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A stereoselective total synthesis of (±)-pseudoclovene-B

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Abstract—A stereocontrolled approach to the construction of the tricyclo[6.3.1.0^{1,6}]dodecane ring system related to the sesquiterpene pseudoclovene-B (**3**) is delineated. Starting from the indanone **4**, the bromophenol **5** was prepared in a straightforward manner. An aryl participated intramolecular cyclisation of **5** afforded the tricyclic dienone **6** which was stereoselectively converted into the A/B *cis*-fused ketone **7** through the intermediates **13** and **14** or through the intermediate **15**. The tosylhydrazone derivative of **7** was treated with methyl lithium to furnish (±)-pseudoclovene-B in high yield.

Tricyclic sesquiterpenes derived from acid treatment of caryophyllene and caryolan-1-ol possess[1–3] novel skeletal features and have been the subject of considerable synthetic activity. Clovene (**1**),[1,2] an acid-induced rearrangement product of caryophyllene and isoclovene (**2**),[2,4] a product of dehydration of caryolan-1-ol with polyphosphoric acid, incorporate tricyclo[6.3.1.0^{1,5}]dodecane and tricyclo-[6.2.2.0^{5,12}]dodecane frameworks (Fig. 1), respectively, and have attracted considerable attention[5–12] as challenging synthetic targets. The total syntheses of the sesquiterpenes **1**[5–9] and **2**[10–12] have been reported in the literature a number of times. Pseudoclovene-B (**3**), another sesquiterpene hydrocarbon possessing a tricyclo[6.3.1.0^{1,6}]dodecane skeleton was isolated[2] along with **2** and several other sesquiterpenes when caryolan-1-ol was treated with polyphosphoric acid. On the basis of chemical and spectroscopic studies, the structure **3** (Fig. 1) was proposed[13,14] for pseudoclovene-B and this structure was conclusively established[14] through X-ray crystallographic analysis of the corresponding dibromide. The possible mode of fomation of **3** from caryolan-1-ol was investigated by Parker and co-workers and a plausible mechanistic scheme was proposed.[15] A successful total synthesis of pseudoclovene-B must address the following problems: (i) construction of the tricyclo[6.3.1.0^{1,6}]dodecane framework with appropriate substituents at C-4 and C-8, (ii) control of the stereochemistry of the A/B ring junction, and (iii) introduction of the isolated double bond in ring A. We describe herein a short, efficient and highly stereocontrolled total synthesis of (±)-pseudoclovene-B (**3**) and our basic strategy for the desired synthesis from an easily accessible indane derivative has been shown in Scheme 1. The bromophenol **5**, easily prepared from 2,5-dimethyl-7-methoxy-indan-1-one (**4**), was smoothly converted into the bridged tricyclic dienone **6** involving an aryl participated intramolecular cyclisation (Ar_1-6 cyclisation) of **5** in the presence of base. A stereoselective conversion of the dienone **6** into the A/B *cis*-fused ketone **7** was achieved in high yield using the functional groups in the ring A of **6**. The transformation of **7** into (±)-pseudoclovene-B (**3**) was then efficiently accomplished through Shapiro reaction. Aryl participated intramolecular cyclisation of indane derivatives to generate specifically functionalised bridged ring systems related to tricyclic sesquiterpenes has been relatively unexplored.

1. Results and discussion

Our synthesis of (±)-pseudoclovene-B **3** from *m*-cresol is outlined in Scheme 2. Reaction of *m*-cresol with methacryloyl chloride provided the phenolic ester **8** which on Fries rearrangement[16] and concomitant intramolecular cyclisation furnished the hydroxy-indanone **9** in 60% yield. The ketone **9** was easily purified by steam distillation and converted into the corresponding methyl ether **4**. Having a convenient route to **4**, we turned our attention to convert **4** into the bromophenol **5**. Michael reaction of **4** with methyl acrylate in the presence of NaOMe afforded the keto-ester **10** in 76% yield. Reduction of **10** with $LiAlH_4$ followed by hydrogenolysis of the resulting crude diol with Li in liquid ammonia[17] afforded the primary alcohol **11** in high overall yield. Treatment of **11** with PBr_3 furnished the bromoether **12**. The spectral characteristics of the compounds **10**–**12** as revealed through their ^1H and ^{13}C NMR spectra were fully in accord with their structures. Demethylation of **12** with BBr_3 in CH_2Cl_2 afforded the desired bromophenol **5** in excellent yield.

