, H-5), 3.48–3.56 (m, 1 H, THP), 3.60 3.64 (2 d, 2 H, $J_{AB} = 16.3$ Hz, H-2), 3.84–3.94 (m, 1 H, THP), 4.02, 4.03 [2 d, 1 H, $J_{AB} = 11.2$ Hz, $J_{AB} = 11.2$ Hz, –C(*H*)H–OTHP], 4.18 (q, 2 H, $J = 7.3$ Hz, CH_2CH_3), 4.23–4.30 [m, 2 H, –C(H)H–OTHP, C-4], 4.56–4.62 (m, 1 H, acetal). Anal. $C_{23}H_{42}O_6Si$: C, H.

*(4S)-(2Z)-Ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-3-[(diethylphosphoryl)oxy]-7-methyl-6-[(2-tetrahydropyran-2-yloxy)methyl]-2,6-octadienoate* (**18**-Z) *and (4S)-(2E)-ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-3-[(diethylphosphoryl)oxy]-7-methyl-6-[(2-tetrahydropyran-2-yloxy)-methyl]-2,6-octadienoate* (**18**-E). Potassium *tert*-butoxide (561 mg, 5.00 mmol) was added to a solution of **17** (2.13 g, 4.82 mmol) in dry THF (12 ml) under nitrogen at room temperature. After 3 min of stirring, diethyl chlorophosphate (1.01 ml, 7.00 mmol) was added and the reaction mixture was stirred for 20 min. Ether was added and the solution was washed with NH_4Cl (aq., 10%) and water and dried (Na_2SO_4) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc 4 : 1 then 2 : 1) of the residue gave a mixture of **18**-*Z* and **18**-*E* (2.32 g, 83%, *Z* : *E* ca. 9 : 1), which was used in the next step without further separation, but pure fractions (diasteromeric mixture due to THP-group) of **18**-*Z* (oil) and **18**-*E* (oil) were collected for analytical purposes.

18-*Z*: R_f (3 : 1) 0.19; ^1H NMR ($CDCl_3$): δ − 0.04, −0.03, 0.04, 0.04 [4 s, 6 H, $-Si(CH_3)_2-$], 0.89 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.30–1.38 [m, 6 H, $-P(O)(OCH_2CH_3)_2$], 1.44–1.86 (m, 6 H, THP), 1.76 [s, 6 H, $=C(CH_3)_2$], 2.35–2.45, 2.59–2.68 (2 m, 2 H, H-5), 3.44–3.54, 3.83–3.93 (2 m, 2 H, THP), 4.01 [d, 1 H, $J_{AB} = 11.2$ Hz, –C(*H*)H–OTHP], 4.10–4.32 [m, 7 H, $-OCH_2CH_3$, –C(H)*H*–OTHP], 4.49–4.59 (m, 2 H, acetal, H-4), 5.83 (m, 1 H, vinylic); selected ^{13}C NMR data ($CDCl_3$): δ 104.76, 104.81 (2 d, $J_{C,P} = 7$ Hz, C-2), 125.13, 125.38, 134.98, 135.27 (C-6, C-7), 163.99, 164.01 (2 d, $J_{C,P} = 8$ Hz, C-3), 164.12 (C=O). Anal. $C_{27}H_{51}O_9PSi$: C, H.

18-*E*: R_f (3 : 1) 0.21; ^1H NMR ($CDCl_3$): δ − 0.01, 0.00, 0.00 [3 s, 6 H, $-Si(CH_3)_2-$], 0.84, 0.85 (2 s, 9 H, *t*-Bu), 1.25, 1.25 (2 t, 3 H, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.37, 1.37 [2 dt, 6 H, $J_{H,P} = 1.1$ Hz, $-P(O)(OCH_2CH_3)_2$, $J = 7.1$ Hz], 1.44–1.88 (m, 6 H, THP), 1.74, 1.77 [2 s, 6 H, $=C(CH_3)_2$], 2.32–2.44, 2.57–2.67 (2 m, 2 H, H-5), 3.45–3.54, 3.83–3.92 (2 m, 2 H, THP), 3.95, 4.01 [2 d, 1 H, $J_{AB} = 11.0$ Hz, –C(*H*)H–OTHP], 4.13 (q, 2 H, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 4.17–4.27 [m, 4 H, $-P(O)(OCH_2CH_3)_2$], 4.29 [d, 1 H, $J_{AB} = 11.0$ Hz, –C(H)*H*–OTHP], 4.58 (m, 1 H, acetal), 5.64–5.72 (m, 1 H, H-4), 5.85, 5.86 (2 d, 1 H, $J = 1.2$ Hz, vinylic); selected ^{13}C NMR data ($CDCl_3$): δ 103.85, 104.04 (2 d, $J_{C,P} = 3$ Hz, C-2), 125.00, 125.20, 134.62, 134.80 (C-6, C-7), 165.10–165.46 (m, C-3, C=O). Anal. $C_{27}H_{51}O_9PSi$: C, H.

