Synthesis of the *Mammea* Coumarins. Part 4.[1] Stereochemical and Regiochemical Studies, and Synthesis of (−)-Mammea B/BB

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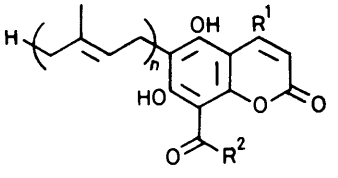
Acylation of phloroglucinol with (*S*)-2-methylbutyryl chloride followed by Pechmann condensation with ethyl 3-oxohexanoate, or acylation of 5,7-dihydroxy-4-propylcoumarin with (*S*)-2-methylbutyryl chloride, gave an 8-(*S*)-acylcoumarin that was *C*-alkylated to afford natural (−)-mammea B/BB; the configuration of the 2-methylbutyryl moiety in the natural coumarins was thus demonstrated to be (*S*). Surangin B was likewise prepared as a mixture of (1′*S*,2″*S*)- and (1′*R*,2″*S*)-stereoisomers. The crystal structure and conformation of a 6-acylcoumarin that establishes the orientation of other synthetic coumarins is reported.

The group of nearly fifty *Mammea* coumarins, natural products isolated principally from the insecticidal tree *Mammea americana* as well as from *M. africana*, *M. longifolia*, *Mesua ferrea* and *Mesua thwaitesii*, share a common 4-alkyl- or 4-aryl-5,7-dioxygenated coumarin skeleton.[2] The aromatic ring also carries an acyl group at the 6- or 8-position, and the remaining position (8- or 6-) is generally substituted with a 3-methylbut-2-enyl (prenyl) group or, less commonly, with a 3,7-dimethylocta-2,6-dienyl (geranyl) residue. Further natural products display oxidative modification of the prenyl group involving cyclisation onto an *ortho* hydroxy group. The general structure of an 8-acyl-4-alkyl *Mammea* coumarin can thus be represented as in (**1**). When the acyl group is 2-methylbutyryl (mammeas -/-B) a chiral centre is introduced into the molecule, and in the insecticidal mammea E series of natural coumarins another chiral centre is present at C-1′ in the 4-(1-acetoxypropyl) moiety. Optical activity is possible in these coumarins, and indeed has been reported in a number of cases, *e.g.* for mammea B/BB (**1a**),[3] and for the geranyl coumarins surangin A (**1b**) and the insecticidal and antibacterial surangin B (**1c**).[4] The inseparable mixture of insecticidal prenylcoumarins mammea E/BA (**1d**) and E/BB (**1e**) has also been reported to have



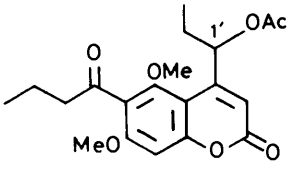
(**1**) **a**; n = 1, R^1 = $(CH_2)_2Me$, R^2 = $CH^{2''}MeCH_2Me$
b; n = 2, R^1 = $(CH_2)_2Me$, R^2 = $CH^{2''}MeCH_2Me$
c; n = 2, R^1 = $CH^{1'}(OAc)CH_2Me$, R^2 = $CH^{2''}MeCH_2Me$
d; n = 1, R^1 = $CH^{1'}(OAc)CH_2Me$, R^2 = CH_2CHMe_2
e; n = 1, R^1 = $CH^{1'}(OAc)CH_2Me$, R^2 = $CH^{2''}MeCH_2Me$

optical activity,[5] as have some mixtures of mammea cyclo F coumarins,[3,6] and 8-(2-methylbutyryl)-4-pentyl-3,4-dihydrocoumarin isolated from *Mammea africana*.[7] No stereochemical investigations have yet been reported in this series, either of the absolute configurations of (**1a**—**c**), or of the relative configuration of (**1c**), with its two chiral centres.

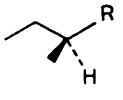
As part of a synthetic programme for the *Mammea* coumarins, we have previously reported syntheses of the majority of the naturally-occurring coumarins of this group, with any optical centres in the (±)-form.[1] We now report our stereochemical investigations that have culminated in the synthesis of natural (−)-mammea B/BB (**4b**), identifying its absolute configuration as (*S*) in the 2-methylbutyryl unit, and our efforts to determine the chirality of the 4-(1-acetoxypropyl) substituent in surangin B (**1c**). In addition we report details herein of an *X*-ray crystallographic determination of the structure of the synthetic 4-(1-acetoxypropyl)-6-acylcoumarin (**2**) which confirms the structure shown, and substantiates the assignment of all our other synthetic coumarins to the 6- or 8-acyl series based on u.v. data and the Gibbs test.

