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A stereocontrolled total synthesis of (±)-zizaene

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Abstract—A stereocontrolled approach to the construction of the tricyclo[6.2.1.0^{1,5}]undecane ring system related to the sesquiterpene zizaene is delineated. Starting from an indanone, a bromophenol was prepared in a straightforward manner. An intramolecular anionic cyclisation then afforded a tricyclic dienone which was stereoselectively converted into a mesylate through various intermediates. Base induced rearrangement furnished a trans-fused ketone as the sole product which was converted into (±)-zizaene through Wittig olefination.

Zizaene (**1**), a tricyclic sesquiterpene hydrocarbon, was isolated[1] from vetiver oil and possesses[1c,2] a tricyclo[6.2.1.0^{1,5}]undecane skeleton. The structure **1** of zizaene was secured through correlation[1d,2,3] with zizan-12-ol (**2**), the stereostructure of which was conclusively established by single crystal X-ray crystallography[4] of the corresponding *p*-bromobenzoate **3**. In view of its novel structural features, zizaene has attracted considerable attention[5–10] as a challenging synthetic target. Besides the construction of the tricyclo[6.2.1.0^{1,5}]undecane framework, the total synthesis of zizaene must address the following problems: (i) control of the stereochemistry of the four asymmetric centres, (ii) introduction of *gem*-dimethyl groups at C-7, and (iii) installation of an exocyclic methylene unit at C-6. The total synthesis of (±)-zizaene (**1**) has been successfully accomplished by Coates et al.[5] and Wiesner et al.[6] Several formal total syntheses of **1** have also been reported in the literature.[7–10] We describe herein a highly stereocontrolled total synthesis of (±)-zizaene (Fig. 1).

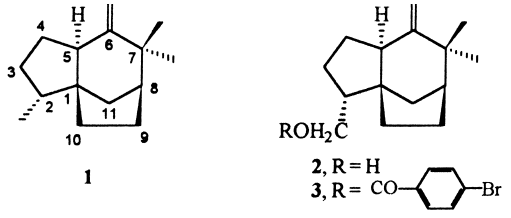

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Figure 1.

1. Results and discussion

Our synthesis of zizaene (**1**) from 3,3-dimethyl-5-methoxyindan-1-one (**4**) is outlined in Scheme 1. The indanone **4** was prepared from 3-methoxyacetophenone following a procedure reported[11] in the literature. Having a convenient route to **4**, we turned our attention to convert **4** into the bromophenol **11**. The indanone was alkylated with methyl bromoacetate using LDA as the base to give the keto-ester **5** in 73% yield which on hydrolysis furnished the keto-acid **6**. This was reduced to the corresponding benzylic alcohol with $NaBH_4$ in aqueous NaOH following a procedure reported by House et al.[12] Catalytic hydrogenolysis of the crude benzylic alcohol in acetic acid containing a few drops of perchloric acid furnished the crystalline acid **7** in high yield. The methyl ester **8**, prepared from **7**, was reduced with $LiAlH_4$ and the resulting primary alcohol **9** was treated with a mixture of Ph_3P and CBr_4 to give the bromoether **10**. Demethylation of **10** with BBr_3 in CH_2Cl_2 provided the desired bromophenol **11** in excellent yield.

In order to effect an intramolecular anionic cyclisation[13] of the bromophenol **11**, a dilute solution of **11** in dry *t*-BuOH was heated with *t*-BuOK (1 equiv.) at 80°C for 10 h. The dienone **12** was isolated as a crystalline compound as the only neutral product of the reaction in 73% yield. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the dienone were in full accord with structure **12**. Conjugate addition of $LiMe_2Cu$ to **12** at 0°C was highly regioselective and stereoselective providing a single enone **13** in 85% yield. The stereochemical assignments at C-1, C-2 and C-8 of **13** followed from subsequent transformations leading to the *cis*-diol **16**, the stereostructure of which was established by single-crystal X-ray crystallography. The enone **13** was converted into the corresponding thioacetal **14** in near quantitative yield. Desulfurisation of the thioacetal **14** was accomplished efficiently with Na and EtOH in liquid ammonia[14] to provide