*(4S)-(2Z)-Ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-7-methyl-6-[(2-tetrahydropyran-2-yloxy)methyl]-3-[(trimethylsilyl)methyl]-2,6-octadienoate* (**19**) *and (4S)-(2Z)-ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-7-methyl-6-[2-(trimethylsilyl)ethyl]-3-[(trimethylsilyl)methyl]-2,6-octadienoate* (**20**). $Ni(acac)_2$ (ca. 40 mg) was added to a solution of **18** (*Z* : *E* 9 : 1) (1.20 g, 2.07 mmol) in dry Et_2O (5 ml) under nitrogen at room temperature and then Me_3SiCH_2MgCl (ca. 4.0 mmol, 1.5 M in Et_2O) and $Ni(acac)_2$ (ca. 40 mg) were added in portions. The reaction was carefully monitored by TLC (heptane–EtOAc 3 : 1). After 2 h the reaction mixture was diluted with ether and washed with 1.0 M HCl, $NaHCO_3$ (sat.) and brine. Drying (Na_2SO_4) and evaporation of the solvent at reduced pressure was followed by column chromatography (heptane–EtOAc 20 : 1) of the residue to give **19** (oil, 560 mg, 53%) as a diastereomeric mixture and **20** (oil, 216 mg, 21%).

19: R_f (3 : 1) 0.59; $[\alpha]_D^{20} + 58°$ (*c* 1.10, $CDCl_3$); ^1H NMR ($CDCl_3$): δ − 0.06, −0.03 [2 s, 6 H, $-Si(CH_3)_2-$], 0.08, 0.09 (2 s, 9 H, TMS), 0.89 (s, 9 H, *t*-Bu), 1.28 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.48–1.88 [m, 7 H, THP,–C(*H*)H–TMS], 1.75, 1.76 [2 s, 6 H, $=C(CH_3)_2$], 2.29–2.48 (m, 2 H, H-5), 2.92, 2.93 [2 d, 1 H, $J_{AB} = 11.6$

Hz, 11.8 Hz, –C(H)*H*–TMS], 3.48–3.55, 3.86–3.93 (2 m, 2 H, THP), 3.96, 4.05 [2 d, 1 H, J_{AB} = 11.2 Hz, 11.4 Hz, –C(*H*)H–OTHP], 4.13 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.10–4.18 (m, 1 H, H-4), 4.26, 4.34 [2 d, 1 H, J_{AB} = 11.4 Hz, J_{AB} = 11.2 Hz, –C(H)*H*–OTHP], 4.57 (m, 1 H, acetal), 5.93 (s, 1 H, vinylic). Anal. $C_{27}H_{52}O_5Si_2$: C, H.

20: R_f (3 : 1) 0.75; $[\alpha]_D^{20}$ + 71° (*c* 1.30, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ – 0.06, – 0.04 [2 s, 6 H, –Si(CH_3)$_2$–], 0.00, 0.08 (2 s, 18 H, TMS), 0.53 (m, 2 H, –CH_2CH_2–TMS), 0.89 (s, 9 H, *t*-Bu), 1.28 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.63, 1.66 [2 s, 6 H, =C(CH_3)$_2$], 1.67 [d, 1 H, J_{AB} = 11.7 Hz, –C(*H*)H–TMS), 1.85–2.14 (m, 2 H, –CH_2CH_2–TMS), 2.14–2.32 (m, 2 H, H-5), 2.98 [dd, 1 H, J_{AB} = 11.7 Hz, J = 0.7 Hz, –C(H)*H*–TMS], 4.07 (m, 1 H, H-4), 4.13 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 5.94 (dd, 1 H, J = 1.0 Hz, 0.7 Hz, vinylic). Anal. $C_{26}H_{54}O_3Si_3$: C, H.

