A Total Synthesis of (±)-Modhephene

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A new approach to the [3.3.3] propellane system *via* a key photochemical oxa-di-π-methane rearrangement has culminated in a synthesis of the sesquiterpene hydrocarbon (±)-modhephene (**1**).

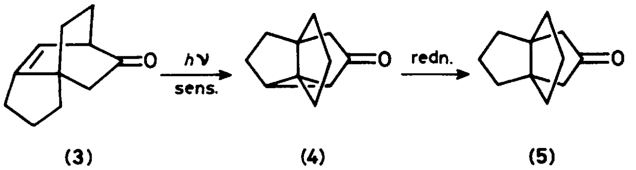
The novel sesquiterpene hydrocarbon modhephene (**1**), bearing the unique carbocyclic [3.3.3] propellane framework, has attracted world-wide synthetic interest and many new and imaginative strategies have been developed towards its synthesis.[1] In this communication, we describe a conceptually new approach to (**1**) and epimodhephene (**2**) in which the pivotal steps are the photochemical oxa-di-π-methane rearrangement of the tricyclic system (**3**) to the strained tetracycle (**4**) and regioselective reductive cleavage to (**5**) bearing the [3.3.3] propellane skeleton, Scheme 1. We emphasize that the (**3**) → (**5**) sequence, although developed in our quest for (**1**), constitutes a new general approach to the [3.3.3] propellanes.[2]

Reaction of the readily available[3] bicyclic enone (**6**) with MeMgI and work-up in aqueous protic media furnished a mixture of highly labile conjugated dienes (**7**) in 86% yield. The crude (**7**) was immediately treated with the ketene equivalent α-chloroacrylonitrile to furnish the Diels–Alder adducts (**8**) and (**9**) (43%). Hydrolysis of (**8**) and (**9**) with ethanolic sodium sulphide furnished the tricyclic ketones (**10**)[†] and (**11**)[†] (58%, 4:1), readily separable on chromatography, which were fully characterised on the basis of their ^{1}H and ^{13}C n.m.r. data (Scheme 2).

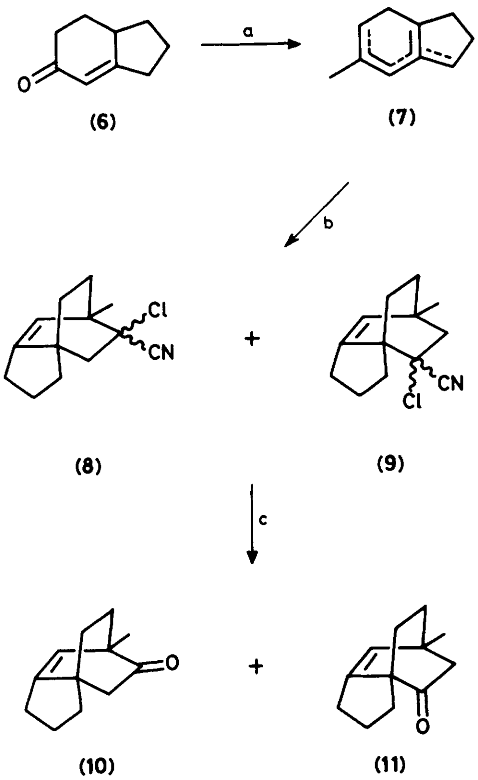
(**1**) (**2**)

Scheme 1

[†] Compound (**10**): $\nu_{max.}$ (neat) 3025 and 1720 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 5.44 (1H, unresolved t) 2.42—1.40 (12H, m), and 1.2 (3H, s); ^{13}C n.m.r. (CDCl$_3$; 25.0 MHz) δ 214.4 (s), 156.2 (s), 120.6 (d), 49.6 (s), 46.9 (s), 45.9 (t), 35.8 (t), 31.9 (t), 31.7 (t), 30.2 (t), 26.1 (t), and 17.8 (q); (**11**): $\nu_{max.}$ (neat) 3025 and 1720 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 5.80 (1H, t, $J \sim 1$ Hz), 2.5—1.4 (12H, m), and 1.25 (3H, s); ^{13}C n.m.r. (CDCl$_3$; 25.0 MHz) δ 211.9, 147.7, 129.2, 59.8, 48.0, 38.2, 35.1, 29.8, 29.6, 28.6, 26.1, and 24.1; (**12**): $\nu_{max.}$ (neat) 3020 and 1720 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 2.4—1.3 (13H, m) and 1.2 (3H, s); ^{13}C n.m.r. (CDCl$_3$; 25.0 MHz) δ 215.4 (s), 62.3 (s), 57.5 (s), 53.4 (t), 50.5 (d), 43.5 (t), 42.9 (s), 38.2 (t), 34.6 (t), 28.6 (t), 24.8 (t), and 19.9 (q); (**13**): $\nu_{max.}$ (neat) 3020 and 1720 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 2.1—1.3 (11H, m), 1.2 (3H, s), 1.0 (3H, s), and 0.84 (3H, s); ^{13}C n.m.r. (CDCl$_3$; 25.0 MHz) δ 219.4 (s), 64.0 (s), 58.5 (s), 52.3 (s), 45.5 (d), 41.4 (s), 40.0 (t), 33.8 (t), 30.7 (t), 29.0 (t), 25.9 (t), 25.1 (q), 19.7 (q), and 17.9 (q); (**14**): $\nu_{max.}$ (neat) 1740 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 3.04—2.61 (two sets of AB quartets, each 2H) and 1.1—0.95 (m, Me); (**15**): $\nu_{max.}$ (neat) 1740 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$; 100 MHz) δ 1.61—1.30 (two sets of m, each 1 H) and 1.1—0.95 (m, Me).

