New Approaches to Quassinoid Synthesis. Structure of a New Michael Adduct

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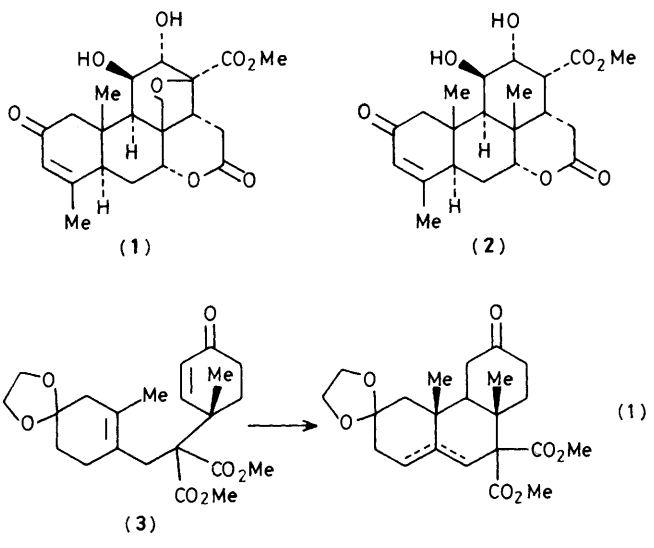
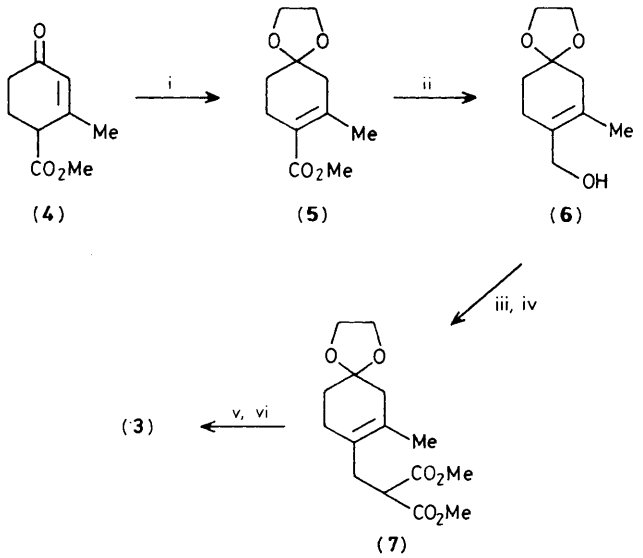
The structure of a new Michael addition product is reported from intermediates in a projected quassinoid synthesis.

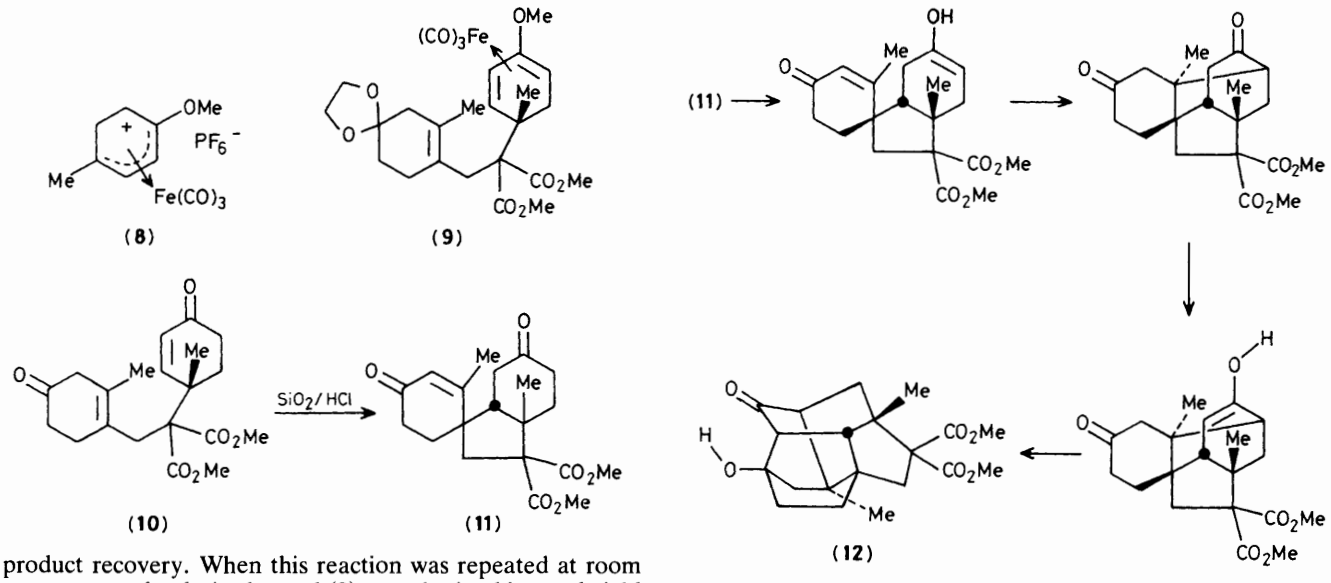
The isolation of the quassinoids Bruceantin (**1**)[1] and Klaineanone (**2**),[2] and the discovery that these compounds possess significant antitumour activity,[3] has resulted in considerable synthetic effort in this area.[4]

