Synthesis of cuparene and herbertene *via* a common intermediate

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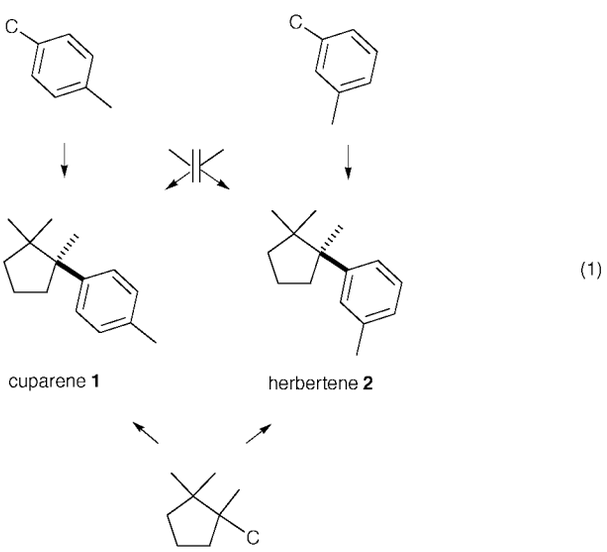
A dihydroisobenzofuran (**13**) was obtained from β-ionone in 10 steps *via* an intramolecular Diels–Alder reaction. On further oxidation, reductive ring opening and decarboxylation, cuparene and herbertene were synthesized.

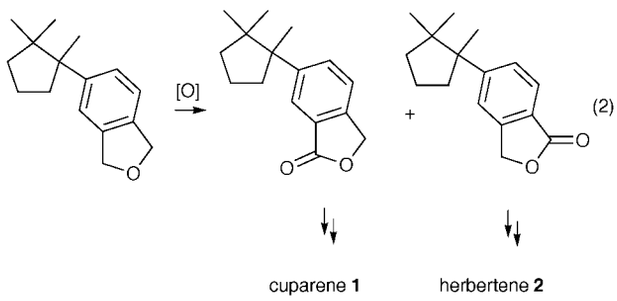
Introduction

Cuparene (**1**) and herbertene (**2**) are prototypes of sesquiterpenes containing interconnecting cyclopentane and benzene rings. Cuparene occurs in the heartwood of conifers (*e.g.*, *Chamaecyparis thyoides*)[1] while herbertene is a constituent of the leafy liverwort *Herberta adunca*.[2] The popularity of cuparene, α-cuparenone, β-cuparenone, and herbertene as synthetic targets is attested by the appearance of more than sixty publications,[3] addressing various aspects of establishing two adjacent quaternary carbon atoms. Because the only difference between cuparene and herbertene is the substitution pattern of the benzene nucleus, any synthetic method relying on the construction of the cyclopentane unit is applicable to a synthesis of the other sesquiterpene when a route to either cuparene or herbertene has been delineated. However, we were intrigued by the possibility of accessing both types of terpenes from a common intermediate for the sake of attendant synthetic economy. Necessarily it entails the employment of a tetrasubstituted cyclopentane derivative for attachment or *de novo* construction of the aromatic ring. The divergent strategy is indicated in eqn. (1).



(1)

To maximize the strategic advantage, we considered the preparation of a series of intermediates possessing a local symmetry. In other words, we desired to delay the branching of the route as long as feasible in order to save our efforts. To that end we focused on a dihydroisobenzofuran, with the expectation that oxidation would give rise to two isomeric phthalides which would be processed further to complete the synthesis of cuparene and herbertene [eqn. (2)].

