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A chemoenzymatic total synthesis of the undecenolide (−)-cladospolide B *via* a mid-stage ring-closing metathesis and a late-stage photo-rearrangement of the *E*-isomer

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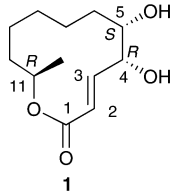
A sixteen-step synthesis of the twelve-membered macrolide (−)-cladospolide B (**2**) from the microbially-derived *cis*-1,2-dihydrocatechol **5** is described. Pivotal steps include the ring-closing metathesis (RCM) of diene **12** to give the ten-membered lactone **13** together with small amounts of the head-to-tail and head-to-head dimers **14** and **15**, respectively. The saturated lactol **19** derived from compounds **13** and **14** readily participates in a Wadsworth–Horner–Emmons reaction to give the *E*-configured α,β-unsaturated ester **20**. This last compound is then converted, through application of a Yamaguchi lactonisation reaction on the derived acid **22**, into the macrolide **23** which, upon removal of the *bis*-acetal protecting group, affords compound **24**, the *E*-isomer of target **2**. Irradiation of a benzene solution of compound **24** results in its partial photoisomerisation to (−)-cladospolide B (**2**).

Introduction

Cladospolides A–D (**1**–**4**, respectively) represent the currently known members of a class of undecenolides isolated from various *Cladosporium* species of fungi.[1–5] Cladospolide B (**2**), together with an isomer (isocladospolide B), has also been isolated from the sponge-derived fungus *Cladosporium herbarum* by Ireland and co-workers.[6] Congeners A–C have been shown to inhibit shoot elongation in rice seedlings, and isomer **3** does so without causing signs of necrosis, thus suggesting that this compound, at least, inhibits gibberellin biosynthesis.[3] Fascinatingly, cladospolide A also inhibits root elongation in lettuce seedlings whilst cladospolide B, which only varies in the configuration about the $\Delta^{2,3}$-double bond and (apparently – see end of Results and discussion section) at C4, has the opposite effect.[2] Cladospolide D (**4**), the structure of which remains to be fully defined, exhibits antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae* with IC_{50} values of 0.15 and 29 μg ml^{-1}, respectively.[4] Compounds **1** and **2** have also been patented as inhibitors of allergy and inflammation.[7]



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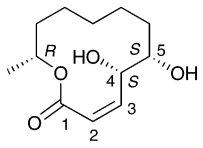

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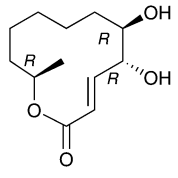

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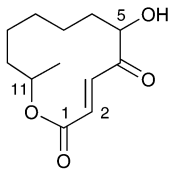

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Recently we disclosed[8] an eleven-step total synthesis of (−)-cladospolide A (**1**) from the *cis*-1,2-dihydrocatechol **5**, a starting material available in large quantity and enantiomerically pure form through microbial dihydroxylation of chlorobenzene. This work represents the shortest of the three distinct total syntheses of compound **1** reported thus far and incorporates a pivotal ring-closing metathesis (RCM) step, a process that has found increasing application in the synthesis of macrolides in recent years.[9] Hitherto, no total synthesis of any of the remaining members of the cladospolide family has been published, although it has been noted[3] that the absolute configuration of cladospolide B has been determined by such means and is as illustrated. Given the dramatic difference in effect that compounds **1** and **2** exert on the growth of lettuce seedlings, the development of a synthesis of the latter would seem worthwhile since such work might offer the capacity to determine which structural features are responsible for the divergent biological properties of these systems. To such ends, we have pursued and now detail a synthesis of (−)-cladospolide B involving preparation of the *E*-isomer and photoisomerisation of this system, in the final step of the reaction sequence, to deliver target **2**. The benefit of this approach is that the *E*-isomer could also be subject to biological evaluation as part of a program to establish a detailed SAR profile for the cladospolides and related systems.

Results and discussion

The early stages of the reaction sequence employed in establishing the present synthesis of (−)-cladospolide B are shown in Scheme 1. This starts with the same enantiomerically pure *cis*-1,2-dihydrocatechol, **5**, used in our total synthesis of cladospolide A, but of necessity, inversion of configuration at C2 is required at some point. In the event, and as part of a more general program to extend the synthetic utility of metabolites such as compound **5**, we have recently reported simple[10] methods for the conversion of this compound into congener **6**. This involves initial and selective hydrogenation of the non-chlorinated double-bond within compound **5** then selective inversion at the centre bearing the allylic hydroxyl group using a Mitsunobu reaction and involving *p*-nitrobenzoic acid as nucleophile. Hydrolysis of the resulting mono-*p*-nitrobenzoate ester then delivered the required *trans*-diol **6** in 59% yield over the three steps just described.

Trans-diol **6** was protected as the corresponding *bis*-acetal **7** (92%) using protocols developed by Frost[11] and Ley.[12] This last compound was obtained in a single diastereoisomeric form and with the illustrated configurations at the anomeric centres as determined by single-crystal X-ray analysis of a derivative (*vide infra*). Chloroalkene **7** was subject to ozonolytic cleavage in the presence of methanol and after reductive work-up with dimethyl sulfide the aldehydic ester **8** was obtained. Wittig methylenation

