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Chemoenzymatic and enantioselective assembly of the (1α,3aβ,6α,7aβ)-octahydro-1,6-methano-1*H*-indene framework associated with 2-isocyanoallopupukeanane: validation of a new synthetic strategy and the identification of enantiomeric switching regimes

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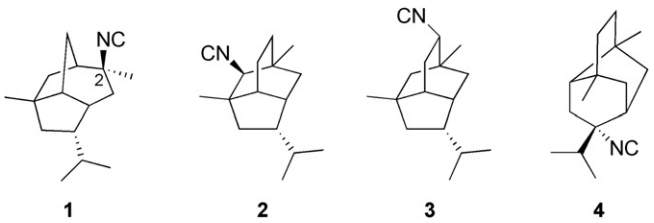
ABSTRACT

The octahydro-1,6-methano-1*H*-indene framework associated with the marine sesquiterpenoid 2-isocyanoallopupukeanane (**1**) has been prepared in enantiomerically pure form from the *cis*-1,2-dihydrocatechol **8** using Diels–Alder cycloaddition, oxa-di-π-methane rearrangement and intramolecular enolate alkylation steps as the key bond-forming events. Three distinct strategies for employing such sequences in the selective synthesis of either enantiomeric form of the target framework have been identified.

1. Introduction

In 1991 Fusetani et al. reported[1] on the elucidation, using 2D NMR spectroscopic techniques, of the structure of 2-isocyanoallopupukeanane (**1**), a sesquiterpenoid isonitrile isolated from two specimens of a *Phyllidia pustulosa* species of nudibranch collected off Hachijo-jima Island, Japan. Such isocyano-containing species, which include the framework-isomeric natural products 2-isocyanopupukeanane (**2**),[2] 9-isocyanopupukeanane (**3**)[2] and 9-isocyanoneopupukeanane (**4**),[3] are found in the secretions of a variety of marine molluscs, where they are presumed to play a defensive role, and are known to be sequestered from the sponge diet of these creatures.[2c] The origins of the isocyano-function have been the subject of various studies[4,5] including a number conducted by one of us (M.J.G.).[5]



1 **2** **3** **4**

As part of a program directed towards developing a comprehensive understanding of the biogenesis of compound **1** we sought to establish methods for synthesising, in either enantiomeric form,[6] the associated octahydro-1,6-methano-1*H*-indene framework incorporating relevant functionality, especially those that would allow for ready installation of isocyano and related groups at the 2-position. In contrast to the situation with compounds **2** and **3**,[7] there have been few studies concerned with the total synthesis of compound **1** or its enantiomer.[8,9] Indeed, the single reported total synthesis of the title natural product was described by Ho et al. in 1999[8] and only provided the racemic modification of the target. More recently (2006), Srikrishna and Satyanarayana have communicated[9] a biogenetically patterned and enantiospecific synthesis of 'allopupukeanones' from 6-methylcarvone that involves, as the key step, the acid-induced Wagner–Meerwein rearrangement of a pupukeanyl cation to the corresponding allopupukeanane species. However, the extension of such chemistry to the preparation of natural product **1** has not been reported thus far.

The approach to the tricyclic framework of *ent*-2-isocyanoallopupukeanane (*ent*-**1**) that we have pursued is outlined in Figure 1, and this incorporates several key transformations used during the course of our development of total syntheses of various triquinane-type sesquiterpenes including hirsutene, hirsutic acid, complicatic acid and phellodonic acid.[10] A pivotal aspect of the present work was the recognition that the framework of target *ent*-**1** (and **1**) is

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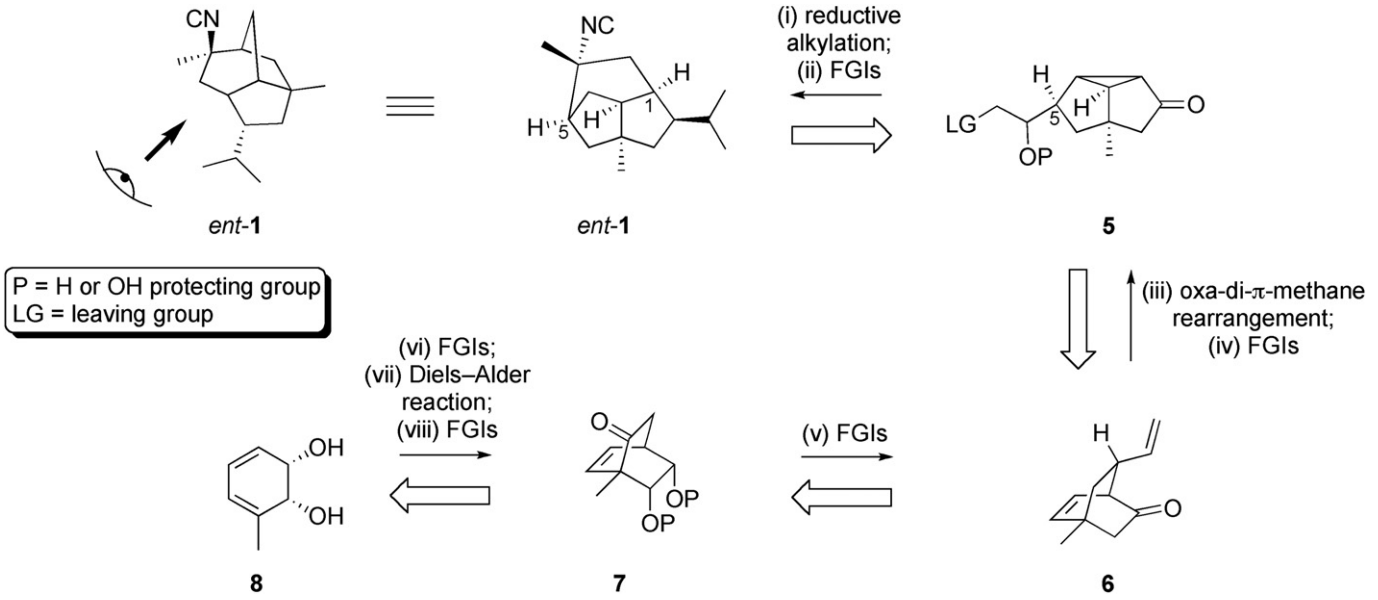


Figure 1. Retrosynthetic analysis of *ent*-2-isocyanoallopupukeanane (*ent*-**1**).

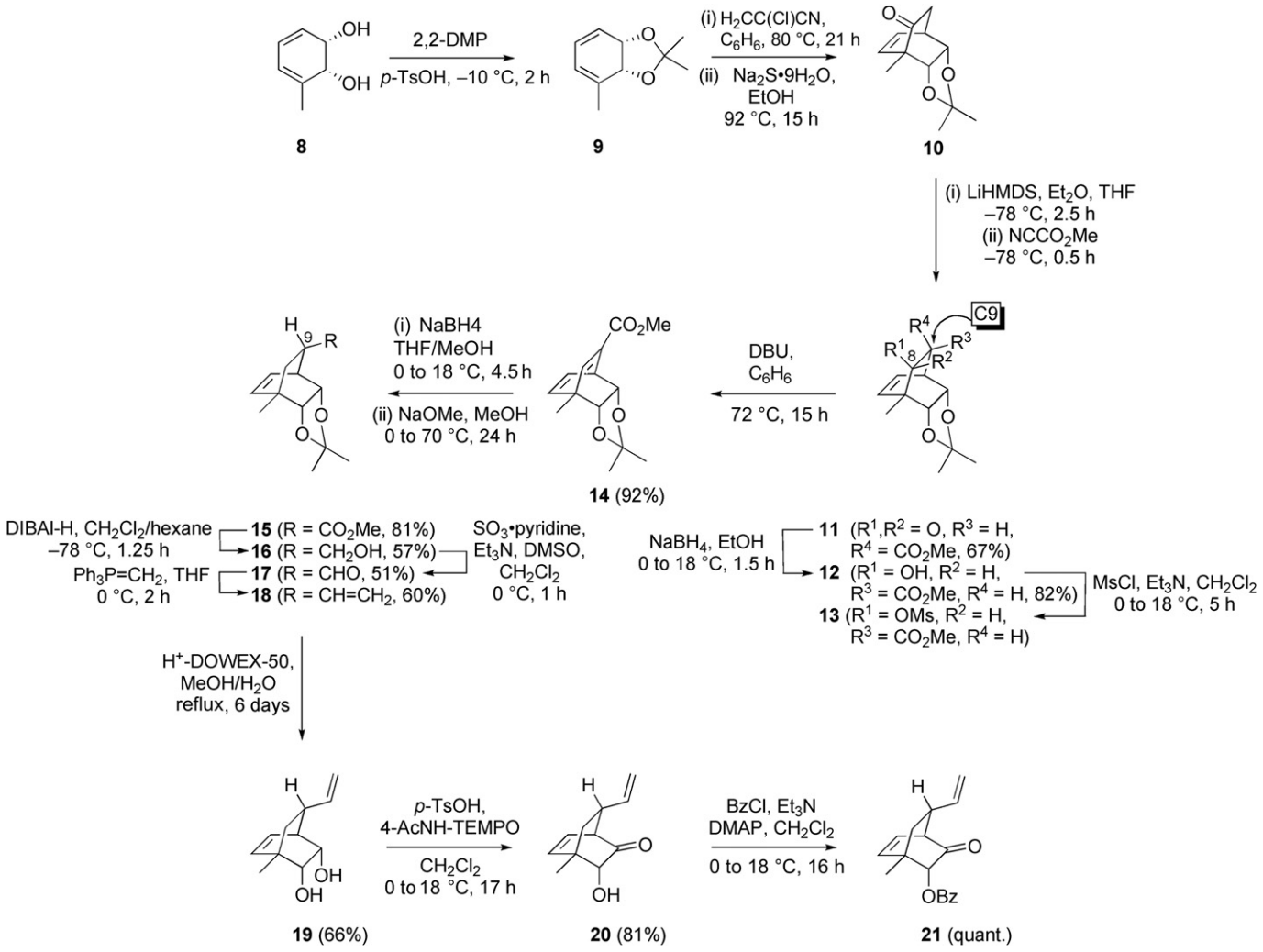
a 1,5-ethano-bridged diquinane and that this could, therefore, be assembled from a precursor of the general form **5** through its subjection to reductive cleavage of the carbonyl-conjugated cyclopropane moiety and in situ intramolecular alkylation of the ensuing enolate by the C5-appended and *endo*-orientated side-chain bearing a leaving group at its terminus. Conventional functional group interconversions (FGIs) of the OP and carbonyl groups within the anticipated product of this sequence should then deliver *ent*-2-isocyanoallopupukeanane (*ent*-**1**) and related compounds. It was expected that compound **5** could, in turn, be obtained via a photochemically promoted oxa-di-π-methane rearrangement[11] of the disubstituted bicyclo[2.2.2]octenone **6** followed by or, if necessary, preceded by manipulation of the associated vinyl group so as to establish the relevant functionality on the side-chain of compound **5**. Access to compound **6** was expected to be gained via conventional manipulations of ketone **7**, versions of which we have obtained previously through Diels–Alder cycloaddition reactions between α-chloroacrylonitrile and hydroxy-protected forms of the *cis*-1,2-dihydrocatechol **8**.[12] Starting material **8** is readily obtained in multi-gram quantities and enantiomerically pure form (>99.8% ee) through the whole-cell biotransformation of toluene using a genetically engineered micro-organism *Escherichia coli* JM109 (pDTG601) that over-expresses the responsible enzyme, viz. toluene-dioxygenase (TDO).[13] In an overall sense, then, there are three critical chemical sequences associated with the implementation of the proposed synthetic plan, namely the Diels–Alder cycloaddition process leading to compounds of the general form **7** and the manipulation of such adducts to give bicyclo[2.2.2]octenone **6**, the photochemical rearrangement of the latter to give, after appropriate FGIs, the cyclopropa-fused diquinane **5** and, finally, a reductive alkylation process leading to the complete tricyclic framework associated with target *ent*-**1**. Each of these pivotal steps is discussed separately in the following sections as is the capacity to adapt the reported chemistry to the synthesis of either enantiomeric form of 2-isocyanoallopupukeanane, viz. **1** and/or *ent*-**1**.