*(4S)-(2Z)-Ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2,6-octadienoate* (**21**) *and (4S)-(2Z)-ethyl 4-hydroxy-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2,6-octadienoate* (**22**). Pyridinium tosylate (100 mg, 0.40 mmol) was added to **19** (466 mg, 0.90 mmol) dissolved in 2-propanol (10 ml). The reaction mixture was stirred at 50°C for 11 h and, after cooling, ether (ca. 100 ml) was added. The solution was washed with $NaHCO_3$ (sat.) and brine, and dried (Na_2SO_4) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc 7 : 1 then 3 : 1) of the residue gave **21** (oil, 234 mg, 60%) and **22** (oil, 30 mg, 11%). Recovered starting material (108 mg, 23%) was also isolated.

21: R_f (3 : 1) 0.40; $[\alpha]_D^{20}$ + 70° (*c* 0.60, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ – 0.02, 0.01 [2 s, 6 H, –Si(CH_3)$_2$–], 0.10 (s, 9 H, TMS), 0.91 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.72, 1.73 [2 s, 6 H, =C(CH_3)$_2$], 1.77 [d, 1 H, J_{AB} = 11.7 Hz, –C(*H*)H–TMS], 2.37 (dd, 1 H, J_{AB} = 14.0 Hz, J = 9.5 Hz, H-5), 2.55 (dd, 1 H, J_{AB} = 14.0 Hz, J = 3.0 Hz, H-5), 2.94 [dd, 1 H, J_{AB} = 11.7 Hz, J = 1.0 Hz, –C(H)*H*–TMS], 4.03 [d, 1 H, J_{AB} = 12.2 Hz, –C(*H*)HOH], 4.13 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.16 (ddd, 1 H, J = 9.5, 3.0, 1.0 Hz, H-4), 4.27 [d, 1 H, J_{AB} = 12.2 Hz, –C(H)*H*OH], 5.89 (dd, 1 H, J = 1.0 Hz, 1.0 Hz, vinylic). Anal. $C_{22}H_{44}O_4Si_2$: C, H.

22: R_f (3 : 1) 0.20; $[\alpha]_D^{20}$ + 89° (*c* 1.06, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 9 H, TMS), 1.27 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 1.76, 1.80 [2 s, 6 H, =C(CH_3)$_2$], 1.83 [d, 1 H, J_{AB} = 11.5 Hz, –C(*H*)H–TMS], 2.11 (dd, 1 H, J_{AB} = 14.6 Hz, J = 9.3 Hz, H-5), 2.14 (s, 2 H, br, –OH), 2.75 (d, 1 H, J_{AB} = 14.6 Hz, H-5), 2.95 [dd, 1 H, J_{AB} = 11.5 Hz, J = 0.9 Hz, –C(H)*H*–TMS], 3.96 [d, 1 H, J_{AB} = 11.6 Hz, –C(*H*)HOH], 4.07 (m, 1 H, H-4), 4.13, 4.14 (2 q, 2 H, J = 7.3 Hz, CH_2CH_3), 4.43 [d, 1 H, J_{AB} = 11.6 Hz, –C(H)*H*OH], 5.94 (s, 1 H, vinylic). Anal. $C_{16}H_{30}O_4Si$: C, H.

