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Chemoenzymatic total syntheses of the linear triquinane-type natural products (+)-hirsutic acid and (−)-complicatic acid from toluene

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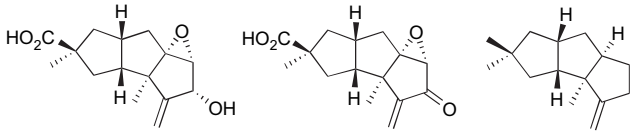
Abstract—Total syntheses of title natural products, **1** and **2**, have been achieved using the *cis*-1,2-dihydrocatechol **7** as starting material. Compound **7** is readily obtained in large quantity and enantiomerically pure form through the whole-cell biotransformation of toluene using the genetically engineered micro-organism *Escherichia coli* JM109 (pDTG601) that over-expresses the enzyme toluene dioxygenase (TDO). Three key chemical steps were employed in these syntheses, the first of which was a high-pressure-promoted Diels–Alder cycloaddition reaction between diene **8** and cyclopentenone to give adduct **9**. The second key step was the photochemically promoted oxa-di-π-methane rearrangement of the bicyclo[2.2.2]octenone derivative, **18**, of **9** to give **20** while the third key step was the reductive cleavage of the last compound so as to afford the linear triquinane **22**. Elaboration of compound **22** to targets **1** and **2** followed conventional and/or established procedures. Single-crystal X-ray analyses were carried out on compounds **10**–**13**, **15**, **18**, **24**, and **34**.

1. Introduction

The sesquiterpenoid natural product (+)-hirsutic acid (**1**) was isolated from the mold *Stereum hirsutum* in 1947 by Heatly et al. who were able to determine the molecular formula of this material but not its linear triquinane-type structure.[1] Scott et al. eventually established this some 20 years later as a result of a combination of chemical and X-ray crystallographic studies.[2,3] The structurally related natural product (−)-complicatic acid (**2**) was first isolated in 1973 from the fungus *Stereum complicatum* that also produces isolable quantities of congener **1**. At that time the latter compound was also identified as the biogenetic precursor to the former.[4] (+)-Hirsutic acid (**1**) is likely, in turn, to be derived in vivo from (+)-hirsutene (**3**), a linear triquininoid hydrocarbon found as a metabolite of the basidiomycete *Coriolis consors*, that is itself produced biogenetically via cation-mediated cyclization processes from the monocyclic sesquiterpene humulene.[5] Compound **2** shows moderate activity against a range of Gram-positive and Gram-negative bacteria as well as certain fungi.[4,6] It also conjugates with the amino acid cysteine and gives a positive Ames test.[6] Unsurprisingly, congeners **1** and **3**, both of which lack the α,β-unsaturated ketone residue embedded in (−)-complicatic acid (**2**), show little comparable activity. Very recently it has been suggested that the linear triquinane-based compounds could act as serotonin 5-HT_6 receptor antagonists for the treatment of Alzheimer's disease.[7]



The title natural products have each been the subject of a number of synthetic endeavors[8] with the first of these being reported in the early 1970s when Matsumoto[9] and Lansbury[10] described various preliminary studies. Very shortly thereafter the former researcher detailed the first total synthesis of (±)-complicatic acid [(±)-**2**] and also described, at that time, that this material could be reduced to (±)-hirsutic acid [(±)-**1**] using $NaBH_4$ in ethanol.[9b] The groups of Trost,[11] Ikegami,[12] Greene,[13] Magnus,[14] Schuda,[15] and Singh[16] have all reported on subsequent studies leading to the establishment of total or formal total syntheses of the racemic modifications of the title acids. Two of these groups[17,18] have also extended their work so as to obtain (+)-hirsutic acid in enantiomerically enriched form while Sakai et al.[19] have established chemoenzymatic routes to

Keywords: Chemoenzymatic; (−)-Complicatic acid; Diels–Alder reaction; *cis*-1,2-Dihydrocatechol; (+)-Hirsutic acid; Oxa-di-π-methane rearrangement; Sesquiterpene; Triquinane.
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enantiomerically enriched samples of a diquinane relevant to the synthesis of (+)-hirsutic acid.

The continued isolation of novel, highly functionalized, and biologically active linear triquinane-type sesquiterpenoids[20] has stimulated the ongoing development of new strategies and tactics for the assembly of the framework associated with this class of natural product.[21] Nevertheless, most such efforts continue to deliver racemic materials. As part of our own program in this area, we reported[22] that the enantiomerically pure *cis*-1,2-dihydrocatechol (**7**) obtained by the whole-cell biotransformation of toluene[23] using a microorganism over-expressing the enzyme toluene dioxygenase (TDO) can be converted into the non-natural or (−)-form of hirsutene (**3**). More recently, we outlined[24] a method for converting the same metabolite into an advanced intermediate associated with the Ikegami[17b] and Greene[18] syntheses of the title acids and thus establishing formal total syntheses of them. Herein, we report full details of this work as well as extensions of it that have allowed us to establish the total syntheses of (−)-complicatic acid and (+)-hirsutic acid. The approach used is outlined in retrosynthetic form in Figure 1 and involves, in the closing stages, various functional group interconversions (FGIs), including the reductive cleavage of a cyclopropyl ketone moiety, being applied to a linear triquinane derivative **4**.

This last compound was, in turn, expected to be accessible through the photochemically promoted oxa-di-π-methane rearrangement of the cyclopentannulated bicyclo[2.2.2]-octenone **5**. A facially selective Diels–Alder cycloaddition reaction between cyclopentenone (**6**) and the *cis*-1,2-dihydrocatechol **7** followed by conventional FGIs was expected to provide the tricyclic framework and relevant functionalities associated with sub-target **5**. The pivotal diene **7** is available in enantiomerically pure form via the above-mentioned biotransformation of toluene and was the starting material used in our previously reported total synthesis of (−)-hirsutene (*ent*-**3**). Overall, then, the approach to be followed contains three critical elements, namely the initial biotransformation of toluene into the *cis*-1,2-dihydrocatechol **7**, the Diels–Alder reaction between compounds **6** and **7**, and then the photochemical rearrangement of a

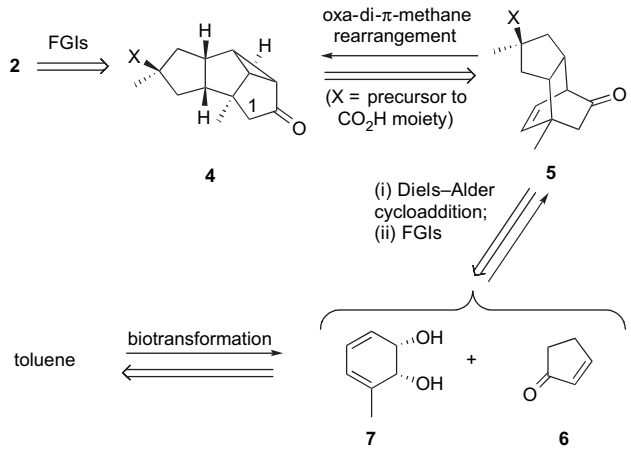


Figure 1. Retrosynthetic analysis of (−)-complicatic acid (**2**).

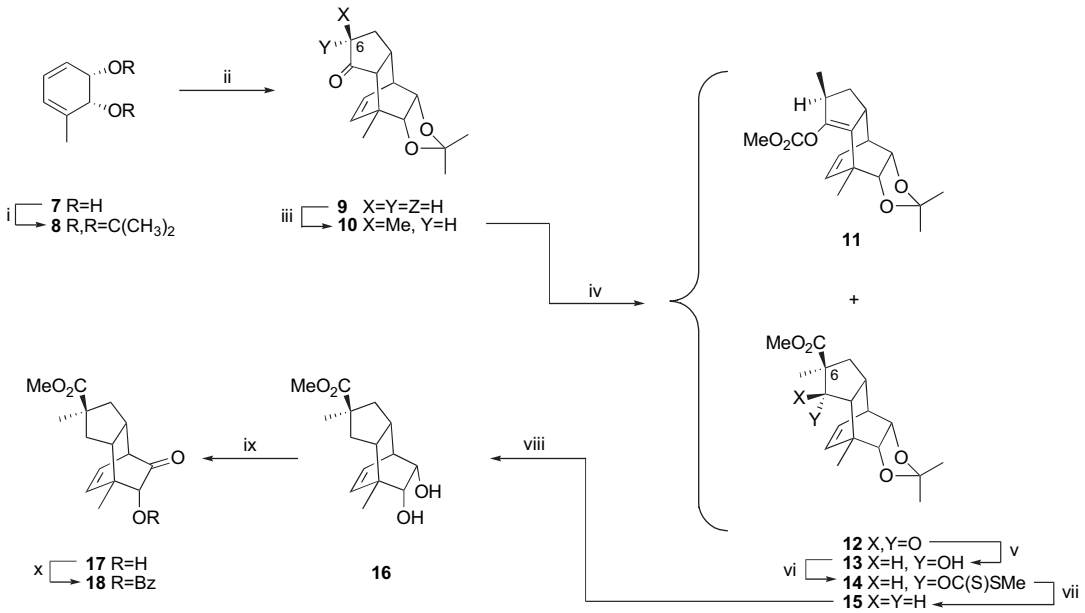
derivative, **5**, of the cycloadduct to give the pivotal triquininoid framework. Such a sequence of events was first introduced by Demuth[25] as a means for assembling the target framework and has subsequently been exploited by others[8] for the same purpose. Indeed, during the course of the studies described here, Singh et al. reported[16] on the use of such a strategy in establishing formal total syntheses of the racemic modifications of the title acids. Our own related work is now detailed in the following section.

2. Results and discussion

2.1. The Diels–Alder cycloaddition reaction and its use in the preparation of a substrate for the oxa-di-π-methane rearrangement

The reaction sequence leading from *cis*-1,2-dihydrocatechol **7** to the substrate for the oxa-di-π-methane rearrangement step is shown in Scheme 1 and begins with the conversion of the starting material into the corresponding and previously reported acetonide derivative **8**. A dichloromethane solution of the latter compound containing 2 molar equiv of cyclopentenone (**6**) was subjected to 19 kbar pressure in a PSIKA high-pressure reactor for 24 h at 18 °C and thus afforded a chromatographically separable mixture of the desired Diels–Alder adduct **9** (73%), its previously reported[22] *syn*-isomer (13%), and a dimer[26] (10%) derived from the starting diene **8**. The structure of compound **9** follows from single-crystal X-ray analyses of various derivatives (vide infra) and is clearly formed through delivery, via an *endo*-transition state, of the dienophile to the face of the diene opposite the sterically demanding acetonide residue. The adjacent nature of the ketone carbonyl and methyl residues about the newly formed cyclohexene ring within adduct **9** is as expected from the operation of the so-called *ortho*-rule.[27] The enolate derived from kinetic deprotonation of ketone **9** using LiHMDS could be stereoselectively *C*-alkylated using methyl iodide, thus producing the desired compound **10** (82% at 92% conversion) that was readily separated from its co-produced *gem*-dimethylated equivalent (15% at 92% conversion). The structure of the former product follows from a single-crystal X-ray analysis (see Section 4). This reveals that the carbon bearing the newly introduced methyl group has the *S*-configuration. Reaction of the ketone **10** with another aliquot of LiHMDS and then treatment of the reaction mixture with methyl cyanoformate (Mander's reagent[28]) afforded a chromatographically separable mixture of the enol carbonate **11** (3%) and the desired keto-ester **12**[29] (88%). The structure of the former product follows from a single-crystal X-ray analysis (see Section 4) and must be generated via O-acylation of the ring-junction enolate arising from deprotonation of precursor **10**. Interestingly, the *C*6-epimer of compound **12**, viz. *C*6-*epi*-**12**, was readily prepared by simply reversing the order of the methylation and acylation steps defined above and thereby obtained in 71% yield over the two steps involved.

The ketone carbonyl unit associated with product **12** had clearly served the synthesis well by virtue of the activating and directing effects it exerted in the Diels–Alder cycloaddition reaction and because it provided the means for installing the adjacent *C*6 methyl and carbomethoxy groups. However,



Scheme 1. *Reagents and conditions*: (i) $(MeO)_2CMe_2$, *p*-TsOH·H_2O, −10 to 18 °C, 1 h; (ii) cyclopentenone (2 mol equiv), dichloromethane, 19 kbar, 18 °C, 24 h; (iii) LiHMDS (1.1 mol equiv), MeI (1.05 mol equiv), THF, 0–18 °C, ca. 4 h; (iv) LiHMDS (1.2 mol equiv), $NCCO_2Me$ (2.0 mole equiv), THF, 0–18 °C, ca. 4 h; (v) $CeCl_3\cdot 7H_2O$ (4 mol equiv), $NaBH_4$ (1 mol equiv), methanol, 0–18 °C, ca. 5 h; (vi) NaHMDS (2 mol equiv), CS_2 (2 mol equiv), MeI (2.1 mol equiv), 0–18 °C, ca. 6 h; (vii) tri-*n*-butyltin hydride (4 mol equiv), AIBN (trace), toluene, 112 °C, ca. 5 h; (viii) DOWEX-50 resin (acidic form), methanol/water, 110 °C, 5 days; (ix) 4-acetamido-TEMPO (2.2 mol equiv), *p*-TsOH·H_2O (2.2 mol equiv), 0–18 °C, ca. 22 h; (x) benzoyl chloride (3.5 mol equiv), DMAP (3.5 mol equiv), triethylamine (4.7 mol equiv), dichloromethane, 0–18 °C, ca. 17 h.

it now needed to be removed and as the preliminary step toward such ends, compound **12** was subjected to Luche conditions[30] using $NaBH_4/CeCl_3\cdot 7H_2O$ in methanol. As a result the alcohol **13** (91%) was obtained in a completely stereoselective manner and its structure was again confirmed by single-crystal X-ray analysis (see Section 4). The *S*-methyl xanthate ester derivative, **14**, of compound **13** was readily prepared by standard methods and this was then treated with tri-*n*-butyltin hydride to complete the Barton–McCombie deoxygenation sequence[31] and thus produce the target 'hydrocarbon' **15**[29] in 97% yield over the last two steps.

