Two Esters of Synadenol, a new Lathyrane Diterpenoid, from the Latex of *Synadenium compactum* (Euphorbiaceae): a Crystal Structure Analysis

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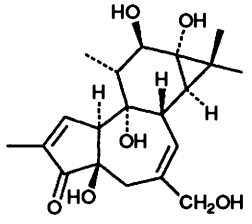
The 2-methylbutanoate tetraacetate and 2-methylbutanoate pentaacetate derivatives of synadenol, a new lathyrane diterpenoid, have been isolated from *Synadenium compactum* N.E. Br. var. *compactum* (Euphorbiaceae). The structure was elucidated using single crystal X-ray crystallography in conjunction with one and two-dimensional high field NMR experiments and mass spectrometry.

The plant family Euphorbiaceae is known for its many toxic species, which often contain compounds related to phorbol **1**, a diterpenoid polyol, the ester derivatives of which are cytotoxic agents, potent irritants and co-carcinogens.[1] The best known diester of phorbol, tetradecanoyl phorbol acetate (TPA) is used extensively as a molecular biological research tool: it is known to stimulate protein kinase C although not through a membrane receptor mediated process as is the case with many hormones which activate this enzyme.[2] Chemically similar to phorbol, but far less well studied, is a group of macrocyclic diterpenes some of which have cytotoxic activity. This group includes ingol **2** which has a lathyrane nucleus.[1] These compounds are of interest because they lack the irritant and co-carcinogenic properties of the phorbol-related diterpenes but some of them have potent biological activity.[3] It is not known whether these compounds act on protein kinase C.

Synadenium compactum N.E. Br. (Euphorbiaceae) is a many branched, small tree native to Kenya and East Africa. It is cultivated in many parts of the world as an ornamental shrub, mainly as *S. compactum* var. *rubrum*, which has purplish-red leaves. *S. compactum* var. *compactum* has dark green leaves and flaking, almost silver coloured bark. Kinghorn[4] has isolated a derivative of 4-deoxyphorbol from the related species *S. grantii* Hook. f., which has been reported as being poisonous.[5,6] *Synadenium cupulare* L. C. Wheeler, which occurs in eastern southern Africa, is reputed to be extremely toxic.[7] We report here the isolation and structure elucidation of a new derivative of the lathyrane diterpene nucleus, designated synadenol, from *Synadenium compactum* var. *compactum*. The compound was isolated as its 2-methylbutanoate tetraacetate **3** and 2-methylbutanoate pentaacetate **4** esters and the structures elucidated using a combination of crystallographic analysis, NMR spectroscopy and mass spectrometry (MS).



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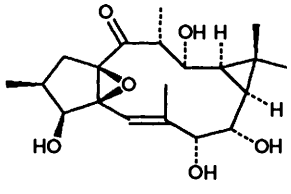

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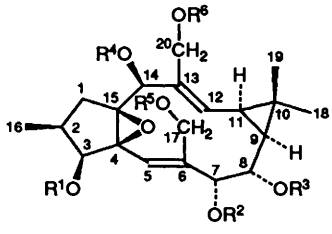

3 $R^1 = R^3 = R^4 = R^6 = Ac$, $R^2 = COCH(Me)Et$, $R^5 = H$
4 $R^1 = R^3 = R^4 = R^5 = R^6 = Ac$, $R^2 = COCH(Me)Et$

Results and Discussion

^1H and ^{13}C NMR data for compound **3** gave an overall indication that the compound was a diterpenoid ester with a lathyrane nucleus and with some similarities to ingol.[8] The nature of the macrocyclic skeleton together with the positions of the acyl groups and their relative stereochemistry was confirmed by single crystal X-ray analysis. Final fractional atomic co-ordinates are given in Table 1 while bond distances and angles are given in Tables 2 and 3 respectively. The molecular structure is shown in Fig. 1 along with the numbering scheme used, which is based on the conventional numbering system for the lathyrane skeleton.

