Total Synthesis of (±)-Pentalenic Acid *via* Intramolecular Double Michael Reaction

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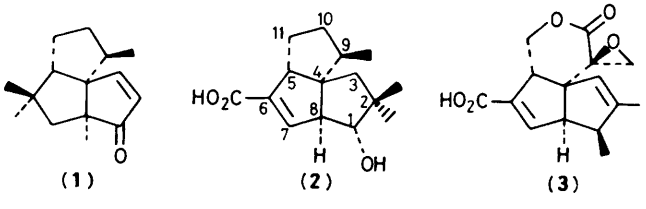
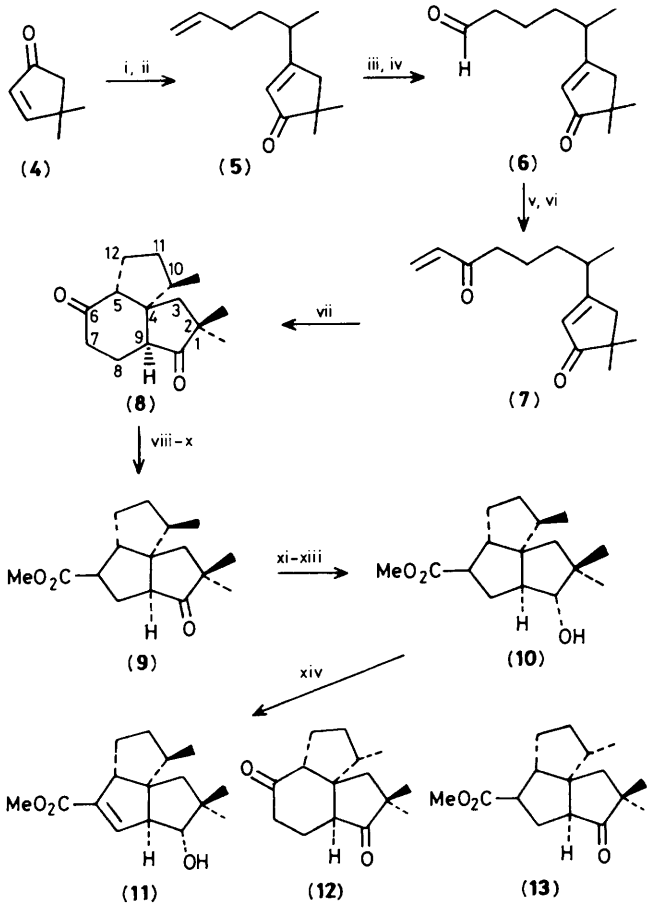
An efficient total synthesis of (±)-pentalenic acid (**2**) has been achieved *via* intramolecular double Michael reaction as the key step.

Recently we reported a synthesis of (±)-3-oxosilphinene (**1**) *via* a tricyclo[7.3.0.0^{1,5}]dodecane derivative constructed by an intramolecular Diels–Alder reaction.[1] We have further planned the extension of this method for the synthesis of other angularly-fused tricyclopentanoid sesquiterpenes and the assembly of the tricyclic ring system by an intramolecular double Michael reaction.[2] We report here a stereoselective total synthesis of (±)-pentalenic acid (**2**),[3,4] a putative precursor in the biosynthesis of the antibiotic pentalenolactone (**3**)[5] according to this strategy.

Coupling between 4,4-dimethylcyclopent-2-enone (**4**)[6] and 5-bromohex-1-ene[7] was carried out under Barbier conditions using ultrasound.[8] The resulting tertiary alcohol was oxidised with pyridinium chlorochromate (PCC) on Florisil to give the enone (**5**). Hydroboration–oxidation of (**5**) utilizing dicyclohexylborane[9] selectively afforded the corresponding primary alcohol, whose oxidation with PCC on Florisil yielded the aldehyde (**6**). Condensation of (**6**) with vinylmagnesium bromide, followed by oxidation with pyridinium dichromate (PDC) gave the bis-enone (**7**)† in excellent yield. Although the intramolecular double Michael reaction using lithium bases[2] failed, the desired tricyclic diketone (**8**),† m.p.