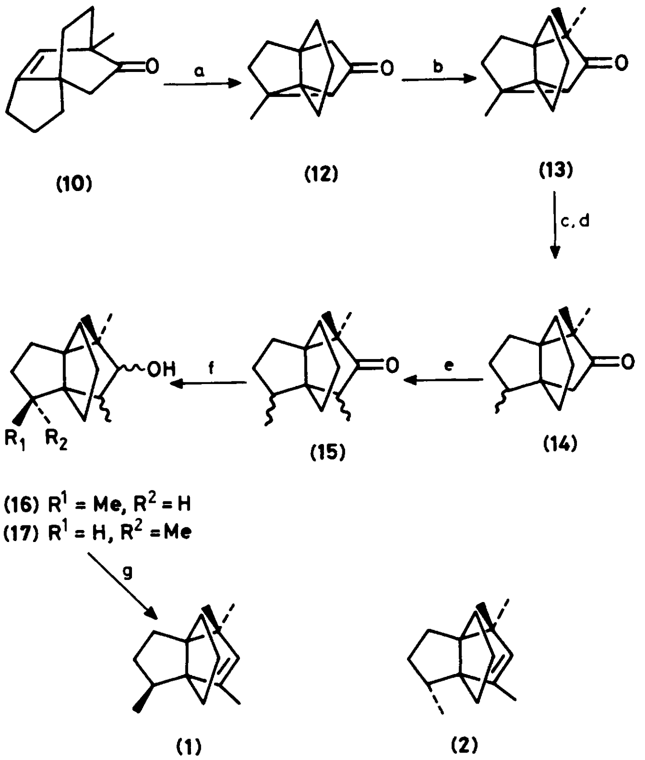


Scheme 1



Scheme 2. a, MeMgI–Et_2O, H_3O^+; b, CH_2=C(Cl)CN, toluene, 80 °C, 14 h; c, $Na_2S·9H_2O$–EtOH, reflux, 10 h.

The major, required β,γ-unsaturated ketone (**10**) was irradiated in acetone with a 450 W Hanovia medium-pressure lamp in a quartz vessel to furnish the strained cyclopropyl ketone (**12**) in 50% yield. The presence of three quaternary C resonances at 62.3 (s), 57.5 (s), and 42.9 (s) and the absence of olefinic C resonances were fully consistent with the tetracyclic structure (**12**)† derived from (**10**) through oxa-di-π-methane rearrangement.[4] The stage was now set for the introduction of the *gem*-dimethyl group at the desired position and this was achieved through exhaustive methylation with $KOBu^t$–MeI to furnish (**13**)† (55%). Reductive C–C bond cleavage in (**13**) was effected through metal–ammonia reduction and (**14**) was obtained as a mixture (~1 : 1) of methyl epimers after pyridinium chlorochromate (PCC) oxidation. The separation of the methyl epimers of (**14**) at this stage proved capricious and was deferred till the penultimate step. Selective methylation of (**14**) with lithium hexamethyldisilazide–MeI proceeded smoothly to give (**15**) (60%) and further reduction with $LiAlH_4$ furnished an epimeric mixture of alcohols (**16**) and (**17**) (70%), which were fortunately amenable to chromatographic separation. However, dehydration of (**16**) and (**17**) presented considerable problems but could be ultimately effected with $POCl_3$–pyridine containing traces of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish (**1**) and (**2**) in 36 and 24% yield, respectively, which were found to be spectroscopically identical with the authentic spectra provided by Professor Paquette (Scheme 3).



Scheme 3. a, hν–acetone, 45 min; b, Bu^tOK–MeI, THF; c, Li–liq. NH_3, NH_4Cl; d, PCC–molecular sieves 4 Å; e, $(Me_3Si)_2$NH–Bu^nLi–MeI, THF, 0 °C; f, $LiAlH_4$–Et_2O, 30 min; g, $POCl_3$–pyridine–DBU, 4 h.

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