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SYNTHESIS OF MAMMEINS AND SURANGIN A

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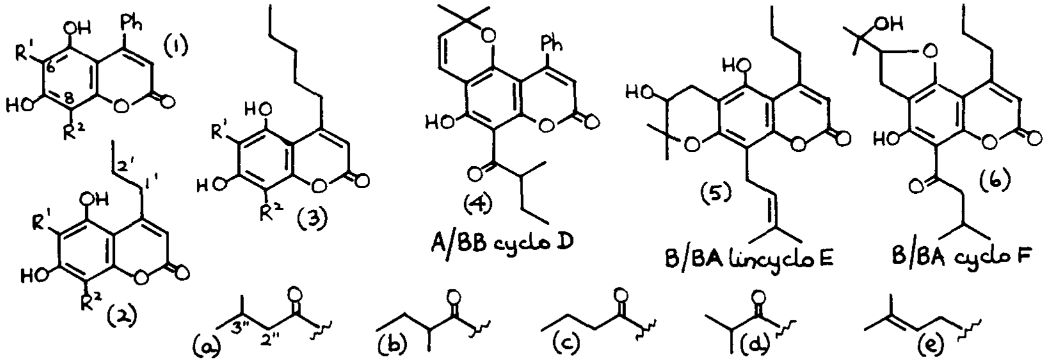
Summary: Syntheses of natural 4-alkyl and 4-aryl coumarins with hexasubstituted aromatic rings, uncouplers of oxidative phosphorylation, are reported. Mammea B/BB, by synthesis, is the (S)-(-)-compound.

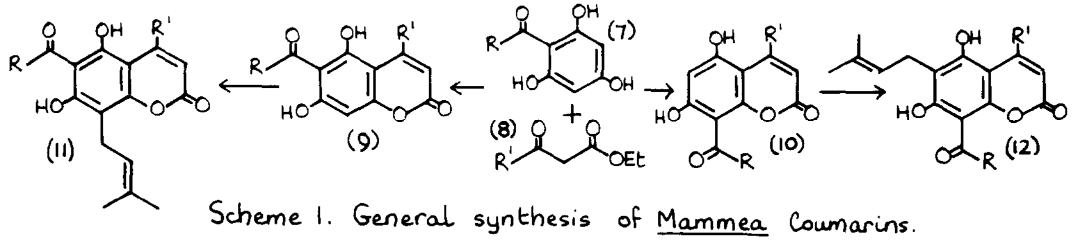
Kernels of the fruit of the West Indian mamey tree, Mammea americana L. (Guttiferae), have been used as insecticidal material and extraction has led to the isolation of coumarins of general type (1)-(6).[1,2] Similar compounds occur in M. africana.[3] Many of these coumarins affect electron transport, uncouple oxidative phosphorylation,[3] and have appreciable anti-cancer activity towards Sarcoma 180 tumor cells.[4] Supply of natural materials has been sparse, and we have undertaken to make them readily available .



A/AA ; [1, R' = (a), R² = (e)]
A/AB ; [1, R' = (b), R² = (e)]
A/AD ; [1, R' = (d), R² = (e)]
A/BA ; [1, R' = (e), R² = (a)]
A/BB ; [1, R' = (e), R² = (b)]
A/BD ; [1, R' = (e), R² = (d)]*
C/BB ; [3, R' = (e), R² = (b)]
C/AB ; [3, R' = (b), R² = (e)]*

B/AA [2, R' = (a), R² = (e)]
B/AB [2, R' = (b), R² = (e)]
B/AC [2, R' = (c), R² = (e)]
B/AD [2, R' = (d), R² = (e)]
B/BA [2, R' = (e), R² = (a)]
B/BB [2, R' = (e), R² = (b)]
B/BC [2, R' = (e), R² = (c)]
B/BD [2, R' = (e), R² = (d)]

