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A chemoenzymatic total synthesis of the phytotoxic undecenolide (−)-cladospolide A

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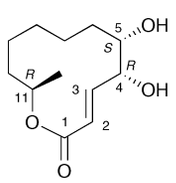
Received 6th February 2004, Accepted 5th May 2004
First published as an Advance Article on the web 23rd June 2004

An eleven-step synthesis of the title compound (**1**) from biocatalytically-derived and enantiomerically pure 'building blocks' alcohol (*R*)-(−)-**9** and ester **13** is described. Attempts to construct the twelve-membered lactone ring of cladospolide A in a direct manner by using a ring-closing metathesis (RCM) reaction failed. However, a ten-membered lactone, **19**, could be constructed by such means and this was then subject to a two-carbon homologation sequence involving, *inter alia*, Wadsworth–Horner–Emmons and Yamaguchi lactonisation reactions in the closing stages of the synthesis. The impact of substituent stereochemistries and protecting groups on the RCM reaction leading to various ten-membered lactones is also described.

Introduction

Cladospolides A–D (**1**–**4**, respectively) comprise the currently known members of a class of undecenolides isolated from various *Cladosporium* species of fungi.[1–4] The first two members were described by Isogai and co-workers[1,2] and the structures, including absolute stereochemistries, established by several means including Mosher ester analysis[5] and a single-crystal X-ray structure determination.[5] Congener **3** was isolated in 1995 by Fukuda and co-workers[3] and its structure inferred by spectroscopic comparisons with compounds **1** and **2**. Cladospolide D was described much more recently (2001)[4] and the configurations at C5 and C11 remain undefined. Cladospolides A–C have been shown to inhibit shoot elongation in rice seedlings and isomer **2** does so without causing signs of necrosis, thus suggesting that this compound, at least, inhibits gibberellin biosynthesis.[3] Remarkably, cladospolide A also inhibits root elongation in lettuce seedlings whilst cladospolide B, which only varies in the configuration about the double bond and at C4, has the opposite effect.[2] Cladospolide D (**4**) exhibits antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae* with IC_{50} values of 0.15 and 29 μg mL^{-1}, respectively.[4] This is the only member of the family to display such properties which may be attributed to the presence of the highly electron-deficient Δ^2-double bond and its consequent capacity to react, in a Michael fashion, with biologically relevant nucleophiles. Cladospolide B, together with the butenolide isocladospolide B, have recently been isolated from the Indonesian sponge-derived fungus I965215 by Ireland and co-workers.[6]



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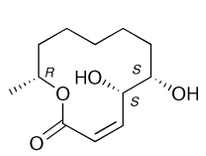

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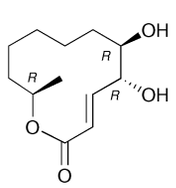

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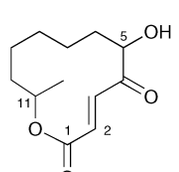

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Despite their rather intriguing biological profiles, the cladospolides have only received limited attention as synthetic targets. The first of only two distinct total syntheses of compound **1** was reported by Mori and Maemoto in 1987[7] and used enantiopure ethyl (*R*)-3-hydroxybutanoate, derived by enzymatic reduction of ethyl acetoacetate, as the source of C11 stereochemistry. Kinetic resolution of a diastereoisomeric mixture of allylic alcohols using Sharpless asymmetric epoxidation chemistry was employed to assemble the *cis-vicinal* diol moiety associated with target **1** while the macrocyclic ring was constructed *via* a Yamaguchi lactonisation reaction. The synthesis was accomplished in 16 steps and 2.6% overall yield. A closely related approach was described by Ichimoto *et al.* in the same year.[8] Solladié's synthesis of cladospolide A was first reported in 1994[9] and cleverly exploited chiral sulfoxides in the construction of a hydroxy-acid that was also subject to a Yamaguchi lactonisation reaction to assemble the undecenolide ring. This synthesis required 20 steps but proceeded in an impressive 5% overall yield. The activities just described would seem to represent the full extent of published work associated with efforts to prepare compounds **1**–**4**.

Our own interest in developing an approach to cladospolide A arose from our recently described total syntheses of the 18-membered macrolide (+)-aspicillin[10] and the nonenolide (−)-microcarpalide.[11] Each of these employed, as the pivotal step, a ring-closing metathesis (RCM) reaction to construct the target macrolides. This method for macrocyclic ring formation has become increasingly popular in the last few years but at the time the work described here was commenced its utilisation in the construction of undecenolide natural products had not been reported.[12] Consequently, we now detail[13] an 11-step and enantioselective total synthesis of cladospolide A, from biocatalytically-derived starting materials, that employs a RCM process as the pivotal step. This work has revealed some constraints that apply in the application of this process to the construction of 10- and 12-membered macrolides.

Results and discussion

The retrosynthetic analysis employed in developing our initial approach to cladospolide A is shown in Fig. 1. Thus, following on from our synthesis of (+)-aspicillin,[10] we supposed that application of RCM chemistry to the triene **5** followed by selective hydrogenation of the non-conjugated double bond within the undecenolide so-formed would lead, after

DOI: 10.1039/b401829j

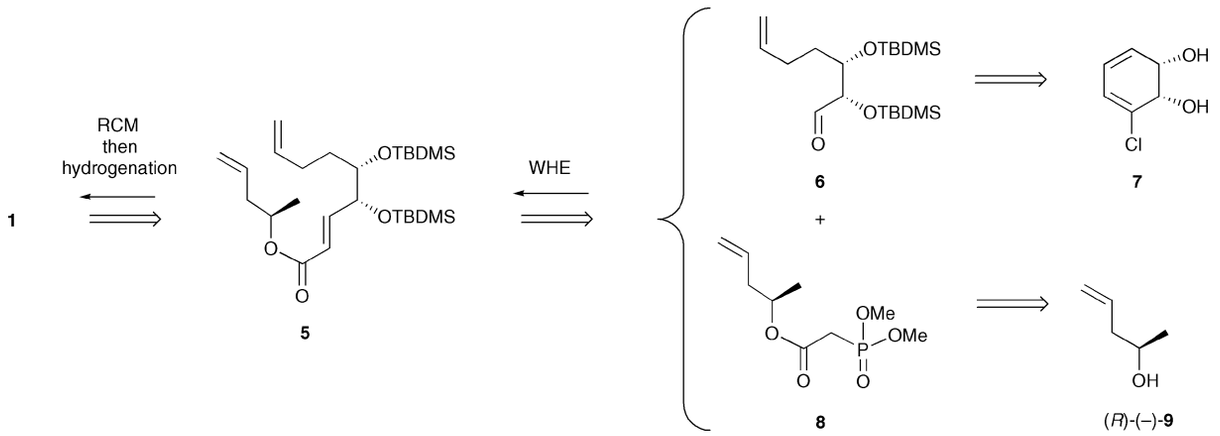
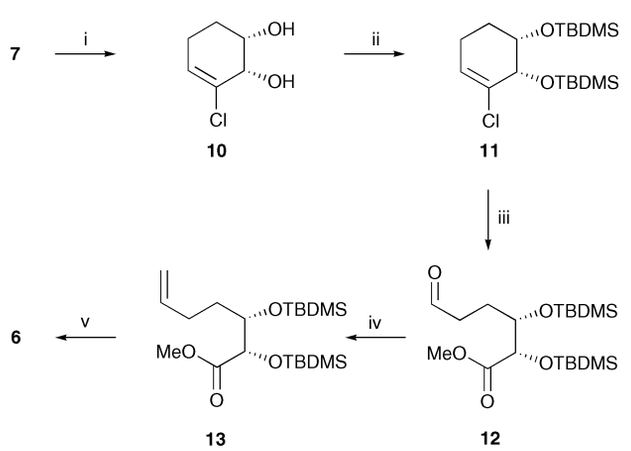


Fig. 1

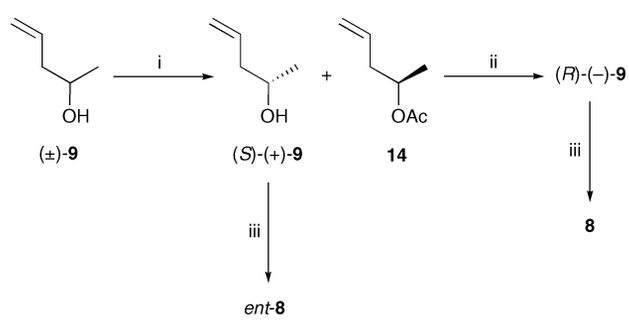
deprotection of the *vicinal*-diol moiety, to target **1**. Compound **5** would, in turn, be prepared through a Wadsworth–Horner–Emmons (WHE) reaction between aldehyde **6** and phosphonoacetate **8**. It was envisaged that the former substrate could be prepared from the *cis*-1,2-dihydrocatechol **7** which is readily obtained on a large scale and in enantiomerically pure form by microbial dihydroxylation of chlorobenzene using a genetically engineered strain of *E. coli* that over expresses the responsible enzyme, *viz*. toluene dioxygenase.[14] The latter substrate should be accessible through *trans*-esterification of methyl phosphonoacetate with the known[15] (*R*)-pent-4-en-2-ol [(*R*)-(−)-**9**]. This combined use of WHE and RCM chemistries was attractive because of the high degree of convergency that should follow.

Construction of the first 'building block' **6** proved straightforward and this was obtained by the route shown in Scheme 1. Thus, in keeping with earlier reports from these laboratories[16] as well as those of Boyd *et al.*[17a] and Hudlicky and co-workers,[17b] *cis*-1,2-dihydrocatechol **7** was reduced to the corresponding tetrahydrocatechol **10** (75%) using dihydrogen in the presence of rhodium on alumina. Protection of the diol moiety within the latter as the *bis*-TBDMS ether **11** (100%) proceeded smoothly under standard conditions.[18] A methanolic solution of compound **11** was then subject to ozonolysis and the resulting ozonide cleaved with sodium borohydride under carefully controlled conditions to give the aldehydic ester **12**. This was subject to a conventional Wittig methylenation reaction and the resulting ω-unsaturated ester **13** was immediately reduced with DIBAL-H to give the targeted aldehyde **6** (55% from **11**).



Scheme 1 *Reagents and conditions*: (i) dihydrogen (1 atm.), 5% Rh on Al_2O_3 (7 mol%), ethanol, 18 °C, 1.5 h; (ii) TBDMS-Cl (4 mol equiv.), imidazole (8 mol equiv.), DMF, 18 °C, 6 h; (iii) O_3 (excess), methanol, −78 °C, *ca*. 20 min, then $NaBH_4$ (1.1 mol equiv.), 0 °C, *ca*. 10 min; (iv) $Ph_3P{=}CH_2$ (2.5 mol equiv.), 4:3 v/v THF–toluene, 0–18 °C, *ca*. 1 h; (v) DIBAL-H (1.8 mol equiv.), hexane, −78 °C, 1 h.