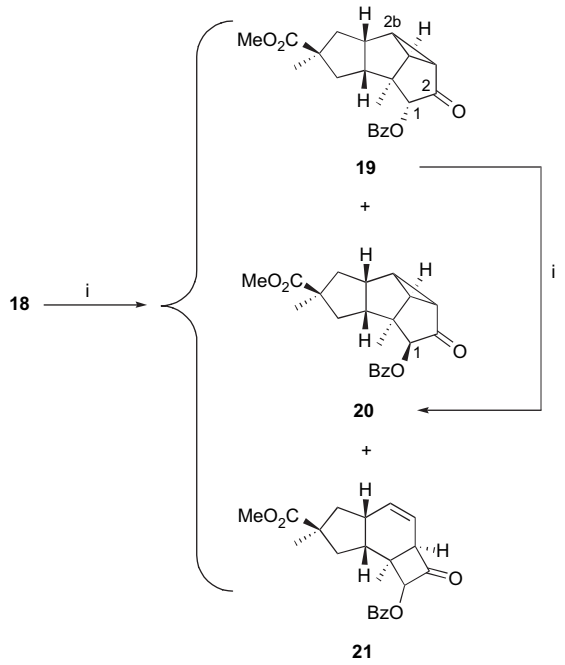
The cleavage of the acetonide residue within compound **15** proved somewhat problematic,[32] presumably because of the very rigid nature of the bicyclo[2.2.2]octene framework to which it is annulated and the consequent poorer than normal orbital overlap attainable during the course of the desired hydrolysis. After examining numerous methods for effecting the desired conversion, the best conditions identified involved exposure of a methanol/water solution of the substrate **15** to freshly activated DOWEX-50 resin and then heating the ensuing mixture at 110 °C for 5 days. By such means the target diol **16** was obtained in 81% yield and as a clear colorless oil. The regioselective oxidation of the hydroxy group remote from the bridgehead methyl group within diol **16** could be achieved using the sterically demanding oxoammonium salt derived from the *p*-toluenesulfonic acid-promoted disproportionation of commercially available 4-acetamido-TEMPO.[33] By such means the acyloin **17** was obtained in 85% yield (at 92% conversion).

If the retrosynthetic analysis defined in Figure 1 was to be followed then the next step in the proposed reaction sequence leading to a substrate for the pivotal photochemically promoted oxa-di-π-methane rearrangement would be the activation and then deletion of hydroxyl group within compound **17** and thus generating a bicyclo[2.2.2]octenone of the general structure **5**. However, since the conditions likely to be appropriate for such a transformation would also be likely to effect cleavage of the carbonyl-conjugated cyclopropane residue generated in the photochemical step, it was decided to delay this deoxygenation process such that a hydroxyl-bearing derivative of **4** would be obtained. This would then be subjected to a two-fold reduction process in an effort to simultaneously remove both the cyclopropane and *C*1-hydroxyl moieties, and thus saving at least one step in the reaction sequence. To such ends, the acyloin **17** was converted into the corresponding benzoate **18**[29] (80%) and this latter material became the substrate for all the photochemical studies detailed below. In principle, this benzoylation step could have been delayed until after the photochemical rearrangement process had been carried out. However, in earlier work[34] we had observed the dimerization of related acyloins and their photoproducts such that poor yields of the latter materials were inevitably observed. Such difficulties were completely avoided by acylation of the offending hydroxyl group and so promoted the conversion **17**→**18** just described.

2.2. The oxa-di-π-methane rearrangement

The title rearrangement is a triplet-mediated photochemical process that is often carried out using acetone as a solvent and in the presence of an even more effective sensitizer such as acetophenone. Accordingly, and following the conditions of Harfoot et al.,[22] an acetone solution of compound **18** and acetophenone that was contained in a Pyrex™ vessel

jacketed by a water-cooled solution of sodium bromide and lead(II) nitrate in water was irradiated with a high-pressure mercury lamp. Depending upon the precise conditions, including reaction time, substrate concentration, and the number of equivalents of acetophenone employed, varying proportions (and yields) of the three photoproducts **19**–**21** were obtained (Scheme 2). Under the optimal conditions defined in Section 4 the last of these products, **21**, which presumably arises via a singlet-mediated 1,3-acyl migration process,[35] was only obtained in trace amounts. Whilst compound **21** was isolated as a single diastereoisomer, the configuration at the benzoyloxy-bearing carbon was not determined. The ratio of products **19** and **20** was highly dependent upon the reaction time employed as shown in Figure 2, which reveals that the former compound is the kinetic product while the latter is the thermodynamic one. In a control experiment, compound **19** was subjected to the original irradiation conditions and shown to be converted, over a period of 36 h, and in 97% yield, into its epimer **20**, presumably via a photoenolization process.[36] The driving force for such a conversion is presumably the relief of steric congestion between the abutting angular methyl and benzoyloxy groups in the former product.



Scheme 2. *Reagents and conditions*: (i) irradiation with high-pressure Hg lamp, acetophenone (2.5 mol equiv), acetone, 5–10 °C, 80 h.

A study of the impact of substrate and acetophenone concentrations on product distribution was carried out. The outcomes of various relevant experiments, which were most conveniently conducted at 350 nm in a Rayonet-type Photochemical Reactor, revealed that the best proportions of the desired compounds **19** and **20** were achieved using 2.5 equiv of acetophenone whilst lowering the amount of this sensitizer to 0.2 equiv resulted in a predominance of the undesired cyclobutanone **21**. The concentration of the substrate was also important with lower ones leading to more satisfactory outcomes. Of course, longer irradiation times ensured that more of the starting material **18** was consumed.

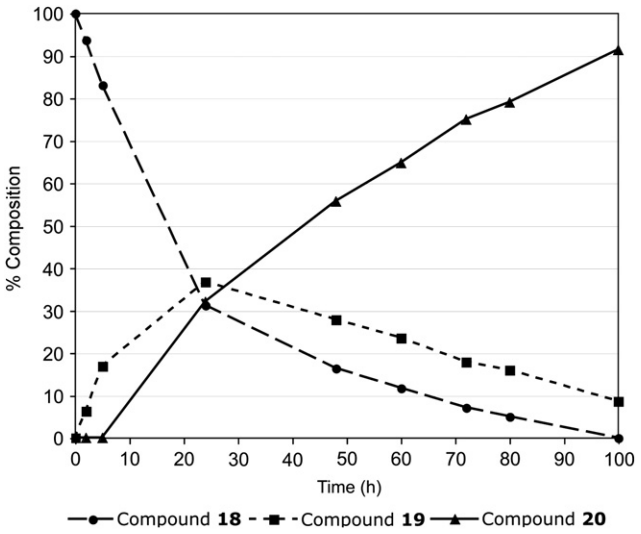
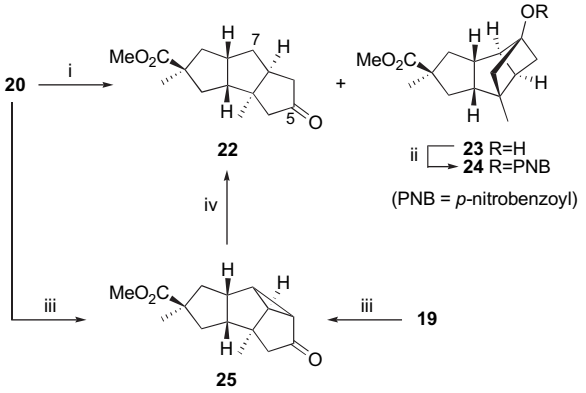


Figure 2. The photochemically promoted oxa-di-π-methane rearrangement of compound **18**—percentage composition of the reaction mixture as a function of time.

2.3. The endgame: elaboration of photoproducts 19 and 20 to (−)-complicatic acid (2) and (+)-hirsutic acid (1)

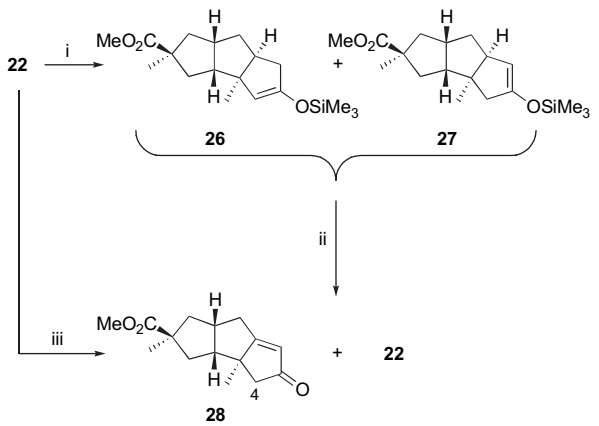
Photoproduct **20** was reacted with samarium(II) iodide (Scheme 3) in the expectation that this reagent should effect reductive cleavage of both the carbonyl-conjugated cyclopropane ring[37] and the *C*1-benzoyloxy group, and so forming the required linear triquinane framework. The anticipated outcome was indeed achieved by subjecting compound **20** to reaction with 4 mol equiv of freshly prepared SmI_2 in THF/methanol between −78 and 18 °C for a total of 3 h. However, the desired product **22** (56%) was accompanied by significant quantities of the cyclobutanol **23** (25%), the structure of which follows from our previously reported[29] single-crystal X-ray analysis of the readily obtained *p*-nitrobenzoyl derivative **24** (75%). The formation of compound **23** under the specified conditions presumably involves initial reductive removal of the *C*1-benzoyloxy group in precursor **20**. This is then followed by



Scheme 3. *Reagents and conditions*: (i) SmI_2 (4.05 mol equiv), THF/methanol, −78 to 18 °C, ca. 3 h; (ii) *p*-nitrobenzoyl chloride (3.5 mol equiv), DMAP (3.5 mol equiv), triethylamine (4.7 mol equiv), dichloromethane, 18 °C, 3 h; (iii) SmI_2 (2.2 mol equiv), THF/methanol, −78 °C, ca. 10 min; (iv) tri-*n*-butyltin hydride (6 mol equiv), AIBN (trace), benzene, 80 °C, ca. 1.5 h.

a cyclopropane ring cleavage process that delivers a derivative of compound **22** bearing samarium at *C*7 and so providing a capacity for this center to add, in an intramolecular sense, to the *C*5-carbonyl residue and thus affording, after work-up, the observed tertiary alcohol. Hoffmann et al. have observed[38] related conversions in that they employed SmI_2 for the pinacolic coupling of 1,4-diketones so as to form cyclobutene-1,2-diols embedded within polycyclic frameworks. In order to avoid the consumption of precious substrate through this unproductive pathway, compound **20** was subjected to less vigorous conditions involving its exposure to just 2 equiv of SmI_2 at −78 °C for 10 min. In this manner the debenzoylated compound **25** was obtained in 98% yield. Analogous treatment of photoproduct **19** delivered the same outcome, affording target **25** in 97% yield. Interestingly, when compound **25** was treated with SmI_2 under the same conditions as employed in the conversion **20**→**22+23** the same products were observed and in yields of 59 and 25%, respectively. Accordingly, alternative methods for cleaving the cyclopropyl residue within compound **25** were sought. Following protocols established by Singh et al.,[16] this material was treated with aliquots of tri-*n*-butyltin hydride (total of 6 molar equiv) and AIBN in refluxing benzene and by such means the target triquinane **22**, now free of any by-products, was obtained in 88% yield (at 87% conversion).

Two distinct pathways (Scheme 4) were investigated for the purposes of converting ketone **22** into the corresponding α,β-unsaturated compound, the double bond of which will serve as the vehicle for introducing the epoxide ring associated with the ultimate targets **1** and **2**. In the first of these a Saegusa oxidation protocol[39] was used and this involved initial treatment of compound **22** with 2,6-lutidine and TMSOTf at 0 °C under conditions closely related to those employed by Crimmins and Mascarella[40] during the course of their synthesis of (±)-silphinene. By such means a ca. 1:4 mixture, as judged by ^{1}H NMR analysis, of silyl enol ethers **26** and **27** was obtained. Without purification, an acetonitrile solution of this mixture was treated with $Pd(OAc)_2$ and *p*-benzoquinone. After 18 h at 18 °C the reaction mixture was worked up to provide a chromatographically separable mixture of the starting ketone **22** (31% recovery) and the



Scheme 4. *Reagents and conditions*: (i) TMSOTf (3 mol equiv), 2,6-lutidine (4 mol equiv), dichloromethane, 0–18 °C, 1 h; (ii) $Pd(OAc)_2$ (2 mol equiv), *p*-benzoquinone (1 mol equiv), acetonitrile, 18 °C, 18 h; (iii) IBX (3.9 mol equiv), *p*-TsOH·H_2O (0.3 mol equiv), toluene/DMSO, 85 °C, 72 h.