*(4S,6R)-(2Z)-Ethyl 4-(*tert*-butyldimethylsilyl)oxy]-6,7-epoxy-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2-octenoate* (**4**). (–)-D-Diethyl tartrate (0.077 ml, 0.45 mmol) and titanium tetraisopropoxide (0.11 ml, 0.37 mmol) were added to a mixture of **21** (586 mg, 1.37 mmol) and powdered molecular sieves (0.22 g, 4 Å, activated at 170°C under vacuum) in dry CH_2Cl_2 (7.5 ml) under nitrogen at – 15°C. The mixture was stirred for 10–15 min at – 15°C and the temperature was then lowered to – 40°C. At this temperature *tert*-butyl hydroperoxide (anhydrous, 0.70 ml, 2.1 mmol, 3.0 M in toluene) was added. After 50 min of stirring at this temperature a solution of $FeSO_4$ (0.67 g) and tartaric acid (0.30 g) in water (4 ml) was added followed by ether (25 ml). Stirring was continued at room temperature for 20 min and the organic phase was then washed with brine and dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc 6 : 1) gave **4** (oil, 595 mg, 98%, 92% d.e. as determined by ^{1}H NMR spectroscopy): R_f (3 : 1) 0.30; $[\alpha]_D^{20}$ + 65° (*c* 0.46, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.06, 0.13 [2 s, 6 H, –Si(CH_3)$_2$–], 0.09 (s, 9 H, TMS), 0.94 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.34 [s, 6 H, >C(CH_3)$_2$], 1.74 [d, 1 H, J_{AB} = 11.7 Hz, –C(*H*)H–TMS], 1.90 (dd, 1 H, J_{AB} = 14.5 Hz, J = 9.5 Hz, H-5), 2.06 (dd, 1 H, J_{AB} = 14.5 Hz, J = 2.7 Hz, H-5), 2.50 (dd, 1 H, J = 3.4, 6.6 Hz, br, –OH), 2.85 [dd, 1 H, J_{AB} = 11.7 Hz, J = 1.0 Hz, –C(H)*H*–TMS], 3.72 [dd, 1 H, J_{AB} = 12.2 Hz, J = 3.4 Hz, –C(H) HOH], 3.82 [dd, 1 H, J_{AB} = 12.2 Hz, J = 6.6 Hz, –C(H)*H*OH], 4.13 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.24 (ddd, 1 H, J = 9.5, 2.7, 1.0 Hz, H-4), 5.87 (dd, 1 H, J = 1.0 Hz, 1.0 Hz, vinylic); ^{13}C NMR ($CDCl_3$): δ – 4.45, – 3.82 [–Si(CH_3)$_2$–], – 0.05 (TMS), 14.57 (CH_2CH_3), 18.30 [–*C*(CH_3)$_3$], 20.66, 22.46 [>C(CH_3)$_2$], 23.12 (–CH_2–TMS), 26.09 [–C(CH_3)$_3$], 36.29 (C-5), 59.48 (CH_2CH), 63.20, 63.94, 65.15, 74.54 (epoxide, –CH_2OH, C-4), 111.52 (C-2), 164.43 (C-3), 167.22 (C=O). Anal. $C_{22}H_{44}O_5Si_2$: C, H.

*(4S,6S)-(2Z)-Ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-6,7-epoxy-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2-octenoate* (**23**). The experiment was performed as described for **4** using **21** (241 mg, 0.562 mmol) as starting material and (+)-L-diethyl tartrate instead of (–)-D-diethyl tartrate. The reaction mixture was stirred for 2 h. Column chromatography (heptane–EtOAc 10 : 1) gave **23** (oil, 216 mg, 86%, 67% d.e. as determined by ^{1}H NMR spectroscopy): R_f (3 : 1) 0.30; $[\alpha]_D^{20}$ + 79° (*c* 0.72, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.06 [s, 3 H, –Si(CH_3)$_2$–], 0.09 (s, 9 H, TMS), 0.10 (s, 3 H, [–Si(CH_3)$_2$–], 0.96 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.35, 1.39 [2 s, 6 H, >C(CH_3)$_2$], 1.70 [d, 1 H, J_{AB} = 12.1 Hz, –C(*H*)H–TMS], 1.82 (dd, 1 H, J_{AB} = 14.5 Hz, J = 3.4 Hz, H-5), 2.31 (dd, 1 H, J_{AB} = 14.5 Hz, J = 9.0 Hz, H-5), 2.93 [dd, 1 H, J_{AB} = 12.1 Hz, J = 1.0 Hz, –C(H)*H*–TMS], 3.66–3.88 (m, 2 H, –CH_2OH), 4.13 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.28 (ddd, 1 H, J = 3.4 Hz, 9.0, 1.0 Hz, H-4), 5.88 (dd, 1 H, J = 1.0 Hz, 1.0 Hz, vinylic); ^{13}C NMR ($CDCl_3$): δ – 4.74, – 3.94 [–Si(CH_3)$_2$–], – 0.18 (TMS),

14.50 (CH_2CH_3), 18.18 [$-C(CH_3)_3$], 20.62, 21.95, 22.68 [$>C(CH_3)_2$, $-CH_2$–TMS], 26.04 [$-C(CH_3)_3$], 38.66 (C-5), 59.45 (CH_2CH_3), 62.26, 63.70, 65.56, 74.63 (epoxide, $-CH_2OH$, C-4), 111.52 (C-2), 164.00 (C-3), 167.09 (C=O). Anal. $C_{22}H_{44}O_5Si_2$: C, H.