2. Results and discussion

2.1. Synthesis of the substrate for the oxa-di-π-methane rearrangement reaction

The first critical chemical sequence associated with the present work started (Scheme 1) with the engagement of the well known[14] acetonide derivative, **9**, of *cis*-1,2-dihydrocatechol **8** in a Diels–Alder cycloaddition reaction with α-chloroacrylonitrile. Hydrolysis of the ensuing mixture of epimeric α-chloronitriles[12] to give the previously reported ketone **10**[12] was achieved most effectively using a modification of conditions originally reported by Evans et al.[15] As a prelude to introducing the vinyl group required in a photochemical substrate of the general form **6**, the enolate anion derived by deprotonation of ketone **10** was treated, in diethyl ether, with 2 mol equiv of Mander's reagent[16] and thus affording the β-ketoester **11** in 67% yield. Reduction of the latter with sodium borohydride in ethanol then gave β-hydroxyester **12** and its stereoisomers C9-*epi*-**12** and C8,C9-di-*epi*-**12** in 82% combined yield.[17] The structure of compound **12** was confirmed by single-crystal X-ray analysis (see Experimental section).

Compound C9-*epi*-**12**, the predominant product of the reduction process, could be converted into isomer **12** (67% yield at 73% conversion) upon treatment with the weakly nucleophilic base DBU. Subjection of a mixture of compounds **12** and C8,C9-di-*epi*-**12** to mesylation under the Crossland–Servis conditions[18] then gave the corresponding mixture of mesylate **13** and isomer C8,C9-di-*epi*-**13**. Treatment of the latter mixture with DBU in hot (72 °C) benzene overnight resulted in elimination of the elements of methanesulfonic acid and formation of the unsaturated ester **14** (92%). Reaction of compound **14** with sodium borohydride in methanol/THF then gave a ca. 1:1 mixture of ester **15** and its epimer C9-*epi*-**15** (81% combined yield) that could be separated from one another by conventional flash chromatographic techniques. Interestingly, treatment of compound C9-*epi*-**15** with sodium methoxide in methanol at 0 to 70 °C for 24 h afforded a ca. 3:1 mixture of the starting material and epimer **15** (89% combined yield) and thus demonstrating that additional quantities of the desired isomer (**15**) could be generated from the unwanted one. Treatment of ester **15** with DIBAL-H in dichloromethane/hexane at −78 °C for 1.25 h afforded a chromatographically separable mixture of alcohol **16** (57%) and aldehyde **17** (30%). The former product could be oxidised to the latter in 51% yield using the Parikh–Doering protocol.[19] Additional quantities of aldehyde **17** could also be obtained by reducing ester C9-*epi*-**15** to aldehyde C9-*epi*-**17** and then epimerising the latter with DBU (47% yield of compound **17** over the two steps). Wittig-type methylenation of aldehyde **17** then gave the required olefin **18** in 60% yield. Cleavage of the acetonide unit within the latter compound was achieved by exposing the substrate to activated DOWEX-50 resin in refluxing aqueous methanol for 6 days. By this



Scheme 1.

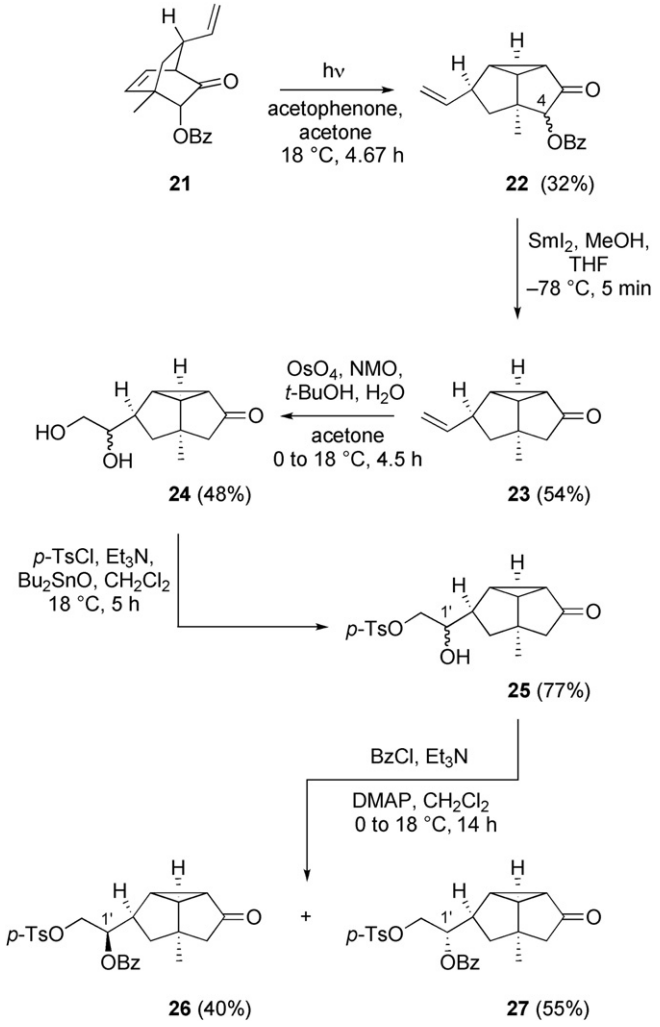
means the diol **19** was obtained in 66% yield. So, despite the harsh conditions required to effect cleavage of the acetonide group, there appeared to be no complications arising from isomerisation of the terminal olefin into a more stable internal position. Selective oxidation of the hydroxyl group remote from the bridgehead methyl group within diol **19** could be achieved using the sterically demanding oxammonium salt derived from reaction of 4-AcNH-TEMPO with *p*-TsOH·H_2O[20] and the ensuing acyloin **20** (81%) was immediately subjected to O-benzoylation using benzoyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine. By such means the keto-ester **21** was obtained in quantitative yield.

While in the original plan (Fig. 1) deletion of the *O*-benzoyl group within keto-ester **21** would now be required in order to produce the photo-substrate **6**, our previous studies[10] had shown that systems related to the former compound readily engage in oxa-di-π-methane rearrangement reactions. Accordingly, and given the capacity to delete the OBz group at a later stage in the synthesis, compound **21** was selected as the substrate to be used in studies of the photochemical rearrangement process. Details are presented in the following section.

2.2. The oxa-di-π-methane rearrangement reaction and chemical manipulation of the photo-product

Following procedures developed earlier,[10] a solution of compound **21** in acetone containing acetophenone (triplet sensitiser) was subjected to irradiation with a medium pressure mercury-vapour lamp at 15 °C for 4.5 h (Scheme 2). By such means a ca. 1:1 mixture of the C4-epimeric forms of compound **22** was obtained, albeit in a disappointing 32% combined yield. This low yield could be attributed to interference from the vinyl group associated with substrate **21**, especially the potential for this moiety to participate in a competing oxa-di-π-methane rearrangement process. The formation of the C4-epimeric forms of product **22** from a single epimeric form of precursor **21** presumably arises from a secondary photochemical process involving photo-enolisation and/or Norrish-type 1 reactions[10] of the primary photo-product. The driving force for the epimerisation of the primary photo-product is the migration of the *O*-benzoyl unit from the *exo*-face to the *endo*-face of the cyclopropa-fused diquinane framework and thereby relieving steric interactions with the adjacent methyl group.

The chemical manipulation of photo-product **22** so as to generate a substrate for examination of the proposed intramolecular enolate alkylation step (Fig. 1) involved initial reductive removal of the *O*-benzoyl residue. This was best accomplished by treating a methanolic solution of compound **22** with 2.2 mol equiv of samarium(II) diiodide at −78 °C for 5 min.[21] The ensuing unsaturated ketone **23** (54%) was subjected to olefin dihydroxylation using the UpJohn conditions[22] and thereby affording an inseparable and 1:1 mixture of the diastereoisomeric forms of the product diol **24** in 48% combined yield. Attempts to improve upon this outcome, in terms of both yield and diastereoselectivity, by using Sharpless asymmetric

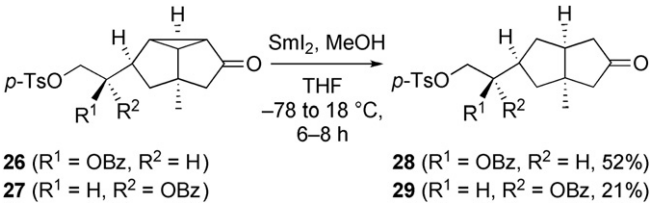


Scheme 2.

dihydroxylation protocols[23] either gave no reaction at all (with AD-mix-β) or resulted in a 1:1:1 mixture of the starting material and the product diols (with AD-mix-α). The selective tosylation of the primary hydroxy group within compound **24** was readily accomplished using *p*-toluenesulfonyl chloride in the presence of dibutyltin oxide[24] and thereby affording the desired epimeric mono-tosylates **25** in 77% combined yield. *O*-Benzoylation of the secondary hydroxyl groups within the epimeric forms of compound **25** was effected under standard conditions (BzCl, DMAP, Et_3N) and the co-formed bis-esters **26** and **27** were readily separated from one another by conventional chromatographic techniques and thereby obtained in yields of 40% and 55%, respectively. The illustrated stereochemistries assigned to products **26** and **27** follow from a single-crystal X-ray analysis of a derivative of the former compound (vide infra).

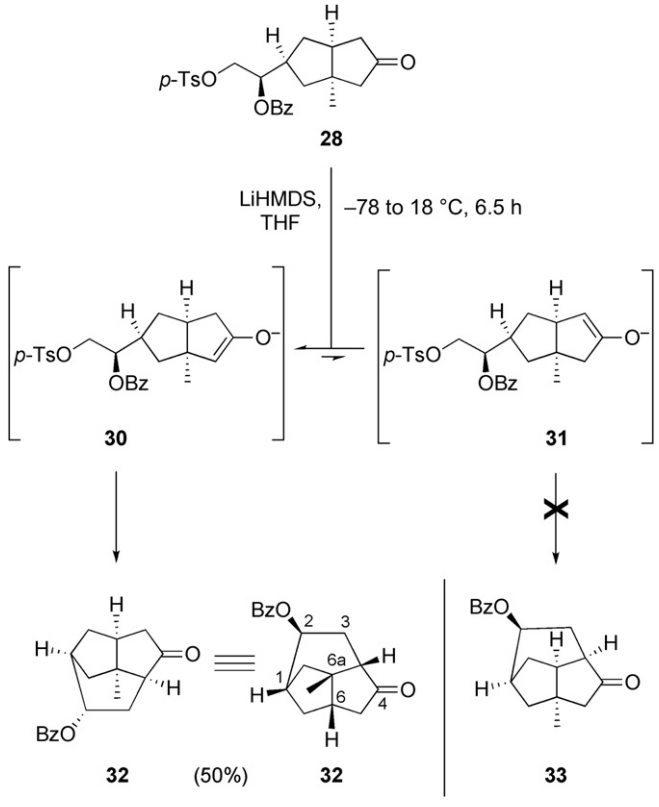
2.3. Completion of the synthesis through intramolecular enolate alkylation

With compounds **26** and **27** in hand studies of the validity of the proposed reductive-cleavage/intramolecular enolate alkylation chemistry (see conversion **5**→**1**, Fig. 1) could begin. The initial experiments simply involved treating each of substrates **26** and **27** with 1.2 mol equiv of samarium(II) diiodide in THF/methanol at −78 to 18 °C for periods of up to 8 h (Scheme 3).[25] However, after quenching the reaction mixtures and then subjecting them to work up, only the products of cyclopropane ring-cleavage, viz. compounds **28** and **29**, were obtained in yields of 52% and 21%, respectively. The lack of any products of intramolecular enolate alkylation processes may be attributed to the limited nucleophilicity and/or the ready protonation of the intermediate samarium enolate.[25,26]



Scheme 3.