With aldehyde **6** in hand attention was focused on production of the phosphonoacetate **8** and the corresponding *S*-enantiomer. Whilst Brown and co-workers have reported[19] generating the necessary chiral alcohol precursor (*R*)-(−)-**9** *via* enantioselective allylation of acetaldehyde, for the purposes of obtaining preparatively useful quantities of this material we turned to enzymatic methods that would be capable of resolving the commercially available racemate (±)-**9**. To these ends, and guided by earlier reports,[20] the racemic material was converted into the corresponding butyrates and five commercially available lipases were screened for their capacity to effect enantioselective hydrolysis of these esters in either aqueous phosphate buffer at pH 7.3 or a hydrocarbon solvent. The enantiomeric excesses of the unreacted esters were determined by chiral capillary GLC at the 24 and 48 h time points and the results of such analyses are summarised in Table 1. These suggested that *Candida antarctica* lipase B (CA or CALB) was especially effective and at the 24 h mark a *ca.* 80% ee of one enantiomeric form of the ester was formed. Comparison of the optical rotation of the isolated and enantiomerically enriched butyrate ester with literature values[21] established that the *S*-isomer had been obtained. This outcome is consistent with expectations, based on both crystallographic studies and molecular modelling of CALB,[22,23] that the *R*-butyrate should be hydrolysed preferentially by this enzyme. Furthermore, a time-course experiment revealed (Table 2) that the highest enantiomeric excesses of residual *S*-butyrate were observed after 2 h. However, whilst this protocol enabled the formation of highly enantiomerically enriched (*R*)-(−)-**9**, recovery and subsequent chemical hydrolysis of the butyrate ester of the (*S*)-enantiomer proved difficult. As a consequence an alternate method for production of the enantiomerically enriched forms of the target alcohols was sought and ultimately identified. Thus, exposure of the racemate (±)-**9** to CALB in vinyl acetate, which serves as both reaction solvent and acyl donor, resulted (Scheme 2) in the recovery of essentially enantiomerically pure



Scheme 2 *Reagents and conditions*: (i) vinyl acetate (neat), CALB, 30 °C, 1 h; (ii) pH 7.3 aq. phosphate buffer, CALB, 30 °C, 16 h; (iii) $(MeO)_2P(O)CH_2CO_2Me$ (2 mol equiv.), DMAP (0.74 mol equiv.), toluene, 112 °C, 18 h.

Table 1 Lipase screening for capacity to effect the enantioselective hydrolysis of the butyrate esters of (±)-**9** at 30 °C

Entry	Lipase/10 mg	Reaction time/h	Medium	Substrate/mg	ee_s (%)
1	None	48	Buffer	102.3	0
2	None	48	Buffer	113.2	0
3	CC	48	Buffer	107.8	−1
4	PP	48	Buffer	102.4	10
5	PS	48	Buffer	103.9	68
6	AK	48	Buffer	101.0	81
7	AK	48	Iso-octane	100.9	1
8	CA	48	Buffer	109.8	66
9	None	24	Iso-octane	102.3	1
10	CC	24	Buffer	103.8	16
11	PP	24	Buffer	101.1	1
12	PS	24	Buffer	104.8	63
13	AK	24	Buffer	102.3	77
14	AK	24	Iso-octane	102.0	0
15	CA	24	Buffer	100.5	79

CC = *Candida cylindriceae* lipase (*ex* Sigma); PP = Porcine pancreatic lipase (*ex* Sigma); PS = lipase PS (*ex* Amano); AK = lipase AK (*ex* Amano); CA = *Candida antarctica* lipase B (*ex* Novo Nordisk); buffer = pH 7.3 aqueous phosphate buffer; ee_s = enantiomeric excess of reaction substrate (as determined by GLC analysis on a chiral column).

Table 2 Time dependence of ee_s in the CALB-catalysed hydrolysis of the butyrate esters of (±)-**9** at 25 °C

Reaction time/h	ee_s[a] (%)
0.5	65
1	70
2	93
4	82
8	81
30	78

[a] ee_s = enantiomeric excess of reaction substrate (as determined by GLC analysis on a chiral column).

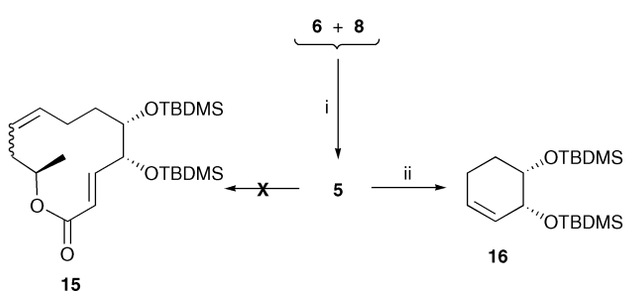
Table 3 Time dependence of ee_p and ee_s in the CALB-catalysed hydrolysis of the acetate esters of (±)-**9** at 30 °C

Reaction time/h	ee_p[a] (%)	ee_s[a] (calculated) (%)
0.25	92	48
0.5	90	80
1	80	99
2	63	100

[a] ee_p = enantiomeric excess of reaction product, *viz.* acetate of **14**; a calculated value for ee_s is recorded because direct measurement was not possible.

(>99.9% ee) alcohol (*S*)-(+)-**9** (60% yield) and the chromatographically separable acetate, **14**, of (*R*)-(−)-**9**, the latter being obtained in 80% yield and *ca.* 75% ee. Time-course experiments revealed (Table 3) that optimal results were obtained after running the reaction at 30 °C for 1–2 h. In order to improve the enantiomeric purity of the acetate, **14**, of the (*R*)-alcohol this was subjected to reaction with CALB in pH 7.3 phosphate buffer thus affording the required compound (*R*)-(−)-**9** in >99.9% ee as judged by chiral GLC analysis of the derived acetate. This two-step resolution protocol could be run on a multi-gram scale and the so-called *E*-value[24] for this process is *ca*. 36. With pure samples of compound (*R*)-(−)-**9** available by such means the corresponding phosphonoacetate, *viz.* **8**, was readily obtained, in 93% yield, by heating the alcohol with trimethyl phosphonoacetate in refluxing toluene and in the presence of the *trans*-acylation catalyst *N*,*N*-dimethylaminopyridine (DMAP).[25] The spectroscopic data obtained on the product phosphonoacetate were fully in accord with the assigned structure.

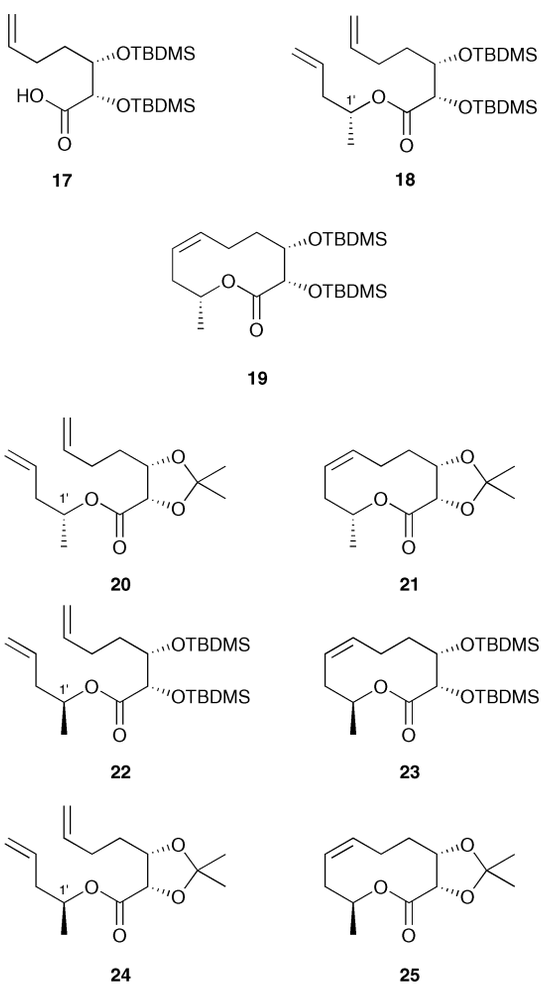
In keeping with the retrosynthetic analysis (Fig. 1) and our earlier work[10] on the synthesis of (+)-aspicillin, the anion derived from compound **8** reacted smoothly with the aldehyde **6** to give triene **5** (81%), the substrate required in the pivotal step of the proposed synthesis, namely the RCM. Unfortunately, and despite many attempts to secure an alternate outcome, exposure of compound **5** to either the Grubbs'-I[26] or Grubbs'-II[27] catalysts failed to give the desired product **15** (Scheme 3). Rather, the unwanted cyclohexene **16** (100%) proved to be the only isolable product of reaction. Clearly this product arises *via* an RCM involving the two olefinic moieties incorporated within the carboxylic acid fragment of ester **5**. Consequently, a number of attempts were made to protect the carbonyl-conjugated double bond through addition of various thiols in a Michael-addition process, specifically *via* nucleophilic epoxidation with hydroperoxy anions and related species and, in desperation, by conjugate reduction with Stryker's reagent.[28] Unfortunately, none of these approaches delivered any useful outcomes and the inability to achieve the desired conversions is attributed, in part at least, to the sterically congested nature of the β-carbon within compound **5**, a situation caused by the proximate and bulky *tert*-butyldimethylsilyloxy groups.



Scheme 3 *Reagents and conditions*: (i) NaH (1.7 mol equiv. wrt **8**), THF, 0–18 °C, *ca.* 2.5 h; (ii) Grubbs'-II catalyst (*ca.* 20 mol%), DCM, 18 °C, 18 h.