*(1R,3S,5S)-Ethyl 5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-3-hydroxymethyl-2,2-dimethyl-6-methylenecyclohexanecarboxylate* (**24**). $BF_3 \cdot OEt_2$ (472 µl, 0.472 mmol, 1.0 M in CH_2Cl_2) was added to a solution of **4** (210 mg, 0.472 mmol) in dry CH_2Cl_2 (25 ml) under nitrogen at 0°C. The reaction mixture was stirred for 10 min after which $NaHCO_3$ (sat., 5 ml) was added followed by ether (50 ml). The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure and column chromatography of the residue (heptane–EtOAc, 5 : 1) gave **24** (oil, 141 mg, 80%): R_f (1 : 1) 0.48; $[\alpha]_D^{20} + 81°$ (*c* 1.10, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.08 [s, 6 H, $-Si(CH_3)_2-$], 0.92 (s, 9 H, *t*-Bu), 0.97, 1.11 [2 s, 6 H, $>C(CH_3)_2$], 1.27 (t, 3 H, $J = 7.0$ Hz, CH_2CH_3), 1.61 (dd, 1 H, $J_{AB} = 13.2$ Hz, $J = 11.7$ Hz, H-4), 2.18 (dd, 1 H, $J_{AB} = 13.2$ Hz, $J = 5.1$ Hz, H-4), 2.38 (dd, 1 H, $J = 3.7$, 8.3 Hz, br, $-CH_2OH$), 3.17 (s, 1 H, H-1), 3.33 [dd, 1 H, $J_{AB} = 11.0$ Hz, $J = 8.3$ Hz, $-C(H)HOH$], 3.64 [dd, 1 H, $J_{AB} = 11.0$ Hz, $J = 3.7$, $-C(H)HOH$], 4.16, 4.17 (2 dq, 2 H, $J_{AB} = 10.5$ Hz, $J = 7.0$ Hz, CH_2CH_3), 4.63 (dddd, 1 H, $J = 11.7$, 5.1, 2.0, 2.0 Hz, H-5), 5.00, 5.28 (2 dd, 2 H, $J = 2.0$, 2.0 Hz, vinylic), 5.72 (s, 1 H, br, *tert*-OH); ^{13}C NMR ($CDCl_3$): δ −4.95 [$-Si(CH_3)_2-$], 14.10 (CH_2CH_3), 18.51 [$-C(CH_3)_3$], 21.24, 25.53 [$>C(CH_3)_2$], 25.96 [$-C(CH_3)_3$], 40.19 (C-2), 42.39 (C-4). 61.91 (CH_2CH_3), 64.12 (C-1), 67.05 (C-5), 67.32 ($-CH_2OH$), 75.88 (C-3), 111.96 ($=CH_2$), 144.10 (C-6), 175.89 (C=O). Anal. $C_{19}H_{36}O_5Si$: C, H.

Acetonide **25**. $BF_3 \cdot OEt_2$ (714 µl, 0.714 mmol, 1.0 M in CH_2Cl_2) was added to a solution of **24** (266 mg, 0.714 mmol) and acetone (2.5 ml) in dry CH_2Cl_2 (27 ml) under nitrogen at 0°C. After 3 min of stirring $NaHCO_3$ (sat., 3 ml) was added followed by ether (50 ml). The organic phase was washed with brine and dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure to give a quantitative yield of **27** (295 mg, pure by ^{1}H NMR spectroscopy). Column chromatography (heptane–EtOAc 10 : 1) gave **25** (oil, 282 mg, 96%): R_f (1 : 1) 0.73; $[\alpha]_D^{20} + 27°$ (*c* 0.30, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.08, 0.09 [2 s, 6 H, $-Si(CH_3)_2-$], 0.92 (s, 9 H, *t*-Bu), 0.97, 1.14 [2 s, 6 H, $>C(CH_3)_2$], 1.26 (t, 3 H, $J = 7.2$ Hz, CH_2CH_3), 1.38, 1.39 (2 s, 6 H, acetonide), 1.80 (dd, 1 H, $J_{AB} = 13.4$ Hz, $J = 6.8$ Hz, H-4), 2.11 (dd, 1 H, $J_{AB} = 13.4$ Hz, $J = 4.3$ Hz, H-4), 3.17 (s, 1 H, H-1), 3.86 [d, 1 H, $J_{AB} = 8.9$ Hz, br, $-C(H)HO-$], 4.07 [d, 1 H, $J_{AB} = 8.9$ Hz, $-C(H)HO-$], 4.11, 4.15 (2 dq, 2 H, $J_{AB} = 10.9$ Hz, $J = 7.2$ Hz, CH_2CH_3), 4.71 (s, 1 H, br, sharpens to dd at 60°C, H-5), 4.86 (m, 1 H, vinylic), 5.10 (s, 1 H, vinylic). Anal. $C_{22}H_{40}O_5Si$: C, H.

