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Preparation of (2*E*,4*E*,6*S*,7*S*,10*E*,12*E*,14*S*,15*S*,1′*S*)-7,15-Bis(1′-hydroxymethylethyl)-6,14-dimethyl-8,16-dioxa-2,4,10,12-cyclohexadecatetraene-1,9-dione. – A Building Block for the Synthesis of Elaiophylin

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The title compound **2**, which is considered to be a possible key intermediate for a synthesis of the antibiotic elaiophylin (**1**), has been obtained by cyclodimerisation of the hydroxy acids **18** and **27** using *Yamaguchi's* method. The hydroxy acids **18** and **27** are synthesised by *Wittig* reaction of the (phosphoranylidene)crotonate **14** with the protected 3,5-dihydroxy-2,4-dimethylpentanals **12** and **23**, respectively. These are constructed, in turn, by diastereoselective *Evans* aldol reaction between (*S*)-3-benzyloxy-2-methylpropanal (**4**) and (*R*)-4-isopropyl-3-propionyl-2-oxazolidinone.

Herstellung von (2*E*,4*E*,6*S*,7*S*,10*E*,12*E*,14*S*,15*S*,1′*S*)-7,15-Bis(1′-hydroxymethylethyl)-6,14-dimethyl-8,16-dioxa-2,4,10,12-cyclohexadecatetraen-1,9-dion. – Ein Baustein für die Synthese von Elaiophylin

Die Titelverbindung **2** wird als Schlüsselprodukt für die Synthese des Antibiotikums Elaiophylin (**1**) erachtet. Sie wurde durch dimerisierende Cyclisierung der Hydroxysäuren **18** und **27** nach der Methode von *Yamaguchi* erhalten. Die Säuren **18** und **27** wurden durch *Wittig*-Reaktion des (Phosphoranyliden)crotonats **14** mit den geschützten 3,5-Dihydroxy-2,4-dimethylpentanalen **12** bzw. **23** hergestellt. Letztere wurden über eine diastereoselektive *Evans*-Aldolisierung zwischen (*S*)-3-Benzyloxy-2-methylpropanal (**4**) und (*R*)-4-Isopropyl-3-propionyl-2-oxazolidinon erhalten.

A) Introduction

In a previous publication[1] we have described the synthesis of a model system for the macrodiolide elaiophylin (**1**).

Using the information which we obtained about the preparation and stability of the central ring, we have now accomplished the synthesis of the diol **2**, a key intermediate for the synthesis of **1**.

B) Preparation of the dihydroxypentanoic acid derivatives 5–7

(*R*)-3-Benzyloxy-2-methyl-1-propanol (**3**), available either from (*S*)-malic acid[2] or from (*S*)-methyl 3-hydroxy-2-methylpropionate[3], was oxidised to give the al-

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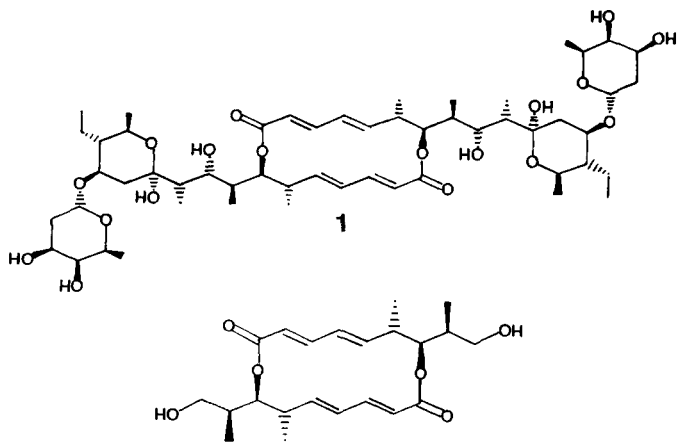
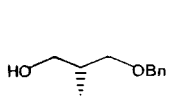


1

2

dehyde **4** using the *Swern* oxidation[4]. Aldol reaction between the (*Z*)-boron enolate of (*R*)-4-isopropyl-3-propionyl-2-oxazolidinone and the aldehyde **4** following *Evans*' method[5] gave the oxazolidinone **5** with greater than 97% diastereoselectivity[6]. The oxazolidinone group had now served its purpose, and was removed by one of two methods. Firstly, after protection of the hydroxy group of **5** using *tert*-butyldimethylsilyl triflate[7] to give the silyl ether **6**, removal of the chiral auxiliary was attempted using various complex hydride reducing agents. This invariably led to partial loss of the silyl protecting group[8]. Reductive cleavage using lithium tetrahydroborate gave the *bis*-protected triol derivative **8** in 33% yield. A second, more satisfactory, procedure involved methanolysis of **5** to give the methyl ester **7** (86%), followed by lithium tetrahydridoaluminate reduction to give the *mono*-protected triol **9** (96%).



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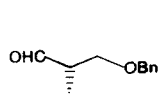

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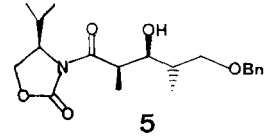

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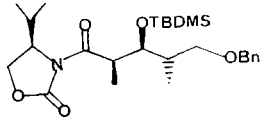

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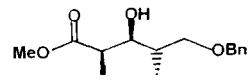

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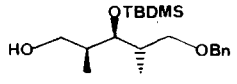

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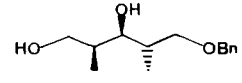

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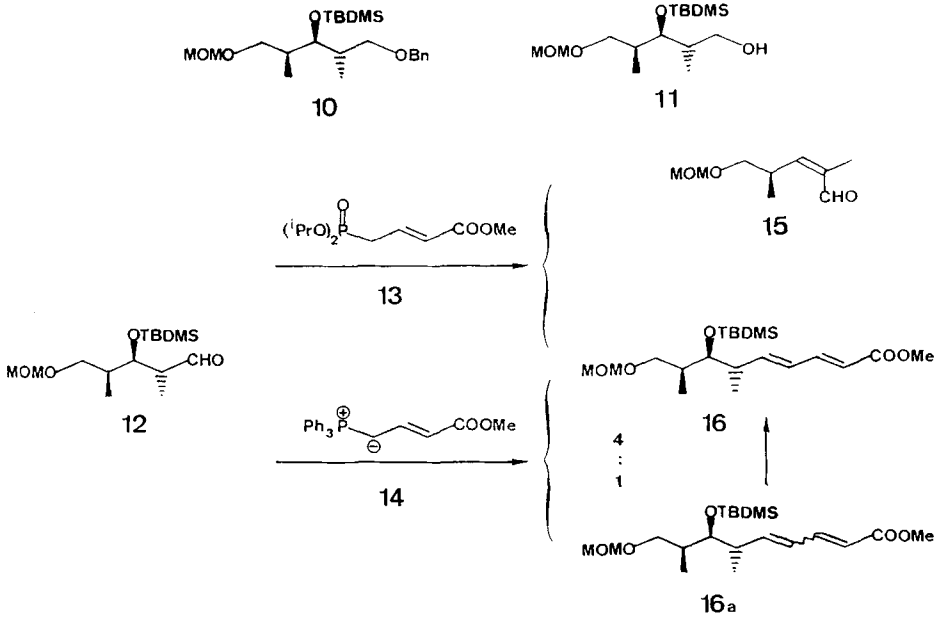
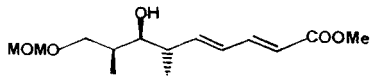
Bn = $CH_2C_6H_5$, TBDMS = Si(*tert*-C_4H_9)(CH_3)$_2$

From this point on the synthesis of the diol **2** was accomplished using two routes, which differed in the choice of protecting groups. The first route used the alcohol **8** as its starting point, whilst the second proceeded from the diol **9** *via* 1,3-dioxane derivatives. The dioxane route proved finally to be more efficient, proceeding from the ester **7** which was available in larger amounts. We describe both routes, however, because the open-chain intermediates derived from the alcohol **8** could be interesting building blocks for the synthesis of other natural products besides elaiophylin. The aim of both routes is next to adjust the oxidation state at carbon atoms 1 and 5 of the pentanoic acid derivatives **8** and **9** for further elaboration of the carbon framework.

