A Stereoselective Route to (±)-Pentalenene and (±)-9-*epi*-Pentalenene

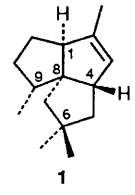
Yong-Jin Wu and D. Jean Burnell*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

The (±)-pentalenene **1** and (±)-*epi*-pentalenene **12** have been synthesised by a novel spiro-annulation strategy that allowed the subsequent formation of two of the five-membered rings by aldol condensations; the order of reduction of two double bonds in a bicyclic intermediate **8** led, in a stereoselective manner, to one C-9 epimer or the other.

Pentalenene **1** is the biosynthetic precursor to the antibiotic sesquiterpenoid pentalenolactone **2**.[1] Many synthetic approaches to **1** have been reported,[2] but a number of these syntheses suffered from poor regiochemical control in the process of ring-formation or lacked selectivity when the relative stereochemistry at C-9 was established. The strategy in the novel route described here was, at the outset, to form the quaternary centre (C-8) of pentalenene from an appropriate ketal by a double acylation method first reported by Kuwajima and coworkers[3] and subsequently modified with improved yields in our laboratory.[4]

Ketalisation of 3-ethyl-5,5-dimethylcyclohex-2-en-1-one with ethylene glycol provided a mixture of poorly separable ketals of which the required isomer **3** was the major component (by GC–MS). Treatment of this mixture of ketals with 1,2-bis(trimethylsiloxy)cyclobutene (3 equiv.) and a large excess of boron trifluoride etherate[4] proceeded, *via* an intermediate cyclobutanone such as **4**, to afford in a single operation the rearranged, spiro-annulated diketones (77%), of which **5** was the major isomer. At −78 °C methyllithium added only once to the spiro diketones, and mono-alcohols, mainly **6**, were obtained in 90% yield. Ozonolysis of **6** must have given **7**, but, without any purification, addition of *p*-toluenesulphonic acid (*p*-TsOH) induced smooth cyclization and concomitant dehydration. These steps rendered the products arising from each of the initial ketal isomers very different chromatographically, and pure (racemic) spiro-compound **8** was easily isolated (in a yield of 65% from the mixture of mono-alcohols). The spectra of **8** confirmed that the double bond that had resulted from dehydration did not move into conjugation with the ring ketone: the IR showed carbonyl absorptions at 1748 and 1672 cm^{-1} and in the ^1H NMR ($CDCl_3$, 300 MHz) only two alkenic resonances (a multiplet at δ 5.757 and a singlet at δ 6.676) were evident. The other, conjugated double bond of **8** was reduced using Birch conditions to furnish the enedione **9** as the only product (81%), but **9** would not cyclise in either acid or base. Catalytic hydrogenation of **9** appeared to proceed with moderate facial selectivity because subsequent aldol ring-closure gave the two possible tricyclic products (84%) in a ratio of 4:1. The ^1H NMR spectrum of the major product included a doublet at δ 1.047 for the methyl on its C-9. The spectrum of the minor product showed the methyl at C-9 as a doublet at δ 0.670. These C-9 methyl signals were irradiated, but only with the minor product was there a nuclear Overhauser enhancement (13%) of the well-resolved signal arising from the proton on its C-4 methine. Thus, the minor product had the relative stereochemistry with the methyl on C-9 *syn* to the proton on C-4, *i.e.* it was isomer **11**. Therefore, the major product was the one with the correct stereochemistry at C-9 for pentalenene, *i.e.* isomer **10**.



