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A TOTAL SYNTHESIS OF (±)-ISOCOMENE AND (±) β-ISOCOMENE BY AN INTRAMOLECULAR ENE REACTION

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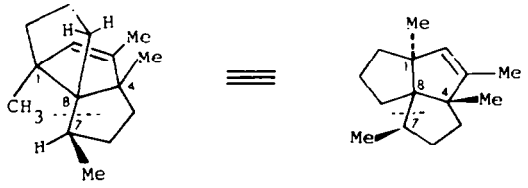
Abstract—The racemic sesquiterpenes isocomene **1** and β-isocomene **22** have been synthesized starting from 1,7-octadien-3-one **10** in a stereoselective manner. In the key step **12**→**13** (Scheme 5) the C-7, C-8-bond was formed by an intramolecular thermal ene reaction. Further transformations of **13** (Scheme 6) involved successively ring contraction **18**→**19**, elimination **21**→**22** and olefin isomerization **22**→**1**.

(−)-Isocomene (berkheyaradulene) has been isolated from the toxic plant *Isocoma Wrightii* by Zalkow *et al* and independently by the group of Bohlmann from the roots of *Berkheya radula*. Based on chemical, spectroscopic and X-ray evidence, both groups assigned structure **1** to this sesquiterpene without specifying its absolute configuration.[1,2] For β-isocomene, isolated from *Berkheya* species, structure **22** has been elucidated.[3] The sterically crowded, polyfused cyclopentanoid network of **1** and **22**



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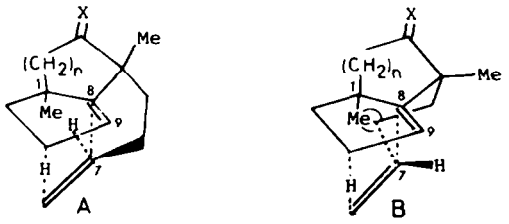
containing one tertiary and three quaternary chiral centers provides considerable challenge as a synthetic target. Very recently several sesquiterpenes have been isolated and shown to possess this unusual carbon skeleton[4] which also constitutes an integral part of the sesterterpene retigeranic acid[5].

In conjunction with a general program exploring the scope and limits of intramolecular ene-reactions for the regio- and stereo-selective preparation of five-membered rings,[6] we have recently published a preliminary note describing a total synthesis of (±)-isocomene.[7] Since then, two independent elegant syntheses of (±)-**1** have been reported by Paquette and Han[8] and by Pirrung.[9]

It is the purpose of this paper to disclose our synthetic approach to (±)-**1** with full experimental detail. Our basic strategy concentrates on the formation of the C-7 , C-8 bond[10] by means of a thermal intramolecular type I-ene reaction. Examination of the endo and exo-transition states *A* and *B* (Scheme 2) indicates a strong repulsion between the C-1-methyl group[10] and the bridging allylic methylene group in the exo-orientation *B*. The desired endo-orientation *A*, which avoids this severe non-bonding interaction, should thus be favored. This strategy led initially to a retrosynthetic analysis (Scheme 3) implicating the stereoselective construction of centers C(7) and C(8)[10] in the key ene reaction **3**→**2**, methylation at C-4[10] in the preceding step **4**→**3** due to the sterically bulky C-

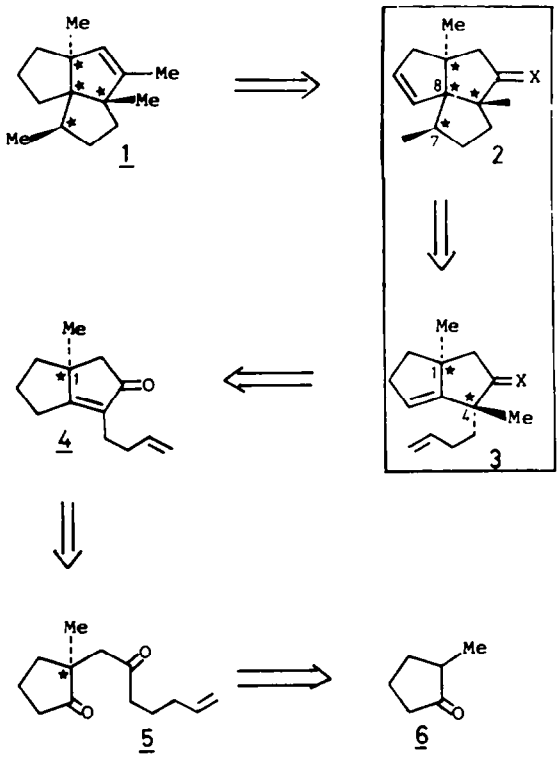


ENDO EXO
(non bonding interaction)

1-methyl group[10], base-induced cyclization **5**→**4**, and appropriate functionalisation of methyl-cyclopentanone **6** giving the 1,4-diketone **5**.

Preparation and Attempted Methylation of the Indenone **4**, *X* = 0

Conversion of **6** to **5** relied on the nucleophile-induced elimination-addition of an α-halo-oxime,[11] a reaction recently employed in a steroid synthesis.[12] The required bromo-oxime **8** was obtained in 78% yield from the known 5-hexenoyl chloride[13] by successive treatment with diazomethane, 47% aq HBr and hydroxylamine. Cleavage of the known silylenol ether **7**[14] with methyllithium in THF followed by slow addition of the bromo-oxime **8** (0.5 equiv) to the resulting enolate solution at −75° furnished the hydroxyoxazine **9** in 77% yield as a single isomer.[15] Stirring an ether solution of **9** with aq. ceric ammonium nitrate (1.2 equiv) at 20° for 18 hr furnished the 1,4-diketone **5** in 45% yield. Although the transformation **7**→**5** represents a new route to 1,4-diketones, it was not further optimized for reasons indicated below. The aldolisation-elimination **5**→**4** was smoothly accomplished in 88% yield by heating **5** with 2.5% NaOH in ethanol/water (1:1) at 80° for 1 hr. However, to our distress, the enone **4** could not be methylated in the desired sense. Successive treatment of pentalenone **4** with a strong base and methyl iodide gave no trace of **3**, X = 0 despite wide variations of the reaction conditions (base, solvent, temperature and reaction time). Our failure to trap any dienolate formed from **4** with deuteroacetic acid, chlorotrimethylsilane or ethyl formate suggests that deprotonation of **4** is disfavored by specific constraints of the pentalene system.

