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A new synthesis of pentalenene using a novel tandem cyclisation involving ketene radical intermediates

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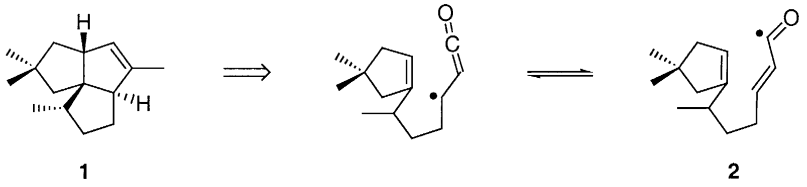
Abstract

A new approach to the synthesis of the angular triquinane (±)-pentalenene, based on sequential 5-*exo*-trig and 5-*exo*-dig radical cyclisations involving ketene intermediates produced from an α,β-unsaturated acyl radical precursor, is described.

The angular triquinane pentalenene **1** and its various oxygenated congeners are biologically important sesquiterpene antibiotics, whose synthesis[1] and biosynthesis[2] have aroused considerable attention in recent years. Paramount among the synthetic approaches that have been developed towards triquinanes, including pentalenene **1**, are those based on tandem radical-mediated cyclisation processes.[3] In our recent studies with α,β-unsaturated acyl radical intermediates[4] we have highlighted the propensity for these species to react via their corresponding α-ketenyl radical counterparts, i.e. R–CH=CH–·CO↔R–·CH–CH=C=O. In this letter we describe the development of this work leading to a new and concise synthesis of (±)-pentalenene based on tandem cyclisation of ketene radical intermediates derived from the α,β-unsaturated acyl radical intermediate **2** (Scheme 1).



1 **2**

Scheme 1.

Thus, following some precedent established by Davies and Doan,[5] we first prepared the β,γ-unsaturated ester **4** via deconjugative alkylation of the α,β-unsaturated ester **3** using lithium 2,2,6,6-tetramethylpiperidinamide (LiTMP) and DMPU at −90°C followed by trapping the resulting enolate

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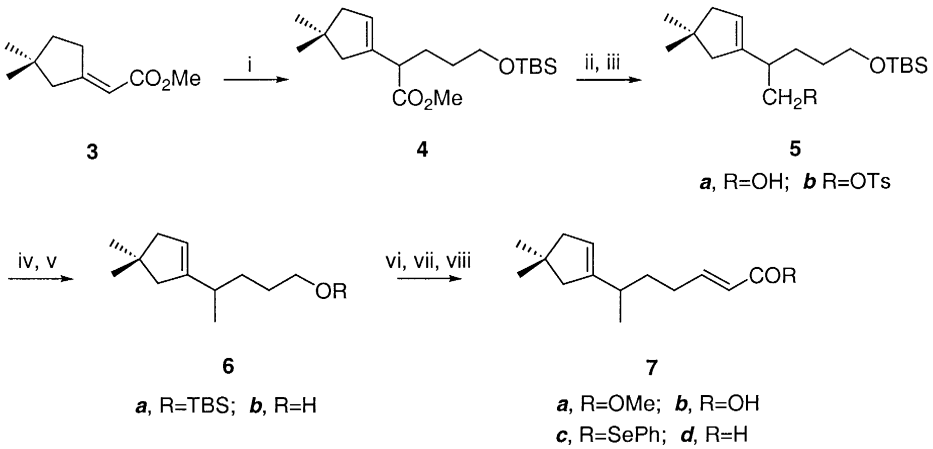
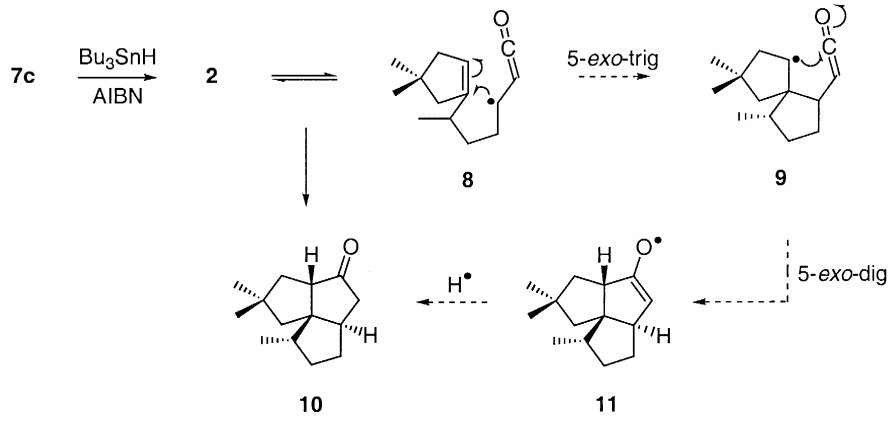
anion with the TBDMS ether of 3-iodo-1-propanol. In this manner, and at this carefully controlled temperature, we obtained almost exclusively the regioisomer **4**, i.e. <5% of other cyclopentene regioisomers.[6] Reduction of the ester **4** using DIBAL, followed by conversion of the resulting carbinol **5a** into the corresponding tosylate **5b**, and a further reduction step, led to the TBS ether **6a** (Scheme 2).