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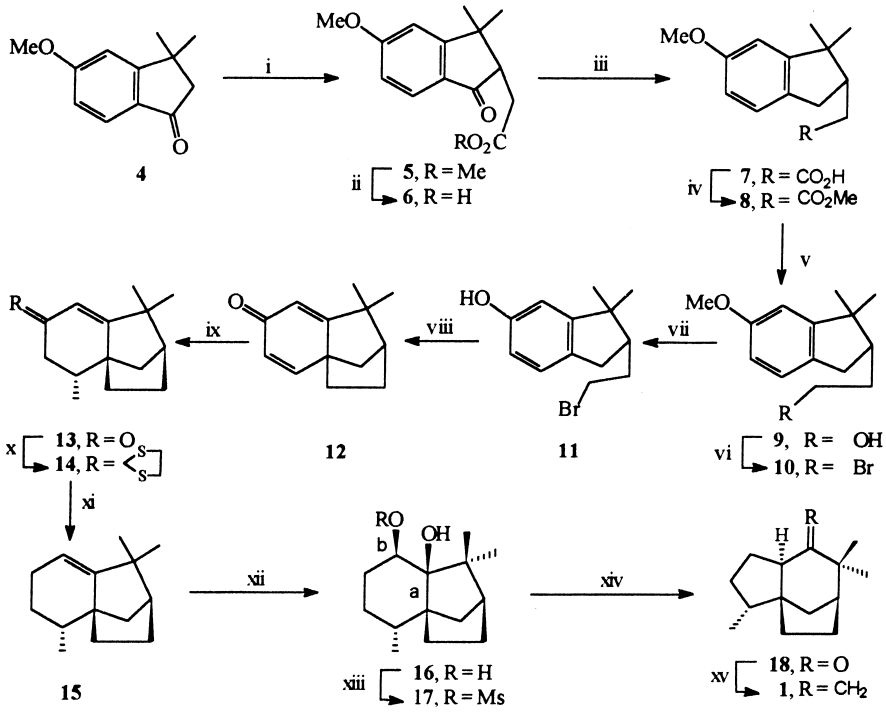

Scheme 1. *Reagents and conditions*: (i) LDA, $BrCH_2CO_2Me$, THF, −10°C to rt, 73%; (ii) KOH, MeOH, reflux, 6 h, H_3O^+, 92%; (iii) $NaBH_4$, aq. NaOH, rt, 24 h, H_3O^+; H_2, 10% Pd–C, AcOH, 89%; (iv) CH_2N_2, Et_2O, 0°C, 94%; (v) LAH, Et_2O, reflux, 4 h, 95%; (vi) Ph_3P, CBr_4, Et_2O, rt, 5 h, 80%; (vii) BBr_3, CH_2Cl_2, 0°C to rt, 16 h, 92%; (viii) *t*-BuOK, *t*-BuOH, 80°C, 10 h, 73%; (ix) $LiMe_2Cu$, Et_2O, 0°C, 2 h, 85%; (x) $HSCH_2CH_2SH$, MeOH, $BF_3{\cdot}Et_2O$, rt, 20 h, 94%; (xi) Na, EtOH, liq. NH_3, 86%; (xii) OsO_4, C_5H_5N, rt, 5 days, 85%; (xiii) MsCl, C_5H_5N, rt, 15 h, 90%; (xiv) *t*-BuOK, *t*-BuOH, 20°C, 10 min, 88%; (xv) *t*-AmOK, $(C_6H_5)_3\,P^+CH_3Br^-$, toluene, 90–92°C, 6 h, 64%.

the olefin **15** in 87% yield. Dihydroxylation of **15** with OsO_4 in pyridine at room temperature afforded the *cis*-diol **16** in high yield and this on treatment with $MeSO_2Cl$ in pyridine furnished the corresponding monomesylate **17** as a crystalline compound in 90% yield. As mentioned before, the relative stereochemistries at C-1, C-2, C-5, C-6 and C-8 of the diol **16** were determined by X-ray crystallography (Fig. 2).[15] The bonds a and b of the mesylate **17** are antiperiplanar and therefore the monomesylate rearranged[16] smoothly on treatment with *t*-BuOK (1 equiv.) in *t*-BuOH at 20°C to provide the ketone **18**[17] as the sole product in high yield. The spectral data of the present compound agreed very well with those reported for (±)-norzizanone **18** in the literature (Scheme 1).[5,6,10]

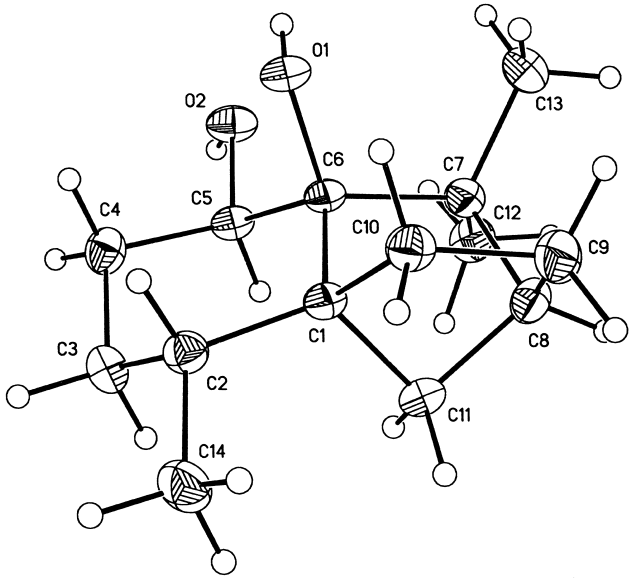

Figure 2. Single-crystal X-ray structure of the diol **16** (an ORTEP drawing).

