A formal synthesis of (+)-pyripyropene A using a biomimetic epoxy-olefin cyclisation: effect of epoxy alcohol/ether on cyclisation efficiency

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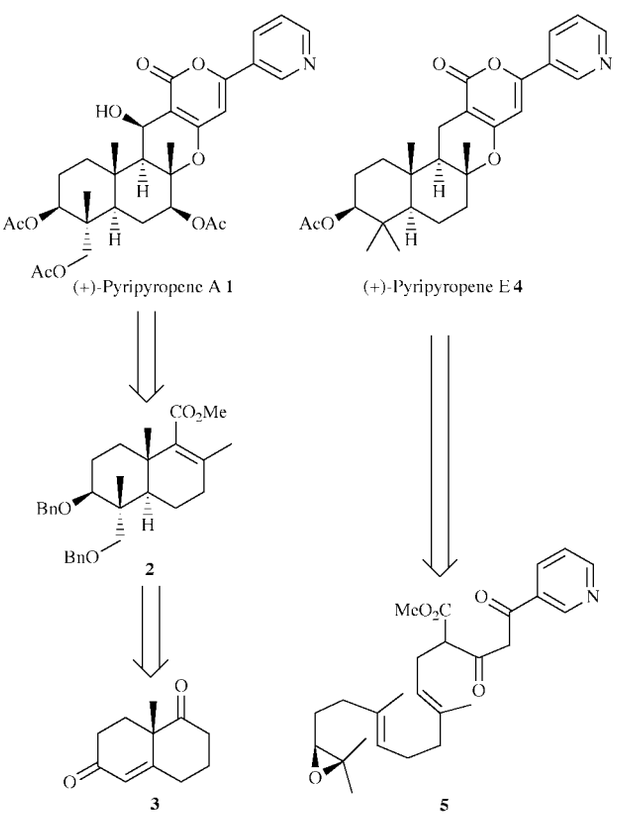
The synthesis of the decalin sub-unit **2** of (+)-pyripyropene A **1** (a key intermediate in the first total synthesis) is described. The key step involves a biomimetic epoxy-olefin cyclisation using an allylsilane as the terminating group. Whilst attempts to cyclise epoxy alcohol **6** were unfruitful, cyclisation of the protected epoxy benzyl ether **7** using $BF_3{\cdot}OEt_2$ was successful, yielding bicyclic ester **25**. Isomerisation of the exocyclic double bond into conjugation with the ester group proved to be problematic, although successful conditions were ultimately found.

Introduction

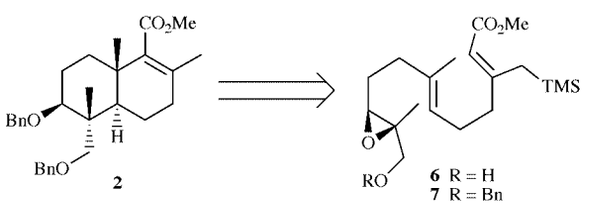
Pyripyropenes A–L, isolated by Õmura and co-workers[1] from a fermentation broth of *Aspergillus fumigatus*, are the most effective naturally occurring inhibitors of acyl-CoA : cholesterol acyltransferase (ACAT), the enzyme responsible for intracellular esterification of cholesterol. Inhibition of the ACAT enzyme represents a new approach to the prevention and treatment of atherosclerosis and hypercholesterolemia[2] since evidence suggests that ACAT inhibitors may lower plasma cholesterol levels and prevent the accumulation of cholesteryl esters in arterial lesions.

The simplest member of the family, pyripyropene E **4**, was biomimetically constructed in a racemic form by Parker and Resnick[3] and, later, in an enantiomerically pure form by Õmura and Smith and co-workers.[4] Both approaches utilised an epoxide initiated polyene cyclisation[5] to deliver the pyripyropene skeleton, the latter using the cyclisation of substrate **5**. The most active member of the family, (+)-pyripyropene A **1**, was synthesised by Õmura and Smith from the (+)-Wieland–Miescher ketone **3** in 19 steps (Scheme 1).[4] Although a biomimetic polyene cyclisation has been used to prepare pyripyropene E **4**, it was surprising that this strategy had not been adopted for pyripyropene A **1** as the required epoxide contains a neighbouring alcohol group and as such could be easily obtained in enantiomerically pure form by Sharpless epoxidation.[6]

We envisioned a short biomimetic route to the decalin sub-unit **2**, a key intermediate in the Õmura–Smith synthesis (prepared in 10 steps from **3**), utilising the cyclisation of epoxy-allylsilanes of type **6** or **7** (Scheme 2).[7] Previously, Weiler had shown that allylsilanes bearing esters were sufficiently nucleophilic to undergo epoxy-olefin cyclisation in good yield.[8] The advantages of such a sequence are rapid construction of the carbocyclic ring system and excellent stereochemical control at the four stereocentres present in the target decalin **2**.



Scheme 1



Scheme 2

Results and discussion

First generation synthesis

Initially, the synthesis and cyclisation of epoxy-allylsilane **6** was attempted. The cyclisation substrate, epoxy alcohol **6**, was synthesised in 5 steps from geranyl bromide **8** (Scheme 3). Initial alkylation of geranyl bromide **8** with the dianion of methyl acetoacetate[9] afforded the β-keto ester **9** and subsequent reaction with NaH and $(EtO)_2POCl$ gave the known enol phosphate **10** in good yield.[10] Regioselective hydroxylation[11]

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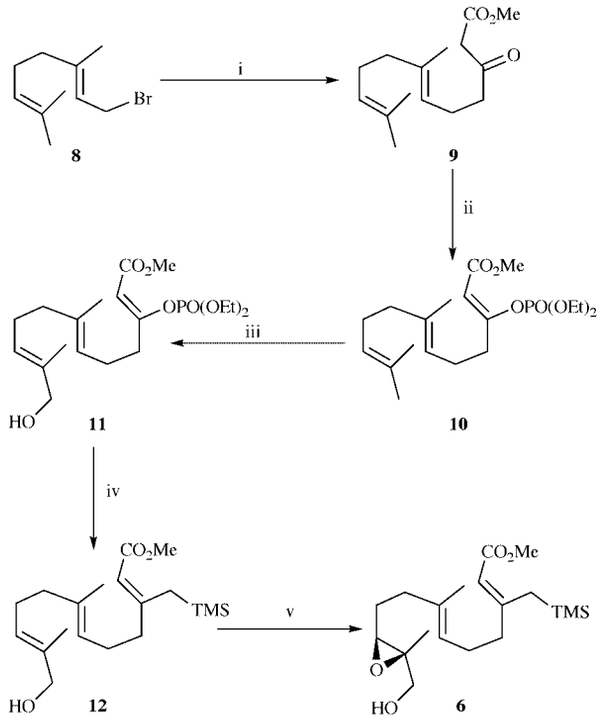
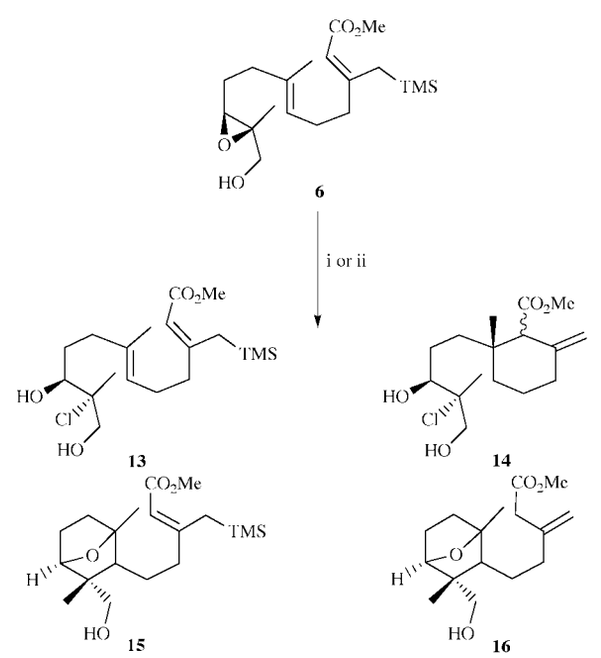