Sufficient quantities of compound **28** were obtained by the means just described to allow for an investigation of the intramolecular enolate alkylation reaction under more conventional conditions. Thus, treatment of a THF solution of ketone **28** maintained at −78 °C with 1.2 mol equiv of lithium hexamethyldisilazide (LiHMDS) (Scheme 4) and then allowing the reaction mixture to warm to 18 °C provided, after work up and chromatographic



Scheme 4.

purification, compound **32** in 53% yield. All the spectroscopic data obtained on this material were in full accord with the assigned structure but final confirmation of this was secured by a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 2 while other details of this analysis are presented in the Experimental section. The formation of this product must arise through selective formation of precursor enolate **30**, which then engages in intramolecular alkylation with the tosyloxy-bearing side-chain to give ketone **32** incorporating the tricyclic framework of 2-isocyanoallopupukeanane but carrying the methyl group in the C6a rather than the desired C6 position. Interestingly, no evidence could be obtained for the formation of the isomeric ketone **33** that would arise from intramolecular alkylation of intermediate **31**.

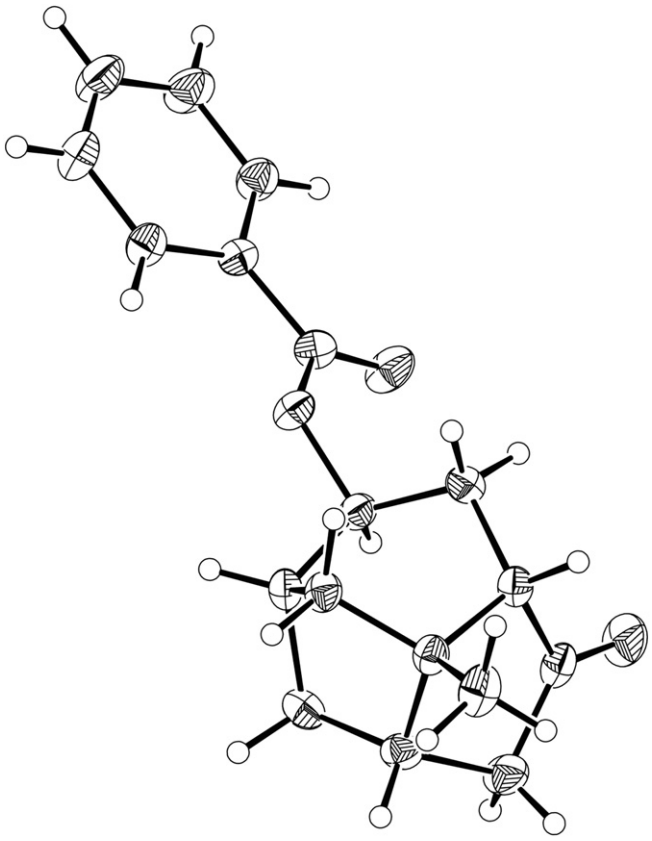


Figure 2. Molecular structure of compound **32** ($C_{18}H_{20}O_3$). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Presumably, the selective formation of enolate **30** over isomer **31** under the conditions of thermodynamic control[27] defined above is a reflection of the reduction in torsional strain (between the angular methyl and the *syn*-1,2-related methylene proton adjacent to the carbonyl group) associated with the conversion **28**→**30**. This reduction is greater than that which would be encountered in the equivalent process leading to **31** (where the corresponding reduction in torsional strain would 'only' be that arising from loss of the interaction between the angular hydrogen and the *syn*-1,2-related methylene proton adjacent to the carbonyl group). In principle, carrying out enolate formation under conditions of kinetic control (viz. adding the substrate ketone **28** to a solution of the base)[27] might be expected to lead to enolate **31** and thence the tricyclic product **33**, which bears a pseudo-enantiomeric relationship to isomer **32**. Unfortunately, a lack of sufficient quantities of ketone **28** has prevented us from conducting the relevant experiments. Current efforts are directed towards achieving a much more efficient route to compound **28** and the results of these will be reported in due course.

2.4. Potentially enantiodivergent routes to the octahydro-1,6-methano-1*H*-indene framework associated with 2-isocyanoallopupukeanane

The lack of certainty regarding the absolute configuration of the naturally occurring form of 2-isocyanoallopupukeanane[6] has prompted us to consider ways in which either enantiomeric form of this compound could be synthesised using the now validated strategy shown in Figure 1. Three distinct ways of achieving this seem possible. First of all, the enantiomeric form of the starting material, viz. compound *ent*-**8**, is available from *p*-iodotoluene using methodology reported by Boyd et al.[28] Accordingly, the optical antipodes of all of compounds **9**–**29** and **32** are automatically available using the chemistries reported herein. Another possible mode of entry into the other enantiomeric series would involve reversing the facial selectively of the initial Diels–Alder cycloaddition reaction involving *cis*-1,2-dihydrocatechol **8** and/or its derivatives since an α-face addition process affords the pseudo-enantiomeric form of the compound (e.g., ketone **10**) arising from the corresponding β-face addition reaction. In recent work[10a,b,29] we have shown that such facial selectivities can be controlled, to some extent at least, by using either compound **8** or a protected form thereof (e.g., acetonide **9**) as the 4π-addend in the cycloaddition process. A third possible mode of enantiomeric 'switching' arises from the pseudo-symmetrical nature of ketonic systems such as compound **28**. In particular, if the non-methylated variant of this diquinane could be obtained from the known, benzene-derived *cis*-1,2-dihydrocatechol[13] then this could be desymmetrised using the relevant Koga–Simpkins type-base[30] to generate either enantiomeric form of the corresponding enolate and thence, through intramolecular alkylation, either enantiomeric form of the title framework.[31] The required methyl group could then be introduced through a conventional dehydrogenation/conjugate addition reaction sequence. Efforts to examine all of these possibilities are now underway in our laboratories. Results will be reported in due course.

3. Experimental section

3.1. General experimental procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini machine operating at 300 or 75 MHz, respectively. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous sodium carbonate. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were normally recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on KBr plates (for liquids) or as a KBr disk (for solids). Low-resolution ESI mass spectra were recorded in positive-ion mode on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a Fisons VG AUTOSPEC instrument. Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Optical rotations were measured at the sodium-D line (λ=589 nm) between 17 and 20 °C and at the concentrations (*c*, in g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of vanillin/sulfuric acid/ethanol (1 g:1 g:18 mL) or phosphomolybdic acid/ceric sulfate/sulfuric acid (concd)/water (37.5 g:7.5 g:37.5 g:720 mL). The retardation factor (R_f) values cited here have been rounded to the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[32] with silica gel 60 (0.040–0.0063 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were either used as supplied or, in the case of liquids, distilled when required. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, dichloromethane, acetonitrile and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[33] Spectroscopic

grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

3.2. Specific chemical transformations

*3.2.1. Compound **11**.* LiHMDS (28.8 mL of a 1 M solution in THF, 28.8 mmol, 2 mol equiv) was diluted with diethyl ether (132 mL) then cooled to −78 °C. A solution of ketone **10**[12] (3.00 g, 14.40 mmol) in diethyl ether (12 mL) was then added to the reaction mixture via syringe pump at the rate of 15 mL/h. After addition was complete, the resulting mixture was stirred at −78 °C for 2.5 h then methyl cyanoformate (Mander's reagent) (2.45 g or 2.30 mL, 28.8 mmol, 2 mol equiv) was added via syringe pump at 0.45 mL/h. The ensuing mixture was stirred at −78 °C for 0.5 h after which it was poured into dichloromethane/water (300 mL of a 1:1 v/v mixture). The separated aqueous phase was extracted with dichloromethane (3×100 mL) and the combined organic layers were washed with brine (1×150 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The orange oil thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.2) gave *β-ketoester **11*** (2.56 g, 67%) as a white, crystalline solid. This material was used in the subsequent steps of the synthesis (see below). For the purposes of analysis a sample of this material was recrystallised (ethyl acetate/hexane) to give colourless crystals, mp=115–116 °C, $[\alpha]_D$ +210.0 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 266.1163; C, 63.43; H, 6.91. $C_{14}H_{18}O_5$ requires $M^{+\bullet}$, 266.1154; C, 63.15; H, 6.81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (br dd, *J*=8.1 and 6.4 Hz, 1H), 5.71 (br dt, *J*=8.1 and 1.5 Hz, 1H), 4.49 (br dd, *J*=7.1 and 3.4 Hz, 1H), 4.08 (dd, *J*=7.1 and 1.5 Hz, 1H), 3.71 (s, 3H), 3.46–3.41 (complex m, 1H), 2.92 (d, *J*=1.6 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.0 (C), 167.8 (C), 133.0 (CH), 129.2 (CH), 110.9 (C), 79.4 (CH), 78.1 (CH), 54.6 (C), 52.8 (CH_3), 50.4 (CH), 38.3 (CH), 25.3 (CH_3), 25.0 (CH_3), 14.6 (CH_3); IR ν_{max} (KBr) 2979, 2949, 2937, 2891, 1747, 1725, 1374, 1262, 1243, 1207, 1163, 1088, 1063, 1034, 973, 714 cm^{-1}; MS (EI, 70 eV) *m*/*z* 266 ($M^{+\bullet}$, 48%), 251 [$(M-CH_3^{\bullet})^+$, 45], 235 (24), 176 (100), 148 (93), 121 (71), 108 (69), 100 (89), 91 (63), 85 (65), 43 (68).

*3.2.2. Compound **12**. Method A*: A solution of β-ketoester **11** (101 mg, 380 μmol) in ethanol (17.4 mL) was cooled to 0 °C then treated, in one portion, with sodium borohydride (14.4 mg, 380 μmol, 1 mol equiv). The ensuing mixture was stirred at 0 °C for 0.5 h then allowed to warm to 18 °C. After 1 h at this temperature the reaction mixture was treated with ammonium chloride (5 mL of a saturated aqueous solution) and, after a further 5 min, with distilled water (50 mL) then concentrated under reduced pressure to ca. 1/3 of its original volume. The residue so obtained was diluted with dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic phases were then washed with brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A [R_f=0.4(4) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] yielded an inseparable 1:1.7 mixture of *compounds **12*** and *C8,C9-di-epi-**12*** (25 mg, 24%) as a clear, colourless oil. Found: $M^{+\bullet}$, 268.1306. $C_{14}H_{20}O_5$ requires $M^{+\bullet}$, 268.1311. ^{1}H NMR (300 MHz, $CDCl_3$) δ (compound **12**) spectrum identical with that derived from a pure sample (see below); ^{1}H NMR (300 MHz, $CDCl_3$) δ (compound C8,C9-di-*epi*-**12**) 6.03 (dd, *J*=8.1 and 6.0 Hz, 1H), 5.78–5.70 (complex m, 1H), 4.40 (ddd, *J*=7.3, 3.2 and 0.8 Hz, 1H), 4.35 (dd, *J*=7.3 and 0.8 Hz, 1H), 3.79 (br d, *J*=4.4 Hz, 1H), 3.69 (s, 3H), 3.22–3.14 (complex m, 1H), 2.28 (dd, *J*=4.4 and 1.8 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H) (signal due to OH proton obscured or overlapping); ^{13}C NMR (75 MHz, $CDCl_3$) δ (compound **12**) spectrum identical with that derived from a pure sample (see below); ^{13}C NMR (75 MHz, $CDCl_3$) δ (compound C8,C9-di-*epi*-**12**) 173.7 (C), 134.9 (CH), 129.7 (CH), 108.5 (C), 78.6 (CH), 77.7 (CH), 75.0 (CH), 52.3 (CH_3), 49.9 (CH), 43.9 (C), 37.5 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.7 (CH_3); MS (EI, 70 eV) *m*/*z* 268 ($M^{+\bullet}$, 2%), 253 [$(M-CH_3^{\bullet})^+$, 54], 133 (100), 109 (73), 108 (91), 105 (90), 100 (86), 43 (85).