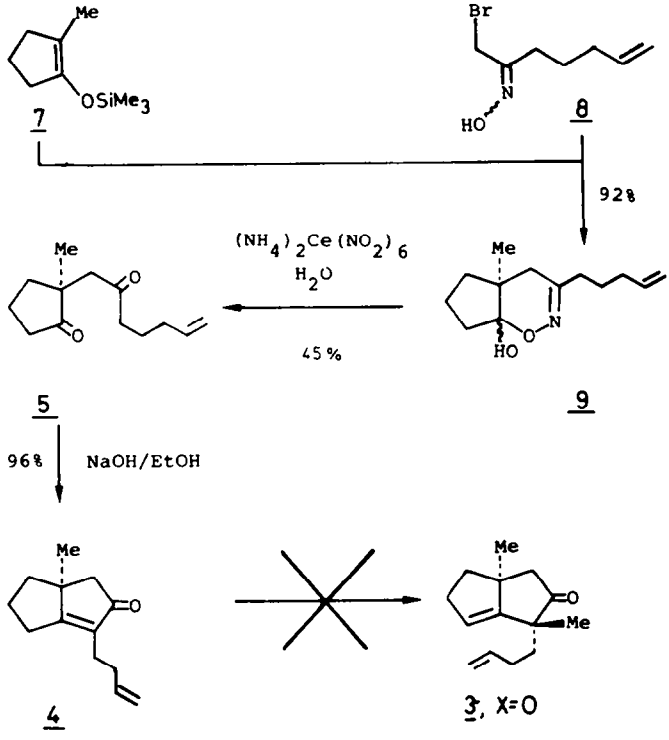


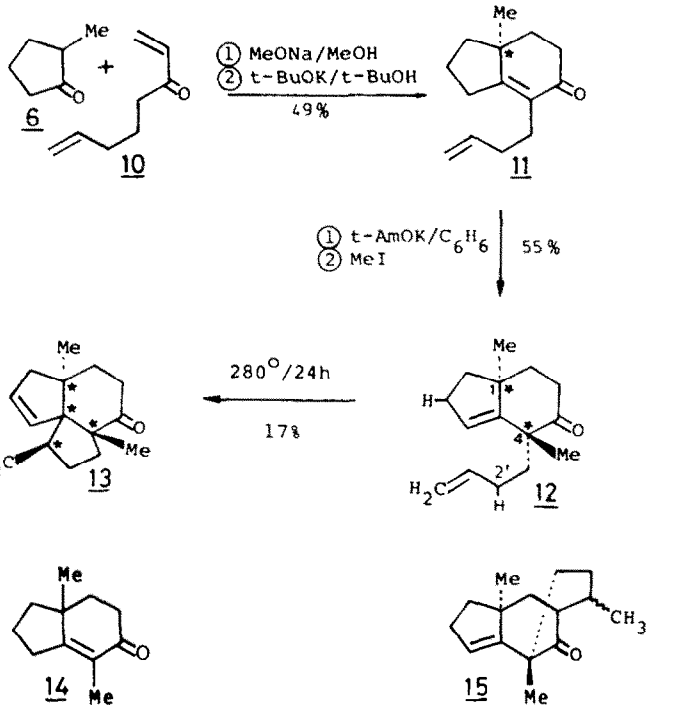
Preparation and thermal cyclization of the indenone **12**

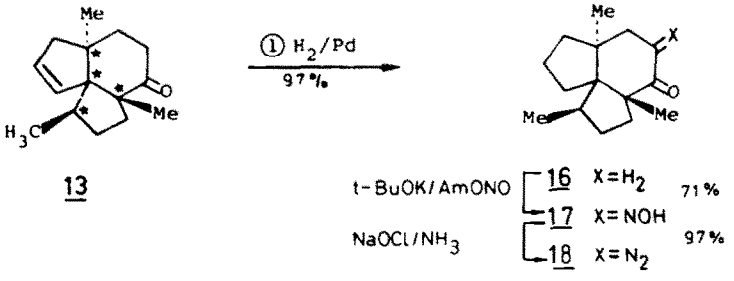
We therefore investigated the deprotonation/methylation of the homologous indenone-system **11**, considering a ring-contraction of the 6-membered ring at a later stage of the synthesis. Dienone **10** was readily available from 5-bromo-1-pentene via addition of the corresponding Grignard reagent to acrolein followed by oxidation of the resulting allylic alcohol with Jones' reagent. Addition of **10** to 2-methylcyclopentanone [16] in 2M methanolic NaOMe at 20° furnished a mixture of 2-methyl-2(3-oxo-7-octenyl)-cyclopentanone and **11**. Completion of the Robinson annelation[17] by treatment of the crude mixture with 0.5M t-BuOK in t-BuOH at 30° gave indenone **11** in 49% yield from **10**. In favorable contrast to pentalenone **4**, methylation of indenone **11** was smoothly achieved by deprotonation with potassium 2-methyl-2-butoxide (1.5 equiv) at 55° in benzene followed by addition of methyl iodide (3 equiv) and heating of the mixture under reflux for 30 min[18] The monomethylated β,γ-unsaturated ketone **12** was obtained in 55% yield as the major product together with its C-4-epimer[10] (11% yield). Thus, alkylation of the dienolate derived from **11** occurred preferentially at the face opposite to the angular C-1 methyl group.[10] This stereochemical assignment agrees with the ^{1}H-NMR spectra of the separated isomers (GC) which show for the minor isomer one methyl singlet at higher field (1.13 ppm) than that of the major product **12** (1.21 ppm); ultimate proof was obtained by the conversion of **12** to (±)-isocomene. The stage was now set for the crucial ene-reaction. Heating crude 1,6-diene **12** at 280° in toluene for 24 h furnished, after chromatography, the expected cyclopent [*d*] indenone **13** with high stereoselectivity. The low yield of **13** (17%) seems to reflect that the steric compression of this molecule is barely matched by the relatively small exergonic nature of the ene-reaction. Accordingly, related reactions became competitive as shown by the isolation of the retro-ene-product **14** (transfer of C-2 proton to 0; 15% yield). In addition, co-occurrence of a Conia cyclization[19] was indicated by obtaining an isomeric mixture (22% yield) tentatively assigned structure **15**.