Scheme 3 *Reagents and conditions*: i, methyl acetoacetate, NaH, ^{n}BuLi, THF, 0 °C, then **8**, 75%; ii, NaH, $(EtO)_2POCl$, Et_2O, 86%; iii, TBHP, SeO_2 (cat.), salicylic acid, DCM, 44%; iv, $TMSCH_2MgCl$, $Ni(acac)_2$ (cat.), Et_2O, 50%; v, TBHP, (+)-DET, $Ti(O^{i}Pr)_4$, DCM, 70%, 90% ee.

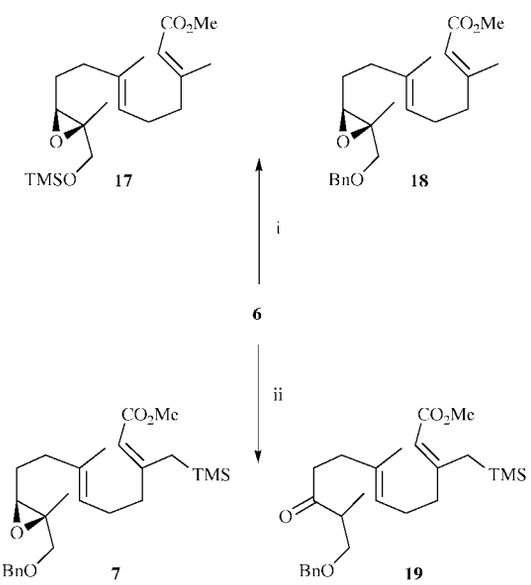
using SeO_2 gave the *trans*-allylic alcohol **11**, which was subjected to a nickel catalysed cross coupling reaction[8,12] with $TMSCH_2MgCl$ to form allylsilane **12**. Subsequent Sharpless epoxidation[6] gave rise to the cyclisation substrate, epoxy alcohol **6**, in 70% yield and 90% ee. Unfortunately, all attempts to cyclise the unprotected epoxy alcohol **6** failed. For example, using $BF_3{\cdot}OEt_2$ only mixtures of unidentifiable acyclic and monocyclic products were obtained and the use of $MeAlCl_2$ (Corey's preferred cyclisation catalyst)[5b–d,13] resulted in the formation of chlorohydrins **13** and **14** as shown in Scheme 4. The use of



Scheme 4 *Reagents and conditions*: i, $MeAlCl_2$, CH_2Cl_2, room temp.; ii, $SnCl_4$, CH_2Cl_2, room temp.

$SnCl_4$ yielded bicyclic ethers **15** and **16** along with chlorohydrin **13**. We were disappointed at the poor results as there are known literature examples of (epoxy alcohol)-olefin cyclisations,[14] however, in each of these cases only a monocyclic product was sought.

We therefore decided to protect the free hydroxy group as a benzyl ether as Tanis *et al*. have demonstrated in the cyclisation of such a benzyl ether, with furan as the terminating group, in the synthesis of (+)-aphidicolin.[15] In a comparison of protecting groups, Tanis found that a benzyl ether gave higher yields than a TBDMS ether in the epoxy–olefin cyclisation reaction and so we elected to make the benzyl ether **7**. However when substrate **6** was subjected to standard benzylation conditions (NaH, BnBr) none of the desired product was obtained; silyl ether **17** and benzyl ether **18** were obtained instead (Scheme 5). Clearly the allylsilane bearing the ester

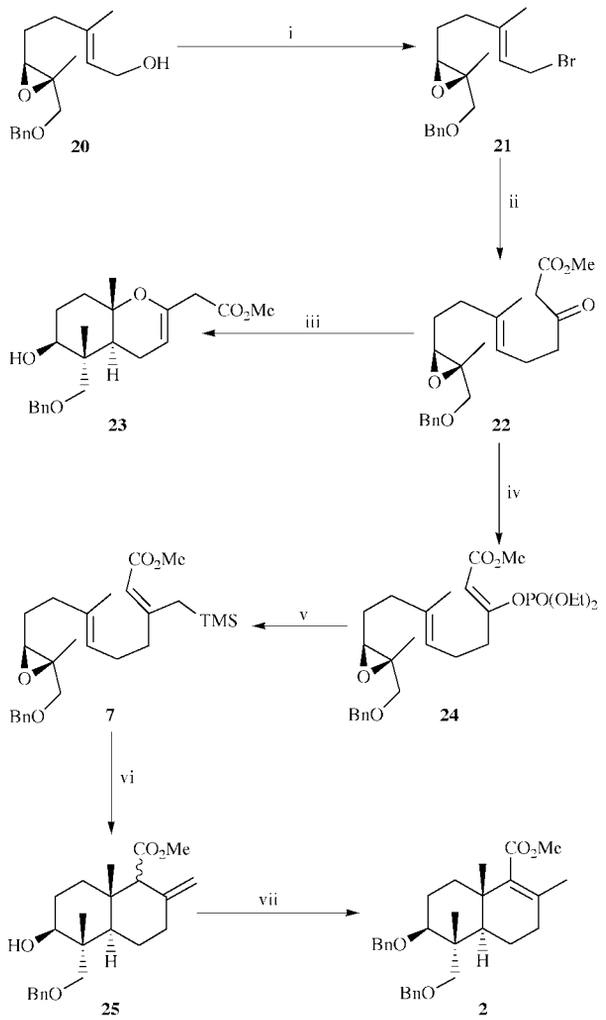


Scheme 5 *Reagents and conditions*: i, NaH, BnBr, THF; ii, $PhCHN_2$, HBF_4 (cat.), CH_2Cl_2, −40 °C, 66% yield (**7**:**19**, 2:1).

moiety was sensitive to the basic conditions employed. The use of mildly acidic conditions was tested ($PhCHN_2$, HBF_4 (cat.))[16] and resulted in formation of the required benzyl ether **7** together with the inseparable rearrangement product **19** arising from acid catalysed epoxide ring opening. Treatment of this mixture of products with $BF_3{\cdot}OEt_2$ did provide decalin **25**, but in rather poor yield. Due to the difficulties experienced in the benzylation step it was decided to introduce the benzyl group at an earlier stage in the synthesis.