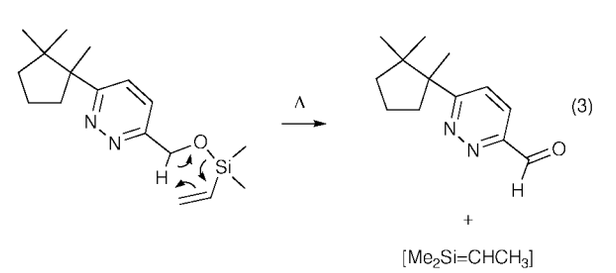


(2)

Results and discussion

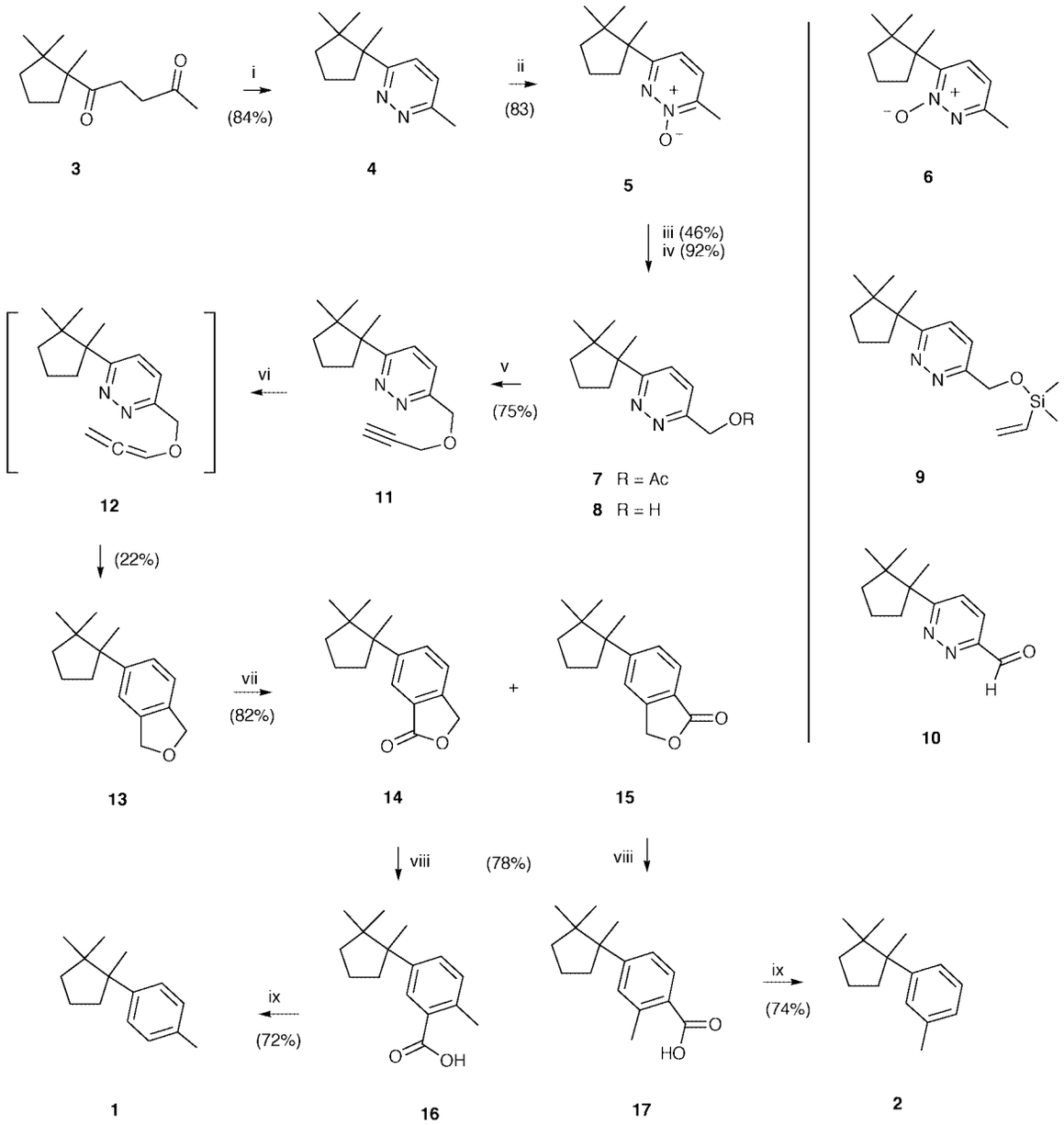
We chose to start our synthesis from diketone **3**, which is readily accessible from β-ionone by epoxidation at the cyclic double bond, boron trifluoride induced rearrangement (ring contraction),[4] and hydrogenation.[5] The cyclocondensation of **3** with hydrazine hydrate in refluxing ethanol in the presence of oxygen yielded pyridazine **4** (Scheme 1). The idea was to functionalize the benzylic methyl group for a subsequent introduction of a pendant group, and execution of an intramolecular Diels–Alder reaction. At this point, we investigated the dienophilicity of **4**, but failed to observe any reaction with either methyl vinyl ketone or acrylic acid. Eventually, the conversion of **4** to the *N*-oxide **5** with MCPBA was effected. Because of the differential steric shieldings, the regioisomer **6** was not formed in the oxidation.