Conversion of the ene-product **13** *to* (±)*-isocomene* (**1**)

Having correctly assembled all four chiral centers of **13**, we turned our attention to the envisaged ring-




6
10
① MeONa/MeOH
② t-BuOK/t-BuOH
49%
11
① t-AmOK/C6H6
② MeI
55%
280°/24h
17%
13
12
14
15


13
① H2/Pd
97%
t-BuOK/AmONO
16 X=H2
17 X=NOH
71%
NaOCl/NH3
18 X=N2
97%
80%
hν/MeOH
LiAlH4
96%
19
20: X=OH
21: X=Se-C6H4-o-NO2
ArSeCN,
Bu3P/Py
58%
① NaIO4
② 80°
TsOH/CH2Cl2/25°
75%
22
(±)-1

contraction. Hydro-genation (**13** → **14**; H_2, Pd/C, methanol; 97% yield), nitrosation of **14** with i-amylnitrite in the presence of t-BuOK to furnish keto-oxime **17** (m.p. 134–136°, 71% yield), and treatment with saturated aq NH_3, 5M NaOH and aq NaOCl[20] gave the diazoketone **18** (97% yield). Irradiation of **18** in methanol[21] under N_2 using a quartz apparatus with a mercury high-pressure lamp led to the ring-contracted ester **19**, obtained in 80% yield as a 4:1 mixture of epimers. The remaining task, requiring reduction of the carbomethoxy- to a methyl-group and introduction of unsaturation at the C-2, C-3 position,[10] was accomplished in the following manner. Reduction of **19** with $LiAlH_4$ gave primary alcohol **20** which was converted to selenide **21** (74% yield) upon treatment with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine in pyridine[22]. Oxidation of **21** ($NaIO_4$ in THF/MeOH/H_2O)[23] furnished a crude selenoxide; fragmentation required heating in refluxing hexane for 30 min[24] giving the exocyclic alkene **22** (58% yield) which was identified as (±)-β-isocomene by comparison of its IR ¹H-NMR, and mass spectra with those of natural (−)-β-isocomene. Finally, olefin-isomerisation of **22** catalyzed by p-toluene-sulfonic acid hydrate in CH_2Cl_2 at 20° gave pure (±)-isocomene **1** (75% yield) which was identified by comparison with the natural product using GC and spectral evidence.

EXPERIMENTAL

General. "Usual work-up" means pouring the reaction mixture into sat aq NH_4Cl or sat aq NaCl, extraction with ether or CH_2Cl_2, washing the combined organic layers successively with sat aq $NaHCO_3$ and sat aq NaCl, drying with solid Na_2SO_4 and removal of the solvent *in vacuo*. Preparative chromatography was carried out on silica gel Merck 0.05–0.20. Gas chromatograms (GC): 1 atm N_2; glass columns (3 mm ID × 3 m), stationary phases on Chromosorb W (acid washed 80–100 mesh); retention time in min (area%). Melting points (m.p.) are not corrected. IR spectra: ν_{max} in cm^{-1}. UV spectra: ethanol, λ_{max} in nm (log ε). NMR spectra: in $CDCl_3$, internal standard tetramethylsilane (δ = 0 ppm); abbreviations: s singlet, d doublet, t triplet, qa quartet, m multiplet, J spin–spin coupling constant (Hz), ¹H-NMR at 100 MHz, ^{13}C-NMR at 25.2 MHz. Mass spectra (MS): signals are given in *m/e* (rel.%); high resolutions MS (HR) were obtained using a Varian SM 1 or MAT 212 instrument.