Second generation synthesis

The known allylic alcohol **20**, derived from geraniol in 5 steps,[15] was converted to bromide **21** upon treatment with $MsCl–Et_3N$ followed by LiBr at −78 °C (Scheme 6). Low temperature and a controlled amount of LiBr were required to minimise opening of the epoxide ring whilst ensuring displacement of any allylic chloride present. Initially, the allylic alcohol **20** was treated with $MsCl–Et_3N$ at −40 °C followed by 3 equivalents of LiBr at room temperature for 30 min.[17] These conditions resulted in the formation of the required allylic bromide **21** in 65% yield and a 10% yield of the inseparable allylic chloride.[18] A third product was identified as the bromohydrin resulting from bromide addition to the epoxide ring.[19] The use of 10 equivalents of LiBr for 30 min reduced the amount of allylic chloride (3%) but, as expected, led to an increase in bromohydrin formation (13%). In an attempt to reduce these side products, the reaction was carried out at −78 °C throughout both the mesylation and bromination steps. Optimum conditions (i, $MsCl–Et_3N$,



Scheme 6 *Reagents and conditions*: i, MsCl, Et_3N, THF, −78 °C, 1 h, then LiBr (3 equiv.), acetone, −78 °C, 40 min, 79%; ii, methyl acetoacetate, NaH, ^nBuLi, THF, 0 °C, then **21**, 78%; iii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 61%; iv, NaH, $(EtO)_2POCl$, Et_2O, 93%; v, $TMSCH_2MgCl$, $Ni(acac)_2$ (cat.), Et_2O, 0 °C, 54%; vi, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 54%; vii, NaH, BnBr, THF, reflux, 51%.

−78 °C, 1 h; ii, 3 equivalents LiBr, −78 °C, 40 min) resulted in formation of the desired allylic bromide **21** in 79% yield along with 7% of the allylic chloride. A small amount of bromohydrin was removed by chromatography. The relatively unstable bromide **21** was then employed in the alkylation step with the dianion of methyl acetoacetate[9] to afford β-keto ester **22** in 78% yield. Treatment of this compound with $BF_3{\cdot}OEt_2$ resulted in cyclisation, but, as expected, through oxygen rather than carbon to furnish the oxabicycle **23**.[20] Conversion of β-keto ester **22** to enol phosphate **24** [NaH, $(EtO)_2POCl$, Et_2O][10] followed by coupling with $TMSCH_2MgCl$ in the presence of nickel(II) bisacetylacetonate[8,12] furnished the cyclisation substrate (*Z*)-allylsilane **7**. It was necessary to conduct the cross coupling reaction at 0 °C using 2.5 equivalents of $TMSCH_2MgCl$ for approximately 10 min to reduce chlorohydrin formation. Using these optimised conditions, with 20 mol% of nickel catalyst, the required epoxy allylsilane **7** was isolated in 54% yield.

Treatment of the allylsilane **7** with $BF_3{\cdot}OEt_2$ (optimum Lewis acid) at room temperature gave the required decalin in 54% yield as a 3:2 mixture of epimeric hydroxy esters **25**. Other Lewis acids *e.g.* $SnCl_4$ or $MeAlCl_2$ resulted in chlorohydrin formation rather than cyclisation. All that remained to complete the formal synthesis was isomerisation of the exocyclic double bond and benzylation of the free alcohol.

Table 1 Variation of alkene isomerisation with time

Time/h[a]	Yield of **2** (%)	Yield of **28** (%)
0.5	14	34
1	32	42
2	45	15
3	47	19
4	51	21

[a] Time of reflux of substrate **25** with NaH prior to addition of BnBr.

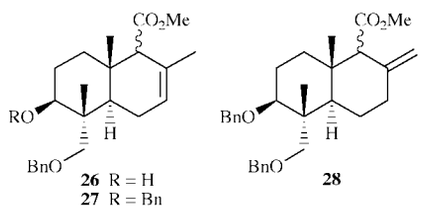


Fig. 1

Initial attempts to isomerise the exocyclic double bond of alcohol **25** with DBU–MeOH or KO^{t}Bu–^{t}BuOH failed, with starting material being recovered. Treatment with KH–THF followed by a ^{t}BuOH quench resulted in isomerisation to the trisubstituted alkene **26** instead (Fig. 1). Fortuitously, benzylation of alcohol **25** by reaction with excess NaH in refluxing THF prior to the addition of BnBr resulted in partial isomerisation to the conjugated alkene **2**. Increasing the time of reflux with NaH to 4 hours led to a 51% yield of alkene **2** (Table 1). Evidently the diene enolate is quenched by a proton at the γ position, but if the protonation regenerates a base, the tetrasubstituted alkene isomerises to the thermodynamically more stable trisubstituted alkene.[21] Decalin **2** was spectroscopically identical[22] to the data reported by Ōmura and Smith.[4]

The remaining unchanged exocyclic double bond isomer **28**,[23] recovered in 21% yield, was subjected to a range of isomerisation conditions. Refluxing the substrate in EtOH in the presence of $RhCl_3$[24] again resulted in the formation of the trisubstituted isomer, alkene **27**. Frejd *et al.* reported similar isomerisation problems in a related system during the synthesis of a Taxol A-ring building block.[14a] It was reported that the considerable isomerisation difficulties encountered were overcome by heating the exocyclic double bond isomer to 185 °C in neat DBU for 1 hour resulting in 58% conversion. Similar conditions (150 °C, neat DBU) were used with alkene **27** but only partial isomerisation occurred after 1 hour and prolonged heating resulted in decomposition of the substrate.

Conclusion

The synthesis of decalin subunit **2**, using a biomimetic epoxyolefin cyclisation of enantiomerically pure allylsilane **7**, was achieved in 11 steps from geraniol, thus completing the formal synthesis of (+)-pyripyropene A **1**. The shorter synthetic route to **2**, *via* cyclisation of the unprotected epoxy alcohol **6**, proved unsuccessful, as treatment with Lewis acids resulted in monocyclisation or no cyclisation at all.

Experimental

Optical rotations were measured on a Perkin-Elmer 141 or an AA-10 polarimeter. Values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed using a Perkin-Elmer 2400 CHN elemental analyser. Infrared spectra were recorded on a Perkin-Elmer 157G spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-250 FT spectrophotometer supported by an Aspect 4000 data system and a Bruker WH-400 spectrophotometer supported

by an Aspect 2000 data system. The chemical shifts (δ_H) were recorded on the δ scale and were measured relative to the residual proton signal of the deuterated solvent. *J* values are given in Hz. Chemical shifts (δ_C) are quoted in ppm referenced to the appropriate solvent peak and are assigned as s, d, t, q for C, CH, CH_2, CH_3. Degenerate peaks are prefixed by the number of carbons. Mass spectra were obtained using either a Kratos MS 25 or MS 80 spectrometer supported by a DS 55 data system. High resolution mass spectra were obtained using a Kratos MS 80 spectrometer supported by a DS 90 data system. Chemical ionisation used ammonia as the reagent. Thin layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated plates and BDH silica (mesh 40–63) was used for column chromatography. Petrol refers to light petroleum (bp 40–65 °C) and ether refers to diethyl ether. Where necessary, solvents and reagents were dried and distilled before use. Boron trifluoride–diethyl ether was purified by the addition of *ca*. 5% ether and distillation at reduced pressure from calcium hydride. THF was refluxed over potassium benzophenone ketyl under a nitrogen atmosphere until anhydrous. Diethyl ether was distilled from sodium benzoquinone ketyl under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride.