Next, **5** was treated with acetic anhydride at refluxing temperature to provide the Polonovski product **7** which was then saponified. Several attempts at using the benzylic alcohol **8** thus obtained did not succeed to generate the desired products. For example, pyrolysis of the silyl ether **9** furnished aldehyde **10**, presumably due to intervention of a more favorable retroene decomposition [eqn. (3)]. Finally, **8** was derivatized to the propargyl ether (prop-2-ynyl ether) **11**, subjected to isomerization with t-BuOK to afford an allenyl ether **12** which was directly thermolyzed in a sealed tube at 200 °C. The Diels–Alder reaction[6] followed by elimination of dinitrogen occurred, albeit in low yield.



(3)

At this point we had passed the most crucial stage of our



Scheme 1 *Reagents and conditions:* (i) $N_2H_4{\cdot}H_2O$, EtOH (AIR), Δ; (ii) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C; (iii) Ac_2O, Δ; (iv) NaOH, EtOH, H_2O, Δ; (v) HC≡CCH_2Br, 50% NaOH–CH_2Cl_2, *n*-Bu_4NBr; (vi) *t*-BuOK, *t*-BuOH, Δ; (vii) PCC, THF, Δ; (viii) Me_3SiCl, NaI, MeCN, Δ; (ix) Cu, quinoline, 220 °C.

synthesis, and were ready to process the dihydroisobenzofuran **13** by oxidation. This desymmetrization operation was carried out with PCC in 1,2-dichloroethane at 80–90 °C. An equimolar mixture of phthalides **14** and **15** was obtained. We were rather disappointed at not having been able to separate the lactone mixture but even in capillary GC they elute very closely. Accordingly, these lactones were submitted to a reductive ring cleavage using Me_3SiCl–NaI in refluxing acetonitrile.[7] The two different carboxylic acids **16** and **17** thus produced were now separable by recrystallization in hexane. Our use of the procedure was based on a conjecture that the benzylic iodides would undergo reduction under the reaction conditions.

The final step was decarboxylation. Thus, in heating with copper powder in quinoline each acid provided the corresponding hydrocarbon in reasonable yield. The products were identified as cuparene and herbertene.

As a corollary, we should mention an assay for a short approach to cuparene using the enedione derived from rearrangement of β-ionone monoepoxide. This route involves a Wittig reaction with ethylidenetriphenylphoshorane to give the dienone and a subsequent electrocyclization to afford a cyclohexadienol. Unfortunately, the photoinduced cyclization[8] was not realized.

Our previous efforts in demonstrating the power of symmetry considerations in facilitating synthesis design[9] has resulted in an elaboration of α-cuparenone.[10] The present work illustrates a new approach to both the cuparane and herbertane series while taking advantage of local symmetry of an intermediate. Subesquent to our preliminary report,[11] a paper describing the creation of the aromatic ring of herbertene in emulation of our Diels–Alder method has appeared.[12] Their modification, however, could not reach cuparene.

Experimental

IR spectra were measured on a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian UNITY-300 instrument at 300 and 75 MHz respectively; chemical shifts are reported in parts per million downfield from TMS. The EIMS were obtained from a TRIO-2000 mass spectrometer. Melting points were uncorrected. Merck Kieselgel 60 of 70–230 mesh was used for column

chromatography. During workup of reactions, organic solutions were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* using a Buchi rotary evaporator.