The macrocyclic skeleton differs from the related diterpene, ingol **2**, in four respects: there is an additional double bond at C-12; the keto function at C-14 is reduced to an alcohol (esterified in the compounds isolated here); and the methyl groups at C-17 and C-20 are hydroxylated (esterified at C-20 in **3**, and at C-17 and C-20 in **4**). This is the first report of the ketone function at C-14 in the ingol related lathyranes being reduced to an alcohol although euphoscopin, epieuphoscopin and euphornin (jatrophanes lacking the C-9, C-11 bond which forms the cyclopropane ring), and a lathyrane, euphohelionone, with a *trans* cyclopropane ring and a C-4, C-12 epoxide have been reported as having hydroxy groups at C-14.[9] In synadenol, the double bonds are both *trans* and the cyclopropane ring is *cis* fused to the macrocyclic ring as occurs in related compounds.

In an attempt to determine the absolute configuration of

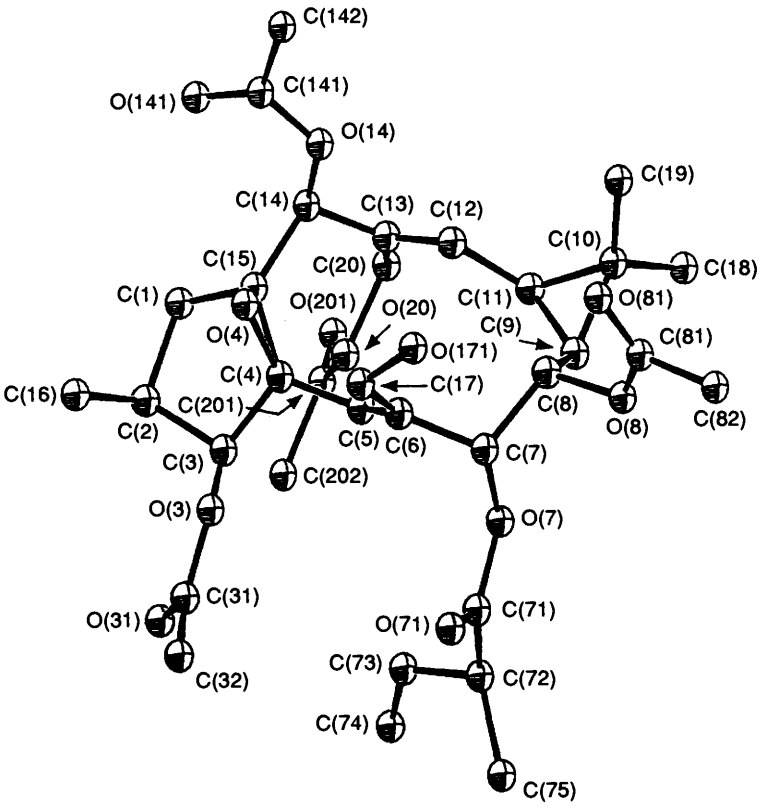

Fig. 1 Crystal structure of 3,8,14,20-tetraacetyl-7-(2-methylbutanoyl)-synadenol. The numbering scheme is based on the conventional system for the lathyrane nucleus and only one position of the disordered O-17 atom is shown for clarity.

compound **3**, the method of equal refinement with co-ordinate inversion was used. However, there was no significant statistical difference between the two enantiomers after equal stages of refinement. The structure presented in Fig. 1 is the enantiomer with the same relative configuration as revised for the X-ray structure of ingol tetraacetate.[10] The enantiomer in Fig. 1 has the absolute configuration 2*S*, 3*S*, 4*S*, 7*R*, 8*S*, 9*S*, 11*R*, 14*S*, 15*S*. While the relative configuration of C-7 (α) is the same as in ingol tetraacetate, it is opposite to that found in related lathyrol and jatrophane diterpenes from some other Euphorbia species.[9,11–14] The substitution at C-8 is α while it is β at C-14. Thus C-14 has the same relative configuration as found in the jatrophanes euphornin and euphohelionone, but opposite to that in the euphoscopins.[9] In addition, the euphoscopins, epieuphoscopins and euphohelionone have the opposite configuration (α) at C-2.