C) MOM route

Protection of the free hydroxy group of **8** with chloromethyl methyl ether gave the fully protected triol **10**. Selective removal of the benzyl group using $Pd(OH)_2/H_2$ gave the alcohol **11** which, upon subsequent *Swern* oxidation[4], gave the aldehyde **12** in good yield. Treatment of this aldehyde with the enolate of the phosphonate **13** gave, at most, a 10% yield of the desired diene **16**. The major product was the unsaturated aldehyde **15**, the result of silanol elimination[9]. Evidently the enolate of **13** is too basic, for despite changes in the protecting group and variations in the conditions, the diene **16** could not be obtained in reasonable yield. *Wittig* reaction with the apparently less basic ylide **14**[10] gave a four to one mixture of the *E,E*-diene **16** and the three other possible stereoisomers **16a**, with one or two *Z* double bonds. The latter could be separated and partially isomerised to **16**, using iodine in dichloromethane.





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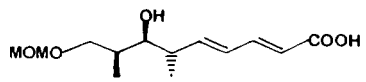

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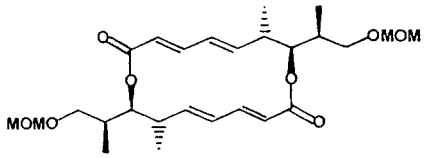

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Bn = $CH_2C_6H_5$, MOM = CH_2OCH_3, TBDMS = Si(*tert*-C_4H_9)$(CH_3)_2$

All attempts to cleave the silyl ether group in **16** with fluoride ion or mild bases were unsuccessful. With aqueous acid (0.1 N HCl in MeOH), however, it was possible to cleave the silyl ether, without cleavage of the MOM-protecting group to a significant extent, though to obtain high yields it was necessary to work the reaction up at 50% conversion. Hydrolysis of the ester **17** with 1 N potassium hydroxide finally gave the hydroxy acid **18**.

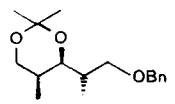
Cyclisation of the hydroxy acid **18** was achieved using the conditions employed for the model system[1]. Treatment of **18** with 2,4,6-trichlorobenzoyl chloride, and dimerisation of the mixed anhydride[11] under high dilution conditions, gave the crystalline macrodiolide **19** in 37% yield. Cleavage of the acetal with dimethylboron bromide[12] gave the title compound **2**.

D) Dioxane route

Protection of the diol **9** using 2,2-dimethoxypropane gave the dioxane derivative **20**. Removal of the benzyl group was achieved using lithium in ammonia following the procedure of *Kishi*[13], to give the alcohol **21** (86% from the diol **9**). Attempted hydrogenolysis of **20** using $Pd(OH)_2$ as catalyst gave a mixture of C-3 epimers, **21** and **22**, the result of acetal equilibration. *Swern* oxidation[4] of the alcohol **21** gave the aldehyde **23**, which was treated with the ylide **14** to give an analogous mixture of products (89%) to that obtained from the aldehyde **12**. The required *E,E*-diene **24** could not be easily separated from the other double-bond isomers, so purification was postponed to the next stage. The dioxane protecting group was removed by treatment with a catalytic amount of *p*-toluenesulfonic acid in methanol to give the diol **25** which could easily be separated from the other isomers by a single recrystallisation. The yield of pure diol from the diene **24** was 47%.

Selective protection of the primary hydroxy group of the diol **25** was achieved using 1-tritylpyridinium tetrafluoroborate[14] to give the hydroxy ester **26**. The mother liquors from the purification of the diol **25** could be treated with the same reagent to give a mixture of trityl-protected diene alcohols from which, after isomerisation using iodine in hexane, the pure hydroxy ester **26** could be isolated.

Thus the effective yield of diol **25** from the diene **24** was increased to 60%. The ester was hydrolysed to give the hydroxy acid **27** which was then converted into the mixed anhydride with 2,4,6-trichlorobenzoyl chloride, followed by cyclisation to give the macrodiolide **28** in 49% overall yield from the diol **25**. Removal of the trityl groups was then accomplished using *p*-toluenesulfonic acid in methanol to give the title compound **2** in 65% yield.



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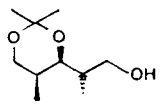

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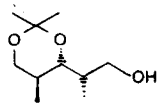

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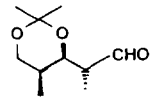

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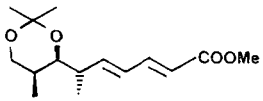

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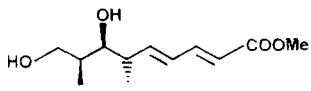

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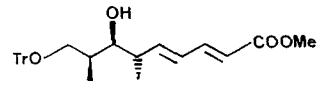

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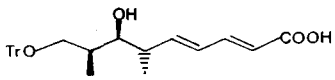

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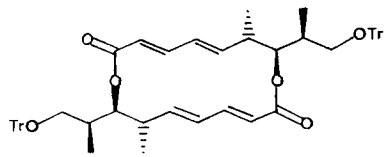

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Tr = $C(C_6H_5)_3$

The overall yield of the dioxane route (12% from the aldol adduct **5**) is four times as large as that from the MOM route. In addition, more of the intermediates are crystalline and there are no steps for which the use of partial conversion is necessary to achieve satisfactory yields.

Oxidation of the alcohol groups in **2** using *Swern's*[4] conditions gives the corresponding dialdehyde in high yield, and coupling with a suitable side chain should give the aglycone of elaiophylin[15] (**1**). The compounds **2**–**6**, **8**–**11**, **15**–**19**, and **25** showed no activity against bacteria, fungi, or yeast. Evidently the amphiphilic nature of elaiophylin[17], and possibly the ionophoric nature of the side chains, is responsible for its biological activity.

We thank Dr. *A. von Wartburg* and Dr. *W. Pache* (Sandoz AG, Basel) for carrying out the biological tests, and the staff of the analytical department of the ETH organic chemistry institute for obtaining the analytical data. We thank Dr. *H.-F. Chow* and Dr. *I. Paterson* for helpful discussion. This work was supported by a grant from the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* (Project Nr. 2.306–0.81). R.F.W.J. thanks the *Royal Society* for a fellowship in the European Exchange Programme.

Experimental

Melting points were determined with a Büchi/Tottoli melting point apparatus and are uncorrected. – The temperature of kugelrohr distillations is that of the air bath. – Merck Kieselgel 60 (silica, mesh size 0.040–0.063) was used for flash chromatography [18]. – Specific rotations were determined with a Perkin-Elmer 241 polarimeter using $CHCl_3$ as solvent at 25°C. The concentration is given in g/100 ml. – IR spectra were recorded using a Perkin-Elmer 297 spectrometer either as KBr discs or in $CHCl_3$ solution. – ^{1}H-NMR spectra were obtained with either a Varian EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument. ^{13}C NMR spectra were obtained using a Varian CFT-20 instrument. All spectra were recorded using TMS as internal standard in $CDCl_3$ as solvent. Signals marked with an asterisk (*) disappear on addition of D_2O. – Mass spectra were recorded at 70 eV on a Hitachi-Perkin-Elmer RMV 6M instrument. All reaction solvents, except for tetrahydrofuran (THF), were of *purissimum* quality. THF was distilled from potassium/benzophenone ketyl immediately before use. All reactions were carried out in oven-dried glassware under argon. Unless otherwise stated, organic extracts were dried with $MgSO_4$ and then concentrated using a rotary evaporator. Buffer solution of pH = 7 was prepared by dissolving potassium dihydrogen phosphate (85 g) and sodium hydroxide (14.5 g) in water (1 l).