Preparation of methyl (2*Z*,6*E*,10*E*)-3-[(diethoxyphosphoryl)-oxy]-12-hydroxy-7,11-dimethyldodeca-2,6,10-trienoate 11

To selenium dioxide (55 mg, 0.50 mmol) and salicylic acid (135 mg, 0.99 mmol) in dry dichloromethane (6 mL), chilled in an ice–water bath, was added *tert*-butyl hydroperoxide (7.9 mL of a 5 M solution in decane, 39.7 mmol) in one portion. To this mixture was added a solution of the known enol phosphate **10**[10] (3.85 g, 9.92 mmol) in dry dichloromethane (6 mL) over 5 min. The resulting colourless solution was stirred for 25 h at room temperature. The solution was diluted with dichloromethane (15 mL) and added to a solution of ferrous sulfate heptahydrate (9 g, 32.5 mmol) in water (100 mL) at 0 °C. The two-phase mixture was stirred for 30 min then separated. The aqueous phase was extracted with dichloromethane (3 × 30 mL). The organic layers were combined and washed with 1 M NaOH (50 mL), water (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The reaction mixture was dissolved in ice cold ethanol (30 mL), and $NaBH_4$ (0.56 g, 14.88 mmol) was carefully added. Stirring continued for 2 h after the addition, then the reaction was quenched by the addition of 1 M HCl (20 mL). The solution was poured into water (20 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 60% EtOAc–petrol) to yield the allylic alcohol **11** (1.77 g, 44%) as a pale yellow oil. R_f 0.16 (60% EtOAc–petrol) (Found: C, 56.5; H, 8.3. $C_{19}H_{33}PO_7$ requires C, 56.4; H, 8.2%); ν_{max}/cm^{-1} (thin film) 3602 (OH), 2984 (CH), 1729 (C=O, ester), 1666 (C=C), 1272 (P=O), 1035 (P–O–C); δ_H (250 MHz; $CDCl_3$) 1.34 (6 H, t, *J* 7.0, 2 × OCH_2CH_3), 1.59 (3 H, s, CH_3C=C), 1.62 (3 H, s, CH_3C=C), 1.97–2.47 (8 H, m, 4 × CH_2C=C), 3.67 (3 H, s, CO_2CH_3), 3.95 (2 H, s, CH_2OH), 4.23 (4 H, quint, *J* 7.0, 2 × OCH_2CH_3), 5.07 (1 H, t, *J* 7.0, C*H*=C), 5.32 (1 H, s, C*H*CO_2Me), 5.32 (1 H, m, C*H*=C(Me)CH_2OH); δ_C (63 MHz; $CDCl_3$) 13.7 (q), 16.0 (2 × q), 16.1 (q), 24.8 (t), 25.9 (t), 35.1 (t), 39.1 (t), 51.1 (q), 64.8 (t), 64.9 (t), 68.7 (t), 104.8 (d), 122.1 (d), 125.3 (d), 135.0 (s), 136.6 (s), 161.5 (s), 164.3 (s); *m*/*z* (EI) 404 (M^+, 2%), 386 (3), 252 (20), 220 (24), 155 (100), 127 (23), 99 (35) (Found: M^+, 404.1962. $C_{19}H_{33}PO_7$ requires *M* 404.1964).

Preparation of methyl (2*Z*,6*E*,10*E*)-12-hydroxy-7,11-dimethyl-3-[(trimethylsilyl)methyl]dodeca-2,6,10-trienoate 12

To a solution of trimethylsilylmethylmagnesium chloride (52.6 mL of a 1 M solution in diethyl ether, 52.6 mmol) under an atmosphere of nitrogen was added anhydrous nickel(II) acetylacetonate (450 mg, 1.75 mmol). The resulting dark-brown mixture was stirred for 5 min before a solution of enol phosphate **11** (3.54 g, 8.76 mmol) in diethyl ether (170 mL) was added slowly. The reaction was stirred for 1 h at room temperature before being quenched by careful addition of 1 M hydrochloric acid (until acidic). After dilution with diethyl ether (150 mL), the solution was washed with 1 M hydrochloric acid (100 mL), brine (2 × 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc–petrol) afforded the allylsilane **12** (1.47 g, 50%) as a yellow oil. R_f 0.24 (20% EtOAc–petrol) (Found: C, 67.3; H, 10.0. $C_{19}H_{34}SiO_3$ requires C, 67.5; H, 10.1%); ν_{max}/cm^{-1} (thin film) 3064 (OH), 2953 (CH), 1707 (C=O, ester), 1623 (C=C); δ_H (250 MHz; $CDCl_3$) 0.04 (9 H, s, 3 × $SiCH_3$), 1.59 (3 H, s, CH_3C=C), 1.65 (3 H, s, CH_3C=C), 1.98–2.18 (8 H, m, 4 × CH_2C=C), 2.41 (2 H, s, CH_2TMS), 3.65 (3 H, s, CO_2CH_3), 3.98 (2 H, s, CH_2OH), 5.09 (1 H, t, *J* 7.0, C*H*=C), 5.37 (1 H, t, *J* 7.0, C*H*=C(Me)CH_2OH), 5.53 (1 H, s, C*H*CO_2CH_3); δ_C (63 MHz; $CDCl_3$) −0.9 (3 × q), 13.6 (q), 16.0 (q), 26.1 (2 × t), 26.4 (t), 39.2 (t), 40.5 (t), 50.5 (q), 68.7 (t), 111.1 (d), 123.2 (d), 125.6 (d), 134.8 (s), 135.8 (s), 164.4 (s), 167.7 (s); *m*/*z* (EI) 338 (M^+, 4%), 323 (5), 305 (5), 253 (32), 149 (95), 107 (34), 73 (100) (Found: M^+, 338.2286. $C_{19}H_{34}SiO_3$ requires *M* 338.2277).

