Enantiospecific first total synthesis of cucumin-H

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Enantiospecific first total synthesis of the linear triquinane sesquiterpene cucumin-H has been described. (R)-Limonene has been employed as the chiral starting material and a combination of Claisen rearrangement, intramolecular cyclopropanation and Nazarov reactions are employed for the regio- and stereospecific construction of the triquinane framework.

Keywords: Cucumanes, triquinanes, limonene, Nazarov cyclisation, Claisen rearrangement, intramolecular cyclopropanation

The polyquinane natural products have aroused a great deal of interest among synthetic chemists in the last three decades. Indeed, polyquinanes have spearheaded the drive and provided the impetus for the development of new strategies for cyclopentannulations. Among the polyquinanes, triquinanes are the most commonly encountered in sesquiterpenes. The linear triquinanes, bearing thermodynamically favoured cis, anti, cis-tricyclo[6.3.0.0\textsuperscript{2,6}]undecane moiety as the fundamental ring system are the most abundant and four different types, hirsutane, capnellane, pleurotellane and ceratopicanes have been encountered earlier. In 1998, research groups of Steglich and Anke\textsuperscript{2} reported the isolation and structure determination of eight new linear triquinane sesquiterpenes 1-8 from mycelial cultures of the agaric Macrocystidia cucumis, Chart I. Of these eight sesquiterpenes, four belong to the hirsutane group (cucumins A-D, 1-4), one to the ceratopican group (cucumin-H, 8) and the remaining three contains a new triquinane framework cucumane (cucumins E-G, 5-7). Cucumin-H 8 is the second member of the ceratopican group to be isolated from Nature, whose first member ceratopicanol 9 was reported in 1988 by Hanssen and Abraham\textsuperscript{3} from the agar cultures of Ascomycete ceratocystis piceae Ha 4/82. Structure of cucumin-H 8 was determined through incisive high-field NMR studies. However, due to paucity of the material, assignment of the absolute configuration and evaluation of the biological profile were not addressed.

Presence of an interesting tricyclo[6.3.0.0\textsuperscript{2,6}]undecane framework, three quaternary carbon atoms (of which two are vicinal) and a γ-hydroxyenone moiety made cucumin-H 8 attractive and challenging synthetic target. In continuation of our interest in the enantiospecific synthesis of natural products\textsuperscript{4} starting from the readily available monoterpene (R)-limonene 10, we have undertaken the enantiospecific total synthesis of cucumin-H 8. Herein we describe the details of our investigations, which also established the absolute configuration of the natural cucumin-H\textsuperscript{5}.

Retrosynthetic analysis of cucumin-H 8 is depicted in Scheme I. It was envisioned that Nazarov cyclisation\textsuperscript{6} based cyclopentannulation of the bicyclic ketone 11 provides a convenient route for the triquinane enone 12, which could be further elaborated into cucumin-H 8. For the enantiospecific synthesis of the bicyclic ketone 11 containing two vicinal quaternary carbon atoms, intramolecular cyclopropanation of the diazoketone derived from the acid 13, followed by regioselective cleavage of the cyclopropane ring in the tricyclic ketone 14 and degradation of the isopropenyl group in 15 was contemplated. The γ,δ unsaturated acid 13 could be obtained from the allyl alcohol 16 by a Claisen rearrangement. Three step synthesis of the allyl alcohol 16 from (R)-limonene 10 has already been developed in our laboratory\textsuperscript{4a}.

Accordingly, the synthetic sequence has been initiated with the conversion of (R)-limonene 10 into the alcohol 16 employing the procedure developed...
earlier\textsuperscript{4a}, Scheme II. Thus, controlled ozonolysis of the ring olefin in (R)-limonene \textbf{10} followed by intramolecular aldol condensation of the resultant ketoaldehyde using piperidine and acetic acid in refluxing benzene furnished the aldehyde \textbf{17}, which on Luche reduction with sodium borohydride and cerium trichloride heptahydrate in methanol generated the allyl alcohol \textbf{16}. The regio- and stereospecific formation of $\gamma, \delta$-unsaturated carbonyl compounds, coupled with the ease of creation of a quaternary carbon atom from a $\gamma, \gamma$-disubstituted allyl alcohol via [3,3]-sigmatropic rearrangement\textsuperscript{7} synthetically very useful reaction. An \textit{ortho}ester variant of the Claisen rearrangement, developed by Jonhson and coworkers\textsuperscript{8}, was chosen for generation of the acid \textbf{13}. Thus, thermal activation of the allyl alcohol \textbf{16} at 180$^\circ$C with triethyl \textit{ortho}acetate and a catalytic amount of propionic acid in a sealed tube furnished the $\gamma, \delta$-unsaturated ester \textbf{18} in 80\% yield. The structure of the ester \textbf{18} was established from its spectral data. Stereochemistry of the quaternary carbon atom in the ester \textbf{18} was assigned based on the steric crowding due to the isopropenyl group in the transition state.

For the annulation of the second five-membered ring as well as creation of the second quaternary carbon atom, an intramolecular cyclopropanation reaction\textsuperscript{9} of the diazoketone \textbf{19} was contemplated. Thus, refluxing a solution of the ester \textbf{18} in aqueous methanolic sodium hydroxide led to the hydrolysis of the ester moiety to furnish the acid \textbf{13} in 94\% yield.
Reaction of the acid 13 with oxalyl chloride at RT followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane furnished the diazoketone 19. Anhydrous copper sulfate and copper catalysed decomposition of the diazoketone 19 in refluxing cyclohexane, under irradiation with a tungsten lamp, led to the insertion of the resultant keto carbenoid into the ring olefin moiety to furnish the tricyclic ketone 14 in 70% yield (from the acid 13), in a regio- and stereospecific manner. The structure of the tricyclic ketone 14 was established from its spectral data. The stereochemistry of the new chiral centre was assigned on the basis of the approach of the carbenoid from the \textit{syn} face of the olefin as it cannot approach from the \textit{anti} face. For the regioselective cleavage of the C-2 C-3 cyclopropane bond, reduction using alkali metal in liquid ammonia was contemplated. It is well established\textsuperscript{10} that in the reductive cleavage of the cyclopropyl ketones using lithium-liquid ammonia conditions, of the two cyclopropane bonds, the one which has better overlap with the carbonyl \(\pi\)-orbital will be cleaved. Reaction of the tricyclic ketone 14 with lithium in liquid ammonia and THF furnished the bicyclic ketone 15 in 85% yield.

After successfully creating two new chiral centres, the original chiral centre was disposed off by converting it into a ketone group. Thus, isomerization of the isopropenyl group in the diquinane 15 using p-toluenesulfonic acid (PTSA) generated the enone 20 in quantitative yield, whose structure rest secured from spectral data and was confirmed by comparison of the spectral data with that reported by Mehta and Karra\textsuperscript{11}. Incidentally, Mehta and Karra have already converted the enone 20 into (–)-ceratopicanol 9, hence the present synthesis of the diquinane 20.
constitutes a formal total synthesis of (−)-ceratopicanol 9. Ozonolysis of the isopropylidene moiety followed by reductive workup with dimethyl sulfide transformed the enone 20 into the dione 21 in 90% yield. In the dione 21, the C-7 ketone is sterically less crowded than the C-2 ketone, which has been exploited for the regioselective deoxygenation of the C-7 ketone employing a two step methodology via the thiketal 22. Reaction of the dione 21 with ethanedithiol in the presence of a catalytic amount of boron trifluoride diethyl etherate in benzene, regioselectively, generated the thiketal 22 in 80% yield along with 5% of bis-thiketal 23. Reaction of the thiketal 22 with a freshly prepared Raney nickel in refluxing ethanol led to desulfurization furnishing the bicyclic ketone 11 in quantitative yield.

A modified version of the Nazarov reaction6 via a 2-alkyne-1,4-diol was chosen for the annulation of the third cyclopentane ring, Scheme III. Consequently, reaction of the bicyclic ketone 11 with 1-lithio-3-(tetrahydropranyloxy)propyne, generated from propargyl THP ether and n-butyllithium in anhydrous THF at –70°C, furnished the addition product 24. Hydrolysis of the THP ether in 24 with pyridinium p-toluenesulfonate (PPTS) in methanol generated the diol 25. Treatment of the diol 25 with an excess of methanesulfonic acid and phosphorous pentoxide12 furnished the annulated product triquinane enone 12 in low yield (10-25%), whose structure was established from its spectral data, in particular the 13 lines 13C NMR spectrum with characteristic13 three quaternary carbon signals at δ 202.7, 181.3 and 153.3 due to the enone moiety.