The foregoing results clearly required a revision of the originally proposed approach (Fig. 1) to (−)-cladospolide A. One possibility would be to couple the carboxylic acid, **17**, derived from ester **18** with alcohol (*R*)-(−)-**9** so as to form ester **18** which can only engage in one mode of RCM, namely that leading to compound **19**. Hydrogenation of the double bond within this last compound would then lead to a saturated lactone which could be reduced to the corresponding lactol. The open-chain form of this last species would then be expected to participate in a WHE reaction to deliver a substrate that could participate in a macrolactonisation reaction and thereby furnish a protected form of (−)-cladospolide A. In seeking to establish such a route, the saponification of ester **13** with sodium hydroxide was examined and it became apparent that elevated temperatures (50 °C) were required and the yields of

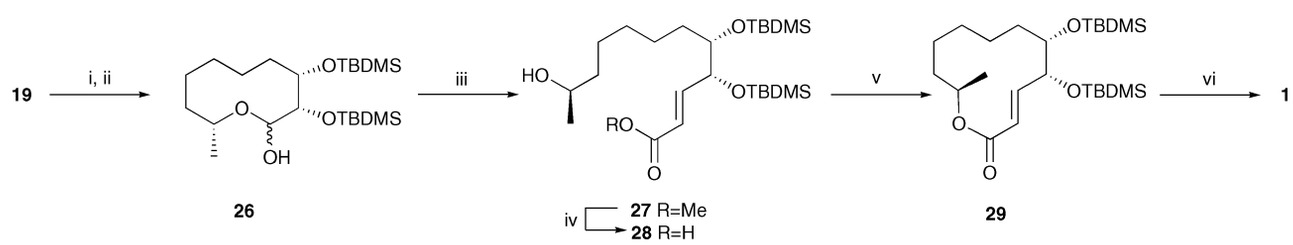
the acid **17** obtained on acidic work-up were rather modest (65%), presumably because undesired desilylation reactions were occurring. Attempts to couple various activated forms of this acid with alcohol (*R*)-(−)-**9** failed to deliver the required ester **18** in preparatively useful quantities. Success was finally realised when the Yonemitsu modification[29] of the Yamaguchi esterification reaction[30] was employed and under such conditions (see Experimental) compound **18** was obtained in quantitative yield. Subjection of this last compound to RCM using Grubbs'-II catalyst[27] afforded the expected unsaturated lactone **19**, as a single geometric isomer and presumably with the illustrated *Z*-configuration, in 73% yield (at 75% conversion). In an effort to improve on the yields obtained in this step the acetonide **20** was prepared by standard methods but this reacted even less efficiently in the RCM process delivering product **21** in only 40% yield (at 85% conversion). Intriguingly, changing the stereochemistry at the carbon (C1′) bearing the methyl group had a significant impact on the efficiency of this type of reaction. Thus, the C1′-epimer of **18**, namely compound **22**, which was readily prepared from acid **17** and alcohol (*S*)-(+)-**9**, engages in reaction with Grubbs'-II catalyst to give lactone **23** in 84% yield. The related acetonide **24** was converted into the corresponding lactone **25** in 65% yield and in this case small amounts of what is presumed to be the corresponding *E*-isomer of the product were observed.



In an effort to develop some understanding of the origins of the rather distinct behaviours of substrates **18**, **20**, **22** and **24** in these RCM reactions, we undertook molecular mechanics and AM1 semi-empirical single-point energy calculations to determine the relative energies of the respective products, namely compounds **19**, **21**, **23** and **25**. These calculations, which were carried out using the Spartan program and involved conformational searching using a Monte Carlo algorithm, revealed that each macrolide existed in multiple low energy conformations. The non-weighted average energy of all of these was determined and by such means it was established that the order of stability of the product macrolides was **19** > **23** ⩾ **25** > **21**. This correlates to some extent, at least, with the yields of 73, 84, 65 and 40%, respectively, observed for the reactions leading to these products. Such results support the proposition that the transition state for the RCM reaction might be product-like and that, therefore, the ground-state energies of the products should give some guide as to the ease with which they can be formed by such means. It seems to follow, therefore, that, at least in the present cases, the entropic advantages conferred on the RCM process through the use of an acetonide moiety are significantly out-weighed by the increased strain (relative to TBS-protected equivalents) that this same unit is likely to engender at the transition state for the reaction. In more general terms, it seems likely that theoretical determinations of the relative stabilities of the products of RCM reactions leading to 10-membered macrolides will provide a useful guide as to the protecting group regimes most likely to be useful in delivering the targeted products in an efficient manner.

Despite the rather disappointing yields observed in the RCM process leading to it, sufficient quantities of compound **19** could be accumulated to allow for completion of a synthesis of target **1**. Thus, the double bond within lactone **19** could be removed by hydrogenation (Scheme 4) under standard conditions and the resulting saturated equivalent (93%) reduced to lactol **26** with DIBAL-H. This last compound proved to be rather unstable but, nevertheless, readily participated in a WHE reaction with the anion derived from trimethyl phosphonoacetate to give the *E*-configured α,β-unsaturated ester **27** (45% from **19**). Saponification of this ester proceeded smoothly using sodium hydroxide at 18 °C to give, after acidic work-up, the seco-acid **28** which was not isolated but immediately subjected to a Yamaguchi lactonisation protocol[30] and thus affording the targeted lactone **29** in 89% (from ester **27**). Interestingly, attempts to effect the desired lactonisation reaction using the Yonemitsu protocol[29] did not yield any cyclised material at all.

The acquisition of lactone **29** provided a bis-TBS ether-protected form of (−)-cladospolide A and attention was thus focused on the final deprotection step so as to reveal the natural product. In the event this step proved troublesome because the compound was both acid- and base-sensitive. The use of TBAF[18] as a fluoride ion source only resulted in decomposition



Scheme 4 *Reagents and conditions*: (i) dihydrogen (1 atm.), 10% Pd on C (cat.), ethanol, 18 °C, 11 h; (ii) DIBAL-H (*ca.* 2 mol equiv.), toluene, −78 °C, 0.5 h; (iii) $(MeO)_2P(O)CH_2CO_2Me$ (2.4 mol equiv.), NaH (1.7 mol equiv.), THF, 0–18 °C, *ca.* 2 h; (iv) NaOH (2.5 M aq. solution, 42 mol equiv.), ethanol, 18 °C, 18 h; (v) 2,4,6-trichlorobenzoyl chloride (1 mol equiv.), triethylamine (1.2 mol equiv.), THF, 18 °C, 2 h then DMAP (5 mol equiv.), toluene, 112 °C, 1 h; (vi) $Zn(BF_4)_2$ (1.2 mol equiv.), MeCN, 18 °C, 24 h.

(perhaps *via* retro-aldol-type processes) while use of the milder TASF[31] reagent generated a variety of unidentified silicon-containing materials. Exposure of lactone **29** to 1% HCl in ethanol only resulted in lactone cleavage and formation of the ethyl analogue of methyl ester **27**. Some success was observed when a HF-pyridine complex was used but the yields of target **1** were poor (20%). In the end the use of zinc tetrafluoroborate in acetonitrile at 18 °C, as described by Ranu *et al.*,[32] give the best result. Thus, under these conditions and after column chromatography, (−)-cladospolide A (**1**) was obtained as a white, crystalline solid in 73% yield. The physical and spectral data acquired on this material were in excellent agreement with those reported[1] for the natural product.

The synthesis detailed above provides target **1** in 11 steps and 4% overall yield from the biocatalytically-derived and enantiomerically pure starting materials *cis*-1,2-dihydrocatechol **7** and alcohol (*R*)-(−)-**9**. The procedures used here should be amenable to the preparation of the other cladospolides and works directed towards such ends are now underway in these laboratories.

Experimental

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 or Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at 20 °C unless otherwise stated. For spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference while the central peak (δ 77.0) of the $CDCl_3$ 'triplet' was used as the reference for proton-decoupled spectra. Spectral data are recorded as follows: chemical shift (δ) [relative integral, multiplicity, coupling constant(s) *J* (Hz)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet or quintet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer or a Perkin-Elmer Spectrum *One* instrument. Samples were analyzed as KBr discs (for solids) or as thin films on KBr plates (for liquids/oils). Low and high resolution MS spectra were recorded on an AUTOSPEC spectrometer or a Kratos Analytical Concept ISQ instrument, the latter being located at the University of Tasmania. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at the sodium D line (598 nm) using spectroscopic grade chloroform (unless otherwise specified) at 20 °C and at the concentrations (*c*) (g 100 mL^{-1}) indicated. Measurements were carried out in a cell with a path length of 1 dm. Melting points (mp) were recorded on a Reichert hot-stage apparatus and are uncorrected. Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia. Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F254 plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with an anisaldehyde–sulfuric acid–ethanol (3 mL:4.5 mL:200 mL) dip or, occasionally, with a phosphomolybdic acid–ceric sulfate–sulfuric acid–water (37.5 g:7.5 g:37.5 mL:720 mL) dip, followed by heating. The quoted retardation factors (R_f) have been rounded to the first decimal place. Flash chromatography was conducted according to the method of Still and co-workers[33] using silica gel 60 (mesh size 0.040–0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated. Many starting materials and reagents were available from the Aldrich Chemical Company or EGA-Chemie and were used as supplied or, in the case of stable liquids, simply distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen in flame-dried apparatus. Tetrahydrofuran (THF) and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. Dichloromethane was distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was heated at reflux over calcium hydride for 16 h then distilled and stored over 3 Å molecular sieves. Organic solutions obtained from work-up of reaction mixtures were dried with anhydrous magnesium sulfate ($MgSO_4$) then concentrated under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 40 °C. Buffer solution of pH 7.3 was prepared by dissolving potassium dihydrogenphosphate (85 g) and sodium hydroxide (14.5 g) in water (950 mL). GC analyses were carried out using an Agilent/HP 6890-5973 gas chromatograph fitted with a 25QC2/CYDEX-B 0.25 mm capillary column supplied by SGE (Melbourne) and heated at 50–80 °C. Peaks were detected using a flame ionisation detector operating at 300 °C and helium was employed as carrier gas (flow rate *ca.* 35 cm s^{-1}). Molecular mechanics and AM1 semi-empirical calculations were carried out using the Spartan '02 for Macintosh program as supplied by Wavefunction Inc. of Irvine, CA.

(1*S*,2*S*)-3-Chloro-3-cyclohexene-1,2-diol (10)

5% Rh on alumina (1.20 g, 7 mol%) was added to a magnetically stirred solution of diol **7** (10.4 g, 71 mmol) in absolute ethanol (350 mL), and the reaction vessel was evacuated then flushed three times with dihydrogen. The resulting black slurry was then stirred at 18 °C for 1.5 h under dihydrogen whereupon TLC analysis indicated the absence of starting material. As a consequence, the reaction mixture was filtered through a pad of Celite™ and the filtrate concentrated under reduced pressure to give an off-white solid. This material was subject to flash chromatography (2:15:3 v/v/v methanol–diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.3, diethyl ether) gave the title compound **10**[16,17] (7.90 g, 75%) as white crystals, mp 115–116 °C; $[\alpha]_D$ −174 (*c* 0.30, methanol); (Found: C, 48.64; H, 6.15; Cl, 23.93. $C_6H_9ClO_2$ requires C, 48.50; H, 6.10; Cl 23.86%); ν_{max}/cm^{-1} 3270, 2932, 2834, 1651, 1462, 1432, 1356, 1332, 1295, 1155, 1124, 1096, 1054, 1002, 984, 923, 820, 787, 690, 591; δ_H 5.99 (1 H, dd, *J* 3.5 and 4.5), 4.16 (1 H, m), 3.94 (1 H, dt, *J* 3.8 and 9.2), 2.70 (2 H, broad s), 2.31 (1 H, m), 2.11 (1 H, m), 1.88–1.70 (2 H, complex m); δ_C 131.0 (C), 128.4 (CH), 70.5 (CH), 68.9 (CH), 25.2 (CH_2), 23.8 (CH_2); *m*/*z* (EI) 150 and 148 ($M^{+\bullet}$, 2 and 7%), 106 and 104 (45 and 100%). Calc. for $C_6H_9{}^{35}ClO_2$ (M): 148.0290. Found: 148.0291.