Preparation of methyl (2*Z*,6*E*)-9-[(2*S*,3*S*)-3-(hydroxymethyl)-3-methyloxiran-2-yl]-7-methyl-3-[(trimethylsilyl)methyl]nona-2,6-dienoate 6

An oven dried two necked round-bottomed flask equipped with a magnetic stir bar and a pressure equalising addition funnel was charged with 480 mg of 3 Å powdered, activated molecular sieves and dichloromethane (15 mL). The flask was cooled to −20 °C before (L)-(+)-diethyl tartrate (49 μL, 0.29 mmol) and titanium isopropoxide (53 μL, 0.18 mmol) were added sequentially with stirring. The reaction mixture was stirred at −20 °C as *tert*-butyl hydroperoxide (1.07 mL of a 5 M solution in decane, 5.37 mmol) was added through the addition funnel at a moderate rate (over *ca*. 5 min). The resulting mixture was stirred at −20 °C for 30 min. The allylic alcohol **12** (1.21 g, 3.58 mmol), dissolved in dichloromethane (5 mL), was then added dropwise through the same addition funnel over a period of 10 min. The reaction mixture was stirred at −20 °C for 6 h and then treated with a solution of triethanolamine (48 μL, 0.36 mmol) in dichloromethane (5 mL). The solution was stirred for 30 min then filtered through a *ca*. 1.5 cm pad of flash silica gel covered with Celite. The filter cake was rinsed with ethyl acetate (100 mL) and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc–petrol) afforded the epoxide **6** (887 mg, 70%, 90% ee) as a yellow oil. $[\alpha]_D^{22}$ −8.2 (*c* 6.25 in CH_2Cl_2); R_f 0.13 (20% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 3593 (br, OH), 2954 (CH), 1708 (C=O, ester), 1623 (C=C); δ_H (250 MHz; $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 1.25 (3 H, s, CH_3COC), 1.59 (3 H, s, CH_3C=CH), 1.62–1.68 (2 H, m, CH_2CHO), 1.99–2.21 (6 H, m, 3 × CH_2C=C), 2.38 (2 H, s, CH_2TMS), 2.99 (1 H, t, *J* 6.1, C*H*OC), 3.48–3.67 (2 H, m, CH_2OH), 3.62 (3 H, s, CO_2CH_3), 5.12 (1 H, t, *J* 6.7, C*H*=C), 5.50 (1 H, s, C*H*CO_2CH_3); δ_C (63 MHz; $CDCl_3$) −0.8 (3 × q), 14.2 (q), 16.0 (q), 26.1 (t), 26.4 (t), 26.7 (t), 36.2 (t), 40.5 (t), 50.5 (q), 59.8 (d), 60.9 (s), 65.4 (t), 111.1 (d), 123.8 (d), 135.1 (s), 164.1 (s), 167.7 (s); *m*/*z* (EI) 354 (M^+, 6%), 339 (25), 323 (20), 253 (43), 211 (25), 186 (45), 149 (100), 107 (65), 82 (60), 73 (100) (Found: M^+, 354.2230. $C_{19}H_{34}SiO_4$ requires *M* 354.2226).

Preparation of (2*S*,3*S*)-3-[(*E*)-5-bromo-3-methylpent-3-enyl]-2-methyl-2-(benzyloxymethyl)oxirane 21

To a solution of the known allylic alcohol **20**[15] (294 mg, 1.07 mmol) and triethylamine (0.25 mL, 1.82 mmol) in tetrahydrofuran (4 mL) at −78 °C was added methanesulfonyl chloride

(0.12 mL, 1.60 mmol) over 10 min. After the addition was complete, the reaction was maintained at −78 °C and stirred for a further 60 min during which time a white precipitate had formed. A solution of anhydrous lithium bromide (0.28 g, 3.21 mmol) in acetone (2 mL) was then added and the resulting suspension was stirred at −78 °C for 40 min. The suspension was filtered through a pad of Celite followed by *in vacuo* concentration of the filtrate. The residue was diluted with ethyl acetate (20 mL) and water (10 mL). After separation, the aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (5 × 30 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (silica gel, 15% EtOAc–petrol) afforded the allylic bromide **21** (308 mg, 79% (+7% allylic chloride)) as a colourless oil. $[\alpha]_D^{22}$ +9.1 (*c* 1.54 in CH_2Cl_2); R_f 0.30 (15% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 2968 (CH), 1657 (C=C); δ_H (250 MHz; $CDCl_3$) 1.33 (3 H, s, C*H*$_3$COC), 1.60–1.80 (2 H, m, C*H*$_2$-CHOC), 1.74 (3 H, s, C*H*$_3$C=CH), 2.10–2.30 (2 H, m, C*H*$_2$C(Me)=CH), 2.85 (1 H, t, *J* 6.4, C*H*OC), 3.42 (1 H, d, *J* 11.0, C*H*HOBn), 3.51 (1 H, d, *J* 11.0, CH*H*OBn), 3.99 (2 H, d, *J* 8.5, C*H*$_2$Br), 4.51 (1 H, d, *J* 11.9, OC*H*HPh), 4.57 (1 H, d, *J* 11.9, OCH*H*Ph), 5.57 (1 H, t, *J* 8.5, C*H*CH$_2$Br), 7.27–7.40 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) 14.6 (q), 16.0 (q), 26.4 (t), 29.2 (t), 36.2 (t), 60.0 (s), 60.3 (d), 73.2 (t), 74.6 (t), 121.2 (d), 127.7 (3 × d), 128.4 (2 × d), 138.1 (s), 142.3 (s); *m*/*z* (CI) 356 ($M^+ + NH_4$, 100%), 312 (35), 259 (25), 151 (30), 111 (30) (Found: M^+, 339.0974. $C_{17}H_{23}O_2Br$ requires *M* 339.0960).

Preparation of methyl (*E*)-7-methyl-9-[(2*S*,3*S*)-3-methyl-3-(benzyloxymethyl)oxiran-2-yl]-3-oxonon-6-enoate 22

Sodium hydride (256 mg of a 60% oil dispersion, 6.40 mmol) was stirred in tetrahydrofuran (10 mL) at 0 °C under an atmosphere of nitrogen. Methyl acetoacetate (0.57 mL, 5.33 mmol) was added dropwise and the colourless solution was stirred at 0 °C for 10 min. To this solution was added *n*-butyllithium (3.67 mL of a 1.6 M solution in hexane, 5.87 mmol) dropwise and the yellow–orange solution was stirred for a further 10 min. To this solution was then added a solution of the allylic bromide **21** (0.90 g, 2.67 mmol) in tetrahydrofuran (8 mL) and the reaction was allowed to warm to room temperature with stirring. The reaction was left to stir for 17 h before being quenched with 1 M hydrochloric acid (8 mL) and ethyl acetate (10 mL). After separation, the aqueous layer was extracted with ethyl acetate (4 × 30 mL) and the combined organic layers were washed with water (3 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc–petrol) afforded the β-keto ester **22** (776 mg, 78%) as a yellow oil. $[\alpha]_D^{22}$ −3.7 (*c* 0.54 in CH_2Cl_2); R_f 0.45 (40% EtOAc–petrol) (Found: C, 70.3; H, 8.3. $C_{22}H_{30}O_5$ requires C, 70.6; H, 8.0%); ν_{max}/cm^{-1} (thin film) 2955 (CH), 1748 (C=O, ester), 1717 (C=O), 1629 (C=C); δ_H (250 MHz; $CDCl_3$) 1.31 (3 H, s, C*H*$_3$COC), 1.58–1.67 (2 H, m, C*H*$_2$CHOC), 1.61 (3 H, s, C*H*$_3$C=CH), 2.00–2.31 (4 H, m, C*H*$_2$C(Me)=CH, C*H*$_2$CH=C), 2.54 (2 H, t, *J* 7.3, C*H*$_2$C=O), 2.82 (1 H, t, *J* 6.4, C*H*OC), 3.40 (1 H, d, *J* 11.0, C*H*HOBn), 3.41 (2 H, s, C*H*$_2$CO$_2$Me), 3.48 (1 H, d, *J* 11.0, CH*H*OBn), 3.71 (3 H, s, CO$_2$C*H*$_3$), 4.50 (1 H, d, *J* 11.9, OC*H*HPh), 4.56 (1 H, d, *J* 11.9, OCH*H*Ph), 5.10 (1 H, t, *J* 7.2, C*H*=C), 7.25–7.35 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) 14.5 (q), 16.0 (q), 22.1 (t), 26.8 (t), 36.3 (t), 42.9 (t), 49.1 (t), 52.3 (q), 59.8 (s), 60.6 (q), 73.1 (t), 74.8 (t), 122.8 (d), 127.6 (3 × d), 128.4 (2 × d), 135.7 (s), 138.2 (s), 167.6 (s), 202.3 (s); *m*/*z* (CI) 392 ($M^+ + NH_4$, 100%), 244 (20), 227 (10), 108 (10) (Found: $M^+ + NH_4$, 392.2443. $C_{22}H_{34}NO_5$ requires *M* 392.2437).