To improve the efficiency of the cyclisation reaction, the reaction was carried out with the enynol 26. Dehydration of the THP ether 24 using phosphorous oxychloride and pyridine furnished the ether 27 which on hydrolysis with PPTS in methanol gave the enynol 26. Treatment of the enynol 26 with 2 equivalents of methanesulfonic acid furnished the enone 12 in 70% yield. On the other hand, formation of varying amounts of the rearranged alcohol 28 was observed in addition to triquinane 12, when the diol 25 was treated with 2 equivalents of Eaton’s reagent, Scheme IV. The structure of the alcohol 28 was deduced from its spectral data. X-ray diffraction analysis of a crystalline derivative was opted for unambiguous assignment of the structure of the rearranged alcohol 28. Thus, treatment of the alcohol 28 with p-nitrobenzoyl chloride, pyridine and a catalytic amount of DMAP in methylene chloride furnished the p-nitrobenzoate 29, m.p. 50-52°C, in 98% yield. Single crystal X-ray diffraction analysis of the p-nitrobenzoate 29 confirmed the structure of the rearranged alcohol 28. An ORTEP diagram is depicted in Figure 1.

Formation of the rearranged alcohol 28 can be readily explained via a series of bond migrations as depicted in Scheme V. First protonation of the tertiary hydroxy group generates the bicyclic tertiary carbonium ion 30, which rearranges to the bicyclo[3.2.1]octyl carbonium ion 31. Deprotonation and further bond migration furnishes the rearranged alcohol 28. Finally, it was found that reaction of the diol 25 with 4 equivalents of Eaton’s reagent (15% phosphorous pentoxide in methanesulfonic acid) in 0.01 M solution of anhydrous methylene chloride for one hour furnishes the enone 12 in 70% yield. Interestingly, even the rearranged alcohol 28 on treatment with 2 equivalents of methanesulfonic acid furnished the triquinane 12. Formation of the triquinane 12 from the rearranged alcohol 28 is surprising, as the alcohol 28 has to be converted first into enynol 26 for the cyclisation to proceed to generate the triquinane enone 12.

Next, attention was turned towards the conversion of the triquinane 12 into cucumin-H 8, Scheme VI. Treatment of the enone 12 with an excess of the sodium hydride and methyl iodide in THF at RT furnished the ceratopicanenone 32 in 75% yield, whose structure was established from the spectral data. A reduction-protection-allylic oxidation-deprotection protocol was explored for the region-controlled conversion of the enone 32 into cucumin-H 8. Consequently, regiospecific 1,2-reduction of the enone 32 with LAH at low temperature (−70°C) generated a 1:1:2 inseparable epimeric mixture of the allylic alcohols 33. As the conversion of the allylic alcohol 33 into its tert-butyl(dimethyl)silyl (TBDMS) ether under various conditions was unsuccessful, it was converted into the acetate 34 in moderate yield using acetic anhydride, pyridine and a catalytic amount of DMAP.

Oxidation of the acetate 34 using di-tertiary butyl chromate14 in carbon tetrachloride gave the enedione 35 in excellent yield and in a highly regioselective manner. The structure of the enedione 35 was established from its spectral data. Subsequently, it was contemplated to explore the selective reduction of the enedione 35. The enedione 35 was prepared by direct oxidation of the enone 32. Thus, oxidation of the enone 32 with ditertiarybutyl chromate in
Scheme IV

Figure 1 — ORTEP diagram of the p-nitrobenzoate 29

Scheme V

Reagents: (a) NaH, MeI; (b) LAH; (c) Ac₂O, py, DMAP; (d) tBu₂CrO₄; (e) NaBH₄; (f) DIAD, PPh₃, PNB-OH; (g) K₂CO₃.

Scheme VI
refluxing carbon tetrachloride furnished the enedione 35 in 81% yield. Stereoselective reduction of the enedione 35 with sodium borohydride and cerium trichloride heptahydrate in methanol furnished, exclusively, the alcohol 36 in 95% yield, which is a regioisomer of cucumin-H 8. The structure of the alcohol 36 was established from its spectral data. However, NMR spectrum could not differentiate, unambiguously, whether the alcohol produced is a regioisomer or a stereoisomer of cucumin-H 8. Theoretical calculations (MNDO and AM1 level) indicated that exo sides of both the C-3 and C-7 ketones in enedione 35 are equally preferred (leading to the hydroxy enones 8 and 36) for the hydride attack over the endo face of the C-3 ketone (leading to 37). Whereas the endo face of the C-7 ketone (leading to 38) is hindered for the hydride attack. To unambiguously establish the stereochemistry of the hydroxy enone 36, we have resorted to single crystal X-ray diffraction analysis and a Mitsunobu reaction15 was employed for converting the alcohol 36 into a crystalline derivative. Treatment of the alcohol 36 with triphenylphosphine, disopropyl azodicarboxylate (DIAD) and p-nitrobenzoic acid in THF at RT cleanly furnished the p-nitrobenzoate 39, m.p. 115-117°C, in 85% yield, whose structure was established from the spectral data. Single crystal X-ray diffraction analysis of the p-nitrobenzoate 39 unambiguously established the stereostructure of the benzoate 39. An ORTEP diagram is depicted in Figure 2. Hydrolysis of the ester in the compound 39 with potassium carbonate in methanol at RT furnished the alcohol 38 in 95% yield.

Finally, controlled reduction of the enedione 35 with 2.3 M LAH solution in THF furnished a 4:1 mixture of cucumin-H 8 and its epimer 37 via regioselective reduction of the C-3 ketone, which were separated by column chromatography on silica gel. The structure of the epicucumin-H 37 was established from its spectral data. The stereochemistry of the alcohol group in cucumin-H 8 and epicucumin-H 37 was ascertained on the basis of the chemical shift due to the CHOH signal (δ 4.51 for cucumin-H 8 and 4.35 for epicucumin-H 37) in the 1H NMR spectrum in comparison to those in the alcohols 36 and 38 (4.51 for alcohol 37 and 4.33 for alcohol 38).

Structure of cucumin-H was established by comparing the spectral data with that of the natural compound. Synthetic (–)-cucumin-H 8 exhibited the optical rotation [α]D23 −26.0 (c 1.0, CHCl3) {lit.2 [α]D18 −25.0 (c 1.03, CHCl3)}, UV, IR, 1H and 13C NMR (Table I) (in methanol d4) and mass spectra, as well as the sign of the CD curves identical with those of natural cucumin-H 8. Present synthesis in addition to confirming the stereostructure of the natural product, also established the absolute configuration of cucumin-H 8.

In conclusion the first enantiospecific total syntheses of the natural enantiomer of the triquinane sesquiterpene cucumin-H 8 and its three regio- and stereoisomers 36-38 have been accomplished starting from the readily and abundantly available monoterpene (R)-limonene 10. A combination of stereoselective orthoester Claisen rearrangement, intramolecular diazoketone cyclopropanation and regiospecific cyclopropane ring cleavage was employed for generating the requisite two vicinal quaternary carbon atoms. A modified Nazarov reaction was exploited for the annulation of the third cyclopentane ring. The present sequence in addition to the stereostructure, also established the absolute configuration of the natural product.