{[(1*S*,2*S*)-3-Chloro-3-cyclohexene-1,2-diyl]bis(oxy)}bis[(1,1-dimethylethyl)]dimethylsilane (11)

A mixture of diol **10** (1.78 g, 12 mmol), TBDMS-Cl (7.29 g, 48 mmol) and imidazole (6.60 g, 97 mol) was treated with DMF (20 mL) and the resulting solution stirred at 18 °C for 6 h then partitioned between water (50 mL) and ethyl acetate (20 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 40 mL) and the combined organic fractions washed successively with NaOH (1 × 20 mL of a 1 M aqueous solution), water (1 × 20 mL) and brine (1 × 20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (hexane elution) and concentration of the relevant fractions (R_f 0.3 in 2:98 v/v ethyl acetate–hexane) gave the title compound **11** (4.53 g, 100%) as a clear, colourless oil, $[\alpha]_D$ −13 (*c* 7.40); ν_{max}/cm^{-1} 2955, 2929, 2894, 2857, 1649, 1472, 1463, 1362, 1255, 1144, 1115, 1080, 1021, 997, 965, 917, 869, 833, 776, 674, 590; δ_H 5.81 (1 H, dd, *J* 2.8 and 4.5), 4.03 (1 H, d, *J* 3), 3.77 (1 H, dt, *J* 3.1 and 11.6), 2.28–1.90 (3 H, complex m), 1.54 (1 H, m), 0.93 (9 H, s), 0.92 (9 H, s), 0.17 (3 H, s), 0.14 (3 H,

s), 0.10 (3 H, s), 0.09 (3 H, s); δ_C 132.2 (C), 126.5 (CH), 74.0 (CH), 72.4 (CH), 26.2 (3 × CH_3), 26.0 (3 × CH_3) 25.2 (CH_2), 24.1 (CH_2), 18.5 (C), −4.2 (CH_3), −4.3 (CH_3), −4.4 (CH_3), −4.6 (CH_3) (one signal obscured or overlapping); *m/z* (EI) 377 and 375 [$(M - H^{\bullet})^+$, each <1%], 363 and 361 [$(M - CH_3^{\bullet})^+$, 2 and 5], 341 [$(M - Cl^{\bullet})^+$, 9], 321 and 319 (30 and 81), 218 (31), 147 (100), 113 (52). Calc. for $C_{19}H_{37}O_2Si_2$ $(M - Cl^{\bullet})^+$: 341.2332. Found: 341.2325.

(2*S*,3*S*)-2,3-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-6-heptenoic acid methyl ester (13)

A magnetically stirred solution of alkene **11** (109 mg, 0.29 mmol) in methanol (6 mL) was cooled to −78 °C then treated with a stream of ozone until a blue colour persisted and TLC analysis indicated the absence of starting material (*ca.* 20 min). The excess ozone was removed by purging the reaction mixture with a stream of nitrogen (10 min) and the resulting colourless solution was then placed in an ice-bath. After 15 min $NaBH_4$ (12.6 mg, 0.33 mmol) was added in two portions over 10 min whereupon TLC analysis indicated the disappearance of the ozonolysis product. As a result, the reaction mixture was quenched with NH_4Cl (1 × 5 mL of a saturated aqueous solution) then extracted with dichloromethane (3 × 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give aldehyde **12** as an unstable, yellow oil. δ_H 9.80 (1 H, s), 4.10 (1 H, d, *J* 6), 4.01 (1 H, dd, *J* 6 and 15), 3.71 (3 H, s), 2.56–2.48 (2 H, complex m), 2.03–1.8 (2 H, complex m), 0.88 (9 H, s), 0.84 (9 H, s), 0.08 (9 H, s), 0.07 (3 H, s). This material was used immediately in the next step of the reaction sequence.

A magnetically stirred solution of methyltriphenylphosphonium bromide (299 mg, 0.74 mmol) in THF (2 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with potassium bis(trimethylsilyl)amide (1.52 mL of a 0.5 M solution in toluene, 0.76 mmol). The resulting yellow mixture was allowed to warm to 18 °C over 0.5 h then re-cooled to 0 °C and treated, *via* cannula, with a solution of aldehyde **12** (obtained as described immediately above) in THF (6 mL). After 1 h at 18 °C the reaction mixture was treated with NH_4Cl (10 mL of a saturated aqueous solution) and water (10 mL) then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with water (1 × 5 mL) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (2:98 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.6 in 5:95 v/v ethyl acetate–hexane) gave the title compound **13** (72 mg, 61% over 3 steps) as a yellow oil, $[\alpha]_D$ −9 (*c* 0.30); ν_{max}/cm^{-1} 2953, 2930, 2857, 1755, 1472, 1255, 1123, 835, 777; δ_H 5.80 (1 H, m), 5.05–4.91 (2 H, complex m), 4.10 (1 H, d, *J* 5.4), 3.95 (1 H, dd, *J* 5.2 and 10.3), 3.70 (3 H, s), 2.16–2.04 (2 H, complex m), 1.82–1.55 (2 H, complex m), 0.90 (9 H, s), 0.87 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s), 0.05 (3 H, s), 0.04 (3 H, s); δ_C 172.8 (C), 138.6 (CH), 114.4 (CH_2), 75.6 (CH), 74.0 (CH), 51.6 (CH_3), 32.1 (CH_2), 28.4 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C), 18.0 (C), −4.6 (CH_3), −4.7 (CH_3), −5.1 (CH_3), −5.3 (CH_3); *m/z* (EI) 387 [$(M - CH_3^{\bullet})^+$, 4.8%], 345 [$(M - C_4H_9^{\bullet})^+$, 72], 318 (19), 285 (16), 261 (17), 199 (69), 147 (38), 73 (100). Calc. for $C_{19}H_{39}O_4Si_2$ $(M - CH_3^{\bullet})^+$: 387.2387. Found: 387.2389.

(2*S*,3*S*)-2,3-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-6-heptenal (6)

DIBAL-H (1.0 µL of a 1 M solution in hexane, 1.00 mmol) was added in three portions over 1 h to a magnetically stirred solution of ester **13** (222 mg, 0.55 mmol) in hexane (16 mL) maintained at −78 °C under a nitrogen atmosphere. The reaction mixture was then quenched with NH_4Cl (10 mL of a saturated aqueous solution) and sufficient HCl (1 M aq. solution) added to dissolve the precipitate so formed (*ca.* 2 mL). The mixture was extracted with diethyl ether (2 × 15 mL) and the combined organic fractions washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title aldehyde **6** (183mg, 90%) as a light-yellow oil. This material was pure enough to use in the next step of the reaction sequence. A portion of this material was subjected to flash chromatography (2.5:97.5 v/v ethyl acetate–hexane elution) to give a spectroscopically pure sample of compound **6** as a clear, colourless oil. ν_{max}/cm^{-1} 2954, 2930, 2858, 1736, 1642, 1472, 1361, 1255, 1117, 1004, 911, 832, 777, 671; δ_H 9.61 (1 H, m), 5.79 (1 H, m), 5.06–4.94 (2 H, complex m), 3.94–3.88 (2 H, complex m), 2.14–2.03 (2 H, complex m), 1.75–1.56 (2 H, complex m), 0.92 (9 H, s), 0.88 (9 H, s), 0.08 (9 H, br s), 0.07 (3 H, s); δ_C 203.5 (CH), 138.0 (CH), 114.8 (CH_2), 80.7 (CH), 74.8 (CH), 32.7 (CH_2), 29.2 (CH_2), 25.7(9) (3 × CH_3), 25.7(7) (3 × CH_3), 18.2 (C), 18.1 (C), −4.3 (CH_3), −4.7 (CH_3 – two signals overlapping), −4.9 (CH_3); *m/z* (EI) 373 [$(M + H)^+$, 0.06%], 357 [$(M - CH_3^{\bullet})^+$, 0.6], 343 (0.5), 315 [$(M - C_4H_9^{\bullet})^+$, 6], 231 (79), 199 (82), 73 (100). Calc. for $C_{19}H_{41}O_3Si_2$ $(M + H)^+$: 373.2594. Found: 373.2595.

General procedure used in screening of lipases for enantioselective hydrolysis of the butyrate esters derived from alcohol (±)-9

A mixture of the specified amount (see Table 1) of the butyrate ester[20] of alcohol (±)-**9** in the relevant medium (2 mL) was treated with the appropriate lipase (10 mg). The resulting suspension was kept at 30 °C on an orbital shaker for the specified time then diluted with ethyl acetate (1 mL) and agitated by vigorous shaking. The emulsified supernatant was removed by pipette and placed in a centrifuge tube which was spun at 200 rpm for 3 min. The resulting clear and now lipase-free supernatant was removed and subjected to chiral GLC analysis (see introductory comments to Experimental section for details) to determine the enantiomeric excess of the residual ester {R_t for *S*-enantiomer = 5.2 min at 80 °C; R_t for *R*-enantiomer = 5.8 min at 80 °C; R_t for *R*-4-penten-2-ol [(−)-**9**] = 7.9 min at 80 °C}. Results from the relevant experiments are shown in Table 1.

Time-course experiment associated with the CALB-catalysed hydrolysis of the butyrate esters derived from alcohol (±)-9

A vigorously stirred mixture of the butyrate esters (509 mg) derived from alcohol (±)-**9** and pH 7.3 buffer (10 mL) was treated with CALB (50 mg). The resulting slurry was stirred at 25 °C and aliquots (1.0 mL) were removed for analysis at the time points specified in Table 2. Each aliquot was placed in a centrifuge tube with ethyl acetate (500 µL), treated with $NaHCO_3$ (1 mL of a saturated aqueous solution) and vigorously shaken. The tubes were spun at 200 rpm for 3 min, frozen at −20 °C then the liquid supernatant was removed and subject to chiral GLC analysis to determine the enantiomeric excess (ee_s) of the residual ester.

(*S*)-4-Penten-2-ol [(*S*)-(+)-9] and acetic acid (*R*)-1-methylbut-3-enyl ester (14)

(a) Time-course experiment. (±)-4-Penten-2-ol [(±)-**9**] (502 mg, 5.83 mmol) was dissolved in vinyl acetate (502 mg, 537 µL, 5.83 mmol) and CALB (53 mg) then added in one portion. The resulting slurry was stirred at 30 °C and aliquots (1 drop) were removed for analysis at the times specified in Table 3. These aliquots were diluted with ethyl acetate (200 µL) then placed in a centrifuge tube and spun at 200 rpm for 3 min. The supernatant was decanted into vials for chiral GLC analysis. Results from the relevant experiments are shown in Table 3.

