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SYNTHESIS OF THE INSECTICIDAL 1'-ACETOXY-MAMMEINS AND SURANGIN B

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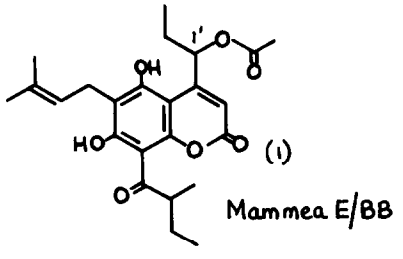
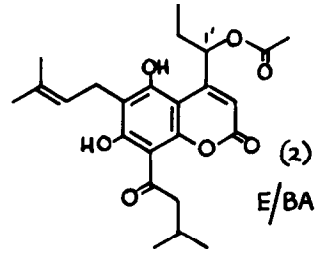
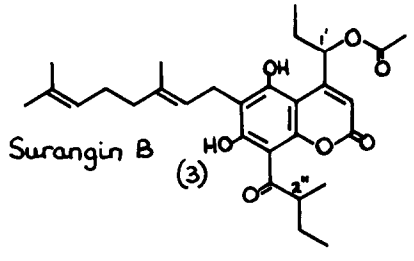
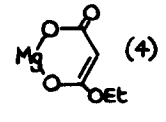
Summary: Methods are examined for the synthesis of 4-(1'-acetoxy) alkylcoumarins having hexasubstituted aromatic rings. This has led to synthesis of the three insecticidal coumarins mammea E/BB, mammea E/BA and surangin B.

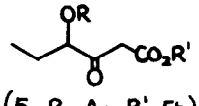
Although many coumarins from Mammea americana (preceding communication) uncouple oxidative phosphorylation, topical insecticidal activity resides mainly in non-crystalline liquors during isolation.[1] Eventually the latter yielded a crystalline mixture of two coumarins, mammea E/BB (1) and E/BA (2), more active topically than the liquors themselves.[1] About this time, surangin B (3) was reported from M.longifolia[2] and the 1'-acetoxy group led us to predict topical insecticidal activity: on testing, this was confirmed.[1] We now report the first synthesis of these structures. Synthetic constraints



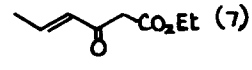


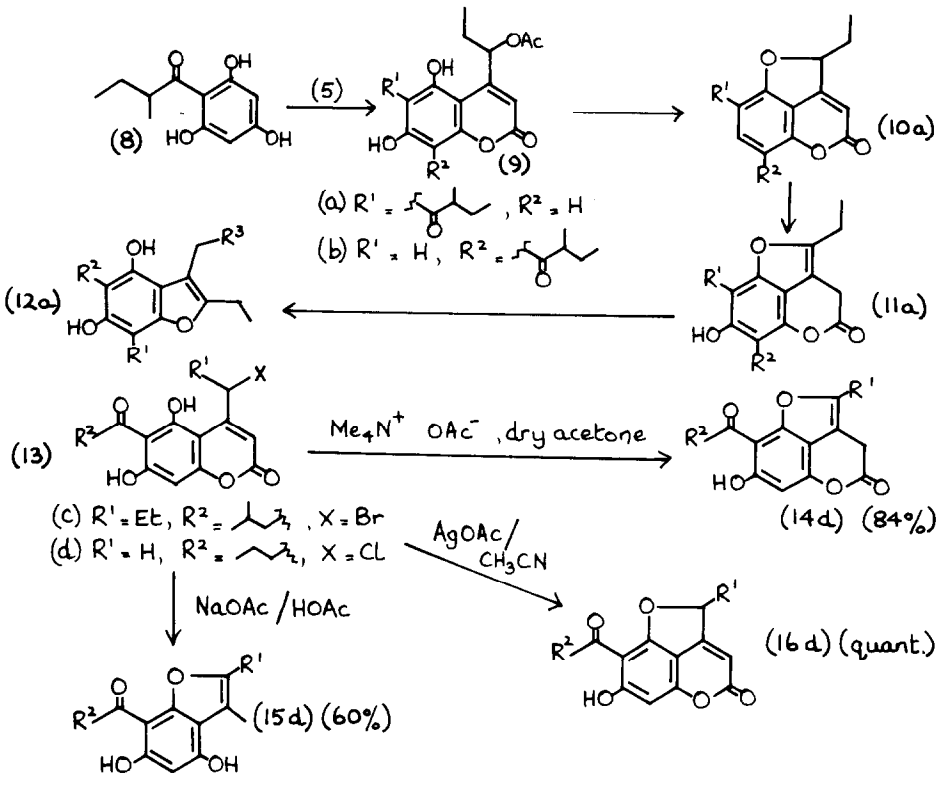






(5, R = Ac, R' = Et)
(6, R = H, R' = Me)