**Experimental Section**

**Ethyl (1S,3S)-3-isopropenyl-1-methyl-2-methylencyclopentylacetate, 18.** A solution of the allyl alcohol1a 16 (2.0 g, 13.1 mmol), triethyl orthoacetate (7.4 mL, 40 mmol) and a catalytic amount of propionic acid was placed in a sealed tube and heated to 180°C for 5 days in an oil bath. The reaction mixture was then cooled, diluted with ether (20 mL), washed with 3 N aqueous HCl (5 mL) followed by saturated aqueous NaHCO3 solution (5 mL) and brine, and dried (anhyd. Na2SO4). Evaporation of the solvent and purification of the residue over a silica gel column using CH2Cl2-hexane (1:5) as eluent furnished...
the ester 18 (2.3 g, 80%) as oil. [α]$_D^{25}$ = -14.7° (c 3.4, CHCl$_3$); IR (neat): 2958, 2926, 2870, 1735 (C=O), 1628, 1451, 1370, 1339, 1313, 1260, 1172, 1104, 1033, 889 (C=CH$_2$) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$+CCl$_4$): δ 4.84 (1 H, d, $J = 2.7$ Hz), 4.85-4.75 (2 H, m) and 4.76 (1 H, d, $J = 2.4$ Hz) [2 × C=CH$_2$], 4.09 (2 H, q, $J = 7.2$ Hz, OCH$_2$CH$_3$), 3.30-3.20 (1 H, m, H-3'), 2.45 and 2.36 (2 H, 2 × d, $J = 14.4$ Hz, CH$_2$CO), 1.90-1.50 (4 H, m), 1.62 (3 H, s, olefinic-CH$_3$), 1.25 (3 H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 1.13 (3 H, s, tert-CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$+CCl$_4$): δ 171.5 (C, OC=O), 160.8 (C, C-2'), 146.0 (C, C=CH$_2$), 113.1 (CH$_2$, C=CH$_2$), 105.7 (CH$_2$, C=CH$_2$), 59.8 (CH$_2$, OCH$_2$CH$_3$), 53.9 (CH, C-3'), 46.0 (CH$_2$, C-2), 44.1 (C, C-1'), 37.8 (CH$_2$, C-5), 28.5 (CH$_2$, C-4'), 27.5 (CH$_3$), 18.2 (CH$_3$), 14.5 (CH$_2$, OCH$_2$CH$_3$); MS: m/z (%) (C$_{13}$H$_{24}$O$_2$) 210 (5), 194 (8), 168 (10), 150 (10), 149 (M − COOEt, 10), 137 (10), 123 (8), 111 (25), 110 (30), 95 (15), 85 (45), 83 (80), 43 (100).

[(15S,3S)-3-Isopropenyl-1-methyl-2-methylene-cyclopentyl]acetic acid, 13. To a magnetically stirred solution of the ester 18 (2.0 g, 9.0 mmol) in methanol (20 mL) was added 10% aqueous NaOH (20 mL) and refluxed for 8 hr. The reaction mixture was cooled to RT and washed with CH$_2$Cl$_2$ (10 mL). The aqueous layer was then acidified with 3 N HCl (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The CH$_2$Cl$_2$ extract was washed with brine and dried (anhyd. Na$_2$SO$_4$). Evaporation of the solvent furnished the acid 13 (1.65 g, 94%), which was recrystallised from hexanes. m.p. 34-36°C; [α]$_D^{23}$ = -5.8° (c 2.4, CHCl$_3$); IR (neat): 3073, 2963, 2874, 1708 (C=O), 1645, 1453, 1410, 1373, 1312, 1280, 1244, 1191, 1106, 937, 891 (C=CH$_2$) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$+CCl$_4$): δ 4.87 (1 H, d, $J = 2.7$ Hz) and 4.85-4.75 (3 H, m) [2 × C=CH$_2$], 3.24 (1 H, qt, $J = 7.5$ and 3.0 Hz), 2.47 and 2.38 (2 H, 2 × d, $J = 14.4$ Hz), 1.95-1.75 (2 H, m), 1.75-1.60 (3 H, m), 1.63 (3 H, s, olefinic-CH$_3$), 1.16 (3 H, s, tert-CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$+CCl$_4$): δ 178.5 (C, OC=O), 160.6 (C), 145.9 (C), 113.2 (CH$_2$), 105.9 (CH$_2$), 53.8 (CH), 45.9 (CH$_2$), 43.9 (C), 37.8 (CH$_3$), 28.3 (CH$_2$), 27.4 (CH$_3$), 18.2 (CH$_3$); MS:
m/z (%) 194 (M+, 2), 179 (M – CH₃, 5), 151 (3), 135 (M – C₂H₅O₂, 100), 119 (30), 107 (30), 105 (15), 93 (20), 91 (30), 79 (25). Anal. Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34%. Found: C, 73.79; H, 8.82%.

(1R,3R,6S,9S)-9-Isopropenyl-6-methyltricyclo-[4.3.0.0¹³]nonan-4-one, 14. To a magnetically stirred solution of the acid 13 (1.5 g, 7.7 mmol) in anhydrous benzene (4 mL) was added oxalyl chloride (2.2 mL, 25 mmol) and stirred for 2 hr at RT. Evaporation of the excess oxalyl chloride and solvent under reduced pressure afforded the acid chloride, which was taken in anhydrous ether (5 mL) and added drop wise to a cold, magnetically stirred solution of diazomethane (prepared from 8 g of N-nitroso-N-methylurea and 50 mL of 60% aqueous KOH solution and 30 mL of ether) and the reaction mixture was stirred for RT for 1.5 hr. Careful evaporation of the excess diazomethane and solvent on a hot water bath and purification of the residue over a neutral alumina column using CH₂Cl₂-hexane (1:2) as eluent furnished the diazoketone 19 (1.52 g) as yellow oil. IR (neat): 3074, 2959, 2871 2102 (N=N), 1643 (C=O), 1454, 1360, 1320, 1169, 1071, 891 (C=CH₂) cm⁻¹.

To a magnetically stirred refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (1.335 g, 21 mmol) in anhydrous cyclohexane (20 mL) over a period of 30 min and the reaction mixture was refluxed for 5 hr. It was then cooled, copper and copper sulfate were filtered off using a sintered funnel. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:25 to 1:20) as eluent furnished the tricyclic ketone 14 (1.02 g, 70% from the acid 13) as oil. [α]D²⁵ = –114.5° (c 1.65, CHCl₃); IR (neat): 3072, 2954, 2871, 1720 (C=O), 1644, 1462, 1411, 1375, 1280, 1249, 1321, 1189, 1051, 1045, 960, 938, 892 (C=CH₂), 772 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.72 (1 H, s) and 4.70 (1 H, s) [C=CH₂], 2.68 (1 H, t, J = 8.4 Hz, H-9), 2.16 and 1.94 (2 H, 2 × d, J = 18.3 Hz, H-5), 2.20-2.05 (1 H, m), 1.90-1.70 (2 H, m), 1.72 (3 H, s, olefinic-CH₂), 1.72-1.60 (1 H, m), 1.50 (1 H, dd, J = 9.2 and 4.0 Hz), 1.45-1.30 (2 H, m), 1.11 (3 H, s, tert-CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 212.4 (C, C=CH₂), 146.9 (C, C=CH₂), 111.3 (CH₂, C=CH₂), 50.0 (CH), 47.8 (CH₂), 47.4 (C), 44.8 (C), 39.4 (CH₂), 39.2 (CH), 30.2 (CH₂), 22.7 (CH₃), 20.6 (CH₂), 17.4 (CH₂); MS: m/z (%) 191 (M+ 1, 35), 190 (M+ 5, 5), 175 (M – CH₃, 12), 147 (30), 135 (30), 133 (33), 121 (100), 119 (30), 107 (30), 105 (60), 93 (30), 91 (80). Anal. Calcd for C₁₅H₂₄O: C, 82.06; H, 9.53%. Found: C, 81.86; H, 9.85%.

(1S,5S,6S)-6-Isopropenyl-1,5-dimethylbicyclo-[3.3.0]octan-3-one, 15. To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (200 mL) in a two necked flask, equipped with Dewar condenser, was added freshly cut lithium (175 mg, 25 mmol) followed by a solution of the tricyclic ketone 14 (1.0 g, 5.26 mmol) in anhydrous THF (5 mL). The resulting blue coloured solution was stirred for 15 min at –33°C and then the reaction was quenched with solid NH₄Cl. After evaporation of ammonia, the residue was taken in water (10 mL) and extracted with ether (3 × 10 mL). The combined ether extract was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:25) as eluent gave the bicyclic ketone 15 (859 mg, 85%) as a solid, which was recrystallised from hexanes. m.p. 41-43°C; [α]D²⁷ +140.0° (c 3.05, CHCl₃); IR (neat): 3082, 2962, 2872, 1742 (C=O), 1639, 1448, 1406, 1380, 1228, 1182, 890 (C=CH₂) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.84 (1 H, s) and 4.69 (1 H, s) [C=CH₂], 2.50 (1 H, d, J = 12.0 Hz), 2.41 (1 H, dd, J = 13.5 and 7.5 Hz), 2.34 and 2.16 (2 H, 2 × d, J = 18.6 Hz), 2.05 (1 H, d, J = 18.6 Hz), 2.00-1.60 (4 H, m), 1.73 (3 H, s, olefinic-CH₃), 1.03 (3 H, s) and 0.84 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃): δ 217.4 (C, C=O), 144.5 (C, C=CH₂), 113.1 (CH₃, C=CH₂), 54.6 (CH), 53.7 (CH₂), 51.4 (C), 50.4 (CH₂), 49.3 (C), 36.5 (CH₂), 26.6 (CH₂), 23.9 (CH₃), 23.6 (CH₂), 17.3 (CH₃); MS: m/z (%) 192 (M+, 20), 177 (M – CH₃, 15), 110 (40). Anal. Calcd for C₁₅H₂₆O: C, 81.20; H, 10.48%. Found: C, 80.86; H, 10.59%.