(b) Preparative experiment. (±)-4-Penten-2-ol [(±)-**9**] (9.85 g, 0.11 mol, 1 equiv.) was dissolved in vinyl acetate (9.84 g, 0.11

mol, 1 mol equiv.) and the resulting solution treated with CALB (1 g). The ensuing slurry was stirred at 30 °C for 1 h and then filtered through a glass frit to remove the immobilised enzyme particles. The filtrate was loaded onto a tall pad of TLC-grade silica which was then eluted with dichloromethane. In this manner two fractions, A and B, were obtained.

Concentration of fraction A (R_f 0.7 in 1:9 v/v ethyl acetate–hexane) at 0 °C using a water aspirator and a dry-ice condenser gave acetate **14** (5.63 g, 80%, 75% ee).

Concentration of fraction B (R_f 0.3 in 1:9 v/v ethyl acetate–hexane) at 0 °C using a water aspirator and a dry-ice condenser gave alcohol (*S*)-(+)-**9** (2.74 g, 60%, 99% ee as determined by analysis of the derived acetate; R_t for *S*-enantiomer = 9.1 min at 50 °C; R_t for *R*-enantiomer = 11.2 min at 50 °C).

(*R*)-4-Penten-2-ol [(*R*)-(−)-9]

A slurry of phosphate buffer (50 mL, pH 7.3), CALB (2.10 g) and acetate **14** (17.6 g, 0.14 mol, 75% ee), obtained as described immediately above, was stirred vigorously at 30 °C for 16 h then cooled to 18 °C and filtered through a pad of Celite™. The filter cake was washed with diethyl ether (6 × 100 mL) and the separated aqueous layer extracted with dichloromethane (3 × 200 mL). The combined organic fractions were then washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure at 0 °C on a rotary evaporator fitted with a water aspirator and a dry-ice condenser. The resulting light-yellow oil was subject to flash column chromatography (1:3 v/v ether–pentane elution) and concentration of the relevant fractions (R_f 0.3 in 1:9 v/v ethyl acetate–hexane) by evaporation at atmospheric pressure then afforded the title compound (*R*)-(−)-**9** (7.23 g, 60%) as a *ca.* 50 mol% solution in diethyl ether. GLC analysis of the derived acetate established it was of >99% ee.

(Dimethoxyphosphinyl)acetic acid (1*R*)-1-methyl-3-butenyl ester (8)

A magnetically stirred solution of DMAP (42 mg, 0.34 mmol) in toluene (10 mL) maintained at 18 °C under a nitrogen atmosphere was treated, dropwise, with alcohol (*R*)-(−)-**9** (200 μL, 0.46 mmol). Trimethyl phosphonoacetate (150 μL, 0.93 mmol) was then added dropwise and the resulting solution heated at reflux for 18 h. The cooled reaction mixture was quenched with NH_4Cl (5 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 10 mL). The organic fractions were combined, washed with water (1 × 5 mL) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark-yellow residue which was purified by flash column chromatography (ethyl acetate elution). Concentration of the relevant fractions (R_f 0.5) gave the title compound **8** as a light-yellow oil (101 mg, 93%). $[\alpha]_D$ +79 (*c* 1.13); ν_{max}/cm^{-1} 2957, 2854, 1733, 1642, 1454, 1272, 1116, 1032, 850, 805; δ_H 5.69 (1 H, m), 5.03 (2 H, m), 4.93 (1 H, m), 3.76 (3 H, m), 3.72 (3 H, m), 2.90 (2 H, d, *J* 21.6), 2.27 (2 H, m), 1.18 (3 H, d, *J* 6.3); δ_C 164.8 (C, d, *J* 6.0), 133.0 (CH), 117.7 (CH_2), 71.6 (CH), 53.0 (CH_3, d, *J* 2.3), 52.9 (CH_3, d, *J* 2.3), 39.9 (CH_2), 33.5 (CH_2, d, *J* 134.5), 19.2 (CH_3); *m/z* (EI) 237 [$(M + H)^+$, 4%], 195 [$(M - C_3H_5^{\bullet})^+$, 3], 169 (22), 151 (100), 109 (55). Calc. for $C_9H_{18}O_5P$ $(M + H)^+$: 237.0892. Found: 237.0895.

Compound *ent*-**8**, $[\alpha]_D$ −77 (*c* 0.85), was prepared from (*S*)-(+)-**9** and trimethyl phosphonoacetate by the method defined above. The derived NMR, IR, and MS spectral data were identical with those obtained from ester **8**.

(2*E*,4*R*,5*S*)-4,5-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-2,8-nonadienoic acid (1*R*)-1-methyl-3-butenyl ester (5)

A magnetically stirred suspension of NaH (13.8 mg of a 60% dispersion in mineral oil, 0.58 mmol) in THF (1 mL) maintained at 0 °C under a nitrogen atmosphere was treated, *via* cannula, with a solution of compound **8** (80 mg, 0.34 mmol) in THF (1 mL). The resulting mixture was allowed to warm to 18 °C over 0.66 h then re-cooled to 0 °C and a solution of aldehyde **6** (109 mg, 0.29 mmol) in THF (1.5 mL) was added *via* cannula at 0 °C. After re-warming to 18 °C over 1.25 h, the reaction mixture was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and the separated aqueous layer extracted with diethyl ether (3 × 10 mL). The organic fractions were combined, washed with water (1 × 5 mL) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil that was subjected to flash chromatography (2:98 v/v ethyl acetate–hexane elution). Concentration of the relevant fractions (R_f 0.1) gave the title compound **5** (173 mg, 81% from compound **6**). $[\alpha]_D$ −3 (*c* 0.70); ν_{max}/cm^{-1} 3078, 2932, 2891, 2858, 1721, 1650, 1644, 1467, 1361, 1257, 1168, 1109, 987, 914, 835, 776; δ_H 6.92 (1 H, dd, *J* 5.7 and 15.8), 5.93 (1 H, dd, *J* 1.5 and 15.8), 5.88–5.69 (2 H, complex m), 5.13–4.92 (5 H, complex m), 4.14 (1 H, m), 3.66 (1 H, m), 2.34 (2 H, m), 2.11 (2 H, m), 1.62 (2 H, m), 1.25 (3 H, d, *J* 6.3), 0.91 (9 H, s), 0.89 (9 H, s), 0.07 (3 H, s), 0.04(3) (3 H, s), 0.03(8) (3 H, s), 0.03(1) (3 H, s); δ_C 165.7 (C), 148.7 (CH), 138.5 (CH), 133.6 (CH), 121.9 (CH), 118.0 (CH_2), 114.4 (CH_2), 75.5 (CH), 75.3 (CH), 70.0 (CH), 40.4 (CH_2), 32.7 (CH_2), 29.0 (CH_2), 26.0(0) (3 × CH_3), 25.9(9) (3 × CH_3), 19.6 (CH_3), 18.3 (C), 18.2 (C), −4.0(5) (CH_3), −4.1(4) (CH_3), −4.3 (CH_3), −4.6 (CH_3); *m/z* (EI) 483 [$(M + H)^+$, >1%], 467 [$(M - CH_3^{\bullet})^+$, 1], 425 [$(M - C_4H_9^{\bullet})^+$, 39], 398 (38), 284 (33), 225 (31), 199 (82), 151 (43), 147 (58), 73 (100). Calc. for $C_{25}H_{47}O_4Si_2$ $(M - CH_3^{\bullet})^+$: 467.3013. Found: 467.3014.

[(1*S*,2*R*)-3-Cyclohexene-1,2-diyl-bis(oxy)]bis[(1,1-dimethylethyl)]dimethylsilane (16)

Grubbs'-II catalyst (7.5 mg, 0.01 mmol) was added to a magnetically stirred solution of compound **5** (24 mg, 0.05 mmol) in degassed dichloromethane (50 mL) maintained under a nitrogen atmosphere at 18 °C. The reaction mixture was stirred for a further 18 h whereupon TLC analysis indicated the absence of starting material. $P(CH_2OH)_3$ (100 mg) and silica (*ca.* 2 g) were added and the resulting mixture stirred at 18 °C for a further 1 h then filtered and concentrated under reduced pressure to give a dark-yellow oil. Subjection of this material to flash chromatography (2:98 v/v diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.7) gave the title compound **16** (17 mg, 100%) as a clear, colourless oil. $[\alpha]_D$ −119 (*c* 0.46); ν_{max}/cm^{-1} 3029, 2932, 2888, 2857, 1467, 1392, 1252, 1117, 1022, 955, 869, 834, 776; δ_H 5.69 (1 H, m), 5.58 (1 H, m), 4.07 (1 H, m), 3.78 (1 H, dt, *J* 2.8 and 9.7), 2.19 (1 H, m), 2.05–1.84 (2 H, complex m), 1.55 (1 H, m), 0.91 (18 H, s), 0.09 (3 H, s), 0.08 (9 H, s); δ_C 128.8, 128.7, 71.0, 68.6, 26.6, 26.1(4), 26.1(3), 24.3, 18.5, −4.1, −4.2, −4.3, −4.6 (one signal obscured or overlapping); *m/z* (EI) 341 [$(M - H^{\bullet})^+$, 0.9%], 327 [$(M - CH_3^{\bullet})^+$, 6], 285 [$(M - C_4H_9^{\bullet})^+$, 8], 184 (34), 147 (100), 127 (62), 79 (53), 73 (59). Calc. for $C_{17}H_{35}O_2Si_2$ $(M - CH_3^{\bullet})^+$: 327.2176. Found: 327.2173.

(2*S*,3*S*)-2,3-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-6-heptenoic acid (1*R*)-1-methyl-3-butenyl ester (18)

A magnetically stirred solution of ester **13** (216 mg, 0.54 mmol) in ethanol (20 mL) maintained at 18 °C was treated with a solution of NaOH (108 mg, 2.7 mmol) in water (2 mL). The ensuing mixture was heated to 50 °C for 13 h then cooled, treated with NH_4Cl (1 × 10 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude acid **17**, $[\alpha]_D$ −5 (*c* 0.10); ν_{max}/cm^{-1} 3078, 2953, 2930, 2896, 2858, 1723, 1642, 1471, 1463, 1255, 1126, 836, 777; δ_H 9.60 (1 H, broad s), 5.78 (1 H, m), 4.99 (2 H, m), 4.17 (1 H, d, *J* 3.6), 3.93 (1 H, m),

2.09 (2 H, m), 1.69 (2 H, m), 0.91 (9 H, s), 0.88 (9 H, s), −0.09 (3 H, s), −0.10 (3 H, s), −0.13 (6 H, s); δ_C 175.2 (C), 138.4 (CH), 138.1 (CH_2), 75.9 (CH), 74.5 (CH), 32.1 (CH_2), 29.1 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 18.2 (C), 18.0 (C), −4.5 (CH_3), −4.7 (CH_3), −5.0 (CH_3), −5.2 (CH_3); *m/z* (EI) 331 [$(M - C_4H_9^{\bullet})^+$, 80%], 199 (88), 171 (71), 147 (47), 75 (66), 73 (100).