The position of the oxygen atom at C-17 was disordered between two sites [O(171) and O(172)] in approximately equal ratios. This disorder may be the result of competition between intra- and inter-molecular hydrogen bonding sites. Although the position of the hydrogen atom at O(17) was not located, the distance between O(171) and O(81) (3.1 Å) suggests an intramolecular hydrogen bond. Similarly, intermolecular hydrogen bonding may occur between the pairs O(171) and O(201) (3.0 Å) and O(172) and O(141) (3.1 Å) of symmetry related molecules.

Detailed assignments of the NMR spectra were made with the aid of two-dimensional experiments. From the ^{1}H-^{1}H COSY NMR spectrum of **3**, the multiplet resonating at 2.37 ppm was correlated with the multiplet at 2.23 ppm, the doublet at 0.92 ppm and the broad doublet at 5.14 ppm. No further correlations from these positions were noted and it was assumed that the adjacent carbon atoms were quaternary. These signals could be assigned to 2-H, the methylene group at C-1, the methyl group at C-16 and 3-H respectively in the cyclopentane ring. A weak correlation was observed between the alkenic signal at 5.25 ppm (5-H) and that at 4.55 ppm (17b-H) which was also coupled to the signal at 4.02 ppm (17a-H). Correlations were observed linking the signals 5.07 to 1.39 to 1.63 to 5.44 ppm and these could be assigned to 8-H, 9-H, 11-H and 12-H respectively. The three-proton singlets at 1.06 and 1.19 ppm corresponded to the geminal methyl groups on the cyclopropane ring, a similar arrangement occurring in ingol **2**.[8] Also, the chemical shifts for 9-H (1.39 ppm) and 11-H (1.63 ppm) were in broad agreement with those observed in ingol. A further singlet at 5.47 ppm was assigned to a methine proton at position 14. This signal showed correlations in a long range COSY experiment with those at 2.23 ppm (1-H) and to one of the components of an AB signal assigned to the methylene group at C-20.

The ^{1}H NMR signals at 2.49 (sextet, 1 H, *J* 7.2 Hz), 1.53 (m, 1 H), 1.71 (m, 1 H), 0.91 (t, 3 H, *J* 7.2 Hz) and 1.21 ppm (d, 3 H, *J* 7.2 Hz) assigned to the 2-methylbutanoyl group, and four acetyl methyl signals gave a total of five acyl groups.

In the ^{1} H NMR spectrum, it is interesting to note the wide separation of the AB signals arising from the methylene protons at C-17 (4.02 and 4.55 ppm), which may reflect a preferred conformation in this region due to intramolecular hydrogen bonding involving the hydroxy function at C-17. One of the signals (4.02 ppm, 17a-H) is a sharp doublet of doublets coupling to the geminal proton and to the hydroxy proton at 3.23 ppm, suggesting that exchange of the hydroxy proton is limited. On acetylation of this group (see below), the AB signal collapses to a broad multiplet at 4.8–5.0 ppm.

^{13}C NMR assignments were made with the aid of DEPT and two-dimensional ^{13}C–^{1}H chemical shift correlation experiments. The signal for C-7 was not detected in either the one- or the two-dimensional experiments.

The chemical ionisation MS had an apparent molecular ion at [M + 1] − 18 (*m*/*z* 617), corresponding to dehydration of

Table 1 Fractional atomic coordinates for 3,8,14,20-tetraacetyl-7-(2-methylbutanoyl)-synadenol