Results and Discussion

The methods developed earlier in the synthesis of racemic *Mammea* coumarins[1] were considered suitable for application in the synthesis of optically active mammea B/BB (**1a**). The requirement was thus for optically active 2-methylbutyric acid as a starting material. Both (*R*)- and (*S*)-configurations have been reported for the 2-methylbutyryl residues contained in various natural product structures. The choice of enantiomeric series in which to initiate our studies was thus influenced by the ready commercial availability of (*S*)-(−)-2-methylbutan-1-ol (**3a**) which could be oxidised to provide (*S*)-(+)-2-methylbutyric acid (**3b**).



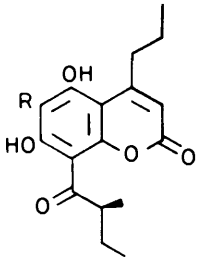
(**2**)



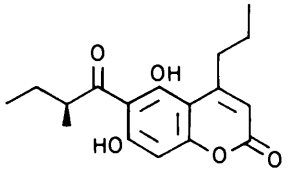
(**3**) **a**; R = CH_2OH
b; R = CO_2H
c; R = COCl
d; R = $COC_6H_2(OH)_3$-2,4,6

Three previously reported methods of oxidation (*i.e.* $KMnO_4$–KOH, CrO_3–AcOH, and $Na_2Cr_2O_7$–H_2SO_4) have been shown to result in some degree of racemisation.[8] The best of these, for example, was said to convert (*S*)-(−)-2-methylbutan-1-ol (**3a**), $[\alpha]_D$ −5.8° (neat), to (*S*)-(+)-2-methylbutyric acid (**3b**) having $[\alpha]_D$ +4.4° (neat) {lit.,[9] $[\alpha]_D$ +19.2° (neat)}. After some initial disappointing experimentation we found that distilled commercially available (**3a**), $[\alpha]_D$ −4.81° (neat), could be oxidised without appreciable racemisation using aqueous potassium permanganate–sodium carbonate to give (**3b**) having $[\alpha]_D$ + 16.04° (neat). This material was treated with thionyl chloride and the (*S*)-(+)-2-methylbutyryl chloride (**3c**) produced was used in two alternative approaches to mammea B/BB.

Firstly, phloroglucinol was acylated with (**3c**) in the presence of aluminium trichloride to afford (*S*)-(+)-(2-methylbutyryl)-phloroglucinol (**3d**) in good yield. Pechmann condensation of (**3d**) with ethyl 3-oxohexanoate in glacial acetic acid containing sulphuric acid gave, as expected, a mixture of *ca.* equal proportions of 8- and 6-(*S*)-acylcoumarins, (**4a**) and (**5**) respectively, from which the required (*S*)-(−)-5,7-dihydroxy-8-(2-methylbutyryl)-4-propylcoumarin (**4a**), $[\alpha]_D^{25}$ −5.4° (*c* 0.46, in ethanol), was obtained (27%) by crystallisation. Alternatively, acylation of 5,7-dihydroxy-4-propylcoumarin with the (*S*)-acid chloride (**3c**), mediated by aluminium trichloride, again afforded a mixture of the acylcoumarins (**4a**) and (**5**) but containing predominantly the desired 8-acyl isomer (**4a**).



(**4**) **a**; R = H
b; R = $CH_2CH{=}CMe_2$

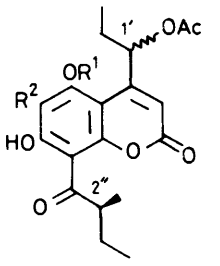


(**5**)

Crystallisation gave (**4a**) (26%) of better optical purity than from the Pechmann condensation, having $[\alpha]_D^{25}$ −7.33° (*c* 0.6, in ethanol). Finally the (*S*)-(−)-8-acylcoumarin (**4a**) was *C*-alkylated with prenyl bromide in 10% aqueous potassium hydroxide to give the (*S*)-(−)-coumarin (**4b**) having an optical rotation at two wavelengths of the same sign and very similar magnitude to that reported[3] for natural mammea B/BB. The absolute configuration of the 2-methylbutyryl unit in mammea B/BB is thus shown to be (*S*), and we suggest that it is likely that this subunit in other *Mammea* coumarins also possesses the (*S*)-configuration.