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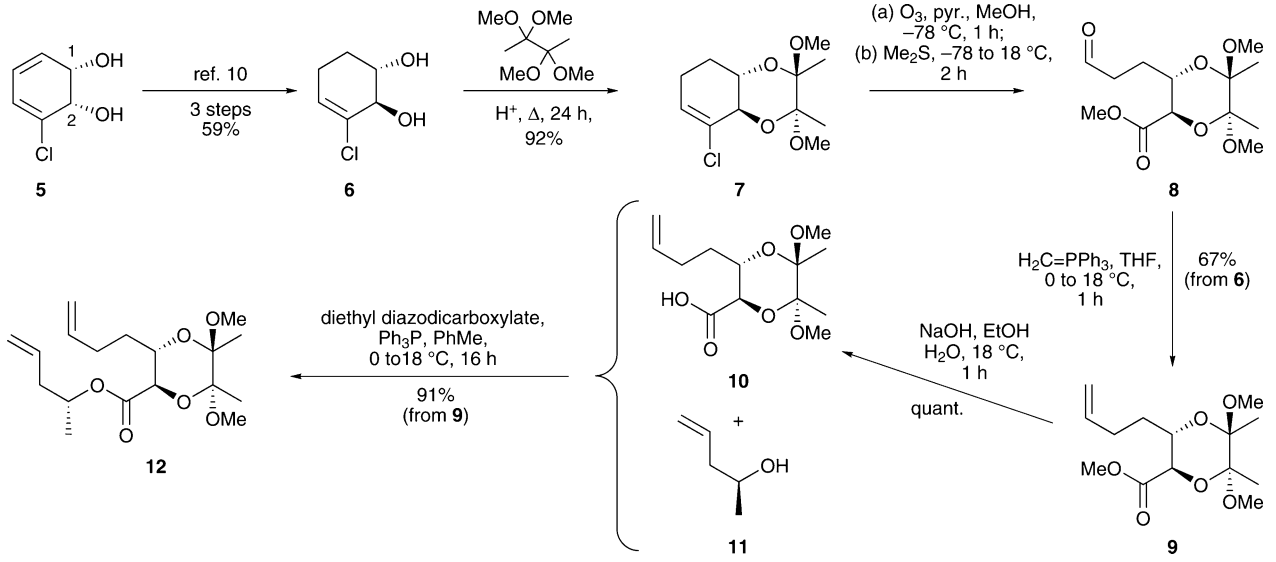
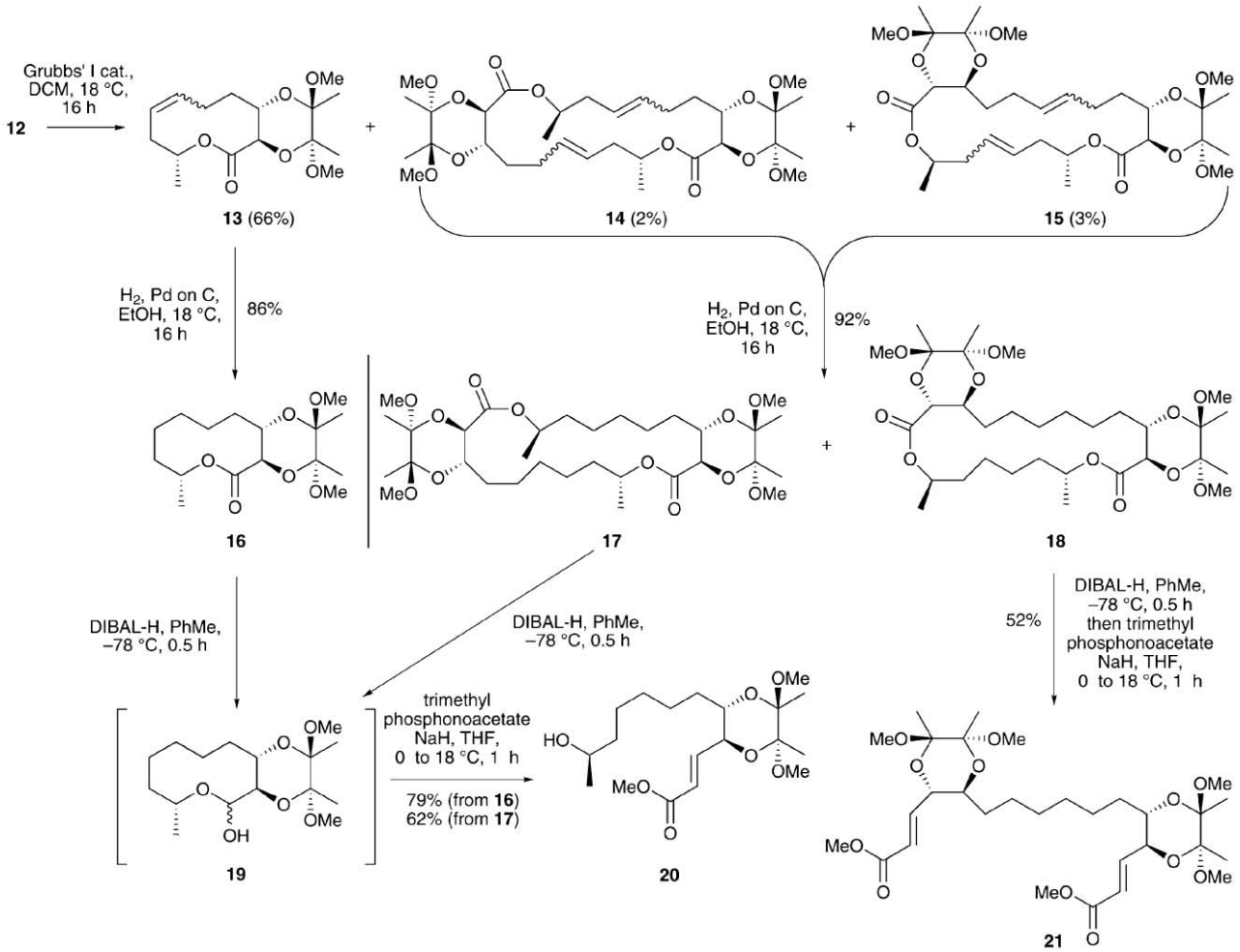


Scheme 1

of aldehyde **8** gave the corresponding unsaturated ester **9** (67% overall yield from diol **6**), which was saponified under the usual conditions to give, after acidic work-up, the corresponding free acid **10** (quantitative). Esterification of the last compound under Mitsunobu conditions with the enantiomerically pure secondary alcohol **11**, available in multi-gram quantities through lipase-mediated resolution of the corresponding racemic material,[8] afforded the doubly-unsaturated ester **12** in 91% overall yield from ester **9**.

Following the strategy used in our recently reported synthesis of cladospolide A,[8] diene **12** was subjected (Scheme 2) to a RCM reaction using Grubbs' second-generation catalyst[13] in dichloromethane at room temperature. In this manner the *Z*-isomer of target lactone **13** was obtained as the sole monomeric



Scheme 2

product of reaction (18%), and the structure of this compound was established in an unequivocal manner through single-crystal X-ray analysis (see Fig. 1 and the Experimental section). However, the major products of reaction were the chromatographically inseparable head-to-tail and head-to-head "dimers" of substrate **12**, namely *bis*-lactones **14** and **15**, respectively, which were obtained in 62% combined yield. The structures of these products follow from the chemical studies detailed below. Fortunately, when the RCM reaction of diene **12** was carried out using Grubbs' first-generation[13] catalyst, the predominant product was the unsaturated lactone **13** (66%) although now obtained as a chromatographically inseparable 1.3 : 1 mixture of *E*- and *Z*-isomers. Under such conditions compounds **14** and **15** were still observed, albeit now in only *ca.* 5% combined yield. The outcomes of the RCM processes just described demonstrate that the *bis*-acetal moiety involved represents an effective protecting group for a *trans*-diol during the course of constructing unsaturated nonenolides by such means. It is also worth noting that the reason for employing a RCM reaction at this stage is because in our earlier studies[8] we had not been able to construct the twelve-membered undecenolide ring of target **1** directly by such means.