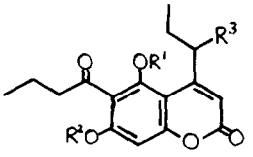




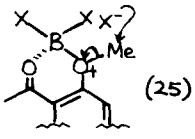
(preceding publication) are considerably increased by the 1'-acetoxy substituents.

Condensation of ethyl 3-oxo-4-acetoxyhexanoate (5) [from 2-acetoxybutyroyl chloride and (4)][3] with (2-methylbutyroyl)phloroglucinol (8) under our standard conditions (5% sulphuric in acetic acid) gave only traces of the desired coumarin together with small amounts of the benzofuran ester (12a; $R^3=CO_2Me$) (Me is solvent derived) and its decarboxylated relative (12a; $R^3=H$). Attempts to use (6) and (7) in a Pechmann reaction were not successful although 4-halogeno-acetoacetates gave limited yields of 1'-halogenocoumarins e.g. (13c,d). Their utility was limited however, as attempts to displace the 1'-halogen by acetoxy in (13d) for example, led to participation by the 5-hydroxyl forming (14d), (15d) and (16d).

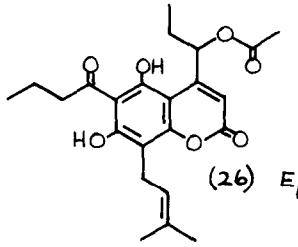
In an attempt to avoid such intervention, the diacetate (17) was made and then 1'-brominated using N-bromosuccinimide. Treatment of (18) with tetramethylammonium acetate again gave (14; $R^1=Et$, $R^2=Pr^n$) as its O-acetate. Attention was turned to the more durable methoxy protecting group and (19) was readily converted into (20) (quant.) with NBS and azo-bisisobutyronitrile. Tetramethylammonium acetate then gave the acetoxydimethyl ether (21) (82%).[4] Boron tribromide or trichloride at -78°C removed one methyl ether giving a mixture of (22) and (23) (90%) but increasing stringency of conditions failed to remove the second: presumably complexation (25) is required to facilitate



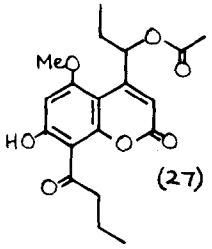
(17) $R' = R^2 = Ac$, $R^3 = H$
(18) $R' = R^2 = Ac$, $R^3 = Br$
(19) $R' = R^2 = Me$, $R^3 = H$
(20) $R' = R^2 = Me$, $R^3 = Br$
(21) $R' = R^2 = Me$, $R^3 = OAc$
(22) $R' = H$, $R^2 = Me$, $R^3 = OAc$
(23) $R' = Me$, $R^2 = H$, $R^3 = OAc$
(24) $R' = R^2 = H$, $R^3 = OAc$



(25)