*Acetonide of (3S,5S)-ethyl 3-[(*tert*-butyldimethylsilyl)-oxy]-5-hydroxy-5-hydroxymethyl-2,6,6-trimethylcyclohex-1-enecarboxylate* (**3**) *and acetonide of (1S,3S,5S)-ethyl 5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-3-hydroxymethyl-2,2-dimethyl-6-methylenecyclohexanecarboxylate* (**26**). A solution of **25** (190 mg, 0.460 mmol) in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.0 ml) was stirred under nitrogen at 185°C for 1 h. After cooling, ether (100 ml) was added and the solution was washed with 1.0 M HCl (10 ml), $NaHCO_3$ (sat.) and brine and dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to give 180 mg of an oil. GLC analysis (RSL 150 capillary column, 9.7 m, 200°C) of this crude product showed 7% of **25** (retention time: 3.38 min), 9% of **26** (3.92 min) and 83% of the conjugated product **3** (4.30 min). This mixture could not be fully separated by column chromatography (heptane–EtOAc 150 : 1 then 100 : 1) although pure fractions of **3** (oil, 114 mg, 60%) and **26** (oil, 5 mg, 3%) were collected together with a fraction containing a mixture of the three compounds (57 mg, 30%).

3: R_f (1 : 1) 0.72; $[\alpha]_D^{20} + 2°$ (*c* 1.29, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.09 [s, 6 H, $-Si(CH_3)_2-$], 0.90 (s, 9 H, *t*-Bu), 1.08, 1.17 [2 s, 6 H, $>C(CH_3)_2$], 1.32 (t, 3 H, $J = 7.0$ Hz, CH_2CH_3), 1.36, 1.46 (2 s, 6 H, acetonide), 1.70 [d, 3 H, $J = 1.0$ Hz, $-C(CH_3)=C<$], 1.89 (dd, 1 H, $J_{AB} = 13.2$ Hz, $J = 8.3$ Hz, H-4), 2.22 (dd, 1 H, $J_{AB} = 13.2$ Hz, $J = 5.8$ Hz, H-4), 3.76, 3.93 (2 d, 2 H, $J_{AB} = 8.7$ Hz, $-CH_2O-$), 4.24 (q, 2 H, $J = 7.0$ Hz, CH_2CH_3), 4.34 (ddq, 1 H, $J = 8.3$, 5.8, 1.0 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ −4.84, −4.20 [$-Si(CH_3)_2-$], 14.30 (CH_2CH_3), 17.09 [$-C(CH_3)=C<$], 18.03 [$-C(CH_3)_3$], 21.56, 24.89 [$>C(CH_3)_2$], 25.82 [$-C(CH_3)_3$], 26.26, 28.07 [$>C(CH_3)_2$ of the acetonide], 38.88 (C-6), 38.90 (C-4), 60.36 (CH_2CH_3), 68.68, 69.76 ($-CO_2O-$, C-3), 84.78 (C-5), 109.58 [$>C(CH_3)_2$ of the acetonide], 135.04, 135.52 (C-1, C-2), 169.76 (C=O); High resolution MS, *m/z*: Calcd. [*M*] 412.263 ± 0.003. Found [M^+] 412.265. Anal. $C_{22}H_{40}O_5Si$: C, H.