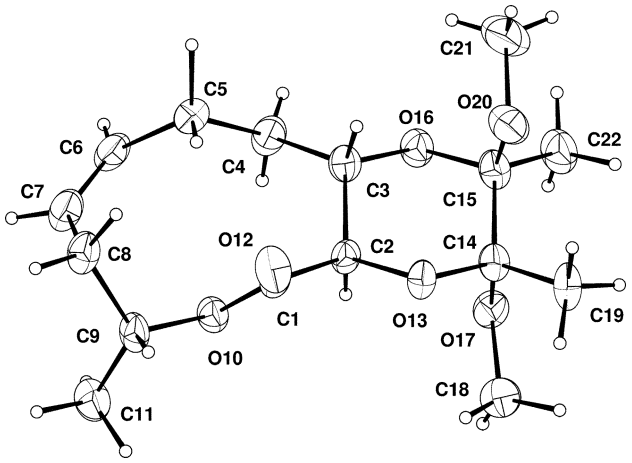
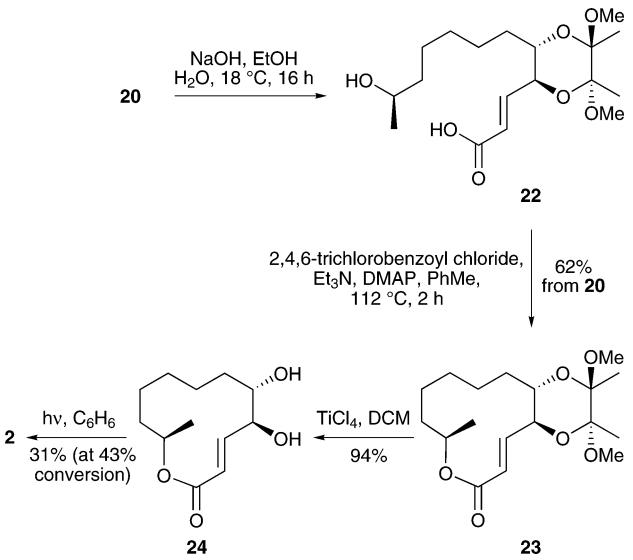


Fig. 1 Anisotropic displacement ellipsoid plot of the *Z*-isomer of compound **13** with labelling of selected atoms. Ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii.

Continuation of the synthesis of target **2** involved (Scheme 2) conventional hydrogenation of the mixture of *E*- and *Z*-isomers of lactone **13**, thus giving the saturated equivalent **16** in 86% yield. Similarly, hydrogenation of the mixture of dimers **14** and **15** afforded the now chromatographically separable products **17** (35%) and **18** (57%), respectively. Independent subjection of compounds **16** and **17** to reduction with DIBAL-H in toluene at −78 °C afforded lactol **19**, which was immediately committed to a Wadsworth–Horner–Emmons reaction with the anion generated through deprotonation of trimethyl phosphonoacetate with sodium hydride. In this way the *E*-configured α,β-unsaturated ester **20** was obtained, as a single geometric isomer, in 79 and 62% overall yield from precursors **16** and **17**, respectively. Subjection of the head-to-head "dimer" **15** to the same reduction–olefination sequence afforded the *bis*-ester **21** (52%), thereby confirming the structural assignments of the precursors **14** and **15** as head-to-tail and head-to-head "dimers", respectively.

The end-game associated with the synthesis of cladospolide B (**2**) is shown in Scheme 3. Thus, saponification of ester **20** under the usual conditions followed by acidic work-up gave the ω-hydroxy-acid **22**, which was subjected to Yamaguchi lactonisation in refluxing toluene to afford the macrolide **23** in 62% yield (from precursor **20**) as a white crystalline solid. All the NMR and mass spectral data obtained for product **23** were fully consistent with the assigned structure, but final confirmation



Scheme 3

followed from a single-crystal X-ray analysis (see Fig. 2 and the Experimental section) that served to highlight the successful acquisition of the target undecenolide framework. Removal of the *bis*-acetal protecting group within compound **23** was not entirely straightforward and amongst the various reagents and reaction conditions examined for this purpose, those involving $TiCl_4$ in dichloromethane at 0 °C proved most effective, as evidenced by the delivery, in 94% yield, of the *E*-isomer, **24**, of target **2**.

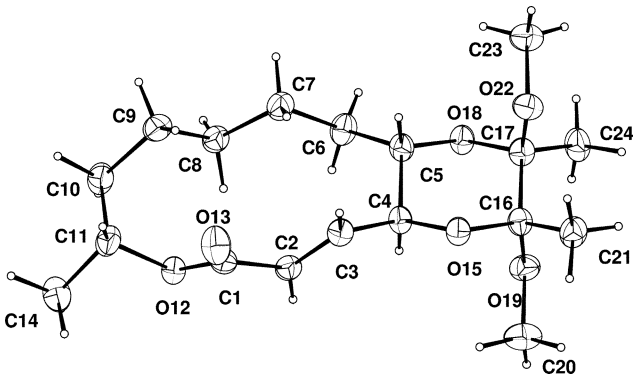


Fig. 2 Anisotropic displacement ellipsoid plot of compound **23** with labelling of selected atoms. Ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii.

While little work has been done on the photoisomerisation of carbonyl-conjugated double-bonds contained within medium-ring macrolides[14] we wondered if this sort of process might be occurring naturally as part of a plant growth regulating process capable of being influenced by the presence (or absence) of incident light. To investigate these possibilities, a deoxygenated benzene solution of compound **24** in a Pyrex vessel was irradiated, in a Rayonet photo-reactor, with 300 nm light. In this manner, isomerisation to target **2** was observed. Under the best conditions we have identified so far, irradiation of the substrate for 16 h at *ca.* 18 °C led to an 4 : 1 mixture of compounds **24** (57% recovery) and (−)-cladospolide B (**2**) (31% at 43% conversion) which could be separated from one another using semi-preparative HPLC techniques. The NMR, IR, and mass spectral data derived from the synthetic sample of cladospolide B were in good agreement with those reported[2] in the literature for the natural product. The most diagnostic features observed in the ^{1}H NMR spectrum of compound **2** were those resonances due to the olefinic protons associated with the unsaturated ester moiety, which appeared at δ 6.24 and 5.78, each as a doublets of doublets with a mutual

coupling of J 12.2, as would be expected for *cis*-related protons associated with a common double-bond. This contrasts with a coupling of J 16.1 observed for the equivalent protons in the *E*-isomer **24**. Significantly, the $[a]_D$ of the synthetic sample of compound **2** was −162 (*c* 0.1, MeOH) which is opposite in sign and of considerably greater magnitude than that recorded[3] for the natural product, *viz*. $[a]_D$ +45 (*c* 0.4, MeOH). We also note that the specific rotation of the synthetic material did not vary a great deal with concentration. Such results clearly imply that the absolute configuration of (+)-cladospolide B has been misassigned and is, in fact, opposite to that shown in structure **2**. The distinct difference in the magnitude of these two values suggests that the natural material may only be enantiomerically enriched with the 4*R*,5*R*,11*S*-form and is not an enantiomerically pure material. Alternatively, and perhaps more likely, the natural product is contaminated with some other material that has a very large and negative rotation.

Interestingly, exposure of a dichloromethane solution of (−)-cladospolide B (**2**) to traces of trifluoroacetic acid (TFA) did not result in any clean isomerisation to **24**; only slow decomposition was observed.

Conclusions

The present work, when considered together our earlier syntheses of (−)-cladospolide A[8] and (+)-aspicillin,[15] serves to demonstrate the utility of *cis*-1,2-dihydrocatechols as building blocks in the assembly of various macrolides. This utility follows from a capacity to "stitch" such building blocks into larger ring systems through the sequential application of ozonolysis, methylenation and RCM reactions. As such, simple extensions of the work detailed herein should enable access to the remaining members of the cladospolide family as well as related systems likely to be of interest in a biological sense. Work directed towards such ends is 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 ^{1}H NMR 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 ^{13}C NMR spectra. ^{1}H NMR 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; 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 analysed 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 per 100 mL) 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 F_{254} 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. Flash chromatography was conducted according to the method of Still and co-workers[16] 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 4 Å molecular sieves. Organic solutions obtained from work-up of reaction mixtures were dried with anhydrous magnesium sulfate ($MgSO_4$) then filtered and concentrated under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 40 °C. Semi-preparative HPLC separations were performed on a system comprising two Waters 510 pumps linked in series and the first of these was fitted with a Rheodyne 7125 injector incorporating a 1 mL loop. A Waters 7.8 × 300 mm μ-Porasil column (irregular particle size) was used and eluting materials were detected using a Waters 481 UV/Vis detector set at 250 nm. A solvent flow rate of 2 mL min^{-1} was used and the detector was interfaced with a computer supporting V3.3 of the Waters Maxima Software.