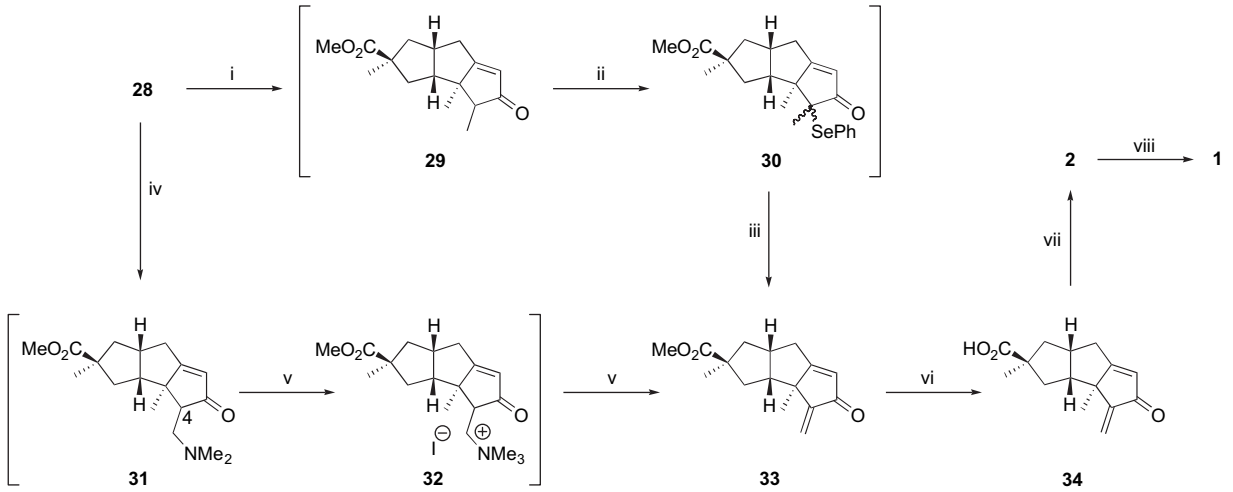
previously reported and desired enone **28** (85% at 69% conversion). An operationally simpler as well as superior method (89% yield) for achieving the conversion **22**→**28** involved subjecting the former material to reaction with IBX[41] in toluene/DMSO at 85 °C as described by Nicolaou et al.[42] The various conditions explored in optimizing this process revealed that the presence of an acid source is critical to its success.

The spectral data obtained on enone **28** compare favorably with those reported in the literature.[17b,18] Since compound **28** is an advanced intermediate associated with the Ikegami[17b] and Greene[18] syntheses of the title acids the acquisition of it, by the means just described, constitutes formal total syntheses of both of these natural products.

For the purpose of extending the work detailed above so as to establish the total syntheses of (+)-hirsutic acid and (−)-complicatic acid, the introduction of an exocyclic methylene at *C*4 of compound **28** was investigated (Scheme 5). Two distinct protocols were investigated, the first being one employed by Ikegami et al.[17b] and involving an initial C-methylation of the enolate obtained by deprotonation of enone **28** with LDA. The monomethylated and previously reported compound **29**[17b] so formed (as a single diastereoisomer although of undefined configuration at *C*4) was itself deprotonated with LDA and the resulting enolate was treated with phenylselenyl chloride to give compound **30**, which has previously been described by Ikegami.[17b] This material was obtained as a mixture of diastereoisomers. Treatment of compound **30** with H_2O_2 provided low yields of the target dienone **33**. Improvements in this elimination step could be achieved by using $NaIO_4$ as oxidant but almost inevitably product **33** (61% from **28**) was contaminated with often-significant quantities of its chromatographically inseparable precursor **29**. As a result a new method for achieving the conversion **28**→**33** was developed and involved trapping of the enolate anion of the starting material with Eschenmoser's salt[43] ($H_2C{=}NMe_2^+I^-$) so as to generate the tertiary amine **31** (79% at 95% conversion), a compound that could be purified and characterized by IR and ^{1}H NMR spectroscopy as well as mass spectrometry. Quaternization of amine **31** using methyl iodide followed by treatment of the ensuing methiodide salt **32** with basic alumina, so as to effect a Hofmann-type elimination reaction, provided the target alkene **33** in 76% yield.[44]

Cleavage of the methyl ester residue associated with compound **33** was achieved using LiI in refluxing DMF and after acidic work-up the crystalline dienone acid **34** was obtained in 73% yield at 78% conversion. The spectral data, including specific rotation, recorded for this material matched those reported by Greene et al.[18] and final confirmation of structure followed from a single-crystal X-ray analysis. The derived ORTEP is shown in Figure 3.

Regio- and stereo-selective nucleophilic epoxidation of compound **34** could be achieved by using a three-fold excess of alkaline hydrogen peroxide in methanol at −50 to −36 °C. In this manner (−)-complicatic acid (**2**) was obtained, as an oil, in a modest 35% yield. Various attempts to improve this outcome were to no avail. For example, the use of higher reaction temperatures and/or additional



Scheme 5. *Reagents and conditions*: (i) LDA (2 mol equiv), MeI (10 mol equiv), THF, −78 to 0 °C, ca. 1.5 h; (ii) LDA (2 mol equiv), PhSeCl (3 mol equiv), THF, −78 to 18 °C, ca. 1.5 h; (iii) $NaIO_4$ (5 mol equiv), THF/water/methanol, 18 °C, 1 h; (iv) LiHMDS (1.5 mol equiv), Eschenmoser's salt (3 mol equiv), THF, −78 to 18 °C, ca. 17 h; (v) MeI (12 mol equiv), diethyl ether/dichloromethane, 18 °C, 16 h, then basic alumina, dichloromethane, 18 °C, 0.5 h; (vi) LiI (15 mol equiv), DMF, 153 °C, 34 h; (vii) H_2O_2 (3 mol equiv), NaOH (3 mol equiv), methanol/water, −50 to 36 °C, ca. 1 h; (viii) $NaBH_4$ (19 mol equiv), −35 to 0 °C, ca. 0.5 h.

quantities of alkaline hydrogen peroxide led to complex mixtures of material, which appeared to contain significant quantities of a bis-epoxide, at least as judged by mass spectral analysis of the crude reaction mixture. A slightly better outcome was achieved when the nucleophilic epoxidation process was followed by immediate treatment of the crude reaction mixture with $NaBH_4$. By such means (+)-hirsutic acid (**1**) was obtained, after chromatographic purification using silica gel, in 46% yield and as white needles. The spectral and other data derived from the samples of targets **1** and **2** obtained by the pathway just described matched those reported by others. In particular, the specific rotation $\{[\alpha]_D\}$ of compound **2** was −77 (*c* 0.3 in $CHCl_3$), which compares favorably with the value of −79 (*c* 1.1 in $CHCl_3$) recorded for the originally isolated natural product.[2b] Similarly, the $[\alpha]_D$ obtained for the synthetically derived (+)-hirsutic acid compares favorably with that recorded for the natural product,[4] +113 (*c* 0.2, $CHCl_3$) versus +116 (*c* 1.05, $CHCl_3$). Less favorable comparisons apply to the melting points for compound **1**,[4] 168–171 versus 178.5–180 °C, although other synthetically derived samples have ones closer in value (e.g., 170 °C[17b]) to that which we observed.

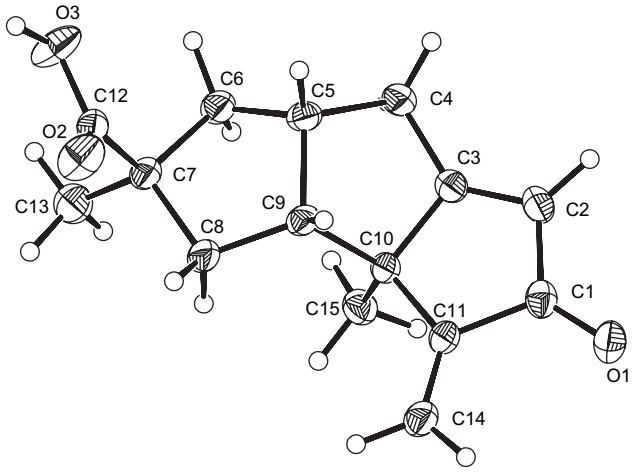


Figure 3. Molecular structure of compound **34** with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

3. Conclusions

This study, when considered in conjunction with our earlier work,[22] establishes that by controlling the facial selectivity of the Diels–Alder reactions involving diene **7** either enantiomeric form of the linear triquinane framework can be obtained. Furthermore, the reaction sequences involved allow for the stereocontrolled introduction of functionality at most positions on the triquinane framework and should be capable, therefore, of exploitation in the preparation of many members of the hirsutene class of sesquiterpenoid natural product. Work directed toward such ends is currently underway in our laboratories and results will be reported in due course.

On a more specific note, it is worth reflecting on the rather remarkable role that the methyl group of toluene plays in this synthesis. First of all, this seemingly innocuous group controls the regio-, stereo-, and enantio-selectivity of the TDO-mediated dihydroxylation of toluene to give metabolite **7**. This same group then controls the regioselectivity of the Diels–Alder cycloaddition reaction, the oxidation reaction leading to the acyloin **17** and the IBX-mediated process leading to the enone **28**. Never has an 'innocent' methyl group been so 'guilty' of controlling so much.

4. Experimental section

4.1. General experimental procedures

Melting points were measured on either a Stanford Research Systems Optimelt automated melting point system or a Reichert hot-stage microscope apparatus and are

uncorrected. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 MHz, Varian Inova 500 MHz, or Varian Inova 600 MHz spectrometer. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as KBr disks (for solids) or as thin films on KBr plates (for oils). Low-resolution mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph–MS or a VG Quattro II triple quadrupole MS instrument using electron impact techniques. High-resolution mass spectra were recorded on an AUTOSPEC instrument. Flash chromatographic separations were carried out using the protocols defined by Still et al.[45] Dichloromethane (DCM) and acetonitrile were distilled from calcium hydride while THF was distilled, under nitrogen, from sodium benzophenone ketyl. Toluene was distilled from chips of sodium metal. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

4.2. Synthetic studies

4.2.1. (3a*R*,7a*S*)-3a,7a-Dihydro-2,2,4-trimethyl-1,3-benzodioxole (8). Acetonide **8** was prepared from diol **7**[46] using previously described[46,47] protocols. The spectral data derived from compound **8** (83%) matched those reported earlier.[46,47]

4.2.2. (3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4-trimethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (9). A solution of acetonide **8** (505 mg, 3.04 mmol) and cyclopentenone (**6**) (500 μL, 6.18 mmol) in dichloromethane (12 mL) was pressurized to 19 kbar in a PSIKA high-pressure reactor. After 24 h at ca. 18 °C the reaction mixture was removed from the reactor and concentrated under reduced pressure. The resulting dark-yellow oil was subjected to flash chromatography (silica, 5:95→1:4 v/v ethyl acetate/hexane gradient elution) thus affording two fractions, A and B.

Concentration of fraction A resulted in a solid, recrystallization (*iso*-propanol) of which afforded the *title compound* ***9*** (549 mg, 73%) as a white needles, mp=79–80 °C, $[\alpha]_D$ +172 (*c* 1.0, $CHCl_3$). (Found: $M^{+\bullet}$, 248.1405. C, 72.25; H, 8.21. $C_{15}H_{20}O_3$ requires: $M^{+\bullet}$, 248.1412. C, 72.55; H, 8.12%.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (br t, *J*=8.3 Hz, 1H), 5.77 (d, *J*=8.3 Hz, 1H), 4.25 (ddd, *J*=7.2, 3.3, and 0.9 Hz, 1H), 3.81 (dd, *J*=7.2 and 1.3 Hz, 1H), 2.92 (m, 1H), 2.46 (m, 1H), 2.15–1.97 (complex m, 3H), 1.91 (d, *J*=9.5 Hz, 1H), 1.68 (m, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 219.7, 135.5, 129.8, 108.9, 82.7, 78.9, 52.3, 41.9, 40.7, 39.5, 36.3, 25.5, 25.1, 25.0, 18.7; IR ν_{max} 2939, 2886, 1732, 1458, 1372, 1264, 1167, 1073, 1053, 889, 728 cm^{-1}; MS *m*/*z* (EI, 70 eV) 248 ($M^{+\bullet}$, 13%), 233 (69), 190 (89), 161 (82), 134 (85), 119 (81), 105 (89), 100 (87), 91 (83), 85 (86), 77 (59), 43 (100).

Concentration of fraction B (R_f=0.4 in 3:7 v/v ethyl acetate/hexane) afforded a yellow oil that was subjected to further flash chromatography (silica, 0:1→1:9 v/v ethyl acetate/hexane gradient elution) thus affording two fractions, C and D.

Concentration of fraction C afforded the *syn*-isomer of compound **9**, viz. (3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4-trimethyl-4,8-etheno-5*H*-indeno-[5,6-*d*]-1,3-dioxol-5-one[22] (99.5 mg, 13%) as a clear, colorless oil [R_f=0.4(1) in 3:7 v/v ethyl acetate/hexane]. The spectral data derived from this material were identical with those reported previously.[22]

Concentration of fraction D afforded the Diels–Alder dimer of the starting diene **8**, viz. [3a*R*-(3aα,5aβ,6α,6aβ,9aβ,10α,10aβ,10bβ)]-3a,5a,6,6a,9a,10,10a,10b-octahydro-2,2,4,6,8,8-hexamethyl-6,10-ethenonaphtho[1,2-*d*:6,7-*d*′]-bis[1,3]dioxole (102 mg, 10%) as a clear colorless oil, $[\alpha]_D$ +57 (*c* 0.3, $CHCl_3$). (Found: $M^{+\bullet}$, 332.1973. $C_{20}H_{28}O_4$ requires: $M^{+\bullet}$, 332.1988.) [R_f=0.3(9) in 3:7 v/v ethyl acetate/hexane.] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (br t, *J*=6.3 Hz, 1H), 5.65 (d, *J*=8.1 Hz, 1H), 5.45 (m, 1H), 4.32 (ddd, *J*=8.1, 5.4, and 0.9 Hz, 1H), 4.12 (dd, *J*=5.1 and 1.5 Hz, 1H), 4.06 (br d, *J*=5.1 Hz, 1H), 3.87 (dd, *J*=7.2 and 2.2 Hz, 1H), 2.83 (m, 1H), 2.25 (br d, *J*=9.0 Hz, 1H), 2.04 (m, 1H), 1.74 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.1, 133.0, 127.9, 122.4, 108.5, 107.5, 82.8, 79.2, 78.4, 73.6, 43.5, 40.4, 39.0, 35.5, 27.9, 26.8, 25.5, 25.1, 19.6, 19.4; IR ν_{max} 2981, 2935, 2874, 1454, 1370, 1240, 1209, 1161, 1062, 1025, 882, 725 cm^{-1}; MS *m*/*z* (EI, 70 eV) 332 ($M^{+\bullet}$, 2%), 317 (10), 274 (14), 216 (52), 109 (81), 108 (100), 80 (53).