In order to effect an aryl participated intramolecular cyclisation[18] of the bromophenol **5**, a dilute solution of **5** in dry *t*-BuOH was heated with *t*-BuOK (1 equiv.) at 80°C

Keywords: terpenes; cyclisation; hydrogenation; conjugate addition; Shapiro reaction.

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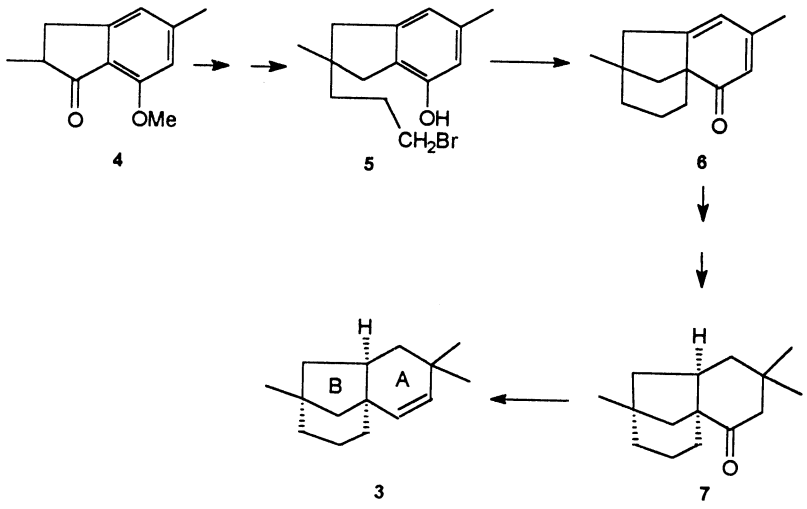


Scheme 1.

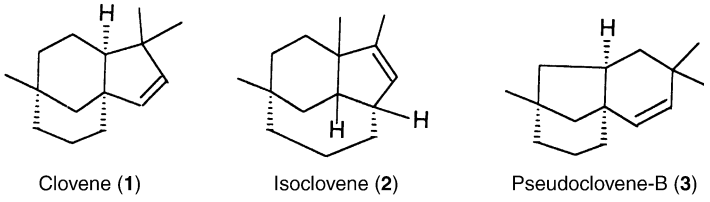
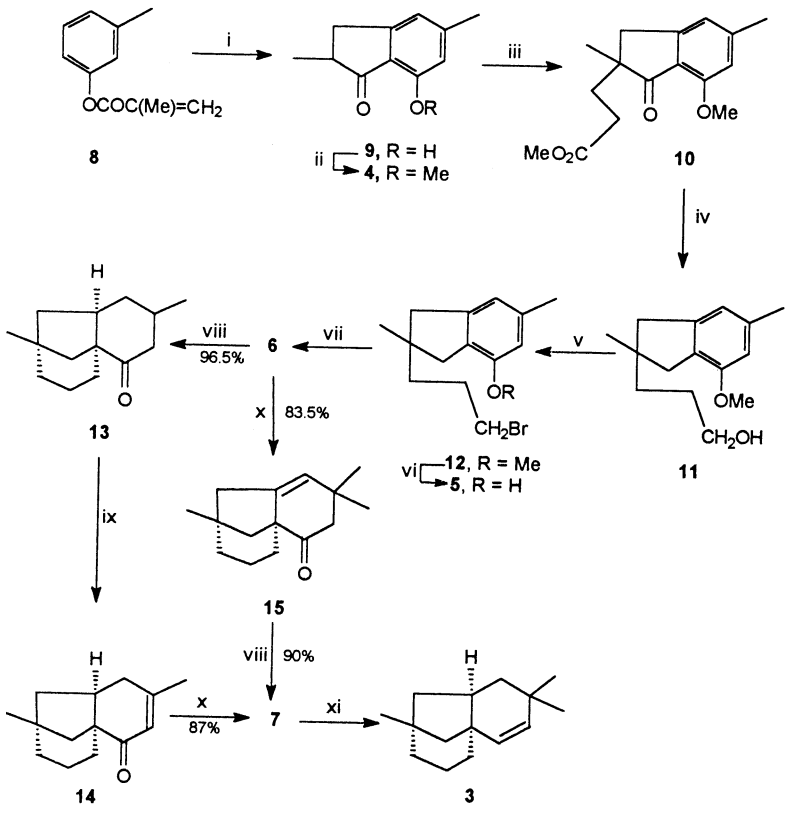