Atom	*x*	*y*	*z*
C(73)	−0.2788(13)	−0.0060(14)	0.8089(8)
C(74)	−0.3330(20)	−0.0164(15)	0.7368(12)
C(75)	−0.4339(11)	−0.0757(10)	0.8875(9)
C(1)	0.1960(9)	0.1947(6)	0.7698(6)
C(2)	0.0747(9)	0.2364(6)	0.7713(6)
C(3)	−0.0014(8)	0.1744(6)	0.8142(5)
C(4)	0.0773(8)	0.1250(5)	0.8643(5)
C(5)	0.0259(8)	0.0532(5)	0.8997(5)
C(6)	0.0001(8)	0.0407(5)	0.9724(5)
C(7)	−0.0542(8)	−0.0377(5)	0.9973(5)
C(8)	0.0367(8)	−0.1011(5)	1.0157(5)
C(9)	0.0760(9)	−0.1556(5)	0.9510(5)
C(10)	0.1879(9)	−0.2008(6)	0.9531(5)
C(11)	0.1716(8)	−0.1354(5)	0.8946(5)
C(12)	0.2318(8)	−0.0549(5)	0.8987(5)
C(13)	0.2563(8)	−0.0097(6)	0.8380(5)
C(14)	0.2974(8)	0.0772(5)	0.8447(5)
C(15)	0.1972(9)	0.1379(6)	0.8370(5)
C(16)	0.0777(11)	0.3217(7)	0.8051(6)
C(17)	0.0230(11)	0.1030(7)	1.0333(7)
C(18)	0.1844(10)	−0.2875(6)	0.9284(6)
C(19)	0.2741(9)	−0.1878(6)	1.0194(6)
O(4)	0.1584(5)	0.1749(4)	0.9061(3)
O(3)	−0.0880(6)	0.2110(4)	0.8638(4)
C(31)	−0.1888(10)	0.2332(7)	0.8317(6)
O(31)	−0.1997(8)	0.2337(6)	0.7637(5)
C(32)	−0.2743(10)	0.2619(8)	0.8870(7)
O(7)	−0.1316(5)	−0.0705(4)	0.9411(3)
C(71)	−0.2419(9)	−0.0401(6)	0.9396(6)
O(71)	−0.2752(8)	0.0067(6)	0.9859(5)
C(72)	−0.3056(11)	−0.0656(8)	0.8711(7)
O(8)	−0.0118(5)	−0.1582(4)	1.0714(3)
C(81)	0.0236(9)	−0.1526(6)	1.1428(6)
O(81)	0.0903(8)	−0.1027(5)	1.1639(5)
C(82)	−0.0325(10)	−0.2136(7)	1.1918(6)
C(20)	0.2416(8)	−0.0374(6)	0.7560(5)
O(20)	0.1358(6)	0.0013(4)	0.7276(4)
C(201)	0.1206(10)	−0.0002(7)	0.6511(6)
O(201)	0.1917(8)	−0.0310(5)	0.6115(5)
C(202)	0.0111(10)	0.0404(7)	0.6290(7)
O(14)	0.3556(6)	0.0857(4)	0.9164(3)
C(141)	0.4214(9)	0.1516(6)	0.9247(5)
O(141)	0.4298(7)	0.2035(4)	0.8770(4)
C(142)	0.4857(10)	0.1498(7)	0.9977(6)
O(171)	0.0496(12)	0.0717(8)	1.1042(8)
O(172	−0.0634(23)	0.1126(14)	1.0792(14)

Table 2 Bond lengths (Å) for 3,8,14,20-tetraacetyl-7-(2-methylbutanoyl)-synadenol

C(1)–C(2)	1.559(14)	C(1)–C(15)	1.515(13)
C(2)–C(3)	1.548(13)	C(2)–C(16)	1.532(14)
C(3)–C(4)	1.507(12)	C(3)–O(3)	1.460(11)
C(4)–C(5)	1.466(12)	C(4)–C(15)	1.477(13)
C(4)–O(4)	1.449(10)	C(5)–C(6)	1.336(12)
C(6)–C(7)	1.505(12)	C(6)–C(17)	1.514(14)
C(7)–C(8)	1.515(12)	C(7)–O(7)	1.441(10)
C(8)–C(9)	1.526(12)	C(8)–O(8)	1.473(11)
C(9)–C(10)	1.489(13)	C(9)–C(11)	1.523(13)
C(10)–C(11)	1.508(13)	C(10)–C(18)	1.499(13)
C(10)–C(19)	1.551(13)	C(11)–C(12)	1.502(12)
C(12)–C(13)	1.338(12)	C(13)–C(14)	1.517(13)
C(13–C(20)	1.531(13)	C(14)–C(15)	1.534(13)
C(14)–O(14)	1.441(11)	C(15)–O(4)	1.438(11)
C(17)–O(171)	1.390(17)	C(17)–O(172)	1.293(25)
O(3)–C(31)	1.342(12)	C(31)–O(31)	1.211(13)
C(31)–C(32)	1.467(15)	O(7)–C(71)	1.366(12)
C(71)–O(71)	1.190(12)	C(71)–C(72)	1.478(15)
C(72)–C(73)	1.509(20)	C(72)–C(75)	1.514(17)
C(73)–C(74)	1.430(21)	O(8)–C(81)	1.332(12)
C(81)–O(81)	1.188(12)	C(81)–C(82)	1.478(14)
C(20)–O(20)	1.465(11)	O(20)–C(201)	1.365(12)
C(201)–O(201)	1.191(12)	C(201)–C(202)	1.481(15)
O(14)–C(141)	1.334(11)	C(141)–O(141)	1.207(11)
C(141–C(142)	1.489(14)		