Scheme 2. *Reagents:* (i) LiTMP, DMPU, $I(CH_2)_3OTBS$, THF, −90°; (ii) DIBAL, toluene, −78°, 49% (two steps); (iii) TsCl, DMAP, Et_3N, CH_2Cl_2, 88%; (iv) $LiEt_3BH$, THF, 97%; (v) $AcOH/H_2O$/THF, 93%; (vi) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, then $Ph_3P{:}CHCO_2Me$, 80%; (vii) $LiOH{\cdot}H_2O$, THF/H_2O, 98%; (viii) NPSP, *n*-Bu_3P, CH_2Cl_2, −30°, 57%

After deprotection of **6a** (to **6b**), application of the Ireland one-pot Swern–Wittig procedure[7] then converted **6b** into the *E*-α,β-unsaturated ester **7a** in a satisfying 80% yield. Finally, saponification of the ester **7a** and treatment of the resulting carboxylic acid **7b** with *N*-(phenylseleno)phthalimide (NPSP) in the presence of *n*-Bu_3P led to the key selenyl ester precursor **7c** to the α,β-unsaturated acyl radical intermediate **2**.

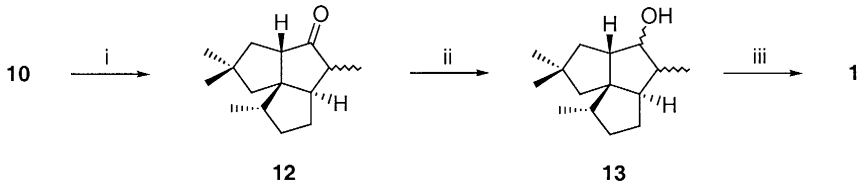
When a solution of **7c** in benzene was heated with Bu_3SnH in the presence of catalytic AIBN, work up and chromatography gave the α-methyl epimer of the tricyclic ketone **10** as the major product (~45%),[6] together with small amounts of the corresponding β-methyl epimer of **10** (~10%), and also the aldehyde **7d** resulting from competing in situ reduction of the ester starting material (~25%). The relative stereochemistry assigned to the triquinoid ketone **10** followed from inspection and comparison



Scheme 3.

of its NMR spectroscopic data with those in the literature.[8] The tricyclic ketone **10** is produced from the selenyl ester **7c** by way of formation of the acyl radical **2** and 5-*exo*-trig radical cyclisation involving the α-ketenyl radical counterpart **8** leading initially to the spiro-ketene radical intermediate **9**. A 5-*exo*-dig radical cyclisation into the ketene electrophore in **9** then leads to the enolate radical **11** which, on quenching by H·, produces **10** (Scheme 3).

The synthesis of (±)-pentalenene **1** was completed following deprotonation and α-methylation of **10**, using LDA and MeI, leading to **12**, reduction of **12** to the corresponding carbinol **13**, and finally dehydration of **13** in hot benzene in the presence of PTSA (Scheme 4).



Scheme 4. *Reagents*: (i) LDA, THF, then MeI, 37%; (ii) $NaBH_4$, MeOH, 52%; (iii) *p*-TsOH, benzene, Δ, 70%

The synthetic (±)-pentalenene displayed spectroscopic data which were identical to those reported in the literature and from an earlier synthesis reported from our laboratory.[9]

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6. All new compounds showed satisfactory spectroscopic data together with microanalytical and/or mass spectrometry data. Selected spectroscopic data: Compound **10**: ν_{max}/cm^{-1} (film) 1737; δ_H (500 MHz) 0.97 (d, *J* 6.9, 3H, C*H*$_3$CH), 0.99 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.30–1.38 (m, 3H, 3×C*H*H), 1.63 (dd, *J* 7.0, 12.9, 1H, C(O)CHC*H*H), 1.72 (dd, *J* 12.9, 9.5, 1H, C(O)CHC*H*H), 1.79–1.86 (m, 2H, 2×C*H*H), 1.86–1.95 (m, 1H, CH_3C*H*), 2.07–2.14 (m, 2H, C*H*H and C(O)C*H*H), 2.40–2.47 (m, 2H, C(O)C*H* and CH_2C*H*CH_2), 2.78 (dd, *J* 18.6, 9.2, 1H, C(O)C*H*H); δ_C (500 MHz) 15.5 (*C*H$_3$CH), 29.2 (CH_3), 29.5 (CH_3), 31.3 (CH_2), 34.4 (CH_2), 41.2 (quat. *C*Me$_2$), 42.9 (CH), 44.6 (CH_2), 45.8 (CH), 46.8 (CH_2), 47.9 (CH_2), 59.4 (CH), 62.7 (quat. C), 222.9 (C=O); *m/z* 206.1678 (M^+ $C_{14}H_{22}O$ requires M^+, 206.1671).
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