A magnetically stirred solution of the acid **17**, obtained as described above, in toluene (18 mL) maintained at 0 °C under a nitrogen atmosphere was treated sequentially with DMAP (69 mg, 0.56 mmol), alcohol (*R*)-(−)-**9** (290 μL of a 2.3 M solution in diethyl ether, 0.67 mmol) and triethylamine (390 μL, 2.8 mmol) then cooled to 0 °C and 2,4,6-trichlorobenzoyl chloride (95 μL, 0.56 mmol) added dropwise. The ensuing white slurry was stirred for an additional 0.75 h then the reaction mixture treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark-yellow residue. Subjection of this material to gravity column chromatography (2:98 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.3 in 5:95 v/v ethyl acetate–hexane) gave the title compound **18** (158 mg, 65 %) as a clear, colourless oil. $[\alpha]_D$ −5 (*c* 0.80); ν_{max}/cm^{-1} 3079, 2931, 2857, 1752, 1642, 1468, 1380, 1255, 1123, 994, 914, 835, 777; δ_H 5.86–5.69 (2 H, complex m), 5.14–4.92 (5 H, complex m), 4.14 (1 H, d, *J* 3.2), 3.95 (1 H, m), 2.34 (2 H, m), 2.09 (2 H, m), 1.67 (2 H, m), 1.24 (3 H, d, *J* 6.3), 0.92 (9 H, s), 0.89 (9 H, s), 0.09 (3 H, s), 0.08 (3 H, s), 0.07 (3 H, s), 0.06 (3 H, s); δ_C 171.4 (C), 138.6 (CH) 133.5 (CH), 117.9 (CH_2), 114.4 (CH_2), 76.3 (CH), 74.7 (CH), 70.6 (CH), 40.2 (CH_2), 32.2 (CH_2), 29.3 (CH_2), 25.9 (3 × CH_3), 25.7 (3 × CH_3), 19.3 (CH_3), 18.3 (C), 18.1(C), −4.3 (CH_3), −4.7(8) (CH_3), −4.8(2) (CH_3), −5.2 (CH_3); *m/z* (EI) 456 ($M^{+\bullet}$, >1%), 441 [$(M - CH_3^{\bullet})^+$, >1], 399 [$(M - C_4H_9^{\bullet})^+$, 35%], 372 (23), 331 (98), 315 (42), 273 (12), 258 (22), 199 (100), 171 (41), 155 (39), 133 (54), 115 (37), 73 (76). Calc. for $C_{20}H_{39}O_4Si_2$ $(M - C_4H_9^{\bullet})^+$: 399.2387. Found: 399.2391.

(3*S*,4*S*,7*Z*,10*R*)-3,4-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-3,4,5,6,9,10-hexahydro-10-methyl-2*H*-oxecin-2-one (19)

A magnetically stirred solution of diene **18** (125 mg, 0.27 mmol) in degassed dichloromethane (140 mL) maintained under a nitrogen atmosphere was treated, *via* cannula, with a solution of Grubbs'-II catalyst (35 mg, 0.04 mmol, 15 mol%) in dichloromethane (10 mL). The resulting mixture was stirred at 18 °C for 24 h then $P(CH_2OH)_3$ (*ca.* 50 mg) and silica gel (*ca.* 200 mg) were added to the reaction mixture. The resulting slurry was stirred at 18 °C for 1 h then filtered through a pad of TLC-grade silica gel which was washed with dichloromethane (1 × 10 mL). The combined filtrates were concentrated under reduced pressure and the light-yellow oil thus obtained subject to flash chromatography (2:98 v/v diethyl ether–hexane elution) and thereby affording two fractions, A and B.

Concentration of fraction A [R_f 0.3(0) in 5:95 v/v ethyl acetate–hexane] afforded the starting diene **18** (32 mg, 26% recovery) which was identical, in all respects, with an authentic sample.

Concentration of fraction B [R_f 0.2(8) in 5:95 v/v ethyl acetate–hexane] gave the title compound **19** (61 mg, 73% yield at 75% conversion) as a clear, colourless oil. $[\alpha]_D$ +0.8 (*c* 7.40); ν_{max}/cm^{-1} 2931, 2857, 1729, 1465, 1374, 1255, 1155, 1073, 957, 885, 837, 777, 716, 674; δ_H 5.47–5.33 (2 H, complex m), 5.10 (1 H, m), 4.28 (1 H, d, *J* 0.7), 3.98 (1 H, dd, *J* 4.7 and 10.9), 2.73 (1 H, m), 2.38 (1 H, m), 2.04–1.82 (3 H, complex m), 1.68–1.53 (1 H, complex m), 1.32 (3 H, d, *J* 6.5), 0.93 (9 H, s), 0.89 (9 H, s), 0.09 (3 H, s), 0.07 (3 H, s), 0.06 (3 H, s), 0.04 (3 H, s); δ_C 172.6 (C), 133.7 (CH), 124.7 (CH), 78.4 (CH), 74.5 (CH), 70.5 (CH), 34.6 (CH_2), 32.1 (CH_2), 25.8 (3 × CH_3), 25.6 (3 × CH_3), 22.7 (CH_2), 20.2 (CH_3), 18.3 (C), 18.0 (C), −4.8 (CH_3), −4.9 (CH_3), −5.1 (CH_3), −5.4 (CH_3); *m/z* (EI) 428 ($M^{+\bullet}$, 2%), 413 [$(M - CH_3^{\bullet})^+$, 3], 371 [$(M - C_4H_9^{\bullet})^+$, 76], 239 (80), 211 (43), 171 (53), 147 (69), 95 (64), 75 (58), 73 (100). Calc. for $C_{22}H_{44}O_4Si_2$ $M^{+\bullet}$: 428.2778. Found: 428.2777.

(4*R*,5*S*)-5-But-3-enyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (precursor to ester 20)

TBAF (1.1 mL of a 1 M solution in THF, 1.1 mmol) was added dropwise to a magnetically stirred solution of ester **13** (223 mg, 0.55 mmol) in THF (6 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was brought to 18 °C, stirred at this temperature for 2 h, then treated with water (5 mL) and $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous fraction was extracted with diethyl ether (2 × 10 mL) and the combined organic fractions then washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. This material was dissolved in 2,2-dimethoxypropane (6 mL) containing *p*-toluenesulfonic acid (9 mg) and the resulting and magnetically stirred solution maintained under a nitrogen atmosphere at 18 °C for 18 h. $NaHCO_3$ (10 mL of a saturated aqueous solution) was added to quench the reaction mixture and the separated aqueous fraction was extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give methyl (4*R*,5*S*)-5-but-3-enyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (42 mg, 35% from **13**). A magnetically stirred solution of this compound (39 mg, 0.18 mmol) in ethanol (3 mL) was treated with NaOH (100 mg, 2.5 mmol) dissolved in water (2 mL) and maintained at 18 °C for 3 h. The ensuing mixture was acidified with HCl (4 mL of a 1 M aqueous solution) and extracted with dichloromethane (3 × 10 mL). The combined organic fractions were washed with brine (1 × 5 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an off-white solid which was resuspended in dichloromethane (10 mL), filtered through glass wool and concentrated under reduced pressure to give the title carboxylic acid (35 mg, 100 %) as a pale-yellow solid. Mp 91–94 °C, $[\alpha]_D$ −5 (*c* 0.01); (Found: C, 63.00; H, 9.15. $C_{12}H_{20}O_4$ requires: C, 63.14; H, 8.83%); ν_{max}/cm^{-1} 3436, 3076, 2983, 2934, 1607, 1440, 1373, 1243, 1218, 1167, 1077, 912, 869, 757; δ_H 5.80 (1 H, m), 5.05 (2 H, m), 4.58 (1 H, m), 4.40 (1 H, m), 2.40–2.05 (3 H, complex m), 1.80 (1 H, m), 1.60 (3 H, s), 1.40 (3 H, s) (signal due to CO_2H not observed); *m/z* (EI) 185 [$(M - CH_3^{\bullet})^+$, 100%], 125 (19), 116 (12), 97 (51), 79 (33), 69 (30), 59 (62). Calc. for $C_9H_{13}O_4$ $(M - CH_3^{\bullet})^+$: 185.0814. Found 185.0818.

(4*R*,5*S*)-5-But-3-enyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (1*R*)-1-methylbut-3-enyl ester (20)

A magnetically stirred solution of (4*R*,5*S*)-5-but-3-enyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (26 mg, 0.13 mmol) in toluene (4 mL) maintained at 0 °C under a nitrogen atmosphere was treated with DMAP (16 mg, 0.13 mmol), alcohol (*R*)-(−)-**9** (60 μL of a 4.5 M solution in diethyl ether, 0.27 mmol) and triethylamine (92 μL, 0.66 mmol). 2,4,6-Trichlorobenzoyl chloride (22 μL, 0.14 mmol) was added dropwise over 1 min and the resulting white slurry stirred for an additional 0.75 h at 0 °C then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark-yellow residue. Subjection of this material to gravity column chromatography (2:98 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.3 in 1:3 v/v ethyl acetate–hexane) gave the title compound **20** (19 mg, 54 %) as a clear, colourless oil. $[\alpha]_D$ +30 (*c* 0.50); ν_{max}/cm^{-1} 3078, 2982, 2935, 1754, 1642, 1452, 1377, 1265, 1192, 1093, 995, 916, 869, 790; δ_H 4.23 (2 H, m), 5.16–4.94

(5 H, m), 4.52 (1 H, d, *J* 6.7), 4.32 (1 H, m), 2.44–2.09 (4 H, complex m), 1.72–1.52 (2 H, complex m), 1.62 (3 H, s), 1.38 (3 H, s), 1.25 (3 H, d, *J* 6.3); δ_C 169.9 (C), 137.4 (CH), 133.3 (CH), 118.1 (CH_2), 115.2 (CH_2), 110.3 (C), 77.2 (CH), 77.1 (CH), 71.2 (CH), 40.2 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 27.0 (CH_3), 25.7 (CH_3), 19.5 (CH_3); *m/z* (EI) 253 [$(M - CH_3^{\bullet})^+$, 85%], 155 (14), 125 (26), 116 (16), 97 (100), 79 (39), 69 (89). Calc. for $C_{14}H_{21}O_4$ $(M - CH_3^{\bullet})^+$: 253.1440. Found: 253.1439.