1-Bromo-6-hepten-2-one oxime **8**. 5-hexenoyl chloride[13] (3.34 g, 25 mmol) was added dropwise to a stirred dry solution of an excess of diazomethane in ether at 0°. After 15 min at 0° aq 47% HBr (23 ml) was added to the reaction mixture over 10 min at 0°. Stirring of the mixture at 20°C for 15 min followed by the usual work-up furnished 1-bromo-6-heptenone (4.16 g, 87% yield) as a colorless oil; IR (film): 3080w, 1720s, 1640m, 920s.-¹H-NMR: 1.72 (m, 2H); 2.08 (m, 2H); 2.67 (t, J = 7); 3.90 (s, 2H): 5.05 (m, 2H); 5.8 (m, 1H). A mixture of the crude 1-bromo-6-heptenone (4.1 g, 21.6 mmol), hydroxylamine hydrochloride (4.3 g, 62 mmol), potassium acetate (5.4 g, 55 mmol) and acetic acid 90 ml) was stirred at 20°C for 16 h. After the usual work-up the remaining acetic acid was removed from the residue by addition of CCl_4 and subsequent evaporation twice *in vacuo* to furnish the bromoxime **8** as a semisolid mixture of syn- and anti-isomers (4.01 g, 90% yield). IR (film): 3300–2600 broad, 1715s, 1640m, 920s.- ¹H-NMR: 1.8 (m, 2H); 2.16 (m, 2H); 2.5 (m,2H); 4.00 (s,1.33 H); 4.08 (s, 0.66 H); 5.1 (m, 2H); 5.8 (m, 1H); 9.5 (s, broad, 1H).

4,4a,5,6,7,7a-Hexahydro-7a-hydroxy-4-methyl-3-(4-pentenyl)-cyclopent[e]-1,2-oxazine **9**. 1.8 M methyllithium in hexane (17.2 ml, 31 mmol) was added dropwise to a solution of 1-methyl-2-trimethylsilyloxy-1-cyclopentene[14] (5,4 g, 31 mmol) in THF (40 ml) at 20°. After stirring the mixture at 20° for 1 hr a solution of the bromoxime **8** (3.1 g, 14 mmol) in THF (30 ml) was added to the stirred mixture at −75°. The reaction mixture furnished after stirring at −75° for 1 hr followed by the usual work-up and chromatography (SiO_2 ethylacetate/ethanol 9:1) the hydroxyoxazine **9** as an oily residue (2.56 g, 77% yield). IR (film) = 3200–2900 (broad), 1645w, 1625w. ¹H-NMR: 1.2 (s, 3H), 1.4–1.85 (8H); 2.1 (m 2H); 2.35–2.85 (4H); 5.05 (m, 2H; 5.8 (m, 1H). MS: 223 ($C_{13}H_{21}NO_2^+$, 45), 194 (14), 180 (27), 169 (100); HR: M^+ Found: 223.1570. $C_{13}H_{21}NO_2$ requires: 223. 1586. ^{13}C-NMR: 148.2 (s), 137.3 (d), 115.1 (t), 44.0 (t), 43.8 (s), 42.2 (t), 36.5 (t), 33.5 (t), 26.4, 24.2, 22.8, 21.9.

2-Methyl-2-(2-oxo-6-heptenyl)-cyclopentanone **5**. A solution of the hydroxyoxazine **9** (1.46 g, 6.55 mmol) in ether (35 ml) was stirred with 0.22 M aq ceric ammonium nitrate (35 ml, 7.86 mmol) at 20°C for 18 hr. Evaporation of the dried organic phase and chromatography of the residue furnished the pure 1,4-diketone **5** (0.615 g, 45% yield) oil. IR (film): 3050w, 1745s, 1710s, 1640m, 950s. ¹H-NMR: 1.0 (s, 3H); 1.7 (m, 2H); 2.0 (m, 6H); 2.4 (m, 4H); 2.7 (d, 1H, J = 18); 2.82 (d, 1H, J = 18); 5.0 (m, 2H); 5.8 (m, 1H). ^{13}C-NMR: 221.3 (s), 207.9 (s), 137.7 (d), 115.0 (t), 50.3 (t), 45.6 (s), 42.0 (t), 37.0 (t), 34.9 (t), 33.0 (t), 22.9 (t), 22.8 (t), 18.9 (t). MS: 208 ($C_{13}H_{20}O_2^+$, 1), 196 (6), 192 (5), 179 (6), 168 (11), 166 (24), 164 (19), 161 (7), 154 (15), 148 (7), 147 (7), 139 (11), 131 (14), 129 (15), 112 (11). 111 (23), 97 (48), 96 (30), 86 (62), 84 (100). HR: M^+ Found 208.1471. $C_{13}H_{20}O_2$ requires: 208.1463.

1-(3-Butenyl)-2,3,3a,4,5,6-hexahydro-3a-methyl-pentalen-2-one **4**. A solution of the 1,4-diketone **5** (624 mg, 3 mmol) in ethanol (30 ml) was added at once to 5% aq sodium hydroxide (30 ml)[25]. Heating of the mixture under argon at 80° for 1 hr, followed by concentration in vacuo neutralisation with 1 M HCl, work-up and bulb-to-bulb distillation (bath 80–100°/0.5 Torr) gave the pentalenone **4** (500 mg, 88% yield), oil. IR (film): 3070w, 1695s, 1660s, 915s, ¹H-NMR: 1.12 (s, 3H); 1.4 (m, 1H); 1.8–2.8 (11H); 5.0 (m, 2H); 5.8 (m, 1H). ^{13}C-NMR: 208.7 (s), 186.2 (s), 137.7 (d), 133.6 (s), 114.7 (t), 50.7 (t) 47.8 (s), 36.9 (t), 32.1 (t), 25.5 (qa), 23.6 (t), 23.2 (t). MS: 190 ($C_{13}H_{18}O^+$, 48), 175 (32), 161 (63), 149 (23), 148 (100), 147 (82). HR: M^+ Found: 190.1362. $C_{13}H_{18}O$ requires: 190.1358.