Figure 1.



Scheme 2. *Reagents and conditions*: (i) NaCl–$AlCl_3$ melt, 180–190°C, 5 min, 60%; (ii) MeI, K_2CO_3, Me_2CO, reflux, 10 h, 90%; (iii) $CH_2{=}CHCO_2Me$, NaOMe, MeOH, reflux, 6 h, 76%; (iv) $LiAlH_4$, Et_2O, reflux, 4 h then Li, liq. NH_3, NH_4Cl, 85%; (v) PBr_3, benzene, 70°C, 4 h, 75%; (vi) BBr_3, CH_2Cl_2, 0°C to rt, 18 h, 88%; (vii) *t*-BuOK, *t*-BuOH, 80°C, 10 h, 78%; (viii) H_2, 10% Pd–C, EtOH, 96.5% (**6→13**) and 90% (**15→7**); (ix) Br_2, AcOH, 15°C then LiBr, Li_2CO_3, DMF, 120–125°C, 6 h, 75%; (x) $LiMe_2Cu$, Et_2O, 0°C, 2 h, 83.5% (**6→15**) and 87% (**14→7**); (xi) $NH_2NHSO_2C_6H_4Me$, MeOH, HCl (trace), reflux, 2 h then MeLi, Et_2O, 20°C, 8 h, 73%.

for 10 h. The dienone **6** was isolated as the only neutral product of the reaction in 78% yield. The IR, ^1H and ^{13}C NMR spectra of the dienone were in full accord with structure **6**. Catalytic hydrogenation of the dienone **6** proceeded stereoselectively with rapid uptake of two moles of hydrogen to furnish the A/B *cis*-fused ketone **13** as the sole product in near quantitative yield. The construction of the basic tricarbocyclic framework of pseudoclovene-B **3** was thus accomplished in a stereocontrolled manner. *cis*-Stereochemistry has been assigned to **13** since catalytic hydrogenation of closely related systems had generated[5,19–21] exclusively *cis*-stereochemistry at 6/5 ring junctures. The assignment of *cis*-stereochemistry to **13** was confirmed by subsequent transformation of **13** into pseudoclovene-B possessing *cis*-stereochemistry at the A/B ring junction. Bromination of the ketone **13** in glacial AcOH and subsequent dehydrobromination of the resulting α-bromoketone with LiBr and Li_2CO_3 in DMF furnished the enone **14** in 75% overall yield. Conjugate addition of $LiMe_2Cu$ to **14** at 0°C provided the saturated ketone **7** as a crystalline compound in high yield. The saturated ketone **7** was also prepared by an alternative route. Conjugate addition[22] of $LiMe_2Cu$ to the dienone **6** at 0°C was highly regioselective providing the enone **15** in 87% yield. The spectral and analytical data of the compound **15** agree with the assigned structure. Catalytic hydrogenation of **15** yielded the saturated ketone **7** as the sole product.

In order to complete the desired synthesis of pseudoclovene-B (**3**), the last step to be carried out was the introduction of the required double bond in ring A and a Shapiro reaction proved successful. The tosylhydrazone derivative of **7** was treated with MeLi (2.5 equiv.)[23] in Et_2O at room temperature for 8 h. Chromatography of the crude product over neutral alumina and elution with hexane afforded the tricyclic hydrocarbon **3** in 73% yield from **7**. The identity of the present compound was secured through ^1H, ^{13}C NMR, IR and microanalytical data. The spectral data of **3** also agreed very well with those reported in the literature.