Our attention was next turned to the configuration of the 4-(1-acetoxypropyl) substituent of the insecticidal mammea E coumarins, exemplified by surangin B (**1c**). In our previous synthetic studies both this centre (C-1′) and C-2″ were present in both *R*- and *S*-forms, and we had therefore prepared a mixture of the four optical isomers of (**1c**), *i.e.* (±)-surangin B and its diastereoisomer, also racemic, which could not at that time be separated.[1c] It was decided to re-synthesize (**1c**) now containing an optically active 2-methylbutyryl moiety and reduce the mixture to only two of the four possible stereoisomers; using the (*S*)-2-methylbutyryl group, for example, would lead to the (1′*S*,2″*S*) and (1′*R*, 2″*S*) diastereoisomers that it was hoped with further effort might be separable. If it is assumed that the 2-methylbutyryl substituent in surangin B has the same (*S*)-configuration as found in mammea B/BB (see above), then one of these components would correspond to natural (−)-surangin B and determination of the relative configuration at C-1′ and C-2″ (for example by *X*-ray methods) would reveal the absolute stereochemistry at C-1′. Conversely, in the (presumably less likely) instance of surangin B (**1c**) having the (2″*R*)-configuration, the same component of the diastereoisomer mixture would correspond to the (+)-enantiomer of surangin B and determination of the relative configuration would still allow deduction of the absolute stereochemistry of the natural material.

Accordingly (±)-4-(1-acetoxypropyl)-5,7-dihydroxycoumarin was subjected to acylation by (*S*)-(+)-2-methylbutyryl chloride in the presence of aluminium trichloride to produce the (1′*RS*,2″*S*)-8-(2-methylbutyryl)coumarin (**6a**). Alkylation



(**6**) **a**; $R^1 = R^2 = H$
b; $R^1 = (CH_2CH{=}CMeCH_2)_2H$, $R^2 = H$
c; $R^1 = H$, $R^2 = (CH_2CH{=}CMeCH_2)_2H$

with geranyl chloride in 5% aqueous potassium hydroxide, as in the non-optically active series, gave a mixture of *O*- and *C*-alkylated coumarins. These were separated by h.p.l.c. to afford, along with the 5-*O*-geranylcoumarin (**6b**), the 6-*C*-geranyl product (**6c**) as a mixture of (1′*S*, 2″*S*) and (1′*R*, 2″*S*) diastereoisomers that it was anticipated would contain natural (−)-surangin B. Unfortunately this mixture could not be separated further by fractional crystallisation or h.p.l.c., including the use of a Pirkle chiral stationary phase.[10]

Having been thwarted in this synthetic approach we next obtained a small sample of natural surangin B.[11] Crystals deposited from either dichloromethane–hexane or ethanol–water have, however, not to date proved amenable to an *X*-ray crystallographic analysis, and the configuration at C-1′ remains undetermined.

All of the structural assignments of synthetic acylcoumarins prepared during our programme to either the 6- or 8-acyl series are based on u.v. spectral correlations and the Gibbs test (which identifies materials with an unsubstituted carbon *para* to a phenolic group on an aromatic ring).[1a] To substantiate these assignments an *X*-ray analysis of an acylcoumarin was required and, after several other derivatives were examined unsuccessfully, the 4-(1-acetoxypropyl)-6-butyryl-5,7-dimethoxycoumarin (**2**)[1b] was found to afford suitable crystals. The coumarin (**2**) crystallised from hexane–chloroform in white orthorhombic crystals, space group $P2_12_12_1$, a = 8.543(1), b = 10.273(1), and c = 22.812(2) Å, with four molecules per unit cell.

The *X*-ray structure was solved by direct methods using diffractometer data (see the Experimental section) to R = 5.47% over 1 773 independent observed reflections. The structure was confirmed as the 6-acyl derivative (**2**) while Figure 1 shows the conformation of the molecule and carries the atomic numbering scheme adopted for crystallographic purposes (and

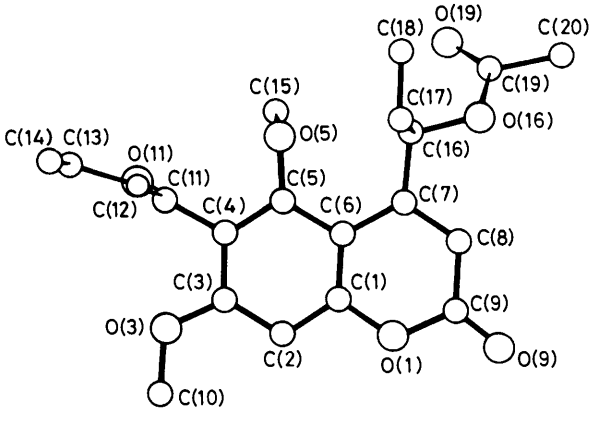


Figure. Crystal structure of compound (**2**) and crystallographic numbering scheme.