26: R_f (1 : 1) 0.73; $[\alpha]_D^{20} - 5°$ (*c* 0.20, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.08, 0.08 [2 s, 6 H, $-Si(CH_3)_2-$], 0.92 (s, 9 H, *t*-Bu), 1.01, 1.02 [2 s, 6 H, $>C(CH_3)_2$], 1.28 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.39, 1.45 (2 s, 6 H, acetonide), 1.73 (dd, 1 H, $J_{AB} = 13.0$ Hz, $J = 11.4$ Hz, H-4), 2.06 (dd, 1 H, $J_{AB} = 13.0$ Hz, $J = 5.4$ Hz, H-4), 3.35 (s, 1 H, H-1), 3.59, 3.96 (2 d, 2 H, $J_{AB} = 8.8$ Hz, $-CH_2O-$), 4.15, 4.18 (2 dq, 2 H, $J_{AB} = 10.9$ Hz, $J = 7.1$ Hz, CH_2CH_3), 4.34 (m, 1 H, H-5), 4.86, 5.23 (2 m, 2 H, vinylic); ^{13}C NMR ($CDCl_3$): δ −4.99, −4.93 [$-Si(CH_3)_2-$], 14.23 (CH_2CH_3), 18.29 [$-C(CH_3)_3$], 19.23, 21.57 [$>C(CH_3)_2$], 25.84 [$-C(CH_3)_3$], 26.32, 27.70 [$>C(CH_3)_2$ of the acetonide], 40.69 (C-2), 44.16 (C-4), 54.27 (C-1), 60.00 (CH_2CH_3), 69.68, 70.14 ($-CH_2O-$, C-5), 86.17 (C-3), 109.78 [$>C(CH_3)_2$ of the acetonide], 145.21 (C-6), 171.37 (C=O). Anal. $C_{22}H_{40}O_5Si$: C, H.

Acetonide of (3S,5S)-ethyl 3,5-dihydroxy-5-hydroxymethyl-2,6,6-trimethylcyclohex-1-ene-carboxylate (**27**).

Tetrabutylammonium fluoride (320 µl, 0.320 mmol, 1.0 M in THF) was added to a solution of **3** (65 mg, 0.158 mmol) in dry THF (0.5 ml) under nitrogen at room temperature. After 2 h of stirring, ether (100 ml) was added and the solution was washed with brine and dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure. Column chromatography (heptane–EtOAc 3 : 1) of the residue gave **27** (oil, 42 mg, 89%): R_f (1 : 1) 0.32; $[\alpha]_D^{20} + 10°$ (*c* 0.87, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 1.09, 1.17 [2 s, 6 H, $>C(CH_3)_2$], 1.32 (t, 3 H, $J = 7.0$ Hz, CH_2CH_3), 1.36, 1.46 (2 s, 6 H, acetonide), 1.78 [d, 3 H, $J = 1.0$ Hz, $-C(CH_3)=C<$], 1.88 (dd, 1 H, $J_{AB} = 13.1$ Hz, $J = 8.5$ Hz, H-4), 2.38 (dd, 1 H, $J_{AB} = 13.1$ Hz, $J = 6.1$ Hz, H-4), 3.76, 3.95 (2 d, 2 H, $J_{AB} = 8.8$ Hz, $-CH_2O-$), 4.25 (q, 2 H, $J = 7.0$ Hz, CH_2CH_3), 4.32 (m, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 14.30 (CH_2CH_3), 16.31 [$-C(CH_3)=C<$], 21.56, 25.04 [$>C(CH_3)_2$], 26.24, 27.95 [$>C(CH_3)_2$ of the acetonide], 38.71 (C-6), 39.15 (C-4), 60.49 (CH_2CH_3), 68.36, 69.81 ($-CH_2O-$, C-3), 84.64 (C-5), 109.76 [$>C(CH_3)_2$ of the acetonide], 133.78, 136.55 (C-1, C-2), 169.57 (C=O). Anal. $C_{16}H_{26}O_5$: C, H.

*(4S)-(2Z)-Ethyl 4-[(*tert*-butyldimethylsilyl]oxy]-8-hydroxy-7,7-dimethyl-6-oxo-3-[(trimethylsilyl)methyl]-2-octenoate* (**28**). The experiment was performed as described for **24** using **23** (189 mg, 0.425 mmol) as the starting material. Column chromatography (heptane–EtOAc 10 : 1) gave **28** (oil, 59 mg, 31%), and *(4S,6S)-(2Z)-ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-7-fluoro-6-hydroxy-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)-methyl]-2-octenoate* (oil, 23 mg, 12%). A small fraction, ca. 10 mg, of less polar products was also collected.