In conclusion, in the present work a stereocontrolled total synthesis of the bridged tricyclic sesquiterpene (±)-pseudoclovene-B has been successfully accomplished involving an aryl participated intramolecular cyclisation of an appropriate indane derivative as a key step.

2. Experimental

2.1. General

The compounds described and having asymmetric centres are all racemates. Melting points and boiling points are uncorrected. IR spectra were recorded on Perkin–Elmer model PE 298 and Shimadzu FTIR-8300 spectrophotometers. ^1H 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 ^1H 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. *m*-Cresyl methacrylate (8). A solution of *m*-cresol (10.8 g, 0.1 mol) in dry benzene (10 mL) was added dropwise with shaking to methacryloyl chloride (10.7 g, 0.102 mol) in benzene (20 mL) at 5°C. The mixture was refluxed for 6 h, cooled, diluted with water (25 mL), and extracted with ether (3×30 mL). The organic extract was washed successively with water (25 mL), cold 5% aqueous KOH (2×20 mL) and water (2×25 mL), and dried. Evaporation of the solvent followed by distillation of the residue at 98–100°C/10 mm Hg furnished the unsaturated ester (14.8 g, 84%) as a colourless oil; (Found: C, 74.75; H, 6.98. $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86%); ν_{max} (film) 1738, 1637, 1614, 1589 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23 (1H, t, *J*=7.7 Hz, Ar*H*), 7.00 (1H, d, *J*=7.7 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 6.90 (1H, d, *J*=7.7 Hz, Ar*H*), 6.31 (1H, bs, vinyl proton), 5.70 (1H, bs, vinyl proton), 2.33 (3H, s, Ar*Me*), 2.03 (3H, s, =C*Me*); δ_C (75 MHz, $CDCl_3$) 165.7, 150.7, 139.3, 135.8, 128.9, 126.8, 126.3, 122.0, 118.4, 21.1, 18.2.

2.1.2. 2,5-Dimethyl-7-hydroxyindan-1-one (9). An intimate mixture of anhydrous $AlCl_3$ (25 g) and NaCl (5 g) was stirred over a free flame until molten. The ester **8** (5 g) was added to this melt at 140°C with stirring. The temperature was rapidly raised to 180°C and maintained at 180–190°C for 5 min. After cooling, the reaction mixture was decomposed with cold dil. HCl (6N, 150 mL) and the product was isolated by steam distillation. The steam volatile part was extracted with ether (3×30 mL). The ether extract was washed with water (2×20 mL), dried and concentrated. The residue was evaporatively distilled at 136–138°C/1 mm Hg to afford the indanone **9** (3 g, 60%) as a colourless oil; (Found: C, 75.15; H, 7.08. $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86%); ν_{max} (film) 3337, 1672, 1626, 1597 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.91 (1H, s, ArO*H*), 6.70 (1H, s, Ar*H*), 6.54 (1H, s, Ar*H*), 3.32–3.24 (1H, m), 2.76–2.58 (2H, m), 2.35 (3H, s, Ar*Me*), 1.31 (3H, d, *J*=6.5 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 211.4, 157.1, 153.6, 149.3, 119.6, 118.0, 113.9, 41.8, 34.7, 22.2, 16.0.

2.1.3. 2,5-Dimethyl-7-methoxyindan-1-one (4). A mixture of the hydroxy-indanone **9** (5 g, 28.4 mmol), dry acetone (30 mL), anhydrous K_2CO_3 (4 g) and MeI (10 g, 70.5 mmol) was refluxed with stirring under nitrogen for 10 h. It was then cooled, diluted with water (30 mL), and extracted with ether (3×30 mL). The ether extract was washed with cold 5% aqueous KOH (15 mL) and water (2×20 mL), dried, and concentrated. Evaporative distillation of the crude product at 140–142°C/2 mm Hg furnished the indanone **4** as a colourless oil (4.86 g, 90%); (Found: C, 75.65; H, 7.23. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%); ν_{max} (film) 1699, 1608, 1587 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.79 (1H, s, Ar*H*), 6.58 (1H, s, Ar*H*), 3.93 (3H, s, ArO*Me*), 3.32–3.23 (1H, m), 2.70–2.57 (2H, m), 2.41 (3H, s, Ar*Me*), 1.27 (3H, d, *J*=7 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 206.7, 157.9, 156.4, 147.9, 122.1, 118.9, 109.9, 55.5, 42.2, 34.5, 22.3, 16.8.