Table 1. Bond lengths in Å with standard deviations in parentheses

C(1)–C(2)	1.368(6)	C(9)–O(1)	1.372(6)
C(1)–C(6)	1.403(6)	C(9)–O(9)	1.197(5)
C(1)–O(1)	1.381(5)	C(10)–O(3)	1.439(6)
C(2)–C(3)	1.385(7)	C(11)–C(12)	1.521(8)
C(3)–C(4)	1.395(6)	C(11)–O(11)	1.195(6)
C(3)–O(3)	1.370(6)	C(12)–C(13)	1.468(9)
C(4)–C(5)	1.372(6)	C(13)–C(14)	1.427(11)
C(4)–C(11)	1.494(6)	C(15)–O(5)	1.414(7)
C(5)–C(6)	1.427(6)	C(16)–C(17)	1.542(9)
C(5)–O(5)	1.367(5)	C(16)–O(16)	1.466(6)
C(6)–C(7)	1.458(6)	C(17)–C(18)	1.464(9)
C(7)–C(8)	1.361(7)	C(19)–C(20)	1.480(7)
C(7)–C(16)	1.518(6)	C(19)–O(16)	1.337(6)
C(8)–C(9)	1.436(7)	C(19)–O(19)	1.213(6)

Table 2. Bond angles in degrees with standard deviations in parentheses

C(2)–C(1)–C(6)	123.9(4)	C(8)–C(9)–O(1)	117.2(4)
C(2)–C(1)–O(1)	115.0(4)	C(8)–C(9)–O(9)	126.4(5)
C(6)–C(1)–O(1)	121.1(4)	O(1)–C(9)–O(9)	116.2(5)
C(1)–C(2)–C(3)	118.5(4)	C(4)–C(11)–C(12)	113.4(4)
C(2)–C(3)–C(4)	120.7(4)	C(4)–C(11)–O(11)	122.1(5)
C(2)–C(3)–O(3)	125.2(4)	C(12)–C(11)–O(11)	124.6(5)
C(4)–C(3)–O(3)	114.1(4)	C(11)–C(12)–C(13)	117.1(6)
C(3)–C(4)–C(5)	119.8(4)	C(12)–C(13)–C(14)	116.0(7)
C(3)–C(4)–C(11)	119.5(4)	C(7)–C(16)–C(17)	109.9(4)
C(5)–C(4)–C(11)	120.5(4)	C(7)–C(16)–O(16)	108.0(4)
C(4)–C(5)–C(6)	121.6(4)	C(17)–C(16)–O(16)	107.1(5)
C(4)–C(5)–O(5)	118.2(4)	C(16)–C(17)–C(18)	114.3(6)
C(6)–C(5)–O(5)	120.2(4)	C(20)–C(19)–O(16)	111.2(4)
C(1)–C(6)–C(5)	115.4(4)	C(20)–C(19)–O(19)	125.6(5)
C(1)–C(6)–C(7)	118.0(4)	O(16)–C(19)–O(19)	123.3(5)
C(5)–C(6)–C(7)	126.7(4)	C(1)–O(1)–C(9)	122.2(4)
C(6)–C(7)–C(8)	118.6(4)	C(3)–O(3)–C(10)	117.9(4)
C(6)–C(7)–C(16)	121.6(4)	C(5)–O(5)–C(15)	114.2(4)
C(8)–C(7)–C(16)	119.4(4)	C(16)–O(16)–C(19)	117.9(4)
C(7)–C(8)–C(9)	122.7(5)		

Table 3. Selected torsion angles

C(2)–C(3)–O(3)–C(10)	12.7
C(5)–C(4)–C(11)–O(11)	87.7
C(4)–C(5)–O(5)–C(15)	−84.8
C(8)–C(7)–C(16)–O(16)	20.5

used in the remainder of this paragraph). Bond lengths and angles are listed in Tables 1 and 2, respectively, together with their standard deviations. In general these adopt expected values although it is interesting that the substituents at C(5) and C(7) create the greatest strain in the coumarin ring with C(5)–C(6) and C(6)–C(7) much the longest bonds and the C(5)–C(6)–C(7) bond angle of 126.7° showing the largest distortion. The foreshortened bond lengths in the side chains are associated with their greater thermal motion. As expected the coumarin ring system is completely planar with no atom further than 0.06 Å away from the mean plane. The conformation of the substituents on the ring is demonstrated in Table 3 showing the appropriate torsion angles. The methoxy at C(3) is located in the ring plane allowing potential conjugation. However, the overcrowding at C(4) and C(5) has forced both substituents to be twisted approximately 90° to be perpendicular to the ring plane totally destroying any potential conjugation. The conformation of the substituent at C(7) is such that the oxygen atom [O(16)] is sited in the plane of the coumarin ring and *anti* to C(6).