(1S,5R)-6-Isopropylidene-1,5-dimethylbicyclo-[3.3.0]octan-3-one, 20. To a magnetically stirred solution of the enone 15 (1.8 g, 9.37 mmol) in anhydrous CH₂Cl₂ (5 mL) was added PTSA (172 mg, 1.0 mmol) and stirred for 2 days at RT. The reaction mixture was then diluted with CH₂Cl₂ (10 mL), washed with saturated aqueous NaHCO₃ solution (3 mL) and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the
residue over a silica gel column using ethyl acetate-hexane (1:25) as eluent furnished the enone$^1$ 20 (1.78 g, 99%) as colourless oil. $\delta^2$ H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 2.74 and 2.24 (2 H, 2 × d, $J = 18.7$ Hz), 2.45-2.35 (2 H, m), 2.21 and 1.99 (2 H, 2 × d, $J = 18.3$ Hz), 1.71 (3 H, s) and 1.60 (3 H, s) [2 × olefinic-CH$_2$]; 13C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 217.4 (C, C=O), 140.9 (C, C-6), 125.1 (C, Me$_2$C=C), 50.5 (C) and 50.4 (C) [C-1 and 5], 50.3 (CH$_3$) and 49.9 (CH$_3$) [C-2 and 4], 34.5 (CH$_2$) and 29.3 (CH$_3$) [C-7 and 8], 22.8 (CH$_2$), 22.0 (CH$_2$), 21.8 (CH$_3$), 20.5 (CH$_3$); MS: m/z (%) (C$_2$H$_5$O$_2$) 192 (M$^+$, 25), 191 (M – 1, 100), 173 (25), 163 (20), 149 (60), 147 (20), 135 (35), 133 (35), 123 (30), 121 (40), 107 (50), 91 (35).

(1R,5S)-1,5-Dimethylbicyclo[3.3.0]octane-2,7-dione, 21. Dry oxygen in oxygen gas was passed through a cold (–70°C) suspension of the enone 20 (1.7 g, 8.85 mmol) and NaHCO$_3$ (50 mg) in 1:5 MeOH-CH$_2$Cl$_2$ (6 mL) till pale blue colour appeared. Excess oxygen was flushed off with oxygen and dimethyl sulfdide (3.3 mL, 45 mmol) was added to the reaction mixture. It was slowly warmed up to RT and magnetically stirred for 5 hr. The reaction mixture was diluted with methylene chloride and washed with water followed by brine and dried. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent gave the diketone 21 (1.32 g, 90%), which was recrystallised from hexane. m.p. 108-110°C; $\delta^2$ H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 2.39 (1 H, $d$, $J = 19.2$ Hz), 2.46 (2 H, t, $J = 7.8$ Hz), 2.22 (2 H, s), 2.06 (1 H, d, $J = 19.3$ Hz), 1.92 (2 H, dd, $J = 8.4$ and 7.8 Hz), 1.16 (3 H, s) and 1.07 (3 H, s) [2 × tert-CH$_3$]; 13C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 219.5 (C, C-2), 214.1 (C, C-7), 55.5 (C, C-1), 50.6 (CH$_2$), 46.6 (CH$_2$), 46.2 (C, C-5), 34.4 (CH$_2$), 31.1 (CH$_3$), 21.9 (CH$_3$), 16.9 (CH$_3$); MS: m/z (%) 166 (M$^+$, 30), 123 (15), 111 (35), 110 (25), 96 (15), 95 (15). Anal. Calcd for C$_{10}$H$_{14}$O$_2$: C, 72.26; H, 8.49%. Found: C, 72.12; H, 8.49%.

(1R,5S)-1,5-Dimethylbicyclo[3.3.0]octane-spiro-[7,2'-1,3-dithiolan-2-one, 22. A solution of the diketone 21 (1.3 g, 7.83 mmol), ethanediol (0.65 mL, 7.88 mmol) and BF$_3$•OEt$_2$ (0.1 mL, 1.0 mmol) in anhydrous benzene (3 mL) was magnetically stirred at 0-5°C for 40 min. The reaction was quenched with aqueous NaHCO$_3$ solution and extracted with ether. The ether extract was washed with 5% aqueous NaOH solution and brine, and dried (anhyd. Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:25) as eluent first furnished the bisdithioketal 23 (124 mg, 5%) as a viscous liquid. $\delta^2$ H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 3.40-3.10 (4 H, m) and 3.20 (4 H, s) [2 × SCH$_2$CH$_2$S], 2.53 (1 H, d, $J = 14.1$ Hz), 2.39 (1 H, td, $J = 12.6$ and 7.2 Hz), 2.31 (2 H, s), 2.24 (1 H, dd, $J = 14.4$ and 1.8 Hz), 2.10 (1 H, dd, $J = 13.2$, 6.3 and 1.2 Hz), 1.70 (1 H, dd, $J = 13.2$ and 6.0 Hz), 1.52 (1 H, td, $J = 12.9$ and 6.6 Hz), 1.34 (3 H, s), 1.16 (3 H, s) [2 × tert-CH$_3$]; 13C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 82.2 (C, C-2), 68.5 (C, C-7), 61.8 (CH$_3$), 59.9 (CH$_2$), 59.4 (C), 50.6 (C), 42.3 (CH$_2$), 41.7 (CH$_2$), 40.3 (CH$_2$), 39.6 (CH$_2$), 38.6 (CH$_2$), 38.5 (CH$_2$), 26.3 (CH$_3$), 20.1 (CH$_3$); MS: m/z (%) 319 (M$^+$ + 1, 4), 318 (M$^+$, 25), 185 (12), 134 (M – C$_2$H$_5$SO$_2$), 131 (100), 119 (20), 105 (12), 91 (18), 61 (17); HRMS: m/z Calcd for C$_{14}$H$_{18}$SO$_2$ (M + 1): 319.0682. Found: 319.0690.

Further elution of the column with ethyl acetate-hexane (1:20) furnished the mono-dithioketal 22 (1.5 g, 80%), which was recrystallised from hexane. m.p. 81-83°C; $\delta^2$ H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 3.28 (4 H, s, SCH$_2$CH$_2$S), 2.75 (1 H, d, $J = 14.7$ Hz, H-8A), 2.60-2.25 (2 H, m), 2.43 (2 H, s), 2.24 (1 H, d, $J = 14.7$ Hz, H-8B), 2.03 (1 H, ddd, $J = 15.0$, 9.0 and 6.0 Hz), 1.71 (1 H, ddd, $J = 13.5$, 9.6 and 6.0 Hz), 1.14 (3 H, s) and 0.99 (3 H, s) [2 × tert-CH$_3$]; 13C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 221.8 (C, C=O), 67.1 (C, C-7), 59.4 (C, C-1), 57.9 (CH$_2$), 57.0 (CH$_2$), 50.0 (C, C-5), 40.1 (CH$_2$) and 40.0 (CH$_2$) [SCH$_2$CH$_2$S], 35.2 (CH$_2$), 32.4 (CH$_3$), 23.2 (CH$_3$), 17.4 (CH$_3$); MS: m/z (%) 244 (M + 2, 11), 243 (M + 1, 17), 242 (M$^+$, 100), 214 (M – C$_2$H$_5$), 186 (80), 158 (40), 132 (30), 126 (80). Anal.: Calcd for C$_{12}$H$_{18}$OS$_2$: C, 59.46; H, 7.49%. Found: C, 59.32; H, 7.49%.