We now report our initial findings on the synthesis of (**2**) using the intramolecular coupling reaction shown in equation (1). Acetal (**3**) was prepared in high yield from Hagemanns ester (**4**) as shown in Scheme 1. Treatment of Hagemanns ester (**4**) with ethylene glycol and toluene-*p*-sulphonic acid in boiling benzene gave the acetal (**5**),[5] which was reduced with $LiAlH_4$ in diethyl ether to the allylic alcohol (**6**).[5] Reaction of (**6**) with hexamethylphosphorous triamide in CCl_4 gave an unstable allylic chloride,[6] which was immediately treated with sodio dimethyl malonate giving the ester (**7**) (58%). Addition of the iron tricarbonyl salt (**8**) to a solution of the potassium salt of (**7**) in tetrahydrofuran (THF) at 0 °C gave very low





Scheme 1. *Reagents:* i, $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_3H$, C_6H_6; ii, $LiAlH_4$; iii, $CCl_4/P(NMe_2)_3$; iv, $CH(CO_2Me)_2/NaH/THF$; v, KH/THF/room temp.; vi, (**8**).



Scheme 2

product recovery. When this reaction was repeated at room temperature the desired acetal (**9**) was obtained in good yield (68%).

Removal of iron from (**9**) was achieved using trimethylamine *N*-oxide in hot benzene and the resulting dienol ether was selectively hydrolysed to the enone (**3**) with oxalic acid in wet MeOH. When the acetal (**3**) was treated with toluene-*p*-sulphonic acid in acetone at room temperature, the diketone (**10**) was obtained as a very unstable oil, readily cyclising in acid to the spirocyclic ketone (**11**) in good yield (66%).

The spirocyclic ketone (**11**) was heated in benzene containing a catalytic amount of toluene-*p*-sulphonic acid in the hope of inducing a ring expansion. A single new compound (**12**)† was obtained from this reaction, as was evident from the ^{13}C n.m.r. spectrum.‡ Compound (**12**) is presumably formed by an intramolecular Michael addition, followed by an aldol condensation as shown in Scheme 2.

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† This compound has been fully analysed (i.r., m.s., n.m.r., C, H, N analysis).

‡ ^{13}C N.m.r. spectral assignments from δ values and off-resonance splittings (q, t, d, s) for a solution of (**12**) in $CDCl_3$ containing Me_4Si (there are no other signals) are listed below: 18.43 (q, Me), 21.23 (q, Me), 28.87 (t, CH_2), 33.49 (t, CH_2), 37.71 (t, CH_2), 40.08 (t, CH_2), 40.46 (s, C), 41.10 (s, C), 44.44 (s, C), 46.56 (t, CH_2), 51.36 (d, CH), 52.27 (q, Me), 52.52 (q, Me), 54.26 (d, CH), 55.30 (d, CH), 67.54 (s, C), 74.78 (s, C), 171.39 (s, C=O), 172.21 (s, C=O), 219.34 (s, C=O).

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