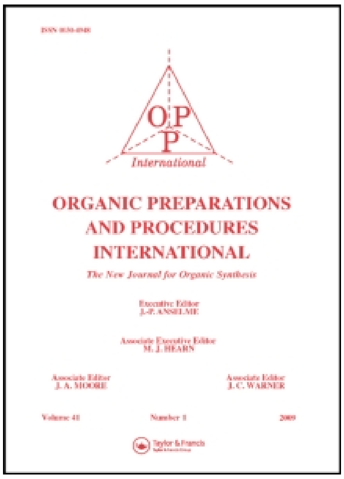

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SYNTHESIS OF (+)-OBTUNONE. A NEW ROUTE TO THE CADINANE SKELETON

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SYNTHESIS OF (±)-OBTUNONE.
A NEW ROUTE TO THE CADINANE SKELETON

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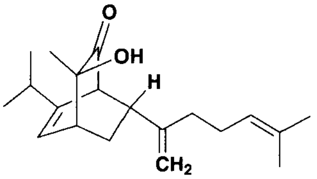
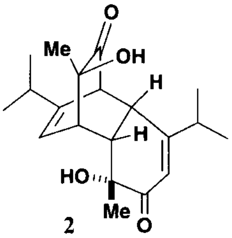
Kuo and coworkers recently reported the isolation of the novel diterpene obtunone (**1**) and the known[2] dimer **2** from the heartwood of *Chamaecyparis Obtusa* var. *formosana*.[1] Although obtunone is formally a diterpene, the authors suggested that it is biosynthesized by the Diels-Alder reaction of the hydroxycyclohexadienone corresponding to acetate **3** and myrcene (**4**).



1 (obtunone)

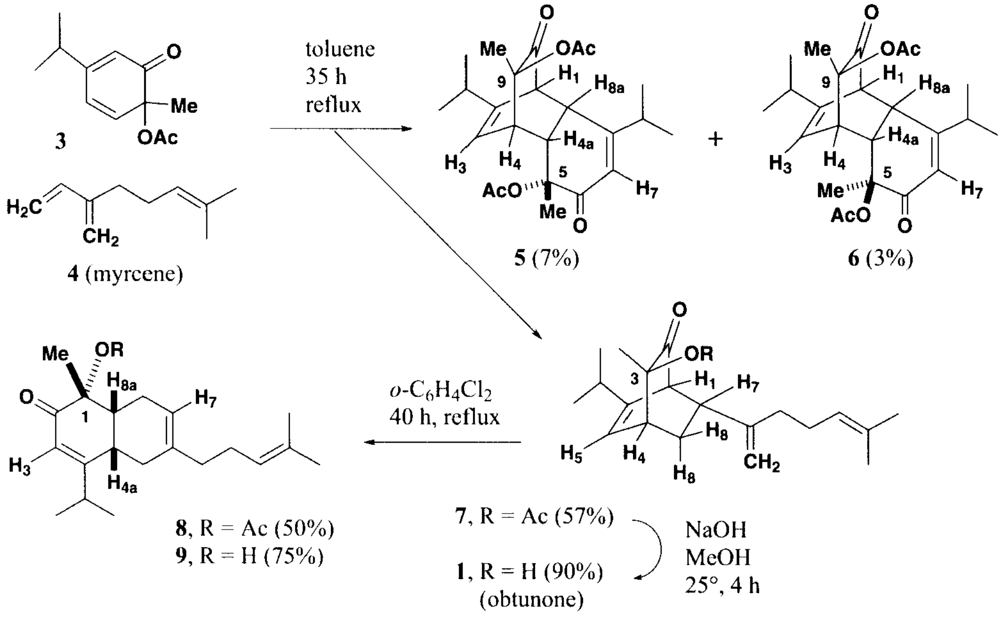


2

The inverse electron demand Diels-Alder reactions of 6-acetoxy-6-methyl-2,4-cyclohexadienones with conjugated cycloalkadienes have been extensively explored,[3-6] suggesting that the Diels-Alder reaction of acetate **3** and the acyclic diene myrcene (**4**) should provide a practical route to obtunone (**1**). Reaction of acetate **3**[7,8] and myrcene in toluene at reflux for 35 h afforded 7% of dimer **5**,[8] the diacetate of **2**, 3% of dimer **6** and 57% of obtunone acetate (**7**). The stereochemistry at the quaternary carbons of **5** was established by the NOEs between C_9-Me and H_3, and between C_5-Me and both H_{4a} and H_{8a}. The stereochemistry at the quaternary carbons of **6** was established by the NOEs between H_3 and both C_5-Me and C_9-Me. The structure of obtunone acetate was established by NOEs between H_5 and C_3-Me and between H_1 and H_7.