It had not earlier been possible to assign unambiguously all the signals in the ^{1}H n.m.r. spectrum of (**2**) at 99.8 MHz in $CDCl_3$). In particular the allocation of two singlets at δ 6.24 and 6.62 between the protons at C-8 and C-3 was uncertain. A complete assignment was, however, possible in a different solvent and using the nuclear Overhauser enhancement. When the spectrum was recorded in C_6D_6 at 250 MHz these same signals were observed at δ 6.15 and 6.50, the latter now as a doublet, *J* 0.9 Hz; the same small allylic coupling was also discerned in an eight line signal at δ 6.3 corresponding to the methine proton at C-1′ (recorded as a double doublet at 99.8 MHz in $CDCl_3$). The two methoxy groups gave rise to separate signals at δ 3.0 and 3.7 (at 99.8 MHz in $CDCl_3$ the resonance due to the methoxy groups was a six-proton singlet), and irradiation of the singlet at δ 3.7 resulted in enhancement of only the signal at δ 6.3 (1′-H) whereas irradiation of the singlet at δ 3.0 led to enhancement only of the singlet at δ 6.15. These observations suggest that the singlet at δ 6.15 corresponds to 8-H whilst the doublet at δ 6.50 can be assigned to 3-H, and also that the methoxy groups at C-7 and C-5 give rise to the resonances at δ 3.0 and 3.7, respectively. The enhancement of only 1′-H on irradiation of the 5-methoxy group is consistent with the conformation found for (**2**) in the solid state (see above).

Table 4. Atomic co-ordinates with standard deviations in parentheses

Atom	*x/a*	*y/b*	*z/c*
C(1)	0.422 9(6)	0.190 7(4)	0.322 7(2)
C(2)	0.499 2(6)	0.291 1(4)	0.349 8(2)
C(3)	0.573 4(5)	0.266 9(4)	0.402 7(2)
C(4)	0.575 8(5)	0.141 8(4)	0.426 4(2)
C(5)	0.498 8(5)	0.042 5(4)	0.398 4(2)
C(6)	0.413 6(5)	0.064 1(4)	0.345 4(2)
C(7)	0.319 1(5)	−0.030 9(4)	0.313 8(2)
C(8)	0.254 0(7)	0.004 6(5)	0.261 8(2)
C(9)	0.267 9(6)	0.133 7(5)	0.238 2(2)
C(10)	0.622 6(8)	0.493 4(4)	0.422 3(3)
C(11)	0.651 2(6)	0.119 4(4)	0.484 7(2)
C(12)	0.543 6(8)	0.148 3(8)	0.536 2(3)
C(13)	0.615 6(11)	0.154 4(10)	0.594 6(3)
C(14)	0.516 3(10)	0.196 9(12)	0.641 1(3)
C(15)	0.635 7(9)	−0.152 8(5)	0.409 0(3)
C(16)	0.275 6(7)	−0.161 0(5)	0.340 9(2)
C(17)	0.143 7(9)	−0.141 9(6)	0.386 2(3)
C(18)	0.100 4(11)	−0.260 4(8)	0.418 0(3)
C(19)	0.279 8(6)	−0.360 7(5)	0.286 2(2)
C(20)	0.199 2(7)	−0.434 7(5)	0.239 4(3)
O(1)	0.349 3(4)	0.223 2(3)	0.270 8(1)
O(3)	0.647 7(4)	0.358 4(3)	0.436 3(2)
O(5)	0.501 7(4)	−0.078 5(3)	0.423 3(1)
O(9)	0.208 2(5)	0.173 5(4)	0.194 2(2)
O(11)	0.782 5(5)	0.080 5(4)	0.489 1(2)
O(16)	0.213 1(4)	−0.244 3(3)	0.294 3(2)
O(19)	0.392 5(5)	−0.398 0(4)	0.313 8(2)

Experimental

General directions are as in Parts 1 and 2.[1] (*S*)-(−)-2-Methylbutan-1-ol was supplied by Aldrich Chemical Co. Ltd., and optical rotations were measured on an ETL-NPL Automatic Polarimeter Type 143A.