(26) E/AC

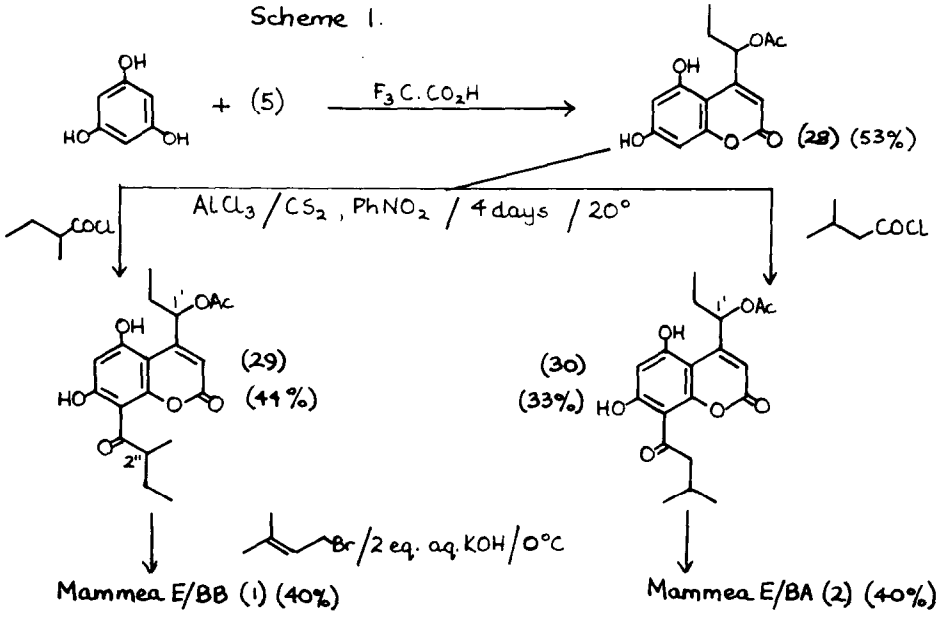


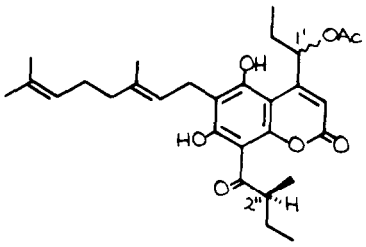
(27)

demethylation. The mixture of monomethyl ethers was therefore silylated and the mixed 1'-acetoxy trimethylsilyl/methyl ethers again demethylated with BBr_3. This gave (24) in 30% yield with 65% recovery of monomethyl ethers. Prenylation using prenyl bromide in the presence of 2 equiv. of aqueous 5% KOH at 0°C then gave mammea E/AC (26) (21%), the first, (though being 6-acyl not natural), 1'-acetoxycoumarin of the mammea series to be synthesised.[5]

Attempts to apply the methodology to the 8-acyl series proceeded in excellent yield as far as the monomethyl ether (27). The silylation stratagem could not now be effective, and despite many attempts, the second demethylation could not be accomplished whilst retaining the aliphatic acetoxy. The 1'-acetoxy-8-acyl series was successfully synthesised as in Scheme 1. Acylation

Scheme 1.





(31)

of the 1'-acetoxycoumarin (28), (made as shown) in the presence of aluminium chloride gave, in both series, predominantly 8-acyl coumarins which were separated from the 6-acyl. Prenylation by our established method then gave E/BB and E/BA, the former being a pair of (±)-diastereomers, the latter, a racemate.

Alkylation of (29) with geranyl chloride to reach surangin B required increase in severity of the reaction conditions, whilst avoiding hydrolysis of the 1'-acetate. Success was achieved by using 2 equiv. of aqueous 5% KOH at 40 - 45°C for 24 h under N_2, when surangin B (3), a pair of (±)-diastereomers (10%) was isolated: its p.m.r. spectrum was closely similar to that published for the natural product.[2] 5-O-Geranylated and 6,6-bisgeranylated side products also formed. Using (S)-(+)-2-methylbutyroyl chloride we have made (29) in 1'(R/S)-2"(S)-form: geranylation then gave surangin B as the 1'(R)-2"(S)/1'(S)-2"(S) pair of diastereomers (31). The stereochemistry of natural surangin B is at present unknown, but likely to be 2"(S) (preceding communication).

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References and Footnotes

1. L. Crombie, D.E. Games, N.J. Haskins and G.F. Reed, J.Chem.Soc., Perkin Trans.1, 1972, 2255.

2. B.S. Joshi, V.N. Kamat, T.R. Govindachari and A.K. Ganguly, Tetrahedron, 1969, 25, 1453.

3. P. Pollet and S. Gelin, Synthesis, 1978, 142; Tetrahedron, 1978, 34, 1453. The best of five recent methods tried (88% yield).

4. The X-ray structure of coumarin (21) has been determined in our laboratory by Dr. M.J. Begley, providing a reference point for the 6-acyl orientation.

5. For some model studies on simpler systems see C.W. Bird, H.I. Butler and A. Hawi, Chem.Ind. (London), 1984, 154.

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