Unsuccessful attempts to convert the 1-(3-butenyl)-2,3,3a,4,5,6-hexahydro-3a-methyl-pentalen-2-one (**4**) to 1-(3-butentyl-1,2,3,3a,4,5-hexahydro-1,3a-dimethyl-pentalen-2-one (**3**, X = 0). The pentalenone **4** was treated with 1 to 10 equiv of a variety of bases (and solvents) such as potassium t-amylate (t-amyl alcohol, benzene, in presence or absence of 18-C-6-crown ether), potassium t-butoxide (t-butanol, DMSO, DME), sodium hydride (HMPA), potassium hydride (DME, THF), sodium methylsulfinyl-methide (DMSO), lithium diisopropylamide (THF), potassium 2,2,6,6-tetramethylpiperidide (benzene) and potassium bis(trimethylsilyl) amide (toluene) at temperatures between −60°C to +100° for 1 hr to 3 weeks. Subsequent addition of an excess of methyl iodide and keeping of the solution between +20 to +100° for 1 hr to 3 weeks gave after the usual work-up variable amounts of unchanged 4 together with highly polar decomposition products but no dimethyl-pentalenone 3, X = 0. Also all attempts failed to trap any dienolates, formed from **4** by the described base treatment, using an excess of either deuteroacetic acid, chlorotrimethylsilane or ethyl formate.

1,7-Octadien-3-one (**10**). A solution of 5-bromo-1-pentene (30 g, 0.2 mol) in ether (20 ml) was added over 1 hr to a stirred suspension of magnesium turnings (6 g, 0.25 mol) in ether (100 ml). Then freshly distilled acrolein (15.4 g, 0.27 mol) was added to this solution at −10° over 30 min. The mixture was stirred at −10° for additional 30 min, to give after the usual work-up and distillation 1,7-octadien-3-ol (20 g, 80% yield), b.p. 90°/40 Torr. IR (film): 3380 broad, 3080w, 1645m, 1000s, 920s. ¹H-NMR: 1.2–1.7 (4H); 1.8-2.3 (2H); 2.95 (s, broad, 1H); 4.06 (m, 1H); 4.7–5.3 (4H); 5.4–6.0 (2H). ^{13}C-NMR: 141.3 (d), 138.4 (d), 114.5 (t), 114.3 (t), 73.0 (d), 36.5 (t), 33.6 (t), 24.7 (t). Ms: 126 ($C_8H_{14}O^+$, 0.3), 125 (0.6), 111 (2), 73 (9), 67 (14), 57 (100); HR: M^+ Found: 126.1028. $C_8H_{14}O$ requires: 126.1044. 2M Jones reagent (20 ml) was added over 20 min to a stirred solution of 1,7- octadien-3-ol (5.04 g, 40 mmol) in benzene/acetone (1:1, 60 ml) at −5° to 0°. Stirring of the mixture at 0° for 30 min followed by the usual work-up and distillation furnished the dienone **10** (4.4 g, 89% yield), b.p. 65°/20 Torr. IR (film): 3075w, 1700s, 1680s, 1640m, 1615m, 995s, 965s, 915s. ¹H-NMR: 1.54–1.90 (2H); 1.90–2.2 (2H); 2.5–2.7 (2H), 4.7–5.1 (2H); 5.5–6.6 (4H). ^{13}C-NMR: 198.9, 137.4, 135.8, 126.5,

114.2, 40.2, 32.6, 22.5. MS: 124 ($C_8H_{12}O^+$,4), 109 (6), 95 (9), 83 (17), 70 (83), 55 (100); HR: M^+ Found: 124.0884. $C_8H_{12}O$ requires: 124.0888. The polymerisable dienone **10** (4.4 g) was stored at −30°C after addition of p-hydroquinone (20 mg).

4 - (3 - *Butenyl*) - 1,2,3,6,7,7a - *hexahydro* - 7a - methyl - 5H - inden - 5 - one (**11**). 1,7-Octadien - 3 - one (**10**) (8.68 g, 70 mmol) was added over 1.5 hr to a stirred solution of 2-methylcyclopentanone (6)[16] (8.23 g, 84 mmol) in freshly prepared 2M NaOMe in methanol (5 ml, 10 mmol) at −75°. The mixture was allowed to warm up slowly to +20°, then stirred at +20°, for additional 12 hr, followed by the usual work-up and distillation (75 to 100°/0.05 Torr) to give an oil (8.7 g); spectral analysis (IR, ^{1}H-NMR, ^{13}C-NMR) showed 2-methyl - 2 - (3 - oxo - 7 - octenyl) - cyclopentanone to be its main constituent. A solution of this oil (8.6 g) in t-butanol (10 ml) was added over 2 hr at +30° to stirred 0.5M t-BuOK in t-BuOH (170 ml, 85 mmol) under argon. The mixture was stirred at +30° for 30 min, then poured into aq. 1M HCl at 0° to give after work-up and distillation the indenone **11** (6.9 g, 49% yield from **10**), oil, b.p. 79–80°/0.1 Torr. IR (film): 3070w, 1660s, 1640s, 1355m, 995m, 910s. UV: 247 (4.06). ^{1}H-NMR: 1.13 (s, 3H); 1.0–2.9 (14H); 4.7–5.2 (2H); 5.75 (m, 1H). ^{13}C-NMR: 197.6 (s), 171.4 (s), 138.2 (d), 130.7 (s), 114.4 (t), 42.8 (s), 41.6 (t), 35.8 (t), 33.9 (t), 32.7 (t), 29.6 (t), 25.7 (t), 22.6 (qa), 21.7 (t). Ms: 204 ($C_{14}H_{20}O^+$, 100), 189 (42), 163 (55), 150 (84). HR: M^+ Found: 204.1511. $C_{14}H_{20}O$ requires: 204.1514.

