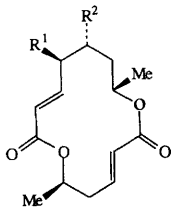
Enantioselective synthesis of the 13-membered macrodiolide bartanol

John A. O'Neill,[a] Stephen D. Lindell,[b] Thomas J. Simpson[a] and Christine L. Willis*,[a]

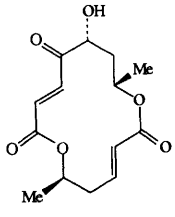
[a] *School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK*
[b] *AgrEvo UK Limited, Chesterford Park, Saffron Waldon, Essex CB10 1XL, UK*

The enantioselective synthesis of the unusual 13-membered ring macrodiolide bartanol 7 from poly[(*R*)-hydroxybutyrate] is described confirming the 6*R*,11*R*,13*R* configuration of the natural product. The use of a novel ylide 29 with a MEM-ester protecting group is developed to enable a mild, one-pot cleavage of both the acid and alcohol protecting groups in 30 prior to macrocyclisation to the bartanol framework. The outcome of a Wittig chain extension reaction on a mixture of lactols 19 and 22 using this ylide was found to be dependent on the solvent.

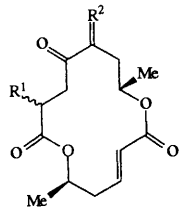
A group of 14-membered ring macrodiolides has been isolated from the culture filtrates of *Cytospora* sp. ATCC 20502 including colletodiol **1**,[1] colletoketol (or grahamimycin A) **2**, grahamimycin A_1 **3**, grahamimycin B **4**,[2] colletallol **5** and colletol **6**.[3] The structures of these metabolites have been elucidated by a combination of spectroscopic methods,[4] X-ray crystallography[5] and total synthesis.[6] Biosynthetic studies have established that colletodiol **1** is polyketide derived and is formed *via* C_6- and C_8-hydroxy acids of tri- and tetra-ketide origins respectively.[7] In the course of studies on the later stages of colletodiol biosynthesis in *Cytospora*,[8] extracts of the culture filtrate were examined for the presence of minor metabolites which might provide further information on the biosynthetic pathway. Two new macrodiolides, bartanol **7** and bartallol **8**,



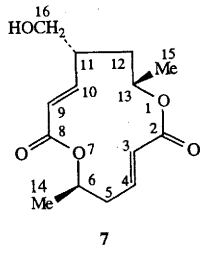
1 $R^1 = R^2 = OH$
5 $R^1 = OH, R^2 = H$
6 $R^1 = H, R^2 = OH$



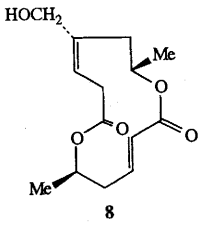
2



3 $R^1 = H, R^2 = O$
4 $R^1 = OH, R^2 = H, OH$



7

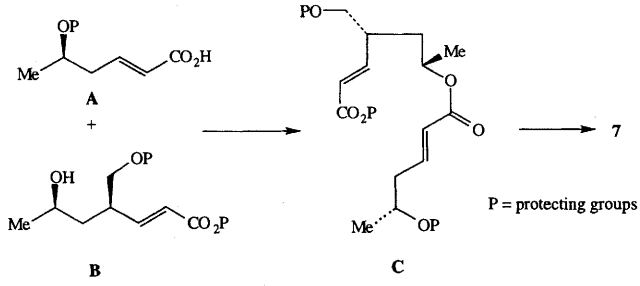


8

were isolated and their structures determined by a detailed study of their high field ^1H and ^{13}C NMR spectra.[3] Unlike the other macrodiolides isolated from *Cytospora* sp. ATCC 20502, bartanol and bartallol have a novel rearranged 13-membered macrocyclic ring. These compounds are of particular interest since they represent the first examples of macrodiolides in which the ring size has been established by a ring-contraction process on a preformed macrocycle. The first total synthesis of bartanol is now described, which not only confirms the absolute configuration of the natural product but also provides valuable material for biological assessment.

Results and discussion

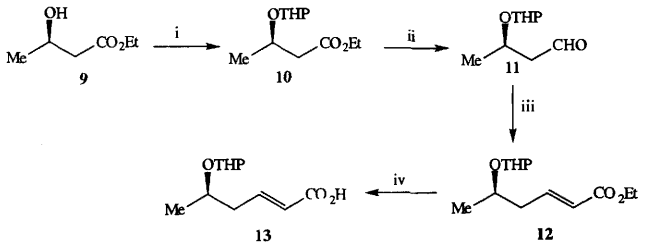
The group of 14-membered ring macrodiolides, including colletodiol, have been the subject of many synthetic studies during recent years. A widely used synthetic strategy has involved a convergent approach involving the macrocyclisation of a suitably protected C_6- and C_8-fragment, *e.g.* in the total synthesis of colletodiol **1**,[9] grahamimycin A_1 **3**,[10] colletallol **5**[11] and colletol **6**.[12] We favoured a similar convergent approach for the synthesis of bartanol **7** based on coupling a C_6-acid **A** with a C_8-alcohol **B** to give **C**, followed by deprotection and cyclisation (Scheme 1).



Scheme 1 Proposed synthetic strategy to bartanol **7**

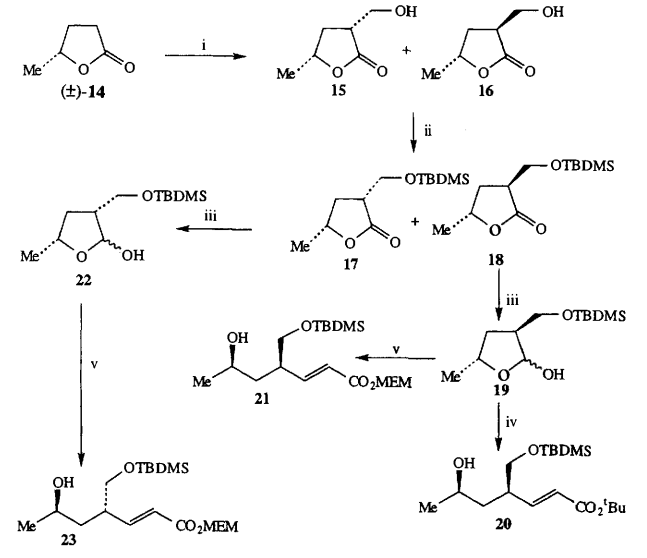
In the structural assignment of **7**,[3] the absolute configuration at C-6 and C-13 was assumed to be *R* by analogy with isolated co-metabolites from *Cytospora*. In our total synthesis of bartanol, the configurations at these key centres are both derived from ethyl (3*R*)-3-hydroxybutyrate **9**, which is readily obtained by acid catalysed depolymerisation of poly[(3*R*)-3-hydroxybutyrate] in ethanol.[13] The required homochiral C_6-acid **13** was prepared from ethyl (3*R*)-3-hydroxybutyrate in 72% overall yield as shown in Scheme 2. An acid labile protecting group was required for the alcohol and the tetrahydropyranyl derivative was selected. Reduction of the ester **10** with diisobutylaluminium hydride (DIBAL H) in toluene at −78 °C gave the aldehyde **11** in 93% yield which on treatment with ethoxycarbonylmethylidene(triphenyl)-phosphorane in tetrahydrofuran (THF) gave the required *trans* alkene **12** as the sole product. Saponification of the ester with sodium hydroxide gave the C_6-acid **13**.

Bartanol **7** has previously been assigned the structure with a 9*E* double bond and the *R*-configuration at C-11 by



Scheme 2 *Reagents:* i, Dihydropyran, toluene-*p*-sulfonic acid, CH_2Cl_2; ii, DIBAL-H, toluene, −78 °C; iii, Ph_3PCHCO_2Et, THF; iv, NaOH, THF, H_2O

spectroscopic techniques.[3] Hence for the synthesis of the C_8-fragment **20** of bartanol outlined in Scheme 3, the *anti*-(3*S**,



Scheme 3 *Reagents:* i, Lithium diisopropylamide, H_2CO, THF; ii, Bu^tMe_2SiCl, imidazole, CH_2Cl_2; iii, DIBAL-H, Et_2O, −78 °C; iv, $Ph_3PCHCO_2Bu^t$, THF; v, Ph_3PCHCO_2MEM, toluene

5*R**)-furan-2-one **16** was required to give the correct relative configuration at C-11 and C-13 of the 13-membered ring macrolide. In addition a *trans* double bond must be selectively introduced into **20** and it was envisaged that this could be effected *via* a Wittig chain extension of the lactols **19** using a stabilised ylide. Investigations into the synthesis of the C_8-fragment were initially carried out on racemic material from commercially available (±)-γ-valerolactone (Scheme 3). Hydroxymethylation of **14** was accomplished by first generating the lithium enolate with lithium diisopropylamide (LDA) in THF at −20 °C and then passing gaseous formaldehyde through the solution,[14] giving a 3:2 mixture of epimers at C-3 (by ^1H NMR spectroscopy) in 84% yield. The mixture was separated by HPLC and the structures of the products assigned on the basis of NOE studies. In the less polar compound, the NOE enhancements between 3-H, 4β-H and 5-H revealed that they are all on the same face of the molecule and hence was assigned as the *syn* (3*R**,5*R**) diastereoisomer **15** (Table 1). In the more polar (3*S**,5*R**) diastereoisomer **16**, NOE enhancements were observed as expected only between 3-H and 4α-H, 5-H and 4β-H and the geminal protons on C-4.