† I.r. ($CHCl_3$) and 500 MHz ^{1}H n.m.r. ($CDCl_3$) data: (**7**) i.r. 1700 cm^{-1} (C=O); n.m.r., δ 1.10 (6H, s, 2 × Me), 1.15 (3H, d, *J* 7.1 Hz, Me), 2.45 (2H, s, 4-H_2), 5.86 (1H, br. s, 2-H), 5.83 (1H, dd, *J* 10.7, 1.5 Hz, olefinic H), 6.22 (1H, dd, *J* 17.3, 1.5 Hz, olefinic H), and 6.35 (1H, dd, *J* 17.3, 10.7 Hz, olefinic H); (**8**) i.r. 1735 and 1710 cm^{-1} (C=O); n.m.r. δ 0.92 (3H, d, *J* 6.3 Hz, 10-Me), 1.17 and 1.24 (each 3H, each s, 2-Me_2), 1.57 and 1.86 (each 1H, each d, each *J* 13.4 Hz, 3-H_2), and 2.51(1H, dd, *J* 5, 2.5 Hz, 9-H); (**9**) i.r. 1730 cm^{-1} (C=O); n.m.r. δ 0.97 (3H, d, *J* 6.7 Hz, 9-Me), 1.06 and 1.14 (each 3H, each s, 2-Me_2), 1.75 and 2.11 (each 1H, each d, each *J* 12.8 Hz, 3-H_2), 2.51 (1H, t, *J* 7.9 Hz, 8-H), 2.63 (1H, q, *J* 7.3 Hz, 6-H), and 3.65 (3H, s, OMe).



Scheme 2. *Reagents and conditions:* i, CH_2=CH[CH_2]$_2$CHBrMe, Li powder, ultrasound, diethyl ether (70% yield); ii, PCC, Florisil, CH_2Cl_2, 18 °C (95%); iii, dicyclohexylborane, tetrahydrofuran (THF), 0 °C; 30% H_2O_2, NaOH, 40—50 °C (94%); iv, PCC, Florisil, CH_2Cl_2, 18 °C (91%); v, CH_2=$CHMgBr$, THF, −78 °C; aq. NH_4Cl (73%); vi, PDC, CH_2Cl_2, 18 °C (100%); vii, Me_3SiCl, Et_3N, $ZnCl_2$, CH_2Cl_2, 160 °C; 10% $HClO_4$, THF, 18 °C (52%); viii, HCO_2Et, NaOMe, diethyl ether, 0 °C (71%); ix, *p*-$MeC_6H_4SO_2N_3$, Et_3N, CH_2Cl_2, 18 °C (100%); x, *hν*, MeOH (100%); xi, KOH, MeOH, 18 °C; xii, NaH; Li, NH_3, MeOH, THF; xiii, CH_2N_2, MeOH [85% from (**9**)]; xiv, LDA, PhSeCl, THF, −78 to −30 °C; 30% H_2O_2, AcOH, THF, 0 °C (75%).

62—63 °C, was obtained in 52% yield along with its stereoisomer (**12**), m.p. 73—74 °C, (10% yield) by heating (**7**) together with an excess of Me_3SiCl, Et_3N, and $ZnCl_2$[10,11] in CH_2Cl_2 at 160 °C for 24 h in a sealed tube. Careful inspection by t.l.c. during the reaction indicated that the bis-enone (**7**) was directly converted into the tricyclic compounds (**8**) and (**12**), which were gradually transformed into a mixture of silyl enol ethers. Thus the annulation does not proceed *via* intramolecular Diels–Alder reaction of the siloxydiene but *via* intramolecular double Michael reaction. This is the first example of the intramolecular tandem conjugate addition of bis-enones.

Transformation of the tricyclo[7.3.0.$0^{1,5}$]dodecane (**8**) into the tricyclo[6.3.0.$0^{4,8}$]undecane (**9**)† was performed *via* Wolff rearrangement.[12] 500 MHz ^1H n.m.r. spectroscopy showed no nuclear Overhauser effect (n.O.e.) between 8-H and 9-Me in compound (**9**), while about 10% n.O.e. was observed for its isomer (**13**), derived from the minor product (**12**). This revealed therefore that the four contiguous asymmetric centres around the spiro atom of the major product (**8**) were correctly arranged as shown and this was confirmed by conversion of (**9**) into the natural product. The fifth asymmetric centre at the 1-position was correctly introduced by Birch reduction of the carbonyl group after conversion of the ester (**9**) into the corresponding acid. Treatment of the resulting alcoholic acid with diazomethane, followed by phenylselenylation of (**10**) with PhSeCl and lithium di-isopropylamide (LDA) and the successive oxidative elimination[13] furnished (±)-methyl pentalenate (**11**). The spectral data of (**11**) were identical with those of the authentic compound. Since the ester (**11**) has previously been hydrolysed to give (±)-pentalenic acid (**2**),[4a] the total synthesis of the triquinane is thus accomplished.

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