(S)-(+)-2-*Methylbutyric Acid* (**3b**).—Freshly distilled (*S*)-(−)-2-methylbutan-1-ol (**3a**) {61.6 g, 0.7 mol; $[\alpha]_D^{25}$ −4.81° (neat)}, and sodium carbonate (15 g) in water (150 ml) was stirred vigorously at 0 °C during the addition of potassium permanganate (142 g) in water (2.75 l) dropwise over 3—4 h. Stirring was continued for a further 12 h before the solution was

filtered and the filtrate evaporated to low volume, acidified, and extracted with ether. The combined extracts were dried and evaporated, and the residue was distilled to afford (*S*)-(+)-2-methylbutyric acid (**3b**) (39.12 g, 55%), $[\alpha]_D^{25}$ +16.04° (neat) {lit.,[9] $[\alpha]_D^{25}$ +19.2° (neat)}, that had an identical ^{1}H n.m.r. spectrum to that of the commercially available racemic material.

(S)-(+)-2-*Methylbutyryl Chloride* (**3c**).—(*S*)-(+)-2-Methylbutyric acid (**3b**) (30.6 g, 0.3 mol) and thionyl chloride (36 g, 0.3 mol) were heated together at reflux for 2 h. Distillation afforded (*S*)-(+)-2-methylbutyryl chloride (**3c**) (28.75 g, 80%), b.p. 114—120 °C (lit.,[9] 119—120 °C); $[\alpha]_D^{25}$ +12.07° (neat); δ 0.98 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.25 (3 H, d, *J* 7 Hz, *Me*CH), 1.5—1.9 (2 H, m, MeCH_2CH), 2.84 (1 H, m, CH_2CH).

(S)-(+)-(2-*Methylbutyryl*)*phloroglucinol* (**3d**).—This was prepared by our general method (see Part 1[1]) from phloroglucinol (6.3 g, 0.05 mol) and (*S*)-(+)-2-methylbutyryl chloride (**3c**) (6.0 g, 0.05 mol), in nitrobenzene (30 ml) and carbon disulphide (30 ml) in the presence of aluminium trichloride (27.6 g, 0.2 mol). The usual work-up gave (*S*)-(+)-(2-methylbutyryl)phloroglucinol (**3d**) (8.8 g, 84%), $[\alpha]_D^{25}$ +17.23° (*c* 18.9, in ethanol), which had an identical ^{1}H n.m.r. spectrum to racemic material (see Part 1[1]).

(S)-(−)-5,7-*Dihydroxy*-8-(2-*methylbutyryl*)-4-*propylcoumarin* (**4a**).—(*a*) To (*S*)-(+)-(2-methylbutyryl)phloroglucinol (**3d**) (7.0 g, 33 mmol) in the minimum of glacial acetic acid was added ethyl 3-oxohexanoate (5.2 g, 33 mmol) followed by conc. sulphuric acid (1 ml). The mixture was allowed to stand for 4 days and the solid deposited was collected by filtration, washed with water, dried, and recrystallised from chloroform–methanol to afford (*S*)-(−)-5,7-dihydroxy-8-(2-methylbutyryl)-4-propylcoumarin (**4a**) (2.76 g, 27%), m.p. 254—256 °C [m.p. 248—250 °C for racemic material (see Part 1[1])], $[\alpha]_D^{25}$ −5.4° (*c* 0.46, in ethanol), which had an identical ^{1}H n.m.r. spectrum to racemic material (see Part 1[1]). The remaining material (3 g, 30%) consisted of a mixture of (**4a**) and its 6-(2-methylbutyryl)coumarin isomer.

(*b*) To 5,7-dihydroxy-4-propylcoumarin (3.85 g, 17.5 mmol) and aluminium trichloride (9.3 g, 70 mmol) stirred in nitrobenzene (40 ml) at 0 °C was added dropwise (*S*)-(+)-2-methylbutyryl chloride (**3c**) (2.1 g, 17.5 mmol). Stirring was continued for 4 days at room temperature, and the mixture was then poured into water and the nitrobenzene removed by steam distillation. The aqueous solution and residue were extracted with ether, and the combined extracts dried and evaporated to leave a residue that was chromatographed on a silica column. Elution with chloroform followed by chloroform–methanol (49:1 v/v) afforded a mixture (2 g, 38%) of predominantly (**4a**) with its 6-(2-methylbutyryl)coumarin isomer. Recrystallisation from chloroform–methanol gave (*S*)-(−)-5,7-dihydroxy-8-(2-methylbutyryl)-4-propylcoumarin (**4a**) (1.4 g, 26%), m.p. 254—256 °C, $[\alpha]_D^{25}$ −7.33° (*c* 0.6, in ethanol), $[\alpha]_D^{25}$ −6.66° (*c* 0.6, in acetone), having identical properties, apart from optical rotation, to that prepared in (*a*) above. The mother liquors afforded a mixture (0.6 g, 11%) of (**4a**) and its 6-acyl isomer, and further elution of the column led to recovery of some unchanged 5,7-dihydroxy-4-propylcoumarin.