(2*R*,3*R*,4a*S*,8a*R*)-8-chloro-2,3,4a,5,6,8a-hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*]-[1,4]dioxine (7)

A magnetically stirred solution of *trans*-diol **6**[10] (153 mg, 1.03 mmol), $CH(OMe)_3$ (450 μL, 4.16 mmol) and $[CH_3C(OMe)_2]_2$ (221 mg, 1.24 mmol) in MeOH (5 mL) maintained under a nitrogen atmosphere at 18 °C was treated with (+)-camphorsulfonic acid (14 mg, 0.06 mmol) and the resulting mixture heated at reflux for 16 h. The cooled reaction mixture was treated with solid $NaHCO_3$ (~2 g) then filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (1 : 9 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.4) gave the *title compound 7* (248 mg, 92%) as a white crystalline solid. Recrystallisation ($CHCl_3$) of a sample of this compound gave analytically pure material as white needles, mp 78–81 °C, $[a]_D$ −276 (*c* 0.5) [Found: $(M - CH_3O\cdot)^+$, 231.0788. C, 55.02; H, 7.10; Cl, 13.57. $C_{12}H_{19}{}^{35}ClO_4$ requires $(M - CH_3O\cdot)^+$, 231.0788. C, 54.86; H, 7.29; Cl, 13.49%]. ν_{max}/cm^{-1} 2956, 2880, 2834, 1460, 1379, 1120, 1044, 1025, 941, 916, 873, 838, 778; δ_H ($CDCl_3$, 300 MHz) 5.78 (1 H, m), 4.20 (1 H, m), 3.85 (1 H, ddd, J 3.8, 8.7 and 12.4), 3.29 (3 H, s), 3.25 (3 H, s), 2.22 (2 H, m), 1.87–1.65 (2 H, complex m), 1.35 (3 H, m), 1.31 (3 H, m); δ_C ($CDCl_3$, 75 MHz) 128.8 (C), 126.5 (CH), 100.7 (C), 99.9 (C), 70.1 (CH), 69.2 (CH), 47.9 (CH_3), 47.8 (CH_3), 25.3 (CH_2), 24.6 (CH_2), 17.7 (CH_3), 17.6 (CH_3); *m*/*z* (EI, 70 eV) 249 and 247 [$(M - CH_3^{\bullet})^+$, 2 and 5%], 233 and 231 (11 and 24), 117 (10), 116 (35), 114 (87), 101 (62), 79 (100).

Methyl (2*R*,3*S*,5*R*,6*R*)-3-(but-3-enyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylate (9)

A magnetically stirred solution of alkene **7** (1.12 g, 4.27 mmol) in MeOH (85 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 then removed by purging the reaction mixture with a stream of nitrogen (10 min) and the resulting colourless solution was placed in an ice-bath and treated with Me_2S (313 μL, 4.26 mmol). After 1 h the reaction mixture was warmed to 18 °C whereupon TLC analysis indicated the disappearance of the ozonolysis product. The reaction mixture was diluted with water (50 mL) and then extracted with ethyl acetate (4 × 100 mL). The combined organic fractions were washed with $CuSO_4$ (1 × 50 mL of a saturated aqueous solution), water (1 × 50 mL) and brine (1 × 50 ml) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *aldehyde* ***8*** as an unstable, yellow oil. This material was used immediately in the next step of the reaction sequence.

A magnetically stirred solution of methyltriphenylphosphonium bromide (2.23 g, 6.40 mmol) in THF (45 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with potassium bis(trimethylsilyl)amide (12.8 mL of a 0.5 M solution in toluene, 6.4 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 **8** (obtained as described immediately above) in THF (20 mL). After 1 h at 18 °C the reaction mixture was treated with NH_4Cl (10 mL of a saturated aqueous solution) then extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with water (1 × 10 mL) and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.4 in 1 : 4 v/v ethyl acetate–hexane) gave the *title compound* ***9*** (823 mg, 67% from diol **6**) as a clear, colourless oil, $[\alpha]_D$ −168 (*c* 0.8) [Found: $(M - CH_3O\cdot)^+$, 257.1381. $C_{14}H_{24}O_6$ requires $(M - CH_3O\cdot)^+$, 257.1389]. ν_{max}/cm^{-1} 2951, 1749, 1440, 1378, 1121, 1038, 889; δ_H ($CDCl_3$, 300 MHz) 5.75 (1 H, m), 5.03–4.89 (2 H, complex m), 4.13 (1 H, d, *J* 9.9), 3.85 (1 H, td, *J* 3.8 and 9.9), 3.73 (3 H, s), 3.26 (3 H, s), 3.22 (3 H, s), 2.32 (1 H, m), 2.06 (1 H, m), 1.60–1.47 (2 H, complex m), 1.32 (3 H, s), 1.27 (3 H, s); δ_C ($CDCl_3$, 75 MHz) 169.3 (C), 137.8 (CH), 114.9 (CH_2), 98.8 (C), 98.5 (C), 72.7 (CH), 67.7 (CH), 52.2 (CH_3), 48.2 (CH_3), 47.9 (CH_3), 29.7 (CH_2), 28.9 (CH_2), 17.6 (CH_3), 17.3 (CH_3); *m/z* (EI, 70 eV) 272 (3%) 271 (17), 258 (54), 257 [$(M - CH_3O\cdot)^+$, 100].

(2*R*,3*S*,5*R*,6*R*)-3-(But-3-enyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylic acid (10)

A magnetically stirred solution of ester **9** (2.48 g, 8.6 mmol) in ethanol (170 mL) maintained at 18 °C was treated with NaOH (29 mL of a 1.5 M aqueous solution, 10.5 mmol). The resulting mixture was kept at 18 °C for 1 h then acidified with HCl (50 mL of a 1 M aqueous solution) and extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude *acid* ***10*** (2.36 g, 100%) as a light-yellow solid. Recrystallisation ($CHCl_3$) of a sample of this material gave analytically pure material, mp 109–110 °C, $[\alpha]_D$ −147 (*c* 0.4) [Found: $(M - CH_3O\cdot)^+$, 243.1238. C, 56.92; H, 8.23. $C_{13}H_{22}O_6$ requires $(M - CH_3O\cdot)^+$, 243.1232. C, 56.92; H, 8.08%]. ν_{max}/cm^{-1} 3200, 2931, 1737, 1375, 1119, 1034; δ_H ($CDCl_3$, 300 MHz) 5.79 (1 H, dm, *J* 17.2), 5.03 (1 H, dm, *J* 17.2), 4.96 (1 H, dm, *J* 10.3), 4.18 (1 H, d, *J* 10.3), 3.77 (1 H, td, *J* 2.5 and 10.3), 3.29 (3 H, s), 3.24 (3 H, s), 2.42–2.28 (1 H, complex m), 2.19–2.04 (1 H, complex m), 1.99–1.84 (1 H, complex m), 1.72–1.56 (1 H, complex m), 1.37 (3 H, s), 1.30 (3 H, s); δ_C ($CDCl_3$, 75 MHz) 171.3 (C), 137.8 (CH), 115.1 (CH_2), 99.3 (C), 98.5 (C), 72.1 (CH), 67.6 (CH), 48.5 (CH_3), 48.1 (CH_3), 29.7 (CH_2), 28.9 (CH_2), 17.6 (CH_3), 17.3 (CH_3); *m/z* (EI, 70 eV) 243 [$(M - CH_3O\cdot)^+$, 27%], 126 (31), 116 (46), 101 (64), 81 (49), 75 (100).