Table 3 Bond angles (°) for 3,8,14,20-tetraacetyl-7-(2-methylbutanoyl)-synadenol

C(15)–C(1)–C(2)	105.6(8)	C(3)–C(2)–C(1)	102.9(8)
C(16)–C(2)–C(1)	113.1(9)	C(16)–C(2)–C(3)	115.5(9)
C(4)–C(3)–C(2)	107.8(8)	O(3)–C(3)–C(2)	114.0(8)
O(3)–C(3)–C(4)	106.4(7)	C(5)–C(4)–C(3)	116.5(8)
C(15)–C(4)–C(3)	107.0(8)	C(15)–C(4)–C(5)	129.4(8)
O(4)–C(4)–C(3)	112.4(7)	O(4)–C(4)–C(5)	120.1(7)
O(4)–C(4)–C(15)	58.9(6)	C(6)–C(5)–C(4)	128.8(8)
C(7)–C(6)–C(5)	120.5(8)	C(17)–C(6)–C(5)	122.8(9)
C(17–C(6)–C(7)	116.6(8)	C(8)–C(7)–C(6)	111.8(8)
O(7)–C(7)–C(6)	112.2(7)	O(7)–C(7)–C(8)	108.5(7)
C(9)–C(8)–C(7)	116.8(8)	O(8)–C(8)–C(7)	108.9(7)
O(8)–C(8)–C(9)	103.6(7)	C(10)–C(9)–C(8)	122.2(8)
C(11)–C(9)–C(8)	125.2(8)	C(11)–C(9)–C(10)	60.1(6)
C(11)–C(10)–C(9)	61.1(6)	C(18)–C(10)–C(9)	116.6(9)
C(18–C(10)–C(11)	118.8(8)	C(19)–C(10)–C(9)	120.2(8)
C(19)–C(10)–C(11)	120.0(8)	C(19)–C(10)–C(18)	111.7(8)
C(10)–C(11)–C(9)	58.8(6)	C(12)–C(11)–C(9)	119.7(8)
C(12)–C(11)–C(10)	122.9(8)	C(13)–C(12)–C(11)	123.6(8)
C(14)–C(13)–C(12)	122.1(8)	C(20)–C(13)–C(12)	124.8(9)
C(20)–C(13)–C(14)	113.1(8)	C(15)–C(14)–C(13)	112.2(8)
O(14)–C(14)–C(13)	107.8(7)	O(14)–C(14)–C(15)	111.4(7)
C(4)–C(15)–C(1)	109.7(8)	C(14)–C(15)–C(1)	118.7(8)
C(14)–C(15)–C(4)	125.4(8)	O(4)–C(15)–C(1)	113.7(8)
O(4)–C(15)–C(4)	59.6(6)	O(4)–C(15)–C(14)	115.8(8)
O(171)–C(17)–C(6)	115(1)	O(172)–C(17)–C(6)	113(1)
		C(15)–O(4)–C(4)	61.6(6)
C(31)–O(3)–C(3)	116.7(7)	O(31)–C(31)–O(3)	121(1)
C(32)–C(31)–O(3)	112.7(9)	C(32)–C(31)–O(31)	126(1)
C(71)–O(7)–C(7)	116.8(7)	O(71)–C(71)–O(7)	122(1)
C(72)–C(71)–O(7)	111.9(9)	C(72)–C(71)–O(71)	126(1)
C(73)–C(72)–C(71)	108(1)	C(75)–C(72)–C(71)	111(1)
C(75)–C(72)–C(73)	114(1)	C(74)–C(73)–C(72)	119(2)
C(81)–O(8)–C(8)	118.4(8)	O(81)–C(81)–O(8)	123(1)
C(82)–C(81)–O(8)	112.1(9)	C(82)–C(81)–O(81)	125(1)
O(20)–C(20)–C(13)	106.7(8)	C(201)–O(20)–C(20)	116.0(8)
O(201)–C(201)–O(20)	120(1)	C(202)–C(201)–O(20)	111(1)
C(202)–C(201)–O(201)	128(1)	C(141)–O(14)–C(14)	116.1(7)
O(141)–C(141)–O(14)	123.3(9)	C(142)–C(141)–O(14)	111.2(8)
C(142)–C(141)–O(141)	125(1)		