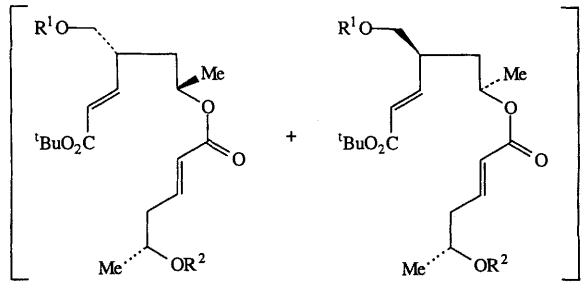
By analogy with the synthesis of grahamimycin A_1 described by Seebach,[10] we selected the *tert*-butyldimethylsilyl (TBDMS) ether as the protecting group for the primary alcohol and the *tert*-butyl ester for the carboxylic acid. Hence the alcohol in the (3*S**,5*R**)-furan-2-one **16** was protected as the TBDMS ether under standard conditions. An alternative approach to **18** was to protect the mixture of alcohols **15** and **16** as the TBDMS ethers and then to separate the mixture of ethers **17** and **18** by flash chromatography. Reduction of the TBDMS protected

Table 1 NOE enhancements observed for alcohols **15** and **16**

Irradiated signal	Enhancements (%)	
	15	**16**
3-H	4β-H (2) 5-H (1.5)	4α-H (2)
4β-H	3-H (3) 4α-H (10) 5-H(3)	3-H (2.5) 4α-H (11)
4α-H	4β-H (11)	3-H (2) 4β-H (11)
5-H	4β-H (2) 3-H (~1)	4β-H (2)

anti (3*S**,5*R**)-furan-2-one **18** with DIBAL-H gave a 1:1 mixture of epimeric lactols **19** in 98% yield which on reaction with *tert*-butoxycarbonylmethylidene(triphenyl)phosphorane in refluxing THF gave the unsaturated ester **20** as the sole product in 46% yield.

With quantities of the required C_6-acid **13** and C_8-alcohol **20** in hand, to complete the synthesis of 13-membered ring macrocycle it was necessary to couple **13** and **20** and then to deprotect the remaining secondary alcohol and carboxylic acid and cyclise. The coupling between the C_6-acid **13** and C_8-alcohol **20** proceeded smoothly with 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give the expected mixture of diastereoisomeric esters **24**. The tetrahydropyran (THP) protecting group in **24** was cleaved efficiently using dimethylaluminium chloride in dichloromethane[15] to give the hydroxy ester **25** without removal of the

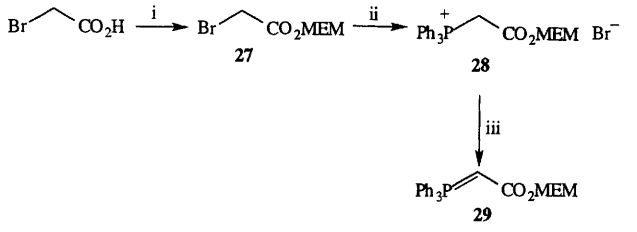


24 R^1 = TBDMS, R^2 = THP
25 R^1 = TBDMS, R^2 = H
26 $R^1 = R^2 = H$

TBDMS protecting group. Trifluoroacetic acid has been employed by Seebach *et al.*[10] to remove a *tert*-butyl ester in the synthesis of grahamimycin A_1. However, repeated attempts to hydrolyse the *tert*-butyl ester in either **24** or **25** using trifluoroacetic acid under a variety of conditions returned a complex mixture of products from which none of the desired hydroxy acid could be isolated. The only product which could be identified was the mixture of diastereoisomeric alcohols **26** in which the TBDMS protecting group had been cleaved, leaving the *tert*-butyl ester intact. The stability of the *tert*-butyl ester was surprising in light of its previous application to the synthesis of grahamimycin A_1. The major difference in this case is that the *tert*-butyl ester is on the C_8-fragment whereas in the synthesis of grahamimycin A_1 it was used in protection of the C_6-moiety. The branching in the C_8-moiety may result in additional steric hindrance which prevents hydrolysis of the *tert*-butyl ester. Therefore it was apparent that the *tert*-butyl ester was not a suitable choice of protecting group for the acid in fragment **B** (Scheme 1) in the total synthesis of bartanol **7** and a different group was required. Ideally we wanted a protecting group for the ester which could be cleaved under the same conditions as the THP ether in fragment **C** (Scheme 1). Kim *et*

al.[16] have used magnesium bromide to cleave a range of acetal protecting groups including THP ethers and 2-methoxyethoxymethyl (MEM) esters in the presence of TBDMS ethers. The use of the C_8-MEM ester **21** rather than the *tert*-butyl ester **20** solved the problems associated with deprotection of the carboxylic acid as described below.

The synthetic route to the racemic C_8-MEM ester **21** from the (3*S**,5*R**)-furan-2-one **18** *via* a Wittig reaction is shown in Scheme 3. The ylide **29** required in the Wittig chain extension reaction was prepared in three steps from bromoacetic acid (Scheme 4). Treatment of the acid with 2-methoxyethoxymethyl



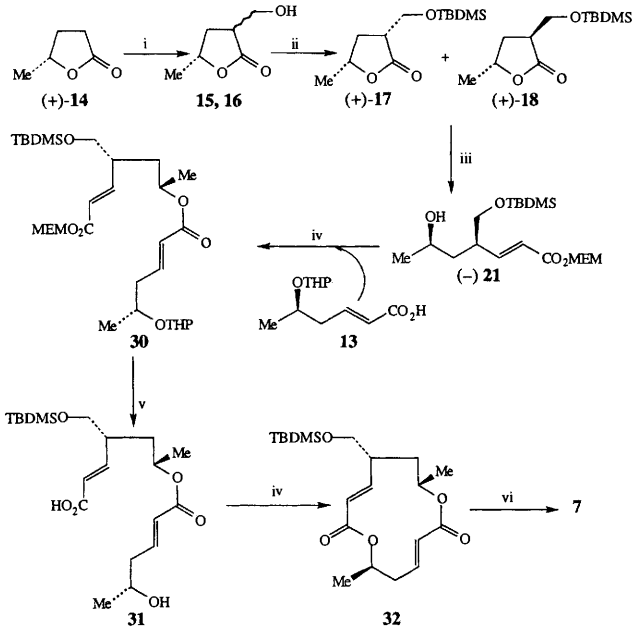
Scheme 4 *Reagents:* i, MEMCl, Et_3N, $CHCl_3$; ii, PPh_3, toluene; iii, $NaHCO_3$, EtOAc

chloride gave the bromo ester **27** which, on reaction with triphenylphosphine followed by sodium hydrogen carbonate, gave the required ylide **29**. Reduction of the (3*S**,5*R**)-furan-2-one **18** with DIBAL-H followed by treatment of the resultant mixture of lactols **19** with the ylide **29** in THF at reflux gave the required (4*R**,6*R**)-MEM ester **21**, but in only 10% yield (Scheme 3). Treatment of a mixture of lactols **19** and **22** with the ylide in toluene at 80 °C gave, as expected, the (4*R**,6*R**)- and (4*S**,6*R**)-diastereoisomers **21** and **23** which were separable by flash chromatography. Interestingly, when the Wittig chain extension reaction was performed in refluxing acetonitrile on approximately a 1 : 1 mixture of lactols **19** and **22**, the (4*R**,6*R**)-MEM ester **21** was obtained as the sole product in 20% yield. One possible explanation for this unexpected observation is that epimerisation of the *syn* (3*R**,5*R**)-furan-2-one **22** to the more stable *anti* (3*S**,5*R**)-isomer **19** is occurring prior to reaction with the ylide. Further Wittig chain extension reactions on a series of 2-substituted γ-valerolactones are being investigated in our laboratories.

The yield of unsaturated ester **21** was rather disappointing, particularly in view of the fact that on monitoring the reactions by TLC, only a single product was apparent. Further studies revealed that **21** (and **23**) are unstable, and washing with either water or dilute acid led to decomposition. Nonetheless having established a procedure for the synthesis of racemic C_8-MEM ester **21**, the approach was now used in the preparation of homochiral material and subsequently of bartanol **7** as described below.