(*R*)-Pent-4-en-2-yl (2*R*,3*S*,5*R*,6*R*)-3-(but-3-enyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylate (12)

A magnetically stirred solution of the acid **10** (1.46 g, 5.33 mmol) in toluene (20 mL) maintained at 0 °C under a nitrogen atmosphere was treated sequentially with (*S*)-pent-4-en-2-ol (**11**)[8] (789 μL, 7.98 mmol) and triphenylphosphine (2.10 g, 7.99 mmol) then cooled to 0 °C and diethyl diazodicarboxylate (1.26 mL, 7.99 mmol) added dropwise. The resulting mixture was allowed to warm to 18 °C over 16 h then treated with $NaHCO_3$ (20 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 30 mL). The combined organic fractions were washed with water (1 × 10 mL) then 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 (1 : 9 v/v diethyl ether–hexane elution) and concentration of the relevant fractions (R_f 0.4) gave the *title compound* ***12*** (1.67 g, 91%) as a clear, colourless oil, $[\alpha]_D$ −162 (*c* 0.7) [Found: $(M - CH_3O\cdot)^+$, 311.1863. $C_{18}H_{30}O_6$ requires $(M - CH_3O\cdot)^+$, 311.1858]. ν_{max}/cm^{-1} 2951, 2858, 1744, 1120; δ_H ($CDCl_3$, 300 MHz) 5.82–5.63 (2 H, complex m), 5.08–4.90 (5 H, complex m), 4.04 (1 H, d, *J* 9.8), 3.83 (1 H, m), 3.25 (3 H, s), 3.21 (3 H, s), 2.38–2.21 (3 H, complex m), 2.12–2.00 (1 H, complex m), 1.56–1.50 (2 H, complex m), 1.30 (3 H, s), 1.26 (3 H, s), 1.23 (3 H, d, *J* 6.3); δ_C ($CDCl_3$, 75 MHz) 168.5 (C), 137.9 (CH), 133.3 (CH), 118.0 (CH_2), 114.8 (CH_2), 98.7 (C), 98.5 (C), 72.5 (CH), 71.2 (CH), 67.8 (CH), 48.1 (CH_3), 47.8 (CH_3), 40.0 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 19.3 (CH_3), 17.6 (CH_3), 17.3 (CH_3); *m/z* (EI, 70 eV) 312 (14%), 311 [$(M - CH_3O\cdot)^+$, 31], 257 (20), 243 (14), 194 (20), 153 (17), 126 (46), 109 (100).

(*E*/*Z*,2*R*,3*R*,4a*R*,7*R*,12a*S*)-2,3,7,8,12,12a-Hexahydro-2,3-dimethoxy-2,3,7-trimethyl-4a*H*-[1,4]dioxino[2,3-*c*]oxecin-5(11*H*)-one (13)

Method A: Grubbs' second-generation catalyst (226 mg, 0.23 mmol) was added to a magnetically stirred solution of compound **12** (613 mg, 1.79 mmol) in degassed dichloromethane (1.80 L) maintained under a nitrogen atmosphere at 18 °C. The reaction mixture was stirred at this temperature for 18 h whereupon TLC analysis indicated the absence of starting material. DMSO (610 μL) was added to the reaction mixture, which was stirred at 18 °C for a further 16 h then filtered through a pad of TLC-grade silica gel. The pad was then eluted with 1 : 4 v/v ethyl acetate–hexane to give two fractions, A and B.

Concentration of fraction A (R_f 0.2) afforded the *lactone* ***Z-13*** (102 mg, 18%) as colourless plates, mp 147 °C, $[\alpha]_D$ −134 (*c* 0.6) [Found: $(M - CH_3O\cdot)^+$, 283.1539. C, 61.29; H, 8.05. $C_{16}H_{26}O_6$ requires $(M - CH_3O\cdot)^+$, 283.1545. C, 61.13; H, 8.34%]. ν_{max}/cm^{-1} 2947, 1750, 1463, 1379, 1122, 1039; δ_H ($CDCl_3$, 300 MHz) 5.61 (1 H, m), 5.46 (1 H, m), 5.11 (1 H, m), 4.09 (1 H, d, *J* 9.3), 3.68 (1 H, m), 3.22 (3 H, s), 3.21 (3 H, s), 2.56 (1 H, m), 2.32–1.94 (2 H, complex m), 1.90–1.82 (1 H, complex m), 1.80–1.72 (1 H, complex m), 1.68–1.54 (1 H, complex m), 1.32 (3 H, s), 1.27 (3 H, d, *J* 6.3), 1.24 (3 H, s); δ_C ($CDCl_3$, 125 MHz) 168.5 (C), 133.3 (CH), 126.6 (CH), 98.9 (C), 98.7 (C), 73.5 (2 × CH), 71.3 (CH), 48.2 (CH_3), 47.8 (CH_3), 30.5 (2 × CH_2), 22.9 (CH_2), 17.6 (2 × CH_3), 17.2 (CH_3); *m/z* (EI, 70 eV) 313 [$(M - H)^{+\bullet}$, <1%], 283 [$(M - CH_3O\cdot)^+$, 72], 225 (12), 211 (10), 166 (62), 123 (67), 122 (78), 101 (78), 95 (73), 81 (80), 68 (86), 55 (84), 43 (100).

Concentration of fraction B (R_f 0.1) afforded an inseparable and *ca.* 3 : 5 mixture of *compound* ***14*** and *compound* ***15*** (348 mg, 62%) as a clear, colourless oil [Found: $(M - CH_3O\cdot)^+$, 597.3276. $C_{32}H_{52}O_{12}$ requires $(M - CH_3O\cdot)^+$, 597.3275]. ν_{max}/cm^{-1} 2945, 1746, 1379, 1121, 1042; *m/z* (EI, 70 eV) 597 [$(M - CH_3O\cdot)^+$, 7%], 565 (23), 416 (18), 332 (29), 283 (12), 207 (15) 194 (33), 189 (19), 166 (29), 149 (37), 148 (46), 121 (48), 116 (85), 101 (86), 81 (87), 68 (71), 67 (70), 55 (53) 43 (100).