the alcohol group which is commonly observed in diterpenes of the ingol and phorbol type.[15] The fragmentation from the putative pseudomolecular ion *m/z* 635 in the MS can be observed with loss of 18 mass units for the dehydration of one alcohol group (*m/z* 635 to 617 and 293 and 275), and the loss of 102 mass units for the 2-methylbutyrate (575 to 473 and 395 to 293) and 4 × 60 mass units for the four acetates (635 to 575, 473 to 413 to 353 to 293 and 575 to 515 to 455 to 395).

On acetylation with acetic anhydride in pyridine, **3** was converted into **4**. The 400 MHz ^{1}H NMR spectrum of acetylated **3** was identical with **4** isolated from the plant material. The NMR assignments and COSY connectivities for **4** are in broad agreement with those of **3**. However, with chemical ionisation MS, a small pseudomolecular ion at *m/z* 677 corresponding to the addition of CH_3CO was observed.

Thus, compounds **3** and **4**, isolated from the latex of *Synadenium compactum* var. *compactum*, were identified as the 7-(2-methylbutanoyl)-3,8,14,20-tetraacetyl and 7-(2-methylbutanoyl)-3,8,14,17,20-pentaacetyl esters of synadenol, a novel diterpenoid with a lathyrane nucleus.

Experimental

Isolation of Synadenol Diterpenes.—Latex (250 cm^3) of *S. compactum* was collected near Manzini, Swaziland, and stored

as a 50:50 mixture with methanol below 0 °C until use. The identity of the tree was confirmed by Mrs. S. Holmes at the Royal Botanic Gardens, Kew, Richmond, Surrey, UK and a voucher specimen has been placed in the Herbarium at Kew. The latex/methanol mixture was evaporated under reduced pressure to a soft mass. This was extracted with acetone (6 × 300 cm^3). The acetone extract was filtered and evaporated to dryness under reduced pressure at 40 °C. The resinous extract was redissolved in methanol–water 90:10 (300 cm^3) and partitioned against hexane (3 × 200 cm^3). The hexane fractions were combined and backwashed with methanol–water (2 × 100 cm^3). The aqueous methanol fractions were combined and diluted with water (500 cm^3). The mixture was then partitioned against diethyl ether (500 cm^3 and 4 × 300 cm^3). The ether fractions were bulked, extracted with 1% aqueous sodium carbonate (2 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure at 40 °C. The residue (6 g) was divided into four equal portions each of which was fractionated on a Florisil 200–300 mesh gravity column (120 g) using a step gradient of hexane–ethyl acetate, with aliquots of 200 cm^3 and a change of 5% at each step. Fractions, collected as 10 cm^3 aliquots, were each tested by TLC using the solvent system cyclohexane–ethyl acetate–diethyl ether (1:1:1). Like fractions were bulked, evaporated to dryness and redissolved in hexane. A fraction eluted with hexane–ethyl acetate (70:30) yielded colourless prisms of **3** (12.9 mg) from hexane after being stored at <0 °C for some months. Subsequent fractions [using eluents up to hexane–ethyl acetate (60:40)] contained no pure compounds, and were bulked and evaporated to dryness for preparative HPLC. Preparative HPLC was carried out on a DuPont Model 830 Preparative HPLC system using a Zorbax SIL column 25 × 2.1 cm, particle size 8–15 μm, and hexane–THF (90:10) (20 cm^3 min^{-1}) as eluting solvent. The sample was prepared in hexane–THF (1:1; 25 mg cm^{-3}), and injected in 1 cm^3 portions. The eluent was passed through a UV detector at 225 nm and fractions were collected following visual observation of the UV trace. Compound **4** was eluted 22 min after injection. Twenty injections were made, and like fractions were bulked. Fractions from the preparative HPLC were analysed by GLC using a Perkin–Elmer Sigma-3 instrument equipped with a 39 m × 0.25 mm OV-1 capillary column. The oven temperature was set at 280 °C and the injector/detector temperatures at 300 °C. Compound **4** had a retention time of 9.8 min. Final yields of **3** and **4** were 10 and 65 mg respectively.