2.1.4. 2,5-Dimethyl-2-(2-methoxycarbonylethyl)-7-methoxyindan-1-one (10). A solution of the indanone **4** (4.4 g, 23 mmol) in MeOH (10 mL) was added with stirring under nitrogen to a solution of NaOMe (prepared from Na (0.24 g, 10.4 g-at.)) in MeOH (25 mL). Methyl acrylate (4 g, 46.5 mmol) was then added dropwise at room temperature and the resulting mixture was refluxed for 6 h. It was then cooled, diluted with water (40 mL), and extracted repeatedly with ether (3×60 mL). The combined ether extract was washed with water (2×30 mL), dried and concentrated. The residue was distilled at 164–166°C/0.5 mm Hg to afford the keto-ester **10** (4.86 g, 76%) as a colourless oil; (Found: C, 69.80; H, 7.39. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30%); ν_{max} (film) 1736, 1699, 1607, 1587 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.78 (1H, s, Ar*H*), 6.59 (1H, s, Ar*H*), 3.92 (3H, s, ArO*Me*), 3.63 (3H, s, CO_2*Me*), 2.95, 2.81 (2H, 2×d, *J*=17.3 Hz, ArCH_2), 2.41 (3H, s, Ar*Me*), 2.31–2.24 (2H, m), 1.97–1.88 (2H, m), 1.20 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 207.0, 173.7, 158.2, 154.9, 148.2, 121.9, 118.9, 110.1, 55.5, 51.4, 48.3, 39.8, 33.1, 29.5, 23.8, 22.3.

2.1.5. 2,6-Dimethyl-2-(3-hydroxypropyl)-4-methoxyindane (11). A solution of the keto-ester **10** (4.7 g, 17 mmol) in dry ether (25 mL) was added dropwise at room temperature to a stirred suspension of $LiAlH_4$ (1.2 g, 31.6 mmol) in ether (50 mL). After the addition, the mixture was stirred and refluxed for 4 h and then cooled. Excess of hydride was carefully destroyed by addition of saturated aqueous Na_2SO_4 and the mixture was filtered through celite. The residue was washed thoroughly with ether (3×25 mL). The combined filtrate was washed with brine (30 mL), dried and concentrated. The crude product (4.13 g, ν_{max} (film) 3400–3300 cm^{-1}) was dissolved in dry ether (30 mL) and added under nitrogen to distilled liquid ammonia (200 mL). To this mixture was added Li metal (0.9 g, 130 g-at.) with stirring during 5 min. After stirring for another 15 min, an excess of NH_4Cl was added and ammonia was allowed to evaporate. The residue was diluted with water (30 mL) and extracted with ether (3×50 mL). The ether extract was washed with water (2×25 mL), dried and concentrated. The residue was distilled to afford the alcohol **11** (3.4 g, 85%) as a colourless oil, bp (bath temperature) 130–132°C/0.5 mm Hg; (Found: C, 76.64; H, 9.55. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); ν_{max} (film) 3364, 1614, 1591 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.61 (1H, s, Ar*H*), 6.47 (1H, s, Ar*H*), 3.79 (3H, s, ArO*Me*), 3.61 (2H, t, *J*=6 Hz, CH_2OH), 2.76, 2.61 (2H, 2×d, *J*=15.5 Hz, ArCH_2), 2.68, 2.61 (2H, 2×d, *J*=15.6 Hz, ArCH_2), 2.31 (3H, s, Ar*Me*), 1.78 (1H, bs, O*H*), 1.63–1.47 (4H, m, CH_2CH_2CH_2OH), 1.08 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 155.8, 144.9, 137.5, 127.2, 117.8, 108.8, 63.6, 55.0, 46.4, 42.7, 42.3, 38.1, 28.7, 26.5, 21.6.