In order to complete the desired synthesis of **1**, the last step to be carried out was the introduction of the exocyclic methylene group at C-6. Wittig olefination of the ketone **18** under appropriate experimental conditions[18] employing potassium *t*-amylate as the base proved successful. The Wittig reagent methylenetriphenylphosphorane was generated at 88–90°C using a fivefold excess of methyltriphenylphosphonium bromide and an equimolar amount of potassium *t*-amylate in the minimum amount of toluene to bring the mixture to homogeneity. The ketone **18** was added to the solution of the reagent at 90°C and the reaction was allowed to proceed at 90–92°C for 6 h. Chromatography of the crude product over silica gel and elution with pentane afforded pure (±)-zizaene (**1**) in good yield. The identity of the present compound was secured through ^1H NMR, ^{13}C NMR, IR, and microanalytical data. The spectral data of our synthetic zizaene are also in good agreement with those reported[3,5,6] in the literature.

In conclusion, in the present work a stereocontrolled total synthesis of the sesquiterpene hydrocarbon (±)-zizaene has been achieved using a base induced pinacol type rearrangement as a key step.

2. Experimental

2.1. General

The compounds described as having asymmetric centres are all racemates. Melting points and boiling points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker DPX-300 spectrometer with $SiMe_4$ as internal standard. The chemical shifts (δ ppm) are reported relative to $SiMe_4$ (δ_H 0.00) for ^{1}H and the central line of residual $CHCl_3$ (δ_C 77.0) for ^{13}C. Moisture sensitive reactions were carried out using standard syringe-septum technique. Anhydrous solvents were obtained by standard procedures. All solvent extracts were dried over anhydrous Na_2SO_4. Product purities were routinely checked by TLC. Ether refers to diethyl ether and light petroleum refers to the fraction of petroleum ether in the boiling point range 40–60°C.

2.1.1. 3,3-Dimethyl-5-methoxyindan-1-one (4). The indanone **4** was prepared[11] from 3-methoxyacetophenone as a crystalline compound, mp 63–64°C (lit.,[11] mp 59–60°C); IR and ^{1}H NMR data of **4** are consistent with the literature values;[11] δ_C (75 MHz, $CDCl_3$) 204.1, 166.8, 165.5, 128.5, 125.1, 114.9, 107.0, 55.5, 53.0, 38.3, 29.8.

2.1.2. 2-Methoxycarbonylmethyl-3,3-dimethyl-5-methoxyindan-1-one (5). To a stirred solution of diisopropylamine (2.53 g, 25 mmol) in dry THF (15 mL) at −10°C was added under nitrogen BuLi (1.5 M in hexane, 15 mL, 22.5 mmol). After 20 min, the indanone **4** (3.92 g, 20.6 mmol) in THF (6 mL) was added and the mixture was stirred at −10°C for 90 min. Methyl bromoacetate (3.67 g, 24 mmol) was then added dropwise and the resulting mixture was stirred at −10°C for 3 h and at room temperature for 12 h. It was then poured into ice, acidified with dil. HCl and extracted with ether (3×40 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (25 mL), water (2×30 mL) and dried. The residue remaining upon evaporation of the solvent was distilled to afford the keto-ester **5** (3.95 g, 73%) as a colourless oil, bath temperature (bp) 158–160°C/0.5 mm Hg; [Found: C, 68.52; H, 7.03. $C_{15}H_{18}O_4$ requires C, 68.69; H, 6.92%]; ν_{max} (film) 1738, 1705, 1597 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.66 (1H, d, *J*=7.9 Hz, 7-Ar*H*), 6.91–6.88 (2 H, m, 4- and 6-Ar*H*), 3.90 (3H, s, ArO*Me*), 3.76 (3H, s, CO_2*Me*), 3.04–2.90 (2H, m), 2.49–2.41 (1H, m), 1.50 (3H, s, *Me*), 1.16 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 203.3, 173.3, 165.6, 165.4, 127.0, 125.3, 115.0, 107.0, 55.9, 55.6, 51.8, 41.5, 30.9, 27.9, 26.8.