Hydrolysis of obtunone acetate (**7**) with NaOH in MeOH at 25° for 4 h gave 95% of (±)-obtunone (**1**) with spectral data identical to those reported for the natural product.[1] Hydrolysis of dimeric diacetates **5** and **6** provided mixtures of the corresponding diol and a phenol resulting from elimination of acetic acid as has been observed in related systems.[9]

Obtunone (**1**) and acetate **7** are 5-vinylbicyclo[2.2.2]oct-2-enes, which should undergo a Cope rearrangement on heating to give the more stable *cis* decalin ring system.[6] Heating **7** in *o*-dichlorobenzene at reflux for 40 h yielded 50% of Cope rearrangement product **8**. Similar treatment of **1** gave 75% of **9**. These *cis* decalins have the cadinane sesquiterpene skeleton with an additional prenyl group attached to the side chain.



We have completed the first synthesis of the novel diterpene obtunone (**1**) by the Diels-Alder reaction of acetoxycyclohexadienone **3** and myrcene **4** and demonstrated that the Cope rearrangement of these adducts provides an efficient new route to the cadinane sesquiterpene skeleton.

EXPERIMENTAL SECTION

NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra were recorded in cm^{-1}. Acetate **3** was prepared from carvacrol by oxidation with $Pb(OAc)_4$.[7,8]

Diels-Alder Reaction of Acetate 3 and Myrcene (4).- A solution of acetate **3** (510 mg, 2.4 mmol) and myrcene (**4**) (600 mg, 4.4 mmol) in toluene (4 mL) was heated at reflux for 35 h under N_2. Removal of the solvent under reduced pressure and chromatography of the residue on silica gel (4:1 hexane/EtOAc) gave 260 mg (43%) of recovered myrcene (**4**), followed by 320 mg (38%, 57% based on recovered **3**) of obtunone acetate (**7**), 165 mg (33%) of recovered acetate **3**, 10 mg (2%, 3% based on recovered **3**) of dimer **6** and 25 mg (5%, 7% based on recovered **3**) of dimer **5**.

The data for (±)-(1α,4α,4aα,5β,8aα,9*S**)-4,4a,5,8a-tetrahydro-5,9-bis(acetyloxy)-5,9-dimethyl-2,8-bis(1-methylethyl)-1,4-ethanonaphthalene-6,10(4*H*)-dione (**5**): ^1H NMR 5.88 (s, 1, H_7), 5.82 (br d, 1, $J = 6.9$, H_3), 3.56 (dd, 1, $J = 6.9$, 1.6, H_4), 3.39 (dd, 1, $J = 8.5$, 1.8, H_{8a}), 3.33 (dd, 1, $J = 8.5$, 1.8, H_1), 3.29 (dd, 1, $J = 2.5$, 1.8), 2.46 (sept, 1, $J = 7.0$), 2.19 (s, 3), 2.11 (s, 3), 1.82 (sept d, $J = 7.0$), 1.66 (s, 3), 1.45 (s, 3), 1.13 (d, 3, $J = 7.0$), 1.11 (d, 3, $J = 7.0$), 0.94 (d, 3, $J = 7.0$), 0.88 (d, 3, $J =$

7.0); ^{13}C NMR 206.0, 195.1, 170.0 (2 C), 163.1, 147.6, 123.5, 122.0, 83.0, 80.3, 56.1, 41.8, 41.4, 39.9, 33.4, 32.0, 26.6, 22.9, 22.3, 22.1, 21.8, 20.6, 19.9, 18.9; IR 1738, 1701, 1367, 1245. A 1D NOESY experiment with irradiation of C_5-CH_3 at δ 1.66 showed absorptions for H_{4a} at δ 3.33, H_{8a} at δ 3.39 and H_7 at δ 5.88. Irradiation of C_9-CH_3 at δ 1.45 showed absorptions for H_4 at δ 3.56 and H_3 at δ 5.82. The data are identical to those previously reported.[8]