(−)-*Mammea B/BB* (**4b**).—To (*S*)-(−)-5,7-dihydroxy-8-(2-methylbutyryl)-4-propylcoumarin (**4a**) [4 g, 13.16 mmol; prepared as in (*b*) above] in 10% aqueous potassium hydroxide (14.7 ml, 26.32 mmol potassium hydroxide) vigorously stirred at 0 °C under an atmosphere of nitrogen was added 3-methylbut-2-enyl bromide (2 g, 13.4 mmol) dropwise over 1.5 h. After this time the solution was poured into dilute hydrochloric acid and the mixture extracted with ether. The combined ether extracts were dried and evaporated to afford a residue that was chromatographed on a silica gel column, eluting with chloroform, to give (−)-mammea B/BB (1.20 g, 25%), m.p. 121—122 °C from hexane (lit.,[12] 122 °C), $[\alpha]_{589}^{25}$ −2.78°, $[\alpha]_{546}^{25}$ −3.87° (*c* 4.57, in chloroform) {lit.,[3] $[\alpha]_{589}^{25}$ −2.93°, $[\alpha]_{546}^{25}$ −4.14° (*c* 4.34, in chloroform)}, which had an identical ^{1}H n.m.r. spectrum to racemic material (see Part 1[1]). Also recovered was some unchanged starting coumarin (**4a**) (1.5 g, 29%).

(1′RS,2″S)-4-(1-*Acetoxypropyl*)-5,7-*dihydroxy*-8-(2-*methylbutyryl*)*coumarin* (**6a**).—To a stirred suspension of (±)-4-(1-acetoxypropyl)-5,7-dihydroxycoumarin (6.8 g, 25 mmol) and aluminium trichloride (13.34 g, 100 mmol) in nitrobenzene (50 ml) was added (*S*)-(+)-2-methylbutyryl chloride (**3c**) (3.0 g, 25 mmol). Stirring was continued for 3 days before the mixture was poured onto ice–water and the solvent removed by steam distillation. The remaining solution was cooled and extracted with ether. The combined ether extracts were dried and evaporated to leave a residue that was chromatographed on a silica gel column, eluting with chloroform followed by chloroform–methanol (99:1 v/v), to afford first some *O*-acylated material and then (1′*RS*,2″*S*)-4-(1-acetoxypropyl)-5,7-dihydroxy-8-(2-methylbutyryl)coumarin (**6a**) (3.54 g, 40%), $[\alpha]_D^{25}$ +16.83° (*c* 3, in chloroform), as a 1:1 mixture of diastereoisomers having an identical ^{1}H n.m.r. spectrum to the (1′*RS*,2″*RS*) material (see Part 3[1]).

(1′RS,2″S)-4-(1-*Acetoxypropyl*)-6-(3,7-*dimethylocta*-2,6-*dienyl*)-5,7-*dihydroxy*-8-(2-*methylbutyryl*)*coumarin* (**6c**).—To (1′*RS*,2″*S*)-4-(1-acetoxypropyl)-5,7-dihydroxy-8-(2-methylbutyryl)coumarin (**6a**) (3.0 g, 8.28 mmol) in 5% aqueous potassium hydroxide (18 ml, 16.56 mmol of potassium hydroxide) stirred at 45 °C under nitrogen was added (2*E*)-3,7-dimethylocta-2,6-dienyl chloride (1.44 g, 8.28 mmol) dropwise over 24 h. The cooled mixture was then poured onto ice–dilute hydrochloric acid and extracted with ether. The combined organic extracts were dried and evaporated to leave a residue that was chromatographed on a silica column eluting with light petroleum (b.p. 60—80 °C)–chloroform (1:1 v/v) to give a mixture of the 5-*O*-geranylcoumarin (**6b**) and the 6-*C*-geranyl compound (**6c**). This was further separated by h.p.l.c. on a silica column, eluting with ethyl acetate–hexane (3:37 v/v), to give (1′*RS*,2″*S*)-4-(1-acetoxypropyl)-5-[(2*E*)-3,7-dimethylocta-2,6-dienyloxy]-7-hydroxy-8-(2-methylbutyryl)coumarin (**6b**) (0.4 g, 10%) and (1′*RS*,2″*S*)-4-(1-acetoxypropyl)-6-[(2*E*)-3,7-dimethylocta-2,6-dienyl]-5,7-dihydroxy-8-(2-methylbutyryl)-coumarin (**6c**) (0.45 g, 11%); both materials had ^{1}H n.m.r. spectra identical to the (1′*RS*,2″*RS*) materials (see Part 3[1]).