4.2.3. (3a*R*,4*R*,4a*R*,6*S*,7a*R*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6-tetramethyl-4,8-etheno-5*H*-indeno-[5,6-*d*]-1,3-dioxol-5-one (10). A magnetically stirred solution of ketone **9** (2.00 g, 8.05 mmol) in THF (80 mL) was cooled to 0 °C and then treated, dropwise, with LiHMDS (8.8 mL of a 1.0 M solution in THF, 8.80 mmol). The resulting mixture was maintained at 0 °C for 0.75 h and then warmed to 18 °C over a period of 1.25 h. The reaction mixture was then re-cooled to 0 °C and treated, dropwise, with iodomethane (526 μL, 8.45 mmol). The ensuing mixture was stirred at 0 °C for 0.75 h, then warmed to 18 °C over 1.25 h, quenched with NH_4Cl (20 mL of a saturated aqueous solution), and then diluted with dichloromethane (80 mL). The separated aqueous phase was extracted with dichloromethane (2×20 mL) and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing orange-colored semi-solid was subjected to flash chromatography (silica, 5:95→15:85 v/v ethyl acetate/hexane gradient elution) thus affording three fractions, A–C.

Concentration of fraction A afforded the *gem*-dimethylated derivative of compound **9**, viz. (3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (310 mg, 15% at 92% conversion) as a white crystalline solid, mp=101–105 °C, $[\alpha]_D$ +88 (*c* 1.0, $CHCl_3$). (Found: $M^{+\bullet}$, 276.1727. $C_{17}H_{24}O_3$ requires: $M^{+\bullet}$, 276.1725.) (R_f=0.4 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95 (m, 1H), 5.82 (br d, *J*=8.4 Hz, 1H), 5.27 (ddd, *J*=7.2, 3.3, and

0.9 Hz, 1H), 3.81 (dd, J=7.2 and 1.2 Hz, 1H), 2.86 (m, 1H), 2.48 (m, 1H), 2.14 (d, J=10.5 Hz, 1H), 1.87 (dd, J=12.9 and 8.9 Hz, 1H), 1.56 (s, 3H), 1.34 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 221.3, 135.9, 129.8, 109.0, 83.2, 78.9, 49.6, 47.0, 40.7, 40.4, 33.4, 26.4, 25.5, 25.0, 22.1, 18.7 (one signal obscured or overlapping); IR ν_{max} 2963, 2933, 2871, 1731, 1455, 1373, 1324, 1269, 1254, 1208, 1166, 1054, 1073, 891, 875, 820, 732 cm^{-1}; MS m/z (EI, 70 eV) 276 ($M^{+\bullet}$, 13%), 261 (38), 218 (90), 176 (78), 134 (80), 105 (100).

Concentration of fraction B afforded the *title compound* ***10*** (1.58 g, 82% at 92% conversion) as a white crystalline solid, mp=67–69 °C, $[\alpha]_D$ +172 (c 0.5, $CHCl_3$). (Found: $M^{+\bullet}$, 262.1568. $C_{16}H_{22}O_3$ requires: $M^{+\bullet}$, 262.1569.) (R_f=0.3 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.16 (br t, J=8.3 Hz, 1H), 5.71 (d, J=8.3 Hz, 1H), 4.26 (ddd, J=7.8, 3.5, and 0.7 Hz, 1H), 3.83 (dd, J=7.2 and 1.2 Hz, 1H), 2.93 (m, 1H), 2.31 (br t, J=9.4 Hz, 1H), 2.13 (m, 1H), 1.95 (d, J=9.3 Hz, 2H), 1.63 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.93 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 219.5, 134.9, 129.7, 108.2, 82.2, 78.6, 52.4, 43.7, 41.8, 40.4, 34.4, 33.2, 25.0, 24.6, 18.4, 13.8; IR ν_{max} 2974, 2932, 2874, 1732, 1455, 1373, 1266, 1207, 1164, 1078, 1055, 886, 732 cm^{-1}; MS m/z (EI, 70 eV) 262 ($M^{+\bullet}$, 10%), 247 (43), 204 (86), 175 (57), 162 (72), 134 (100), 105 (96), 100 (82), 92 (60), 91 (63), 43 (69).

Concentration of fraction C afforded the starting ketone **9** (169 mg, 8% recovery) as a white crystalline solid [R_f=0.2(5) in 3:7 v/v ethyl acetate/hexane]. This material was identical, in all respects, with an authentic sample.

4.2.4. Methyl (3a*R*,4*R*,6*S*,7a*R*,8*S*,8a*S*)-4,6,7,7a,8,8a-hexahydro-2,2,4,6-tetramethyl-4,8-etheno-3a*H*-indeno-[5,6-*d*]-1,3-dioxol-5-yl carbonate (11) and methyl (3a*R*, 4*R*,4a*R*,6*S*,7a*R*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6-tetramethyl-5-oxo-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate (12). A magnetically stirred solution of compound **10** (1.94 g, 7.41 mmol) in THF (75 mL) was cooled to 0 °C and then treated, dropwise, with LiHMDS (8.9 mL of a 1.0 M solution in THF, 8.90 mmol). The resulting mixture was maintained at 0 °C for 0.75 h, warmed to 18 °C over 1.25 h, and then re-cooled to 0 °C and treated dropwise with Mander's reagent[28] (1.18 mL, 14.9 mmol). Stirring was continued at 0 °C for 0.75 h, then the reaction mixture was warmed to 18 °C over 1.25 h, and quenched with NH_4Cl (20 mL of a saturated aqueous solution) and diluted with dichloromethane (80 mL). The separated aqueous phase was extracted with dichloromethane (3×20 mL) and the combined organic phases were then washed with water (2×10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 5:95→15:85 v/v ethyl acetate/hexane gradient elution) thus affording two fractions, A and B.

Concentration of fraction A afforded the *title enol carbonate* ***11*** (71 mg, 3%) as white needles, mp=100–104 °C, $[\alpha]_D$ +50 (c 0.9, $CHCl_3$). (Found: $M^{+\bullet}$, 320.1631. $C_{18}H_{24}O_5$ requires: $M^{+\bullet}$, 320.1624.) (R_f=0.5 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97 (d, J=8.1 Hz, 1H), 5.81 (dd, J=8.1 and 6.8 Hz, 1H), 4.36 (dd, J=7.2 and 3.6 Hz, 1H), 4.02 (br d, J=6.8 Hz, 1H), 3.82 (s, 3H), 2.85 (m, 1H), 2.70 (m, 2H), 1.80–1.55 (complex m, 2H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.10 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 145.5, 138.0, 130.9, 127.2, 109.5, 80.6, 80.3, 55.2, 42.6, 41.7, 40.1, 39.3, 37.7, 25.5, 25.0, 16.3(5), 16.3(2); IR ν_{max} 2958, 2939, 2881, 1764, 1693, 1456, 1441, 1371, 1272, 1245, 1207, 1182, 1072, 1045, 1010, 950, 896, 871, 818, 783, 729 cm^{-1}; MS m/z (EI, 70 eV) 320 ($M^{+\bullet}$, 5%), 305 (4), 247 (51), 203 (100), 187 (69), 186 (95), 161 (60), 144 (92), 101 (77).

Concentration of fraction B afforded a solid that was recrystallized (ethyl acetate) to give the *title keto-ester* ***12*** (2.09 g, 88%) as a white needles, mp=91–94 °C, $[\alpha]_D$ +105 (c 1.0, $CHCl_3$). (Found: $M^{+\bullet}$, 320.1621. $C_{18}H_{24}O_5$ requires: $M^{+\bullet}$, 320.1624.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.97 (br t, J=ca. 5.0 Hz, 1H), 5.84 (d, J=5.0 Hz, 1H), 4.28 (dd, J=4.2 and 2.1 Hz, 1H), 3.82 (d, J=4.2 Hz, 1H), 3.66 (s, 3H), 2.88 (m, 1H), 2.57 (m, 2H), 2.26 (d, J=6.0 Hz, 1H), 1.57 (s, 3H), 1.34 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.2, 173.0, 136.5, 130.0, 109.6, 83.3, 79.1, 58.4, 52.9, 51.8, 41.3, 39.7, 38.2, 34.8, 25.8, 25.3, 18.9, 18.8; IR ν_{max} 2976, 2935, 2878, 1753, 1728, 1456, 1375, 1267, 1208, 1151, 1069, 889, 736 cm^{-1}; MS m/z (EI, 70 eV) 320 ($M^{+\bullet}$, 18%), 305 (60), 262 (89), 247 (74), 202 (78), 173 (55), 157 (59), 134 (78), 105 (84), 100 (100), 92 (62), 91 (66), 85 (59), 69 (52), 43 (71), 41 (58).

4.2.5. Methyl (3a*R*,4*R*,4a*R*,6*R*,7a*R*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6-tetramethyl-5-oxo-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate (6-*epi*-12). *Step i:* a magnetically stirred solution of ketone **9** (202 mg, 0.82 mmol) in THF (2.5 mL) was cooled to −78 °C and then treated, dropwise over 0.5 h, with LiHMDS (1.22 mL of 1.0 M solution in THF, 1.22 mmol). The ensuing mixture was stirred at −78 °C for 1.5 h and then treated with Mander's reagent[28] (71 μL, 0.90 mmol) before being allowed to warm to 18 °C over 14 h. The reaction mixture was then treated with water (5 mL) and dichloromethane (5 mL), and the separated aqueous phase was extracted with dichloromethane (2×5 mL). The combined organic fractions were washed with $NaHCO_3$ (1×2 mL of a saturated aqueous solution) and brine (1×2 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 1:9→1:3 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions gave a light-yellow oil tentatively identified as a mixture of *methyl (3aR,4R,4aR,6R,7aR,8S,8aS)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4-trimethyl-5-oxo-4,8-etheno-4H-indeno[5,6-d]-1,3-dioxole-6-carboxylate* and its *various tautomers* (191 mg, 78%) (R_f=0.3 in 3:7 v/v ethyl acetate/hexane). This material was subjected, without full characterization, to step ii of the reaction sequence as detailed immediately below.

Step ii: a magnetically stirred suspension of NaH (15 mg, 0.63 mmol) in THF (5 mL) was cooled to 0 °C and then treated with a sample of the material obtained in step i (94 mg, 0.31 mmol) dissolved in THF (1.5 mL). The

ensuing mixture was warmed to 18 °C and then allowed to stir at this temperature for 0.75 h before being treated with iodomethane (96 mL, 1.54 mmol). After a further 1 h, the reaction mixture was treated with NH_4Cl (5 mL of a saturated aqueous solution) and dichloromethane (5 mL). The separated aqueous phase was extracted with dichloromethane (2×5 mL) and the combined organic extracts were washed with water (1×5 mL) and brine (1×5 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The white solid so obtained was subjected to flash chromatography (silica, 1:9→3:7 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions afforded the *title keto-ester C6-epi-**12*** (90 g, 91%) as white needles, mp=92–96 °C, $[\alpha]_D$ +11 (*c* 0.2, $CHCl_3$). (Found: $M^{+\bullet}$, 320.1637. $C_{18}H_{24}O_5$ requires: $M^{+\bullet}$, 320.1624.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.01 (m, 1H), 5.76 (br d, *J*=8.4 Hz, 1H), 4.27 (br dd, *J*=7.5 and 4.8 Hz, 1H), 3.81 (dd, *J*=7.5 and 1.2 Hz, 1H), 3.68 (s, 3H), 2.95 (m, 1H), 2.48 (m, 1H), 2.36 (dd, *J*=13.5 and 7.2 Hz, 1H), 2.13 (d, *J*=9.9 Hz, 1H), 1.92 (dd, *J*=13.8 and 9.2 Hz, 1H), 1.57 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.2, 172.2, 135.1, 129.8, 109.2, 82.9, 78.8, 58.2, 52.5, 50.7, 41.2, 39.5, 36.9, 33.6, 25.5, 25.0, 22.3, 18.6; IR ν_{max} 2936, 2876, 1748, 1728, 1458, 1375, 1268, 1209, 1165, 1065, 999, 883, 728 cm^{-1}; MS *m*/*z* (EI, 70 eV) 320 ($M^{+\bullet}$, 8%), 305 (55), 262 (87), 220 (60), 202 (55), 173 (61), 157 (73), 134 (96), 105 (100).