NMR Spectroscopy.—NMR experiments were performed on JEOL GX400 and GX270 instruments using solutions of 2 and 65 mg in 0.6 cm^3 for **3** and **4** respectively. The two-dimensional spectra were obtained using the standard pulse sequences available on the instruments.[16] The 399.65 MHz ^1H NMR spectra for **3** and **4** were collected with 128 scans using a frequency width of 4000 Hz and 32 K data points to give a digital resolution of 0.24 Hz/pt. The 399.65 MHz ^1H–^1H COSY spectra were zero filled once in the column direction to give a final data matrix of 1024 × 512 complex points. A Blackman–Harris window function was applied before transformation. The number of scans per slice, frequency width (Hz) and corresponding resolution (Hz/pt) were 128, 3201.0 and 6.2 for **3** and 16, 2100.8 and 4.1 for **4**. In the 399.65 MHz long-range COSY spectrum for **3** a fixed delay was inserted in the pulse sequence to optimise small couplings. 64 Scans were accumulated with a frequency width of 2100.8 Hz to give a resolution of 4.1 Hz. *J* Values are recorded in Hz.

The 67.8 MHz noise-decoupled ^{13}C and DEPT spectra were collected with a frequency width of 18050.5 Hz and 16 K data points to give a resolution of 2.2 Hz/pt. 26502 and 3600 scans were accumulated for the ^{13}C spectra of **3** and **4** respectively. The 67.8 MHz ^{13}C–^1H heteronuclear shift correlation spectra were zero filled once in the column direction to give final matrices of 1024 × 128 complex points. For compound **4**, 48 scans were accumulated for each slice with row and column frequencies of 13404.8 and 1600.2 Hz giving resolutions of 26.2 and 12.5 Hz/pt respectively.

Mass Spectrometry.—Isobutane chemical ionisation spectra were obtained on a V.G. 7070E instrument.