3-Methyl-6-(1,2,2-trimethylcyclopentan-1-yl)pyridazine (4)

A solution of hydrazine hydrate (0.6 g, 18.7 mmol) in 95% ethanol (20 mL) was mixed with diketone **3** (2.0 g, 9.4 mmol) while being stirred magnetically. The mixture was refluxed for 31 h, cooled to room temperature, and the solvent was removed *in vacuo*. The crude product was chromatographed over silica gel using EtOAc–*n*-hexane (1 : 8) as eluent to give pyridazine **4** (1.6 g, 84%). IR (film): 2873, 2858, 1460, 1424 cm^{-1}; ^{1}H-NMR δ 7.27 (d, 1H, J = 9 Hz), 7.14 (d, 1H, J = 9 Hz), 2.80–2.60 (m, 1H), 2.58 (s, 3H), 1.82–1.40 (m 5H), 1.27 (s, 3H), 1.06 (s, 3H), 0.49 (s, 3H); ^{13}C-NMR δ 165.5 (s), 157.0 (s), 125.8 (d), 124.6 (d), 51.8 (s), 44.7 (s), 39.8 (t), 35.9 (t), 25.8 (q), 24.2 (q), 23.4 (q), 21.6 (q), 19.7 (t); MS *m*/*z* 204 (M^+, 18), 187 (17), 163 (11); HRMS (EI) 204.1617 (204.1628 Calcd for $C_{13}H_{20}N_2$).

3-Methyl-6-(1,2,2-trimethylcyclopentan-1-yl)pyridazine *N*-oxide (5)

To an ice-cooled solution of pyridazine **4** (1.3 g, 6.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added MCPBA (1.5 g, 8.8 mmol). After removal of the ice bath, the mixture was stirred for 4 h, and filtered. The filtrate was washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed over silica gel using CH_2Cl_2 as eluent to give **5** (1.18 g, 83.2%). IR (film): 2964, 2870, 1560, 1446, 1370 cm^{-1}; ^{1}H-NMR δ 7.45 (d, 1H, J = 8.4 Hz), 7.01 (d, 1H, J = 8.4 Hz), 2.70–2.60 (m, 1H), 2.48 (s, 3H), 1.85–1.45 (m, 5H), 1.29 (s, 3H), 1.11 (s, 3H), 0.63 (s, 3H); ^{13}C-NMR δ 166.7 (s), 140.4 (s), 133.1 (d), 115.5 (d), 51.9 (s), 44.7 (s), 39.7 (t), 35.5 (t), 26.0 (q), 24.0 (q), 23.2 (q), 19.3 (t), 17.7 (q); MS *m*/*z* 220 (M^+, 8), 204 (15), 203 (100), 151 (87), 135 (15).

3-Acetoxymethyl-6-(1,2,2-trimethylcyclopentan-1-yl)pyridazine (7)

A solution of the *N*-oxide **6** (1.38 g, 6.3 mmol) in Ac_2O (6 mL) was refluxed for 12 h, cooled to room temperature, and evaporated to dryness. The residue was redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. After removal of the solvent *in vacuo* and chromatography (silica gel, *n*-hexane–EtOAc 8 : 1) the pyridazine (**7**) was obtained (1.1 g, 46.2%). IR (film): 2980, 1710 cm^{-1}; ^{1}H-NMR δ 7.45 (d, 1H, J = 13.8 Hz), 7.42 (d, 1H, J = 13.8 Hz), 5.38 (s, 2H), 2.90–2.70 (m, 1H), 2.13 (s, 3H), 1.90–1.40 (m, 5H), 1.34 (s, 3H), 1.13 (s, 3H), 0.54 (s, 3H); ^{13}C-NMR δ 170.6 (s), 167.8 (s), 155.4 (s), 125.1 (d), 124.7 (d), 65.2 (t), 52.3 (s), 45.0 (s), 39.9 (t), 36.1 (t), 26.0 (q), 24.3 (q), 23.5 (q), 20.8 (q), 19.8 (t); MS *m*/*z* 262 (M^+, 6), 247 (21), 193 (100); HRMS (EI) 262.1689 (262.1682 Calcd for $C_{15}H_{22}N_2O_2$).