(2S)-3-Benzyloxy-2-methylpropanal (**4**): A solution of DMSO (3.75 ml, 48 mmol) in dichloromethane (11 ml) was added to a solution of oxalyl chloride (2.2 ml, 24 mmol) in dichloromethane (35 ml) cooled to −65°C. After 2 min, a solution of the alcohol **3** (4.0 g, 22 mmol) in dichloromethane (9 ml) was added slowly. After a further 15 min, triethylamine (15.4 ml) was added and the mixture then allowed to warm to 0°C. The mixture was poured into water and extracted with dichloromethane (twice) and the combined organic extracts were washed with 0.5 N HCl (twice), saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. The organic extracts were dried and evaporated to yield the crude aldehyde **4** (4.09 g, 23 mmol) which was used without further purification. A sample was kugelrohr-distilled; b.p. 80°C/0.1 Torr; $[\alpha]_D$ = +30 (c = 1.29). – IR ($CHCl_3$): 1720 (s, CHO). – ^{1}H NMR (90 MHz): δ = 1.10 (d, J = 7 Hz, 3H, CH_3), 2.4–2.8 (m, 1H, 2-H), 3.65 (d, J = 6 Hz, 2H, 3-H_2), 4.50 (s, 2H, OCH_2Ph), 7.1–7.5 (m, 5H, Ar), 9.75 (d, J = 2 Hz, 1H, 1-H). – ^{13}C NMR: δ = 10.70, 46.81, 70.15, 73.30, 127.62, 128.42, 203.75. – MS: m/z = 134 (3%, $M^+ - CHO - CH_3$), 108 (23%), 107 (74%, OCH_2Ph^+), 92 (15%), 91 (100%, $C_7H_7^+$).

$C_{11}H_{14}O_2$ (178.2) Calc. C 74.15 H 7.92 Found C 73.95 H 8.07

(4R,2'R,3'S,4'S)-3-(5'-Benzyloxy-3'-hydroxy-2',4'-dimethylpentanoyl)-4-isopropyl-2-oxazolidinone (**5**): A solution of 1 N dibutylboron triflate in dichloromethane (23.8 ml, 24 mmol) and diisopropylethylamine (4.4 ml, 26 mmol) were successively added to a solution of (4*R*)-4-isopropyl-3-propionyl-2-oxazolidinone [5] (4.0 g, 22 mmol) in dichloromethane (44 ml) cooled to 0°C. After 1 h the solution was cooled to −78°C and the aldehyde **4** (3.95 g, 22 mmol) was added. The mixture was stirred at −78°C for 1 h and then at 0°C for 1.5 h, before being poured into phosphate buffer (pH = 7, 100 ml). The mixture was extracted with ether and the organic extracts were washed with saturated brine. After evaporation of solvent the residual oil was dissolved in methanol (72 ml) and then cooled to 0°C. Aqueous hydrogen peroxide (35%, 24 ml) was added slowly, and the solution was then stirred for 1 h at 0°C. The solvent was partially evaporated and the residue extracted with ether. The organic extracts were washed with saturated aqueous sodium hydrogen carbonate and saturated brine before being evaporated. The residue was then purified by flash chromatography using ether/petroleum ether (1:1) as eluant to give the aldol adduct **5** (5.93 g, 78%); m. p. 107.5–108°C; $[\alpha]_D$ = +45 (c = 0.98). – IR (KBr): 3500 (m, OH), 1780 (s, C=O),

1768 (s, C=O), 1675 (s, C=O). – ^{1}H NMR (300 MHz): δ = 0.88 and 0.90 [2d, *J* = 10 Hz, 6H, CH(C*H*$_3$)$_2$], 0.97 (d, *J* = 6.0 Hz, 3H, 2′-CH$_3$), 1.24 (d, *J* = 6.9 Hz, 3H, 4′-CH$_3$), 1.91–1.97 (m, 1H, 4′-H), 2.36–2.42 [m, 1H, C*H*(CH$_3$)$_2$], 3.54* (d, *J* = 3 Hz, OH), 3.58 (d, *J* = 5.5 Hz, 2H, 5′-H$_2$), 3.84 (ddd, *J* = 3.2, 4.6, and 6.5 Hz, 1H, 3′-H), 3.96 (dq, *J* = 3.5 and 6.9 Hz, 1H, 2′-H), 4.19 (dd, *J* = 10.9 and 18.2 Hz, 1H, 5-H), 4.21 (dd, *J* = 5.3 and 9.1 Hz, 1H, 5-H), 4.40–4.45 (m, 1H, 4-H), 4.50 (s, 2H, OCH$_2$Ph), 7.24–7.36 (m, 5H, Ar). – ^{13}C NMR: δ = 10.42 (q), 13.64 (q), 14.39 (q), 17.66 (q), 28.10 (d), 35.83 (d), 40.13 (d), 58.29 (d), 63.03 (d), 73.14 (t), 73.83, 74.20, 127.33 (d), 128.10 (d), 137.88 (s), 153.35 (s), 176.44 (s). – MS: *m/z* = 365 (0.5%, M$^+$ + 2), 364 (0.5%, M$^+$ + 1), 240 (26%), 91.5 (100%).

$C_{20}H_{29}NO_5$ (363.5) Calc. C 66.09 H 8.04 N 3.85 Found C 66.13 H 7.95 N 3.80

On a larger scale (100 mmol) it was observed that the yield of the required product was lower (50–60%). Consistent results could best be obtained by initial mixing of the diisopropylethylamine and dibutylboron triflate, followed by cooling of this solution to –78 °C, before addition of the propionyloxazolidinone and subsequent warming to 0 °C. In addition it was found that the crude product could be purified effectively by precipitation from ether solution using hexane.

(4R,2R,3′S,4′S)-3-[5′-Benzyloxy-3′-(tert-butyldimethylsilyloxy)-2′,4′-dimethylpentanoyl]-4-isopropyl-2-oxazolidinone (**6**): 2,6-Lutidine (1.59 ml, 13.8 mmol) and *tert*-butyldimethylsilyl triflate (1.89 ml, 8.3 mmol) were added to a solution of the aldol adduct **5** (2.00 g, 5.5 mmol) in dichloromethane (5.5 ml). The solution was stirred for 1.5 h at room temperature and then poured into a mixture of ether and saturated sodium hydrogen carbonate solution. The organic phase was separated and washed with saturated brine, dried (Na_2SO_4), and evaporated to give the silyl ether **6** (2.66 g, 100%), m. p. 60.5–62 °C. A sample was recrystallised from ether/hexane; $[\alpha]_D$ = –72 (*c* = 1.13). – IR (KBr): 1765 (s, C=O), 1700 (s, C=O). – ^{1}H NMR (300 MHz): δ = 0.05 [2s, 6H, Si(CH$_3$)$_2$], 0.83 and 0.86 [2d, *J* = 7.0 Hz, 6H, CH(C*H*$_3$)$_2$], 0.88 [s, 9H, C(CH$_3$)$_3$], 1.01 (d, *J* = 7.1 Hz, 3H, 4′-CH$_3$), 1.21 (d, *J* = 6.7 Hz, 3H, 2′-CH$_3$), 1.90–2.05 (m, 1H, 4′-H), 2.25–2.35 [m, 1H, C*H*(CH$_3$)$_2$], 3.20 (dd, *J* = 5.8 and 9.3 Hz, 1H, 5′-H), 3.76 (dd, *J* = 8.5 and 8.9 Hz, 1H, 3′-H), 4.00–4.06 (m, 3H, 5-H$_2$ and 2′-H), 4.23 (ddd, *J* = 2.6, 3.9, and 6.6 Hz, 1H, 4-H), 4.40 and 4.42 (2 d, *J* = 7 Hz, 2H, OCH$_2$Ph), 7.24–7.33 (m, 5H, Ar). – ^{13}C NMR: δ = –3.91, 14.72, 15.50, 17.94, 18.37, 26.11, 28.40, 39.07, 41.41, 58.49, 62.92, 72.08, 72.86, 75.03, 127.35, 128.31, 138.76, 153.38, 176.14. – MS: *m/z* = 477 (< 1%, M$^+$), 420 (14%, M$^+$ – C$_4$H$_9$), 91 (100%).