Method B: Grubbs' first-generation catalyst (46 mg, 0.06 mmol) was added to a magnetically stirred solution of

compound **12** (317 mg, 0.92 mmol) in degassed dichloromethane (920 mL) maintained under a nitrogen atmosphere at 18 °C. The reaction mixture was stirred at this temperature for 18 h after which time TLC analysis indicated the absence of starting material. DMSO (215 μL) was added to the reaction mixture, which was then stirred at 18 °C for a further 16 h before being concentrated under reduced pressure. Subjection of the residue to flash chromatography (1 : 4 v/v ethyl acetate–hexane elution) gave two fractions, A and B.

Concentration of fraction A (R_f 0.2) afforded compound **13** (191 mg, 66%) as an inseparable and *ca.* 1.3 : 1 mixture of *E*- and *Z*-isomers.

Concentration of fraction B (R_f 0.1) afforded an inseparable and *ca.* 2 : 3 mixture of compounds **14** and **15** (14 mg, 5%).

(2*R*,3*R*,4a*R*,7*R*,12a*S*)-Octahydro-2,3-dimethoxy-2,3,7-trimethyl-4a*H*-[1,4]dioxino[2,3-*c*]-oxecin-5(7*H*)-one (16)

10% Palladium on carbon (9 mg, 10 wt%) was added to a magnetically stirred solution of alkene **13** (89 mg, 0.28 mmol) in absolute ethanol (3 mL). A balloon of dihydrogen was attached and the reaction vessel evacuated and flushed twice with dihydrogen. The resulting black suspension was stirred under an atmosphere of dihydrogen at 18 °C for 14 h, then filtered through a pad of Celite™. Concentration of the filtrate under reduced pressure gave a grey-yellow oil that was subjected to flash chromatography (1 : 9 v/v diethyl ether–hexane elution). Concentration of the relevant fractions (R_f 0.3 in 1 : 4 v/v ethyl acetate–hexane) then gave the *title compound* ***16*** (77 mg, 86%) as a clear, colourless oil, $[\alpha]_D$ −160 (*c* 0.2) [Found: $(M - CH_3O\cdot)^+$, 285.1706. $C_{16}H_{28}O_6$ requires $(M - CH_3O\cdot)^+$, 285.1702]. ν_{max}/cm^{-1} 2944, 1752, 1456, 1378, 1183, 1123, 1038; δ_H ($CDCl_3$, 500 MHz) 5.51 (1 H, m), 4.19 (1 H, d, *J* 8.8), 3.63 (1 H, tm, *J* 9.8), 3.24 (3 H, s), 3.20 (3 H, s), 1.74–1.54 (8 H, complex m), 1.44–1.34 (2 H, complex m), 1.33 (3 H, s), 1.27 (3 H, d, *J* 6.3), 1.26 (3 H, s); δ_C ($CDCl_3$, 125 MHz) 168.9 (C), 99.1(7) (C), 99.1(1) (C), 73.5 (CH), 71.8 (CH), 70.5 (CH), 48.3 (CH_3), 47.8 (CH_3), 31.9 (CH_2), 28.4 (CH_2), 26.9 (CH_2), 22.7 (CH_2), 20.4 (CH_3), 19.4 (CH_2), 17.7 (CH_3), 17.3 (CH_3); *m/z* (EI, 70 eV) 285 (41%), 271 (10), 168 (32), 139 (22), 116 (68), 101 (69), 81 (72), 68 (68), 55 (59), 43 (100).

Compounds 17 and 18

Hydrogenation of compounds **14** and **15** under the same conditions as employed in the conversion **13** → **16** afforded a grey-yellow oil on work-up. Subjection of this material to flash chromatography (1 : 4 v/v diethyl ether–hexane to 3 : 7 v/v ethyl acetate–hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.4 in 3 : 7 v/v ethyl acetate–hexane) gave *compound* ***17*** (161 mg, 35%) as a clear, colourless oil, $[\alpha]_D$ −96 (*c* 0.4), [Found: $(M - CH_3O\cdot)^+$, 601.3593. $C_{32}H_{56}O_{12}$ requires $(M - CH_3O\cdot)^+$, 601.3588]. ν_{max}/cm^{-1} 2940, 2860, 1746, 1458, 1379, 1120, 1041; δ_H ($CDCl_3$, 500 MHz) 5.02 (2 H, m), 4.06 (2 H, d, *J* 9.3), 3.81 (2 H, dt, *J* 1.0 and 8.8), 3.27 (6 H, s), 3.21 (6 H, s), 1.62–1.40 (8 H, complex m), 1.37–1.24 (12 H, complex m), 1.32 (6 H, s), 1.26 (6 H, s), 1.22 (6 H, d, *J* 5.9); δ_C ($CDCl_3$, 125 MHz) 168.8 (C), 98.7 (C), 98.5 (C), 72.4 (CH), 71.9 (CH), 68.8 (CH), 48.2 (CH_3), 47.8 (CH_3), 35.6 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 24.7 (CH_2), 24.4 (CH_3), 19.8 (CH_2), 17.7 (CH_3), 17.3 (CH_3); *m/z* (EI, 70 eV) 601 [$(M - CH_3O\cdot)^+$, 5%], 569 (26), 452 (29), 420 (94), 336 (43), 285 (21), 168 (46), 150 (91), 116 (85), 101 (100).

Concentration of fraction A [R_f 0.3(5) in 3 : 7 v/v ethyl acetate–hexane)] gave *compound* ***18*** (258 mg, 57%) as white needles, mp 160 °C, $[\alpha]_D$ −187 (*c* 0.2) [Found: $(M - CH_3O\cdot)^+$, 601.3573. C, 60.84; H, 8.71. $C_{32}H_{56}O_{12}$ requires $(M - CH_3O\cdot)^+$, 601.3588. C, 60.74; H, 8.92%]. ν_{max}/cm^{-1} 2936, 2858, 1747, 1457, 1379, 1121, 1039; δ_H ($CDCl_3$, 500 MHz) 4.99 (2 H, m), 4.08 (2 H, d, *J* 9.8), 3.79 (2 H, m), 3.26 (6 H, s), 3.22 (6 H, s), 1.70 (2 H, m), 1.57 (2 H, m), 1.47 (2 H, m), 1.43–1.52 (14 H, complex m), 1.34 (6 H, s), 1.28 (6 H, s), 1.25 (6 H, d, *J* 6.3); δ_C ($CDCl_3$, 125 MHz) 168.9 (C), 98.9 (C), 98.6 (C), 73.1 (CH), 72.0 (CH), 69.1 (CH), 48.2 (CH_3), 47.8 (CH_3), 36.1 (CH_2), 30.4 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 25.1 (CH_3), 19.9 (CH_2), 17.7 (CH_3), 17.4 (CH_3); *m/z* (EI, 70 eV) 601 [$(M - CH_3O\cdot)^+$, 3%], 569 (14), 452 (10), 420 (43), 336 (15), 208 (100), 116 (75), 101 (99), 69 (85).