3-Hydroxymethyl-6-(1,2,2-trimethylcyclopentan-1-yl)pyridazine (8)

To aqueous NaOH (0.23 g, 2.9 mmol in 5 mL H_2O) was added a solution of pyridazine **7** (0.76 g, 2.9 mmol) in ethanol (0.45 mL). The mixture was refluxed for 4 h, ethanol was evaporated, water was added, and the mixture was extracted with ether, which was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed over silica gel using *n*-hexane–EtOAc (1 : 1) as eluent to afford **8** (0.58 g, 92%). IR (film) 3350, 2964, 2888, 1464, 1369, 1083 cm^{-1}; ^{1}H-NMR δ 7.48 (d, 1H, J = 9 Hz), 7.42 (d, 1H, J = 9 Hz), 4.91 (s, 2H), 2.80–2.60 (m, 1H), 1.85–1.40 (m, 5H), 1.28 (s, 3H), 1.07 (s, 3H), 0.48 (s, 3H); ^{13}C-NMR δ 167.3 (s), 159.1 (s), 125.6 (d), 124.2 (d), 63.2 (t), 52.1 (s), 44.8 (s), 39.8 (t), 35.9 (t), 25.9 (q), 24.2 (q), 23.4 (q), 19.7 (t); MS *m*/*z* 220 (M^+, 25), 189 (34), 151 (100), 124 (16); HRMS (EI) 220.1573 (220.1577 Calcd for $C_{13}H_{20}ON_2$).

[6-(1,2,2-Trimethylcyclopentan-1-yl)pyridazin-3-yl]methyl prop-2-ynyl ether (11)

A mixture of alcohol **9** (0.58 g, 2.6 mmol), aqueous 50% NaOH (1 mL), prop-2-ynyl bromide (0.74 g, 7.9 mmol), and a catalytic amount of tetrabutylammonium bromide in dichloromethane (8 mL) was stirred at room temperature for 10 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography using EtOAc–*n*-hexane (1 : 10) as eluent furnished the prop-2-ynyl ether **11** (0.51 g, 75%). IR (film) 3307, 2960, 2873, 1438, 1464, 1368, 1111 cm^{-1}; ^{1}H-NMR δ 7.50 (d, 1H, J = 9 Hz), 7.46 (d, 1H, J = 9 Hz), 4.91 (s, 2H), 4.28 (d, 2H, J = 2.4 Hz), 2.90–2.70 (m, 1H), 2.47 (d, 1H, J = 2.4 Hz), 1.90–1.50 (m, 5H), 1.36 (s, 3H), 1.14 (s, 3H), 0.55 (s, 3H); ^{13}C-NMR δ 167.5 (s), 157.2 (s), 125.2 (d), 124.6 (d), 79.0 (d), 75.1 (s), 70.8 (t), 58.2 (t), 52.2 (s), 45.0 (s), 39.9 (t), 36.1 (t), 26.0 (q), 24.4 (q), 23.5 (q), 19.8 (t); MS *m*/*z* 258 (M^+, 13), 190 (14), 189 (100); HRMS (EI) 258.1718 (258.1733 Calcd for $C_{16}H_{22}ON_2$).

