A Stereoselective Total Synthesis of (±)-Pentalenene

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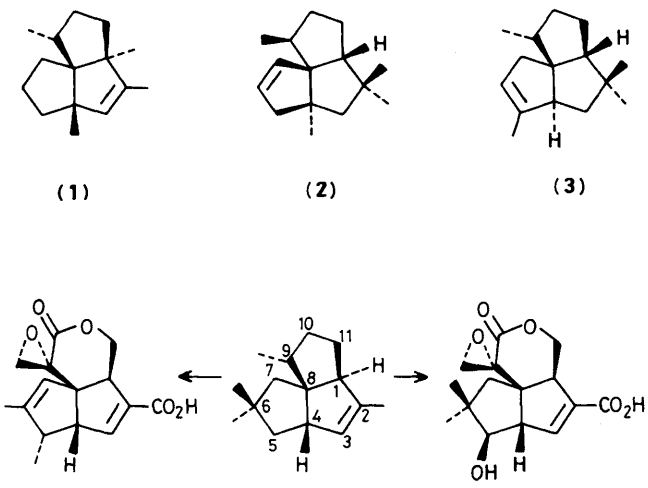
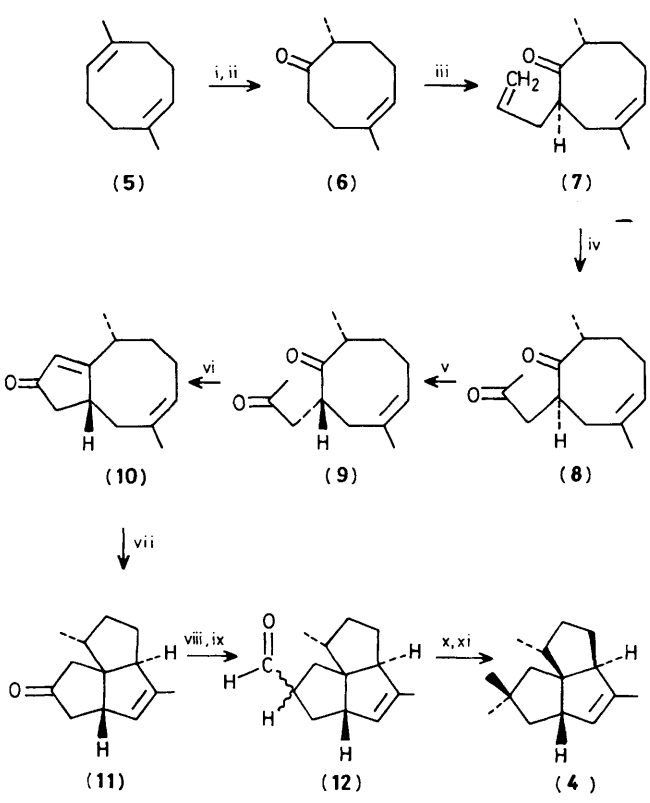
A short, stereoselective synthesis of triquinane sesquiterpene hydrocarbon (±)-pentalenene (**4**) from commercially available 1,5-dimethylcyclo-octa-1,5-diene (**5**) involving a transannular cyclisation as the pivotal step is described.

Angularly fused triquinane natural products *e.g.*, isocomene (**1**),[1a] silphenene (**2**),[1b] senoxydene (**3**),[1c] pentalenene (**4**)[1d] among many others,[1e,f] have received a great deal of attention from synthetic chemists during the past few years due to their unique molecular architecture, embellished with a variety of methyl substituents.[2] Among these the sesquiterpene hydrocarbon pentalenene (**4**), isolated[1d] from *Streptomyces griseochromogenes* has held special attraction due to its novel biosynthetic origin[3a] and its role as the key precursor of the pentalenolactone family of antibiotics,[3b] Scheme 1. From the synthetic point of view, the challenge of pentalenene (**4**) resides in the efficient formation of the tricyclo[6.3.0.$0^{4,8}$]un-



Scheme 1



Scheme 2. *Reagents and conditions:* i, 9-borabicyclo[3.3.1]nonane, THF, 70%; ii, PCC–molecular sieves 4 Å, CH_2Cl_2, 87%; iii, $(Me_3Si)_2NH$–Bu^nLi, $CH_2{=}CHCH_2Br$, −78 °C, THF, 75%; iv, $PdCl_2$, CuCl, O_2; *N,N*-dimethylformamide, 80%; v, KOH–MeOH, 82%; vi, NaH, THF, 70%; vii, BF_3–Et_2O, HCO_2H, 55%; viii, $Ph_3P^+CH_2OMeCl^-$–t-$C_5H_{11}O^-Na^+$–Et_2O; ix, 35% $HClO_4$–Et_2O, 80% [from (**11**)]; x, KH–MeI, THF, 0—10 °C, 63%; xi, N_2H_4, Na, $(HOCH_2CH_2)_2O$, $(HOCH_2)_2$, 33%.

decane framework and the generation of four contiguous asymmetric centres around the spiro carbon atom (C-8).[4] We report here a new synthesis of (**4**) which employs a transannular C^+–π type of cyclisation within a bicyclo[6.3.0]undecane system as the key transformation to generate the angular triquinane framework.[4d,5] Our synthesis is notable for its conceptual simplicity, brevity, and apparent generality (Scheme 2).