$C_{26}H_{43}NO_5Si$ (477.7) Calc. C 65.37 H 9.07 N 2.93 Found C 65.32 H 8.94 N 2.77

Methyl (2R,3S,4S)-5-benzyloxy-3-hydroxy-2,4-dimethylpentanoate (**7**): Sodium methoxide (2.04 g, 37.8 mmol) was suspended in methanol (270 ml) and the mixture was cooled to 0 °C. The oxazolidinone **5** (12.48 g, 34.3 mmol) was then added in one portion. The mixture was stirred for 20 min and then poured into phosphate buffer (pH = 7, 600 ml). The solution was extracted with dichloromethane (3 × 250 ml) and the combined organic extracts were dried and evaporated. The residue was purified by flash chromatography (15 × 5 cm column, eluant 1.5 l ether/hexane, 1:1) to give the methyl ester **7** (7.90 g, 86%). The chiral auxiliary could be recovered by flushing the column with methanol (600 ml). A sample of the ester **7** was kugelrohr-distilled; b. p. 150 °C/0.1 Torr; $[\alpha]_D$ = –16.7 (*c* = 1.0). – IR ($CHCl_3$): 3500 (m, OH), 1735 (s, CO_2Me). – ^{1}H NMR (300 MHz): δ = 0.92 (d, *J* = 7 Hz, 3H, CH$_3$), 1.19 (d, *J* = 7 Hz, 3H, CH$_3$), 1.89 (m, 1H, 4-H), 2.61 (dq, *J* = 4 and 7 Hz, 1H, 2-H), 3.46* (d, *J* = 3.6 Hz, 1H, OH), ABX system (δ$_A$ = 3.55, δ$_B$ = 3.63, *J*$_{AB}$ = 9.1 Hz, CH$_2$OBn), 3.69 (s, 3H, CO_2Me), 3.88 (m, 1H, 3-H), 4.51 (s, 2H, OCH$_2$Ph), 7.23–7.37 (m,

5H, Ar). – MS: m/z = 267 (< 1%, $M^+ + H$), 235 (1%, $M^+ - OCH_3$), 180 (3%), 142 (24%), 108 (20%), 107 (17%), 92 (17%), 91 (100%).

$C_{15}H_{22}O_4$ (266.3) Calc. C 67.65 H 8.33 Found C 67.93 H 8.53

(2S,3R,4S)-5-Benzyloxy-3-(tert-butyldimethylsilyloxy)-2,4-dimethyl-1-pentanol (**8**): Lithium tetrahydroborate (225 mg, 11.7 mmol) was added to a solution of the silyl ether **6** (4.48 g, 9.4 mmol) in THF (30 ml). The mixture was stirred for 2 d and then poured into phosphate buffer (pH = 7), then it was extracted with dichloromethane. The organic extracts were dried (Na_2SO_4), evaporated, and the residue was then purified by flash chromatography (eluant ether/hexane, 1:3) to give firstly the starting material **6** (0.63 g, 1.3 mmol, 14%) and then the alcohol **8** (1.09 g, 3.1 mmol, 33%); $[\alpha]_D$ = −3.4 (c = 1.07). – IR ($CHCl_3$): 3700–3250 (w, OH). – ^{1}H NMR (300 MHz): δ = 0.04 and 0.06 [2 s, 6H, $Si(CH_3)_2$], 0.87 (d, J = 10.7 Hz, 3H, CH_3), 0.88 [s, 9H, $C(CH_3)_3$], 0.97 (d, J = 7.0 Hz, 3H, CH_3), 1.85–1.89 (m, 1H, 2-H or 4-H), 2.03–2.07 (m, 1H, 2-H or 4-H), 3.31 (dd, J = 7.0 and 9.1 Hz, 1H), 3.47–3.58 (m, 2H), 3.56 (dd, J = 5.4 and 9.1 Hz, 1H), 3.76 (dd, J = 2.9 and 5.7 Hz, 1H), 4.46 and 4.50 (2d, J = 11.5 Hz, OCH_2Ph), 7.24–7.34 (m, 5H, Ar). – ^{13}C NMR: δ = −4.18, 11.84, 15.03, 18.33, 26.07, 37.77, 39.02, 66.21, 73.01, 73.10, 73.68, 127.35, 127.51, 127.60, 128.33, 138.58. – MS: m/z = 295 (< 1%, $M^+ - C_4H_9$), 203 (6%, $M^+ - BnOCH_2CHCH_3$), 91 (100%).

$C_{20}H_{36}O_3Si$ (352.6) Calc. C 68.13 H 10.29 Found C 68.74 H 10.53

(2S,3R,4S)-5-Benzyloxy-2,4-dimethyl-1,3-pentanediol (**9**): Lithium tetrahydridoaluminate (2.89 g, 76.2 mmol) was suspended in ether (100 ml) and cooled in an ice/water bath. The methyl ester **7** (7.9 g, 29.7 mmol) in ether (70 ml) was added dropwise over a period of 40 min. The cooling bath was removed after a further 45 min, and the mixture was then stirred for 2 h. The cooling bath was replaced and the reaction quenched by the addition of water (3 ml), aqueous potassium hydroxide (15% solution, 3 ml), and finally water (9 ml). The suspension was stirred for 15 min and then $MgSO_4$ was added, before filtration and washing of the solid with ether (150 ml). The filtrate was evaporated to give the diol **9** (6.76 g, 96%) as an oil which solidified on standing. A sample was recrystallised from hexane; m. p. 52–53.6 °C; $[\alpha]_D$ = +39.3 (c = 0.98) [lit.[13] $[\alpha]_D$ = +38.4 (c = 0.94)]. – IR ($CHCl_3$): 3460 (s, OH). – ^{1}H NMR (300 MHz): δ = 0.79 (d, J = 6.9 Hz, 3H, CH_3), 0.97 (d, J = 7.0 Hz, CH_3), 1.75 (m, 1H, 2-H or 4-H), 2.01 (m, 1H, 2-H or 4-H), 2.55* (m, 1H, OH), 3.46–3.80 (m, 5H, CH_2OH, $CHOH$ and CH_2Ph), 3.96* (br. s, OH), 4.53 (s, 2H, OCH_2Ph), 7.25–7.36 (m, 5H, Ar). – MS: m/z = 220 (< 1%, $M^+ - H_2O$), 179 (3%, $M^+ - CH_3CHCH_2OH$), 108 (28%, $BnOH^+$), 107 (38%), 91 (100%).

$C_{14}H_{22}O_3$ (238.3) Calc. C 70.56 H 9.30 Found C 70.83 H 9.22

(2S,3S,4S)-5-Benzyloxy-3-(tert-butyldimethylsilyloxy)-1-(methoxymethoxy)-2,4-dimethylpentane (**10**): A solution of the alcohol **8** (1.05 g, 2.9 mmol) diisopropylethylamine (1.5 ml), and chloromethyl methyl ether (0.5 ml) in dichloromethane (10 ml) was stirred at room temperature for about 12 h. The solution was diluted with dichloromethane and washed successively with 1 N HCl and saturated brine, before being dried and evaporated. The residue was purified by flash chromatography (eluant ether/hexane, 1:3) to give the pure MOM ether **10** (0.89 g, 77%) as a colourless oil; $[\alpha]_D$ = −13.4 (c = 1.46). – IR ($CHCl_3$): 2900 (CH). – ^{1}H NMR (300 MHz): δ = 0.03 and 0.04 [2s, 6H, $Si(CH_3)_2$], 0.88 [s, 9H, $C(CH_3)_3$], 0.90 (d, J = 6.9 Hz, 3H, CH_3), 0.98 (d, J = 6.9 Hz, 3H, CH_3), 1.91–1.96 (m, 2H, 2-H and 4-H), 3.25–3.35 (m, 2H), 3.33 (s, 3H, OCH_3), 3.43 (dd, J = 6.8 and 9.4 Hz, 1H), 3.53 (dd, J = 4.8 and 9.0 Hz, 1H), 3.72 (dd, J = 2.6 and 6.2 Hz, 1H), 4.46 and 4.49 (2d, J = 10.0 Hz, OCH_2Ph), 4.58 (s, 2H, OCH_2O), 7.24–7.33 (m, 5H, Ar). – ^{13}C NMR: δ = 0.00 (q), 18.77 (q), 22.52 (s), 30.26 (q), 40.53 (d), 42.71 (d), 59.11 (q), 75.34 (t), 77.09 (t), 77.79

(t), 100.60 (t), 131.32, 131.55, 132.33, 142.97 (s). – MS: m/z = 365 (< 1%, $M^+ - OCH_3$), 91 (100%).