28: R_f (3 : 1) 0.29; $[\alpha]_D^{20} + 42°$ (*c* 0.58, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.04, 0.05 [2 s, 6 H, $-Si(CH_3)_2-$], 0.10 (s, 9 H, TMS), 0.87 (s, 9 H, *t*-Bu), 1.13, 1.14 [2 s, 6 H, $-C(CH_3)_2-$], 1.28 (t, 3 H, $J = 7.0$ Hz, CH_2CH_3), 1.48 [d, 1 H, $J_{AB} = 11.8$ Hz, $-C(H)$–TMS], 2.34 (t, 1 H, $J = 6.8$ Hz, br, –OH), 2.48 (dd, 1 H, $J_{AB} = 17.4$ Hz, $J = 1.9$ Hz, H-5), 2.84 (dd, 1 H, $J_{AB} = 17.4$ Hz, $J = 8.7$ Hz, H-5), 2.96 [dd, 1 H, $J_{AB} = 11.8$ Hz, $J = 1.2$ Hz, $-C(H)$–TMS], 3.55, 3.58 (2 dd, 2 H, $J_{AB} = 11.3$ Hz, $J = 6.8$ Hz, H-8), 4.14 (q, 2 H, $J = 7.0$ Hz, Et), 4.65 (ddd, 1 H, $J = 1.9$, 8.7, 1.5 Hz, H-4), 5.96 (dd, 1 H, $J = 1.2$, 1.5 Hz, vinylic); ^{13}C NMR ($CDCl_3$): δ −4.93, −4.31 [$-Si(CH_3)_2-$], −0.49 (TMS), 14.39 (CH_2CH_3), 18.03 [$-C(CH_3)_3$], 21.09, 21.14, 22.99 [$-C(CH_3)_2-$, $-CH_2$–TMS), 25.84 [$-C(CH_3$], 45.83 (C-5), 49.20 (C-7), 59.36 (CH_2CH_3), 69.44, 71.58 (C-8, C-4), 110.95 (C-2), 164.31 (C-3), 167.43 (C-1), 213.71 (C-6). Anal. $C_{22}H_{44}O_5Si_2$: C, H.

Data for (4*S*,6*S*)-(2*Z*)-ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-7-fluoro-6-hydroxy-6-hydroxymethyl-7-methyl-3-[(trimethylsilyl)methyl]-2-octenoate: R_f (3 : 1) 0.38; $[\alpha]_D^{20} + 39°$ (*c* 0.58, $CDCl_3$); ^1H NMR ($CDCl_3$): δ 0.07 [s, 3 H, $-Si(CH_3)_2-$], 0.10 (s, 9 H, TMS), 0.16 [s, 3 H, $-Si(CH_3)_2-$], 0.94 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, $J = 7.1$ Hz, CH_2CH_3), 1.39, 1.40 [2 d, 6 H, $J_{H,F} = 22.7$ Hz, $J_{H,F} = 22.8$ Hz, $-C(CH_3)_2F$], 1.85 [d, 1 H, $J_{AB} = 11.7$ Hz, $-C(H)$–TMS], 1.88 (dd, 1 H, $J_{AB} = 14.8$ Hz, $J = 9.0$ Hz, H-5), 1.95 (dd, 1 H, $J_{AB} = 14.8$ Hz, $J = 2.4$ Hz, H-5), 2.83 [dd, 1 H, $J_{AB} = 11.7$ Hz, $J = 1.0$ Hz, $-C(H)$–TMS], 3.65, 3.84 (2 d, 2 H, $J_{AB} = 11.8$ Hz, $-CH_2OH$), 4.13, 4.14 (2 dq, 2 H, $J_{AB} = 10.9$ Hz, $J = 7.1$ Hz, CH_2CH_3), 4.60 (ddd, 1 H, $J = 9.0$, 2.4, 1.0 Hz, H-4), 5.84 (dd, 1 H, $J = 1.0$, 1.0 Hz, vinylic); ^{13}C NMR ($CDCl_3$): δ −5.03, −3.48 [$-Si(CH_3)_2-$], −0.28 (TMS), 14.37 (CH_2CH_3), 17.92 [$-C(CH_3)_3$], 22.60, 22.61 [2 d, $J_{C,F} = 25$ Hz, $J_{C,F} = 24$ Hz, $-C(CH_3)_2F$], 22.87 ($-CH_2$–TMS), 25.83 [$-C(CH_3)_3$], 38.61 (d, $J_{C,F} = 3$ Hz, C-5), 59.45 (CH_2CH_3), 64.66 (d, $J_{C,F} = 3$ Hz, $-CH_2OH$), 75.27 (C-4), 75.84 (d, $J_{C,F} = 22$ Hz, C-6), 99.89 (d, $J_{C,F} = 171$ Hz, C-7), 111.84 (C-2), 164.21 (C-3), 167.16 (C=O). Anal. $C_{22}H_{45}FO_5Si_2$: C, H.

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