2.1.3. 2-Carboxymethyl-3,3-dimethyl-5-methoxyindan-1-one (6). The ester **5** (3.8 g) was hydrolysed by refluxing for 6 h with a solution of KOH (4 g) in MeOH (32 mL) and water (3 mL). Usual work-up followed by purification on a silica gel column using ether–light petroleum (1:4) as eluent furnished the keto-acid **6** (3.31 g, 92%) as an oil; [Found: C, 67.51; H, 6.38. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%]; ν_{max} (film) 1703, 1699, 1597 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.69 (1H, d, *J*=9.0 Hz, 7-Ar*H*), 6.92 (1H, dd, *J*=9.0, 2.4 Hz, 6-Ar*H*), 6.92 (1H, d, *J*=2.4 Hz, 4-Ar*H*), 3.92 (3H, s, ArO*Me*), 3.02–2.92 (2H, m), 2.58–2.48 (1H, m), 1.52 (3H, s, *Me*), 1.19 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 204.1, 177.7, 165.9, 165.8, 126.8, 125.7, 115.2, 107.0, 55.7, 55.7, 41.8, 31.3, 27.8, 27.0.

2.1.4. 1,1-Dimethyl-2-carboxymethyl-6-methoxyindane (7). To a stirred solution of the keto-acid **6** (3.2 g, 12.9 mmol) in aqueous NaOH (1.5N, 16 mL) was added $NaBH_4$ (0.57 g, 15 mmol) in small portions during 20 min. The mixture was stirred at room temp. for 24 h, cooled to 0°C and acidified with 3N HCl. Extraction with ether afforded a gummy material (3 g) which was dissolved in AcOH (25 mL) and hydrogenated over Pd–C (10%, 0.6 g) in the presence of a few drops of $HClO_4$. Uptake of hydrogen ceased after 1 h. The mixture was filtered, diluted with water (50 mL) and extracted with $CHCl_3$ (3×60 mL). The organic extract was washed with brine, water and dried. Evaporation of the solvent followed by crystallisation of the solid residue from a mixture of ether and light petroleum afforded the acid **7** (2.69 g, 89%) as white needles, mp 121–122°C; [Found: C, 71.70; H, 7.85. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%]; ν_{max} (KBr) 1703, 1608 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.08 (1H, d, *J*=8.8 Hz, 4-Ar*H*), 6.71–6.68 (2H, m, 5- and 7-Ar*H*), 3.79 (3H, s, ArO*Me*), 3.11–3.04 (1H, m), 2.63–2.45 (3H, m), 2.41–2.33 (1H, m), 1.32 (3H, s, *Me*), 1.00 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 179.9, 158.9, 153.6, 132.7, 124.9, 111.8, 108.0, 55.4, 47.3, 45.6, 35.6, 34.8, 26.5, 23.4.

2.1.5. 1,1-Dimethyl-2-methoxycarbonylmethyl-6-methoxyindane (8). The acid **7** (2.6 g) was treated with an ethereal solution of CH_2N_2 (excess) at 0°C to provide the methyl ester **8** (2.59 g, 94%) as an oil, bp 135–137°C/0.4 mm Hg; [Found: C, 72.70; H, 8.22. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%]; ν_{max} (film) 1738, 1610 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.06 (1H, d, *J*=8.9 Hz, 4-Ar*H*), 6.70–6.66 (2H, m, 5- and 7-Ar*H*), 3.78 (3H, s, ArO*Me*), 3.70 (3H, s, CO_2*Me*), 3.04–2.97 (1H, m), 2.59–2.44 (3H, m), 2.38–2.29 (1H, m), 1.29 (3H, s, *Me*), 0.98 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 173.8, 158.9, 153.7, 132.8, 124.8, 111.7, 107.9, 55.3, 51.5, 47.5, 45.5, 35.6, 34.7, 26.5, 23.3.

2.1.6. 1,1-Dimethyl-2-(2-hydroxyethyl)-6-methoxyindane (9). A solution of the ester **8** (2.3 g, 9.26 mmol) in anhydrous ether (15 mL) was added dropwise at room temperature to a stirred suspension of $LiAlH_4$ (0.6 g, 15.8 mmol) in ether (25 mL). After the addition, the mixture was refluxed for 4 h and then cooled. Excess of hydride was carefully destroyed by addition of saturated aq. Na_2SO_4 and the mixture was filtered through celite. The residue was washed thoroughly with ether (3×20 mL). The combined filtrate was washed with brine, dried and concentrated. The residue was evaporatively distilled to afford the primary alcohol **9** (1.94 g, 95%) as a colourless oil, bp 130–132°C/0.6 mm Hg; [Found: C, 76.50; H, 9.21. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15%]; ν_{max} (film) 3366, 1610 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.06 (1H, d, *J*=7.8 Hz, 4-Ar*H*), 6.69–6.66 (2H, m, 5- and 7-Ar*H*), 3.85–3.66 (2H, m, CH_2OH), 3.78 (3H, s, ArO*Me*), 2.94–2.87 (1H, m), 2.54–2.45 (1H, m), 2.14–1.54 (4H, m), 1.29 (3H, s, *Me*), 0.96 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 158.8, 154.6, 133.3, 124.7, 111.5, 107.9, 62.3, 55.3, 48.0, 45.6, 35.5, 32.7, 26.4, 23.4.