5-(1,2,2-Trimethylcyclopentan-1-yl)-1,3-dihydroisobenzofuran (13)

A solution of ether **11** (0.51 g, 2 mmol) and potassium *tert*-butoxide (1.0 g, 8.9 mmol) in *tert*-butanol (2-methylpropan-2-ol) (10 mL) was refluxed for 5 h. After cooling to room temperature, the solvent was removed *in vacuo*. The crude product was diluted with ether, washed with NH_4Cl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the crude allenyl ether **12** (0.5 g). This product and a catalytic amount of hydroquinone (0.01 g) in benzene (6 mL) was heated to 200 °C for 20 h. The cooled mixture was diluted with ether and acidified with 10% HCl. After stirring for 1 h at room temperature, the organic layer was separated and dried over Na_2SO_4. Concentration *in vacuo* and chromatography furnished **13** (0.1 g, 22.4%). IR (film) 2970, 1693, 1457, 1380, 1047 cm^{-1}; ^{1}H-NMR δ 7.27 (d, 1H, J = 8 Hz), 7.21 (s, 1H), 7.13 (d, 1H, J = 8 Hz), 5.09 (s, 4H), 2.60–2.40 (m, 1H), 1.80–1.40 (m, 5H), 1.27 (s, 3H), 1.07 (s, 3H), 0.56 (s, 3H); ^{13}C-NMR δ 147.0 (s), 138.5 (s), 136.0 (s), 126.1 (d), 119.8 (d), 119.3 (d), 73.6 (t), 73.4 (t), 50.6 (s), 44.1 (s), 39.6 (t), 37.0 (t), 26.4 (q), 24.6 (q), 19.6 (t); MS *m*/*z* 230 (M^+, 18), 229 (100), 97 (11), 71 (16); HRMS (EI) 230.1626 (230.1671 Calcd for $C_{16}H_{22}O$).

6-(1,2,2-Trimethylcyclopentan-1-yl)-1,3-dihydroisobenzofuran-1-one (14) and 5-(1,2,2-trimethylcyclopentan-1-yl)-1,3-dihydroisobenzofuran-1-one (15)

A mixture of the dihydroisobenzofuran **13** (1.27 g, 5.5 mmol), PPC (2.38 g, 16.2 mmol) in dry THF (10 mL) was heated at 60–70 °C for 20 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated. The crude product was chromatographed over silica gel using EtOAc–*n*-hexane (1 : 1) as eluent to give a mixture of lactones **14** and **15** (1.1 g, 81.8%). IR (film) 2970, 2877, 1772, 1616, 1458 cm^{-1}; ^{1}H-NMR δ 7.90–7.30 (m, 6H), 5.28 (s, 2H), 2.60–2.40 (m, 2H), 1.95–1.40 (m, 10H), 1.31 (s, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 0.56 (s, 3H), 0.54 (s, 3H); ^{13}C-NMR δ 171.7 (s), 171.2 (s), 155.3 (s), 149.4 (s), 146.4 (s), 143.7 (s), 133.2 (d), 128.2 (d), 125.2 (s), 124.5 (d), 123.8 (d), 123.0 (s), 121.0 (d), 120.2 (d), 69.7 (t), 69.5 (t), 51.4 (s), 50.9 (s), 44.5 (s), 44.3 (s), 39.6 (t), 39.5 (t), 37.0 (t), 26.3 (q), 24.5 (q), 24.2 (q), 24.1 (q), 19.6 (t); MS *m*/*z* 244 (M^+, 25), 175 (25), 174 (98), 162 (72), 145 (100), 143 (27); HRMS (EI) 244.1459 (244.1464 Calcd for $C_{16}H_{20}O_2$).

2-Methyl-5-(1,2,2-trimethylcyclopentan-1-yl)benzoic acid (16) and 2-methyl-4-(1,2,2-trimethylcyclopentan-1-yl)benzoic acid (17)

To a stirred mixture of **14**–**15** (0.24 g, 1 mmol) and sodium iodide (3 g, 20 mmol) in dry acetonitrile (10 mL) was added

chlorotrimethylsilane (2.16 g, 20 mmol) slowly. The reaction mixture was refluxed for 4 days. The cooled reaction mixture was taken up in ether, washed with water, sodium thiosulfate solution (10%), and brine. The ether solution was dried, evaporated, and the residue (0.19 g, 78.4%) was recrystallized from *n*-hexane to separate the less soluble **16** from the more soluble **17**.