2.1.6. 2-(3-Bromopropyl)-2,6-dimethyl-4-methoxyindane (12). Phosphorous tribromide (2 g, 7.4 mmol) in benzene (3 mL) was added dropwise at 0°C to a stirred solution of **11** (3.28 g, 14 mmol) in benzene (15 mL). The mixture was stirred at 70°C for 4 h, cooled, and poured into crushed ice. The product was extracted with benzene (3×20 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), water (2×20 mL), and dried. The residue remaining upon removal of the solvent was evaporatively distilled at 130–132°C/0.5 mm Hg to afford the bromide **12** (3.12 g, 75%) as a colourless oil; (Found: C, 60.74; H, 7.35. $C_{15}H_{21}BrO$ requires C, 60.61; H, 7.12%); ν_{max} (film) 1614, 1591, 1493, 1462, 1315 cm^{-1} δ_H (300 MHz, $CDCl_3$) 6.61 (1H, s, Ar*H*), 6.48 (1H, s, Ar*H*), 3.79 (3H, s. ArO*Me*), 3.39 (2H, t, *J*=6.8 Hz, CH_2Br), 2.79–2.58 (4H, m, 2×ArCH_2), 2.32 (3H, s, Ar*Me*), 1.94–1.84 (2H, m), 1.63–1.56 (2H, m), 1.09 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 155.9, 144.7, 137.6, 127.1, 117.8, 108.9, 55.1, 46.5, 42.6, 42.3, 40.8, 34.5, 29.1, 26.6, 21.6.

2.1.7. 2-(3-Bromopropyl)-2,6-dimethyl-4-hydroxyindane (5). To a stirred solution of **12** (3 g, 10.1 mmol) in CH_2Cl_2 (15 mL) at 0°C was added dropwise BBr_3 (2.6 g, 10.38 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0°C for 2 h and at room temperature for 16 h. It was then poured into ice and extracted with CH_2Cl_2 (2×20 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), water (2×15 mL), and dried. Evaporation of the solvent followed by chromatography of the residue on a silica gel column (70 g) using ether–light petroleum (1:19) as eluent furnished the bromophenol **5** (2.52 g, 88%) as a colourless oil which solidified on standing to furnish colourless crystals, mp 50–51°C; (Found: C, 59.20; H, 6.89. $C_{14}H_{19}BrO$ requires C, 59.37; H, 6.76%); ν_{max} (film) 3393, 1626, 1591 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.59 (1H, s, Ar*H*), 6.43 (1H, s, Ar*H*), 4.75 (1H, bs, ArO*H*), 3.39 (2H, t, *J*=6.8 Hz, CH_2Br), 2.80–2.55 (4H, m, 2×ArCH_2), 2.26 (3H, s, Ar*Me*), 1.94–1.84 (2H, m), 1.63–1.58 (2H, m), 1.09 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 151.7, 145.2, 137.9, 124.8, 118.0, 113.5, 46.4, 43.0, 41.6, 40.7, 34.5, 29.1, 26.5, 21.2.

2.1.8. 4,8-Dimethyltricyclo[6.3.1.0^{1,6}]dodeca-3,5-dien-2-one (6). To a stirred solution of *t*-BuOK (prepared from K (0.34 g, 8.72 g-at.)) in *t*-BuOH (650 mL) at 80°C was added dropwise under nitrogen a solution of the bromophenol **5** (2.4 g, 8.47 mmol) in *t*-BuOH (10 mL). The mixture was stirred at 80°C for 10 h and then ca. 500 mL of *t*-BuOH was removed under reduced pressure. The residue was diluted with water (150 mL) and extracted repeatedly with ether (3×150 mL). The combined ether extract was washed with water (2×80 mL), dried and concentrated. The residue was evaporatively distilled at 114–116°C/0.5 mm Hg to afford the dienone **6** as a colourless oil (1.34 g, 78%); (Found: C, 83.03; H, 8.79. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97%); ν_{max} (film) 1666, 1647 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.83 (1H, bs, vinyl proton), 5.65 (1H, bs, vinyl proton), 2.50, 2.21 (2H, 2×d, *J*=18.6 Hz, =CCH_2), 2.02 (3H, d, *J*=0.9 Hz, vinyl methyl), 1.83–1.45 (8H, m), 1.10 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 206.7, 163.3, 154.6, 120.1, 117.2, 60.2, 44.9, 43.0, 38.4, 37.5, 37.2, 27.0, 22.7, 21.7.