Concentration of fraction B [R_f=0.4(1) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] gave *compound C9-epi-**12*** (56 mg, 58%) as a white, crystalline solid, mp=84–86 °C, $[\alpha]_D$ +26.5 (*c* 0.9, $CHCl_3$). Found: $(M-CH_3^{\bullet})^+$, 253.1076. $C_{14}H_{20}O_5$ requires $(M-CH_3^{\bullet})^+$, 253.1076. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35–6.29 (m, 1H), 5.74 (dd, *J*=8.2 and 1.2 Hz, 1H), 4.17 (dd, *J*=7.2 and 3.6 Hz, 1H), 3.83 (dd, *J*=7.2 and 1.2 Hz, 1H), 3.72 (d, *J*=8.6 Hz, 1H), 3.67 (s, 3H), 3.11–3.06 (complex m, 1H), 2.75 (d, *J*=8.6 Hz, 1H), 2.10 (br s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 131.9 (CH), 131.5 (CH), 109.6 (C), 80.3 (CH), 78.3 (CH), 71.8 (CH), 51.9 (CH_3), 47.8 (CH), 44.9 (C), 36.2 (CH), 25.3 (CH_3), 24.9 (CH_3), 18.2 (CH_3); IR ν_{max} (KBr) 3481, 2977, 2934, 2876, 1737, 1454, 1437, 1371, 1346, 1260, 1203, 1171, 1080, 1056, 1031, 883, 836, 731 cm^{-1}; MS (EI, 70 eV) *m*/*z* 268 ($M^{+\bullet}$, <1%), 253 [$(M-CH_3^{\bullet})^+$, 26], 133 (63), 109 (61), 108 (100), 105 (47), 80 (43), 43 (40).

*Method B (epimerisation of compound C9-epi-**12**)*: DBU (58 μL, 220 μmol) was added to a solution of compound C9-*epi*-**12** (59 mg, 220 μmol) in benzene (1.1 mL) and the reaction mixture heated at 72 °C for 21 h then cooled to 18 °C and diluted with dichloromethane (10 mL). The solution thus obtained was washed with HCl (2×10 mL of a 2 M aqueous solution), sodium bicarbonate (1×10 mL of a saturated aqueous solution) and brine (1×10 mL) before being dried, filtered and concentrated under reduced pressure. The resulting light-yellow solid (52 mg), which was comprised of a 1:3.4 mixture of β-hydroxyesters C9-*epi*-**12** and **12** (as determined by ^{1}H NMR analysis), was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A [R_f=0.4(4) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] yielded *compound **12*** (29 mg, 67% at 73% conversion) as a white, crystalline solid, mp=132.2–132.4 °C, $[\alpha]_D$ +47.9 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 268.1312; C, 62.69; H, 7.54. $C_{14}H_{20}O_5$ requires $M^{+\bullet}$, 268.1311; C, 62.67; H, 7.51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (ddd, *J*=8.1, 6.7 and 0.8 Hz, 1H), 5.77 (dd, *J*=8.1 and 1.2 Hz, 1H), 4.23 (ddd, *J*=7.3, 3.4 and 1.2 Hz, 1H), 3.91 (dd, *J*=3.3 and 1.2 Hz, 1H), 3.87 (dd, *J*=7.4 and 1.2 Hz, 1H), 3.74 (s, 3H), 3.20–3.15 (complex m, 1H), 2.33 (t, *J*=3.4 Hz, 1H), 1.59 (s, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C), 133.4 (CH), 131.2 (CH), 109.5 (C), 80.6 (CH), 75.7 (CH), 73.0 (CH), 52.4 (CH), 52.3 (CH_3), 44.9 (C), 36.4 (CH), 25.4 (CH_3), 24.9 (CH_3), 17.8 (CH_3); IR ν_{max} (KBr) 3461, 2976, 2927, 2876, 1731, 1374, 1266, 1248, 1206, 1163, 1078, 1066, 1029, 882, 730 cm^{-1}; MS (EI, 70 eV) *m*/*z* 268 ($M^{+\bullet}$, 8%), 253 [$(M-CH_3^{\bullet})^+$, 49], 133 (100), 109 (64), 108 (63), 105 (69), 100 (67), 43 (71).

Concentration of fraction B [R_f=0.4(1) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] afforded β-hydroxyester C9-*epi*-**12** (16 mg, 27% recovery) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

*3.2.3. Compound **14**. Step i*: Triethylamine (2.27 g, 22.44 mmol, 1.5 mol equiv) was added to a magnetically stirred solution of a ca. 4:1 mixture[34] of alcohols **12** and C8,C9-di-*epi*-**12** (4.01 g, 14.96 mmol) in dichloromethane (75 mL) and the resulting mixture cooled to 0 °C then treated, dropwise over 5 min, with methanesulfonyl chloride (1.89 g, 16.46 mmol, 1.1 mol equiv). The ensuing mixture was stirred at 0 °C for 1 h then at 18 °C for 4 h after which it was diluted with dichloromethane (25 mL). The resulting solution was washed with ice-cold water (1×100 mL), hydrochloric acid (1×100 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1×100 mL of a saturated aqueous solution) and brine (1×100 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to give an off-white solid

(4.89 g). This material, which was comprised (as determined by ^{1}H NMR analysis) of a ca. 4:1 mixture of the *mesylates of alcohols* ***12*** (viz. **13**) and *C8,C9-di-epi-**12***, was used directly in the step ii of the reaction sequence.

Step ii: DBU (2.40 mL, 16.07 mmol, 2.6 mol equiv) was added to a solution of the above-mentioned mixture of mesylates (2.14 g, 6.18 mmol) in benzene (30 mL). The resulting mixture was heated to 72 °C for 15 h then cooled to 18 °C and diluted with dichloromethane (20 mL). The ensuing solution was washed with hydrochloric acid (1×50 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1×50 mL of a saturated aqueous solution) and brine (1×50 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (1.62 g) thus obtained was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.8) then gave *compound **14*** (1.42 g, 92%) as a light-yellow oil, $[\alpha]_D$ +43.7 (*c* 1, $CHCl_3$). Found: $(M-CH_3^{\bullet})^+$, 235.0968. $C_{14}H_{18}O_4$ requires $(M-CH_3^{\bullet})^+$, 235.0970. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.34–6.28 (complex m, 1H), 5.99–5.95 (complex m, 1H), 4.30–4.25 (complex m, 2H), 3.93–3.89 (complex m, 1H), 3.71 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 150.1 (CH), 138.1 (C), 136.2 (CH), 132.1 (CH), 113.2 (C), 82.9 (CH), 79.9 (CH), 51.7 (CH), 47.7 (C), 41.7 (CH_3), 25.8 (CH_3), 25.5 (CH_3), 19.0 (CH_3); IR ν_{max} (KBr) 2977, 2949, 2934, 2905, 1718, 1456, 1437, 1380, 1371, 1263, 1242, 1211, 1162, 1058, 1037, 881, 755, 744, 717 cm^{-1}; MS (EI, 70 eV) *m*/*z* 235 [$(M-CH_3^{\bullet})^+$, 33%], 163 (90), 119 (75), 100 (96), 91 (64), 85 (100), 43 (85).

*3.2.4. Compound **15**. Method A*: A solution of α,β-unsaturated ester **14** (897 mg, 3.59 mmol) in THF/MeOH (124 mL of a 7:1 v/v mixture) was cooled to 0 °C and sodium borohydride (489 mg, 12.93 mmol, 3.6 mol equiv) was then added in one portion. The ensuing mixture was stirred at 0 °C to 18 °C for 4.5 h then re-cooled to 0 °C and quenched with ammonium chloride (100 mL of a saturated aqueous solution). The resulting mixture was extracted with dichloromethane (3×50 mL) and the combined organic extracts were washed with brine (1×100 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A [R_f=0.8(4) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] gave *compound **15*** (333 mg, 37%) as a clear, colourless oil, $[\alpha]_D$ −1.6 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 252.1357. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (ddd, *J*=8.1, 6.3 and 0.9 Hz, 1H), 5.83 (dd, *J*=8.1 and 0.9 Hz, 1H), 4.22 (ddd, *J*=7.2, 3.3 and 0.9 Hz, 1H), 3.88 (dd, *J*=7.2 and 1.2 Hz, 1H), 3.69 (s, 3H), 3.16–3.10 (complex m, 1H), 2.47 (ddd, *J*=11.4, 5.4 and 3.0 Hz, 1H), 1.65 (dd, *J*=13.5 and 5.4 Hz, 1H), 1.31 (dd, *J*=13.5 and 11.4 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 136.7 (CH), 130.0 (CH), 107.9 (C), 82.6 (CH), 76.1 (CH), 52.0 (CH_3), 40.8 (CH), 38.5 (C), 37.3 (CH), 31.4 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2976, 2955, 2936, 2900, 2873, 1733, 1458, 1435, 1374, 1343, 1297, 1265, 1239, 1205, 1165, 1070, 1055, 1021, 997, 885, 724 cm^{-1}; MS (EI, 70 eV) *m*/*z* 252 ($M^{+\bullet}$, 13%), 237 [$(M-CH_3^{\bullet})^+$, 44], 221 [$(M-CH_3O^{\bullet})^+$, 16], 194 (66), 135 (100), 134 (60), 117 (55), 105 (55), 91 (64).

Concentration of fraction B [R_f=0.7(9) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] yielded *compound C9-epi-**15*** (398 mg, 44%) as a clear, colourless oil, $[\alpha]_D$ −26.2 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 252.1363. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dd, *J*=8.1 and 6.3 Hz, 1H), 5.88 (dd, *J*=8.1 and 0.6 Hz, 1H), 4.24 (ddd, *J*=7.2, 3.3 and 0.9 Hz, 1H), 3.84 (dd, *J*=7.2 and 1.2 Hz, 1H), 3.65 (s, 3H), 3.23–3.18 (complex m, 1H), 2.50 (ddd, *J*=10.2, 5.1 and 2.4 Hz, 1H), 1.59 (dd, *J*=13.5 and 5.1 Hz, 1H), 1.39 (dd, *J*=13.5 and 10.2 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (C), 136.9 (CH), 127.8 (CH), 108.6 (C), 82.7 (CH), 78.8 (CH), 52.0 (CH_3), 39.6 (CH), 38.1 (C), 37.5 (CH), 32.3 (CH_2), 25.5 (CH_3), 25.0 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2971, 2956, 2931, 2873, 1738, 1373, 1285, 1254, 1203, 1167, 1063, 885, 714 cm^{-1}; MS (EI, 70 eV) *m*/*z* 252 ($M^{+\bullet}$, 7%), 237 [$(M-CH_3^{\bullet})^+$, 61], 221 [$(M-CH_3O^{\bullet})^+$, 27], 194 (84), 162 (84), 135 (100), 134 (83), 117 (70), 105 (70), 100 (81), 93 (70).