The data for (±)-(1α,4α,4aα,5α,8aα,9*S**)-4,4a,5,8a-tetrahydro-5,9-bis(acetyloxy)-5,9-dimethyl-2,8-bis(1-methylethyl)-1,4-ethanonaphthalene-6,10(4*H*)-dione (**6**): mp. 170-172°; ^{1}H NMR 5.84 (s, 1, H_7), 5.70 (d, 1, J = 7.0, H_3), 3.75 (dd, 1, J = 7.0, 1.8, H_4), 3.24 (br s, 1, H_1), 3.23 (br d, 1, J = 8.0, 1.8, H_{8a}), 2.71 (dd, 1, J = 8.0, 1.8, H_{4a}), 2.43 (sept, 1, J = 6.7), 2.14 (s, 3), 1.90 (s, 3), 1.89 (sept, 1, J = 6.7), 1.55 (s, 3), 1.46 (s, 3), 1.10 (d, 6, J = 6.7), 0.93 (d, 3, J = 6.7), 0.86 (d, 3, J = 6.7); ^{13}C NMR 204.9, 195.9, 170.0, 169.1, 162.8, 146.9, 124.0, 121.1, 82.5, 80.8, 55.2, 42.0, 41.3, 39.9, 33.5, 32.2, 23.5, 21.9, 21.6, 21.4, 20.5, 20.0, 19.1, 17.4; IR 1738, 1705, 1368, 1236. A 1D NOESY experiment with irradiation of C_5-CH_3 at δ 1.55 showed absorptions for H_4 at δ 3.75, H_{4a} at δ 2.71 and H_3 at δ 5.70. Irradiation of C_9-CH_3 at δ 1.46 showed absorptions for H_4 at δ 3.75 and H_3 at δ 5.70.

The data for (±)-(1α,3α,4α,7*S**)-3-acetyloxy-3-methyl-6-(1-methylethyl)-7-(5-methyl-1-methylene-4-hexenyl)-bicyclo[2.2.2]oct-5-en-2-one (obtunone acetate, **7**): ^{1}H NMR 6.03 (dt, 1, J = 7.3, 1.5), 5.09 (m, 1), 4.78 (s, 1), 4.71 (s, 1), 3.75 (ddd, 1, J = 7.3, 3.1, 2.5), 3.14 (br s, 1), 2.71 (dd, 1, J = 9.2, 7.0), 2.05 (s, 3), 2.01-2.18 (m, 5), 1.90 (ddd, 1, J = 13.0, 9.2, 3.1), 1.68 (s, 3), 1.60 (s, 3), 1.51 (s, 3), 1.44 (ddd, 1, J = 13.0, 7.0, 2.5), 0.98 (d, 3, J = 6.8), 0.92 (d, 3, J = 6.8); ^{13}C NMR 204.9, 169.8, 149.7, 145.0, 131.8, 125.2, 123.6, 110.0, 80.1, 54.9, 39.6, 38.3, 36.2, 33.1, 26.8, 26.5, 25.6, 21.8, 20.9, 20.8, 19.8, 17.7; IR 1736, 1367, 1238. A 1D NOESY experiment with irradiation of H_5 at δ 6.03 showed absorptions for H_4 at δ 3.75, C_3-CH_3 at δ 1.51 and C_{17}-CH_3 at δ 0.98. Irradiation of H_{16} at δ 4.71 showed absorptions for H_{16} at δ 4.78 and $H_{8\alpha}$ at δ 1.44. Irradiation of H_4 at δ 3.75 showed absorptions for H_5 at δ 6.03 and C_3-CH_3 at δ 1.51. Irradiation of H_7 at δ 2.71 showed absorptions for H_1 at δ 3.14 and $H_{8\beta}$ at δ 1.90.

(±)-(1α,3α,4α,7*S)-3-Hydroxy-3-methyl-6-(1-methylethyl)-7-(5-methyl-1-methylene-4-hexenyl)-bicyclo[2.2.2]oct-5-en-2-one (Obtunone, 1)**.- A solution of obtunone acetate (**7**) (70 mg, 0.20 mmol) in methanol (1 mL) was treated with aqueous NaOH (0.2 mL, 1 N). The reaction mixture was stirred for 4 h at 25°, acidified with 1 N HCl, and concentrated partially under reduced pressure. The aqueous solution was extracted with ether (3 x 2 mL), which was washed with brine (1 mL) and dried over Na_2SO_4. Removal of the solvent, followed by chromatography of the residue on silica gel (3:1 hexane/EtOAc) yielded 58 mg (95%) of obtunone (**1**): ^{1}H NMR 6.05 (ddd, 1, J = 7.3, 1.8, 1.8), 5.09 (m, 1), 4.77 (s, 1), 4.71 (s, 1), 3.09 (dd, 1, J = 1.8, 1.8), 2.83 (ddd, 1, J = 7.3, 2.4, 2.4), 2.70 (ddd, 1, J = 10.2, 6.0, 2.4), 2.39 (ddd, 1, J = 13, 10.2, 3.0), 2.11 (m, 5), 1.68 (s, 3), 1.60 (s, 3), 1.35 (ddd, 1, J = 13, 6.0, 2.4), 1.24 (s, 3), 0.99 (d, 3, J = 6.8), 0.91 (d, 3, J = 6.8); ^{13}C NMR 213.2, 150.2, 144.7, 131.9, 125.3, 123.8, 109.8, 72.2, 55.4, 42.8, 39.9, 36.3, 33.1, 26.6, 26.1, 25.9, 25.6, 21.0, 19.9, 17.7; IR 3429, 1725, 1130. A 1D NOESY experiment with irradiation of H_5 at δ 6.05 showed absorptions for H_4 at δ 2.83, C_3-CH_3 at δ 1.24 and C_{17}-CH_3 at δ 0.99. Irradiation of H_{16} at δ 4.71 showed an absorption for