Cyclisation of methyl (*E*)-7-methyl-9-[(2*S*,3*S*)-3-methyl-3-(benzyloxymethyl)oxiran-2-yl]-3-oxonon-6-enoate 22

To a solution of β-keto ester **22** (474 mg, 1.27 mmol) in dry dichloromethane (12 mL), toluene (12 mL), hexane (12 mL), was added triethylamine (0.55 mL, 3.93 mmol). The mixture was cooled to −78 °C, and a solution of boron trifluoride–diethyl ether (0.98 mL, 7.75 mmol) in dichloromethane (25 mL) was added over a period of 2 h. The resulting solution was allowed to stir for a further 2 h at −78 °C and then poured into ethyl acetate (200 mL) and saturated aqueous sodium hydrogen carbonate (200 mL). The organic phase was separated, washed with 0.1 M hydrochloric acid (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc–petrol) afforded the oxacycle **23** (291 mg, 61%) as a pale yellow oil. $[\alpha]_D^{22}$ −13.9 (*c* 0.58 in CH_2Cl_2); R_f 0.50 (50% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 3496 (br, OH), 2946 (CH), 1739 (C=O, ester), 1684 (C=C); δ_H (250 MHz; $CDCl_3$) 0.88 (3 H, s, C*H*$_3$CO), 1.18 (3 H, s, C*H*$_3$C), 1.49–2.00 (7 H, m, C*H*$_2$CHOH, C*H*$_2$CH$_2$CHOH, CHC*H*$_2$CH=C, C*H*CH$_2$CH=C), 2.95 (2 H, br s, C*H*$_2$CO$_2$Me), 3.26 (1 H, d, *J* 8.6, C*H*HOBn), 3.34 (1 H, br s, O*H*), 3.44 (1 H, d, *J* 8.6, CH*H*OBn), 3.66 (3 H, s, CO$_2$C*H*$_3$), 3.73 (1 H, dd, *J* 11.1 and 4.1, C*H*OH), 4.47 (1 H, d, *J* 12.2, OC*H*HPh), 4.53 (1 H, d, *J* 12.2, OCH*H*Ph), 4.58 (1 H, dd, *J* 2.6 and 2.0, C=C*H*), 7.24–7.40 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) 11.0 (q), 19.2 (q), 19.3 (t), 27.1 (t), 37.2 (t), 40.1 (t), 41.5 (s), 42.3 (d), 51.9 (q), 73.7 (t), 76.0 (d), 76.0 (s), 79.3 (t), 97.8 (d), 127.6 (d), 127.9 (2 × d), 128.5 (2 × d), 137.7 (s), 145.3 (s), 171.0 (s); *m*/*z* (EI) 374 (M^+, 20%), 265 (20), 149 (20), 91 (100), 55 (25) (Found: M^+, 374.2093. $C_{22}H_{30}O_5$ requires *M* 374.2086).

Preparation of methyl (2*Z*,6*E*)-3-[(diethoxyphosphoryl)oxy]-7-methyl-9-[(2*S*,3*S*)-3-methyl-3-(benzyloxymethyl)oxiran-2-yl]-nona-2,6-dienoate 24

A solution of the β-keto ester **22** (100 mg, 0.27 mmol) in diethyl ether (1 mL) was added to a suspension of sodium hydride (21 mg of a 60% oil dispersion, 0.54 mmol) in diethyl ether (2 mL) under an atmosphere of nitrogen at 0 °C. After stirring for 20 min, diethyl phosphorchloridate (58 μL, 0.40 mmol) was introduced and stirring was continued for 2.5 h at room temperature. The reaction mixture was stirred with excess ammonium chloride, filtered through Celite, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 40% EtOAc–petrol) afforded the enol phosphate **24** (127 mg, 93%) as a yellow oil. $[\alpha]_D^{22}$ −2.9 (*c* 2.55 in CH_2Cl_2); R_f 0.15 (40% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 2985 (CH), 1728 (C=O, ester), 1666 (C=C), 1281 (P=O), 1034 (P–O–C); δ_H (250 MHz; $CDCl_3$) 1.30 (3 H, s, C*H*$_3$COC), 1.34 (6 H, *J* 7.0, 2 × OCH$_2$C*H*$_3$), 1.58–1.66 (2 H, m, C*H*$_2$CHOC), 1.61 (3 H, s, C*H*$_3$C=CH), 2.00–2.46 (6 H, m, C*H*$_2$C(Me)=CH, C*H*$_2$CH=C, C*H*$_2$CH$_2$CH=C), 2.82 (1 H, t, *J* 6.4, C*H*OC), 3.39 (1 H, d, *J* 10.7, C*H*HOBn), 3.48 (1 H, d, *J* 10.7, CH*H*OBn), 3.66 (3 H, s, CO$_2$C*H*$_3$), 4.23 (4 H, quint, *J* 7.0, 2 × OC*H*$_2$CH$_3$), 4.49 (1 H, d, *J* 11.9, OC*H*HPh), 4.56 (1 H, d, *J* 11.9, OCH*H*Ph), 5.12 (1 H, t, *J* 7.0, C*H*=C), 5.32 (1 H, s, C*H*CO$_2$Me), 7.25–7.35 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) 14.4 (q), 16.0 (q), 16.1 (2 × q), 24.8 (t), 26.8 (t), 35.1 (t), 36.2 (t), 51.1 (q), 59.8 (s), 60.5 (d), 64.7 (t), 64.8 (t), 73.1 (t), 74.7 (t), 104.9 (d), 122.4 (d), 127.6 (3 × d), 128.3 (2 × d), 136.1 (s), 138.2 (s), 161.5 (s), 164.3 (s); *m*/*z* (CI) 510 (M^+, 0.5%), 319 (20), 155 (82), 91 (100) (Found: M^+, 510.2389. $C_{26}H_{39}PO_8$ requires *M* 510.2383).