Enantioselective synthesis of bartanol 7

The synthesis of the homochiral C_8-fragment requires (*R*)-(+)-γ-valerolactone (+)-**14** as the starting material which was prepared in 43% yield from ethyl (3*R*)-3-hydroxybutyrate as previously described.[13] Hydroxymethylation of the lactone (+)-**14** followed by protection of the resultant alcohols **15** and **16** with *tert*-butyldimethylsilyl chloride and imidazole gave approximately a 1 : 1 mixture of diastereoisomeric lactones in 78% yield over the two steps (Scheme 5). The products were separable by flash chromatography, giving the less polar (3*S*,5*R*)-3-*tert*-butyldimethylsiloxymethyl-5-methyltetrahydrofuran-2-one (+)-**18** {$[\alpha]_D$ +9.6 (*c* 2.9 in CH_2Cl_2)} and the more polar (3*R*,5*R*)-isomer (+)-**17** {$[\alpha]_D$ + 13.6 (*c* 3.1 in CH_2Cl_2)}. However this chromatographic separation led to considerable decomposition and from the studies described above on the racemic material, it was apparent that it was not necessary to separate the diastereoisomers prior to the chain



Scheme 5 *Reagents:* i, LDA, H_2CO, THF; ii, Bu^tMe_2SiCl, imidazole, CH_2Cl_2; iii, DIBAL-H, Et_2O, −78 °C then Ph_3PCHCO_2MEM, CH_3CN; iv, DCC, DMAP, toluene-*p*-sulfonic acid; v, $MgBr_2$, Et_2O; vi, 1% HCl

extension reaction. Hence the mixture of protected hydroxymethyl lactones (+)-**17** and (+)-**18** was reduced with DIBAL-H at −78 °C and the resultant mixture of lactols was then immediately treated with the MEM ylide **29** in refluxing acetonitrile to give the required 2-methoxyethoxymethyl (2*E*,4*R*,6*R*)-4-(*tert*-butyldimethylsiloxymethyl)-6-hydroxyhept-2-enoate (−)-**21** {$[\alpha]_D$ −12.6 (*c* 4.1 in $CHCl_3$)} as the sole product in 38% yield over the two steps.

The homochiral C_6-acid **13** and C_8-alcohol (−)-**21** were coupled using DCC–DMAP in dichloromethane to give the required seco ester **30**. The reaction was slow, giving only 37% isolated yield of **30** after 2 weeks, along with unreacted starting materials. Previous studies on DCC couplings by Holmberg and Keck[17] have shown that yields of esters may be reduced by the formation of *N*-acylureas. Addition of an acid inhibits the formation of the *N*-acylurea and indeed the rate of reaction between **13** and (−)-**21** was enhanced by the addition of toluene-*p*-sulfonic acid (PTSA) giving a 49% yield of seco ester **30** after 12 h. A key step in the synthesis of bartanol was the desired simultaneous deprotection of both the THP ether and the MEM ester in **30**. This was achieved in one pot using magnesium bromide in diethyl ether overnight at room temperature to give **31**. The resultant hydroxy acid **31** was immediately cyclised under DCC–DMAP conditions with 10 mol% PTSA added as catalyst to give bartanol TBDMS ether **32** in 33% overall yield from **30**. Finally, the TBDMS protecting group was cleaved using 1% HCl in ethanol to give bartanol **7**, with $[\alpha]_D$ +33.9 (*c* 0.4 in $CHCl_3$), which is in good agreement with the $[\alpha]_D$ +32.2 (*c* 1.9 in $CHCl_3$) of the natural product[3] isolated from *Cytospora*. The ^1H NMR spectra of the synthetic material and the natural product were identical.

In conclusion, the first enantioselective total synthesis of bartanol **7** has been described which confirms the 6*R*,11*R*,13*R* configuration of the natural product. The starting material for the synthesis is the relatively inexpensive poly[(*R*)-hydroxybutyrate] which was used for the preparation of both key fragments **13** and (−)-**21**. The synthesis is convergent and requires only eight steps from either hydroxybutyrate **9** or lactone (+)-**14**. A particularly valuable feature of the synthesis of bartanol was the development and use of the novel ylide **29** with a MEM ester protecting group which enabled the mild,

one-pot cleavage of the alcohol and acid protecting groups in **30**. Previous syntheses of related macrodiolides[9–12] have required sequential deprotection procedures. In addition, the surprising results from the reaction of the mixture of lactols **19** and **22** with the MEM ylide **29** in different solvents [in toluene the expected mixture of Wittig chain extension products **21** and **23** were formed, whereas in acetonitrile only the (4*R**,6*R**)-MEM ester **21** was obtained] warrants further investigation.

Experimental

General experimental details have been previously described.[3]

Ethyl (3*R*)-3-(tetrahydropyran-2-yloxy)butanoate 10

Ethyl (3*R*)-3-hydroxybutyrate [ethyl (3*R*)-3-hydroxybutanoate] **9** (6.6 g, 50 mmol) and toluene-*p*-sulfonic acid monohydrate (19 mg, 0.1 mmol) were stirred in dichloromethane (50 cm^3) at 0 °C under nitrogen. Dihydropyran (4.62 g, 55 mmol) was added slowly over 15 min and the reaction allowed to warm to ambient temperature after 15 min. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (25 cm^3) and the aqueous layer was then washed with dichloromethane (25 cm^3). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the *title compound* **10** (10.8 g, 100%) as an oil (Found: C, 60.9; H, 9.5. $C_{11}H_{20}O_4$ requires C, 61.09; H, 9.32%); ν_{max}/cm^{-1} 1737; δ_H 1.20 and 1.30 (each 1.5 H, d, *J* 6, CH_3CH), 1.26 and 1.27 (each 1.5 H, t, *J* 7.3, CH_2CH_3), 1.4–1.9 (6 H, m, $OCHCH_2CH_2CH_2$), 2.39, 2.42, 2.56 and 2.67 (each 0.5 H, m, CH_2CO_2), 3.5 and 3.88 (each 1 H, m, $OCHOCH_2$), 4.13 (2 H, q, *J* 7.3, CH_2CH_3), 4.19 and 4.25 (each 0.5 H, m, CH_3CH) and 4.69 and 4.74 (each 0.5 H, m, OCHO); *m*/*z* 115 (M^+ − 101, 34%), 101 (41), 85 (100) and 74 (40).

(3*R*)-3-(Tetrahydropyran-2-yloxy)butanal 11

DIBAL-H in toluene (1 mol dm^3; 10 cm^3, 10 mmol) was added to a solution of ethyl (3*R*)-3-(tetrahydropyran-2-yloxy)butanoate **10** (2.16 g, 10 mmol) in dry toluene (100 cm^3) maintaining the temperature below −70 °C under nitrogen. After 0.5 h the reaction was allowed to warm to ambient temperature, water (50 cm^3) and saturated aqueous ammonium chloride solution (50 cm^3) were added and the reaction stirred vigorously for 1 h. The precipitated alumina was then removed by filtering through a bed of Celite, which was then washed with toluene (100 cm^3). The toluene layer was dried over magnesium sulfate and concentrated *in vacuo* to give the aldehyde **11** (1.69 g, 93%) as an oil; ν_{max}/cm^{-1} 1729; δ_H 1.23 and 1.34 (each 1.5 H, d, *J* 6, CH_3CH), 1.45–1.85 (6 H, m, $OCHCH_2H_2CH_2$), 2.48, 2.53, 2.66 and 2.72 (each 0.5 H, m, CH_2CHO), 3.70 and 3.9 (each 1 H, m, CH_2OCHO), 4.27 (1 H, m, CH_3CH), 4.7 (1 H, m, OCHO) and 9.79 and 9.82 (each 0.5 H, m, CHO).

Ethyl (2*E*,5*R*)-5-(tetrahydropyran-2-yloxy)hex-2-enoate 12

Ethoxycarbonylmethylidene(triphenyl)phosphorane (5.65 g, 16.24 mmol) and (3*R*)-3-(tetrahydropyran-2-yloxy)butanal **11** (2 g, 11.6 mmol) were stirred in tetrahydrofuran (30 cm^3) for 3 days at ambient temperature under nitrogen. Hydrochloric acid (2 mol dm^{-3}; 150 cm^3) was added and the reaction mixture extracted with dichloromethane (2 × 150 cm^3). The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to an oil. The crude unsaturated ester **12** was purified by flash chromatography (SiO_2 10% ethyl acetate in petrol) to give an oil (2.17 g, 82.8%); ν_{max}/cm^{-1} 1720 and 1654; δ_H 1.14 and 1.26 (each 1.5 H, d, *J* 6, CH_3CH), 1.26 (3 H, m, CH_2CH_3), 1.5–1.8 (6 H, m, $OCHCH_2CH_2CH_2$), 2.4 (2 H, m, CH_2CH=), 3.5 and 3.9 (each 1 H, m, CH_2OCHO), 4.15 (1 H, m, CH_3CH), 4.2 (2 H, q, *J* 7.1, CH_2CH_3), 4.65 and 4.75 (each 0.5 H, m, OCHO), 5.87 and 5.92 (each 0.5 H, d, *J* 15.6, $=CHCO_2$) and 7.0 (1 H, m, $CH=CHCO_2$); *m*/*z* 141 (M^+ − 101, 10.6%), 113 (10), 101 (2), 95 (7) and 85 (100).