2.1.7. 1,1-Dimethyl-2-(2-bromoethyl)-6-methoxyindane (10). To a stirred mixture of CBr_4 (5.44 g, 16.4 mmol) and the alcohol **9** (1.8 g, 8.2 mmol) in anhydrous ether (35 mL) at 25°C was added Ph_3P (4.3 g, 16.4 mmol) in small portions After stirring at 25°C for 5 h, the reaction mixture was diluted with ether (40 mL) and filtered. The insoluble material was washed with two 20 mL portions of ether. Evaporation of the filtrate followed by purification of the residue on a silica gel column using ether–light petroleum (1:49) as eluent afforded the bromide **10** (1.85 g, 80%) as a colourless oil, bp 128–130°C/0.6 mm Hg; [Found: C, 59.22; H, 6.95. $C_{14}H_{19}BrO$ requires C, 59.37; H, 6.76%]; ν_{max} (film) 1610, 1585, 1485, 1242, 1070 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07 (1H, d, *J*=8.8 Hz, 4-Ar*H*), 6.69 (1H, d, *J*=2.3 Hz, 7-Ar*H*), 6.68 (1H, dd, *J*=8.8, 2.3 Hz, 5-Ar*H*), 3.79 (3H, s, ArO*Me*), 3.61–3.38 (2H, m, CH_2Br), 2.98–2.91 (1H, m), 2.52–2.44 (1H, m), 2.26–1.85 (3H, m), 1.31 (3H, s, *Me*), 0.97 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 159.0, 154.3, 132.7, 124.8, 111.7, 108.0, 55.4, 50.1, 45.6, 34.8, 33.3, 32.8, 26.5, 23.5.

2.1.8. 1,1-Dimethyl-2-(2-bromoethyl)-6-hydroxyindane (11). To a stirred solution of **10** (1.7 g, 6.0 mmol) in dry CH_2Cl_2 (12 mL) at 0°C was added dropwise BBr_3 (1.55 g, 6.2 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at 0°C for 1 h and at room temperature for 16 h. It was then poured into ice and extracted with CH_2Cl_2 (3×20 mL). The organic extract was washed with aqueous $NaHCO_3$, water, and dried. Evaporation of the solvent followed by chromatography of the residue on a silica gel column (45 g) using ether–light petroleum (1:19) as eluent furnished the bromophenol **11** (1.48 g, 92%) as an oil; [Found: C, 57.83; H, 6.46. $C_{13}H_{17}BrO$ requires C, 58.00; H, 6.37%]; ν_{max} (film) 3346, 1614, 1593 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.02 (1H, d, *J*=8.2 Hz, 4-Ar*H*), 6.62–6.59 (2H, m, 5- and 7-Ar*H*), 4.94 (1H, bs, ArO*H*), 3.61–3.38 (2H, m, CH_2Br), 2.97–2.89 (1H, m), 2.51–2.42 (1H, m), 2.24–1.85 (3H, m), 1.28 (3H, s, *Me*), 0.96 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 154.7, 154.6, 132.8, 125.0, 113.3, 109.2, 50.0, 45.5, 34.8, 33.2, 32.8, 26.4, 23.5.

2.1.9. 7,7-Dimethyltricyclo[6.2.1.0^{1,6}]undeca-2,5-dien-4-one (12). A solution of the bromophenol **11** (1.4 g, 5.2 mmol) in *t*-BuOH (5 mL) was added dropwise under nitrogen to a stirred solution of *t*-BuOK [prepared from K (0.21 g, 5.38 mmol)] in *t*-BuOH (400 mL) at 80°C. The mixture was stirred at 80°C for 10 h and then ca. 200 mL of *t*-BuOH was removed under reduced pressure. The residue was diluted with water (250 mL) and extracted with ether (3×200 mL). The ether extract was washed with water (2×100 mL), dried and concentrated. The residue was evaporatively distilled at 110°C/0.4 mm Hg to afford a colourless oil which crystallised from light petroleum to give the dienone **12** (0.71 g, 73%) as colourless plates, mp 72–73°C; [Found: C, 82.83; H, 8.71. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%]; ν_{max} (KBr) 1655, 1626 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.04 (1H, d, *J*=9.6 Hz, C*H*=CHCO), 6.27 (1H, dd, *J*=9.6, 1.5 Hz, CH=C*H*CO), 6.03 (1H, d, *J*=1.5 Hz, COC*H*=C), 2.20–1.25 (7H, m), 1.19 (3H, s, *Me*), 1.13 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 187.6, 181.4, 149.7, 130.6, 118.1, 53.8, 48.6, 42.3, 42.1, 33.8, 28.0, 28.0, 24.2.