Preparation of methyl (2*Z*,6*E*)-7-methyl-9-[(2*S*,3*S*)-3-methyl-3-(benzyloxymethyl)oxiran-2-yl]-3-[(trimethylsilyl)methyl]nona-2,6-dienoate 7

To a solution of trimethylsilylmethylmagnesium chloride (1.26 mL of a 0.87 M solution in diethyl ether, 1.10 mmol) at 0 °C under an atmosphere of nitrogen was added anhydrous nickel(II) acetylacetonate (23 mg, 0.09 mmol). The resulting dark-brown mixture was stirred for 5 min before a solution of enol phosphate **24** (224 mg, 0.44 mmol) in diethyl ether (11 mL) was added slowly. The reaction was stirred at 0 °C for 10 min

before being quenched by careful addition of 1 M hydrochloric acid (until acidic). After dilution with diethyl ether (15 mL), the solution was washed with 1 M hydrochloric acid (10 mL), brine (2 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% EtOAc–petrol) afforded the allylsilane **7** (105 mg, 54%) as a yellow oil. $[\alpha]_D^{22}$ −2.56 (*c* 5.2 in CH_2Cl_2); R_f 0.50 (20% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 2953 (CH), 1708 (C=O, ester), 1623 (C=C); δ_H (250 MHz; $CDCl_3$) 0.04 (9 H, s, 3 × $SiCH_3$), 1.32 (3 H, s, CH_3COC), 1.61 (3 H, s, CH_3C=CH), 1.61–1.69 (2 H, m, CH_2CHOC), 2.04–2.17 (6 H, m, CH_2C(Me)=CH, CH_2CH=C, CH_2CH$_2$CH=C), 2.40 (2 H, s, CH_2TMS), 2.84 (1 H, t, *J* 6.1, C*H*OC), 3.41 (1 H, d, *J* 11.0, C*H*HOBn), 3.50 (1 H, d, *J* 11.0, CH*H*OBn), 3.64 (3 H, s, CO_2CH_3), 4.51 (1 H, d, *J* 12.2, OC*H*HPh), 4.58 (1 H, d, *J* 12.2, OCH*H*Ph), 5.14 (1 H, t, *J* 7.0, C*H*=C), 5.52 (1 H, s, C*H*CO_2Me), 7.25–7.35 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) −0.8 (3 × q), 14.5 (q), 16.1 (q), 26.2 (t), 26.5 (t), 26.9 (t), 36.3 (t), 40.5 (t), 50.5 (q), 59.9 (s), 60.6 (d), 73.1 (t), 74.8 (t), 111.1 (d), 123.7 (d), 127.6 (3 × d), 128.4 (2 × d), 135.2 (s), 138.1 (s), 164.2 (s), 167.7 (s); *m*/*z* (EI) 444 (M^+, 2.5%), 429 (7), 253 (25), 186 (28), 149 (43), 91 (100) (Found: M^+, 444.2682. $C_{26}H_{40}SiO_4$ requires *M* 444.2696).

Preparation of methyl (4a*S*,5*R*,6*S*,8a*S*)-6-hydroxy-5,8a-dimethyl-2-methylene-5-(benzyloxymethyl)perhydronaphthalene-1-carboxylate 25

To a solution of epoxy allylsilane **7** (120 mg, 0.27 mmol) in dichloromethane (9 mL) was slowly added $BF_3{\cdot}OEt_2$ (41 μL, 0.32 mmol) at room temperature. The reaction mixture was stirred for 10 min then quenched with brine (2 mL). The organic layer was diluted with dichloromethane (10 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20% EtOAc–petrol) afforded the bicyclic alcohol **25** (54 mg, 54%) as a yellow oil. $[\alpha]_D^{22}$ +8.1 (*c* 2.95 in CH_2Cl_2); R_f 0.16 (20% EtOAc–petrol); ν_{max}/cm^{-1} (thin film) 3500 (br, OH), 2949 (CH), 1731 (C=O, ester), 1684 (C=C); δ_H (250 MHz; $CDCl_3$) 0.89 (1.5 H, s, CH_3), 0.94 (1.5 H, s, CH_3), 0.95 (1.5 H, s, CH_3), 1.08 (1.5 H, s, CH_3), 1.21–1.68 (7 H, m, CH_2CHOH, CH_2CH$_2$-CHOH, CH$_2$CH_2CH, C*H*CH$_2$CH$_2$), 1.95–2.62 (2 H, m, CH$_2$-CH_2CCH$_2$), 2.76 (1 H, s, C*H*CO_2Me), 3.20 (0.5 H, d, *J* 8.9, C*H*HOBn), 3.34 (0.5 H, d, *J* 8.9, CH*H*OBn), 3.47 (0.5 H, d, *J* 8.9, CH*H*OBn), 3.56 (0.5 H, d, *J* 8.9, C*H*HOBn), 3.62 (1.5 H, s, CO_2CH_3), 3.64 (1.5 H, s, CO_2CH_3), 3.60–3.71 (1 H, m, C*H*OH), 4.46 (1 H, d, *J* 12.2, OC*H*HPh), 4.54 (1 H, d, *J* 12.2, OCH*H*Ph), 4.66 (0.5 H, s, C=C*H*H), 4.73 (0.5 H, s, C=C*H*H), 4.83 (1 H, s, C=CH*H*), 7.29–7.39 (5 H, m, Ph); δ_C (63 MHz; $CDCl_3$) 12.2 (q), 14.6 (q), 21.1 (q), 22.9 (t), 23.1 (t), 26.3 (t), 26.5 (t), 31.7 (t), 35.6 (t), 35.8 (t), 36.6 (t), 37.9 (s), 38.9 (s), 39.8 (d), 41.9 (s), 42.3 (s), 48.3 (d), 51.1 (q), 51.4 (q), 62.7 (q), 63.1 (q), 73.6 (t), 73.8 (t), 75.6 (d), 77.0 (d), 78.8 (t), 81.4 (t), 108.9 (t), 112.9 (t), 127.6 (2 × d), 127.8 (d), 128.5 (2 × d), 137.9 (s), 138.0 (s), 143.0 (s), 143.6 (s), 171.8 (s), 173.0 (s); *m*/*z* (EI) 373 (M^+ + H, 100%), 355 (75), 264 (42), 246 (80), 233 (37), 206 (35), 105 (33), 91 (82) (Found: M^+, 372.2314. $C_{23}H_{32}O_4$ requires *M* 372.2301).