(1R,5S)-1,5-Dimethylbicyclo[3.3.0]octan-2-one, 11. To a magnetically stirred solution of the dithioketal 22 (1.1 g, 4.5 mmol) in anhydrous ethanol...
(5 mL) was added an excess of raney nickel and refluxed for 30 min. The reaction mixture was cooled and filtered through a short silica gel column to remove the catalyst. Evaporation of the solvent and purification of the residue over a silica gel column using CH₂Cl₂-hexane (1:3) as eluent furnished the ketone 11 (675 mg, 98%) as oil. [α]ėD²⁶ = –103.9º (c 2.3, CHCl₃); IR (neat): 2954, 2870, 1737 (C=O), 1603, 1465, 1455, 1309, 1264, 1097, 1040 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 2.29 (2 H, t, J = 7.5 Hz), 2.10-1.90 (1 H, m), 1.90-1.75 (1 H, m), 1.70-1.35 (6 H, m), 1.01 (3 H, s) and 0.89 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CDCl₄): δ 222.2 (C), 150.6 (C), 58.6 (C, C-1), 49.6 (C, C-5), 40.1 (CH₂), 37.1 (CH₂), 35.4 (CH₂), 32.2 (CH₂), 22.9 (CH₃, C-7), 22.86 (CH₃), 17.6 (CH₃); MS: m/z (%) 152 (M⁺, 5), 111 (15), 96 (15), 95 (35), 85 (60), 83 (100); HRMS: m/z Calcd for C₁₀H₁₆O₃Na (M + Na), 175.1099. Found: 175.1109.

(1R,2R,5R)-1,5-Dimethyl-2-[3-(tetrahydro-2-pyran-2-yloxy)-1-propynyl]bicyclo[3.3.0]octan-2-ol, 24. To a cold (−70°C), magnetically stirred solution of propargyl THP ether (1.0 g, 7.0 mmol) in anhydrous THF (3 mL) was added a solution of n-butyllithium (2.5 M in hexane, 2.7 mL, 6.7 mmol) under nitrogen atmosphere and stirred for 0.5 hr. A solution of the ketone 11 (456 mg, 3.0 mmol) in anhydrous THF (2 mL) was added to the reaction mixture and stirred for 6 hr at RT. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with ether (3 × 10 mL). The ether extract was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the tertiary alcohol 24 (700 mg, 80%) as a liquid. [α]ėD²⁶ = –8.6º (c 5.1, CHCl₃); IR (neat): 3432 (OH), 2945, 2869, 1453, 1378, 1291, 1262, 1201, 1183, 1120, 1077, 1025, 945, 903, 871, 813 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 4.81 (1 H, s, OCHO), 4.27 (2 H, s, CH₂-OTHP), 3.80 (1 H, t, J = 9.9 Hz) and 3.55-3.45 (1 H, m, OCH₂), 2.10-1.40 (16 H, m), 1.35-1.15 (1 H, m), 1.04 (3 H, s) and 1.02 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CDCl₄): δ 96.3 (CH), 89.5 (C), 81.6 (C), 80.1 (C), 61.6 (CH₂), 56.2 (C), 54.1 (CH₂), 49.5 (C), 44.6 (CH₂), 38.7 (CH₂), 37.8 (CH₃), 37.4 (CH₂), 30.3 (CH₂), 26.0 (CH₃), 25.6 (CH₂), 24.2 (CH₂), 21.1 (CH₃), 19.1 (CH₃).

(1R,2S,5R)-2-[3-Hydroxyprop-1-yn-1-yl]-1,5-dimethylbicyclo[3.3.0]octan-2-ol, 25. A solution of the THP ether 24 (500 mg, 1.7 mmol) and a catalytic amount of PPTS in methanol (3 mL) was stirred for 6 hr at RT. Methanol was removed under reduced pressure. The residue was taken in ether (20 mL), washed with saturated aqueous NaHCO₃ (5 mL) and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (3:7) as eluent furnished the diol 25 (320 mg, 90%), which was recrystallised from hexane. m.p. 98-100°C; [α]ėD²⁴ = –12.3º (c 1.9, CHCl₃); IR (neat): 3295 (OH), 2945, 2869, 1457, 1377, 1297, 1158, 1104, 1089, 1039, 1025, 1001 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 4.29 (2 H, s, CH₂OH), 3.56 (2 H, br s, OH), 2.05-1.80 (3 H, m), 1.60-1.45 (6 H, m), 1.35-1.15 (1 H, m), 1.05 (3 H, s) and 1.01 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CDCl₄): δ 89.1 (C), 83.9 (C), 80.1 (C), 56.1 (C), 50.7 (CH₂), 49.5 (C), 44.5 (CH₂), 38.4 (CH₂), 37.7 (CH₂), 37.4 (CH₂), 26.0 (CH₃), 24.1 (CH₂), 20.9 (CH₃); MS: m/z (%) 175 (M – H₂O – Me, 4), 98 (6), 97 (45), 96 (40), 95 (100), 90 (15). Anal. Calcd for C₁₉H₂₄O₂: C, 74.96; H, 8.68%. Found: C, 74.61; H, 9.80%.

(1R,8R)-1,8-Dimethyltricyclo[6.3.0.0²⁶]undec-2-(6)-en-3-one, 12. To a suspension of P₂O₅ (140 mg, 1.0 mmol) in MsOH (190 mg, 2.0 mmol) was added a solution of the diol 25 (100 mg, 0.48 mmol) in anhydrous CH₂Cl₂ (20 mL) over a period of 10 min. The reaction mixture was stirred for 1 hr at RT, diluted with water (5 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The CH₂Cl₂ extract was washed with saturated aqueous NaHCO₃ and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (1:20) as eluent furnished the enone 12 (64 mg, 70%) as oil. [α]ėD²⁶ = –53.9º (c 1.3, CHCl₃); IR (neat): 2949, 2867, 1697 (C=O), 1646, 1467, 1444, 1374, 1286, 1211, 978 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 2.70-2.55 (2 H, m), 2.50-2.30 (4 H, m), 2.10-1.95 (1 H, m), 1.75-1.20 (5 H, m), 1.14 (3 H, s) and 1.10 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃+CDCl₄): δ 202.7 (C, C=O), 181.3 (C, C-6), 153.3 (C, C-2), 56.5 (C, C-11), 52.2 (C, C-8), 47.6 (CH₂), 44.0 (CH₂), 40.7 (CH₂), 38.2 (CH₂), 25.3 (CH₂), 24.6 (CH₃), 24.0 (CH₃), 20.5 (CH₃); MS: m/z (%) 190 (M⁺, 60), 175 (M – CH₃, 50), 148 (60), 147 (80), 133 (75), 119 (95), 105 (90), 91 (95); HRMS: m/z Calcd for C₁₉H₂₄O₂Na (M + Na), 213.1256. Found 213.1264.

3-[1R,5R]-1,5-Dimethylbicyclo[3.3.0]oct-2-yn-2-ylprop-2-yn-1-ol, 26. To a magnetically stirred ice
cold solution of the tertiary alcohol 24 (30 mg, 0.1 mmol) in pyridine (0.5 mL) was added freshly distilled POCl₃ (0.1 mL). The reaction mixture was stirred at the same temperature for 1 hr. Water was added to the reaction mixture and extracted with ether (3 × 3 mL). The ether layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent gave the dehydrated product 27 (25 mg).

A solution of the THP ether 27 (20 mg, 0.07 mmol) and a catalytic amount of PPTS in methanol (1 mL) was stirred for 6 hr at RT. Methanol was removed under reduced pressure. The residue was taken in ether (5 mL), washed with saturated aqueous NaHCO₃ (5 mL) and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the alcohol 26 (12.5 mg, 90%) as oil. [α]²⁴ -36.5º (c 2.6, CHCl₃); IR (neat): 3341, 3049, 2951, 2867, 1460, 1444, 1379, 1208, 1019, 809 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.34 and 2.37 (2 H, AB q, J = 17.7 Hz, H-4), 2.10-1.85 (1 H, m), 1.70-1.20 (6 H, m), 1.04 (3 H, s) and 1.03 (3 H, s) [2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃): δ 134.9 (CH, C-3), 132.7 (C, C-2'), 88.3 (C, C-3), 82.6 (C, C-2), 59.7 (C, C-1'), 51.7 (CH₂, C-1), 49.2 (C, C-5'), 48.5 (CH₂, C-4'), 44.3 (CH₃), 38.9 (CH₃), 24.8 (CH₃), 23.6 (CH₂, C-7'), 21.6 (CH₃); MS: m/z (%): 190 (M⁺, 33), 161 (50), 119 (12), 117 (12), 105 (20), 91 (25); HRMS: m/z Calcd for C₁₅H₂₃O (M + 1), 191.1436. Found 191.1429.