4.2.6. Methyl (3a*R*,4*R*,4a*R*,5*S*,6*S*,7a*R*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-5-hydroxy-2,2,4,6-tetramethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate (13). A magnetically stirred solution of $CeCl_3\cdot 7H_2O$ (16.01 g, 43.0 mmol) and ketone **12** (6.88 g, 21.5 mmol) in methanol (107 mL) was cooled to 0 °C and then treated in portions, over 0.5 h, with $NaBH_4$ (1.63 g, 43.0 mmol). The resulting mixture was allowed to warm to 18 °C, stirred at this temperature for 2 h, and then re-cooled to 0 °C and treated with an additional aliquot of $NaBH_4$ (1.68 g, 44.5 mmol). The reaction mixture was then re-warmed to 18 °C, stirred at this temperature for an additional 2 h, and then diluted (*slowly*) with water (20 mL). After hydrogen evolution had ceased the reaction mixture was concentrated under reduced pressure and the residue was extracted with dichloromethane (4×150 mL). The combined organic extracts were washed with water (1×50 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the *title hydroxy-ester **13*** (6.30 g, 91%) as a low-melting solid, $[\alpha]_D$ −20 (*c* 1.0, $CHCl_3$). (Found: $M^{+\bullet}$, 322.1780. $C_{18}H_{26}O_5$ requires: $M^{+\bullet}$, 322.1780.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.10 (m, 2H), 4.28 (dd, *J*=11.5 and 5.9 Hz, 1H), 4.20 (dd, *J*=7.0 and 3.3 Hz, 1H), 3.82 (d, *J*=7.0 Hz, 1H), 3.67 (s, 3H), 2.81 (m, 1H), 2.24–2.08 (complex m, 2H), 1.93 (dd, *J*=10.5 and 5.9 Hz, 1H), 1.56 (d, *J*=6.6 Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 1.08 (br t, *J*=11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.9, 137.7, 130.7, 109.0, 83.3, 79.9, 77.6, 56.6, 52.0, 50.7, 40.6 (two signals overlapping), 37.9, 37.4, 25.4, 24.8, 19.6, 18.3; IR ν_{max} 3541, 2974, 2934, 2877, 1728, 1457, 1377, 1277, 1256, 1207, 1163, 1080, 1054, 1038, 980, 895, 877, 825, 728 cm^{-1}; MS *m*/*z* (EI, 70 eV) 322 ($M^{+\bullet}$, 2%), 307 (62), 264 (99), 222 (100), 187 (87), 186 (99), 144 (87), 117 (60), 106 (81), 91 (68), 85 (60), 43 (89).

4.2.7. Methyl (3a*R*,4*R*,4a*R*,5*S*,6*S*,7a*R*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6-tetramethyl-5-[(methylthio)thiooxomethoxy]-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate (14). A magnetically stirred solution of alcohol **13** (1.91 g, 5.91 mmol) in THF (60 mL) was cooled to 0 °C and then treated with NaHMDS (11.8 mL of a 1.0 M solution in THF, 11.8 mmol). The ensuing mixture was stirred at 0 °C for 1.5 h, warmed to 18 °C over 0.5 h, and then re-cooled to 0 °C, and treated with carbon disulfide (711 μL, 11.8 mmol). After stirring at 0 °C for 1.5 h the reaction mixture was warmed to 18 °C over 0.5 h, then immediately re-cooled to 0 °C, and treated with iodomethane (773 mL, 12.4 mmol). Stirring was continued at 0 °C for 1.5 h, then the reaction mixture was warmed to 18 °C, stirred at this temperature for 0.5 h, then diluted with diethyl ether, (60 mL) and washed with water (1×100 mL), HCl (100 mL of a 1.0 M aqueous solution), and brine (1×50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil. The bulk of this material was subjected, as obtained, to the next step of the reaction sequence as detailed in the following section. For the purposes of characterization, a sample of this material was subjected to flash chromatography (silica, 1:9→3:7 v/v ethyl acetate/hexane gradient elution). Concentration of the relevant fractions afforded the *title xanthate ester **14*** as a light-yellow oil, $[\alpha]_D$ +64 (*c* 0.5, $CHCl_3$). (Found: $M^{+\bullet}$, 412.1387. $C_{20}H_{28}O_5S$ requires: $M^{+\bullet}$, 412.1378.) (R_f=0.3 in 3:7 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.64 (d, *J*=5.1 Hz, 1H), 5.91 (m, 2H), 4.20 (dd, *J*=7.2 and 3.0 Hz, 1H), 3.79 (d, *J*=7.2 Hz, 1H), 3.72 (s, 3H), 2.80 (m, 1H), 2.60 (s, 3H), 2.24–2.05 (complex m, 3H), 1.42 (t, *J*=10.3 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.1, 175.6, 137.2, 125.9, 109.1, 86.2, 83.6, 79.6, 57.0, 52.4, 50.0, 40.3, 40.0, 39.4, 37.5, 25.5, 25.0, 19.6, 19.2, 18.3; IR ν_{max} 2975, 2932, 1730, 1457, 1377, 1286, 1245, 1207, 1057, 877, 729 cm^{-1}; MS *m*/*z* (EI, 70 eV) 412 ($M^{+\bullet}$, 43%), 379 (44), 246 (51), 187 (85), 186 (75), 159 (48), 145 (82), 144 (83), 91 (100), 43 (46).

4.2.8. Methyl (3a*R*,4*R*,4a*R*,6*S*,7a*S*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6-tetramethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate (15). A magnetically stirred solution of xanthate ester **14** (ca. 5.91 mmol, obtained as described immediately above) in dry toluene (100 mL) was treated with AIBN (20 mg, 0.122 mmol) and tri-*n*-butyltin hydride (3.2 mL, 11.9 mmol), and the ensuing mixture was heated under reflux for 1.5 h, then cooled to 18 °C, and treated with additional aliquots of AIBN (20 mg, 0.122 mmol) and tri-*n*-butyltin hydride (3.2 mL, 11.9 mmol). The resulting mixture was again heated under reflux, this time for 3.5 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, hexane then 1:4 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions, the *title acetonide **15*** (1.76 g, 97% from alcohol **13**) as a white crystalline solid, mp=63–64 °C, $[\alpha]_D$ ca. 0 (*c* 1.2, $CHCl_3$). [Found: $(M-CH_3\bullet)^+$, 291.1589. C, 70.16; H, 8.07. $C_{18}H_{26}O_4$ requires: $(M-CH_3\bullet)^+$, 291.1596. C, 70.56; H, 8.55%.] (R_f=0.4 in 3:7 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00 (br t, *J*=8.0 Hz, 1H), 5.74 (dd, *J*=8.0 and 1.0 Hz, 1H), 4.18 (ddd, *J*=8.1, 3.6, and 3.2 Hz, 1H),

3.79 (dd, J=8.1 and 0.9 Hz, 1H), 3.64 (s, 3H), 2.72 (m, 1H), 2.23–2.07 (complex m, 3H), 1.79 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5, 135.6, 130.3, 108.8, 83.4, 79.7, 51.9, 50.8, 45.2, 41.8, 41.5, 40.5, 40.4, 38.7, 25.6, 24.9, 23.8, 19.7; IR ν_{max} 2960, 2932, 2873, 1731, 1456, 1377, 1254, 1206, 1168, 1101, 1065, 1031, 879, 733 cm^{-1}; MS m/z (EI, 70 eV) 291 [$(M-CH_3^{\bullet})^+$, 73%], 248 (77), 206 (95), 189 (83), 188 (92), 173 (73), 159 (100), 146 (92), 145 (91), 144 (92), 131 (90), 109 (64), 105 (70), 100 (77), 91 (82), 43 (67).

4.2.9. Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,8*S*,9*R*)-2,3,3a,4,7,7a-hexahydro-8,9-dihydroxy-2,4-dimethyl-4,7-ethano-1*H*-indene-2-carboxylate (16). A magnetically stirred solution of acetonide **15** (507 mg, 1.65 mmol) in methanol/water (12 mL of a 5:1 v/v mixture) was treated with DOWEX-50 resin [500 mg that had been washed, successively, with $NaHCO_3$ (saturated aqueous solution), water (distilled), HCl (1 M aqueous solution), and water (distilled)]. The ensuing mixture was heated at 110 °C until TLC analysis revealed that the starting material had been consumed (normally 3–5 days). The cooled reaction mixture was filtered and the resin thus retained was washed with methanol (3×10 mL). The combined filtrates were concentrated under reduced pressure, then the residue diluted with NaCl (20 mL of a ca. 1.5 M aqueous solution), and the resulting mixture extracted with dichloromethane (5×20 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the *title diol* ***16*** (357 mg, 81%) as a clear, colorless oil, $[\alpha]_D$ −5.5 (*c* 1.2, $CHCl_3$). [Found: $(M+H)^+$, 267.1595. $C_{15}H_{22}O_4$ requires: $(M+H)^+$, 267.1596.) (R_f=0.2 in 1:1 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.14 (dd, J=8.3 and 6.5 Hz, 1H), 5.85 (dd, J=8.3 and 1.1 Hz, 1H), 3.82 (dd, J=7.4 and 2.3 Hz, 1H), 3.63 (s, 3H), 3.39 (d, J=7.4 Hz, 1H), 2.86 (br s, 1H), 2.73 (br s, 1H), 2.68 (m, 1H), 2.22–2.13 (complex m, 3H), 1.82 (m, 1H), 1.16(8) (s, 3H), 1.16(6) (s, 3H), 0.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5, 136.5, 131.6, 74.7, 71.3, 51.9, 50.1, 45.9, 42.8, 41.9, 41.5, 40.8(7), 40.8(6), 23.7, 19.4; IR ν_{max} 3400, 2933, 1729, 1457, 1404, 1375, 1170, 1099, 1058, 1021, 995, 833, 791, 728 cm^{-1}; MS m/z (EI, 70 eV) 267 [$(M+H)^+$, 1%], 206 (94), 174 (56), 146 (100), 131 (90), 101 (45), 91 (35).

4.2.10. Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,9*R*)-2,3,3a,4,7,7a-hexahydro-9-hydroxy-2,4-dimethyl-8-oxo-4,7-ethano-1*H*-indene-2-carboxylate (17). A magnetically stirred solution of diol **16** (1.13 g, 4.25 mmol) in dichloromethane (100 mL) was cooled to 0 °C and then treated with *p*-TsOH·H_2O (1.76 g, 9.25 mmol). 4-Acetamido-TEMPO (1.97 g, 9.25 mmol) was then added, in portions over 2.5 h, to the reaction mixture, which was then stirred at 0 °C for 2 h. After this time it was warmed to 18 °C, stirred at this temperature for 16 h, then treated with $NaHCO_3$ (50 mL of a saturated aqueous solution), and the separated aqueous phase was extracted with dichloromethane (4×50 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange-colored semi-solid. Subjection of this material to flash chromatography (silica 1:9→1:4 ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A afforded the starting diol **16** (93 mg, 8% recovery) as a white crystalline solid (R_f=0.2 in 1:1 v/v ethyl acetate/hexane). This material was identical, in all respects, with an authentic sample.

Concentration of fraction B afforded the *title acyloin* ***17*** (882 mg, 85% at 92% conversion) as a clear colorless oil, $[\alpha]_D$ +148 (*c* 0.1, $CHCl_3$). (Found: $M^{+\bullet}$, 264.1361. $C_{15}H_{20}O_4$ requires: $M^{+\bullet}$, 264.1362.) (R_f=0.4 in 1:1 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.04 (m, 2H), 3.30 (s, 3H), 3.62 (s, 1H), 3.08 (dm, J=9.9 Hz, 1H), 2.98 (br s, 1H), 2.55 (m, 1H), 2.32–2.14 (complex m, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.4, 177.9, 140.1, 126.2, 74.4, 52.0, 50.8, 50.1, 47.3, 44.7, 41.4, 40.7, 38.7, 23.6, 18.1; IR ν_{max} 3462, 2962, 2931, 2872, 1729, 1463, 1450, 1374, 1325, 1286, 1199, 1171, 1080, 1037, 881, 818, 763, 721, 661 cm^{-1}; MS m/z (EI, 70 eV) 264 ($M^{+\bullet}$, 7%), 233 (10), 199 (40), 140 (100), 43 (50).

4.2.11. Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,9*R*)-9-(benzoyloxy)-2,3,3a,4,7,7a-hexahydro-2,4-dimethyl-8-oxo-4,7-ethano-1*H*-indene-2-carboxylate (18). A magnetically stirred solution of the acyloin **17** (880 mg, 3.33 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1.43 g, 11.7 mmol) in dichloromethane (30 mL) was cooled to 0 °C, and then treated with triethylamine (2.2 mL, 15.7 mmol) and benzoyl chloride (1.35 mL, 11.7 mmol). The ensuing mixture was warmed to 18 °C and then stirred at this temperature for 16 h before being quenched with water (20 mL) and then diluted with dichloromethane (50 mL). The separated organic phase was washed with $NaHCO_3$ (2×20 mL of a saturated aqueous solution) and brine (1×20 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) thus affording, after concentration of the appropriate fractions, a white solid, recrystallization (*iso*-propanol) of which gave the *title benzoate* ***18*** (984 mg, 80%) as white needles, mp=121–123 °C, $[\alpha]_D$ +179 (*c* 1.0, $CHCl_3$). (Found: $M^{+\bullet}$, 368.1625. C, 71.24; H, 6.54. $C_{22}H_{24}O_5$ requires: $M^{+\bullet}$, 368.1624. C, 71.72; H, 6.57%.) (R_f=0.4 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (dm, J=7.8 Hz, 2H), 7.55 (m, 1H), 7.41 (tm, J=7.8 Hz, 2H), 6.23 (br t, J=7.5 Hz, 1H), 6.14 (dd, J=7.5 and 0.6 Hz, 1H), 5.10 (s, 1H), 3.69 (s, 3H), 3.20 (ddd, J=6.5, 2.5, and 1.1 Hz, 1H), 2.73 (m, 1H), 2.49–2.29 (complex m, 3H), 1.30 (s, 3H), 1.16 (s, 3H), 1.13 (partially obscured m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.3, 177.7, 166.1, 139.4, 133.2, 129.9, 129.4, 128.3, 127.0, 74.0, 52.1, 51.6, 50.2, 47.0, 43.8, 41.6, 40.9, 39.2, 23.7, 18.3; IR ν_{max} 2965, 2932, 1740, 1725, 1450, 1325, 1268, 1197, 1172, 1110, 1070, 1028, 985, 710 cm^{-1}; MS m/z (EI, 70 eV) 368 ($M^{+\bullet}$, 1%), 309 (12), 246 (51), 218 (51), 206 (25), 186 (18), 174 (26), 159 (37), 158 (75), 146 (55), 131 (20), 106 (45), 105 (100), 91 (20), 77 (70).