2.1.10. (1*RS*,2*RS*,8*SR*)-2,7,7-Trimethyltricyclo[6.2.1.0^{1,6}]-undec-5-en-4-one (13). A solution of $LiMe_2Cu$ was prepared under nitrogen by dropwise addition of MeLi (1.6 M in ether, 8 mL, 12.8 mmol) to a stirred suspension of CuI (1.22 g, 6.4 mmol) in anhydrous ether (20 mL) at 0°C. A solution of the dienone **12** (0.61 g, 3.24 mmol) in ether (16 mL) was then added over a period of 10 min and the resultant mixture was stirred at 0°C for 2 h. It was then treated with saturated aqueous NH_4Cl (20 mL), stirred for 20 min, diluted with water (20 mL) and extracted with ether (3×40 mL). The ether extract was washed with water (2×30 mL), dried and concentrated. The solid residue was crystallised from pentane to furnish the enone **13** (0.56 g, 85%) as white needles, mp 64–65°C; [Found: C, 82.40; H, 9.75. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%]; ν_{max} (KBr) 1668, 1640 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.69 (1H, s, C*H*=C), 2.69–2.62 (1H, m), 2.30–1.98 (2H, m), 1.80–1.31 (7H, m), 1.13 (3H, s, *Me*), 1.09 (3H, s, *Me*), 1.00 (3H, d, *J*=7.0 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 199.4, 182.1, 116.8, 54.9, 46.9, 43.8, 42.6, 39.7, 33.5, 33.2, 26.9, 24.6, 24.4, 17.5.

2.1.11. (1*RS*,2*RS*,8*SR*)-4,4-Ethyelenedithio-2,7,7-trimethyltricyclo[6.2.1.0^{1,6}]undec-5-ene (14). To a solution of the enone **13** (0.51 g, 2.5 mmol) in MeOH (4 mL) were added ethanedithiol (1.2 g) and $BF_3{\cdot}Et_2O$ (1 mL) and the mixture was stirred at room temp. for 20 h. The reaction mixture was then poured into ice-cold aqueous NaOH (10%, 15 mL) and the product was extracted with ether (3×25 mL). The ether extract was washed with water (2×20 mL), dried and concentrated. The residue was evaporatively distilled at 154–156°C/0.1 mm Hg to give **14** (0.66 g, 94%) as a colourless oil; ν_{max} (film) 1458, 1379, 1360, 1275 cm^{-1}; [Found: C, 68.28; H, 8.79. $C_{16}H_{24}S_2$ requires C, 68.51; H, 8.62%]; δ_H (300 MHz, $CDCl_3$) 5.42 (1H, s, C*H*=C), 3.44–3.26 (4H, m, SCH_2CH_2 S), 2.35–1.15 (10H, m), 1.05 (3H, s, *Me*), 1.04 (3H, d, *J*=6.5 Hz, CH*Me*), 0.99 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 155.5, 118.5, 64.3, 52.1, 47.2, 45.8, 41.1, 40.4, 39.0, 38.6, 33.9, 32.9, 28.8, 25.2, 24.7, 17.5.

2.1.12. (1*RS*,2*RS*,8*SR*)-2,7,7-Trimethyltricyclo[6.2.1.0^{1,6}]-undec-5-ene (15). A solution of the thioacetal **14** (0.6 g, 2.14 mmol) in dry ether (15 mL) was added under nitrogen to distilled liquid ammonia (80 mL). To this mixture was added Na metal (0.9 g, 39 mmol) with stirring for 2 min. After 5 min, EtOH was added dropwise until the blue colour disappeared. The ammonia was allowed to evaporate. The residue was diluted with water (25 mL) and extracted with ether (3×30 mL). The ether extract was washed with water (2×25 mL), dried, and concentrated. The residue was evaporatively distilled to afford **15** as a colourless oil (0.35 g, 86%), bp 98–100°C/4 mm Hg; [Found: C, 88.28; H, 11.46. $C_{14}H_{22}$ requires C, 88.35; H, 11.65%]; ν_{max} (film) 1377, 1360 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.16 (1H, t, *J*=3.5 Hz, C*H*=C), 1.97–1.84 (3H, m), 1.78–1.59 (3H, m), 1.53–1.11 (6H, m), 1.03 (3H, s, *Me*), 0.96 (3H, s, *Me*), 0.87 (3H, d, *J*=7.0 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 154.4, 111.1, 52.9, 47.3, 41.4, 39.5, 35.3, 32.3, 29.0, 26.8, 25.7, 25.2, 21.1, 16.2.