*not yet isolated naturally



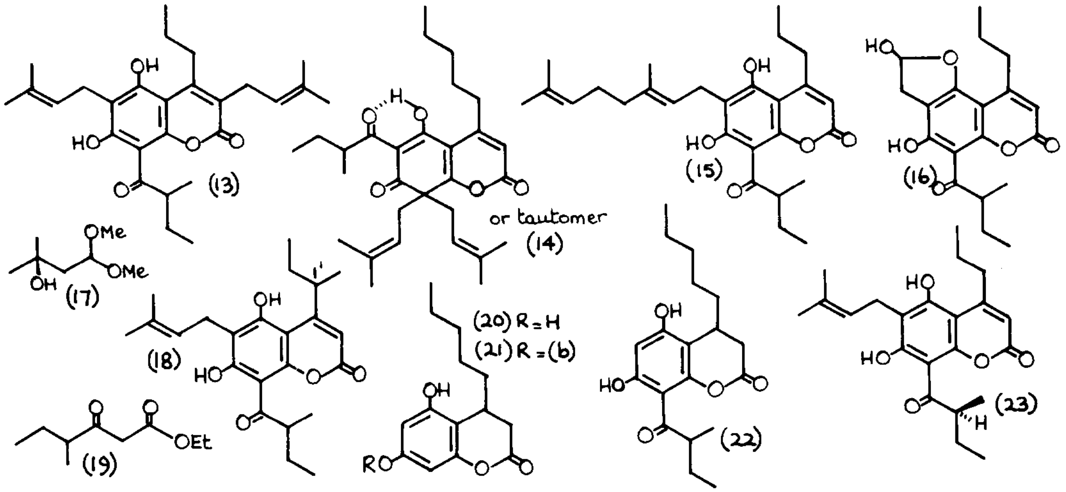
Scheme 1. General synthesis of Mammea Coumarins.

Structures of type (1)-(3) having a hexasubstituted aromatic ring are sterically compressed and being densely functionalised, constraints appear. An acyl group deactivates the phloroglucinol ring towards Pechmann condensation, but stronger acid catalysis causes deacylation and can cyclise the prenyl group. Base conditions can effect 8-acyl to 6-acyl rearrangement *via* lactone opening, and also cause deacylation. Prenylation faces problems of ambident *O*- versus *C*-alkylation. Further constraints appear in connection with the important 1'-acetoxy series (following communication). Our general approach is shown in Scheme 1.

Acylation of phloroglucinol with units (a)-(d) *via* the acid chlorides using 4 mol of aluminium chloride in CS_2-$PhNO_2$, refluxing 1-2 h, gave (7a-7d) in approx. 80% yield.[5] Pechmann reaction (5% sulphuric in acetic acid) with keto-esters (8) gave unbranched 4-alkyl coumarins [6-acyl (9), 8-acyl (10) mixture] in 70% yield; alkyl branching at C-1' however prevented reaction. The 4-phenyl case gave lower yields (35%). The 8-acyl/6-acyl compounds (∿ 2:3) can be separated by crystallisation or chromatography, orientations being recognised by UV-spectra with alkaline shifts.[6] Best prenylation conditions for the sixth aromatic substituent (exclusive *C*-alkylation) used prenyl bromide with 10% potassium hydroxide in water at 0°C. Yields were 20-35%, or 30-45% allowing for material recovered,[7] and similar results were obtained with the dipotassium salt of the phenol in $F_3C.CH_2OH$ at 0°C. In alkylation to give mammea B/BB, (13) was a by-product (1%) and in the case of C/AB, bis-alkylated (14) (6%). The 16 coumarins listed as A/AA to B/BD were synthesised as in Scheme 1.

Alkylation of (10;$R'=Pr^n$, $R=CH(Me)CH_2Me$) with geranyl chloride/10% potassium hydroxide (2 mol) at 40-45°C (24 h) gave (±)-surangin A (15) (7%), spectrally identical with natural from *M. longifolia*:[9] 5-*O*-geranyl product (6%) also formed along with 6,6-bisgeranylated enolic dione (*cf*. 14) (5%). As an alternative to direct geranylation, the masked aldehyde (16), suitable for elaboration, can be obtained from mammea B/BB by OsO_4/$NaIO_4$ degradation (43%).

Using (9) and (10), chromens like (4) were obtained (70-75%) on heating with the dimethylacetal of 3-methyl-3-hydroxybutyraldehyde (17) in pyridine.[8,10] Eight cyclo F compounds of type (6) were made (50-70%) by treating mammeas A/AA, A/AB, B/AA, B/AB, B/AC, B/BA, B/BB and B/BC with *m*-chloroperbenzoic acid in dichloromethane,[2a] and similar reactions in the presence of *p*-TSA[2a] gave linear cyclo E compounds (50%), such as (5), from mammeas B/BA, B/BB and B/BC.