4.2.12. Methyl (1*R*,2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-1-(benzoyloxy)decahydro-4,5b-dimethyl-2-oxo-1*H*-cyclopenta[*a*]-cyclopropa[*cd*]pentalene-4-carboxylate (19), methyl (1*S*, 2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-1-(benzoyloxy)decahydro-4,5b-dimethyl-2-oxo-1*H*-cyclopenta[*a*]cyclopropa[*cd*]-pentalene-4-carboxylate (20) and methyl (1*S*/*R*,2a*R*,

4a*R*,6*S*,7a*R*,7b*S*)-1-(benzoyloxy)-1,2a,4a,5,6,7,7a,7b-octahydro-6,7b-dimethyl-2-oxo-2*H*-cyclobut[*e*]indene-6-carboxylate (21). A deoxygenated solution of compound **18** (217 mg, 0.59 mmol) and acetophenone (172 μL, 1.47 mmol) in acetone (120 mL) that was contained in a Pyrex™ vessel jacketed by a water-cooled (5–10 °C) solution of sodium bromide (750 g) and lead(II) nitrate (8 g) in water (1000 mL) was subjected to irradiation with a Philips 125 W HPL-N lamp for 80 h. The reaction mixture was then concentrated under reduced pressure and the ensuing pale-yellow oil subjected to flash chromatography (silica, 5:95→3:7 v/v ethyl acetate/hexane gradient elution) thus affording three fractions, A–C.

Concentration of fraction A afforded the *title compound* ***19*** (19.2 mg, 9%) as a clear colorless oil, $[\alpha]_D$ +35 (*c* 0.6, $CHCl_3$). (Found: $M^{+\bullet}$, 368.1623. $C_{22}H_{24}O_5$ requires: $M^{+\bullet}$, 368.1624.) [R_f=0.3(5) in 3:7 v/v ethyl acetate/hexane.] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.57 (tt, *J*=7.5 and 1.5 Hz, 1H), 7.43 (tm, *J*=7.5 Hz, 2H), 4.92 (br s, 1H), 3.68 (s, 3H), 2.82 (ddd, *J*=13.8, 9.3, and 2.1 Hz, 1H), 2.65 (m, 1H), 2.53 (t, *J*=6.0 Hz, 1H), 2.39 (m, 1H), 2.23 (m, 2H), 1.79 (dd, *J*=10.2 and 6.0 Hz, 1H), 1.57 (m, 1H), 1.36 (s, 3H), 1.30 (m, 1H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 177.7, 165.6, 133.3, 129.9, 129.4, 128.4, 84.3, 60.1, 52.2, 51.6, 50.9, 44.6, 43.4, 40.8, 40.6, 39.5, 39.0, 25.0, 15.4; IR ν_{max} 2919, 1726, 1451, 1315, 1266, 1197, 1175, 1106, 1069, 1026, 711 cm^{-1}; MS *m*/*z* (EI, 70 eV) 368 ($M^{+\bullet}$, 5%), 309 (12), 263 (38), 246 (68), 218 (47), 206 (52), 203 (56), 159 (63), 158 (93), 146 (75), 145 (55), 106 (81), 105 (95), 77 (100).

Concentration of fraction B afforded the *title compound* ***20*** (178 mg, 82%) as a clear colorless oil, $[\alpha]_D$ −75 (*c* 0.4, $CHCl_3$). (Found: $M^{+\bullet}$, 368.1622. $C_{22}H_{24}O_5$ requires: $M^{+\bullet}$, 368.1624.) [R_f=0.3(0) in 3:7 v/v ethyl acetate/hexane.] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (dm, *J*=7.8 Hz, 2H), 7.57 (tt, *J*=7.8 and 1.5 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 2H), 5.34 (d, *J*=1.5 Hz, 1H), 3.65 (s, 3H), 2.77 (ddd, *J*=13.8, 9.3, and 2.4 Hz, 1H), 2.67–2.49 (complex m, 2H), 2.29 (t, *J*=5.4 Hz, 1H), 2.14–2.04 (complex m, 2H), 1.79 (dd, *J*=10.2 and 5.4 Hz, 1H), 1.55 (t, *J*=12.0 Hz, 1H), 1.36 (s, 3H), 1.33 (m, 1H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.1, 177.8, 165.4, 133.4, 129.9, 129.3, 128.4, 83.1, 54.2, 52.0, 51.5, 49.7, 44.5, 43.0, 40.4, 36.0, 33.6, 32.5, 24.8, 20.6; IR ν_{max} 2928, 1740, 1725, 1451, 1314, 1269, 1176, 1112, 1071, 999, 711 cm^{-1}; MS *m*/*z* (EI, 70 eV) 368 ($M^{+\bullet}$, 66%), 309 (16), 263 (61), 246 (25), 203 (35), 106 (50), 105 (100), 77 (78).

Concentration of fraction C afforded the *title compound* ***21*** (traces[†]) as a clear colorless oil. [Found: $(M-CO-CH_3\bullet)^+$, 325.1436. $C_{22}H_{24}O_5$ requires: $(M-CO-CH_3\bullet)^+$, 325.1440.] (R_f=0.5 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (dm, *J*=7.2 Hz, 2H), 7.60 (tt, *J*=7.2 and 1.5 Hz, 1H), 7.45 (tm, *J*=7.2 Hz, 2H), 5.94 (d, *J*=3.0 Hz, 1H), 5.74 (dm, *J*=10.0 Hz, 1H), 5.63 (ddd, *J*=10.0, 4.8, and 2.7 Hz, 1H), 3.68 (s, 3H), 3.18 (m, 1H), 3.02 (m, 1H), 2.74–2.60 (complex m, 2H), 2.35 (dd, *J*=13.0 and 7.2 Hz, 1H), 1.67 (dd, *J*=13.0 and 1.5 Hz, 1H), 1.29 (s, 3H), 1.19 (s, 3H), 1.18 (partially obscured m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.3, 178.8, 165.0, 133.6, 133.3, 130.0, 128.7, 128.5, 118.5, 82.9, 57.7, 52.1, 48.4, 43.6, 42.2, 40.4, 38.2, 37.1, 27.7, 19.2; IR ν_{max} 2954, 2873, 1790, 1727, 1451, 1267, 1217, 1165, 1107, 1025, 990, 710 cm^{-1}; MS *m*/*z* (EI, 70 eV) 325 [$(M-CO-CH_3\bullet)^+$, ca. 1%], 246 (28), 206 (37), 159 (50), 158 (99), 146 (72), 145 (59), 106 (53), 105 (67), 77 (100). This material is unstable and decomposes on standing at 18 °C in air for short periods of time.

[†] Sufficient quantities of compound **21** were accumulated from the various experiments described in the text to allow it to be characterized spectroscopically.

4.2.13. Photochemically promoted epimerization of compound 19 and generation of isomer 20. A sample of compound **19** (50.4 mg, 0.14 mmol) was subjected to irradiation for 36 h under the conditions defined immediately above. Work-up followed by chromatographic purification afforded isomer **20** (48.9 mg, 97%) that proved identical, in all respects, with an authentic sample.

4.2.14. Methyl (2*S*,3a*R*,3b*R*,6a*S*,7a*S*)-decahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (22) and methyl (2*S*,2a*R*,2b*S*,4*S*,5a*R*,6*S*,6a*R*)-decahydro-2-hydroxy-4,6-dimethyl-2,6-methanocyclobuta[*a*]pentalene-4-carboxylate (23).

4.2.14.1. Method 1. A magnetically stirred solution of cyclopropane **20** (67 mg, 0.18 mmol) in THF/methanol (1.5 mL of a 2:1 v/v mixture) was cooled to −78 °C and then treated with samarium(II) iodide (7.28 mL of a 0.1 M solution in THF, 0.73 mmol). The ensuing mixture was stirred at −78 °C for 1 h, then warmed to 18 °C, and stirred at the latter temperature for a further 2 h, after which time the initial blue color of the reaction mixture had been discharged. The reaction mixture so obtained was treated with K_2CO_3 (5 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic fractions were washed with water (1×5 mL) and brine (1×5 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 1:9 v/v diethyl ether/hexane elution) to yield two fractions, A and B.

Concentration of fraction A afforded the *title compound* ***22*** (25.5 mg, 56%) as a clear colorless oil, $[\alpha]_D$ −121 (*c* 0.2, $CHCl_3$) {lit.[18] $[\alpha]_D$ −125 (*c* 1.2, $CHCl_3$)}. (Found: $M^{+\bullet}$, 250.1570. $C_{15}H_{22}O_3$ requires: $M^{+\bullet}$, 250.1569.) (R_f=0.3 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.66 (s, 3H), 2.70 (m, 1H), 2.60–2.34 (complex m, 4H), 2.24–2.06 (complex m, 3H), 2.03 (d, *J*=7.2 Hz, 2H), 1.70 (m, 1H), 1.58–1.44 (complex m, 1H), 1.30 (s, 3H), 1.06 (m, 1H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.2, 178.0, 52.9, 52.0, 51.9, 51.2, 49.1, 46.0, 44.5, 42.9, 41.4, 40.6, 39.6, 24.4, 22.1; IR ν_{max} 2950, 1740, 1460, 1406, 1377, 1306, 1251, 1196, 1168, 1080, 846 cm^{-1}; MS *m*/*z* (EI, 70 eV) 250 ($M^{+\bullet}$, 3%), 248 (2), 192 (100), 133 (75), 105 (61).

Concentration of fraction B afforded the *title compound* ***23*** (11.4 mg, 25%) as a white crystalline solid, mp=79–82 °C, $[\alpha]_D$ +6 (*c* 0.9, $CHCl_3$). (Found: $M^{+\bullet}$, 250.1576. $C_{15}H_{22}O_3$ requires: $M^{+\bullet}$, 250.1569.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.62 (s, 3H),

2.52–2.24 (complex m, 3H), 2.14 (br s, 1H), 2.04 (ddd, J=12.6, 7.2, and 2.7 Hz, 1H), 1.91 (t, J=3.0 Hz, 1H), 1.89 (dd, J=3.6 and 1.5 Hz, 1H), 1.64 (s, 1H), 1.57 (m, 1H), 1.38 (dd, J=9.6 and 1.5 Hz, 1H), 1.24 (s, 3H), 1.06 (m, 1H), 1.01 (s, 3H), 0.93 (m, 1H), 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.4, 77.9, 63.3, 58.5, 51.9, 51.8, 48.0, 44.9, 42.9, 39.5, 39.4, 39.2, 36.9, 24.3, 18.2; IR ν_{max} 3424, 2951, 2870, 1730, 1463, 1450, 1375, 1331, 1312, 1287, 1247, 1222, 1195, 1168, 1106, 1091, 875, 774, 763, 701 cm^{-1}; MS m/z (EI, 70 eV) 250 ($M^{+\bullet}$, 2%), 235 (3), 207 (13), 193 (76), 147 (50), 133 (100).

4.2.14.2. Method 2. A magnetically stirred solution of cyclopropane **25** (293 mg, 1.18 mmol, obtained as described below) in THF/methanol (15 mL of a 2:1 v/v mixture) was cooled to −78 °C and then treated with samarium(II) iodide (24 mL of a 0.1 M solution in THF, 2.4 mmol). The ensuing mixture was treated in the same manner as detailed immediately above in method 1 thus affording a pale-yellow oil upon work-up. Subjection of this material to flash chromatography (silica, 1:9 v/v diethyl ether/hexane elution) yielded two fractions, A and B.

Concentration of fraction A afforded compound **22** (173 mg, 59%) as a clear colorless oil (R_f=0.4 in 3:7 v/v ethyl acetate/hexane). This material was identical, in all respects, with that obtained via method 1.

Concentration of fraction B afforded compound **23** (74 mg, 25%) as a white crystalline solid (R_f=0.2 in 3:7 v/v ethyl acetate/hexane). This material was identical, in all respects, with that obtained via method 1.

4.2.14.3. Method 3. A magnetically stirred solution of cyclopropane **25** (756 mg, 3.04 mmol, obtained as detailed below) and AIBN (10 mg, 0.06 mmol) in benzene (95 mL) was treated, at 18 °C, with tri-*n*-butyltin hydride (1.64 mL, 6.09 mmol). The ensuing mixture was heated at reflux for 1.5 h, then cooled to 18 °C, and treated with further aliquots of AIBN (10 mg, 0.06 mmol) and tri-*n*-butyltin hydride (1.64 mL, 6.09 mmol), and refluxing of the reaction mixture was continued for further 1.5 h. This process was repeated once more and such that a total of 6 equiv of tri-*n*-butyltin hydride was added to the original reaction mixture and a total reflux time of 4.5 h had been applied. The cooled reaction mixture was then concentrated under reduced pressure and the light-yellow oil so obtained subjected to flash chromatography (silica, 0:1→1:4 v/v ethyl acetate/hexane gradient elution) thus providing two fractions, A and B.