(3a*S*,6*R*,8*Z*,11a*S*)-3a,6,7,10,11,11a-Hexahydro-2,2,6-trimethyl-1,3-dioxolo[4,5-*c*]oxecin-4-one (21)

Diene **20** (13 mg, 0.05 mmol) was subjected to the conditions defined above for the ring-closing metathesis of congener **18** (and yielding macrolide **19**). Subjection of the resulting mixture to the specified work-up procedures afforded a light–yellow oil which was subject to flash chromatography (1:3 v/v diethyl ether–hexane elution). In this manner two fractions, A and B, were obtained.

Concentration of fraction A [R_f 0.3(2)] afforded the starting diene **20** (2 mg, 15% recovery) which was identical, in all respects, with an authentic sample.

Concentration of B [R_f 0.3(5)] gave a clear colourless oil tentatively identified as the title compound **21** (4 mg, 40% at 85% conversion). δ_H 5.59–5.38 (2 H, complex m), 4.94 (1 H, m), 4.53 (1 H, m), 4.28 (1 H, m), 2.43–2.04 (4 H, complex m), 1.66–1.58 (2 H, complex m), 1.60 (3 H, m), 1.29 (3 H, m), 1.27 (3 H, m). These data compare favourably with those derived from the more stable congener **19**. It is this comparison which provides the major basis for the assignment of the illustrated structure to compound **21**.

(2*S*,3*S*)-2,3-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-6-heptenoic acid (1*S*)-1-methyl-3-butenyl ester (22)

A magnetically stirred solution of ester **13** (106 mg, 0.27 mmol) in ethanol (10 mL) maintained at 18 °C was treated with a solution of NaOH (212 mg, 5.3 mmol) in water (2 mL). The ensuing mixture was heated to 50 °C for 13 h, then cooled, acidified with NH_4Cl (1 × 10 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude acid **17** which was dissolved in toluene (30 mL) and the resulting solution maintained under a nitrogen atmosphere at 18 °C whilst being treated with DMAP (1.9 mg, 16 mmol), alcohol (*S*)-(+)-**9** (98 μL, *ca.* 0.95 mmol) and triethylamine (1 mL, 7.2 mmol). The resulting mixture was cooled to 0 °C and 2,4,6-trichlorobenzoyl chloride (1 mL, 6.4 mmol) added dropwise. The resulting white slurry was warmed to 18 °C, maintained at this temperature for 0.75 h then diluted with diethyl ether (20 mL) and poured into $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous solution was extracted with diethyl ether (3 × 50 mL) and the combined organic fractions were washed with HCl (1 × 10 mL of 1 M aqueous solution), water (1 × 15 mL) and brine (1 × 15 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to gravity column chromatography (2:98 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.5 in 1:9 ethyl acetate–hexane) gave the title compound **22** (33.5 mg, 65 %) as a clear, colourless oil. $[\alpha]_D$ −10 (*c* 0.90); ν_{max}/cm^{-1} 3078, 2953, 2931, 2893, 2857, 2893, 1753, 1468, 1380, 1254, 1156, 1124, 993, 914, 886, 777; δ_H 5.87–5.66 (2 H, complex m), 5.16–4.88 (5 H, complex m), 4.12 (1 H, d, *J* 3.3), 3.94 (1 H, ddd, *J* 3.4, 4.9 and 6.9), 2.44–1.95 (4 H, complex m), 1.84 −1.52 (2 H complex m), 1.24 (3 H, d, *J* 6.3), 0.91 (9 H, s), 0.88 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s), 0.06(2) (3 H, s), 0.05(5) (3 H, s); δ_C 171.4 (C), 138.6 (CH), 133.6 (CH), 117.9 (CH_2), 114.4 (CH_2), 76.3 (CH), 74.8 (CH), 70.8 (CH), 40.2 (CH_2), 32.1 (CH_2), 29.3 (CH_2), 25.9 (3 × CH_3), 25.7 (3 × CH_3), 19.3 (CH_3), 18.3 (C), 18.1 (C), −4.3 (CH_3), −4.7(9) (CH_3), −4.8(2) (CH_3), −5.2 (CH_3); *m/z* (EI) 455 [$(M - H^{\bullet})^+$, 1%], 399 [$(M - C_4H_9^{\bullet})^+$, 2], 345 (32), 243 (31), 215 (34), 199 (65), 185 (43), 147 (52), 133 (21), 115 (42), 73 (100). Calc. for $C_{20}H_{39}O_4Si_2$ $(M - C_4H_9^{\bullet})^+$: 399.2387. Found: 399.2386.

(3*S*,4*S*,7*Z*,10*S*)-3,4-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-3,4,5,6,9,10-hexahydro-10-methyl-2*H*-oxecin-2-one (23)

Diene **22** (31 mg, 0.07 mmol) was subjected to the conditions defined above for ring-closing metathesis. After subjection of the product mixture to flash chromatography (2:98 v/v diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.4 in 8:92 v/v ethyl acetate hexane), the title compound **23** (25 mg, 84%) was obtained as a clear, colourless oil. $[\alpha]_D$ −27 (*c* 0.80); ν_{max}/cm^{-1} 2954, 2930, 2886, 2859, 1750, 1595, 1460, 1428, 1253, 1173, 1136, 1077, 995, 836, 757; δ_H 5.55 (2 H, m), 5.03 (1 H, m), 4.34–4.20 (2 H, complex m), 3.01 (1 H, m), 2.18 (1 H, m), 1.99 (1 H, m), 1.88–1.56 (2 H, complex m), 1.37 (1 H, m), 1.24 (3 H, d *J* 6.7), 0.95 (9 H, s), 0.90 (9 H, s), 0.12 (3 H, s), 0.07 (3 H, s), 0.06 (6 H, m); δ_C 171.8 (C), 134.9 (CH), 122.7 (CH), 74.9 (CH), 72.9 (CH), 70.7 (CH), 30.6 (CH_2), 26.0 (3 × CH_3), 25.8 (3 × CH_3), 23.6 (CH_2), 18.5 (C), 18.2 (C), 17.8 (CH_3), −4.6 (CH_3), −4.8 (CH_3), −4.9 (CH_3), −5.1 (CH_3) (one signal obscured or overlapping); *m/z* (EI) 428 ($M^{+\bullet}$, <1%), 413 [$(M - CH_3^{\bullet})^+$, 2], 371 [$(M - C_4H_9^{\bullet})^+$, 68], 355 (11), 327 (46), 239 (99), 211 (100), 195 (82), 171 (80), 147 (81). Calc. for $C_{22}H_{44}O_4Si_2$ $M^{+\bullet}$: 428.2778. Found: 428.2785.

(2*S*,3*S*)-2,3-Dihydroxyhept-6-enoic acid (1*R*)-1-methylbut-3-enyl ester (precursor to ester 24)

TBAF (600 μL of a 1 M solution in THF, 0.60 mmol) was added dropwise to a magnetically stirred solution of compound **22** (115 mg, 0.25 mmol) in THF (5 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was brought to 18 °C and stirred for 2 h at this temperature then treated sequentially with water (5 mL) and $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic fractions washed with $NaHCO_3$ (1 × 5 mL of a saturated aq. solution) and brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (2:3 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.3) gave the title compound (43 mg, 76%) as pale-yellow needles. Mp 36–38 °C; $[\alpha]_D$ −5 (*c* 0.53); ν_{max}/cm^{-1} 3431, 3077, 2978, 2929, 1730, 1641, 1445, 1212, 1125, 1078, 995, 915; δ_H 5.87–5.65 (2 H, complex m), 5.14–4.93 (4 H, complex m), 4.18 (1 H, d, *J* 3.7), 3.83 (1 H, dt, *J* 3.4 and 9.9), 2.87 (2 H, broad s), 2.40–2.20 (3 H, complex m), 2.12 (1 H, m), 1.64 (1 H, m), 1.47 (1 H, m), 1.27 (3 H, d, *J* 6.3); δ_C 172.3 (C), 137.9 (CH), 133.1 (CH), 118.3 (CH_2), 115.1 (CH_2), 74.1 (CH), 72.5 (CH), 72.4 (CH), 40.1 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 19.5 (CH_3). Satisfactory MS data could not be obtained for this compound.

(4*R*,5*S*)-5-But-3-enyl-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (1*S*)-1-methylbut-3-enyl ester (24)

A magnetically stirred solution of (2*S*,3*S*)-2,3-dihydroxyhept-6-enoic acid (1*R*)-1-methylbut-3-enyl ester (40 mg, 0.17 mmol) in 2,2-dimethoxypropane (2 mL) was treated, in one portion, with *p*-toluenesulfonic acid (3.4 mg). The resulting mixture was maintained under a nitrogen atmosphere at 18 °C for 18 h then $NaHCO_3$ (10 mL of a saturated aqueous solution) was added to quench the reaction mixture. The separated aqueous fraction was extracted with ethyl acetate (3 × 10 mL) and the organic fractions were combined, washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title compound **24** (18.6 mg, 40%) as a light-yellow oil. $[\alpha]_D$ +24 (*c* 0.20); ν_{max}/cm^{-1} 3078, 2982, 2937, 1753,

1727, 1642, 1452, 1377, 1268, 1190, 1092, 994, 916, 869, 789; δ_H 5.88–5.66 (2 H, complex m), 5.15–4.96 (5 H, complex m), 4.51 (1 H, d, *J* 6.7), 4.31 (1 H, m), 2.45–2.08 (4 H, complex m), 1.72–1.50 (2 H, complex m), 1.61 (3 H, s), 1.38 (3 H, s), 1.26 (3 H, d, *J* 6.2); δ_C 169.7 (C), 137.3 (CH), 133.3 (CH), 118.1 (CH_2), 115.2 (CH_2), 110.3 (C), 71.5 (CH), 40.2 (CH_2), 30.5 (CH_2), 29.4 (CH_2), 27.1 (CH_3), 25.8 (CH_3), 19.6 (CH_3) (two signals obscured or overlapping). Satisfactory EIMS data could not be obtained for this compound.

(3a*S*,6*S*,8*Z*,11a*S*)-3a,6,7,10,11,11a-Hexahydro-2,2,6-trimethyl-1,3-dioxolo-[4,5-*c*]oxecin-4-one (25)

Diene **24** (10.2 mg, 0.04 mmol) was subjected to the conditions defined above for ring-closing metathesis and after purification by flash chromatography (1:3 v/v diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.4 in 1:3 v/v ethyl acetate hexane) a yellow oil, tentatively assigned as the title compound **25** (5.8 mg, 64%), was obtained. δ_H 5.47 (2 H, m), 4.99 (1 H, m), 4.52 (1 H, m), 4.29 (1 H, m), 2.38–2.05 (4 H, complex m), 1.68–1.53 (5 H, complex m), 1.38 (6 H, m); δ_C 169.9 (C), 129.5 (CH), 128.6 (CH), 77.9 (CH), 77.2 (CH), 71.8 (CH), 39.3 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 26.9 (CH_3), 25.7 (CH_3), 19.8 (CH_3) (one signal obscured or overlapping). These data compared favourably with those derived from the more stable congener **23**. At present, it is this comparison that provides the major basis for the assignment of the illustrated structure to compound **25**.