Preparation of methyl (4a*S*,5*R*,6*S*,8a*S*)-2,5,8a-trimethyl-6-(benzyloxy)-5-(benzyloxymethyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate 2

A solution of the bicyclic alcohol **25** (17 mg, 0.046 mmol) in THF (0.7 mL) was treated with NaH (9 mg of a 60% oil dispersion, 0.23 mmol) and the mixture was heated at reflux for 4 h. Benzyl bromide (27 μL, 0.23 mmol) was then added and the reaction was maintained at reflux for a further 2 h, cooled, and carefully quenched with water. The aqueous layer was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc–petrol) afforded the decalin **2** (11 mg, 51%) as a colourless oil. $[\alpha]_D^{22}$ +76.4 (*c* 0.45 in $CHCl_3$) [lit.,[4] +81 (*c* 0.5 in $CHCl_3$)]; R_f 0.18 (5% EtOAc–petrol); ν_{max}/cm^{-1} ($CHCl_3$) 2949 (CH), 1713 (C=O, ester); δ_H (250 MHz; $CDCl_3$) 0.73 (3 H, s, CH_3), 1.22 (3 H, s, CH_3), 1.37–1.93 (7 H, m, CH_2CHOBn, CH_2CH$_2$CHOBn, CH$_2$CH_2CH, C*H*CH$_2$CH$_2$), 1.61 (3 H, s, C=CCH_3), 2.05 (2 H, m, CH_2C(Me)=C), 3.13 (1 H, d, *J* 9.1, C*H*HOBn), 3.36 (1 H, d, *J* 9.1, CH*H*OBn), 3.57 (1 H, dd, *J* 11.0 and 4.6, C*H*OBn), 3.72 (3 H, s, CO_2CH_3), 4.28 (1 H, d, *J* 12.2, OC*H*HPh), 4.36 (1 H, d, *J* 11.9, OC*H*HPh), 4.41 (1 H, d, *J* 12.2, OCH*H*Ph), 4.59 (1 H, d, *J* 11.9, OCH*H*Ph), 7.29 (10 H, m, 2 × Ph) [lit.,[4] δ_H (270 MHz; $CDCl_3$) 0.74 (3 H, s), 1.22 (3 H, s), 0.97–1.92 (7 H, complex m), 1.62 (3 H, s), 2.07 (2 H, m), 3.14 (1 H, d, *J* 9.1), 3.37 (1 H, d, *J* 9.1), 3.57 (1 H, dd, *J* 11.5 and 4.6), 3.73 (3 H, s), 4.29 (1 H, d, *J* 12.3), 4.32 (1 H, d, *J* 11.9), 4.40 (1 H, d, *J* 12.3), 4.60 (1 H, d, *J* 11.9), 7.29 (10 H, m)]; δ_C (63 MHz; $CDCl_3$) 13.2 (q), 17.7 (t), 20.9 (2 × q), 22.8 (t), 31.9 (t), 34.5 (t), 36.4 (s), 42.2 (d), 42.5 (s), 51.1 (q), 71.4 (t), 71.9 (t), 72.9 (t), 79.1 (d), 127.3 (d), 127.4 (d), 127.6 (4 × d), 128.2 (4 × d), 132.9 (s), 137.9 (s), 138.8 (s), 139.3 (s), 170.9 (s); *m*/*z* (EI) 462 (M^+, 2%), 432 (10), 283 (12), 248 (37), 233 (17), 91 (100) (Found: M^+, 462.2752. $C_{30}H_{38}O_4$ requires *M* 462.2770).

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References

1 H. Tomoda, N. Tabata, D.-J. Yang, H. Takayanagi, H. Nishida and S. Õmura, *J. Antibiotics*, 1995, **48**, 495; H. Tomoda, Y.-K. Kim, H. Nishida, R. Masuma and S. Õmura, *J. Antibiotics*, 1994, **47**, 148; S. Õmura, H. Tomoda, Y.-K. Kim and H. Nishida, *J. Antibiotics*, 1993, **46**, 1168; Y.-K. Kim, H. Tomoda, H. Nishida, T. Sunazuka, R. Obata and S. Õmura, *J. Antibiotics*, 1994, **47**, 154; T. Sunazuka and T. Nagamitsu, *J. Synth. Org. Chem. Jpn.*, 1988, **56**, 478.
2 D. R. Sliskovic and A. D. White, *Trends Pharmacol. Sci.*, 1991, **12**, 194.
3 K. A. Parker and L. Resnick, *J. Org. Chem.*, 1995, **60**, 5726.
4 A. B. Smith III, T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y. Harigaya and S. Õmura, *J. Org. Chem.*, 1995, **60**, 8126.
5 For a review, see: (*a*) S. K. Taylor, *Org. Prep. Proc. Int.*, 1992, **24**, 247. For recent examples, see: (*b*) E. J. Corey and M. Sodeoka, *Tetrahedron Lett.*, 1991, **32**, 7005; (*c*) E. J. Corey, G. Luo and L. S. Lin, *J. Am. Chem. Soc.*, 1997, **119**, 9927; (*d*) E. J. Corey, G. Luo and L. S. Lin, *Angew. Chem., Int. Ed.*, 1998, **37**, 1126; for mechanistic studies, see: (*e*) E. J. Corey and D. D. Staas, *J. Am. Chem. Soc.*, 1998, **120**, 3526.
6 B. K. Sharpless, Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko and H. Masamune, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
7 V. K. Aggarwal, P. A. Bethel and R. Giles, *Chem. Commun.*, 1999, 325.
8 L. Weiler and R. J. Armstrong, *Can. J. Chem.*, 1986, **64**, 584.
9 L. Weiler and S. N. Huckin, *J. Am. Chem. Soc.*, 1974, **96**, 1082.
10 L. Weiler and F.-W. Sum, *Can. J. Chem.*, 1979, **57**, 1431.
11 K. B. Sharpless and M. A. Umbreit, *J. Am. Chem. Soc.*, 1977, **99**, 5526.
12 M. Kumada, T. Hayashi and Y. Katsuro, *Tetrahedron Lett.*, 1980, **21**, 3915.
13 E. J. Corey, J. Lee and D. R. Liu, *Tetrahedron Lett.*, 1994, **35**, 9149.
14 (*a*) T. Frejd, L. Pettersson and G. Magnusson, *Tetrahedron Lett.*, 1987, **28**, 2753; (*b*) M. E. Jung, Y. M. Cho and Y. H. Jung, *Tetrahedron Lett.*, 1996, **37**, 3.
15 S. P. Tanis, Y.-H. Chuang and D. B. Head, *J. Org. Chem.*, 1988, **53**, 4929.
16 B. Ganem and L. J. Liotta, *Tetrahedron Lett.*, 1989, **30**, 4759.
17 F. E. Ziegler, S. I. Klein, U. K. Pati and T.-F. Wang, *J. Am. Chem. Soc.*, 1985, **107**, 2730.
18 It was important to reduce the amount of allylic chloride present in the reaction mixture as it was found to be inefficient in the subsequent alkylation reaction.
19 Alternative conditions (CBr_4, PPh_3) resulted in lower yields of the allylic bromide **21** and led to bromohydrin formation.

20 β-Keto esters are known to cyclise through oxygen rather than carbon, see: T. R. Hoye, A. J. Caruso and M. J. Kurth, *J. Org. Chem.*, 1981, **46**, 3550; J. D. White, R. W. Skeean and G. L. Trammell, *J. Org. Chem.*, 1985, **50**, 1939.
21 From molecular modelling (SPARTAN) it was found that **27** was lower in energy than the conjugated tetrasubstituted double bond isomer **2.**
22 By ^{1}H NMR, ^{13}C NMR, mass and IR analyses.
23 The recovered isomer **28** was enriched in one diastereomer after 2 h reflux with NaH. After 4 h reflux, the recovered isomer **28** appeared to be one diastereomer only, suggesting a difference in deprotonation rates for the two diastereomeric esters.
24 J. Andrieux, D. H. R. Barton and H. Patin, *J. Chem. Soc.*, *Perkin Trans. 1*, 1977, 359.

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