4 - (3 - *Butenyl*) - 1,2,4,6,7,7a - *hexahydro* - 4,7a - *dimethyl* - 5 *H* - *inden* - 5 - *one* (**12**). A solution of the conjugated indenone **11** (1.5 g, 7.35 mmol) in benzene (10 ml) was added over 30 min to a stirred suspension of dry potassium 2-methyl-2-butoxide (1.4 g, 11 mmol) in benzene (40 ml) at 5°. Successive stirring of the mixture at 55°C for 1 hr, addition of methyl iodide (2 ml, 22 mmol) over 45 min at 0°, heating under reflux for 30 min, usual work-up and chromatography (SiO_2, toluene/ethylacetate 19:1) furnished apart from unchanged **11** (0.35 g, 23%) a 5:1 mixture of the monomethylated ketone **12** and its C-4-epimer (1.05 g, 66% yield). GC (5% SE 30, 180°): 8.24 (16.3), 9.37 (82.0). For spectral identification a sample of this mixture was separated by preparative GC (10% SE 30) giving the minor C-4-epimer of **12**, oil. IR (CCl_4): 3070w, 3040w, 1705s, 1638m, 1373m, 1178w, 912s. ^{1}H-NMR: 1.13 (s, 3H); 1.23 (s, 3H); 1.4–2.1 (8H); 2.1–2.9 (4H); 4.8–5.2 (2H); 5.41 (t, J = 2.5, 1H); 5.73 (m, 1H). Ms: 218 ($C_{15}H_{22}O^+$, 24), 203 (7), 200 (11), 190 (14), 177 (19), 164 (100), 149 (17). Further elution furnished the major product **12**, oil. IR (CCl_4): 3070w, 3040w, 1705s, 1638m, 1373m, 1057w, 912s. ^{1}H-NMR: 1.21 (s, 3H); 1.23 (s, 3H); 1.4–2.15 (8H); 2.15–2.9 (4H); 4.96 (m, 2H); 5.48 (t, J = 2.5, 1H); 5.75 (m, 1H). ^{13}C-NMR: 214.4 (s), 152.5 (s), 138.0 (d), 125.3 (d), 114.4 (t), 52.6 (s), 45.5 (s), 42.7 (t), 37.7 (t), 36.8 (t), 35.4 (t), 30.1 (t), 28.7 (t), 23.7 (qa), 22.2 (qa). MS: 218 ($C_{15}H_{22}O^+$, 14), 203 (6), 200 (5), 177 (14), 164 (100), 149 (13); HR: M^+ Found: 218.1677. $C_{15}H_{22}O$ requires: 218.1671.

Thermal cyclization of 4 - (3 - *Butenyl*) - 1,2,4,6,7,7a - *hexahydro* - 4,7a - *dimethyl* - 5*H* - *inden* - 5 - *one*: *Preparation of* 1,2,3,3a,5,6,6a,7 - *octahydro* - 1,3a,6 - *trimethyl* - 4H - *cyclopent* [d] *inden* - 4 - *one* (**13**). A solution of the 1,6-diene **12** (1.8 g, 8.25 mmol, containing 16% of its C-4-epimer) in toluene (90 ml, filtered through basic Al_2O_3 activity I) was heated in a sealed Pyrex tube at 280° for 24 hr. Chromatography of the evaporated reaction mixture (SiO_2, toluene/ethylacetate 19:1) furnished a fraction (910 mg) containing **13** and two isomers) followed by the more polar known 1,2,3,6,7,7a - hexahydro - 4,7a - dimethyl - 5H - inden - 5 - one (**14**)[25] (300 mg, 22% yield), oil, b.p. 100° (bath)/0.2 Torr. IR (CCl_4): 1660s, 1600w, 1375m, 1350m, 1325m. UV: 246 (4.11).-^{1}H-NMR: 1.08 (s, 3H); 1.63 (t, J = 1.6, 3H); 1.2-2.1 (6H); 2.1–2.9 (4H. ^{13}C-NMR: 198.3 (s), 170.9 (s), 126.8 (s), 42.8 (s), 41.7 (t), 36.0(t), 33.8 (t), 30.0 (t), 22.4 (qa), 21.7 (t), 11.27 (qa). MS: 164 ($C_{11}H_{16}O^+$, 84), 149 (56), 136 (71), 122 (100); HR: M^+ Found 164.1203. $C_{11}H_{16}O$ requires 164.1201.

The fraction containing **13** (910 mg) was rechromatographed (5% $AgNO_3/SiO_2$, hexane/t-butyl methyl ether) giving an inseparable mixture of two isomers (270 mg, 15% yield) showing the following data, compatible with structure **15** b.p. 120° (bath)/0.05 Torr. IR (film): 3030w, 1720s, 1380m. ^{1}H-NMR: 0.86 (s, 3H); 1.11 (s, 3H); 0.8–2.6 (15H); 5.4 (m, 1H). ^{13}C-NMR: strong signals at 219.2 (s), 157.1 (s), 120.78 (d), 50.7, 49.3, 45.3, 45.2, 42.5, 42.4, 41.3, 30.9, 26.1, 24.0, 23.6, 17.7 qa); weak signals at 156.6 (s), 123.6 (d), 53.8, 48.4, 46.8, 44.1, 38.3, 37.5, 29.8, 29.0, 28.0, 22.0. MS: 218 ($C_{15}H_{22}O^+$, 100), 203 (78), 175 (31), 161 (34), 147 (16), 133 (29). Further elution furnished the desired cyclopent [d] indenone **13** (305 mg, 17% yield) b.p. 120° (bath)/0.05 Torr, IR (film): 3045w, 1705s, 1380m, 720m. ^{1}H-NMR: 0.84 (d, J = 6, 3H); 1.02 (s, 3H); 1.18 (s, 3H); 0.7–2.9 (11H); 5.63 (m, 1H, irradiation at 2.3→d, J = 6); 5.90 (m, 1H, irradiation at 2.3→d, J = 6). MS: 218 ($C_{15}H_{22}O^+$, 100), 203 (71), 185 (10), 161 (25), 147 (24), 133 (20); HR: M^+ Found 218.1663. $C_{15}H_{22}O$ requires: 218.1671.