Readily available 1,5-dimethylcyclo-octa-1,5-diene (**5**) on hydroboration–oxidation followed by pyridinium chlorochromate (PCC) oxidation furnished the enone (**6**) in good yield. Kinetically controlled allylation of the lithium enolate derived from (**6**) exclusively furnished the *trans*-(**7**) in keeping with the recent observation of Clark Still on similar systems.[6] Tsuji oxidation[7] of (**7**)† proceeded uneventfully to give (**8**).† At this stage, to ensure the correct relative stereochemistry at C-4 and C-9 in pentalenene (**4**), the dione (**8**) was subjected to base catalysed equilibration to furnish a 4 : 1 mixture of (**9**)† and (**8**),† respectively. The *cis*-dione (**9**) on exposure to sodium hydride underwent smooth aldol cyclisation to afford the bicyclic enone (**10**)† (80%) along with its C-4 epimer (20%). The key step now was the transannular cyclisation and after much exploratory work employing toluene-*p*-sulphonic acid, Nafion-H, trimethylsilyl trifluoromethanesulphonate, *etc.*, we found that formic acid in the presence of BF_3–diethyl ether effected the desired cyclisation to give the tricyclic ketone (**11**) in 55% isolated yield. The structure of (**11**)† was confirmed by the presence of a cyclopentanone moiety (i.r.: 1730 cm^{-1}) and a quaternary carbon centre (δ 62.1, s) in the ^{13}C n.m.r. spectrum. At this stage, we sought to convert (**11**) into pentalenene through direct geminal dimethylation with Reetz titanium reagent.[8] Reaction of (**11**) with Me_2TiCl_2, provided a complex mixture of C_{14}- and C_{15}-alkenes and although g.c.–mass spectroscopic analysis indicated the presence of (**4**) (~ 10%), it was preparatively unworkable. A more circuitous approach was therefore adopted. Wittig olefination of (**11**) with methoxymethyltriphenylphosphonium chloride and mild acidic hydrolysis of the product gave the C_{14}-aldehyde (**12**).† Methylation of (**12**) with KH–MeI in tetrahydrofuran (THF) established the second quaternary carbon centre at C-6, and the resulting C_{15}-aldehyde (i.r.: 2700, 1720 cm^{-1}; ^1H n.m.r.: δ 9.41, s) on Wolff–Kishner reduction led to (±)-pentalenene (**4**), which was identical (^1H and ^{13}C n.m.r.) with the natural product.

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† Compound (**7**): i.r. (neat) 1710, 1640 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 6.12—5.44(1H,m), 5.44—5.16(1H,t), 5.16—4.84(2H,m), 3.04—1.04(10H, series of m), 1.68(3H,br s), 0.96(3H,d); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz): δ 216.9, 136.5, 135.2, 125.5, 116.6, 56.1, 41.0, 36.0(2C), 33.0, 27.4, 23.4, 19.1; (**8**): i.r. (neat) 1700 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 5.36(1H,t), 3.16—2.36(4H,m), 2.36—1.84(4H,m), 2.15(3H,s), 1.6—1.12(2H,m), 1.69(3H,br s), 1.0(3H,d); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz): δ 218.9, 205.3, 136.2, 126.0, 51.0, 45.2, 41.7, 35.5, 32.9, 29.9, 27.1, 23.8, 19.1; (**9**): i.r. (neat) 1700 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 5.28(1H,t), 3.24—1.0(10H, series of m), 2.0(3H,s), 1.68(3H,br s), 0.88(3H,d); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz): δ 217.6, 206.8, 135.3, 125.1, 49.1, 45.2, 44.5, 33.8. 31.5, 30.0, 26.1, 25.1, 17.6; (**10**): i.r. (neat) 1670, 1595 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 5.92(1H,br s), 5.32(1H,t), 3.12—1.2(10H, series of m), 1.8(3H,br s), 1.1(3H,d); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz): δ 208.5, 192.3, 135.3, 128.8, 125.1, 44.0, 43.3, 38.1, 35.9, 35.2, 26.0, 25.0, 21.8; (**11**): i.r. (neat) 1730 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 5.08(1H,br s), 3.28—1.12 (11H, series of m), 1.64(3H,br s), 0.92(3H,d); ^{13}C n.m.r. ($CDCl_3$, 25.0 MHz): δ 219.0, 144.0, 126.8, 62.1, 60.2, 51.6, 45.9, 43.6, 43.0, 34.8, 28.7, 15.8, 15.2; (**12**): i.r. (neat) 2700, 1720 cm^{-1}.

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