$H_{8\alpha}$ at δ 1.35. Irradiation of H_1 at δ 3.09 showed an absorption for C_{17}-CH_3 at δ 0.91. Irradiation of H_4 at δ 2.83 showed absorptions for H_5 at δ 6.05, $H_{8\beta}$ at δ 2.39, $H_{8\alpha}$ at δ 1.35 and C_3-CH_3 at δ 1.24. Irradiation of H_7 at δ 2.70 showed absorptions for H_1 at δ 3.09 and $H_{8\beta}$ at δ 2.39. Irradiation of $H_{8\beta}$ at δ 2.39 showed absorptions for H_4 at δ 2.83, H_7 at δ 2.70 and $H_{8\alpha}$ at δ 1.35. Irradiation of C_3-CH_3 at δ 1.24 showed absorptions for H_5 at δ 6.05, H_4 at δ 2.83 and OH at δ 2.18. The data are identical to those previously reported.[1]

Cope Rearrangement of Obtunone Acetate (7).- A solution of obtunone acetate (**7**) (20 mg, 0.058 mmol) in *o*-dichlorobenzene (5 mL) was heated at reflux for 40 h under N_2. Chromatography of the solution on silica gel (9:1 hexane/EtOAc) gave 10 mg (50%) of rearranged product **8**: mp. 103-104°; ^{1}H NMR 5.86 (d, 1, *J* = 1.8, H_3), 5.33 (s, 1, H_7), 5.06 (tt, 1, *J* = 6.7, 1.3), 3.21 (ddd, 1, *J* = 9.8, 7.3, 4.3, H_{8a}), 3.01 (br, 1, H_{4a}), 2.40 (sept, 1, *J* = 6.7), 2.34 (br s, 2), 2.11 (s, 3), 2.05-2.09 (m, 2), 1.98 (t, 2, *J* = 7.5), 1.92 (br, 2), 1.72 (s, 3), 1.68 (s, 3), 1.60 (s, 3), 1.08 (d, 3, *J* = 6.7), 1.06 (d, 3, *J* = 6.8); ^{13}C NMR 195.9, 170.4, 170.2, 135.7, 131.8, 123.9, 121.3, 120.3, 86.2, 40.5, 37.7, 35.8, 30.7, 30.1, 26.0, 25.7, 23.6, 22.6, 22.0, 20.4, 20.1, 17.7; IR 3432, 2974, 1724, 1604. A 1D NOESY experiment with irradiation of H_{8a} at δ 3.21 showed absorptions for H_{4a} at δ 3.01, H_8 at 1.92 and C_1-CH_3 at δ 1.72. Irradiation of H_{4a} at δ 3.01 showed absorptions for H_{8a} at δ 3.21, C_1-CH_3 at δ 1.72, and H_5 at δ 2.34.

Cope Rearrangement of Obtunone (1).- A solution of obtunone (**1**) (29 mg, 0.09 mmol) in *o*-dichlorobenzene (4 mL) was heated at reflux for 40 h under N_2. Chromatography of the solution on silica gel (9:1 hexane/EtOAc) gave 22 mg (75%) of rearranged product **9**: ^{1}H NMR 5.90 (d, 1, *J* = 2.5, H_3), 5.36 (s, 1, H_7), 5.07 (tt, 1, *J* = 6.7, 1.5), 3.54 (s, 1, OH), 3.04 (dt, 1, *J* = 9.1, 3.0, H_{4a}), 2.44 (sept, 1, *J* = 6.7), 2.24-2.36 (m, 4), 2.06-2.10 (br t, 2), 1.98 (t, 2, *J* = 7.3), 1.68 (s, 3), 1.61 (s, 3), 1.37 (s, 3), 1.11 (d, 3, *J* = 6.7), 1.07 (d, 3, *J* = 6.7); ^{13}C NMR 203.0, 172.6, 135.1, 131.8, 123.9, 121.2, 120.1, 76.6, 43.7, 37.7, 36.5, 30.9, 30.2, 26.1, 25.7, 24.6, 23.3, 22.5, 20.6, 17.7; IR 2957, 1669, 1105. A 1D NOESY experiment with irradiation of C_1-CH_3 at δ 1.37 showed absorptions for the OH group at δ 3.54, H_{8a} at δ 2.34, and H_{4a} at δ 3.04. Irradiation of H_{4a} at δ 3.04 showed absorptions for H_5 at δ 2.36, H_{8a} at δ 2.34, and C_1-CH_3 at δ 1.37.

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