Concentration of fraction A afforded compound **22** (580 mg, 88% at 87% conversion) as a clear colorless oil (R_f=0.3 in 3:7 v/v ethyl acetate/hexane). This material was identical, in all respects, with that obtained via method 1.

Concentration of fraction B afforded the starting cyclopropane **25** (101 mg, 13% recovery) as a clear colorless oil (R_f=0.2 in 3:7 v/v ethyl acetate/hexane). This material was identical, in all respects, with an authentic sample.

4.2.15. Methyl (2*S*,2a*R*,2b*S*,4*S*,5a*R*,6*S*,6a*R*)-decahydro-4,6-dimethyl-2-[(4-nitrobenzoyl)oxy]-2,6-methanocyclobuta[*a*]pentalene-4-carboxylate (24). A magnetically stirred solution of alcohol **23** (20 mg, 0.08 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (34 g, 0.28 mmol) in dichloromethane (2 mL) was treated with triethylamine (30 μL, 0.22 mmol) and freshly prepared *p*-nitrobenzoyl chloride (52 mg, 0.28 mmol). The ensuing mixture was stirred at 18 °C for 3 h before being quenched with water (2 mL) and then diluted with dichloromethane (10 mL). The separated organic phase was washed with $NaHCO_3$ (1×2 mL of a saturated aqueous solution) and brine (1×2 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing solid was recrystallized (hexane) to give the *title ester* ***24*** (24 mg, 75%) as a white crystalline solid, mp=89–95 °C (with decomposition), $[\alpha]_D$ −19 (*c* 0.5, $CHCl_3$). (Found: $M^{+\bullet}$, 399.1684. $C_{22}H_{25}NO_6$ requires: $M^{+\bullet}$, 399.1682.) (R_f=0.5 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J=9.0 Hz, 2H), 8.16 (d, J=9.0 Hz, 2H), 3.67 (s, 3H), 2.67 (q, J=6.1 Hz, 1H), 2.56–2.34 (complex m, 3H), 2.20–1.98 (complex m, 3H), 1.78 (dd, J=9.3 and 1.5 Hz, 1H), 1.56 (br s, 1H), 1.41 (br dd, J=9.3 and 1.8 Hz, 1H), 1.27 (s, 3H), 1.10 (s, 3H), 1.00 (dd, J=12.3 and 11.1 Hz, 1H), 0.90 (dd, J=12.3 and 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.2, 163.7, 150.4, 136.0, 130.7, 123.5, 81.6, 61.3, 58.2, 51.9, 51.7, 47.5, 42.8, 42.0, 40.1, 39.1, 37.8, 37.7, 24.2, 18.1; IR ν_{max} 2954, 2920, 2862, 1727, 1528, 1349, 1284, 1270, 1224, 1169, 1147, 1118, 872, 831, 718 cm^{-1}; MS m/z (EI, 70 eV) 399 ($M^{+\bullet}$, 2%), 340 (10), 339 (5), 249 (15), 232 (22), 193 (67), 150 (100), 120 (85).

4.2.16. Methyl (2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-decahydro-4,5b-dimethyl-2-oxo-1*H*-cyclopenta[*a*]cyclopropa[*cd*]-pentalene-4-carboxylate (25).

4.2.16.1. Method 1. A magnetically stirred solution of compound **19** (185 mg, 0.50 mmol) in THF/methanol (7.5 mL of a 2:1 v/v mixture) was cooled to −78 °C and then treated, dropwise, with samarium(II) iodide (11 mL of 0.1 M solution in THF, 1.1 mmol) until a blue color persisted (ca. 10 min). The reaction mixture was then treated with K_2CO_3 (10 mL of saturated aqueous solution) and the separated aqueous phase extracted with diethyl ether (3×20 mL). The combined organic fractions were washed with water (1×10 mL) and brine (1×10 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the *title compound* ***25*** (122 mg, 98%) as a clear colorless oil, $[\alpha]_D$ −36 (*c* 1.3, $CHCl_3$). (Found: $M^{+\bullet}$, 248.1414. $C_{15}H_{20}O_3$ requires: $M^{+\bullet}$, 248.1412.) (R_f=0.2 in 3:7 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (s, 3H), 2.76 (ddd, J=13.8, 9.3, and 2.1 Hz, 1H), 2.56 (m, 1H), 2.37 (t, J=5.4 Hz, 1H), 2.30 (dd, J=18.0 and 1.2 Hz, 1H), 2.20–2.08 (complex m, 2H), 2.05–1.94 (complex m, 2H), 1.63 (dd, J=10.2 and 6.3 Hz, 1H), 1.48 (t, J=13.8 Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.5, 178.1, 63.0, 56.5, 52.0, 51.5, 47.1, 44.6, 43.1, 40.6, 40.0, 39.2, 38.6, 25.2, 22.1; IR ν_{max} 2959, 2928, 2872, 1727, 1461, 1378, 1289, 1196, 1160, 1124, 1086, 958, 874, 808 cm^{-1}; MS m/z (EI, 70 eV) 248 ($M^{+\bullet}$, 16%), 206 (90), 174 (72), 146 (100), 131 (82).

4.2.16.2. Method 2. A sample of compound **20** (720 mg, 1.96 mmol) was subjected to react with samarium(II) iodide at −78 °C under the conditions defined immediately above. Work-up provided the title compound **25** (470 mg, 97%) as

a clear colorless oil that was identical, in all respects, with the material generated by method 1.

4.2.17. Methyl (2*S*,3a*R*,3b*S*,7a*S*)-2,3,3a,3b,4,4,7,7a-octahydro-2,3b-dimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (28).

4.2.17.1. Method 1. In an adaptation of protocols defined by Crimmins and Mascarella,[40] a magnetically stirred solution of ketone **22** (51.5 mg, 0.21 mmol) and 2,6-lutidine (96 mL, 0.82 mmol) in dichloromethane (2 mL) was cooled to 0 °C and then treated, dropwise, with TMSOTf (112 μL, 0.62 mmol). The ensuing mixture was warmed to 18 °C, stirred for 1 h at this temperature, and then treated with water (2 mL) and dichloromethane (10 mL). The separated aqueous phase was extracted with dichloromethane (3×5 mL) and the combined organic fractions were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a 4:1 mixture, as judged by ^{1}H NMR spectroscopic analysis, of the silyl enol ethers **26** and **27** as a light-yellow oil. A solution of these ethers in acetonitrile (1.5 mL) was added to a magnetically stirred slurry of palladium(II) acetate (92 mg, 0.41 mmol) and *p*-benzoquinone (23 mg, 0.21 mmol) in acetonitrile (0.5 mmol). The ensuing mixture was stirred at 18 °C for 18 h, then diluted with diethyl ether (15 mL), and filtered through a pad of Celite™ contained in a sintered-glass funnel. The solids thus retained were washed with additional diethyl ether (3×5 mL) and the combined filtrates concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of the fraction A afforded the starting ketone **22** (16 mg, 31% recovery) as a clear colorless oil (R_f=0.4 in 3:7 v/v ethyl acetate/hexane). This material was identical, in all respects, with an authentic sample.

Concentration of the fraction B afforded the title enone **28**[18] (35 mg, 85% at 69% conversion) as a clear colorless oil, $[\alpha]_D$ +56 (*c* 0.6, $CHCl_3$) {lit.[18] $[\alpha]_D$ +57 (*c* 0.7, $CHCl_3$)}. (Found: $M^{+\bullet}$, 248.1416. $C_{15}H_{20}O_3$ requires: $M^{+\bullet}$, 248.1412.) (R_f=0.4 in 1:1 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.68 (m, 1H), 3.66 (s, 3H), 2.84–2.63 (complex m, 2H), 2.52 (ddd, *J*=12.3, 7.5, and 1.5 Hz, 1H), 2.44–2.21 (complex m, 3H), 2.27 (s, 2H), 1.53–1.39 (complex m, 1H), 1.35 (s, 3H), 1.24 (m, 1H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.5, 195.0, 178.0, 122.5, 54.7, 52.5, 52.0, 50.6, 49.2, 46.3, 44.4, 37.1, 32.5, 24.5, 24.4; IR ν_{max} 2960, 1728, 1709, 1635, 1467, 1202, 1169, 1093, 876 cm^{-1}; MS *m/z* (EI, 70 eV) 248 ($M^{+\bullet}$, 100%), 233 (32), 189 (75), 188 (70), 173 (63), 120 (70), 108 (92), 91 (55), 81 (68), 80 (82), 79 (68).

4.2.17.2. Method 2. A magnetically stirred solution of ketone **22** (462 mg, 1.88 mmol) in toluene/DMSO (7.5 mL of a 2:1 v/v mixture) was treated with *p*-TsOH·H_2O (105 mg, 0.55 mmol) and IBX[41] (2.07 g, 7.38 mmol). The resulting solution was heated at 85 °C for 72 h, and then cooled and diluted with diethyl ether (100 mL). The separated organic phase was washed with $NaHCO_3$ (2×5 mL of a 5% w/v aqueous solution), water (2×50 mL), and brine (1×50 mL), and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions, the title enone **28** (408 mg, 89%) as a clear colorless oil (R_f=0.4 in 1:1 v/v ethyl acetate/hexane). This material was identical, in all respects, with that generated via method 1.

4.2.18. Methyl [2*S*-(2α,3aα,3bβ,7aα)]-2,3,3a,3b,4,5,7,7a-octahydro-2,3b-dimethyl-4-methylene-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (33).

4.2.18.1. Method 1. *Step i*: following a procedure established by Ikegami et al.,[17b] a magnetically stirred solution of enone **28** (27 mg, 0.11 mmol) in THF (1 mL) was cooled to −78 °C and then treated with freshly prepared LDA (513 mL of a 0.43 M solution in THF, 0.22 mmol). The ensuing mixture was stirred at −78 °C for 10 min and then treated with iodomethane (68 μL, 1.09 mmol) after which it was allowed to warm to 0 °C over 1 h, then quenched with NH_4Cl (2 mL of a saturated aqueous solution), and extracted with diethyl ether (3×5 mL). The combined organic fractions were washed with brine (1×5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a single diasteroisomeric form of methyl [2*S*-(2α,3aα,3bβ,7aα)]-2,3,3a,3b,4,5,7,7a-octahydro-2,3b,4-trimethyl-5-oxo-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (**29**)[17b] as a clear colorless oil that was immediately used in step ii.

Step ii: a magnetically stirred solution of compound **29** (obtained as described in step i) in THF (1.5 mL) was cooled to −78 °C and then treated with freshly prepared LDA (513 mL of a 0.43 M solution, 0.22 mmol). Stirring was continued at −78 °C for 0.5 h and then the reaction mixture was treated with a solution of phenylselenyl chloride (68.3 mL of a 0.48 M solution in THF, 0.33 mmol). Stirring was continued for 0.25 h and then the reaction mixture was warmed to 18 °C over 0.5 h and quenched with NH_4Cl (2 mL of a saturated aqueous solution). The ensuing mixture was extracted with diethyl ether (3×5 mL) and the combined organic fractions washed with brine (1×5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 3:1 mixture of the two diasteroisomeric forms of methyl [2*S*-(2α,3aα,3bβ,7aα)]-2,3,3a,3b,4,5,7,7a-octahydro-2,3b,4-trimethyl-5-oxo-4-(phenylseleno)-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (**30**)[17b] as a clear colorless oil.

Step iii: a magnetically stirred solution of selenide **30** (obtained as described in step ii) in THF/water/methanol (4 mL of a 1:1:2 v/v/v mixture) was treated with $NaIO_4$ (121 mg, 0.54 mmol) and the ensuing mixture was stirred at 18 °C for 1 h, then diluted with dichloromethane (10 mL) and $Na_2S_2O_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions, the title dienone **33**[17b] (17.4 mg, 61% from **28**) as a clear colorless oil (R_f=0.5 in 1:1 v/v ethyl acetate/hexane). This material was often contaminated with varying amounts of the chromatographically inseparable precursor **29**. As a result, full characterization of compound **33** was carried out using samples prepared by method 2 detailed immediately below.

4.2.18.2. Method 2. *Step i*: a magnetically stirred solution of enone **28** (94 mg, 0.38 mmol) in THF (5 mL) maintained at −78 °C under a nitrogen atmosphere was treated, dropwise, with LiHMDS (566 μL of a 1.0 M solution in THF, 0.57 mmol) and the resulting mixture was stirred at this temperature for 1 h. After this time Eschenmoser's salt (227 mg, 1.13 mmol, ex. Aldrich Chemical Co.) was added, in one portion, to the reaction mixture and this was then allowed to warm to 18 °C and stirred at this temperature for 16 h. The reaction mixture was then quenched with HCl (20 mL of a 3 M aqueous solution), and after 5 min the aqueous phase was separated and extracted with diethyl ether (3×20 mL). The combined organic phases were washed with $NaHCO_3$ (1×20 mL of saturated aqueous solution) and brine (1×10 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the starting enone **28** (5 mg, 5% recovery) as a clear colorless oil and identical, in all respects, with an authentic sample. The aqueous layers obtained as described above were combined and basified to pH 14 using NaOH (4 M aqueous solution) and then extracted with dichloromethane (3×50 mL). The combined organic fractions were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give *methyl [2S-(2α,3aα,3bβ,7aα)]-2,3,3a,3b,4,5,7,7a-octahydro-2,3b-dimethyl-4-[(dimethylamino)methyl]-5-oxo-1H-cyclopenta-[a]pentalene-2-carboxylate* (**31**) (91 mg, 79% at 95% conversion) as a clear colorless oil and as a single diastereoisomer of undetermined configuration at *C*4. (Found: $M^{+\bullet}$, 305.1992. $C_{18}H_{27}NO_3$ requires: $M^{+\bullet}$, 305.1991.) ^1H NMR ($CDCl_3$, 300 MHz) δ 5.63 (d, J=1.5 Hz, 1H), 3.65 (s, 3H), 2.75 (dd, J=15.0 and 8.0 Hz, 1H), 2.68–2.44 (complex m, 3H), 2.40–2.24 (complex m, 5H), 2.20 (s, 6H), 1.47 (dd, J=13.8 and 8.0 Hz, 1H), 1.34 (s, 3H), 1.27 (dd, J=12.0 and 10.5 Hz, 1H), 1.13 (s, 3H); IR ν_{max} 2957, 2923, 2851, 1729, 1700, 1635, 1465, 1373, 1198, 1165, 1093 cm^{-1}; MS *m/z* (EI, 70 eV) 305 ($M^{+\bullet}$, 20%), 260 (12), 201 (16), 200 (15), 170 (18), 141 (16), 77 (27), 58 (100).