2.1.9. (1*SR*,4*RS*,6*RS*,8*RS*)-4,8-Dimethyltricyclo-[6.3.1.0^{1,6}]dodecan-2-one (13). A solution of the dienone **6** (0.65 g, 3.2 mmol) in EtOH (10 mL) was hydrogenated over Pd–C (10%, 0.3 g) at room temperature and atmospheric pressure. Uptake of hydrogen (170 mL) ceased after 15 min. The mixture was filtered from the catalyst. Evaporation of the solvent furnished the saturated ketone **13** (0.64 g, 96.5%) as a colourless oil, bp (bath temperature) 108–110°C/0.6 mm Hg; (Found: C, 81.57; H, 10.55. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%); ν_{max} (film)

1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.36–1.10 (16H, m), 1.03 (3H, s, *Me*), 0.96 (3H, d, *J*=6.5 Hz, CH*Me*); δ_C (75 MHz, $CDCl_3$) 216.1, 55.5, 47.7, 46.9, 45.5, 44.4, 42.5, 40.3, 38.8, 33.0, 31.4, 27.4, 22.1, 19.6.

2.1.10. (1*SR*,6*SR*,8*RS*)-4,8-Dimethyltricyclo[6.3.1.0^{1,6}]-dodec-3-en-2-one (14). A solution of bromine (0.4 g, 2.5 mmol) in AcOH (2 mL) was added dropwise during 10 min to a stirred solution of the ketone **13** (0.5 g, 2.4 mmol) in AcOH (12 mL) at 15°C, allowing each drop of bromine to decolourise before more was added. After the addition, the mixture was stirred at room temperature for 2 h, diluted with water (20 mL) and extracted with $CHCl_3$ (3×25 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (15 mL), water (2×15 mL), and dried. Evaporation of the solvent furnished the crude bromoketone (0.67 g) as a gummy material which was dissolved in dry DMF (10 mL). LiBr (0.4 g, 4.6 mmol) and Li_2CO_3 (0.3 g, 4 mmol) were added and the mixture was stirred at 120–125°C for 6 h under nitrogen. The reaction mixture was cooled, poured into dil. HCl (2N, 10 mL) and extracted with ether (3×25 mL). The ether extract was washed with aqueous $NaHCO_3$ (15 mL), water (2×15 mL), and dried. Evaporation of the solvent and purification of the product on a silica gel column using ether–light petroleum (1:24) as eluent furnished the enone **14** (0.37 g, 75%) as a colourless oil, bp (bath temperature) 108–110°C/0.4 mm Hg; (Found: C, 82.49; H, 9.78. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%); ν_{max} (film) 1655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.84 (1H, bs, COC*H*═C), 2.39–1.09 (13H, m), 1.91 (3H, s, vinyl methyl), 1.03 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 203.0, 159.7, 125.8, 52.7, 45.5, 45.0, 40.5, 40.0, 38.7, 38.2, 34.6, 27.5, 24.1, 19.8.

2.1.11. 4,4,8-Trimethyltricyclo[6.3.1.0^{1,6}]dodec-5-en-2-one (15). A solution of $LiMe_2Cu$ was prepared under argon by dropwise addition of MeLi (1.6 M in ether, 6.2 mL, 9.92 mmol) to a stirred suspension of CuI (0.95 g, 4.99 mmol) in anhydrous ether (15 mL) at 0°C. A solution of the dienone **6** (0.5 g, 2.47 mmol) in ether (15 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 (16 mL), stirred for 20 min, diluted with water (15 mL) and extracted with ether (3×25 mL). The ether extract was washed with water (2×15 mL), dried and concentrated. The residue was evaporatively distilled at 108–110°C/0.4 mm Hg to afford the enone **15** (0.45 g, 83.5%); (Found: C, 82.32; H, 10.18. $C_{15}H_{22}O$ requires C, 82.52; H, 10.16%); ν_{max} (film) 1711 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.29 (1H, bs, C*H*═C), 2.64, 2.09 (2H, 2×d, *J*=14.2 Hz), 2.27, 2.04 (2H, 2×d, *J*=16.9 Hz), 1.78–1.59 (4H, m), 1.52–1.34 (4H, m), 1.13 (3H, s, *Me*), 1.03 (3H, s, *Me*), 0.99 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 214.6, 141.9, 128.6, 56.8, 50.0, 46.4, 41.8, 39.1, 38.9, 37.5, 37.2, 30.8, 30.6, 27.0, 20.4.