Methyl (*E*)-3-{(2*S*,3*S*,5*R*,6*R*)-3-[(*R*)-6-hydroxyheptyl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl}acrylate (20)

Method A: DIBAL-H (408 μL of a 1 M solution in hexane, 0.41 mmol) was added, in portions over 1 h, to a magnetically stirred solution of the lactone **16** (89 mg, 0.28 mmol) in toluene (3 mL) maintained at −78 °C under a nitrogen atmosphere. Stirring was continued for 0.5 h, the reaction then quenched by adding NaK tartrate (5 mL of a 1 M aqueous solution), the resulting mixture warmed to 0 °C over an additional 10 min and then extracted with ethyl acetate (3 × 10 mL). A few drops of 1 M aqueous HCl were added to disperse the emulsion formed during extraction. The combined organic fractions were washed with brine (1 × 5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *lactol* ***19*** as an unstable, yellow oil which was used immediately in the next step of the reaction sequence.

A magnetically stirred suspension of NaH (23 mg of a 60% dispersion in mineral oil, 0.57 mmol) in THF (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated dropwise with trimethyl phosphonoacetate (91 μL, 0.56 mmol). The resulting mixture was warmed to 18 °C over 0.5 h and a solution of the lactol **19** (obtained as described immediately 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 ethyl acetate (10 mL) and quenched with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous fraction was extracted with ethyl acetate (3 × 15 mL) and the combined organic fractions washed with water (1 × 10 ml) and 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 (3 : 7 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.1 in 1 : 4 v/v ethyl acetate–hexane) gave the *title compound* ***20*** (82 mg, 79% from lactone **16**) as a clear, colourless oil, $[\alpha]_D$ −163 (*c* 0.5) [Found: $(M - CH_3O\cdot)^+$, 343.2119. $C_{19}H_{34}O_7$ requires $(M - CH_3O\cdot)^+$, 343.2121]. ν_{max}/cm^{-1} 3399, 2938, 1727, 1660, 1437, 1376, 1307, 1124, 1038; δ_H ($CDCl_3$, 300 MHz) 6.85 (1 H, dd, *J* 5.6 and 15.6), 6.19 (1 H, dd, *J* 1.6 and 15.6), 4.14 (1 H, ddd, *J* 1.6, 5.6 and 9.5), 3.74 (3 H, s), 3.52 (1 H, m), 3.24 (1 H, m), 3.23 (6 H, s), 1.68–1.20 (10 H, complex m), 1.54 (1 H, br s), 1.31 (3 H, s), 1.30 (3 H, s), 1.17 (3 H, d, *J* 6.2); δ_C ($CDCl_3$, 75 MHz) 166.7 (C), 143.0 (CH), 123.1 (CH), 98.7 (C), 98.6 (C), 71.7 (CH), 70.7 (CH), 68.1 (CH), 51.7 (CH_3), 48.0 (CH_3), 47.9 (CH_3), 39.2 (CH_2), 30.5 (CH_2), 29.5 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 23.5 (CH_3), 17.7 (CH_3), 17.5 (CH_3); *m/z* (EI, 70 eV) 343 [$(M - CH_3O\cdot)^+$, 20%], 327 (15), 311 (31), 225 (20), 208 (18), 194 (40), 138 (52), 117 (76), 116 (78), 101 (77), 96 (69), 73 (79), 55 (74), 43 (100).

Method B: Reaction of *bis*-lactone **17** with DIBAL-H in the same manner as described above but using 4 (rather than 1.5) mole equivalents of the reducing agent gave the lactol **19**. This material was immediately subjected to reaction with the anion derived from trimethyl phosphonoacetate (see Method A) and in this way the title compound **20** (62% from lactone **17**) was obtained as a clear, colourless oil. This material proved identical, as judged by ^{13}C and ^1H NMR analysis, with that obtained by Method A.

Compound 21

Reaction of *bis*-lactone **18** with DIBAL-H in the same manner as described above for the conversion **16** → **19** but using 4

(rather than 1.5) mole equivalents of the reducing agent gave the corresponding *bis*-aldehyde on work-up. This material was immediately treated with the anion derived from trimethyl phosphonoacetate in the same manner as described above for the conversion **19** → **20** but using 4 (rather than 2) mole equivalents of the anion. In this way a yellow oil was obtained on work-up. Subjection of this material to flash chromatography (3 : 7 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.6 in 1 : 4 v/v ethyl acetate–hexane) gave *compound **21*** (52% from lactone **18**) as a clear, colourless oil, $[\alpha]_D$ +11 (*c* 0.4) [Found: (M − $CH_3O^{\bullet}$)$^+$, 571.3122. $C_{30}H_{50}O_{12}$ requires (M − $CH_3O^{\bullet}$)$^+$, 571.3118]. ν_{max}/cm^{-1} 2947, 2857, 1728, 1662, 1436, 1376, 1307, 1125, 1039, 978, 889, 853; δ_H ($CDCl_3$, 300 MHz) 6.84 (2 H, dd, *J* 5.8 and 15.7), 6.19 (2 H, dd, *J* 1.4 and 15.7), 4.13 (2 H, ddd, *J* 1.4, 5.8 and 9.5), 3.74 (6 H, s), 3.51 (2 H, m), 3.22 (12 H, s), 1.72–1.20 (12 H, complex m), 1.31 (6 H, s), 1.30 (6 H, s); δ_C ($CDCl_3$, 75 MHz) 166.6 (C), 143.0 (CH), 123.2 (CH), 98.7 (C), 98.6 (C), 71.8 (CH), 70.7 (CH), 51.7 (CH_3), 48.0 (CH_3), 47.9 (CH_3), 30.6 (CH_2), 29.6 (CH_2), 25.1 (CH_2), 17.7 (CH_3), 17.5 (CH_3); *m*/*z* (EI, 70 eV) 571 [(M − $CH_3O^{\bullet}$)$^+$, 11%], 539 (46), 507 (29), 439 (21), 390 (72), 274 (47), 249 (45), 220 (55), 219 (100), 205 (60), 166 (55), 149 (68).

Compound 23

A magnetically stirred solution of methyl ester **20** (129 mg, 0.34 mmol) in ethanol (7 mL) was treated with NaOH (1.1 mL of a 1.5 M aqueous solution, 1.65 mmol). The resulting mixture was allowed to stir at 18 °C for 3 h, diluted with water (10 ml), acidified to pH 3 (with 1 M aqueous HCl) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *carboxylic acid **22*** as a light-yellow oil.