1,2,3,3a,5,6,6a,7,8,9 - *Decahydro* - 1,3a,6 - *trimethyl* - 4H - *cyclopent* [d] *inden* - 4 - *one* (**16**). 10% Pd/C (75 mg) was added to a solution of the octahydrocyclopent [*d*] indenone **13** (300 mg, 1.4 mmol) in methanol (10 ml). The mixture was stirred under H_2 (1 atm) for 18 hr, then filtered and evaporated to give the decahydrocyclopent [d] indenone **16** as an oily residue (294 mg, 97% yield). IR (CCl_4): 1710s, 1380m. ^{1}H-NMR: 0.97 (d, J = 6, 3H); 1.0 (s, 3H); 1.13 (s, 3H); 0.7–1.8 (15 H). MS: 220 ($C_{15}H_{24}O^+$, 53), 218 (51), 203 (57), 178 (40), 177 (40), 165 (100), 163 (93), 150 (98), 135 (41); HR: M^+ Found 220.1825. $C_{15}H_{24}O$ requires: 220.1827.

1,2,3,3a,5,6,6a,7,8,9 - *Decahydro* - 5 - *hydroximino* - 1,3a,6 - *trimethyl* - 4H - *cyclopent* [d] *inden* - 4 - *one* (**17**). A solution of the ketone **16** (290 mg, 1.3 mmol) in t-butanol (2 ml) was added under argon to 0.15M t-BuOK (15 ml, 2.2 mmol). Stirring at 20° for 30 min, successive addition of i-amylnitrite (0.44 ml, 3.25 mmol) over 30 min, stirring at 20° for 20 hr and pouring of the mixture into aq 10% citric acid, usual work-up and chromatography (SiO_2, toluene/ethylacetate 9:1→3:1) gave the keto-oxime **17** (230 mg, 71% yield). A sample of **17** was crystallized (ether/pentane), m.p. 134–136°. IR ($CHCl_3$): 3560w, 3250 broad, 1705s, 1620w, 1470m, 1380m, 960s, 940s. UV: 234 (3.87). ^{1}H-NMR: 1.0 (s, 3H); 1.04 (d, J = 6, 3H); 1.2 (s, 3H); 1.3–2.3 (11H); 2.7 (d, J = 18.5, 1H); 2.84 (d, J = 18.5, 1H).-MS.: 249 ($C_{15}H_{23}NO_2^+$; 15), 232 (28), 221 (20), 204 (100), 190 (21), 163 (47); HR: M^+ Found 249.1726. $C_{15}H_{23}NO_2$ requires: 249.1729.

5 - *Diazo* - *decahydro* - 1,3a,6 - *trimethyl* - *cyclopent* [d] *inden* - 4 - *one* (**18**). 13–15% aq. sodium hypochlorite (30 ml) was added over 30 min to a stirred mixture of the ketoxime **17** (163 mg, 0.65 mmol), THF (12 ml), ether (120 ml), aq conc NH_4OH (16 ml) and aq. 5M NaOH (12 ml). Successive stirring of the reaction mixture for 1 hr, separation of the organic phase, extraction of the aqueous phase with CH_2Cl_2 and evaporation of the dried, combined organic phases furnished the diazoketone **18** (159 mg, 97% yield), yellow oil. IR (CCl_4): 2090s, 1630s, 1470m, 1345s. UV: 266, shoulder (3.74), 288 (3.79). ^{1}H-NMR: 1.02 (d, J = 6, 3H); 1.12 (s, 3H); 1.19 (s, 3H); 1.2–2.2 (11H); 2.35 (d, J = 15, 1H); 2.79 (d, J = 15, 1H). MS: 246 ($C_{15}H_{22}N_2O^+$, 36), 218 (41), 203 (55), 175 (100), 161 (64).

Decahydro - 1,3a,5a - *trimethyl* - *cyclopenta* [c] *pentalene* - 4 - *carboxylic acid methylester* **19**. A stream of N_2 was passed through a solution of the diazo-ketone **18** (159 mg, 0.646 mmol) in methanol (200 ml, Merck, Uvasol) for 45 min in the dark and then for 30 min under irradiation using a mercury high pressure lamp (Phillips 125 W) and a cooled (20°C) quartz apparatus. Evaporation of the reaction mixture and chromatography of the residue (SiO_2, hexane/toluene 1:1) gave the ester **19** (130 mg, 80%) yield as a 4:1-stereoisomer mixture, oil. Gc (3% SP 2330, 140°): 14.4 (80), 15.33 (20). IR (CCl_4): 1730s, 1465m, 1435m, 1380m, 1195s. ^{1}H-NMR: 0.87 (d, J = 6, 0.6H); 0.9 (d, J = 6, 2.4H); 1.02 (s, 2.4H); 1.19 (s, 2.4H), 0.8–2.2 (14.2 H); 2.5 (d × d, J = 7 and 12, 0.8H); 2.7 (d × d, J = 7 and 13, 0.2H); 3.68 (s, 3H). MS: 250 ($C_{16}H_{26}O_2^+$, 100), 235 (18), 219 (7), 191 (7), 175 (9), 164 (11), 149 (59), 141 (27), 135 (27), 122 (55): HR: M^+ Found 250.1927. $C_{16}H_{26}O_2$ requires: 250.1932.