2.1.13. (1*RS*,2*RS*,5*RS*,6*SR*,8*SR*)-2,7,7-Trimethyltricyclo-[6.2.1.0^{1,6}]undecane-5,6-diol (16). A solution of the olefin

15 (0.3 g, 1.6 mmol) and OsO_4 (0.41 g, 1.6 mmol) in pyridine (6 mL) was stored at room temp. for 5 days. A saturated aqueous solution of sodium hydrogen sulfite (20 mL) was then added to the stirred reaction mixture, and stirring was continued at room temperature for 3 h. Water (20 mL) was added and the product was extracted with ether (3×40 mL). The ether extract was washed with dilute HCl (3N, 2×15 mL), water (2×25 mL), and dried. The solid residue remaining upon evaporation of the solvent was crystallised from light petroleum to furnish the diol **16** (0.3 g, 85%) as colourless rods, mp 116–117°C; [Found: C, 75.18; H, 11.02. $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78%]; ν_{max} (KBr) 3470, 3395 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (1H, dd, *J*=10.5, 5.2 Hz, C*H*OH), 2.27–1.01 (14H, m), 1.19 (3H, s, *Me*), 0.97 (3H, s, *Me*), 0.88 (3H, d, *J*=6.4 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 80.0, 72.3, 57.2, 49.7, 43.6, 32.2, 31.5, 31.5, 31.1, 27.3, 24.8, 24.8, 23.0, 17.4.

2.1.14. Preparation of the monomethanesulfonate 17. A solution of the diol **16** (0.25 g, 1.1 mmol) and methanesulfonyl chloride (0.17 g, 1.5 mmol) in pyridine (4 mL) was left at room temp. for 15 h. The reaction mixture was then diluted with water (15 mL) and extracted with ether (3×25 mL). The ether extract was washed with water (2×20 mL), dried, and concentrated under reduced pressure. The solid residue was crystallised from a mixture of ether and light petroleum to afford the monomesylate **17** (302 mg, 90%) as colourless plates, mp 97–98°C; [Found: C, 59.44; H, 8.90. $C_{15}H_{26}O_4S$ requires C, 59.57; H, 8.67%]; ν_{max} (KBr) 3543, 1354, 1167, 939 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.97 (1H, dd, *J*=11.6, 2.4 Hz, C*H*OMs), 3.05 (3H, s, OSO_2 *Me*), 2.11–1.06 (13H, m), 1.19 (3H, s, *Me*), 0.98 (3H, s, *Me*), 0.88 (3H, d, *J*=6.5 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 86.6, 79.5, 58.5, 50.0, 43.8, 40.9, 32.3, 30.9, 30.5, 28.3, 26.9, 24.8, 24.6, 22.6, 17.2.

2.1.15. (1*RS*,2*RS*,5*RS*,8*SR*)-2,7,7-Trimethyltricyclo-[6.2.1.0^{1,5}]undecan-6-one (18). A solution of *t*-BuOK [prepared from K (35 mg, 0.9 mmol)] in *t*-BuOH (7 mL) was added under nitrogen to a magnetically stirred solution of the monomesylate **17** (0.26 g, 0.86 mmol) in *t*-BuOH (3 mL) at 20°C. The reaction mixture was stirred at 20°C for 10 min and then diluted with water (20 mL). The product was extracted with ether (3×30 mL). The ether extract was washed with water (2×20 mL), dried and concentrated. Purification of the residue on a silica gel column using ether–light petroleum (1:19) as eluent furnished the ketone **18** (156 mg, 88%) as a colourless oil; [Found: C, 81.65; H, 10.67. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%]; ν_{max} (film) 1707, 1462, 1385, 1151 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.93 (1H, t, *J*=8.0 Hz, C*H*CO), 2.13–2.00 (2H, m), 1.90–1.80 (3H, m), 1.66–1.15 (7H, m), 1.19 (3H, s, *Me*), 1.04 (3H, s, *Me*), 0.97 (3 H, d, *J*=6.6 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 216.5, 57.5, 54.0, 50.0, 49.0, 41.4, 36.1, 32.1, 30.5, 26.8, 25.7, 22.1, 20.0, 19.2.