1R,8R)-1,8-Dimethyltricyclo[6.3.0.0²⁶]undec-2 (6)-en-3-one, 12. To a solution of MsOH (20 mg, 0.2 mmol) in CH₂Cl₂ (1 mL) was added a solution of the alcohol 26 (10 mg, 0.05 mmol) in CH₂Cl₂ (2 mL). The reaction mixture was stirred for 0.5 hr at RT, diluted with water (5 mL) and extracted with CH₂Cl₂ (2 × 3 mL). The CH₂Cl₂ extract was washed with saturated aqueous NaHCO₃ and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (1:20) as eluent furnished the enone 12 (7 mg, 70%), which exhibited TLC and spectral data identical with those of the sample obtained earlier.

1R,8R)-1,8-Dimethyltricyclo[6.3.0.0²⁶]undec-2 (6)-en-3-one, 12 and 3-[15S,5R)-(4,5-dimethylbicyclo[3.3.0]oct-3-3-en-1-yl)prop-2-yn-1-ol, 28. To a suspension of P₂O₅ (7 mg, 0.05 mmol) in MsOH (48 mg, 0.5 mmol) was added a solution of the dial 25 (50 mg, 0.24 mmol) in anhydrous CH₂Cl₂ (10 mL). The reaction mixture was stirred for 15 min at RT, diluted with water (5 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The CH₂Cl₂ extract was washed with saturated aqueous NaHCO₃ and brine, and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (1:25 to 1:20) as eluent first furnished the triquinane 12 (16 mg, 35%). Further elution of the column with the same solvent as eluent furnished the rearranged alcohol 28 (16 mg, 35%) as oil. [α]²⁶ +11.8º (c 0.85, CHCl₃); IR (neat): 3340 (OH), 3037, 2953, 2866, 1466, 1378, 1310, 1291, 1228, 1143, 1013, 792 cm⁻¹; ¹H NMR (400 MHz, CDCl₃+CCL₄): δ 5.12 (1 H, s, olefinic-H), 4.29 (2 H, s, CH₂OH), 2.63 (1 H, dt, J = 16.5 and 2.3 Hz) and 2.35 (1 H, dt, J = 16.4 and 2.0 Hz) [H-2'], 2.05-1.90 (1 H, m), 1.80-1.70 (2 H, m), 1.59 (3 H, d, J = 1.8 Hz, olefinic-CH₃), 1.45-1.30 (2 H, m), 1.15 (3 H, s, tert-CH₃); ¹³C NMR (75 MHz, CDCl₃+CCL₄): δ 144.7 (C, C-4'), 121.1 (C, C-3), 92.7 (C, C-3), 80.9 (C, C-2), 61.2 (C, C-1), 51.5 (CH₃, C-1), 49.7 (C, C-5), 46.5 (CH₂), 44.0 (CH₂), 37.5 (CH₃), 24.6 (CH₂), 22.9 (CH₃); MS: m/z (%) 190 (M⁺, 15), 175 (M – CH₃, 15), 148 (12), 147 (12), 133 (12), 119 (15), 117 (12), 95 (40), 91 (12), 85 (100); HRMS: m/z Calcd for C₁₀H₁₉O (M + 1), 191.1436. Found 191.1449.

3-[15S,5R)-(4,5-Dimethylbicyclo[3.3.0]oct-3-3-en-1-yl)prop-2-yn-1-yl]-1-y1-4-nitrobenzoate, 29. To a magnetically stirred solution of the alcohol 28 (8 mg, 0.042 mmol) and pyridine (0.03 mL, 0.35 mmol) in anhydrous CH₂Cl₂ (1 mL) was added 4-nitrobenzoyl chloride (35 mg, 0.2 mmol) and the reaction mixture was stirred for 8 hr at RT. It was then diluted with CH₂Cl₂ (5 mL), washed with brine and dried (anhyd. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using CH₂Cl₂-hexane (1:5) as eluent furnished the ester 29 (14 mg, 98%), which was recrystallised from hexane. m.p. 50-52°C; [α]²⁶ -3.33º (c 1.2, CHCl₃); IR (neat): 2954, 2927, 2854, 1734 (OC=O), 1608, 1530, 1447, 1348, 1319, 1269, 1099, 1014, 943, 873, 857, 784, 719 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCL₄): δ 8.31 (2 H, d, J = 8.7 Hz) and 8.24 (2 H, d, J = 8.7 Hz) [aromatic H], 5.11 (1 H, s, olefinic-H), 4.99 (2 H, s, CH₂O), 2.68 and 2.38 (2 H, 2 × d, J = 16.5 Hz, H-2'), 2.10-1.90 (1 H, m), 1.90-1.70 (2 H, m), 1.70-1.65 (1 H, m), 1.60 (3 H, s, olefinic-CH₃), 1.45-1.30 (2 H, m), 1.16 (3 H, s, tert-CH₃); ¹³C NMR (75 MHz,
CDCl$_3$+CCL$_4$: δ 163.8 (C, OC=O), 150.8 (C, C-4), 144.6 (C, C-4°), 135.3 (C, C-1), 130.9 (2 C, CH), 123.6 (2 C, CH), 121.1 (CH, C-3°), 94.9 (C, C-3°), 75.7 (C, C-2), 61.4 (C, C-1°), 54.5 (CH$_2$, C-1°), 49.7 (C, C-5°), 46.4 (CH$_3$), 43.9 (CH$_2$), 37.6 (CH$_2$), 24.7 (CH$_3$), 22.9 (CH$_3$), 13.1 (CH$_3$); MS: m/z 189 (M – C$_2$H$_5$NO$_3$, 4), 172 (8), 158 (13), 157 (100), 150 (NO$_2$C$_6$H$_4$CO$_2$), 30, 143 (15), 129 (20), 115 (15), 104 (13), 91 (15); HRMS: m/z Calcd for C$_{29}$H$_{24}$NO$_3$Na (M + Na), 362.1368. Found 362.1389. Anal. Calcd for C$_{29}$H$_{24}$NO$_3$: C, 70.78; H, 6.24; N, 4.13%. Found: C, 70.87; H, 6.60; N, 2.98%.

(1R,8R)-1,4,4,8-Tetramethyltricyclo[6.3.0.0$^{3,6}$]-undec-2(6)-en-3-one, 32. To an ice-cold magnetically stirred suspension of sodium hydride (50% dispersion in oil, 96 mg, 2.0 mmol washed with dry hexane) in anhydrous THF (2 mL), was added the enone 12 (50 mg, 0.26 mmol) in anhydrous THF (1 mL) and stirred for 1 hr. Methyl iodide (0.3 mL, excess) was added and the reaction mixture was stirred at RT for 1 hr. It was then quenched with water (5 mL) and extracted with ether (3 × 5 mL). The ether extract was washed with brine and dried (anhyd. Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the dimethylated enone 32 (43 mg, 75%) as oil. [α]$_D^{27}$: −57.0° (c 1.0, CHCl$_3$); IR (neat): 2955, 2867, 1698 (C=O), 1648, 1466, 1444, 1379, 1291, 1214, 1136, 975, 922, 824 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$): δ 2.36 (2 H, s) and 2.27 (2 H, s) [H-5 and 7], 2.05-1.95 (1 H, m), 1.70-1.10 (5 H, m), 1.14 (3 H, s), 1.11 (6 H, s) and 1.10 (3 H, s) [4 × tert-CH$_3$]; $^{13}$C NMR (75 MHz, CDCl$_3$+CCL$_4$): δ 207.7 (C, C=O), 177.9 (C, C-6), 150.7 (C, C-2°), 56.2 (C, C-1), 50.3 (C, C-8), 48.0 (CH$_2$), 44.3 (CH$_2$), 42.3 (CH$_2$), 38.2 (CH$_2$), 25.7 (CH$_3$), 25.3 (CH$_3$), 24.8 (CH$_3$), 24.3 (CH$_2$, C-10), 20.7 (CH$_3$); MS: m/z (%): 218 (M$^+$, 5), 203 (M – CH$_3$, 8), 175 (5), 149 (8), 133 (4), 119 (4), 105 (5); HRMS: m/z Calcd for C$_{15}$H$_{23}$O$_2$Na (M + Na), 241.1568. Found 241.1575.