*Method B (epimerisation of compound C9-epi-**15**)*: A solution of ester C9-*epi*-**15** (368 mg, 1.46 mmol) in MeOH (27 mL) was cooled to 0 °C then sodium methoxide [generated from NaH (105 mg, 4.38 mmol, 3 mol equiv) and MeOH (18 mL)] was added. After 5 min, the cooling bath was removed and the reaction mixture heated to 70 °C for 24 h then allowed to cool to 18 °C and quenched with ammonium chloride (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×20 mL) then the combined organic phases were washed with brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:7:12 v/v/v MeOH/ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A [R_f=0.8(4) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] gave ester **15** (62 mg, 36% at 47% conversion) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B [R_f=0.7(9) in 1:7:12 v/v/v MeOH/ethyl acetate/hexane] afforded ester C9-*epi*-**15** (196 mg, 53% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

*3.2.5. Compounds **16** and **17**. Method A (reduction of ester **15**)*: A magnetically stirred solution of ester **15** (50 mg, 198 μmol) in dichloromethane (5.20 mL) was cooled to −78 °C then DIBAL (0.34 mL of a 1 M solution in hexane, 340 μmol, 1.7 mol equiv) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 1.25 h then quenched with potassium sodium tartrate (2 mL of a saturated aqueous solution), warmed to 18 °C and stirred at this temperature for 15 h. The separated aqueous layer was extracted with dichloromethane (3×2 mL) and the combined organic phases were then dried (magnesium sulfate), filtered and concentrated under reduced pressure to yield a clear, colourless oil (46 mg). Subjection of this material to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.4 in 1:4 v/v ethyl acetate/hexane) gave *aldehyde **17*** (13 mg, 30%) as a white, crystalline solid, mp=59–62 °C, $[\alpha]_D$ −31.0 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 222.1253; C, 70.05; H, 8.00. $C_{13}H_{18}O_3$ requires $M^{+\bullet}$, 222.1256; C, 70.25; H, 8.16%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.16 (dd, *J*=8.1 and 6.8 Hz, 1H), 5.88 (d, *J*=8.1 Hz, 1H), 4.05 (ddd, *J*=7.2, 3.2 and 1.0 Hz, 1H), 3.78 (dd, *J*=7.2 and 1.0 Hz, 1H), 3.29–3.27 (complex m, 1H), 2.47 (ddd, *J*=11.2, 5.4 and 2.9 Hz, 1H), 1.70 (dd, *J*=13.6 and 5.4 Hz, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (dd, *J*=13.6 and 11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4 (CH), 137.5 (CH), 129.5 (CH), 108.1 (C), 82.5 (CH), 75.9 (CH), 49.5 (CH), 38.8 (C), 35.4 (CH), 28.1 (CH_2), 25.4 (CH_3), 24.9 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2975, 2955, 2934, 2872, 1722, 1458, 1373, 1264, 1254, 1208, 1165, 1135, 1071, 1058, 971, 884, 824, 729, 699 cm^{-1}; MS (EI, 70 eV) *m*/*z* 223 [$(M+H)^+$, 15%], 222 ($M^{+\bullet}$, 5), 207 [$(M-CH_3^{\bullet})^+$, 46], 164 (63), 135 (98), 117 (65), 93 (67), 92 (100), 91 (63), 43 (75).

Concentration of fraction B (R_f=0.1 in 1:4 v/v ethyl acetate/hexane) afforded *alcohol **16*** (25 mg, 57%) as a clear, colourless oil, $[\alpha]_D$ −17.3 (*c* 0.9, $CHCl_3$). Found: $(M-CH_3^{\bullet})^+$, 209.1179. $C_{13}H_{20}O_3$ requires $(M-CH_3^{\bullet})^+$, 209.1178. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, *J*=8.2 and 6.9 Hz, 1H), 5.80 (d, *J*=8.2 Hz, 1H), 4.39 (dd, *J*=7.3 and 3.2 Hz, 1H), 3.79 (d, *J*=7.3 Hz, 1H), 3.64–3.47 (complex m, 2H), 2.96–2.92 (complex m, 1H), 1.85–1.74 (complex m, 2H), 1.35 (dd, *J*=13.3 and 11.1 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 0.69 (dd, *J*=13.3 and 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (CH), 131.9 (CH), 107.7 (C), 83.1 (CH), 75.6 (CH), 65.0 (CH_2), 38.6 (CH), 38.4

(C), 35.9 (CH), 33.1 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3417, 3044, 2970, 2933, 2869, 1457, 1374, 1269, 1246, 1207, 1165, 1075, 1058, 1028, 885, 730, 705, 691, 513 cm^{-1}; MS (EI, 70 eV) *m/z* 209 [$(M-CH_3^{\bullet})^+$, 25%], 166 (60), 135 (100), 93 (63).

*Method B (oxidation of alcohol **16**)*: A magnetically stirred solution of alcohol **16** (980 mg, 4.37 mmol) in dichloromethane/DMSO (62 mL of a 1:1 v/v mixture) was cooled to 0 °C then treated with triethylamine (3 mL, 21.85 mmol, 5 mol equiv) and sulfur trioxide·pyridine complex (2.09 g, 13.11 mmol, 3 mol equiv). The ensuing mixture was stirred at 0 °C for 1 h, diluted with diethyl ether (50 mL) then washed with hydrochloric acid (1×10 mL of a 1 M aqueous solution), sodium hydrogen carbonate (1×10 mL of a saturated aqueous solution) and brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-orange oil (922 mg) was subjected to column chromatography (silica, 1:5:14 v/v/v MeOH/ethyl acetate/hexane elution) and gave, after concentration of the appropriate fractions, aldehyde **17** (497 mg, 51%) as a white, crystalline solid that was identical, in all respects, with an authentic sample.

*Method C (reduction of ester C9-epi-**15** and epimerisation of the resulting aldehyde C9-epi-**17**). Step i*: A magnetically stirred solution of ester C9-*epi*-**15** (100 mg, 0.40 mmol) in dichloromethane (10 mL) was cooled to −78 °C then DIBAL (0.48 mL of a 1 M solution in hexane, 0.48 mmol, 1.2 mol equiv) was added dropwise over 10 min and the ensuing mixture then stirred at −78 °C for 2 min before being quenched with potassium sodium tartrate (5 mL of a saturated solution), warmed to 18 °C and stirred at this temperature for 5 h. The separated aqueous phase was extracted with dichloromethane (3×10 mL) then the combined organic phases were washed with brine (1×5 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to column chromatography (silica, 1:4→1:1 v/v ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.4 in 1:4 v/v ethyl acetate/hexane) gave aldehyde **17** (4 mg, 5%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f=0.3 in 1:4 v/v ethyl acetate/hexane) afforded *compound C9-epi-**17*** (58 mg, 65%) as a clear, colourless oil, $[\alpha]_D$ +15.3 (*c* 1.15, $CHCl_3$). Found: $(M-CH_3^{\bullet})^+$, 207.1026. $C_{13}H_{18}O_3$ requires $(M-CH_3^{\bullet})^+$, 207.1021. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, *J*=1.1 Hz, 1H), 5.95–5.86 (complex m, 2H), 4.32 (ddd, *J*=7.2, 3.3 and 1.0 Hz, 1H), 3.89 (dd, *J*=7.2 and 1.0 Hz, 1H), 3.25–3.20 (complex m, 1H), 2.44 (dddd, *J*=9.9, 4.7, 2.2 and 1.0 Hz, 1H), 1.64 (dd, *J*=13.6 and 4.7 Hz, 1H), 1.31 (dd, *J*=13.6 and 9.9 Hz, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9 (CH), 137.9 (CH), 127.1 (CH), 108.7 (C), 83.1 (CH), 79.0 (CH), 48.0 (CH), 38.4 (C), 35.9 (CH), 29.6 (CH_2), 25.4 (CH_3), 25.0 (CH_3), 21.5 (CH_3); IR ν_{max} (KBr) 2975, 2954, 2932, 2873, 1726, 1458, 1374, 1277, 1251, 1209, 1166, 1121, 1068, 1023, 884, 728 cm^{-1}; MS (EI, 70 eV) *m/z* 223 [$(M+H)^+$, 20%], 222 ($M^{+\bullet}$, 1), 207 [$(M-CH_3^{\bullet})^+$, 16], 135 (79), 117 (52), 100 (51), 93 (49), 91 (63), 85 (46), 43 (100).

Step ii: DBU (26 μL, 171 μmol, 1 mol equiv) was added to a magnetically stirred solution of aldehyde C9-*epi*-**17** (38 mg, 171 μmol) in benzene (1 mL) and the resulting mixture heated at 70 °C for 16 h, then cooled to 18 °C and diluted with dichloromethane (4 mL) before being washed successively with hydrochloric acid (1×2 mL of a 2 M aqueous solution), sodium hydrogen carbonate (1×2 mL of a saturated aqueous solution) and brine (1×2 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. ^{1}H NMR analysis of the resulting yellow oil (33 mg) established that this was comprised of a ca. 1:4.8 mixture of aldehydes C9-*epi*-**17** and **17**.

*3.2.6. Compound **18**.* $MePPh_3Br$ was dried at 100 °C for 15 h then cooled and stored under nitrogen. Some of the dried material (2.05 g, 5.73 mmol, 3.0 mol equiv) was stirred in THF (19.1 mL) then cooled to 0 °C and treated, dropwise over 0.5 h, with NaHMDS (4.58 mL of a 1 M solution in THF, 4.58 mmol, 2.4 mol equiv). The resulting mixture was stirred at 0 °C for 2.5 h and the bright-yellow reaction mixture so-formed was treated, dropwise over 0.5 h, with a solution of aldehyde **17** (424 mg, 1.91 mmol) in THF (8.50 mL). Stirring was continued at 0 °C for 2 h then the reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and diluted with dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (3×20 mL) then the combined organic phases were washed with brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil thus obtained was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.5) then gave *olefin **18*** (253 mg, 60%) as a clear, colourless oil, $[\alpha]_D$ −45.3 (*c* 0.55, $CHCl_3$). Found: $(M-H^{\bullet})^+$, 219.1382. $C_{14}H_{20}O_2$ requires $(M-H^{\bullet})^+$, 219.1385. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (ddd, *J*=7.8, 6.3 and 1.0 Hz, 1H), 5.83 (ddd, *J*=17.2, 10.3 and 6.9 Hz, 1H), 5.79 (dd, *J*=7.8 and 1.0 Hz, 1H), 5.11–5.01 (complex m, 2H), 4.36 (ddd, *J*=7.4, 3.3 and 1.0 Hz, 1H), 3.81 (dd, *J*=7.4 and 1.0 Hz, 1H), 2.80–2.74 (complex m, 1H), 2.29–2.18 (complex m, 1H), 1.39 (dd, *J*=13.4 and 11.0 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.01 (dd, *J*=13.4 and 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0 (CH), 135.4 (CH), 131.9 (CH), 114.6 (CH_2), 107.6 (C), 83.3 (CH), 75.9 (CH), 40.8 (CH), 39.4 (CH), 38.7 (C), 34.6 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 21.8 (CH_3); IR ν_{max} (KBr) 3045, 2976, 2952, 2937, 2903, 2869, 1638, 1457, 1378, 1371, 1262, 1233, 1207, 1165, 1069, 1056, 995, 912, 885, 861, 809, 729, 707 cm^{-1}; MS (EI, 70 eV) *m/z* 220 ($M^{+\bullet}$, 18%), 219 [$(M-H^{\bullet})^+$, 38], 205 [$(M-CH_3^{\bullet})^+$, 11], 163 (68), 105 (64), 57 (100), 43 (46).