$C_{22}H_{40}O_4Si$ (396.6) Calc. C 66.62 H 10.16 Found C 66.48 H 10.19

(2S,3S,4S)-3-(tert-Butyldimethylsilyloxy)-5-(methoxymethoxy)-2,4-dimethyl-1-pentanol (**11**): A suspension of the benzyl ether **10** (0.74 g, 1.9 mmol) and palladium hydroxide (90 mg) in ethyl acetate (8 ml) was stirred under hydrogen for 1 h and then filtered through Celite®. The filtrate was evaporated and purified by flash chromatography (eluant ether/pentane, 1:3) to give the alcohol **11** (0.47 g, 83%); $[\alpha]_D$ = −7.1 (c = 1.2). – IR ($CHCl_3$): 3700–3300 (w, OH). – ^{1}H NMR (300 MHz): δ = 0.09 and 0.11 [2s, 6H, $Si(CH_3)_2$], 0.92 [s, 9H, $C(CH_3)_3$], 0.94 (d, J = 7.0 Hz, 3H, CH_3), 0.95 (d, J = 7.0 Hz, 3H, CH_3), 1.84–2.00 (m, 2H, 2-H and 4-H), 2.37* (br., 1H, OH), 3.35 (s, 3H, OCH_3), 3.37 (dd, J = 9.6 and 12.7 Hz, 1H), 3.47 (dd, J = 7.2 and 9.4 Hz, 1H), 3.59 (br., 2H), 3.78 (dd, J = 3.2 and 5.5 Hz, 1H), 4.61 (s, 2H, OCH_2O). – ^{13}C NMR: δ = −4.23, −4.09, 12.28, 14.65, 18.34, 26.08, 37.19, 39.54, 55.27, 65.65, 71.05, 75.77, 96.62. – MS: m/z = 217 (20%), 45 (100%, $CH_3O{=}CH_2^+$).

$C_{15}H_{34}O_4Si$ (306.5) Calc. C 58.78 H 11.18 Found C 58.75 H 11.21

(2R,3R,4S)-3-(tert-Butyldimethylsilyloxy)-5-(methoxymethoxy)-2,4-dimethylpentanal (**12**): DMSO (0.41 ml, 5.7 mmol) was added to a solution of oxalyl chloride (0.24 g, 2.7 mmol) in dichloromethane (5 ml) cooled to −60°C. After 5 min the alcohol **11** (0.37 g, 1.2 mmol) in dichloromethane (2 ml) was added, followed by triethylamine (1.68 ml, 12 mmol) after a further 15 min. The mixture was stirred for 5 min at −60°C and then allowed to warm to 0°C. The suspension was poured into water and extracted with dichloromethane. The organic phase was washed with 1 N HCl (twice), saturated aqueous sodium hydrogen carbonate, and saturated brine, before being dried (Na_2SO_4) and evaporated. The crude product (0.40 g) was used without further purification. – ^{1}H NMR (90 MHz): δ = 0.1 [2s, 6H, $Si(CH_3)_2$], 0.90 [s, 9H, $C(CH_3)_3$], 0.95 (d, J = 7 Hz, 3H, CH_3), 1.05 (d, J = 7 Hz, 3H, CH_3), 1.8–2.2 (m, 1H, 4-H), 2.4–2.7 (m, 1H, 2-H), 3.35 (s, 3H, OCH_3), 3.35–3.65 (m, 2H), 4.05 (dd, J = 4 and 6 Hz, 1H), 4.55 (s, 2H, OCH_2O), 9.80 (d, J = 2 Hz, 1H, CHO).

Methyl (2E,4E,6S,7S,8S)-7-(tert-butyldimethylsilyloxy)-9-(methoxymethoxy)-6,8-dimethyl-2,4-nonadienoate (**16**): A mixture of the crude aldehyde **12** (0.40 g) and methyl 4-(triphenylphosphoranediyl)-2-butenoate (**14**) (1.0 g, 2.7 mmol) in toluene (40 ml) was stirred at 80°C for about 12 h. The solution was evaporated and the residue purified by flash chromatography (eluant ether/hexane, 1:5) to give firstly a mixture of the dienes **16** and **16a** (0.11 g, 23% from the alcohol **11**) and then the pure diene **16** (0.29 g, 62%); $[\alpha]_D$ = −6.8 (c = 1.25). – IR ($CHCl_3$): 1700 (m, C=O), 1640 (m, C=C), 1620 (w, C=C). – ^{1}H NMR (300 MHz): δ = −0.04 and −0.01 [2s, 6H, $Si(CH_3)_2$], 0.83 [s, 9H, $C(CH_3)_3$], 0.82–0.84 (br., 3H, CH_3), 0.98 (d, J = 6.9 Hz, 3H, CH_3), 1.77–1.85 (m, 1H, 8-H), 2.35–2.45 (m, 1H, 6-H), 3.23 (dd, J = 6.7 and 9.4 Hz, 1H, 9-H), 3.61 (dd, J = 3.6 and 4.7 Hz, 1H, 7-H), 3.66 (s, 3H, CO_2CH_3), 4.50 (s, 2H, OCH_2O), 5.72 (d, J = 15.2 Hz, 2-H), 6.06 (m, 2H, 4-H and 5-H), 7.15–7.25 (m, 1H, 3-H). – MS: m/z = 355 (< 1%, $M^+ - OMe$), 329 (1%, $M^+ - C_4H_9$), 185 (100%).

$C_{20}H_{38}O_5Si$ (386.6) Calc. C 62.14 H 9.91 Found C 61.99 H 10.01

Isomerisation of **16a** *to* **16**: A solution of the diene **16a** and iodine (5 mg) in dichloromethane (10 ml) was allowed to stand in direct sunlight for 6 h. The solution was then washed with aqueous sodium hydrogen sulfite, dried, and then evaporated. The residue was purified by flash chromatography (eluant ether/hexane, 1:4) to give the *E,E*-diene **16** (27 mg, 31%) and the starting unisomerised diene **16a** (24 mg, 30%).

Methyl (2E,4E,6S,7S,8S)-7-hydroxy-9-(methoxymethoxy)-6,8-dimethyl-2,4-nonadienoate (**17**): A solution of the diene **16** (631 mg, 1.63 mmol) in methanol (30 ml) was stirred with 0.1 N HCl (10 ml) for 4 h at 60°C. The mixture was then extracted with dichloromethane and the organic extracts were dried and evaporated. The residue was purified by flash chromatography (eluant ether/hexane/methanol, 10:10:2) to give the starting silyl ether **16** (324 mg, 51%) and then the alcohol **17** (194 mg, 43%). A sample was kugelrohr-distilled; b. p. 150°C/0.01 Torr; $[\alpha]_D = +5.7$ ($c = 1.23$). – IR ($CHCl_3$): 3700–3300 (br., OH), 1705 (s, C=O), 1640 (m, C=C), 1610 (w, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.95$ (d, $J = 6.9$ Hz, 3H, CH_3), 1.02 (d, $J = 6.8$ Hz, 3H, CH_3), 1.93–1.99 (m, 1H, 8-H), 2.22* (br., 1H, OH), 2.43 (6-line system, 1H, 6-H), 3.36 (s, 3H, OCH_3), 3.56–3.60 (m, 3H, 7-H and 9-H_2), 3.74 (s, 3H, CO_2CH_3), 4.61 (s, 2H, OCH_2O), 5.83 (d, $J = 15.4$ Hz, 2-H), 6.15 (dd, $J = 7.8$ and 15.3 Hz, 1H, 5-H), 6.26 (dd, $J = 11.5$ and 15.3 Hz, 1H, 4-H), 7.28 (dd, $J = 10.2$ and 15.3 Hz, 1H, 3-H). – MS: $m/z = 272$ (<1%, M^+), 241 (<1%, $M^+ - OCH_3$), 140 [100%, $M^+ - MOMCH_2CH(CH_3)CHO$].