Compound **17** mp: 190–192 °C; IR (film) 3340, 2970, 2870, 1672, 1458 cm^{-1}; ^{1}H-NMR δ 7.91 (d, 2H, J = 7.8 Hz), 7.30–7.10 (m, 2H), 2.59 (s, 3H), 2.50–2.40 (m, 1H), 1.80–1.40 (m, 5H), 1.21 (s, 3H), 1.01 (s, 3H), 0.50 (s, 3H); ^{13}C-NMR δ 171.2 (s), 153.4 (s), 140.5 (s), 131.0 (d), 130.7 (d), 125.3 (d), 124.7 (s), 50.8 (s), 44.5 (s), 39.7 (t), 26.7 (t), 26.4 (q), 24.3 (q), 24.2 (q), 22.6 (q), 19.7 (t); MS *m*/*z* 246 (M^+, 73), 245 (100), 176 (90), 145 (39), 115 (19); HRMS (EI) 246.1630 (246.1620 Calcd for $C_{16}H_{22}O_2$).

Compound **16** mp: 156–158 °C; IR (film) 3340, 2970, 2870, 1672, 1458 cm^{-1}; ^{1}H-NMR δ 8.06 (d, 1H, J = 2.7 Hz), 7.43 (dd, 1H, J = 2.7, 8.4 Hz), 7.17 (d, 1H, J = 8.4 Hz), 2.64 (s, 3H), 2.50–2.40 (m, 1H), 1.80–1.40 (m, 5H), 1.27 (s, 3H), 1.01 (s, 3H), 0.55 (s, 3H); ^{13}C-NMR δ 173.4 (s), 145.3 (s), 138.2 (s), 131.7 (d), 131.2 (d), 130.1 (d), 127.3 (s), 50.3 (s), 44.3 (s), 39.7 (t), 26.8 (t), 26.3 (q), 24.2 (q), 21.6 (q), 19.7 (t); MS *m*/*z* 246 (M^+, 38), 245 (100), 176 (95), 145 (60), 115 (21); HRMS (EI) 246.1615 (246.1620 Calcd for $C_{16}H_{22}O_2$).

Cuparene (1)

A mixture of **16** (50 mg, 0.2 mmol), Cu powder (38 mg, 0.6 mmol) and quinoline (6 mL) was stirred at 220 °C for 6 h. On cooling to room temperature, the mixture was filtered and the filtrate was washed with ice-cold HCl (8 mL, 20 g ice), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed over silica gel using *n*-hexane as eluent to give cuparene **(1)** (29.5 mg, 71.9%). ^{1}H-NMR δ 7.22 (d, 2H, J = 8.1 Hz), 7.06 (d, 2H, J = 8.1 Hz), 2.60–2.40 (m, 1H), 2.34 (s, 3H), 1.80–1.40 (m, 5H), 1.23 (s, 3H), 1.07 (s, 3H), 0.57 (s, 3H); ^{13}C-NMR δ 144.5 (s), 134.6 (s), 128.2 (d), 126.9 (d), 50.3 (s), 44.3 (s), 39.8 (t), 36.8 (t), 27.0 (q), 24.4 (q), 20.9 (q), 19.8 (q).

Herbertene (2)

A mixture of acid **17** (80.5 mg, 0.3 mmol), Cu powder (57 mg, 0.9 mmol) and quinoline (8 mL) was manipulated in the same manner as above. The crude product was chromatographed over silica gel using *n*-hexane as eluent to give herbertene (**2**) (51.4 mg. 73.7%). ^{1}H-NMR 7.20–7.10 (m, 3H), 7.00–6.90 (m, 1H), 2.60–2.40 (m, 1H), 2.34 (s, 3H), 1.80–1.40 (m, 5H), 1.25 (s, 3H), 1.05 (s, 3H), 0.55 (s, 3H); ^{13}C-NMR δ 147.5 (s), 136.6 (s), 127.8 (d), 127.4 (d), 126.1 (d), 124.1 (d), 50.5 (s), 44.4 (s), 39.9 (t), 36.9 (t), 26.6 (q), 24.5 (q), 24.4 (q), 21.9 (q), 19.8 (t).

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