*3.2.7. Compound **19**.* DOWEX-50 was activated by washing it twice with MeOH, twice with hydrochloric acid (2 M aqueous solution) and, finally, twice with water. The activated resin (269 mg) thus obtained was added to a magnetically stirred solution of acetonide **18** (269 mg, 1.22 mmol) in MeOH/water (6 mL of a 5:1 v/v mixture) and the resulting suspension heated in an oil bath maintained at 110 °C. After 6 days the reaction mixture was cooled, filtered and the DOWEX washed three times with MeOH. The combined filtrates were concentrated under reduced pressure. The resin was also washed twice with dichloromethane and the filtrate added to the concentrated residue, which was then washed with sodium chloride (1×10 mL of a 1.5 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×10 mL) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The orange oil (201 mg) thus obtained was subjected to column chromatography (silica, 1:4→1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f=0.5 in 1:1 v/v ethyl acetate/hexane) then gave diol **19** (146 mg, 66%) as a clear, colourless oil, $[\alpha]_D$ −76.1 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 180.1144. $C_{11}H_{16}O_2$ requires $M^{+\bullet}$, 180.1150. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (ddd, *J*=8.1, 7.0 and 0.8 Hz, 1H), 5.90 (dd, *J*=8.1 and 0.8 Hz, 1H), 5.82 (ddd, *J*=17.0, 10.3 and 6.7 Hz, 1H), 5.10–5.01 (complex m, 2H), 4.05 (ddd, *J*=7.6, 2.5 and 0.8 Hz, 1H), 3.44 (dd, *J*=7.6 and 0.8 Hz, 1H), 2.80 (br s, 2H), 2.67–2.62 (complex m, 1H), 2.20–2.09 (complex m, 1H), 1.38 (dd, *J*=13.5 and 11.2 Hz, 1H), 1.23 (s, 3H), 1.06 (dd, *J*=13.5 and 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8 (CH), 136.6 (CH), 133.4 (CH), 114.9 (CH_2), 75.6 (CH), 67.9 (CH), 43.8 (CH), 40.2 (C), 40.0 (CH), 35.3 (CH_2), 21.6 (CH_3); IR ν_{max} (KBr) 3374, 2928, 2869, 1637, 1457, 1403, 1372, 1065, 1031, 994, 959, 910, 726, 703, 601 cm^{-1}; MS (EI, 70 eV) *m/z* 180 ($M^{+\bullet}$, 5%), 120 (97), 105 (100), 92 (72), 91 (53).

*3.2.8. Compound **20**.* A magnetically stirred solution of diol **19** (146 mg, 0.81 mmol) in dichloromethane (19.50 mL) was cooled to 0 °C then *p*-TsOH·H_2O (339 mg, 1.78 mmol, 2.2 mol equiv) was

added followed by 4-AcNH-TEMPO (380 mg, 1.78 mmol, 2.2 mol equiv) and the mixture thus obtained was warmed to 18 °C. After 17 h at the latter temperature, the reaction mixture was quenched with sodium hydrogen carbonate (10 mL of a saturated aqueous solution) and extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting orange semi-solid (533 mg) was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.3) then gave *acyloin* ***20*** (118 mg, 81%) as a clear, colourless oil, $[\alpha]_D$ +346.5 (*c* 0.65, $CHCl_3$). Found: $M^{+\bullet}$, 178.0986. $C_{11}H_{14}O_2$ requires $M^{+\bullet}$, 178.0994. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (dd, *J*=7.7 and 6.6 Hz, 1H), 6.11 (d, *J*=7.7 Hz, 1H), 5.68 (ddd, *J*=17.0, 10.3 and 7.3 Hz, 1H), 5.10–4.98 (complex m, 2H), 3.37 (s, 1H), 3.20 (dd, *J*=6.6 and 2.2 Hz, 1H), 2.73 (br s, 1H), 2.61–2.50 (complex m, 1H), 1.80 (dd, *J*=13.4 and 11.7 Hz, 1H), 1.43 (dd, *J*=13.4 and 4.7 Hz, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6 (C), 140.7 (CH), 140.5 (CH), 126.9 (CH), 115.1 (CH_2), 75.1 (CH), 52.7 (CH), 42.2 (C), 39.0 (CH), 37.9 (CH_2), 20.0 (CH_3); IR ν_{max} (KBr) 3448, 2970, 2954, 2931, 2869, 1725, 1639, 1457, 1115, 1068, 990, 915, 776, 709 cm^{-1}; MS (EI, 70 eV) *m*/*z* 178 ($M^{+\bullet}$, 8%), 106 (72), 105 (100), 91 (71), 79 (70), 43 (73), 39 (64), 32 (67).

3.2.9. Compound ***21***. A magnetically stirred solution of acyloin **20** (118 mg, 0.66 mmol) in dichloromethane (21 mL) was cooled to 0 °C then treated with triethylamine (0.46 mL, 3.30 mmol, 5 mol equiv), DMAP (9 mg, 0.07 mmol, 10 mol %) and benzoyl chloride (0.15 mL, 1.32 mmol, 2 mol equiv). The ensuing mixture was allowed to warm to 18 °C and after 16 h it was quenched with sodium hydrogen carbonate (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×20 mL) then the combined organic extracts were washed with brine (1×10 mL) before being dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow semi-solid (301 mg) thus obtained was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.6) gave *keto-ester* ***21*** (199 mg, 0.71 mmol, quant.) as a clear, colourless oil, $[\alpha]_D$ +255.9 (*c* 1, $CHCl_3$). Found: $M^{+\bullet}$, 282.1255. $C_{18}H_{18}O_3$ requires $M^{+\bullet}$, 282.1256. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–7.98 (complex m, 2H), 7.59–7.52 (complex m, 1H), 7.46–7.39 (complex m, 2H), 6.32 (dd, *J*=7.8 and 6.7 Hz, 1H), 6.20 (d, *J*=7.8 Hz, 1H), 5.76 (ddd, *J*=17.2, 10.3 and 7.4 Hz, 1H), 5.16–5.05 (complex m, 2H), 5.08 (s, 1H), 3.26 (ddd, *J*=6.7, 2.9 and 1.1 Hz, 1H), 2.67–2.56 (complex m, 1H), 1.89 (dd, *J*=13.6 and 11.5 Hz, 1H), 1.62 (dd, *J*=13.6 and 4.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3 (C), 166.1 (C), 140.0 (CH), 139.8 (CH), 133.2 (CH), 129.9 (CH), 129.4 (C), 128.3 (CH), 127.6 (CH), 115.6 (CH_2), 74.5 (CH), 53.5 (CH), 41.3 (C), 39.5 (CH), 37.5 (CH_2), 20.1 (CH_3); IR ν_{max} (KBr) 2965, 2925, 2869, 2853, 1741, 1724, 1451, 1328, 1266, 1254, 1177, 1111, 1070, 1029, 921, 708 cm^{-1}; MS (EI, 70 eV) *m*/*z* 282 ($M^{+\bullet}$, 21%), 160 (37), 132 (62), 120 (41), 106 (76), 105 (100), 91 (30), 77 (89), 51 (43).

3.2.10. Compound ***22***. A magnetically stirred and deoxygenated solution of keto-ester **21** (186 mg, 0.66 mmol) and acetophenone (0.23 mL, 1.98 mmol, 3 mol equiv) in acetone (300 mL) was placed in a quartex immersion well photoreactor (Ace Glass Inc., 500 mL) equipped with a Pyrex filter. The mixture was subjected to irradiation, at 18 °C, with a Hanovia 450 W medium pressure mercury-vapour lamp. After 4.67 h the reaction mixture was removed from the photoreactor and concentrated under reduced pressure to give a yellow oil (459 mg) that was subjected to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f=0.5) yielded a mixture of acetophenone and the *C4-α-form of diquinane* ***22*** (49 mg) as a clear, colourless oil. Resubjection of the material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.2) then gave the *C4-α-form of diquinane* ***22*** (29 mg, 15%) as a clear, colourless oil, $[\alpha]_D$ +139.1 (*c* 0.9, $CHCl_3$). Found: $M^{+\bullet}$, 282.1260. $C_{18}H_{18}O_3$ requires $M^{+\bullet}$, 282.1256. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.02 (complex m, 2H), 7.60–7.54 (complex m, 1H), 7.47–7.40 (complex m, 2H), 5.82 (ddd, *J*=17.3, 10.4 and 5.6 Hz, 1H), 5.19–5.02 (complex m, 2H), 5.08 (br s, 1H), 3.46–3.35 (complex m, 1H), 2.61 (ddd, *J*=6.0, 5.1 and 1.0 Hz, 1H), 2.43 (dd, *J*=13.5 and 11.0 Hz, 1H), 2.35–2.30 (m, 1H), 2.24–2.22 (m, 1H), 1.89 (dt, *J*=13.5 and 1.4 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9 (C), 165.6 (C), 139.5 (CH), 133.2 (CH), 129.9 (CH), 129.5 (C), 128.4 (CH), 115.8 (CH_2), 83.5 (CH), 49.9 (C), 49.8 (CH_2), 43.0 (CH), 42.0 (CH), 39.8 (CH), 38.4 (CH), 19.3 (CH_3); IR ν_{max} (KBr) 2970, 2935, 2874, 1722, 1451, 1266 (br), 1177, 1107, 1094, 1069, 1026, 990, 957, 915, 852, 709, 668 cm^{-1}; MS (EI, 70 eV) *m*/*z* 282 ($M^{+\bullet}$, 2%), 160 (25), 132 (45), 106 (55), 105 (71), 91 (37), 77 (100).

Concentration of fraction B (R_f=0.5) gave the *C4-β-form of diquinane* ***22*** (30 mg, 17%) as a clear, colourless oil, $[\alpha]_D$ +60.2 (*c* 0.6, $CHCl_3$). Found: $M^{+\bullet}$, 282.1256. $C_{18}H_{18}O_3$ requires $M^{+\bullet}$, 282.1256. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (complex m, 2H), 7.61–7.55 (complex m, 1H), 7.48–7.42 (complex m, 2H), 5.80 (ddd, *J*=17.0, 10.3 and 7.0 Hz, 1H), 5.44 (t, *J*=1.5 Hz, 1H), 5.11 (dt, *J*=17.0 and 1.5 Hz, 1H), 5.01 (dt, 10.3 and 1.5 Hz, 1H), 3.45–3.35 (complex m, 1H), 2.37 (dd, *J*=5.9 and 4.8 Hz, 1H), 2.28 (dt, *J*=9.8 and 5.9 Hz, 1H), 2.12 (ddd, *J*=14.0, 11.0 and 1.5 Hz, 1H), 2.05–1.98 (complex m, 2H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1 (C), 165.4 (C), 139.2 (CH), 133.3 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 115.3 (CH_2), 82.1 (CH), 49.3 (C), 44.2 (CH), 43.5 (CH_2), 36.4 (CH), 35.8 (CH), 32.6 (CH), 24.3 (CH_3); IR ν_{max} (KBr) 2959, 1739, 1724, 1452, 1331, 1269, 1248, 1177, 1113, 1097, 1071, 1026, 1000, 916, 850, 709 cm^{-1}; MS (EI, 70 eV) *m*/*z* 282 ($M^{+\bullet}$, 11%), 160 (37), 132 (49), 106 (52), 105 (100), 77 (69).

3.2.11. Compound ***23***. A magnetically stirred solution of the C4-α- and β-epimeric forms of compound **22** (296 mg, 1.05 mmol) in THF (10.5 mL) containing MeOH (5.3 mL) was cooled to −78 °C then samarium(II) diiodide (23.1 mL of a 0.1 M solution in THF, 2.31 mmol, 2.2 mol equiv) was added dropwise over 0.5 h. Stirring was continued at −78 °C for 5 min then the reaction mixture was quenched with potassium carbonate (20 mL of a saturated aqueous solution) before being allowed to slowly warm to 18 °C. The separated aqueous phase was extracted with diethyl ether (3×50 mL) and the combined organic phases were washed with brine (1×20 mL) then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil (289 mg) thus obtained was subjected to column chromatography (silica, 1:39 v/v ethyl acetate/dichloromethane elution) and concentration of the appropriate fractions (R_f=0.5) gave *diquinane* ***23*** (93 mg, 54%) as a clear, colourless oil, $[\alpha]_D$ +74.0 (*c* 0.6, $CHCl_3$). Found: $M^{+\bullet}$, 162.1044. $C_{11}H_{14}O$ requires $M^{+\bullet}$, 162.1045. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J*=17.2, 10.3 and 5.8 Hz, 1H), 5.08 (dt, *J*=17.2 and 1.7 Hz, 1H), 4.97 (dt, *J* 10.3 and 1.7 Hz, 1H), 3.37–3.26 (complex m, 1H), 2.45 (ddd, *J*=6.3, 4.9 and 0.8 Hz, 1H), 2.33–2.22 (complex m, 2H), 2.20–2.04 (complex m, 2H), 1.96 (m, 1H), 1.63 (d, *J*=12.6 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5 (C), 139.9 (CH), 115.0 (CH_2), 55.0 (CH_2), 52.4 (CH_2), 46.3 (C), 43.4 (CH), 42.3 (CH), 39.6 (CH), 36.8 (CH), 25.7 (CH_3); IR ν_{max} (KBr) 2954, 2928, 2870, 1724, 1454, 1407, 1331, 1313, 1250, 1197, 1096, 989, 965, 914, 885, 871 cm^{-1}; MS (EI, 70 eV) *m*/*z* 162 ($M^{+\bullet}$, 11%), 120 (50), 105 (100), 77 (45).