$C_{14}H_{24}O_5$ (272.3) Calc. C 61.74 H 8.88 Found C 61.82 H 8.76

(2E,4E,6S,7S,8S)-7-Hydroxy-9-(methoxymethoxy)-6,8-dimethyl-2,4-nonadienoic acid (**18**): A solution of the methyl ester **17** (161 mg, 0.59 mmol) in methanol (15 ml) was treated with 1 N KOH (5 ml) and the mixture was then stirred for 18 h. The solution was diluted with dichloromethane and acidified to pH = 3 with 1 N HCl. The organic phase was separated, dried, and evaporated to give the acid **18** (160 mg, 100%) as a glass which was used without further purification. – IR ($CHCl_3$): 3650–2300 (br., OH), 1715 (s, C=O). – ^{1}H NMR (300 MHz): $\delta = 0.96$ (d, $J = 7.0$ Hz, 3H, CH_3), 1.03 (d, $J = 6.9$ Hz, 3H, CH_3), 1.90–2.00 (m, 1H, 8-H), 2.40–2.52 (6-line system, 1H, 6-H), 3.36 (s, 3H, OCH_3), 3.56–3.62 (m, 3H, 7-H and 9-H_2), 4.61 (s, 2H, OCH_2O), 5.82 (d, $J = 15.3$ Hz, 2-H), 6.17–6.33 (m, 2H, 4-H and 5-H), 7.34 (dd, $J = 10.0$ and 15.4 Hz, 1H, 3-H). – ^{13}C NMR: $\delta = 9.95$, 16.64, 35.22, 41.00, 55.36, 71.95, 76.02, 96.71, 119.41, 128.71, 146.78, 147.91, 171.78. – MS: $m/z = 259$ (1%, $M^+ + 1$), 240 (<1%, $M^+ - H_2O$), 45 (100%).

(2E,4E,6S,7S,10E,12E,14S,15S,1'S)-6,14-Dimethyl-7,15-bis[1'-methyl-2'-(methoxymethoxy)ethyl]-8,16-dioxa-2,4,10,12-cyclohexadecatetraene-1,9-dione (**19**): A solution of the hydroxy acid **18** (1.0 g) in THF (30 ml) was treated with triethylamine (0.6 ml, 4.3 mmol) and 2,4,6-trichlorobenzoyl chloride (0.94 g, 3.87 mmol) and the mixture was then stirred for 2 h at room temperature. The triethylamine hydrochloride was then filtered off using an argon frit and the filtrate diluted with benzene (15 ml). This solution was then added over a period of 5.5 h to a solution of 4-pyrrolidinopyridine (4.1 g, 30 mmol) in benzene (600 ml) using a motor-driven syringe. After the addition was complete, the mixture was stirred for a further 30 min before being diluted with ether and washed, successively, with 1 N HCl, saturated aqueous sodium hydrogen carbonate, and finally saturated brine. The organic phase was dried and evaporated. The residue was purified by flash chromatography (eluant ether/hexane, 1:1) to give the macrodiolide **19** (342 mg, 37%) as white crystals. A sample was recrystallised from ether/hexane; m. p. 158.5–159°C; $[\alpha]_D = +77.2$ ($c = 0.93$). – IR (KBr): 1718 (s, C=O), 1645 (m, C=C), 1632 (m, C=C), 1615 (m, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.97$ (d, $J = 7.0$ Hz, 6H, 2 CH_3), 1.05 (d, $J = 6.7$ Hz, 6H, 2 CH_3), 2.15–2.22 (m, 2H, 1'-H_2), 2.43–2.52 (m, 2H, 6-H and 14-H), 3.32–3.42 (m, 4H, 2 2'-H_2), 3.35 (s, 6H, 2 OCH_3), 4.58 and 4.61 (2d, $J = 8.4$ Hz, 4H, 2 OCH_2O), 4.96 (dd, $J = 1.8$ and 10.3 Hz, 2H, 7-H and 15-H), 5.60 (d, $J = 15.4$ Hz, 2H, 2-H and 10-H), 5.63 (dd, $J = 10.0$ and 15.0 Hz, 2H, 5-H and 15-H), 6.02 (dd, $J = 11.2$ and 15.0 Hz, 2H, 4-H and 12-H), 6.93 (dd, $J = 11.2$ and 15.4 Hz, 2H, 3-H and 11-H). – ^{13}C NMR: $\delta = 9.95$ (q), 15.52 (q), 33.64 (d), 41.69 (d), 55.27

(q), 70.68 (t), 76.17 (d), 96.87 (t), 121.37 (d), 131.10 (d), 144.36 (d), 145.21 (d), 167.61 (s). – MS: m/z = 480 (< 1%, M^+), 449 (< 1%, $M^+ - OCH_3$), 223 (100%, $M^+/2 - OH$).

$C_{26}H_{40}O_8$ (480.6) Calc. C 64.98 H 8.39 Found C 64.71 H 8.32

(2E,4E,6S,7S,10E,12E,14S,15S,1'S)-7,15-Bis-(1'-hydroxymethylethyl)-6,14-dimethyl-8,16-dioxa-2,4,10,12-cyclohexadecatetraene-1,9-dione (**2**): Dimethylboron bromide (2.9 ml, 1.5 N solution in 1,2-dichloroethane) was added dropwise to a solution of the MOM-protected diolide **19** (342 mg) in dichloromethane (7 ml) cooled to –80 °C. The mixture was stirred for 1 h and then transferred using a syringe to a vigorously stirred saturated aqueous solution of sodium hydrogen carbonate (20 ml). This mixture was stirred for 5 min and, after separation of the organic phase, the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated brine, dried, and evaporated. The residue was purified by flash chromatography (eluant ether and then ether/hexane, 1:1) to give the diol **2** (238 mg, 85%) as white crystals. A sample was recrystalised from dichloromethane/hexane; m. p. 186–188 °C (dec.); $[\alpha]_D$ = +107 (c = 8.3). – IR (KBr): 3700–2600 (br., OH), 1718 (s, C=O), 1640 (m, C=C), 1615 (m, C=C). – ^{1}H NMR (300 MHz): δ = 0.86 (d, J = 7.0 Hz, 6H, 2 CH_3), 1.05 (d, J = 6.7 Hz, 6H, 2 CH_3), 1.45–2.0* (br., 2H, 2 OH), 2.09–2.17 (m, 2H, 1'-H_2), 2.47–2.56 (m, 2H, 6-H and 14-H), 3.35 (dd, J = 9.8 and 11.4 Hz, 2H, CH_2OH), 3.48 (dd, J = 5.5 and 11.4 Hz, 2H, CH_2OH), 4.81 (dd, J = 2.1 and 10.3 Hz, 2H, 7-H and 15-H), 5.63 (dd, J = 9.7 and 15.1 Hz, 2H, 5-H and 13-H), 5.67 (d, J = 15.4 Hz, 2H, 2-H and 10-H), 6.10 (dd, J = 11.2 and 15.1 Hz, 2H, 4-H and 12-H), 6.97 (dd, J = 11.2 and 15.4 Hz, 2H, 3-H and 11-H). – ^{13}C NMR: δ = 9.03, 15.11, 35.46, 40.92, 64.65, 76.70, 121.23, 131.78, 144.32, 144.92, 169.08. – MS: m/z = 392 (< 1%, M^+), 374 (< 1%, $M^+ - H_2O$), 179 (100%, $M^+/2 - OH$).

(2S,3S,4S)-5-Benzyloxy-1,3-isopropylidenedioxy-2,4-dimethylpentane (**20**): The diol **9** (9.94 g, 41.7 mmol) was dissolved in dimethoxypropane (170 ml) and then *p*-toluenesulfonic acid (1.1 g) was added. The solution was stirred for 5.5 h until t.l.c. analysis (ether/hexane, 1:1) indicated the absence of starting material. The mixture was poured into saturated aqueous sodium hydrogen carbonate (150 ml) and then extracted with dichloromethane (2 × 100 ml). The organic extracts were dried and evaporated to give the crude acetonide **20** (11.60 g, 100%) which was used without further purification. A sample was kugelrohr-distilled; b. p. 145 °C/0.15 Torr; $[\alpha]_D$ = –29.2 (c = 0.91). – IR ($CHCl_3$): 3000 (s, CH). – ^{1}H NMR (300 MHz): δ = 0.93 (d, J = 6.9 Hz, 3H, CH_3CH), 1.06 (d, J = 6.9 Hz, 3H, CH_3CH), 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.58 (m, 1H, 2-H or 4-H), 1.79 (m, 1H, 2-H or 4-H), ABX system (δ_A = 3.45, δ_B = 3.53, J_{AB} = 8.8 Hz, 2H, CH_2OBn), 3.60 (dd, J = 1.7 and 11.4 Hz, 1H, 1-H_a), 3.76 (dd, J = 2.3 and 10.1 Hz, 1H, 3-H), 4.08 (dd, J = 2.8 and 11.4 Hz, 1H, 1-H_b), AB system (δ_A = 4.45, δ_B = 4.52, J_{AB} = 13.1 Hz, OCH_2Ph), 7.24–7.34 (m, 5H, Ar). – MS: m/z = 263 (9%, $M^+ - CH_3$), 220 (2%, $M^+ - CH_3 - CH_3CO$), 107 (34%), 91 (100%, Bn^+).