(2*E*,5*R*)-5-(Tetrahydropyran-2-yloxy)hex-2-enoic acid 13

The ester **12** (1.45 g, 6 mmol) was added to a solution of sodium hydroxide (814 mg, 20.34 mmol) in tetrahydrofuran (85 cm^3) and water (85 cm^3) and stirred at ambient temperature for 16 h. The reaction was adjusted to pH 1.0 with concentrated hydrochloric acid then extracted with dichloromethane (3 × 170 cm^3), dried over magnesium sulfate then concentrated *in vacuo* to give the unsaturated acid **13** (1.19 g, 92.6%) as an oil; ν_{max}/cm^{-1} 2943, 1699 and 1655; δ_H 1.16 and 1.25 (each 1.5 H, d, *J* 6.2, CH_3CH), 1.4–1.9 (6 H, m, $OCHCH_2CH_2CH_2$), 2.5 (2 H, m, CH_2CH=), 3.53 and 3.84 (each 1 H, m, CH_2OCHO), 3.84 (1 H, m, CH_3CH), 4.67 and 4.74 (each 0.5 H, m, OCHO), 5.89 and 5.92 (each 0.5 H, d, *J* 15.6, $=CHCO_2$) and 7.11 (1 H, m, $CH=CHCO_2$); *m*/*z* 113 (M^+ − 101, 22.5%), 101 (4), 96 (17), 86 (100), 68 (26) and 57 (34).

Hydroxymethylation of (+)-5-methyltetrahydrofuran-2-one [(+)-γ-valerolactone] 14

Diisopropylamine (3.5 cm^3, 25 mmol) and butyllithium in hexane (2.5 mol dm^{-3}; 10 cm^3, 25 mmol) were added to dry tetrahydrofuran (200 cm^3) at room temperature under nitrogen. The reaction was then cooled to −20 °C and (±)-5-methyltetrahydrofuran-2-one **14** (2 g, 20 mmol) was added. After 15 min gaseous formaldehyde was bubbled through the reaction mixture in a stream of nitrogen for 30 min. When no lactone remained by TLC (SiO_2, 80% ethyl acetate in petrol) the reaction was worked up by the addition of hydrochloric acid (0.5 mol dm^{-3}; 200 cm^3). The reaction mixture was extracted with dichloromethane (3 × 400 cm^3), dried over magnesium sulfate and concentrated *in vacuo* to give a mixture of (3R*,4R*) and (3S*,5R*)-3-*hydroxymethyl*-5-*methyltetrahydrofuran*-2-*one* **15** and **16** (2.18 g, 84%) as an oil; ν_{max}/cm^{-1} 3429 and 1757; *m*/*z* 130 (M^+, 2.5%), 115 (8), 100 (13) and 57 (100) (Found: M^+, 130.063. $C_6H_{10}O_3$ requires *M*, 130.063).

A sample of the mixture of **15** and **16** (60 mg) in dichloromethane (0.9 cm^3) was separated by normal phase preparative HPLC (flow rate 21.6 cm^3 min^{-1}, mobile phase 2% propan-2-ol in dichloromethane, detection 240 nm).

(3*R,5*R**)-3-Hydroxymethyl-5-methyltetrahydrofuran-2-one 15.** Compound **15** (12 mg) eluted after 27 min; δ_H 1.45 (3 H, d, *J* 6.1, CH_3CH), 1.8 (1 H, ddd, *J* 12.2, 12.2 and 10.3, $CHCHHCH$), 2.43 (1 H, ddd, *J* 12.2, 9.0 and 5.4, $CHCHHCH$), 2.89 (1 H, dddd, *J* 12.2, 9.0, 5.9 and 3.6, CH_2CHCO), 3.78 (1 H, dd, *J* 11.2 and 5.9, CHHOH), 3.94 (1 H, dd, *J* 11.2 and 3.6, CHHOH) and 4.59 (1 H, ddq, *J* 10.3, 6.1 and 5.4, CH_3CH).

(3*S,5*R**)-3-Hydroxymethyl-5-methyltetrahydrofuran-2-one 16.** Compound **16** (12 mg) eluted after 30 min; δ_H 1.39 (3 H, d, *J* 6.4, CH_3CH), 2.02 (1 H, ddd, *J* 12.9, 9.5 and 4.4, $CHCHHCH$), 2.39 (1 H, ddd, *J* 12.9, 12.9 and 7.8, $CHCHHCH$), 2.9 (1 H, dddd, *J* 12.9, 5.1, 4.9 and 4.4, CH_2CHCO), 3.79 (1 H, dd, *J* 11.2 and 5.1, CHHOH), 3.94 (1 H, dd, *J* 11.2 and 4.9, CHHOH) and 4.59 (1 H, ddq, *J* 6.4, 9.5 and 7.8, CH_3CH).

TBDMS protection of the mixture of 3-hydroxymethyl-5-methyltetrahydrofuran-2-ones 15 and 16

The mixture of lactones **15** and **16** (10.2 g, 78.5 mmol), *tert*-butyldimethylsilyl chloride (15.1 g, 100 mmol) and imidazole (13.62 g, 200 mmol) were stirred in dry *N*,*N*-dimethylformamide (80 cm^3) under nitrogen for 48 h. Diethyl ether (800 cm^3) and water (800 cm^3) were added to the reaction mixture and the aqueous layer washed with diethyl ether (800 cm^3). The combined diethyl ether extracts were washed with water (3 × 800 cm^3) and dried over magnesium sulfate and concentrated *in vacuo* to give a mixture of (3R*,5R*)- and (3S*,5R*)-3-tert-*butyldimethylsiloxymethyl*-5-*methyltetrahydrofuran*-2-*one* **17** and **18** as an oil. The isomers were separated by flash chromatography (SiO_2, 20% diethyl ether in hexane).

(3*S,5*R**)-3-*tert*-Butyldimethylsiloxymethyl-5-methyltetrahydrofuran-2-one 18.** The less polar product, **18**, was isolated as

a gum (2.6 g, 13.6%) (Found: $M^+ - 15$, 229.126. $C_{11}H_{21}O_3Si$ requires M, 229.126); ν_{max}/cm^{-1} 1774; δ_H 0.04 [6 H, s, $(CH_3)_2Si$], 0.86 [9 H, s, $(CH_3)_3CSi$], 1.36 (3 H, d, J 6.4, CH_3CH), 1.96 (1 H, ddd, J 12.9, 9.8 and 6.0, CHCHHCH), 2.4 (1 H, ddd, J 12.9, 6.8 and 5.9, CHCHHCH), 2.76 (1 H, dddd, J 9.8, 5.9, 4.4 and 3.4, CH_2CHCO), 3.76 (1 H, dd, J 10 and 3.4, CHHOH), 3.96 (1 H, dd, J 10 and 3.4, CHHOH) and 4.67 (1 H, ddq, J 6.8, 6.4 and 6.0, CH_3CH); m/z 229 ($M^+ - 15$, 2.5%), 187 (60.7), 75 (100) and 57 (44).

(3*R,5*R**)-3-*tert*-butyldimethylsiloxymethyl-5-methyltetrahydrofuran-2-one 17.** The more polar product, **17**, was also isolated as a gum (1.15 g, 6%) (Found: $M^+ - 15$, 229.126. $C_{11}H_{21}O_3Si$ requires M, 229.126); ν_{max}/cm^{-1} 1774; δ_H 0.05 [6 H, s, $(CH_3)_2Si$], 0.87 [9 H, s, $(CH_3)_3Si$], 1.41 (3 H, d, J 6.1, CH_3CH), 1.90 (1 H, m, CHCHHCH), 2.41 (1 H, m, CHCHHCH), 2.78 (1 H, m, CH_2CHCO), 3.80 (1 H, dd, J 10 and 3.4, CHHOH), 3.91 (1 H, dd, J 10 and 5, CHHOH) and 4.67 (1 H, m, CH_3CH); m/z 229 ($M^+ - 15$, 2.5%), 187 (60.7), 75 (100) and 57 (44).

A mixed fraction containing both isomers was also recovered (1.4 g, 7.3%).