(1R,3R,8R,3′) and (1R,3S,8R)-1,4,4,8-Tetramethyltricyclo[6.3.0.0$^{3,6}$]-undec-2(6)-en-3-ols, 33. To a cold (−70°C) magnetically stirred solution of the enone 32 (27 mg, 0.12 mmol) in dry ether (2 mL) was added LAH (17 mg, 0.45 mmol) in one portion. The reaction mixture was stirred at the same temperature for 1 hr and allowed to warm up to 0°C over a period of 30 min. Ethyl acetate (0.5 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3 × 5 mL). The ether layer was separated, washed with brine and dried (anhyd. Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the alcohol 33 (25.6 mg, 94%) as oil. [α]$_D^{25}$: −20.0° (c 1.2, CHCl$_3$); IR (neat): 3447 (OH), 2952, 1444, 1380, 1217, 1037, 990, 814 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$): δ 3.97 and 3.84 (1 H, s, CHOH), 2.10 (2 H, t, J = 15.9 Hz), 2.05-1.90 (1 H, m), 1.85-1.20 (8 H, m), 1.10 and 1.09 (3 H, s), 1.06 (3 H, s), 1.05 and 1.03 (3 H, s) and 1.02 (3 H, s) [4 × tert-CH$_3$]; $^{13}$C NMR (75 MHz, CDCl$_3$+CCL$_4$): δ 151.3 and 151.0 (C), 146.5 and 145.5 (C), 81.2 and 80.9 (CH), 55.6 and 55.4 (C), 53.9 and 53.8 (C), 47.4 and 47.3 (C), 46.5 and 46.4 (CH$_2$), 44.6 and 44.3 (CH$_2$), 43.4 and 43.3 (CH$_2$), 39.4 and 38.5 (CH$_2$), 29.4 and 29.1 (CH$_3$), 25.3 and 25.2 (CH$_3$), 24.3 and 24.1 (CH$_3$), 23.4 and 23.3 (CH$_3$), 22.7 and 21.1 (CH$_3$); HRMS: m/z Calcd for C$_{15}$H$_{23}$O$_2$Na (M + Na), 243.1713. Found 243.1725.

(1R,3R,8R,3′) and (1R,3S,8R)-1,4,4,8-Tetramethyltricyclo[6.3.0.0$^{3,6}$]-undec-2(6)-ene-3-yl acetates, 34. To a magnetically stirred solution of the alcohol 33 (20 mg, 0.09 mmol) in CH$_2$Cl$_2$ (1 mL) was sequentially added pyridine (80 mg, 1.0 mmol), acetic anhydride (102 mg, 1.0 mmol) and a catalytic amount of DMAP, and stirred for 20 hr at RT. It was then quenched with 1.5 N aq. HCl (1 mL) and extracted with CH$_2$Cl$_2$ (3 × 3 mL). The combined organic phase was washed with saturated aq. NaHCO$_3$ solution and brine, and dried (anhyd. Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the acetate 34 (17 mg, 70%). [α]$_D^{25}$: −25.0° (c 1.2, CHCl$_3$); IR (neat): 2953, 2867, 1736 (C=O), 1465, 1444, 1368, 1239, 1024, 962 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$, mixture of diastereomers): δ 5.26 and 5.18 (1 H, s, CH-OC$_2$H$_5$), 2.03 (3 H, s, CH$_3$C=O), 2.25-1.95 (3 H, m), 1.84 (1 H, d, J = 16.2 Hz), 1.80-1.55 (5 H, m), 1.55-1.35 (1 H, m), 1.13 and 1.11 (3 H, s), 1.07 and 1.04 (3 H, s), 1.02 and 1.01 (3 H, s) and 0.99 and 0.95 (3 H, s) [4 × tert-CH$_3$].

(1S,8S)-1,4,4,8-Tetramethyltricyclo[6.3.0.0$^{3,6}$]-undec-2(6)-ene-3,7-dione, 35. To a magnetically stirred solution of the enone 32 (30 mg, 0.14 mmol) in CCl$_4$ (1 mL) was added a solution of di-tert-butyl chromate (1 mL) in CCl$_4$ [prepared from 1 g of chromium trioxide and 2.5 mL of anhydrous tert-butyl alcohol in 7 mL of CCl$_4$] and the mixture was stirred at 80°C for
9 hr. The reaction mixture was filtered through a short silica gel column. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the enedione 35 (26 mg, 81%), which was recrystallised from hexane. m.p. 88-90°C; [α]D 20: −5.3° (c 0.95, CHCl3); IR (neat): 2928, 2868, 1704 (C=O), 1640, 1449, 1381, 1370, 1327, 1281, 1162, 1128, 1013, 982, 915 cm−1; 1H NMR (300 MHz, CDCl3): δ 2.45 (2 H, s, H-5), 2.00 (2 H, dd, J = 12.9 and 6.3 Hz), 1.65-1.30 (3 H, m), 1.20-0.90 (1 H, m), 1.27 (3 H, s), 1.20 (3 H, s), 1.18 (3 H, s) and 1.13 (3 H, s) [4 × tert-CH3]; 13C NMR (75 MHz, CDCl3): δ 82.103 (C) and 209.0 (C) [C-3 and 7], 173.5 (C, C-2), 167.6 (C, C-6), 64.7 (C, C-8), 51.4 (C, C-4), 49.7 (C, C-1), 39.7 (CH2), 36.8 (CH3), 36.7 (CH2), 25.5 (CH3), 25.2 (CH3), 23.4 (CH2, C-10), 20.1 (CH3), 19.2 (CH3); MS: m/z (%): 232 (M+, 15), 217 (M – CH2, 10), 204 (15), 189 (15), 149 (30), 105 (20), 95 (25), 91 (22). Anal. Calcd for C13H22O2: C, 77.55; H, 8.68%. Found: C, 77.38; H, 8.75%.

(1R,7S,8S)-7-Hydroxy-1,4,4,8-tetramethyltricyclo-[6.3.0.02,6]undec-2(6)-en-3-one, 36. To a magnetically stirred solution of the enedione 35 (12 mg, 0.05 mmol) in methanol (1 mL) at 0°C were added CeCl3·7H2O (10 mg, 0.027 mmol) and NaBH4 (10 mg, 0.27 mmol) successively and stirred for 1 hr at RT. Methanol was evaporated under reduced pressure, water was added to the residue and extracted with ether (3 × 3 mL). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the allyl alcohol 36 (11.5 mg, 95%) as oil. [α]D 20: −67.1° (c 0.7, CHCl3); IR (neat): 3402 (OH), 2960, 2929, 2867, 1681 (C=O), 1644, 1464, 1446, 1380, 1330, 1298, 1269, 1217, 1062, 1026 cm−1; 1H NMR (300 MHz, CDCl3): δ 4.51 (1 H, br s, H-7), 2.45 and 2.26 (2 H, 2 × d, J = 18.3 Hz), 2.20-2.00 (2 H, m), 1.70-1.00 (5 H, m), 1.12 (12 H, s) [4 × tert-CH3]; 13C NMR (75 MHz, CDCl3): δ 208.2 (C, C=O), 177.3 (C, C-6), 150.1 (C, C-2), 82.0 (CH, C-7), 60.2 (C), 52.3 (C), 50.2 (C), 39.8 (CH2), 37.8 (CH2), 34.9 (CH2), 25.8 (CH3), 25.0 (CH3), 24.5 (CH2, C-10), 23.1 (CH3), 20.6 (CH3); MS: m/z (%): 234 (M+, 22), 219 (12), 201 (5), 191 (5), 163 (3), 149 (3), 107 (5), 87 (25), 47 (100); HRMS: m/z Calcd for C13H22O2 (M + 1): 235.1698. Found: 235.1712.