$C_{17}H_{26}O_3$ (278.4) Calc. C 73.35 H 9.41 Found C 73.29 H 9.45

(2S,3S,4S)-3,5-Isopropylidenedioxy-2,4-dimethyl-1-pentanol (**21**): Lithium (3 g, 430 mmol) was added to liquid ammonia (200 ml) cooled to –78 °C. When all the lithium had dissolved, a solution of the benzyl ether **20** (11.15 g, 40 mmol) in dry THF (65 ml) was added over a period of 5 min. The cooling bath was removed and the mixture then stirred at reflux for 40 min. The reaction was then quenched by the careful addition of ammonium chloride (24 g). Ammonia was allowed to evaporate, and then saturated brine (200 ml) was added. The mixture was diluted with water to dissolve the inorganic salts, extracted with ether (200 ml), then with dichloromethane (200 ml). The combined organic extracts were dried and evaporated, and the residue was purified by flash chromatography [15 × 5 cm column,

eluant ether/hexane, 1:3 (1 l) and 1:1 (1.2 l)] to give the alcohol **21** (6.52 g, 86%). A sample was kugelrohr-distilled; b. p. 85°C/0.1 Torr. On standing, the oil crystallised and a sample was recrystallised from hexane; m. p. 66.2–67.0°C; $[\alpha]_D = +2.8$ ($c = 1.85$). – IR ($CHCl_3$): 3500 (s, OH). – ^{1}H NMR (300 MHz): $\delta = 0.77$ (d, $J = 7.0$ Hz, 3H, CH_3CH), 1.10 (d, $J = 6.9$ Hz, 3H, CH_3CH), 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.54 (m, 1H, 2-H or 4-H), 1.88 (m, 1H, 2-H or 4-H), 2.4–3.0* (br., 1H, OH), 3.51–3.64 (m, 3H, 1-H_2 and 5-H_a), 3.81 (dd, $J = 2.4$ and 9.8 Hz, 1H, 3-H), 4.10 (dd, $J = 2.9$ and 11.6 Hz, 1H, 5-H_b). – MS: m/z = 173 (13%, $M^+ - CH_3$), 129 (6%, $M^+ - CH_3CHCH_2OH$), 59 (100%, CH_3CHCH_2OH).

$C_{10}H_{20}O_3$ (188.3) Calc. C 63.80 H 10.71 Found C 63.94 H 10.78

(2R,3R,4S)-3,5-Isopropylidenedioxy-2,4-dimethylpentanal (**23**): A solution of oxalyl chloride (0.70 g, 5.5 mmol) in dichloromethane (20 ml) was cooled to –78°C. DMSO (0.86 g, 11 mmol) in dichloromethane (5 ml) was then added over a period of 2.5 min and the mixture was stirred for a further 1.5 min. A solution of the alcohol **21** (0.94 g, 5 mmol) in dichloromethane was added over a period of 3 min and the mixture was stirred for 15 min. Triethylamine (3.50 ml, 25 mmol) was then added and the reaction mixture was allowed to warm to 0°C over a period of 45 min when it was poured into water (100 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (100 ml). The combined organic extracts were washed, successively, with 0.5 N HCl (2 × 100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), and finally with saturated brine (100 ml) before being dried and evaporated. The crude product (0.906 g) was used in the next step without purification. – ^{1}H NMR (90 MHz): $\delta = 0.95$ (d, $J = 7$ Hz, 3H, CH_3CH), 1.12 (d, $J = 7$ Hz, CH_3CH), 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.3–2.7 (m, 1H, $CHCHO$), 3.65 (dd, $J = 2$ and 12 Hz, 5-H_a), 4.0–4.3 (m, 2H, 3-H and 5-H_b), 9.75 (d, $J = 2$ Hz, CHO).

Methyl (2E,4E,6S,7S,8S)-7,9-isopropylidenedioxy-6,8-dimethyl-2,4-nonadienoate (**24**): A solution of the crude aldehyde **23** (0.906 g) and the phosphorane **14** (4.0 g, 11.1 mmol) in toluene (200 ml) was stirred at 105°C for 15 h. The mixture was cooled and then filtered through flash silica (8 × 3 cm deep), washing with ether/hexane (1:1, 100 ml). The filtrate was evaporated and the residue was purified by flash chromatography (15 × 3 cm column, eluant ether/hexane, 1:5) to give the product as a mixture of isomers (1.19 g, 89%). A pure sample of the *E,E*-diene **24** exhibited the following data: $[\alpha]_D = -46.4$ ($c = 1.24$). – IR ($CHCl_3$): 1720 (s, C=O), 1640 (m, C=C), 1615 (w, C=C). – ^{1}H NMR (300 MHz): $\delta =$ 0.96 (d, $J = 6.9$ Hz, 3H, CH_3CH), 1.08 (d, $J = 6.9$ Hz, CH_3CH), 1.37 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.57 (m, 1H, 8-H), 2.36 (m, 1H, 6-H), 3.58–3.64 (m, 2H, 7-H and 9-H_a), 3.74 (s, 3H, CO_2CH_3), 4.08 (dd, $J = 2.7$ and 11.5 Hz, 9-H_b), 5.80 (d, $J = 15.2$ Hz, 1H, 2-H), 6.18 (m, 2H, 4-H and 5-H), 7.27 (m, 1H, 3-H). – MS: $m/z = 253$ (4%, $M^+ - CH_3$), 193 (2%, $M^+ - CH_3 - CH_3CO_2H$), 129 (69%), 59 (100%, $CO_2CH_3^+$).

$C_{15}H_{24}O_4$ (268.3) Calc. C 67.14 H 9.01 Found C 67.15 H 9.06

Methyl (2E,4E,6S,7S,8S)-7,9-dihydroxy-6,8-dimethyl-2,4-nonadienoate (**25**): The acetonide **24** (1.18 g, 4.4 mmol), as a mixture of isomers, was dissolved in methanol (50 ml). *p*-Toluenesulfonic acid (40 mg) was added and the solution was stirred for 24 h at room temperature, before being cooled in an ice/water bath. Saturated aqueous sodium hydrogen carbonate (30 ml) was added and the mixture was then evaporated ($T < 30$°C). The residue was diluted with water (10 ml) and extracted with ethyl acetate (2 × 50 ml). The combined organic extracts were washed with saturated brine (30 ml) and then evaporated. The crude product was crystallised from hexane/ether (10 ml total volume) to give the pure *E,E*-diene **25** (474 mg, 47%). The mother liquor was evaporated and purified by flash chromatography (15 × 3 cm column, eluant ethyl acetate/hexane, 1:1) to give the starting acetonide **24**

(76 mg, 6%) as a mixture of isomers, and a mixture of diols (399 mg, 40%) homogeneous by t.l.c. The pure *E,E*-diol **25** exhibited the following data: m. p. 84–86°C; $[\alpha]_D = -41.7$ ($c = 1.05$). – IR ($CHCl_3$): 3500 (s, OH), 1720 (s, C=O), 1645 (m, C=C), 1620 (m, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.97$ (d, $J = 7.0$ Hz, 3H, CH_3CH), 1.02 (d, $J = 6.8$ Hz, CH_3CH), 1.85 (s, 2H, 2 OH) and (m, 1H, 8-H), 2.42 (m, 1H, 6-H), 3.61 (dd, $J = 2.7$ and 8.5 Hz, 1H, 7-H), 3.74 (s, 3H, OCH_3), 5.84 (d, $J = 15.4$ Hz, 1H, 2-H), 6.08 (dd, $J = 8.6$ and 15.3 Hz, 1H, 5-H), 6.28 (dd, $J = 10.8$ and 15.3 Hz, 1H, 4-H), 7.27 (dd, $J = 10.8$ and 15.4 Hz, 1H, 3-H). – MS: $m/z = 169$ (1%, $M^+ - CH_3CHCH_2OH$), 140 [100%, $M^+ - HOCH_2CH(CH_3)CHO$].