(3*S,5*R**)-3-*tert*-Butyldimethylsilyloxymethyl-5-methyltetrahydrofuran-2-ol 19**

The (3*S**,5*R**) lactone **18** (488 mg, 2 mmol) in dry diethyl ether (20 cm^3) was cooled to −78 °C under nitrogen. DIBAL-H in hexane (1 mol dm^{-3}; 2.5 cm^3, 2.5 mmol) was added slowly over 15 min, and then after 30 min the reaction was warmed to room temperature. Water (10 cm^3) and saturated ammonium chloride (10 cm^3) were added and the reaction stirred vigorously for 30 min. The reaction mixture was filtered through Celite, and the filter bed washed with diethyl ether (50 cm^3). The aqueous layer was washed with diethyl ether (50 cm^3) and the combined ether layers were dried over magnesium sulfate and concentrated *in vacuo* to give the title compound **19** (482 mg, 98%) as a 1:1 mixture of isomeric lactols; ν_{max}/cm^{-1} 3409; δ_H 0.03 and 0.06 (each 3 H, s, $SiCH_3$), 0.87 and 0.88 (each 4.5 H, s, $SiCCH_3$), 1.21 and 1.31 (each 1.5 H, d, J 6, CH_3CH), 1.55 and 2.05 (each 0.5 H, m, CH_3CHCHH), 1.8 (1 H, m, CH_3CHCHH), 2.38 and 2.43 (each 0.5 H, m, $CHCH_2OSi$), 3.51 (1 H, m, CHHOSi), 3.78 and 3.86 (each 0.5 H, m, CHHOSi), 4.23 and 4.38 (each 0.5 H, m, CH_3CH) and 5.26 and 5.43 (each 0.5 H, m, CHOH); m/z (CI, methane), 245 ($M^+ - 1$, 10%), 229 (85), 189 (4), 115 (23) and 97 (79).

***tert*-Butyl (2*E*,4*R**,6*R**)-4-*tert*-butyldimethylsiloxymethyl-6-hydroxyhept-2-enoate 20**

tert-Butoxycarbonylmethylidene(triphenyl)phosphorane (1.63 g, 4.33 mmol) and the lactol **19** (410 mg, 1.67 mmol) were heated to reflux in tetrahydrofuran (8 cm^3) for 16 h under nitrogen. Diethyl ether (100 cm^3) was added and the reaction washed with hydrochloric acid (2 mol dm^{-3}; 100 cm^3). The ether layer was dried over magnesium sulfate and concentrated *in vacuo* to an oil. Purification by flash chromatography, eluting with 20% ethyl acetate in petrol, gave the unsaturated ester **20** as a gum (266 mg, 46.3%); ν_{max}/cm^{-1} 3420, 1720 and 1655; δ_H 0.07 (6 H, s, CH_3Si), 0.91 (9 H, s, CH_3CSi), 1.20 (3 H, d, J 6.2, CH_3CH), 1.49 [9 H, s, $CO_2C(CH_3)_3$], 2.58 (2 H, m, $CHCH_2CH$), 3.58 (2 H, m, CH_2OSi), 3.8 (1 H, m, CH_3CHCH_2), 5.81 (1 H, d, J 15.7, $CHCHCO_2$) and 6.72 (1 H, dd, J 15.7 and 8.9, $CHCHCO_2$); m/z 344 (M^+, 6%), 231 (15), 213 (31), 89 (54), 75 (100) and 57 (58).

***tert*-Butyl (2*E*,4*R**,6*R**,2′*E*,5′*R*)-4-(*tert*-butyldimethylsiloxymethyl)-6-[5′-(tetrahydropyran-2″-yloxy)hex-2′-enoyloxy]hept-2-enoate 24**

The alcohol **20** (45 mg, 0.13 mmol), the acid **13** (35 mg, 0.16 mmol), dicyclohexylcarbodiimide (66 mg, 0.32 mmol) and 4-dimethylaminopyridine (4 mg, 0.4 mmol) were stirred in dry diethyl ether (1 cm^3) under nitrogen for 4 days. The reaction mixture was then filtered through Celite and the filter bed washed with diethyl ether (10 cm^3). The filtrate was concentrated *in vacuo* to an oil, and the mixture purified by flash chromatography (SiO_2, 20% ethyl acetate in petrol) to give the title compound **24** as an oil (52 mg, 75%); ν_{max}/cm^{-1} 1713, 1655; δ_H 0.02 (6 H, s, $SiCH_3$), 0.86 (9 H, s, $SiCCH_3$), 1.1–1.3 (6 H, m, 6′-H_3 and 7-H_3), 1.45 (9 H, s, CO_2CCH_3), 1.5–2.0 (8 H, m, 5-H_2, 3″-H_2, 4″-H_2 and 5″-H_2), 2.4 (3 H, m, 4-H and 4′-H_2), 3.2 (1 H, m, 6″-H), 3.5 (2 H, m, $TBDMSOCH_2$), 3.9 (2 H, m, 6″-H and 5′-H), 4.64 and 4.72 (each 0.5 H, m, 2″-H), 4.92 (1 H, m, 6-H), 5.70 (1 H, d, J 16, 2-H), 5.81 and 5.84 (each 0.5 H, d, J 15.6, 3′-H), 6.65 (1 H, dd, J 16 and 9.2, 3-H) and 6.92 (1 H, m, 9-H); m/z (CI, isobutane) 541 ($M^+ + 1$, 0.2%), 457 (7), 401 (87), 271 (37) and 85 (100).

***tert*-Butyl (2*E*,4*R**,6*R**,2′*E*,5′*R*)-4-(*tert*-butyldimethylsiloxymethyl)-6-(5′-hydroxyhex-2′-enoyloxy)hept-2-enoate 25**

The ester **24** (52 mg, 0.096 mmol) in dichloromethane (2 cm^3) was cooled to −20 °C under nitrogen. A solution of dimethylaluminium chloride in hexane (1 mol dm^{-3}; 250 mm^3, 0.25 mmol) was added and the reaction stirred at −20 °C for 30 min, then allowed to warm to ambient temperature for 3 h. Dichloromethane (30 cm^3) and aqueous sodium hydrogen carbonate (10 cm^3) were added to the reaction which was stirred at ambient temperature for a further 30 min. The reaction mixture was filtered through Celite and the filter bed washed with dichloromethane (10 cm^3). The dichloromethane layer was dried over magnesium sulfate and concentrated *in vacuo* to give a mixture of the alcohols **25** (39 mg, 94%) as an oil; ν_{max}/cm^{-1} 3440, 1719 and 1655; δ_H 0.01 (6 H, s, $SiCH_3$), 0.86 (9 H, s, $SiCCH_3$), 1.22 and 1.23 (each 3 H, d, J 6.1, 6′-H_3 or 7-H_3), 1.45 (9 H, s, CO_2CCH_3), 1.57 and 1.85 (each 1 H, m, 5-H_2), 2.35 (2 H, m, 4′-H_2), 2.7 (1 H, m, 4-H), 3.53 (2 H, d, J 6.1, $TBDMSOCH_2$), 3.9 (1 H, m, 5′-H), 4.95 (1 H, m, 6-H), 5.75 (1 H, d, J 15.8, 2-H), 5.88 (1 H, d, J 15.5, 2′-H), 6.67 (1 H, dd, J 15.8 and 7.3, 3-H) and 6.94 (1 H, dt, J 15.5 and 7.5, 3′-H).

***tert*-Butyl (2*E*,4*R**,6*R**,2′*E*,5′*R*)-6-(5′-hydroxyhex-2′-enoyloxy)-4-hydroxymethylhept-2-enoate 26**

The ester **25** (47 mg, 0.87 mmol) was stirred in dry tetrahydrofuran (1 cm^3) and trifluoroacetic acid (77 mm^3, 1 mmol) for 7 days under nitrogen. Dichloromethane (10 cm^3) and saturated aqueous sodium hydrogen carbonate (10 cm^3) were added and the reaction was washed with dichloromethane (3 × 10 cm^3), dried over magnesium sulfate and concentrated *in vacuo* to an oil. The mixture was purified by flash chromatography (SiO_2, 60% ethyl acetate in petrol) to give the title compounds **26** as an oil (5 mg, 17%); δ_H 1.25 (6 H, m, 6′-H_3 and 7-H_3), 1.46 (9 H, s, CO_2CCH_3), 1.6–1.9 (2 H, m, 5-H_2), 2.35 (2 H, m, 4′-H_2), 2.48 (1 H, m, 4-H), 3.6 (2 H, m, $TBDMSOCH_2$), 3.96 (1 H, m, 5′-H), 4.94 and 5.02 (each 0.5 H, m, 6-H), 5.75–5.9 (2 H, m, 2-H and 2′-H), 6.7 (1 H, m, 3-H) and 6.95 (1 H, m, 3′-H); m/z (CI, ammonia) 360 ($M^+ + 18$, 100%), 334 (15), 304 (40), 248 (72) and 192(39).

2-Methoxyethoxymethyl bromoacetate 27

Triethylamine (12.65 cm^3, 125 mmol) was added to a solution of bromoacetic acid (13.9 g, 100 mmol) in dry chloroform (150 cm^3) at 0 °C under nitrogen. 2-Methoxyethoxymethyl chloride (15.57 g, 125 mmol) was added to the reaction mixture at 0 °C over 20 min, the reaction was warmed to ambient temperature and stirred for 2 h. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (150 cm^3) and the aqueous layer washed with chloroform (50 cm^3). The combined chloroform layers were washed with hydrochloric acid (2 mol dm^{-3}, 150 cm^3) and the acid layer washed with chloroform (50 cm^3). The combined chloroform layers were dried over magnesium sulfate and concentrated *in vacuo* to give the *bromo ester* **27** (19.5 g, 85.9%) as an oil (Found: M^+,

182.9477. $C_5H_9O_3{}^{81}Br$ requires *M*, 182.9479); ν_{max}/cm^{-1} 1752; δ_H 3.40 (3 H, s, OCH_3), 3.58 (2 H, m, CH_2OCH_3), 3.84 (2 H, m, OCH_2OCH_2), 4.11 (2 H, s, $BrCH_2CO_2$) and 5.42 (2 H, s, CO_2CH_2O); δ_C 166.91 (CO_2), 90.87 (OCH_2O), 71.37 ($BrCH_2$), 69.96 (OCH_2OCH_2), 59.09 (CH_2OCH_3) and 40.83 (OCH_3); *m/z* 183 [M^+(^{81}Br), 1%], 181 (3), 153 (6), 151 (10), 89 (76) and 59 (100).