(1R,7R,8R)-3-Oxo-1,4,4,8-tetramethyltricyclo-[6.3.0.02,6]undec-2(6)-en-7-y1 4-nitrobenzoate, 39. To a magnetically stirred solution of triphenylphosphine (52 mg, 0.2 mmol) in dry THF (1 mL) was added DIAD (29 mg, 0.14 mmol) and stirred for 15 min at RT. A solution of the allyl alcohol 36 (11 mg, 0.05 mmol) and 4-nitrobenzoic acid (30 mg, 0.18 mmol) in anhydrous THF (1 mL) was added to the reaction mixture and stirred for 8 hr at RT. It was then diluted with ether (5 mL), washed with brine and dried (anhyd. Na2SO4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the ester 39 (7 mg, 85%), which was recrystallised from hexane. m.p. 115-117°C; [α]D 20: +73.5° (c 2.3, CHCl3); IR (neat): 2958, 2930, 2868, 1725 (C=O), 1704 (C=O), 1657, 1607, 1530, 1465, 1382, 1346, 1269, 1100, 1014, 961, 873, 853, 784, 721 cm−1; 1H NMR (300 MHz, CDCl3): δ 8.282 (2 H, d, J = 8.5) and 8.17 (2 H, d, J = 8.5 Hz) [aromatic H], 5.66 (1 H, s, H-7), 2.40 and 2.30 (2 H, 2 × d, J = 18.3 Hz, H-5), 2.06 (1 H, dd, J = 12.5 and 6.0 Hz), 1.95-1.85 (1 H, m), 1.75-1.15 (4 H, m), 1.23 (3 H, s), 1.13 (6 H, s) and 1.06 (3 H, s) [4 × tert-CH3]; 13C NMR (75 MHz, CDCl3): δ 207.5 (C, C=O), 171.3 (C, C-6), 164.1 (C, C=O), 155.4 (C), 151.0 (C), 135.2 (C), 130.8 (2 C, CH), 123.7 (2 C, CH), 84.2 (CH, C-7), 59.7 (C), 53.1 (C), 50.6 (C), 42.2 (CH2), 40.7 (CH3), 36.8 (CH3), 25.8 (CH3), 25.0 (CH3), 24.1 (CH2, C-10), 21.5 (CH3), 18.6 (CH3); MS: m/z (%): 383 (M+, 5), 233 (7), 205 (7), 201 (7), 150 (8), 120 (5), 104 (5). Anal. Calcd for C22H22O4: C, 68.91; H, 6.57; N, 3.65%. Found: C, 68.92; H, 7.16; N, 2.67%.

(1R,7R,8R)-7-Hydroxy-1,4,4,8-tetramethyltricyclo-[6.3.0.02,6]undec-2(6)-en-3-one, 38. To a magnetically stirred solution of the enedione 35 (3 mg, 0.008 mmol) in methanol (1 mL) was added K2CO3 (5 mg) and stirred at RT for 6 hr. Water (3 mL) was added to the reaction mixture and extracted with ether (3 × 3 mL). The combined ether extract was washed with brine and dried (anhyd. Na2SO4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the alcohol 38 (1.7 mg, 95%) as oil. [α]D 20: −12.0° (c 0.5, CHCl3); IR (neat): 3431 (OH), 2956, 2867, 1683 (C=O), 1637, 1467, 1382, 1366, 1287, 1249, 1215, 1081, 1044 cm−1; 1H NMR (300 MHz, CDCl3): δ 4.33 (1 H, s, H-7), 2.51 and 2.33 (2 H, 2 × d, J = 18.3 Hz, H-5), 1.98 (1 H, dd, J = 12.0 and 6.0 Hz), 1.70-1.40 (5 H, m), 1.39 (1 H, d of t, J = 12.3 and 7.8 Hz), 1.17 (3 H, s), 1.15 (3 H, s), 1.13 (3 H, s) and 1.06 (3 H, s) [4 × tert-CH3]; MS: m/z (%): 235 (C13H22O2) 235 (M + 1, 5), 234 (M+, 95%) as oil.
(1S,3S,8S)-3-Hydroxy-1,4,4,8-tetramethyltricyclo[6.3.0.0^3^8]undec-2(6)-en-7-one (cucumin H, 8) and (1S,3R,8S)-3-hydroxy-1,4,4,8-tetramethyltricyclo[6.3.0.0^3^8]undec-2(6)-en-7-one (epicucumin H, 37). To a magnetically stirred ice cold solution of the enedione 35 (18 mg, 0.08 mmol) in dry THF (1 mL) was added a solution of LAH (2.3 M in THF, 0.03 mL, 0.07 mmol). The reaction mixture was stirred at the same temperature for 5 min. Water (3 mL) was added to the reaction mixture and extracted with ether (3 × 3 mL). The ether layer was washed with brine and dried (anhyd. NaSO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent first furnished the unreacted starting material (7.2 mg, 40%). Further elution of the column gave cucumin-H 8 (7 mg, 39%) as a colourless solid. [α]D^25: −26.0° (c 1.0, CHCl₃); UV (CH₃CN): λmax 240 (log ε = 2.83); CD (CH₃CN): λmax (∆ε) 246 (−5.3), 216 (+7.2); IR (neat): 3414, 2957, 2868, 1680 (C=O), 1637, 1467, 1365, 1083 cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 4.51 (1 H, s), 2.33 (1 H, dd, J = 12.5 and 5.5 Hz), 2.22 and 2.09 (2 H, 2 × d, J = 16.0 Hz, H-5), 1.95 (1 H, dd, J = 12.5 and 5.5 Hz), 1.57 (1 H, quintet, J = 6.0 Hz), 1.44 (1 H, d of t, J = 12.5 and 6.0 Hz), 1.40-1.30 (1 H, m), 1.30-1.00 (2 H, m), 1.26 (3 H, s), 1.08 (3 H, s) and 1.07 (3 H, s) [4 × tert-CH₃]; 13C NMR (300 MHz, CDCl₃): δ 4.51 (1 H, br s), 2.26 and 2.11 (2 H, 2 × d, J = 16.2 Hz, H-5), 2.17 (1 H, dd, J = 12.0 and 4.8 Hz), 2.00 (1 H, dd, J = 12.3 and 5.7 Hz), 1.60-1.00 (5 H, m), 1.20 (3 H, s), 1.17 (1 H, 3s), 1.06 (3 H, s) and 1.05 (3 H, s) [4 × tert-CH₃]; 13C NMR (75 MHz, CD₂OD): δ 212.8 (C, C=O), 190.7 (C, C-2), 145.5 (C, C-6), 81.5 (CH, C-3), 64.1 (C), 52.5 (C), 49.6 (C), 39.7 (CH₃), 38.5 (CH₂), 37.8 (CH₂), 27.8 (CH₃), 23.9 (CH₂, C-10), 22.9 (CH₃), 20.2 (CH₃), 19.7 (CH₃); HRMS: m/z Calcd for C₁₃H₂₂O₂Na (M + Na): 257.1517. Found: 257.1527.

**X-ray data:** General Information: The single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 293 (2) K. The X-ray generator was operated at 50 KV and 35 mA using MoKα radiation (λ = 0.7107 Å). The data was collected with ω scan width of 0.3°. A total of 606 frames per set were collected using SMART in three different settings of φ (0°, 90° and 180°) for monoclinic and orthorhombic crystal systems, keeping the sample to detector distance of 6.062 cm and 20 value fixed at −25°. The data were reduced by SAINTPLUS an empirical absorption correction was applied using the package SADABS and XPREP was used to determine the space group. The structures were solved using SIR92 and refined using SHELXL97.

**Crystal data and structure refinement parameters for the compound, 28.** Mol. For. C₃₅H₅₃NO₂: MW = 339.4; colourless; Crystal system: monoclinic; Space group P2₁(1); cell parameters, a = 11.151 (6) Å, b = 6.861 (4) Å, c = 24.007 (1) Å; α = 90°, β = 102.56 (8)°, γ = 90°, V = 1792.7 (2) Å³, Z = 4, Dc = 1.26 g cm⁻³, F(000) = 720, µ = 0.088 mm⁻¹. Total number of l.s. parameters = 201, R1 = 0.114 for 1112 [I > 2σ(I)] and 0.189 for all 2176 data. wR2 = 0.244, GOF = 1.130, restrained GOF = 1.130 for all data.

**Crystal data and structure refinement parameters for the compound 39.** Mol. For. C₅₂H₆₁NO₂: MW = 383.4; colourless; Crystal system: monoclinic; Space group P2₁(1); cell parameters, a = 17.449 (5) Å, b = 11.559 (3) Å, c = 17.582 (5) Å; α = 90°, β = 117.88, γ = 90°, V = 3134.85 (2) Å³, Z = 4, Dc = 1.22 g cm⁻³, F(000) = 1224, µ = 0.09 mm⁻¹. Total number of l.s. parameters = 981, R1 = 0.054 for 4913 [I > 2σ(I)] and 0.090 for all 7649 data. wR2 = 0.111, GOF = 0.878, restrained GOF = 0.878 for all data. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 201351).
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References