$C_{12}H_{20}O_4$ (228.3) Calc. C 63.14 H 8.83 Found C 63.08 H 8.92

Methyl (2E,4E,6S,7S,8S)-7-hydroxy-6,8-dimethyl-9-triphenylmethoxy-2,4-nonadienoate (**26**): The diol **25** (1.14 g, 5 mmol) and 1-tritylpyridinium tetrafluroborate (2.5 g, 6.1 mmol) were dissolved in acetonitrile (20 ml). The solution was stirred for 1 h and the solvent was then evaporated. The residue was filtered through flash silica (9 × 5 cm column, eluant ether/hexane, 1:1) to give, after evaporation of the solvent, the *mono*-trityl ether **26** as a foam (2.53 g), homogeneous by t.l.c. (ether/hexane, 1:1), though evidently contaminated with a small amount of the *bis*-trityl compound. A sample was recrystallised from methanol with a trace of water; m. p. 120.5–121°C; $[\alpha]_D = -19.5$ ($c = 1.13$). – IR ($CHCl_3$): 3500 (m, OH), 1720 (s, C=O), 1640 (m, C=C), 1595 (m, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H, CH_3CH), 1.03 (d, $J = 7.0$ Hz, CH_3CH), 1.84 (m, 1H, 8-H), 2.28* (d, $J = 3.2$ Hz, 1H, OH), 2.32 (br. q, $J = 6.8$ Hz, 1H, 6-H), ABX system ($\delta_A = 3.11$, $\delta_B = 3.25$, $J_{AB} = 9.1$ Hz), 3.73 (s, 3H, OCH_3), 5.77 (d, $J = 15.3$ Hz, 1H, 2-H), 6.10 (m, 2H, 4-H and 5-H), 7.2–7.32 and 7.39–7.4 (m, 16H, Ar and 3-H). – MS: $m/z = 469$ (< 1%, $M^+ - H$), 393 (< 1%, $M^+ - C_6H_5$), 259 (12%), 243 (100%).

$C_{12}H_{20}O_4$ (470.2) Calc. C 79.12 H 7.28 Found C 79.06 H 7.29

(2E,4E,6S,7S,8S)-7-Hydroxy-6,8-dimethyl-9-triphenylmethoxy-2,4-nonadienoic acid (**27**): The crude methyl ester **26** was dissolved in THF (25 ml) and then methanol (75 ml) followed by 1 N KOH (25 ml) were added. The solution was stirred for 16 h and the solvent was then evaporated. The residue was diluted with water (20 ml) and acidified to pH = 1 with 0.5 N HCl, before being extracted with dichloromethane (2 × 100 ml). The organic extracts were dried, evaporated, and the residue was then filtered through a column of flash silica (7 × 3 cm column, eluant ethyl acetate/hexane, 1:3, 1.2 l). The filtrate was evaporated to yield the acid **27** as a foam (2.41 g) which could not entirely be freed of solvent, even after heating in high vacuum for 15 h; m. p. 63–65°C; $[\alpha]_D = -1.4$ ($c = 0.85$). – IR ($CHCl_3$): 3600–2300 (br., OH), 1690 (s, C=O), 1640 (m, C=C), 1615 (m, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.97$ (d, $J = 6.8$ Hz, 3H, CH_3CH), 1.04 (d, $J = 7.0$ Hz, CH_3CH), 1.85 (m, 1H, 8-H), 2.32 (br. q, $J = 6.8$ Hz, 1H, 6-H), ABX system ($\delta_A = 3.12$, $\delta_B = 3.25$, $J_{AB} = 9.0$ Hz), 5.76 (d, $J = 15.3$ Hz, 1H, 2-H), 6.15 (m, 2H, 4-H and 5-H), 7.2–7.44 (m, 16H, Ar and 3-H), – MS: $m/z = 302$ (< 1%, $M^+ - 2\ C_6H_5$), 274 (2%), 260 (4%), 243 (5%), 183 (16%), 149 (24%), 41 (100%).

$C_{30}H_{32}O_4$ (456.6) Calc. C 78.92 H 7.06 Found C 78.88 H 7.16

(2E,4E,6S,7S,10E,12E,14S,15S,1'S)-6,14-Dimethyl-7,15-bis[1'-methyl-2'-(triphenylmethoxy)-ethyl]-8,16-dioxa-2,4,10,12-cyclohexadecatetraene-1,9-dione (**28**): The crude hydroxy acid **27** (2.41 g) was dissolved in dry THF (20 ml), and then 2,4,6-trichlorobenzoyl chloride (1 N solution in THF, 5.2 ml, 5.2 mmol) was added, followed by triethylamine (0.8 ml, 5.7 mmol). The mixture was stirred for 2 h and then filtered through an argon frit to remove the triethylamine hydrochloride. The solid was washed with toluene (10 ml) and the combined

filtrates and washings were diluted to a total volume of 200 ml with toluene. This solution was then added over a period of 7.5 h to a solution of 4-pyrrolidinopyridine (7.4 g, 50 mmol) in toluene (1.5 l) using a dropping funnel with a ground glass tap. After the addition was complete, the mixture was stirred for a further 75 min, before being diluted with ether (400 ml) and washed with 0.5 N HCl (300 ml), saturated aqueous sodium hydrogen carbonate (300 ml), and finally saturated brine (300 ml). The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (15 × 5 cm column, eluant ether/hexane, 1:5, 1 l, and 2:1, 600 ml) to give the diolide **28** (1.07 g, 49% from the diol **25**). A sample was recrystallised from ethyl acetate/hexane; m. p. 97–100°C; $[\alpha]_D = +113.3$ ($c = 0.54$). – IR (KBr): 1720 (s, C=O), 1640 (s, C=C), 1615 (m, C=C). – ^{1}H NMR (300 MHz): $\delta = 0.88$ (d, $J = 6.9$ Hz, 6H, 2 CH_3), 1.00 (d, $J = 6.6$ Hz, 6H, 2 CH_3), 1.97 (br. q, $J = 6.6$ Hz, 2H, 1'-H), 2.40 (m, 2H, 6-H and 14-H), 3.03 (m, 4H, 2 2'-H_2), 4.98 (dd, $J =$ 1.6 and 10.3 Hz, 2H, 7-H and 15-H), 5.47 (d, $J = 15.3$ Hz, 2H, 2-H and 10-H), 5.63 (dd, $J = 9.8$ and 15.0 Hz, 2H, 5-H and 15-H), 5.93 (dd, $J = 11.2$ and 15.0 Hz, 2H, 4-H and 12-H), 6.89 (dd, $J = 11.2$ and 15.3 Hz, 2H, 3-H and 11-H), 7.15–7.44 (m, 30H, Ar). – MS: $m/z = 393$ (2%), 361 (2%), 243 [100%, $(C_6H_5)_3C^+$].

$C_{60}H_{60}O_6$ (877.1) Calc. C 82.16 H 6.89 Found C 82.69 H 6.85

(2E,4E,6S,7S,10E,12E,14S,15S,1'S)-7,15-Bis(1'-hydroxymethylethyl)-6,14-dimethyl-8,16-dioxa-2,4,10,12-cyclohexadecatetraene-1,9-dione (**2**): The trityl-protected diolide **28** (1.05 g, 1.2 mmol) was dissolved in a mixture of methanol (38 ml) and THF (22 ml). *p*-Toluenesulfonic acid (42 mg) was added and the solution was stirred for 16 h. Solid sodium hydrogen carbonate (0.6 g) was added and the solvent was evaporated. The residue was purified by flash chromatography (15 × 3.5 cm column, eluant ethyl acetate/hexane, 1:1, 500 ml, and then ethyl acetate, 400 ml) to give the diolide diol **2** (304 mg, 65%), identical in all respects with the material prepared by the other route.

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