2-Methoxyethoxymethoxycarbonylmethyl(triphenyl)-phosphonium bromide 28

Triphenylphosphine (20.98 g, 80 mmol) and methoxyethoxymethyl bromoacetate **27** (18.16 g, 80 mmol) were stirred in dry toluene (80 cm^3) for 48 h under nitrogen. Vacuum filtration followed by drying *in vacuo* at 1 mmHg gave the title compound **28** (1.9 g, 43%); δ_H 3.31 (3 H, s, CH_2OCH_3), 3.44 (2 H, m, CH_2OCH_3), 3.63 (2 H, m, OCH_2OCH_2), 5.22 (2 H, s, CO_2CH_2O), 5.45 (2 H, d, *J* 32, PCH_2CO_2) and 7.6–8.0 (15 H, m, Ar-H).

2-Methoxyethoxymethoxycarbonylmethylidene(triphenyl)-phosphane 29

2-Methoxyethoxymethoxycarbonylmethyl(triphenyl)phosphonium bromide **28** (2.2 g, 4.5 mmol) was dissolved in water (22.5 cm^3), then saturated aqueous sodium hydrogen carbonate (22.5 cm^3) was added with vigorous stirring. The reaction mixture was extracted with ethyl acetate (2 × 45 cm^3). The ethyl acetate extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the *ylide* **29** as an oil (1.46 g, 79.5%) (Found: $M^+ + 1$, 409.1569. $C_{24}H_{26}O_4P$ requires *M*, 409.1568); ν_{max}/cm^{-1} 1734 and 1627; δ_H 3.05 (1 H, d, *J* 21.7, $PCHCO_2$), 3.37 (3 H, s, OCH_3), 3.54 (2 H, m, $OCH_2CH_2OCH_3$), 3.68 (2 H, m, $OCH_2CH_2OCH_3$), 4.75 (2 H, m, CO_2CH_2O) and 7.4–7.7 (15 H, m, Ar-H); *m/z* (CI, CH_4) 409 ($M^+ + 1$, 1.7%), 367 (2), 279 (100), 262 (53), 201 (46), 185 (45), 89 (63) and 59 (57).

2-Methoxyethoxymethyl (2*E*,4*R,6*R**)-4-*tert*-butyldimethylsiloxymethyl-6-hydroxyhept-2-enoate 21**

The MEM ylide **29** (1.46 g, 3.57 mmol) and the lactols **19** (545 mg, 2.2 mmol) were heated to reflux in tetrahydrofuran (10 cm^3) for 5 h under nitrogen. Diethyl ether (150 cm^3) was added and the reaction mixture washed with hydrochloric acid (2 mol dm^{-3}; 50 cm^3). The ether layer was dried over magnesium sulfate and concentrated *in vacuo* to an oil. The *unsaturated ester* **21** was purified by flash chromatography (SiO_2, 0 to 40% ethyl acetate in petrol) to give a gum (85 mg, 10.3%) (Found: $M^+ - 17$, 359.2268. $C_{18}H_{35}O_5Si$ requires *M*, 359.2254); ν_{max}/cm^{-1} 3440, 1722 and 1651; δ_H 0.02 (6 H, s, $SiCH_3$), 0.85 (9 H, s, $SiCCH_3$), 1.16 (3 H, d, *J* 6.2, CH_3CH), 1.55 (2 H, m, $CHCH_2CH$), 2.60 (1 H, m, $CH_2CH{=}CH$), 3.35 (3 H, s, OCH_3), 3.53 (2 H, m, $OCH_2CH_2OCH_3$), 3.58 (2 H, m, CH_2OSi), 3.77 (3 H, m, $OCH_2CH_2OCH_3$ and CH_3CH), 5.36 (2 H, s, CO_2CH_2O), 5.87 (1 H, d, *J* 15.6, $CHCO_2$), 6.86 (1 H, dd, *J* 15.6 and 15.8, $CHCHCO_2$); δ_C 165.64 (CO_2), 151.17 ($CHCHCO_2$), 121.74 ($CHCO_2$), 89.26 (OCH_2O), 71.38 (CH_2OCH_2), 69.37 (CH_2OCH_3), 66.08 (CH_2OSi), 65.73 (CH_3CH), 59.01 (CH_2OSi), 42.56 (OCH_3), 40.77 (CH_2CHCH_2OSi), 25.76 ($SiCCH_3$), 24.30 (CH_3CH), 18.17 ($SiCCH_3$) and −5.38 ($SiCH_3$); *m/z* (CI, CH_4) 359 ($M^+ - 18$, 7%), 329 (3), 301 (5), 271 (52), 229 (12), 213 (16), 89 (100), 75 (24) and 59 (54).

Wittig reaction of lactol mixture 19 and 22 in toluene

The lactol mixture **19** and **22** (123 mg, 0.5 mmol) and MEM ylide **29** (2.04 g, 5 mmol) in dry toluene (5 cm^3) were heated to 80 °C for 4 h under nitrogen. The reaction was cooled to room temperature and ethyl acetate (50 cm^3) added. The reaction mixture was washed with hydrochloric acid (2 mol dm^{-3}; 25 cm^3), then dried over magnesium sulfate and concentrated *in vacuo* to an oil. The reaction mixture was purified by flash chromatography (SiO_2, 20 to 50% ethyl acetate in petrol). The (4*R**,6*R**) ester **21** (22 mg, 11.7%) eluted first, spectral data as before. This was followed by 2-*methoxyethoxymethyl* (2E,4S*,6R*)-4-tert-*butyldimethylsiloxymethyl*-6-*hydroxyhept*-2-*enoate* **23** as a gum (19 mg, 10.1%) (Found: $M^+ - 17$, 359.2268. $C_{18}H_{35}O_5Si$ requires *M*, 359.2254); ν_{max}/cm^{-1} 3445, 1724 and 1651; δ_H 0.05 (6 H, s, $SiCH_3$), 0.88 (9 H, s, $SiCCH_3$), 1.19 (3 H, d, *J* 5.4, CH_3CH), 1.62 (2 H, m, $CHCH_2CH$), 2.58 (1 H, m, $CHCH_2OSi$), 3.38 (3 H, s, OCH_3), 3.55 (2 H, m, CH_2OCH_3), 3.64 (2 H, m, CH_2OSi), 3.81 (2 H, m, OCH_2OCH_2), 3.9 (1 H, m, CH_3CH), 5.39 (2 H, s, OCH_2O), 5.87 (1 H, d, *J* 15.9, $CHCO_2$), 6.95 (1 H, dd, *J* 15.9 and 7.8, $CHCHCO_2$); δ_C 165.67 (CO_2), 151.30 ($CHCHCO_2$), 121.32 ($CHCO_2$), 89.33 (OCH_2O), 71.43 ($CO_2CH_2OCH_2$), 69.43 (CH_2OCH_3), 65.43 (CH_2OSi), 65.34 (CH_3CH), 59.06 ($CHCH_2OSi$), 41.69 ($CHCH_2CH$), 40.69 (OCH_3), 25.77 ($SiCCH_3$), 23.43 (CH_3CH), 18.20 [$SiC(CH_3)_3$], and −5.54 ($SiCH_3$); *m/z* (CI, CH_4) 359 ($M^+ - 17$, 6.2%), 329 (9), 271 (71), 33 (30) and 89 (100).

Wittig reaction of lactol mixture 19 and 22 in acetonitrile

The MEM ylide **29** (20.4 g, 50 mmol) and the diastereoisomeric mixture of lactols **19** and **22** (2.4 g, 9.75 mmol) were heated to reflux in dry acetonitrile (50 cm^3) for 3 h under nitrogen. The crude reaction mixture was purified by flash chromatography (SiO_2, 0% to 30% diethyl ether in petrol) to give the unsaturated ester **21** (735 mg, 20%) as an oil. Spectral data as before.

Hydroxymethylation of (*R*)-(+)-5-methyltetrahydrofuran-2-one (+)-14

Diisopropylamine (8.75 cm^3, 62.5 mmol) and butyllithium in hexane (2.5 mol dm^{-3}; 25 cm^3, 62.5 mmol) were added to dry tetrahydrofuran (500 cm^3) at room temperature under nitrogen. The reaction was then cooled to −20 °C and (*R*)-5-methyltetrahydrofuran-2-one (+)-**14** (5 g, 50 mmol) was added. After 15 min gaseous formaldehyde was bubbled through in a stream of nitrogen for 30 min. When no lactone remained by TLC (SiO_2, 80% ethyl acetate in petrol) the reaction was worked up by the addition of hydrochloric acid (0.5 mol dm^{-3}; 500 cm^3). The reaction was extracted with dichloromethane (3 × 500 cm^3), dried over magnesium sulfate and concentrated *in vacuo* to an oil (5.24 g, 80.6%).