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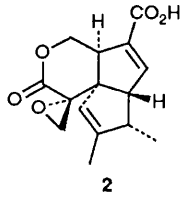

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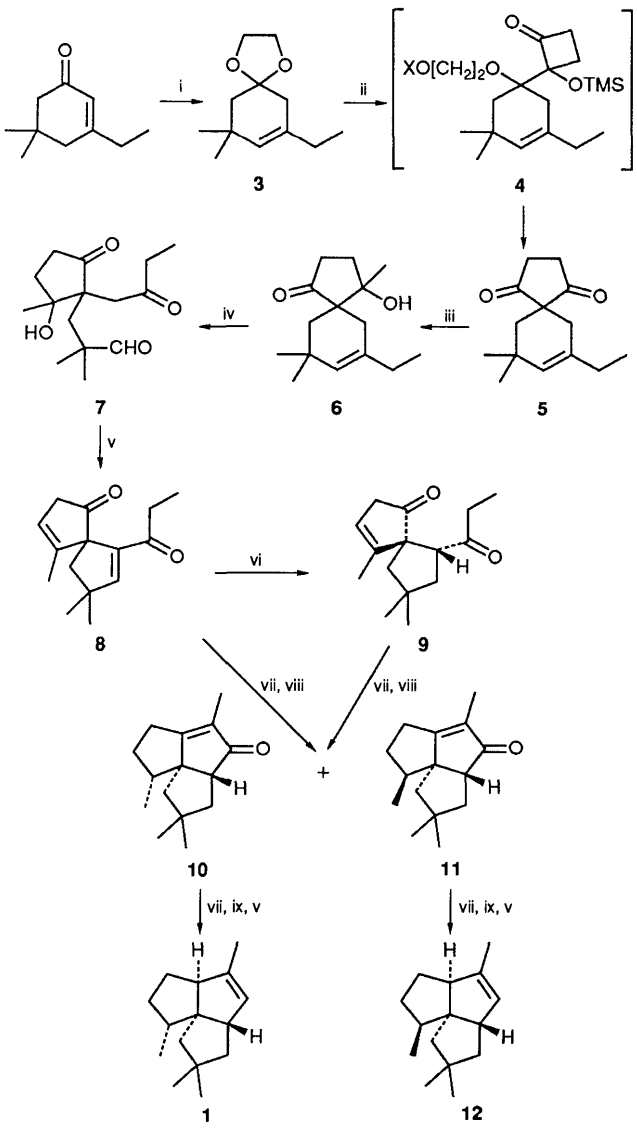

Scheme 1 *Reagents and conditions*: i, $(CH_2OH)_2$, *p*-TsOH; ii, 1,2-bis(trimethylsiloxy)cyclobutene (3 equiv.), $BF_3{\cdot}Et_2O$ (15 equiv.), −78 °C to 20 °C; iii, MeLi (5 equiv.), −78 °C; iv, O_3, CH_2Cl_2, then $(Me)_2S$; v, *p*-TsOH, C_6H_6, reflux; vi, Li metal, NH_3, then MeOH; vii, H_2, Pd on carbon; viii, $(Me)_3CO^-K^+$; ix, $NaBH_4$, MeOH

Catalytic hydrogenation directly on **8** reduced the nonconjugated double bond first, and reduction continued easily with a second equivalent of hydrogen to yield a saturated product quantitatively. Aldol condensation of this material also gave a mixture of the same epimeric tricyclic products, but, in contrast to the Birch reduction followed by hydrogenation route, in this case **11** was the major product and **10** was the minor one. The ratio was 1 : 5.6 for **10** to **11**, respectively.

Catalytic hydrogenation, sodium borohydride reduction and acid-catalysed dehydration resulted in a 76% yield of (±)-pentalenene **1** from **10**, and, in the same way, (±)-9-*epi*-pentalenene **12** was obtained from **11** in a similar yield (81%). The spectra of **1** and **12** were in complete agreement with spectra (^1H and ^{13}C NMR and IR) of the authentic molecules kindly provided by Dr E. Piers of the University of British Columbia. The overall yield of **1** from the ketal **3** was 23%, and the yield of **12** from **3** was 30%, the stereochemistry of the major product being dependent on the order in which the double bonds of **8** has been reduced.

Thus, this spiro-annulation approach was both short and relatively efficient, and the strategy should be amenable to the synthesis of other angularly fused triquinanes.

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