The unstable acid obtained as described above was immediately dissolved in THF (3 mL) containing triethylamine (57 μL, 0.41 mmol) and the resulting and magnetically stirred solution cooled to 0 °C, treated with 2,4,6-trichlorobenzoyl chloride (54 μL, 0.35 mmol) and warmed to 18 °C. After 1 h TLC analysis indicated that all of the starting material had been consumed. The reaction mixture was diluted with toluene (30 mL) and added, over *ca.* 10 minutes and *via* cannula, to a solution of DMAP (210 mg, 1.72 mmol) in refluxing toluene (30 mL). The resulting mixture was heated at reflux for 1 h then cooled, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with $CuSO_4$ (1 × 5 mL of a saturated aqueous solution), water (1 × 5 ml) and brine (1 × 5 mL), and then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (1 : 9 v/v ethyl acetate–hexane elution) and concentration of the relevant fractions (R_f 0.2) gave the *macrolactone **23*** (73 mg, 62%) as white, crystalline solid. Recrystallisation (hexane) of a sample of this material gave analytically pure material, mp 159–160 °C, $[\alpha]_D$ −152 (*c* 0.3) [Found: (M − $CH_3O^{\bullet}$)$^+$, 311.1862. $C_{18}H_{30}O_6$ requires (M − $CH_3O^{\bullet}$)$^+$, 311.1858]. ν_{max}/cm^{-1} 2942, 1718, 1462, 1376, 1246, 1122, 1039, 857; δ_H ($CDCl_3$, 300 MHz) 6.86 (1 H, dd, *J* 7.1 and 16.1), 6.16 (1 H, dd, *J* 1.2 and 16.1), 5.06 (1 H, m), 4.22 (1 H, ddd, *J* 1.2, 6.8 and 8.3), 3.41 (1 H, m), 3.24 (3 H, s), 3.21 (3 H, s), 1.74–1.01 (10 H, complex m), 1.29 (3 H, s), 1.28 (3 H, s), 1.27 (3 H, d, *J* 6.6); δ_C ($CDCl_3$, 75 MHz) 167.0 (C), 143.2 (CH), 123.7 (CH), 99.4 (C), 98.7 (C), 73.9 (CH), 72.9 (CH), 72.8 (CH), 48.0 (CH_3), 47.8 (CH_3), 32.2 (CH_2), 30.5 (CH_2), 27.5 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 19.1 (CH_3), 17.8 (CH_3), 17.4 (CH_3); *m*/*z* (EI, 70 eV) 342 ($M^{+\bullet}$, <1%), 311 [(M − $CH_3O^{\bullet}$)$^+$, 52], 117 (65), 116 (78), 101 (77), 83 (60), 73 (70), 55 (90), 43 (100).

E-Isomer of (−)-cladospolide B (24)

A magnetically stirred solution of compound **23** (60 mg, 0.17 mmol) in dichloromethane (2 ml) was cooled to 0 °C and treated with distilled $TiCl_4$ (23 μL, 0.21 mmol). The resulting orange solution was maintained at 0 °C for 1.5 h, quenched with $NaHCO_3$ (1 ml of a saturated aqueous solution) and extracted with ethyl acetate (3 × 10 ml). The combined organic fractions were washed with water (1 × 2 ml) and brine (1 × 2 ml) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (7 : 3 v/v ethyl acetate–hexane elution) followed by concentration of the relevant fractions (R_f 0.3) gave *compound **24*** (37 mg, 94%) as a clear, colourless oil, $[\alpha]_D$ −20 (*c* 0.2) [Found: (M − H_2O)$^{+\bullet}$, 210.1256. $C_{12}H_{20}O_4$ requires (M − H_2O)$^{+\bullet}$, 210.1256]. ν_{max}/cm^{-1} 3394, 2937, 2863, 1712, 1647, 1464, 1259, 1165, 1116, 1049, 1029; δ_H ($CDCl_3$, 600 MHz) 6.94 (1 H, dd, *J* 5.9 and 16.1), 6.12 (1 H, dd, *J* 1.5 and 16.1), 5.12 (1 H, m), 4.12 (1 H, ddd, *J* 1.5, 5.9 and 7.3), 3.32 (1 H, m), 2.25 (2 H, br s), 1.76–1.60 (3 H, complex m), 1.52–1.32 (5 H, complex m), 1.29 (3 H, d, *J* 6.8), 1.22 (1 H, m), 1.02 (1 H, m); δ_C ($CDCl_3$, 150 MHz) 166.9 (C), 146.6 (CH), 122.4 (CH), 77.8 (CH), 77.6 (CH), 72.8 (CH), 33.0 (CH_2), 32.4 (CH_2), 28.1 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 18.8 (CH_3); *m*/*z* (EI, 70 eV) 228 ($M^{+\bullet}$, <1%), 210 [(M − H_2O)$^{+\bullet}$, 7], 199 (39), 184 (28), 171 (100).

(−)-Cladospolide B (2)

A magnetically stirred solution of compound **24** (37 mg, 0.16 mmol) in degassed benzene was irradiated for 16 h at 300 nm in a Rayonet photoreactor. Evaporation of the solvent and subjection of the resulting clear, colourless oil to semi-preparative HPLC purification (7 : 3 v/v ethyl acetate–hexane elution) provided two fractions, A and B.

Concentration of fraction A (R_t 12.3 min) gave compound **24** (21 mg, 57% recovery) identical, in all respects, with authentic material.

Concentration of fraction B (R_t 9.9 min) gave the *title compound **2*** (5 mg, 31% at 43% conversion) as a white solid, mp 108–109 °C {lit.[3] mp [for (+)-cladospolide B] 109–110 °C}, $[\alpha]_D$ −162 (*c* 0.1, MeOH). ν_{max}/cm^{-1} 3409, 2926, 2855, 1707, 1633, 1460, 1377, 1279, 1047, 838; δ_H ($CDCl_3$, 500 MHz) 6.24 (1 H, dd, *J* 8.3 and 12.2), 5.78 (1 H, dd, *J* 1.5 and 12.2), 5.27 (1 H, m), 4.89 (1 H, m), 3.78 (1 H, m), 3.64–3.41 (2 H, br m), 1.80–1.27 (10 H, complex m), 1.29 (3 H, d, *J* 6.3); δ_C ($CDCl_3$, 150 MHz) 165.8, 148.5, 121.9, 74.4, 73.9, 67.4, 31.9, 30.5, 25.6, 24.1, 21.3, 19.6; *m*/*z* (EI, 70 eV) 228 [($M^{+\bullet}$, <<1%), 169 (29), 109 (28), 102 (100), 84 (65), 55 (57).

Crystallographic studies

Crystal data for compound *Z*-13. $C_{16}H_{26}O_6$, M = 314.378, T = 200(1) K, trigonal, space group $P3_1$, Z = 9, a = 18.6850(2), b = 18.6850(2), c = 12.2539(1) Å, V = 3705.02(6) Å^3, D_X = 1.268 Mg m^{-3}, 5629 unique data ($2\theta_{max}$ = 55°), 5022 with $I > 3.00\sigma(I)$; R = 0.038, wR = 0.048, S = 1.292.

Crystal data for compound 23. $C_{18}H_{30}O_6$, M = 342.43, T = 200(1) K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.0435(1), b = 16.1734(4), c = 16.3288(4) Å, V = 1860.13(7) Å^3, D_X = 1.223 Mg m^{-3}, 1903 unique data ($2\theta_{max}$ = 50°), 1399 with $I > 2.00\sigma(I)$; R = 0.0276, wR = 0.0297, S = 1.1307.

Structure determination. Images were measured on a Nonius KappaCCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[17] Structure solution was by direct methods (SIR92).[18] The crystals of compound *Z*-**13** were twinned so the structure was refined using RAELS2000.[19] Full details will be reported elsewhere.[20] The structure of compound **23** was refined using the CRYSTALS program package.[21] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference

numbers 253914 and 253913 for compounds *Z*-**13** and **23** respectively). See http://www.rsc.org/suppdata/ob/b4/b417685e/ for crystallographic data in .cif or other electronic format.

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