The hydroxy lactones **15** and **16** (5.24 g, 40.3 mmol), *tert*-butyldimethylsilyl chloride (12.08 g, 80 mmol) and imidazole (10.89 g, 160 mmol) were stirred in dry dichloromethane (80 cm^3) under nitrogen for 16 h. The reaction mixture was washed with water (80 cm^3) and the aqueous layer washed with dichloromethane (80 cm^3). The combined dichloromethane extracts were dried over magnesium sulfate and concentrated *in vacuo* to give a mixture of lactones (+)-**17** and (+)-**18** (9.6 g, 97%) as an oil, which were separated by flash chromatography.

(3*S*,5*R*)-3-*tert*-Butyldimethylsiloxymethyl-5-methyltetrahydrofuran-2-one (+)-18. Compound (+)-**18** (1.50 g, eluted first as an oil 15.3%); $[\alpha]_D^{21}$ +9.6 (*c* 2.9 in CH_2Cl_2) (Found: $M^+ - 15$, 229.126. $C_{11}H_{21}O_3Si$ requires *M*, 229.126); ν_{max}/cm^{-1} 1774; δ_H 0.04 (6 H, s, CH_3Si), 0.86 (9 H, s, CH_3CHSi), 1.36 (3 H, d, *J* 6.4, CH_3CH), 1.96 (1 H, ddd, *J* 12.9, 9.8 and 6.0, $CHCHHCH$), 2.4 (1 H, ddd, *J* 12.9, 6.8 and 5.9, $CHCHHCH$), 2.76 (1 H, dddd, *J* 9.8, 5.9, 4.4 and 3.4, CH_2CHCO), 3.76 (1 H, dd, *J* 10 and 3.4, $CHHOH$), 3.96 (1 H, dd, *J* 10 and 4.4, $CHHOH$) and 4.67 (1 H, ddq, *J* 6.8, 6.0 and 6.4, CH_3CH); *m/z* 229 ($M^+ - 15$, 2.5%), 187 (60.7), 75 (100) and 57 (44).

(3*R*,5*R*)-3-*tert*-Butyldimethylsiloxymethyl-5-methyltetrahydrofuran-2-one (+)-17. Compound (+)-**17** eluted second as an oil (1.78 g, 18.1%); $[\alpha]_D^{21}$ +13.6 (*c* 3.1 in CH_2Cl_2) (Found: $M^+ - 15$, 229.126. $C_{11}H_{21}O_3Si$ requires *M*, 229.126); ν_{max}/cm^{-1} 1774; δ_H 0.05 (6 H, s, CH_3Si), 0.87 (9 H, s, CH_3CHSi), 1.41 (3 H, d, *J* 6.1, CH_3CH), 1.90 and 2.41 (each 1 H, m, $CHCH_2CH$), 2.78 (1 H, m, CH_2CHCO), 3.80 (1 H, dd, *J* 10 and

3.4, C*H*HOH), 3.91 (1 H, dd, *J* 10 and 5, C*H*HOH) and 4.67 (1 H, m, CH_3CH); *m/z* 229 ($M^+ - 15$, 2.5%), 187 (60.7), 75 (100) and 57 (44).

A mixed fraction of both isomers was also recovered (314 mg, 3.2%).

2-Methoxyethoxymethyl (2*E*,4*R*,6*R*)-4-*tert*-butyldimethylsiloxymethyl-6-hydroxyhept-2-enoate (−)-21

The lactone mixture (+)-**17** and (+)-**18** (2.2 g, 9 mmol) in dry diethyl ether (90 cm^3) was cooled to −78 °C under nitrogen. DIBAL-H in hexane (1 mol dm^{-3}, 11.25 cm^3, 11.25 mmol) was added, keeping the temperature below −70 °C. After 30 min the reaction was warmed to room temperature and water (45 cm^3) and saturated aqueous ammonium chlorode (45 cm^3) added with vigorous stirring. After a further 30 min the precipitated alumina was removed by filtration through Celite and the filter bed washed with diethyl ether (300 cm^3). The ether layer was dried over magnesium sulfate and concentrated *in vacuo* to give the mixture of lactols (2.11 g, 95.6%) as an oil.

The MEM ylide **29** (21.05 g, 51.6 mmol) and the diastereoisomeric mixture of lactols (2.11 g, 8.6 mmol) were heated to reflux in dry acetonitrile (52 cm^3) for 3 h under nitrogen. The crude reaction mixture was purified by flash chromatography (SiO_2, 0% to 30% diethyl ether in petrol) to give the unsaturated ester (−)-**21** as an oil (1.233 g, 38%); $[\alpha]_D$ −12.6 (*c* 4.1 in $CHCl_3$) (Found: $M^+ - 17$, 359.2268. $C_{18}H_{35}O_5Si$ requires *M*, 359.2254); ν_{max}/cm^{-1} 3440, 1722 and 1651; δ_H 0.02 (6 H, s, SiCH_3), 0.85 (9 H, s, SiCCH_3), 1.16 (3 H, d, *J* 6.2, CH_3CH), 1.55 (2 H, m, CHCH_2CH), 2.60 (1 H, m, CH_2CH=CH), 3.35 (3 H, s, OCH_3), 3.53 (2 H, m, $OCH_2CH_2OCH_3$), 3.58 (2 H, m, CH_2OSi), 3.77 (3 H, m, $OCH_2CH_2OCH_3$ and CH_3CH), 5.36 (2 H, s, CO_2CH_2O), 5.87 (1 H, d, *J* 15.6, C*H*CO_2), 6.86 (1 H, dd, *J* 15.6 and 5.8, C*H*CHCO_2); δ_C 165.64 (*C*O_2), 151.17 (*C*HCHCO_2), 121.74 (*C*HCO_2), 89.26 (OCH_2O), 71.38 (CH_2OCH_2), 69.37 (CH_2OCH_3), 66.08 (CH_2OSi), 65.73 (CH_3CH), 59.01 (*C*H-CH_2OSi), 42.56 (OCH_3), 40.77 (*C*H_2CHCH_2OSi), 25.76 (SiCCH_3), 24.30 (*C*H_3CH), 18.17 (SiCCH_3) and −5.38 (SiCH_3); *m/z* (CI, CH_4) 359 ($M^+ - 17$, 7%), 329 (3), 301 (5), 271 (52), 229 (12), 213 (16), 89 (100), 75 (24) and 59 (54).

2-Methoxyethoxymethyl (2*E*,4*R*,6*R*,2′*E*,5′*R*)-4-*tert*-butyldimethylsiloxymethyl-6-[5-(tetrahydropyran-2-yloxy)hex-2-enoyloxy]hept-2-enoate 30

The hydroxy ester (−)-**21** (688 mg, 1.83 mmol), the THP acid **13** (593 mg, 2.75 mmol), dicyclohexylcarbodiimide (852 mg, 4.13 mmol) and 4-dimethylaminopyridine (49 mg, 0.4 mmol) were stirred in dry dichloromethane (15 cm^3) for 14 days. The precipitated urea was removed by filtration and the reaction mixture was purified by flash chromatography (SiO_2, 40% ethyl acetate in petrol) giving two products.

The required ester **30** eluted first as an oil; (385 mg, 36.8%, 85.2% wrt recovered starting material); ν_{max}/cm^{-1} 1720 and 1655; δ_H 0.02 (6 H, s, SiCH_3), 0.87 (9 H, s, SiCCH_3), 1.13–1.26 (6 H, m, 6′-H_3 and 7-H_3), 1.6–20 (8 H, m, 5-H_2, 3″-H_2, 4″-H_2 and 5″-H_2), 2.3–2.6 (3 H, m, 4-H and 4′-H_2), 3.37 (3 H, s, OCH_3), 3.55 (4 H, m, CH_2OCH_3 and TBDMSOCH_2), 3.78 (2 H, m, CH_2OCH_2), 3.91 (1 H, m, 5′-H), 4.64 and 4.71 (each 0.5 H, m, 2″-H), 4.91 (1 H, m, 6-H), 5.37 (2 H, AB, OCH_2O), 5.81 (1 H, d, *J* 15.9, 2-H), 5.84 (1 H, m, 2′-H), 6.84 (1 H, dd, *J* 15.9 and 9.1, 3-H) and 6.95 (1 H, m, 3′-H); *m/z* (CI, methane) 572 (M^+, 0.1%), 557 (0.2), 511 (1), 475 (3), 413 (6), 359 (8), 337 (25), 271 (59), 212 (45) and 85 (100). This was followed by unreacted alcohol **35** (391 mg, 56.8%).