3.2.12. Compound ***24***. A magnetically stirred solution of diquinane **23** (52 mg, 321 μmol) in acetone/water (2 mL of a 1:1 v/v mixture) was cooled to 0 °C then *N*-methylmorpholine *N*-oxide (45 mg, 385 μmol, 1.2 mol equiv) and osmium tetroxide (1.22 mL of a 0.1 M solution in *tert*-butanol, 122 μmol, 0.38 mol equiv) were added. The ensuing mixture was allowed to warm to 18 °C and after 4.5 h at

this temperature it was quenched with sodium hydrogensulfite (4 mL of a saturated aqueous solution) then stirred at 18 °C for another hour. The resulting mixture was diluted with diethyl ether (4 mL) and just enough water to dissolve any solids. Solid sodium chloride was then added to saturate the aqueous phase which, after separation, was extracted with diethyl ether (3×10 mL) then dichloromethane (3×10 mL). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. Subjection of the resulting clear, colourless oil to column chromatography (silica, ethyl acetate→1:9 v/v MeOH/ethyl acetate gradient elution) and concentration of the appropriate fractions (R_f=0.4 in 1:9 v/v methanol/ethyl acetate) then gave a 1:1 mixture of the *epimeric forms of diol* ***24*** (30 mg, 48%) as a clear, colourless oil. Found: $M^{+\bullet}$, 196.1098. $C_{11}H_{16}O_3$ requires $M^{+\bullet}$, 196.1099. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (dd, J=11.3 and 2.2 Hz, 0.5H), 3.66–3.58 (complex m, 0.5H), 3.50 (br s, 2H), 3.45 (dd, J=11.3 and 7.4 Hz, 0.5H), 3.40–3.30 (complex m, 1.5H), 2.71–2.55 (complex m, 1H), 2.54–2.48 (complex m, 1H), 2.43–2.30 (complex m, 1H), 2.27–1.80 (complex m, 5H), 1.37 (s, 1.5H), 1.36 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6 (C), 217.4 (C), 74.2 (CH), 74.1 (CH), 66.2 (CH_2), 65.4 (CH_2), 56.4 (CH_2), 56.0 (CH_2), 48.8 (CH_2), 48.6 (CH_2), 46.6 (C), 46.2 (C), 43.8 (2×CH), 42.9 (CH), 42.8 (CH), 39.3 (CH), 39.1 (CH), 37.1 (CH), 35.4 (CH), 25.9 (CH_3), 25.8 (CH_3); IR ν_{max} (KBr) 3405, 2951, 2928, 2871, 1709, 1454, 1408, 1379, 1360, 1335, 1312, 1254, 1200, 1161, 1101, 1076, 1041, 964, 920, 879, 813, 735 cm^{-1}; MS (EI, 70 eV) m/z 196 ($M^{+\bullet}$, 2%), 178 [$(M-H_2O^{\bullet})^+$, 14], 165 (75), 136 (96), 95 (94), 94 (88), 93 (100), 91 (77), 43 (75).

3.2.13. Compound ***25****.* Dibutyltin(IV) oxide (8 mg, 32 μmol, 20 mol %) then triethylamine (21 μL, 153 μmol, 1 mol equiv) were added to a magnetically stirred solution of a 1:1 mixture of the epimeric forms of diol **24** (30 mg, 153 μmol) in dichloromethane (0.45 mL). Stirring was continued at 18 °C for 10 min then a solution of *p*-toluenesulfonyl chloride (29 mg, 152 μmol, 1 mol equiv) in dichloromethane (ca. 0.25 mL) was added dropwise over 10 min. After 5 h at 18 °C, the reaction mixture was diluted with dichloromethane (0.4 mL) then filtered through a plug of Celite™ and the filtrate concentrated under reduced pressure to give a light-yellow oil (67 mg). This was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and thus affording three fractions, A, B and C.

Concentration of fraction A (R_f=0.4) yielded the *C1′S-epimeric form of mono-tosylate* ***25*** (9 mg, 17%) as a clear, colourless oil, $[\alpha]_D$ +26.4 (*c* 0.64, $CHCl_3$). Found: $M^{+\bullet}$, 350.1182. $C_{18}H_{22}O_5S$ requires $M^{+\bullet}$, 350.1188. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 2H), 7.36 (d, J=8.0 Hz, 2H), 4.17 (dd, J=10.4 and 4.6 Hz, 1H), 4.13 (dd, J=10.4 and 2.7 Hz, 1H), 3.56–3.50 (complex m, 1H), 2.77–2.71 (complex m, 1H), 2.49 (dd, J=5.9 and 5.3 Hz, 1H), 2.45 (s, 3H), 2.37 (ddd, J=17.8, 2.3 and 1.2 Hz, 1H), 2.26–2.12 (complex m, 2H), 1.94–1.88 (complex m, 1H), 1.85 (dd, J=9.8 and 5.3 Hz, 1H), 1.81 (d, J=13.4 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3 (C), 145.1 (C), 132.4 (C), 130.0 (CH), 128.0 (CH), 72.7 (CH_2), 71.4 (CH), 56.0 (CH_2), 48.6 (CH_2), 46.3 (C), 43.8 (CH), 42.3 (CH), 38.9 (CH), 34.6 (CH), 25.9 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3418, 2954, 2926, 2870, 1715, 1598, 1453, 1406, 1357, 1309, 1189, 1176, 1098, 1019, 972, 957, 917, 878, 855, 814, 667, 555 cm^{-1}; MS (EI, 70 eV) m/z 350 ($M^{+\bullet}$, 1%), 165 (31), 155 (33), 136 (100), 105 (45), 93 (51), 91 (80).

Concentration of fraction B (R_f=0.35) afforded a ca. 1:1.5 mixture of the C1′*S*- and C1′*R*-epimeric forms of mono-tosylate **25** (29 mg, 54%) as a clear, colourless oil.

Concentration of fraction C (R_f=0.3) gave *C1′R-epimeric form of mono-tosylate* ***25*** (3 mg, 6%) as a clear, colourless oil, $[\alpha]_D$ +25.7 (*c* 0.35, $CHCl_3$). Found: $M^{+\bullet}$, 350.1188. $C_{18}H_{22}O_5S$ requires $M^{+\bullet}$, 350.1188. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J=8.0 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 4.06 (dd, J=10.5 and 2.7 Hz, 1H), 3.90 (dd, J=10.5 and 6.3 Hz, 1H), 3.58–3.52 (complex m, 1H), 2.73–2.66 (complex m, 1H), 2.55–2.48 (complex m, 2H), 2.45 (s, 3H), 2.40 (dd, J 17.8 and 2.2 Hz, 1H), 2.18–2.02 (complex m, 3H), 1.99 (dd, J=9.5 and 5.2 Hz, 1H), 1.37 (s, 3H), 1.33 (d, J=13.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3 (C), 145.1 (C), 132.7 (C), 129.9 (CH), 127.9 (CH), 73.1 (CH_2), 71.3 (CH), 56.4 (CH_2), 48.6 (CH_2), 46.6 (C), 43.6 (CH), 42.1 (CH), 39.0 (CH), 35.7 (CH), 25.8 (CH_3), 21.7 (CH_3); IR ν_{max} (KBr) 3420, 2956, 2918, 2870, 2850, 1712, 1598, 1453, 1358, 1312, 1189, 1176, 1097, 972, 957, 946, 918, 880, 853, 815, 667, 555 cm^{-1}; MS (EI, 70 eV) m/z 350 ($M^{+\bullet}$, 5%), 165 (47), 136 (100), 93 (68), 91 (95), 43 (67), 32 (48).

3.2.14. Compounds ***26*** *and* ***27****. Method A*: A magnetically stirred solution of a ca. 1:1.5 mixture of the C1′*S*- and C1′*R*-epimeric forms of mono-tosylate **25** (29 mg, 83 μmol) in dichloromethane (2.9 mL) was cooled to 0 °C then triethylamine (58 μL, 414 μmol, 5 mol equiv) was added followed by DMAP (834 μg, 8.28 μmol, 10 mol %) and benzoyl chloride (20.7 μL, 166 μmol, 2 mol equiv). The resulting mixture was allowed to warm to 18 °C then stirred at this temperature for 14 h before being quenched with sodium hydrogen carbonate (1 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (5×2 mL) then the combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The clear, colourless oil (51 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f=0.5) gave *compound* ***27*** (15 mg, 40%) as a clear, colourless oil, $[\alpha]_D$ +14.2 (*c* 0.38, $CHCl_3$). Found: $M^{+\bullet}$, 454.1447. $C_{25}H_{26}O_6S$ requires $M^{+\bullet}$, 454.1450. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, J=8.3 and 1.2 Hz, 2H), 7.73 (d, J=8.3 Hz, 2H), 7.59–7.55 (complex m, 1H), 7.42 (dd, J=8.3 Hz, 2H), 7.20 (d, J=8.3 Hz, 2H), 4.98 (m, J=11.1 Hz, 1H), 4.44 (dd, J=11.2 and 2.6 Hz, 1H), 4.24 (dd, J=11.2 and 2.2 Hz, 1H), 3.24 (m, 1H), 2.54 (dd, J=5.9 and 5.3 Hz, 1H), 2.40 (dd, J=18.1 and 1.0 Hz, 1H), 2.34 (s, 3H), 2.30 (d, J=18.1 Hz, 1H), 2.20 (ddd, J=13.2, 10.7 and 2.0 Hz, 1H), 2.11–2.06 (complex m, 1H), 1.95 (dd, J=9.8 and 5.3 Hz, 1H), 1.55 (d, J=13.2 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8 (C), 165.5 (C), 144.9 (C), 133.3 (CH), 132.3 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.3 (CH), 127.9 (CH), 73.0 (CH), 69.7 (CH_2), 55.3 (CH_2), 48.7 (CH_2), 46.5 (C), 42.3 (CH), 41.1 (CH), 39.0 (CH), 34.0 (CH), 25.8 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2956, 2927, 1720, 1599, 1452, 1364, 1270, 1190, 1177, 1109, 1097, 1070, 1026, 962, 946, 922, 881, 814, 793, 714, 667, 554 cm^{-1}; MS (EI, 70 eV) m/z 454 ($M^{+\bullet}$, 4%), 149 (18), 118 (55), 105 (100), 91 (27), 77 (34), 57 (32), 43 (35).