(3*S*,4*S*,10*R*)-3,4-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-10-methyl-2-oxecanone (precursor to lactol 26)

10% Palladium on charcoal (23 mg, 20 wt%) was added to a magnetically stirred solution of alkene **19** (112 mg, 0.260 mmol) in absolute ethanol (3 mL). A balloon of dihydrogen was attached and the reaction vessel evacuated and flushed with dihydrogen three times. The resulting black suspension was stirred under an atmosphere of dihydrogen at 18 °C for 11 h, then filtered through a pad of Celite™. Concentration of the filtrate under reduced pressure gave a grey-yellow oil which was subjected to flash chromatography (1:9 v/v diethyl ether–hexane elution). Concentration of the relevant fractions (R_f 0.3 in 5:95 v/v ethyl acetate–hexane) gave the title compound (104 mg, 93%) as a clear, colourless oil. $[a]_D$ −2 (*c* 0.77); ν_{max}/cm^{-1} 2931, 2857, 1724, 1470, 1363, 1276, 1253, 1171, 1154, 1082, 976, 836, 777, 675; δ_H 5.03 (1 H, m), 4.27 (1 H, d, *J* 1.2), 4.01 (1 H, m), 1.93–1.35 (10 H, complex m), 1.26 (3 H, d, *J* 6.5), 0.93 (9 H, s), 0.88 (9 H, s), 0.08 (3 H, s), 0.06 (6 H, s), 0.04 (3 H, s); δ_C 172.7 (C), 77.7 (CH), 75.4 (CH), 72.5 (CH), 31.5 (CH_2), 31.1 (CH_2), 26.0 (3 × CH_3), 25.7 (3 × CH_3), 25.5 (CH_2), 23.7 (CH_2), 21.4 (CH_2), 20.7 (CH_3), 18.4 (C), 18.2 (C), −4.6 (CH_3), −4.7 (CH_3), −4.9 (CH_3), −5.2 (CH_3); *m/z* (EI) 430 ($M^{+\bullet}$, 2%), 415 [(M − $CH_3^{\bullet}$)$^+$, 3], 373 [(M − $C_4H_9^{\bullet}$)$^+$, 54%], 304 (27), 241 (56), 213 (51), 147 (58), 133 (45), 109 (50), 73 (100). Calc. for $C_{22}H_{46}O_4Si_2$ $M^{+\bullet}$: 430.2935. Found: 430.2936.

(2*E*,4*R*,5*S*,11*R*)-4,5-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-11-hydroxy-2-dodecenoic acid methyl ester (27)

DIBAL-H (500 µL of a 1 M solution in hexane, 0.50 mmol) was added to a magnetically stirred solution of the lactone derived from the hydrogenation of compound **19** (119.4 mg, 0.28 mmol) in toluene (6 mL) maintained at −78 °C under a nitrogen atmosphere. Stirring was continued for 0.5 h then the reaction quenched by adding NaK tartrate (10 mL of a 1 M aqueous solution) and the resulting mixture warmed to 0 °C over an additional 0.5 h. The separated aqueous fraction was extracted with diethyl ether (3 × 30 mL) and the combined organic fractions washed with water (1 × 5 mL) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give lactol **26** as an unstable, yellow oil which was used immediately in the next step of the reaction sequence. Thus, a magnetically stirred suspension of NaH (19 mg of a 60% dispersion in mineral oil, 0.48 mmol) in THF (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated dropwise with trimethyl phosphonoacetate (135 µL, 0.66 mmol). The mixture was warmed to 18 °C over 0.5 h and a solution of the lactol **26** (obtained as described above) in THF (3 mL) was added *via* cannula at 0 °C. After re-warming to 18 °C over a period of 1 h, the reaction mixture was diluted with diethyl ether (10 mL) and quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous fraction was extracted with diethyl ether (3 × 10 mL) and the combined organic fractions washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (2:3:5 v/v/v dichloromethane–diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.3) gave the title compound **27** (66 mg, 48% from saturated lactone) as a clear, colourless oil. $[a]_D$ −3 (*c* 0.43); ν_{max}/cm^{-1} 3369, 2931, 2857, 1728, 1660, 1466, 1255, 1166, 1111, 836, 776; δ_H 6.96 (1 H, dd, *J* 5.4 and 15.7), 5.96 (1 H, dd, *J* 1.5 and 15.7), 4.14 (1 H, m), 3.76 (1 H, m), 3.73 (3 H, s), 3.63 (1 H, m), 1.59 (1 H, broad s), 1.54–1.23 (10 H, complex m), 1.17 (3 H, d, *J* 6.2), 0.90 (9 H, s), 0.86 (9 H, s), 0.05 (3 H, s), 0.02 (6 H, s), 0.01 (3 H, s); δ_C 166.7 (C), 149.2 (CH), 120.9 (CH), 76.1 (CH), 75.5 (CH), 68.0 (CH), 51.5 (CH_3), 39.3 (CH_2), 33.4 (CH_2), 29.9 (CH_2), 26.0 (3 × CH_3), 25.9 (3 × CH_3), 25.8 (CH_2), 25.0 (CH_2), 23.5 (CH_3), 18.3 (C), 18.2 (C), −4.1 (CH_3), −4.3 (CH_3), −4.4 (CH_3), −4.7 (CH_3); *m/z* (EI) 473 [(M − $CH_3^{\bullet}$)$^+$, 0.3%], 431 [(M − $C_4H_9^{\bullet}$)$^+$, 7], 399 (56), 259 (55), 171 (30), 147 (76), 109 (44), 89 (40), 75 (57) 73 (100). Calc. for $C_{21}H_{43}O_5Si_2$ (M − $C_4H_9^{\bullet}$)$^+$: 431.2649. Found: 431.2653.

(3*E*,5*R*,6*S*,12*R*)-5,6-Bis{[(1,1-dimethylethyl)dimethylsilyl]oxy}-12-methyloxacyclododec-3-en-2-one (29)

A magnetically stirred solution of methyl ester **27** (28 mg, 0.06 mmol) in ethanol (3 mL) was treated with NaOH (1 mL of a 2.5 M aqueous solution). The ensuing mixture was allowed to stir at 18 °C for 18 h then acidified to pH 3 (with 1 M aqueous HCl) and extracted with ethyl acetate (5 × 12 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the carboxylic acid **28** as a light-yellow oil. This unstable material was immediately dissolved in THF (1 mL) containing triethylamine (10 µL, 0.07 mmol) and the resulting and magnetically stirred solution was treated with 2,4,6-trichlorobenzoyl chloride (9 µL, 0.06 mmol) and, after 2 h, diluted with toluene (70 µL). The ensuing mixture was added, over *ca.* 10 min and *via* cannula, to a solution of DMAP (37 mg, 0.3 mmol) in refluxing toluene (10 mL). The resulting mixture was heated at reflux for 1 h then cooled, quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (5:95 v/v diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.3) gave the macrolactone **29** (22.5 mg, 89%) as a clear, colourless oil. $[a]_D$ −23 (*c* 0.18); ν_{max}/cm^{-1} 2932, 2858, 1723, 1649, 1466, 1364, 1254, 1159, 1074, 1003, 835, 777; δ_H 6.76 (1 H, dd, *J* 4.7 and 15.8), 6.15 (1 H, dd, *J* 1.6 and 15.8), 5.08 (1 H, m), 4.43 (1 H, m), 3.53 (1 H, dm, *J* 8.9), 1.90–1.05 (10 H, complex m), 1.28 (3 H, d, *J* 6.6), 0.92 (9 H, s), 0.90 (9 H, s), 0.09 (3 H, s), 0.06 (3 H, s), 0.05(2) (3 H, s), 0.04(8) (3 H, s); δ_C 168.4 (C), 147.8 (CH), 121.7 (CH), 76.6 (CH), 75.7 (CH), 72.9 (CH), 32.2 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 26.1 (3 × CH_3), 26.0 (3 × CH_3), 25.8 (CH_2), 23.4 (CH_2), 19.4 (CH_3), 18.5 (C), 18.4 (C), −4.4 (2 × CH_3), −4.6(7) (CH_3), −4.7(0) (CH_3); *m/z* (EI) 456 ($M^{+\bullet}$, 3%), 399 [(M − $C_4H_9^{\bullet}$)$^+$, 27%], 371 (13), 241 (34), 216 (51), 198 (62), 147 (87), 109 (53), 73 (100). Calc. for $C_{24}H_{48}O_4Si_2$ $M^{+\bullet}$: 456.3091. Found: 456.3090.

(−)-Cladospolide A (1)

A magnetically stirred solution of lactone **29** (20 mg, 0.04 mmol) in acetonitrile (500 μL) was treated with $Zn(BF_4)_2$ (45 μL of a 5 M aqueous solution) and the resulting mixture maintained at 18 °C for 24 h then diluted with water (2 mL) and extracted with diethyl ether (5 × 2 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (diethyl ether elution) and concentration of the relevant fractions (R_f 0.3) gave the title compound **1** (7.3 mg, 73%) as a white solid. Mp 90–91 °C (lit.[1] mp 92–93 °C), $[\alpha]_D$ −53 (*c* 0.20) {lit.[7] $[\alpha]_D$ −49 (*c* 0.23 in $CHCl_3$)}; ν_{max}/cm^{-1} 3469, 2939, 2865, 1714, 1647, 1461, 1270, 1165, 1126, 1031, 995, 881, 756, 668; δ_H 6.80 (1 H, dd, *J* 5.7 and 16.0), 6.21 (1 H, dd, *J* 1.5 and 16.0), 5.13 (1 H, m), 4.56 (1 H, m), 3.67 (1 H, ddd, *J* 1.5, 3.2 and 9.8), 2.50 (2 H, broad s), 1.84–1.11 (8 H, complex m), 1.29 (3 H, d, *J* 6.4), 0.87 (2 H, m); δ_C 167.7, 145.5, 122.2, 74.7, 72.9, 32.5, 30.7, 28.2, 25.1, 22.6, 19.1 (one signal obscured or overlapping); *m*/*z* (EI) 229 [$(M + H)^+$, 0.4%], 211 (2), 184 (5), 127 (17), 109 (36), 102 (100), 84 (66). Calc. for $C_{12}H_{21}O_4$ $(M + H)^+$: 229.1440. Found: 229.1441.

Acknowledgements

We thank Dr Ken McRae and Ms Filisaty Vounatsos for preliminary experiments and Dr Kate Jolliffe for useful discussions. Dr Gregg Whited (Genencor International Inc., Palo Alto) is warmly thanked for providing us with generous quantities of compound **7**.

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