Step ii: a magnetically stirred solution of amine **31** (275 mg, 0.90 mmol) in diethyl ether/dichloromethane (40 mL of a 3:1 v/v mixture) was treated with iodomethane (678 μL, 10.9 mmol), the resulting solution stirred at 18 °C for 16 h and then concentrated under reduced pressure. The ensuing white residue, presumed to be the methiodide **32**, was dissolved in dichloromethane (5 mL) and the resulting solution treated with basic alumina (ca. 250 mg of 0.063–0.200 mesh and grade 1 activity material). The suspension thus formed was stirred magnetically at 18 °C for 0.5 h and then concentrated under reduced pressure, and the solid mass so obtained was dried under reduced pressure (ca. 6 mm Hg). The resulting solid was loaded onto the top of a flash chromatographic column comprised of alumina and this was subsequently eluted with dichloromethane. Concentration of the relevant fractions then afforded the title dienone **33**[17b] (179 mg, 76%) as a clear, colorless oil $[\alpha]_D$ +91 (*c* 0.3, $CHCl_3$) {lit.[17b] $[\alpha]_D$ +74 (*c* 0.4, $CHCl_3$) for 80% ee material}. (Found: $M^{+\bullet}$, 260.1417. $C_{16}H_{20}O_3$ requires: $M^{+\bullet}$, 260.1412.) (R_f=0.5 in 1:1 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 600 MHz) δ 5.89 (s, 2H), 5.17 (s, 1H), 3.65 (s, 3H), 2.80 (dd, J=7.5 and 3.9 Hz, 1H), 2.70 (m, 1H), 2.55 (dd, J=6.3 and 4.2 Hz, 1H), 2.46–2.36 (complex m, 2H), 2.29 (ddd, J=7.5, 3.6, and 0.6 Hz, 1H), 1.68–1.56 (complex m, 1H), 1.38 (s, 3H), 1.30 (t, J=6.0 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 189.3, 177.9, 153.6, 123.5, 113.3, 54.9, 52.1, 51.7, 48.1, 46.4, 44.9, 37.0, 32.3, 24.5, 23.4; IR ν_{max} 2962, 2925, 1727, 1701, 1622, 1466, 1374, 1307, 1256, 1196, 1165, 1094, 860 cm^{-1}; MS *m/z* (EI, 70 eV) 260 ($M^{+\bullet}$, 65%), 247 (21), 232 (27), 202 (100), 201 (90), 200 (93), 132 (68), 121 (65), 91 (67).

4.2.19. [2*S*-(2α,3aα,3bβ,7aα)]-2,3,3a,3b,4,5,7,7a-Octahydro-2,3b-dimethyl-4-methylene-5-oxo-1*H*-cyclopenta[*a*]-pentalene-2-carboxylic acid (34). A magnetically stirred solution of ester **33** (101 mg, 0.39 mmol) and anhydrous lithium iodide (780 mg, 5.83 mmol) in DMF (15 mL) was heated at reflux for 34 h, then cooled and diluted with water (15 mL). The ensuing mixture was acidified with HCl (10% w/w aqueous solution) to pH 1–2 and then extracted with diethyl ether (5×30 mL). The combined organic fractions were washed with water (1×10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A afforded the starting ester **33** (23 mg, 22% recovery) as a clear colorless oil (R_f=0.5 in 1:1 v/v ethyl acetate/hexane). This material was identical, in all respects, with an authentic sample.

Concentration of fraction B afforded the title acid **34** (69 mg, 73% at 78% conversion) as white needles, mp=137–143 °C (with decomposition) (lit.[15] mp=113–115 °C) $[\alpha]_D$ +77 (*c* 0.7, $CHCl_3$) {lit.[18] $[\alpha]_D$ +74 (*c* 0.4, $CHCl_3$)}. (Found: $M^{+\bullet}$, 246.1256. $C_{15}H_{18}O_3$ requires: $M^{+\bullet}$, 246.1256.) (R_f= 0.2 in 1:1 v/v ethyl acetate/hexane.) ^1H NMR ($CDCl_3$, 500 MHz) δ 5.90 (d, J=0.9 Hz, 1H), 5.89 (s, 1H), 5.16 (s, 1H), 2.86–2.72 (complex m, 2H), 2.55 (ddd, J=7.5, 4.2, and 0.9 Hz, 1H), 2.50–2.36 (complex m, 2H), 2.30 (m, 1H), 1.61 (dd, J=7.5 and 4.8 Hz, 1H), 1.41 (s, 3H), 1.33 (t, J=6.9 Hz, 1H), 1.17 (s, 3H) (signal due to carboxylic acid proton not observed); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7, 189.3, 183.7, 153.5, 123.5, 113.5, 54.7, 51.7, 48.1, 46.2, 44.8, 36.8, 32.3, 24.3, 23.4; IR ν_{max} 2965, 1698, 1646, 1614, 1468, 1404, 1307, 1257, 1197, 1156, 941, 861 cm^{-1}; MS *m/z* (EI, 70 eV) 246 ($M^{+\bullet}$, 100%), 218 (31), 201 (62), 200 (43), 132 (40), 91 (57).

4.2.20. (1a*R*,3a*R*,3b*R*,5*S*,6a*R*,7a*S*)-Decahydro-3a,5-dimethyl-3-methylene-2-oxocyclopenta[4,5]pentaleno[1,6a-*b*]oxirene-5-carboxylic acid [(−)-complicatic acid (2)]. Following a procedure established by Ikegami et al.,[17b] a magnetically stirred solution of acid **34** (27 mg, 0.11 mmol) in methanol (1.5 mL) was cooled to −50 °C and treated with hydrogen peroxide (110 μL of a 30% w/v aqueous solution, 0.33 mmol) and then with NaOH (330 μL of a 1 M aqueous solution, 0.33 mmol). The ensuing mixture was warmed to −36 °C over a period of 0.75 h, poured into NH_4Cl (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3×5 mL). The combined organic fractions were washed with brine (1×2 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the relevant

fractions gave (−)-complicatic acid (**2**) (10 mg, 35%) as a clear colorless oil, $[\alpha]_D$ −77 (*c* 0.3, $CHCl_3$) {lit.[4] $[\alpha]_D$ −79 (*c* 1.1, $CHCl_3$)}. (Found: $M^{+\bullet}$, 262.1215. $C_{15}H_{18}O_4$ requires: $M^{+\bullet}$, 262.1205.) (R_f=0.3 in 1:1 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.08 (s, 1H), 5.30 (s, 1H), 3.44 (s, 1H), 2.74 (m, 1H), 2.56 (ddd, *J*=7.8, 4.5, and 3.9 Hz, 1H), 2.44 (m, 1H), 2.10–1.96 (complex m, 3H), 1.59 (dd, *J*=7.8 and 5.4 Hz, 1H), 1.42 (s, 3H), 1.29 (t, *J*=14.7 Hz, 1H), 1.19 (s, 3H) (signal due to carboxylic acid proton not observed); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.7, 183.7, 152.6, 120.5, 76.4, 60.9, 53.2, 49.6, 46.4, 46.0, 39.2, 36.8, 29.7, 24.1, 17.4; IR ν_{max} 2966, 1729, 1697, 1637, 1469, 1407, 1312, 1227, 1159, 1098, 944, 794, 750 cm^{-1}; MS *m*/*z* (EI, 70 eV) 262 ($M^{+\bullet}$, 4%), 205 (70), 159 (42), 105 (100), 77 (41).

4.2.21. (1a*R*,2*R*,3a*R*,3b*R*,5*S*,6a*R*,7a*S*)-Decahydro-2-hydroxy-3a,5-dimethyl-3-methylenecyclopenta[4,5]pentaleno[1,6a-*b*]oxirene-5-carboxylic acid [(+)-hirsutic acid (1)]. Following a procedure established by Greene et al.,[18] a magnetically stirred solution of acid **34** (25 mg, 0.10 mmol) in ethanol (1.5 mL) was cooled to −35 °C and treated with hydrogen peroxide (450 μL of a 35% w/v aqueous solution, 0.45 mmol) and then with NaOH (450 μL of a 1 M aqueous solution, 0.45 mmol). The reaction mixture was stirred at −35 °C for 4 h, then ethanol (1.5 mL) and sodium borohydride (72 mg, 1.90 mmol) were added to the reaction mixture, which was gradually warmed to 0 °C and then diluted with water (5 mL) followed by dichloromethane (5 mL). The ensuing mixture was then acidified with HCl (2% w/w aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 8:2:1 v/v/v hexane/ethyl acetate/acetic acid elution) afforded a white solid. Recrystallization (dichloromethane/cyclohexene) of this material afforded (+)-hirsutic acid (**1**) (12 mg, 46%) as white needles, mp=168–171 °C (lit.[17b] mp=170 °C) $[\alpha]_D$ +113 (*c* 0.2, $CHCl_3$) {lit.[4] $[\alpha]_D$ +116 (*c* 1.05, $CHCl_3$)}. (Found: $M^{+\bullet}$, 264.1367. $C_{15}H_{20}O_4$ requires: $M^{+\bullet}$, 264.1362.) (R_f=0.1 in 1:1 v/v ethyl acetate/hexane.) ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.27 (s, 1H), 5.00 (s, 1H), 4.60 (s, 1H), 3.47 (s, 1H), 2.65 (m, 1H), 2.49 (dd, *J*=6.0 and 3.9 Hz, 1H), 2.34 (m, 1H), 2.27 (m, 1H), 1.88 (m, 2H), 1.49 (dd, *J*=6.6 and 4.5 Hz, 1H), 1.38 (s, 3H), 1.21 (m, 1H), 1.04 (s, 3H) (signals due to carboxylic acid and hydroxyl protons not observed); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.4, 158.4, 111.9, 75.3, 74.0, 63.6, 53.1, 48.5, 48.4, 46.3, 39.2, 36.5, 29.9, 24.1, 17.0; IR ν_{max} 3397 (br), 2965, 2071, 1698, 1468, 1438, 1405, 1378, 1310, 1260, 1217, 1168, 1099, 1066, 1029, 1000, 916, 888, 684 cm^{-1}; MS *m*/*z* (EI, 70 eV) 264 ($M^{+\bullet}$, 20%), 189 (100), 138 (90), 105 (67), 81 (60), 43 (63).

4.3. X-ray crystallographic studies

4.3.1. Crystal data (for compound 10). $C_{16}H_{22}O_3$, *M*=262.35, *T*=200(1) K, monoclinic, space group $P2_1$, *Z*=2, *a*=9.2693(10), *b*=7.5640(9), *c*=10.1754(11) Å, β=95.655(7)°, *V*=709.96(14)Å^3, D_x=1.227 g cm^{-3}, 1364 unique data ($2\theta_{max}$=50.344°), 1204 with $I>2.0\sigma(I)$; *R*=0.0335, *Rw*=0.0391, *S*=1.1256.

4.3.2. Crystal data (for compound 11). $C_{18}H_{24}O_5$, *M*=320.39, *T*=200(1) K, monoclinic, space group $P2_1$, *Z*=2, *a*=9.8364(2), *b*=7.9963(2), *c*=11.3300(3) Å, β=107.2807(16)°, *V*=850.93(4) Å^3, D_x=1.250 g cm^{-3}, 2084 unique data ($2\theta_{max}$=54.894°), 1653 with $I>2.0\sigma(I)$; *R*=0.0278, *Rw*=0.0318, *S*=1.1543.

4.3.3. Crystal data (for compound 13). $C_{18}H_{26}O_5$, *M*=322.40, *T*=200(1) K, orthorhombic, space group $P2_12_12_1$, *Z*=4, *a*=6.4593(1), *b*=14.2696(2), *c*=18.2058(2) Å, *V*=1678.06(5) Å^3, D_x=1.276 g cm^{-3}, 2220 unique data ($2\theta_{max}$=55°), 1848 with $I>3.0\sigma(I)$; *R*=0.0314, *Rw*=0.0373, *S*=1.1427.

4.3.4. Crystal data (for compound 34). $C_{15}H_{18}O_3$, *M*=246.31, *T*=200(1) K, orthorhombic, space group $P2_12_12_1$, *Z*=4, *a*=6.2051(1), *b*=10.0685(2), *c*=20.7552(5) Å, *V*=1296.70(5) Å^3, D_x=1.262 g cm^{-3}, 1729 unique data ($2\theta_{max}$=54.934°), 1335 with $I>2.0\sigma(I)$; *R*=0.0304, *Rw*=0.0315, *S*=1.2010.

4.3.5. Structural determinations. Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[48] Structural solution was by direct methods (SIR92)[49] and refined using the CRYSTALS program package.[50] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC numbers 633749–633752 for compounds **10**, **11**, **13**, and **34**, 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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