Decahydro-1,3a,5a - *trimethylcyclopenta* [c] - *pentalene* - 4 - *methanol* (**20**). A solution of the ester **19** (37.5 mg, 0.15 mmol) in ether (2 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (6 mg, 0.16 mmol) in ether (6 ml). Stirring of the mixture at 20°C for 1 hr, followed by addition of sat aq NaCl and the usual work-up gave the alcohol **20** (32 mg, 96% yield), solid, m.p. 48–53°. IR (CCl_4): 3600m, 1465m, 1380m, 1265s, 1010s. ^{1}H-NMR: 0.88 (d, J = 6, 0.6H); 0.92 (d, J = 6, 2.4H); 1.02 (s, 3H); 1.08 (s, 3H); 0.8–2.2 (15H), 3.57 (d × d, J = 7.5 and 10, 1H, irradiation at 1.8 gives d, J = 10); 3.80 (d × d, J = 5 and 10, irradiation at 1.8 gives d, J = 10).

MS: 222 ($C_{15}H_{26}O_2^+$, 100), 207 (15), 164 (9), 149 (21), 135 (11); HR: M^+, Found: 222.1976. $C_{15}H_{26}O$ requires: 222 1983.

Decahydro - 1,3a,5a - trimethyl - 4 - [[(2 - nitrophenyl) seleno] methyl] - cyclopenta [c] pentalene (**21**). Tri-n-butylphosphine (99 μl, 0.40 mmol) was added over 15 min under argon to a stirred mixture of the alcohol **20** (43 mg, 0.194 mmol) and *o*-nitrophenylseleno-cyanate (91 mg, 0.40 mmol) in pyridine (1.2 ml). The dark-brown solution was stirred at 20° for 16 hr, then poured into 1M HCl to give after the usual work-up and chromatography (SiO_2 hexane/toluene 2:1) the selenide **21** (58 mg, 74% yield), yellow crystals, m.p. 110–120°. IR (CCl_4): 1590m, 1520s, 1340s, 855w. ^{1}H-NMR: 0.90 (d, J = 6, 0.6 H); 0.93 (d, J = 6, 2.4 H); 1.00 (s, 3 H); 1.10 (s, 3 H); 0.8–2.5 (14 H); 2.5–3.3 (2 H); 7.1–7.7 3 H); 8.32 (d, J = 8, 1 H). MS: 407 ($C_{21}H_{29}NO_2$ $^{80}Se^+$, 50), 405 (26), 403 (12), 205 (100), 186 (8), 163 (13), 149 (60); HR: M^+ Found: 407.1382. $C_{21}H_{29}NO_2$ $^{80}Se^+$ requires: 407.1363.

Decahydro - 1,3a,5a - trimethyl - 4 - methylene - cyclopenta [c] *pentalene*: (d,l) - *β - isocomene* (**22**). A solution of $NaIO_4$ (34 mg, 0.157 mmol) in methanol/water (4:1, 10 ml) was added to a solution of the *o*-nitrophenylselenide **21** (58 mg, 0.143 mmol) in THF (4 ml). The mixture was stirred at 20° for 18 hr, then evaporated. The usual work-up gave a residue which was heated with hexane (10 ml) under reflux for 30 min to furnish after filtration through SiO_2 (hexane) and evaporation of the filtrate the exocyclic alkene **22** (17 mg, 58% yield), semi-crystalline residue. IR (CS_2): 3065w, 1655m, 1380, 882s. ^{1}H-NMR: 0.91 (d, J = 7, 3 H); 0.99 (s, 3 H); 1.09 (s, 3 H); 1.1–2.1 (11 H); 2.1 (d, broad, J = 14.5, 1 H, irradiation at 4.6 gives d, J = 14.5); 2.36 (d × t, J = 14.5 and 2.5, 1 H, irradiation at 4.6 gives d, J = 14.5); 4.63 (m, 2 H). MS: 204 ($C_{15}H_{24}^+$, 29), 189 (45), 161 (21), 147 (33), 133 (26), 121 (38), 108 (100). The spectra are identical to those of natural β-isocomene.[3]

1,2,3,3a,5a,6,7,8 - *Octahydro - 1,3a,4,5a - tetramethylcyclopenta* [c] *pentalene*: (d,l) - *Isocomene* (**1**). A mixture of the exocyclic alkene **22** (4 mg, 0.02 mmol), p-toluenesulfonic acid monohydrate (1 mg) and CH_2Cl_2 (1 ml) was stirred at 20° for 3 hr to give after filtration through SiO_2 (CH_2Cl_2) and evaporation of the filtrate pure (d, l)-isocomene (**1**), oil (3 mg, 75% yield), $AgNO_3/SiO_2$, hexane. GC (3% SP-2330, on Chromosorb W-HP, 80–100 mesh, 100°): 5.40. IR (CCl_4): 3010w, 1670w, 1455s, 1445s, 1378s, 1330w, 1205w, 1182w, 1160w, 1090w, 1080w, 1000m, 850s. ^{1}H-NMR: 0.88 (d, J = 7, 3 H); 1.06 (s, 3 H); 1.0–2.3 (17H); 4.89 (s, broad, 1H). MS: 204 ($C_{15}H_{24}^+$, 20), 189 (22), 175 (6), 163 (16), 162 (100), 161 (15), 149 (7), 148 (12), 147 (36), 135 (12), 134 (14), 133 (16). The IR, ^{1}H-NMR and mass spectra as well as the behaviour on GC (coinjection) and TLC ($SiO_2/AgNO_3$/hexane) of synthetic (d,l)-**1** are identical to those of natural isocomene.

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