Concentration of fraction B (R_f=0.4) afforded *compound* ***26*** (21 mg, 55%) as a white, crystalline solid, mp=134–139 °C. Found: $M^{+\bullet}$, 454.1448. $C_{25}H_{26}O_6S$ requires $M^{+\bullet}$, 454.1450. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.93 (complex m, 2H), 7.70–7.66 (complex m, 2H), 7.60–7.54 (complex m, 1H), 7.45–7.40 (complex m, 2H), 7.15–7.12 (complex m, 2H), 4.87 (dt, J=11.2 and 2.9 Hz, 1H), 4.31 (dd, J=11.4 and 2.9 Hz, 1H), 4.17 (dd, J=11.4 and 2.9 Hz, 1H), 3.34 (m, 1H), 2.51 (t, J=5.4 Hz, 1H), 2.44–2.30 (complex m, partially concealed, 1H), 2.34–2.24 (complex m, partially concealed, 1H), 2.30 (s, 3H), 2.15–2.07 (complex m, partially concealed, 1H), 2.07 (d, J=17.0 Hz, 1H), 1.87 (dd, J=10.2 and 5.4 Hz, 1H), 1.44 (d, J=13.2 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7 (C), 165.1 (C), 145.0 (C), 133.2 (CH), 132.1 (C), 129.9 (CH), 129.8 (CH), 129.5 (C), 128.2 (CH), 127.8 (CH), 73.2 (CH), 69.4 (CH_2), 56.2 (CH_2), 47.8 (CH_2), 46.5 (C), 42.1 (CH), 40.9 (CH), 38.9 (CH), 35.6 (CH), 25.8 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2956, 1723, 1599, 1451, 1361, 1312, 1266, 1189, 1176, 1109, 1096, 1069, 1025, 957, 946, 921, 884, 839, 814, 713, 667, 554 cm^{-1}; MS (EI, 70 eV) m/z 454 ($M^{+\bullet}$, 3%), 283 (16), 118 (72), 105 (100), 91 (36), 77 (41).

Method B: A magnetically stirred solution of the C1′*R*-epimeric form of mono-tosylate **25** (7 mg, 20 μmol) in dichloromethane (0.7 mL) was treated in the same way as described immediately above. The clear, colourless oil (5 mg) thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate

fractions (R_f=0.5) then gave *compound* ***27*** (3 mg, 35%) as a white, crystalline solid. This material was identical, in all respects, with an authentic sample.

3.2.15. Compound ***28***. A solution of diquinane **26** (21 mg, 46 μmol) in THF/MeOH (0.9 mL of a 2:1 v/v mixture) was cooled to −78 °C and samarium(II) diiodide (0.55 mL of a 0.1 M solution in THF, 55 μmol, 1.2 mol equiv) was added dropwise over 5 min. The resulting mixture was stirred at −78 °C until the initial blue colour associated with the reaction mixture had turned yellow (ca. 25 min) then more samarium(II) diiodide (0.55 mL of a 0.1 M solution in THF, 55 μmol, 1.2 mol equiv) was added dropwise over 15 min and the reaction mixture warmed to 0 °C at which point sufficient additional samarium(II) diiodide was added to re-establish a deep-blue colour. The reaction mixture was then warmed to 18 °C and stirred at this temperature until the blue colour had faded. This procedure was repeated twice more at 18 °C until the starting material had been consumed as determined by TLC analysis. The reaction mixture was then quenched with potassium carbonate (1 mL of a saturated aqueous solution) and the separated aqueous phase extracted with diethyl ether (3×5 mL) and then with dichloromethane (3×5 mL). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.6) then gave *diquinane* ***28*** (11 mg, 52%) as a clear, colourless oil. Found: $M^{+\bullet}$, 456.1606. $C_{25}H_{28}O_6S$ requires $M^{+\bullet}$, 456.1607. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–7.88 (complex m, 2H), 7.74–7.68 (complex m, 2H), 7.62–7.55 (complex m, 1H), 7.47–7.40 (complex m, 2H), 7.21–7.15 (complex m, 2H), 5.16–5.06 (m, 1H), 4.22 (dd, J=11.1 and 3.4 Hz, 1H), 4.15 (dd, J=11.1 and 4.6 Hz, 1H), 2.74–2.57 (complex m, 1H), 2.52 (ddd, J=18.8, 8.8 and 1.2 Hz, 1H), 2.34 (s, 3H), 2.36–2.08 (complex m, 4H), 2.07 (dd, J=18.8 and 4.8 Hz, 1H), 1.79 (dd, J=12.9 and 8.0 Hz, 1H), 1.41 (dd, J=12.9 and 11.1 Hz, 1H), 1.41–1.30 (complex m, 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.0 (C), 165.6 (C), 145.0 (C), 133.3 (CH), 132.3 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.8 (CH), 74.3 (CH), 69.5 (CH_2), 52.4 (CH_2), 46.7 (CH), 46.3 (C), 44.2 (CH_2), 42.5 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 3020, 2954, 2918, 2848, 1736, 1727, 1452, 1364, 1269, 1216, 1190, 1177, 1110, 1097, 814, 756, 713, 667, 554 cm^{-1}; MS (EI, 70 eV) m/z 456 ($M^{+\bullet}$, <1%), 285 (11), 179 (21), 162 (25), 105 (100), 91 (34), 77 (32).

3.2.16. Compound ***29***. A solution of diquinane **27** (15 mg, 33 μmol) in THF/MeOH (0.6 mL of a 2:1 v/v mixture) was cooled to −78 °C then samarium(II) diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 mol equiv) was added dropwise over 15 min. The resulting mixture was stirred at −78 °C for 20 min then warmed to 0 °C, stirred at this temperature for 3 h then at 18 °C for 1 h. After this time, the reaction mixture was re-cooled to −78 °C and additional samarium(II) diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 mol equiv) was added dropwise over 2 min. The reaction mixture was stirred at −78 °C for 1 min and then allowed to warm to 18 °C. After 0.5 h at this temperature samarium(II) diiodide (0.4 mL of a 0.1 M solution in THF, 40 μmol, 1.2 mol equiv) was again added and after 0.5 h at 18 °C the reaction mixture was quenched with potassium carbonate (1 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3×5 mL) then saturated with sodium chloride and extracted with dichloromethane (3×5 mL). The combined organic phases were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.5) then gave *diquinane* ***29*** (3 mg, 21%) as a clear, colourless oil. Found: $(M+Na)^+$, 479.1500. $C_{25}H_{28}O_6S$ requires $(M+Na)^+$, 479.1504. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.89 (complex m, 2H), 7.73–7.69 (complex m, 2H), 7.61–7.56 (complex m, 1H), 7.46–7.42 (complex m, 2H), 7.20–7.16 (complex m, 2H), 5.12 (ddd, J=7.8, 4.5 and 3.4 Hz, 1H), 4.21 (dd, J=11.1 and 3.4 Hz, 1H), 4.17 (dd, J=11.1 and 4.5 Hz, 1H), 2.62–2.72 (complex m, 1H), 2.53 (ddd, J=19.0, 9.3 and 1.5 Hz, 1H), 2.34 (s, 3H), 2.34–2.14 (complex m, 4H), 2.05 (ddd, J=19.0, 4.6 and 1.5 Hz, 1H), 1.84 (dd, J=13.2 and 7.8 Hz, 1H), 1.58 (dd, J=13.2 and 10.7 Hz, 1H), 1.22–1.14 (complex m, 1H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0 (C), 165.6 (C), 145.0 (C), 133.4 (CH), 132.4 (C), 129.8 (CH), 129.7 (CH), 129.4 (C), 128.4 (CH), 127.9 (CH), 74.2 (CH), 69.5 (CH_2), 52.4 (CH_2), 46.7 (CH), 46.2 (C), 44.4 (CH_2), 42.4 (CH_2), 39.7 (CH), 36.3 (CH_2), 27.7 (CH_3), 21.6 (CH_3); IR ν_{max} (KBr) 2953, 1738, 1722, 1451, 1364, 1269, 1190, 1177, 1109, 1097, 1070, 1026, 976, 942, 815, 714, 667, 554 cm^{-1}; MS (ESI, +ve) m/z 495 [$(M+K)^+$, 7%], 479 [$(M+Na)^+$, 100], 455 (38), 285 (93), 206 (35), 163 (50), 135 (35), 105 (69).

3.2.17. Compound ***32***. A magnetically stirred solution of diquinane **28** (10 mg, 22 μmol) in THF (0.2 mL) was cooled to −78 °C then LiHMDS (26 μL of a 1 M solution in THF, 26 μmol, 1.2 mol equiv) added dropwise over 5 min. After 0.5 h the reaction mixture was warmed to 0 °C and then, after 1 h, to 18 °C. After 5 h at this temperature the reaction mixture was quenched with water (0.2 mL) and the separated aqueous phase washed with dichloromethane (5×1 mL). The combined organic layers were then dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to column chromatography (silica, 1:3:6 v/v/v MeOH/ethyl acetate/hexane elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f=0.7) gave *compound* ***32*** (3 mg, 53% at 91% conversion) as a white, crystalline solid, mp=128–133 °C. Found: $M^{+\bullet}$, 284.1412. $C_{18}H_{20}O_3$ requires $M^{+\bullet}$, 284.1412. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04–7.99 (complex m, 2H), 7.58–7.52 (complex m, 1H), 7.47–7.40 (complex m, 2H), 4.73 (t, J=8.1 Hz, 1H), 2.56 (dd, J=18.3 and 7.8 Hz, 1H), 2.46–2.17 (complex m, 4H), 2.10 (d, J=9.1 Hz, 1H), 1.96 (d, J=12.3 Hz, 1H), 1.76 (dt, J=13.7 and 9.1 Hz, 2H), 1.45 (dd, J=12.3, 4.5 and 1.1 Hz, 1H), 1.26 (s, 3H), 1.19–1.11 (complex m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.6 (C), 165.8 (C), 132.9 (CH), 130.5 (C), 129.5 (CH), 128.3 (CH), 75.8 (CH), 50.9 (CH), 47.0 (C), 44.3 (CH_2), 43.1 (CH), 41.3 (CH), 38.4 (CH_2), 36.0 (CH_2), 25.8 (CH_2), 25.0 (CH_3); IR ν_{max} (KBr) 2930, 1732, 1717, 1451, 1336, 1313, 1275, 1258, 1179, 1143, 1112, 1068, 1024, 1003, 981, 710 cm^{-1}; MS (EI, 70 eV) m/z 284 [$M^{+\bullet}$, 3%], 163 (45), 162 (89), 134 (52), 106 (44), 105 (100), 93 (89), 92 (63), 77 (83). A sample of this material was recrystallised (ethyl acetate/hexane) to provide a crystal suitable for X-ray analysis. Details of this analysis are presented below and in Figure 2.

Concentration of fraction B (R_f=0.6) gave starting material **28** (1 mg, 9% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

3.3. Single-crystal X-ray analysis of compounds 12 and 32

3.3.1. Data for compound ***12***. $C_{14}H_{20}O_5$, M=268.31, T=200 K, monoclinic, space group $P2_1$, Z=4, a=14.7414(4), b=6.6985(2), c=15.2998(5) Å, β=111.7498(19); V=1403.23(8) Å^3, D_x=1.270 g cm^{-3}, 2697 unique data ($2\theta_{max}$=50°), R=0.0307 [for 2192 reflections with $I>1.5\sigma(I)$]; Rw=0.0376 (all data), S=1.1764.

3.3.2. Data for compound ***32***. $C_{18}H_{20}O_3$, M=284.36, T=200 K, monoclinic, space group $P2_1$, Z=2, a=6.8933(3), b=7.4523(2), c=14.8977(6) Å, β=100.166(2); V=753.29(5) Å^3, D_x=1.254 g cm^{-3}, 1439 unique data ($2\theta_{max}$=50°), R=0.035 [for 1084 reflections with $I>2.0\sigma(I)$]; Rw=0.081 (all data), S=0.82.

3.3.3. Structure determination. Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[35]

Structure solution was by direct methods (SIR92).[36] The structures of compounds **12** and **32** were refined using the CRYSTALS program package.[37] Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 763134 and 760492 for compounds **12** and **32**, respectively). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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