Structure Determination for 4-(1-*Acetoxypropyl*)-6-*butyryl*-5,7-*dimethoxycoumarin* (**2**).—A sample of the coumarin (**2**) prepared as in Part 2,[1] m.p. 120—122 °C from hexane–ether, was recrystallised from hexane–chloroform to give crystals suitable for *X*-ray analysis; δ (250 MHz; C_6D_6) 0.86 (6 H, t, *J* 7.5 Hz, 2 × *Me*CH_2) 1.63 (3 H, s, *Me*CO), 1.6—1.8 (4 H, m, MeCH_2CH_2 and MeCH_2CH), 2.58 (2 H, t, *J* 7 Hz, CH_2CO), 3.0 (3 H, s, 7-OMe), 3.7 (3 H, s, 5-OMe), 6.15 (1 H, s, ArH), 6.3 (ddd, *J* 8.5, 3, and 0.9 Hz, C*H*O), and 6.50 (1 H, d, *J* 0.9 Hz, C=C*H*CO).

The space group and preliminary cell parameters were determined photographically. For the intensity measurement the crystal was then mounted on an Enraf-Nonius CAD4 diffractometer. Accurate lattice parameters were obtained by least squares refinement of the positions of 25 reflections measured on the diffractometer with θ *ca.* 35°. Intensity data were collected with CuK_α radiation using an $\omega - \frac{2}{3}\theta$ scan for $1° \leqslant \theta \leqslant 76°$. A total of 2 391 independent reflections were

measured of which 1 773 had $I \geqslant 3\sigma(I)$ and were considered observed and used in the subsequent refinement. The data were corrected for Lorentz and polarisation factors, but no absorption corrections were applied. Data reduction and subsequent crystallographic calculations were performed using the CRYSTALS[13] system of programs.

Crystal Data.—$C_{20}H_{24}O_7$, M = 376.39. Orthorhombic, a = 8.543(1), b = 10.273(1), c = 22.812(1) Å, U = 2 002.03 Å^3, Z = 4, D_c = 1.25 g cm^{-3}, $F(000)$ = 800. Space group $P2_12_12_1$ uniquely from systematic absences, CuK_α radiation, λ = 1.541 78 Å, μ(Cu-K_α) = 7.96 cm^{-1}.

Structure Solution and Refinement.—The structure was solved by direct methods using the MULTAN[14] program. 270 Reflections with $E > 1.46$ were used and the E map based on the best set of phases suggested the positions of 26 of the 27 non-hydrogen atoms among the largest peaks in the map. Attempted refinement of this model indicated that 3 of these positons were incorrect and a subsequent difference map readily located the 4 missing atoms. Full-matrix isotropic least-squares refinement of these positions gave an R value of 13.1%.

Refinement was continued with anisotropic thermal parameters for all non-hydrogen atoms. A difference map next revealed the approximate positions of many of the hydrogen atoms. Geometric considerations were then used to calculate the accurate positions of all the hydrogen atoms whose location could be fixed in this way. The remaining hydrogen atom positions were taken directly from the peaks in the difference map. The hydrogen atoms were then included in the calculations but without refinement. Analysis of the agreement between F_o and F_c suggested the adoption of a weighting scheme based on a Chebyshev polynomial. Refinement finally converged with the largest parameter shifts 0.2σ after 19 cycles of least squares refinement. The final R value at convergence was 5.47% with R_w 7.74%. A final difference map was calculated which showed no peaks or depressions >0.24 e Å^{-3}. Final atomic co-ordinates are listed in Table 4. Hydrogen positions and temperature factors are available on request from the Cambridge Crystallographic Data Centre.*

* See Instructions for Authors (1987) paragraph 5.6.3 in *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

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Received 3rd *January* 1986; *Paper* 6/022