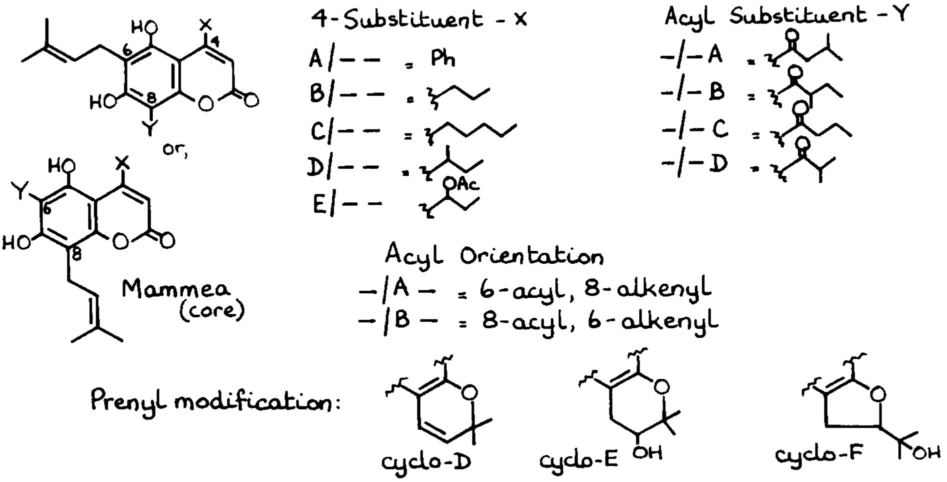
The 1'-branched alkyl case, ferruol A (18) (mammea D/BB), from Mesua ferrea[11], was made by carrying out a Pechmann reaction between (19) and phloroglucinol in 75% sulphuric acid. The 4-(1'-methylpropyl) coumarin (28%) was acylated with 2-methylbutyroyl chloride [aluminium chloride/nitrobenzene (20°C/6 days)] to give largely 8-acyl product (43%). Prenylation (22%) gave ferruol A (18), a pair of diastereomers, with n.m.r. data virtually identical with natural.[11] Dihydromammea C/BB-O (22) from Mammea africana[12] was also synthesised: Pechmann condensation between phloroglucinol and 3-oxo-octanoic ester, gave the expected coumarin (64%), hydrogenated (Pd/C, 50 Ats.) to (20) (62%). Treatment of the latter with 2-methylbutyroyl chloride and 4 mol. aluminium chloride in nitrobenzene for 15 min. gave the 7-O-acyl derivative (21) (53%) along with 5-O-acyl (12%) and bis-O-acyl (14%) products. Sterner conditions caused Fries rearrangement giving (22) (40% overall) with no evidence of 6-acyl product.

Natural mammea B/BB has the (S)-configuration (23) by synthesis. (S)-(+)-2-Methylbutyric acid $[\alpha]_D^{25}$ + 16.0°, as its acid chloride, was used to acylate ($AlCl_3/PhNO_2$) 4-propyl-5,7-dihydroxycoumarin. The 8-acyl was the major product, probably via a Fries mechanism. Prenylation then gave (S)-(-)-mammea B/BB (23), m.p. 121 - 122°, $[\alpha]_{589}$ - 2.78°, $[\alpha]_{546}$ - 3.87° (Lit.[4] for natural $[\alpha]_{589}$ - 2.93°; $[\alpha]_{546}$ - 4.14°).

We thank the Wellcome Foundation Ltd. and SERC for a CASE award (C.J.P.).

References and Footnotes

1. Codification of Mammea americana extractives is as follows:



2. Inter alia (a) L. Crombie, D.E. Games, N.J. Haskins and G.F. Reed, J.Chem.Soc., Perkin Trans.1, 1972, 2241, 2248, 2255; (b) L. Crombie, D.E. Games and A. McCormick, J.Chem.Soc.,(C), 1967, 2545, 2553. (c) C. Djerassi, E.J. Eisenbraun, R.A. Finnegan and B. Gilbert, J.Org.Chem., 1960, 25, 2164, 2169. (d) D.E. Games, Tetrahedron Lett., 1972, 3187.

3. I. Carpenter, E.J. McGarry and F. Scheinmann, J.Chem.Soc.,(C), 1971, 3783.

4. R.A. Finnegan, K.E. Merkel and N. Back, J.Pharm.Sci., 1972, 61, 1599.

5. Smaller $AlCl_3$ ratios, as in the earlier literature, lower the yield in acylations of this type.

6. The criteria were developed from pairs of orientations assessed by Gibbs reactions:[2a] we have lately confirmed them by an X-ray structure mentioned in the following communication.

7. Reaction of similar acyl coumarins with 3-methylbut-3-en-2-ol and BF_3 gave prenylated compounds in 0.3 to 9% yield.[8]

8. D.E. Games and N.J. Haskins, J.Chem.Soc., Chem.Commun., 1971, 1005.

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

10. W.M. Bandaranayake, L. Crombie and D.A. Whiting, J.Chem.Soc.(C)., 1971, 811.

11. T.R. Govindachari, B.R. Pai, P.S. Subramanian, U. Ramdas Rao and N. Muthukumaraswamy, Tetrahedron, 1967, 23, 4161.

12. E.G. Crichton and P.G. Waterman, Phytochemistry, 1978, 17, 1783.

13. This confirmed the orientation. An X-ray study (C.H. Schwalbe, P.G. Waterman and E.G. Crichton, R.S.C. Crystallography Group Meeting, Leeds, September 1981) reached the same conclusion.

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