Addition of toluene-*p*-sulfonic acid. The hydroxy ester (−)-**21** (150 mg, 0.4 mmol), the acid **13** (129 mg, 0.6 mmol), toluene-*p*-sulfonic acid (11.5 mg, 0.06 mmol) and 4-dimethylaminopyridine (74 mg, 0.6 mmol) were stirred in dry dichloromethane (6 cm^3) under nitrogen. Dicyclohexylcarbodiimide (124 mg, 0.6 mmol) in dichloromethane (2 cm^3) was added and the reaction mixture stirred at room temperature overnight. The required ester **30** was purified by direct vacuum flash chromatography (SiO_2, 0 to 30% ethyl acetate in petrol) as an oil (112 mg, 49%).

(3*E*,6*R*,9*E*,11*R*,13*R*)-11-*tert*-Butyldimethylsiloxymethyl-6,13-dimethyl-1,7-dioxacyclotrideca-3,9-diene-2,8-dione 32

The ester **30** (86 mg, 0.15 mmol), magnesium bromide (83 mg, 0.45 mmol) and dry diethyl ether (8.5 ml) were stirred at room temperature overnight. Water (8.5 cm^3) was added and the reaction extracted with dichloromethane (3 × 20 ml), dried over magnesium sulfate and concentrated *in vacuo* to give the hydroxy acid **31** as an oil.

The crude hydroxy acid **31** was dissolved in dry dichloromethane (4 cm^3) with 4-dimethylaminopyridine (24.4 mg, 0.2 mmol) and toluene-*p*-sulfonic acid (1.9 mmol, 0.01 mmol) under nitrogen. Dicyclohexylcarbodiimide (41.3 mg, 0.2 mmol) in dichloromethane (2 cm^3) was added and the reaction stirred at room temperature overnight. The TBDMS ether **32** of bartanol was purified by vacuum flash chromatography (SiO_2, 0 to 20% ethyl acetate in petrol) as an oil (19 mg, 33%) (Found: $M^+ + 1$, 383.2242. $C_{20}H_{35}O_5Si$ requires *M*, 383.2254); ν_{max}/cm^{-1} ($CHCl_3$) 1718 and 1652; δ_H 0.04 (6 H, s, SiCH_3), 0.88 (9 H, s, SiCCH_3), 1.29 (3 H, d, *J* 6.6, 15-H_3), 1.39 (3 H, d, *J* 6.3, 14-H_3), 1.67 and 2.08 (each 1 H, m, 9-H_2), 2.20 and 2.49 (each 1 H, m, 3-H_2), 2.61 (1 H, m, 10-H), 3.44 (1 H, dd, *J* 9.6 and 8.1, 16-H), 3.54 (1 H, dd, *J* 9.6 and 6.1, 16-H), 5.06 (1 H, m, 2-H), 5.25 (1 H, m, 8-H), 5.72 (1 H, d, *J* 15.6, 12-H), 5.76 (1 H, d, *J* 15.9, 5-H), 6.45 (1 H, dd, *J* 15.6 and 9.8, 11-H), 6.55 (1 H, ddd, *J* 15.9, 10.7 and 5.6, 4-H); δ_C 167.7 (C13), 165.52 (C6), 151.04 (C11), 142.3 (C4), 127.89 (C12), 123.04 (C5), 69.43 (C2), 68.43 (C8), 65.01 (C16), 40.95 (C9), 40.21 (C10), 34.30 (C3), 25.82 (SiCCH_3), 20.53 (C14), 19.71 (C15), 18.20 (SiCCH_3), −5.38 (SiCH_3) and −5.48 (SiCH_3); *m/z* (CI, CH_4) 383 ($M^+ + 1$, 19%), 367 (9), 338 (18), 325 (63) and 213 (100).

Synthetic bartonol 7

The TBDMS ether **32** (19 mg, 0.05 mmol) was stirred in hydrochloric acid [1% in ethanol (2.9 g conc. hydrochloric acid in 97.1 g ethanol); 4 cm^3] at room temperature for 30 min. Water (20 cm^3) was added and the reaction extracted with dichloromethane (3 × 20 cm^3), the extract was dried over magnesium sulfate and concentrated *in vacuo* to an oil. Bartanol **7** was purified by flash chromatography (SiO_2, 50 to 100% diethyl ether in petrol) as a gum (5.8 mg, 43.3%); $[\alpha]_D^{22}$ +33.9 (*c* 0.4 in $CHCl_3$), natural bartanol $[\alpha]_D^{22}$ +32.2 (*c* 1.9 in $CHCl_3$) (Found: $M^+ + 18$, 286.165. $C_{14}H_{24}O_5N$ requires *M*, 286.166); ν_{max}/cm^{-1} 3412, 1722 and 1652; δ_H 1.28 (3 H, d, *J* 6.6, 15-H_3), 1.36 (3 H, d, *J* 6.4, 14-H_3), 1.51 (1 H, ddd, *J* 14.7, 2.2 and 1.7, 9-H_R), 2.08 (1 H, ddd, *J* 14.7, 8.8 and 3.7, 9-H_S), 2.13 (1 H, ddd, *J* 12.4, 10.5 and 10.5, 3-H_R), 2.47 (1 H, ddd, *J* 12.4, 5.4 and 3.4, 3-H_S), 2.64 (1 H, m, 10-H), 3.53 (1 H, dd, *J* 15.7 and 6.6, 16-H), 3.58 (1 H, dd, *J* 15.7 and 8.1, 16-H), 5.03 (1 H, qdd, *J* 6.6, 3.7 and 2.2, 8-H), 5.22 (1 H, dqd, *J* 10.5, 6.4 and 3.4, 2-H), 5.73 (1 H, d, *J* 15.6, 12-H), 5.84 (1 H, d, *J* 15.6, 5-H), 6.41 (1 H, dd, *J* 15.6 and 9.8, 11-H), 6.53 (1 H, ddd, *J* 15.6, 10.5 and 5.4, 4-H); δ_C 167.4 (C13), 165.56 (C6), 150.73 (C11), 142.5 (C4), 127.8 (C12), 124.1 (C5), 69.64 (C2), 68.4 (C8), 64.99 (C16), 40.93 (C9), 40.05 (C10), 34.3 (C3), 20.46 (C14) and 19.7 (C15); *m/z* (CI, NH_3) 286 ($M^+ + 18$, 100%).

Acknowledgements

We are grateful to the EPSRC for a studentship (J. A. O'N.) and to AgrEvo UK Limited for financial support.

References

1 T. J. Simpson and G. I. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1985, 1822.

2 S. Gurusiddaiah and R. C. Ronald, *Antimicrob. Agents Chemother.*, 1981, **19**, 1953.
3 K. Hanson, J. A. O'Neill, T. J. Simpson and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2493.
4 J. MacMillan and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1487.
5 R. Amstutz, E. Hungerbuhler and D. Seebach, *Helv. Chim. Acta*, 1981, **64**, 1796.
6 P. Schurrenberger, E. Hungerbuhler and D. Seebach, *Tetrahedron Lett.*, 1984, **25**, 2209.
7 J. MacMillan and M. W. Lunnon, *J. Chem. Soc., Perkin Trans. 1*, 1976, 184.
8 J. A. O'Neill, T. J. Simpson and C. L. Willis, *J. Chem. Soc., Chem. Commun.*, 1993, 737.
9 H. Tsutsui and O. Mitsunobu, *Tetrahedron Lett.*, 1984, **25**, 2159; P. Schurrenberger, E. Hungerbuhler and D. Seebach, *Liebigs Ann. Chem.*, 1987, 733.
10 K. Ohta and O. Mitsunobu, *Tetrahedron Lett.*, 1991, **32**, 517; D. Seebach and W. Seidel, *Tetrahedron Lett.*, 1982, **23**, 159.
11 R. Thijs, F. J. Dommerhalt and B. Zweneburg, *Tetrahedron Lett.*, 1991, **32**, 1499; N. Machinaga and C. Kibayashi, *Tetrahedron Lett.*, 1993, **34**, 841.
12 I. Shimizu and T. Omura, *Chem. Lett.*, 1993, 1759.
13 J. A. O'Neill, S. D. Lindell, T. J. Simpson and C. L. Willis, *Tetrahedron: Asymmetry*, 1994, **5**, 117.
14 P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1972, 1317.
15 Y. Ogawa and M. Shibasaki, *Tetrahedron Lett.*, 1984, **25**, 663.
16 S. Kim and J. H. Park, *Tetrahedron Lett.*, 1987, **28**, 439; S. Kee, S. Kim, Y. H. Park and I. S. Kee, *Tetrahedron Lett.*, 1991, **32**, 3099; S. Kim, I. S. Kee, Y. H. Park and J. H. Park, *Synlett*, 1991, 183.
17 B. Hansen and K. Holmberg, *Acta Chem. Scand.*, 1979, 411; E. P. Boden and G. E. Keck, *J. Org. Chem.*, 1985, **50**, 2394.

Paper 5/06247K
Received 21*st September* 1995
Accepted 19*th October* 1995