2.1.16. (±)-Zizaene (1). To a solution of potassium *tert*-amylate [prepared from potassium (118 mg, 3 mmol)] in dry toluene (2.5 mL) at 80°C was added under argon methyltriphenylphosphonium bromide (1.11 g, 3.1 mmol) and the mixture was stirred at 88–90°C for 30 min. To the resulting bright yellow solution of Wittig reagent was added at 90°C a solution of the ketone **18** (125 mg, 0.60 mmol) in toluene (1 mL) and the mixture was stirred at 90–92°C for 6 h. It was then cooled, diluted with water (15 mL) and extracted with ether (3×20 mL). The combined ether extract was washed with water (2×15 mL), dried and concentrated. The residue was dissolved in pentane and passed through a short silica gel column to remove the triphenylphosphine oxide. Further purification was effected by chromatography on 10 g of silica gel. Elution with pentane afforded (±)-zizaene (**1**) (80 mg, 64%) as a colourless oil; ν_{max} (film) 3082, 2940, 2860, 1638, 1478, 1375, 891 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.73–4.72 (1H, m, vinyl proton), 4.60–4.59 (1H, m, vinyl proton), 2.52–2.48 (1H, m, C*H*C=CH_2), 1.97–1.17 (12H, m), 1.08 (3H, s, *Me*), 1.05 (3H, s, *Me*), 0.95 (3H, d, *J*=7.0 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 157.3, 104.9, 54.8, 49.2, 47.2, 40.4, 40.3, 36.1, 32.6, 31.7, 28.6, 26.1, 25.9, 24.8, 20.0. An analytical sample of **1** was prepared by evaporative distillation at 105–107°C/4 mm Hg; [Found: C, 88.01; H, 11.64. $C_{15}H_{24}$ requires C, 88.16; H, 11.84%]. [Lit.,[5] IR (film) 1640, 1480, 1375 and 895 cm^{-1}, lit.,[5] NMR (CCl_4) 4.71 and 4.56 (t, 1H each, *J*=2 Hz), 1.08 (s, 3H), 1.06 (s, 3H), and 0.96 (d, 3H, *J*=7 Hz)].

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15. Crystallographic data of the diol **16/16** crystallises in the monoclinic *C*2/*c* space group with a=22.632 (8), b=10.945 (4), c=10.194 (2) Å; $\alpha=\gamma=90°$, β=98.99 (2)°; V=2493.9 (13) Å^3, and z=8. The final coordinates were solved by direct methods and refined by full matrix least square method with R=0.0330 and Rw=0.0858, and GOF=1.010 for 242 variables; measured reflections 1705, used reflectios 1631; Bond length ([Å] (standard deviation)): C(5)–C(4) 1.510(3), C(5)–C(6) 1.535(2), C(5)–O(2) 1.436(2), C(4)–C(3) 1.514(3), C(3)–C(2) 1.522(3), C(2)–C(1) 1.532(2); C(2)–C(14) 1.524(3), C(1)–C(6) 1.564(2), C(1)–C(11) 1.543(2), C(1)–C(10) 1.548(2), C(11)–C(8) 1.531(3), C(8)–C(7) 1.550(3), C(8)–C(9) 1.523(3), C(7)–C(6) 1.597(2), C(7)–C(12) 1.535(3), C(7)–C(13) 1.529(3), C(10)–C(9) 1.537(3), C(6)–O(1) 1.439(2). Bond angles ([°] (standard deviation)): O(2)–C(5)–C(4) 111.70(2), C(4)–C(5)–C(6) 112.03(14), C(4)–C(3)–C(2) 110.90(2), C(3)–C(2)–C(1) 112.49(14), C(2)–C(1)–C(11) 118.30(2), C(11)–C(1)–C(10) 100.37(14), C(11)–C(1)–C(6) 100.40(13), O(1)–C(6)–C(5) 106.25(13), C(5)–C(6)–C(1) 112.50(13), C(5)–C(6)–C(7) 114.02(13), C(8)–C(11)–C(1) 94.97(14), C(9)–C(8)–C(7) 111.90(2), C(13)–C(7)–C(12) 107.40(2), C(12)–C(7)–C(8) 107.50(2), C(12)–C(7)–C(6) 114.30(2), C(9)–C(10)–C(1) 104.70(2), O(2)–C(5)–C(6) 107.49(14), C(5)–C(4)–C(3) 109.30(2), C(3)–C(2)–C(14) 110.60(2), C(14)–C(2)–C(1) 113.70(2), C(2)–C(1)–C(10) 113.20(14), C(2)–C(1)–C(6) 115.08(14), C(10)–C(1)–C(6) 107.71(14), O(1)–C(6)–C(1) 107.51(13), O(1)–C(6)–C(7) 113.39(13), C(1)–C(6)–C(7) 103.14(13), C(9)–C(8)–C(11) 101.10(2), C(11)–C(8)–C(7) 102.00(2), C(13)–C(7)–C(8) 113.90(2), C(13)–C(7)–C(6) 112.10(2), C(8)–C(7)–C(6) 101.68(14), C(8)–C(9)–C(10) 102.70(2). Final crystallographic coordinates are deposited in Cambridge Crystallographic Data Centre (CCDC 174746).
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