2.1.12. (1*SR*,6*RS*,8*RS*)-4,4,8-Trimethyltricyclo-[6.3.1.0^{1,6}]dodecan-2-one (7). (a) To a stirred solution of $LiMe_2Cu$ (2.94 mmol) in dry ether (15 mL) at 0°C was added under argon, over a period of 10 min, a solution of the enone **14** (0.3 g, 1.47 mmol) in ether (10 mL) and the resultant mixture was stirred at 0°C for 2 h. It was then treated with saturated aqueous NH_4Cl (10 mL), stirred for 15 min and diluted with water (10 mL). The product was extracted with ether (3×20 mL). The ether extract was washed with water (2×15 mL), dried, and concentrated. The solid residue was crystallised from light petroleum to furnish the ketone **7** (0.28 g, 87%) as colourless needles, mp 57–58°C; (Found: C, 81.68; H, 11.20. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%); ν_{max} ($CHCl_3$) 1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.30–1.10 (15H, m), 1.03 (3H, s, *Me*), 0.98 (3H, s, *Me*), 0.82 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 216.4, 55.2, 51.7, 47.8, 47.0, 45.5, 41.8, 40.8, 38.9, 34.9, 32.6, 31.4, 27.5, 25.1, 19.7.

(b) A solution of the enone **15** (0.35 g, 1.6 mmol) in EtOH (10 mL) was hydrogenated over Pd–C (10%, 0.2 g) at room temperature and atmospheric pressure. Uptake of hydrogen (45 mL) ceased after 30 min. The mixture was filtered from the catalyst. Evaporation of the solvent followed by crystallisation of the residue from light petroleum furnished the ketone **7** (0.32 g, 90%), mp 57–58°C. ^1H and ^{13}C NMR spectra of **7**, prepared by the methods (a) and (b), were identical.

2.1.13. (±)-Pseudoclovene-B (3). To a solution of the ketone **7** (0.4 g, 1.81 mmol) in EtOH (4 mL) were added *p*-toluenesulfonhydrazide (0.35 g, 1.88 mmol) and conc. HCl (one drop) and the mixture was refluxed for 2 h. It was then cooled in an ice-bath and the crystalline tosylhydrazone derivative was collected by suction filtration and dried, mp 167–168°C (700 mg). To a stirred suspension of this material in anhydrous ether (10 mL) at 20°C was added under nitrogen MeLi (1.6 M in ether, 2.5 mL, 4 mmol) during 10 min and the mixture was stirred at room temperature for 8 h. It was then diluted with water (10 mL) and extracted with ether (3×20 mL). The ether extract was washed with water (2×15 mL), dried and concentrated. The residue was chromatographed on neutral alumina (15 g). Elution with hexane afforded (±)-pseudoclovene-B (**3**) (270 mg, 73%) as a colourless oil, bp (bath temperature) 95–97°C/3 mm Hg; (Found: C, 88.02; H, 12.08. $C_{15}H_{24}$ requires C, 88.16; H, 11.84%); ν_{max} (film) 3010, 1456, 1373, 1360, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.35 (2H, s, vinyl protons), 1.91–1.00 (13H, m), 0.96 (3H, s, *Me*), 0.95 (3H, s, *Me*), 0.91 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 135.4, 132.7, 49.6, 45.6, 45.3, 44.8, 40.0, 38.9, 38.7, 38.0, 32.6, 31.1, 28.0, 27.7, 20.6. (Lit.,[14] ν_{max} 3010, ca. 1640 vw, 1375, 1360, and 750 cm^{-1}; τ 4.66 (2H, s), 9.03 (6H) and 9.08 (3H)).

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