3,8,14,20-*Tetraacetyl*-7-(2-*methylbutanoyl*)-*synadenol* **3**.—δ_H(400 MHz; solvent $CDCl_3$; standard Me_4Si) 0.91 (3 H, t, $^3J_{4',3'}$ 7.2, 4'-H), 0.92 (3 H, d, $^3J_{16,2}$ 7.3, 16-H), 1.06 (3 H, s, 19-H), 1.19 (3 H, s, 18-H), 1.21 (3 H, d, $^3J_{2'\text{-Me},2'}$ 7.2, 2'-Me), 1.39 (1 H, dd, $^3J_{9,8}$ 10.8, $^3J_{9,11}$ 9.3, 9-H), 1.53 (1 H, m, 3'a-H), 1.63 (1 H, dd, $^3J_{11,12}$ 12.2, $^3J_{11,9}$ 9.3, 11-H), 1.71 (1 H, m, 3'b-H), 2.02, 2.07, 2.12 and 2.15 (3 H, s, acetate Me), 2.23 (2 H, m, 1-H), 2.37 (1 H, m, 2-H), 2.49 (1 H, sextet, $^3J_{2',3'}$ and $^3J_{2',2'\text{-Me}}$ 7.2, 2'-H), 3.23 (1 H, br d, 17-OH), 4.02 (1 H, dd, $^2J_{17a,17b}$ 12.8, $^3J_{17a,17\text{-OH}}$ 10.5, 17a-H), 4.55 (1 H, br d, $^2J_{17b,17a}$ 12.8, 17b-H), 4.64 (1 H, d, $^2J_{20a,20b}$ 12.9, 20a-H), 4.72 (1 H, d, $^2J_{20b,20a}$ 12.9, 20b-H), 5.07 (1 H, br d $^3J_{8,9}$ 10.8, 8-H), 5.14 (1 H, br d $^3J_{3,2}$ 8.6, 3-H), 5.25 (1 H, m, 5-H), 5.40 (1 H, br s, 7-H), 5.44 (1 H, d, $^3J_{12,11}$ 12.2, 12-H) and 5.47 (1 H, s, 14-H); δ_C(67.8 MHz, solvent $CDCl_3$, standard Me_4Si) 11.4 (Me, C-4'), 15.1 (Me, C-19), 16.5 (Me, C-5'), 17.1 (Me, C-16), 20.4, 20.8, 20.9 and 21.2 (Me, acetate), 23.3 (C_q, C-10), 26.3 (CH, C-11), 26.7 (CH_2, C-3'), 28.7 (Me, C-18), 29.2 (CH, C-2), 30.9 (CH, C-9), 38.6 (CH_2, C-1), 41.2 (CH, C-2'), 60.1 (CH_2, C-17), 61.2 (CH_2, C-20), 71.5 (CH, C-14), 72.8 (CH, C-8), 76.3 (CH, C-3), 77.2 and 77.8 (C_q, C-4 and C-15), 120.5 (CH, C-5), 124.0 and 138.6 (C_q, C-6 and C-13), 132.2 (CH, C-12), 169.4, 170.3, 170.6 and 174.9 (C_q, 5 × ester carbonyl, two coincident); *m/z* 617 ([M + 1 − 18]$^+$, 4%), 575 (75), 515 (17), 473 (19), 455 (17), 413 (30), 395 (10), 353 (40), 293 (52) and 275 (10).

3,8,14,17,20-*Pentaacetyl*-7-(2-*methylbutanoyl*)-*synadenol* **4**.—δ_H(400 MHz; solvent $CDCl_3$; standard Me_4Si) 0.91 (3 H, t, $^3J_{4',3'}$ 7.2, 4'-H), 0.92 (3 H, d, $^3J_{16,2}$ 7.2, 16-H), 1.05 (3 H, s, 19-H), 1.19 (3 H, s, 18-H), 1.21 (3 H, d, $^3J_{2'\text{-Me},2'}$ 7.2, 2'-Me), 1.40 (1 H, dd, $^3J_{9,8}$ 10.8, 9-H), 1.52 (1 H, m, $^3J_{3'a,4'}$ 7.2, 3'a-H), 1.63 (1 H, dd, $^3J_{11,9}$ 9.9, 11-H), 1.71 (1 H, m, 3'b-H), 2.03, 2.05, 2.09, 2.14 and 2.17 (3 H, s, acetate Me), 2.23 (2 H, m, 1-H), 2.35 (1 H, m, $^3J_{2,3}$ 8.1, 2-H), 2.49 (1 H, sextet, $^3J_{2',2'\text{-Me}}$ and $^3J_{2',3'}$ 7.2, 2'-H), 4.60 (1 H, d, $^2J_{20a,20b}$ 12.6, 20a-H), 4.72 (1 H, d, $^2J_{20b,20a}$ 12.6, 20b-H), 4.80–5.00 (3 H, br m, 8-H, 17a- and 17b-H), 5.14 (1 H, d, $^3J_{3,2}$ 8.1, 3-H), 5.31 (1 H, d, $^3J_{12,11}$ 12.4, 12-H), 5.36 (1 H, s, 5-H) and 5.42 (2 H, br s, 7-H, 14-H); δ_C(67.8 MHz, solvent $CDCl_3$, standard Me_4Si) 11.5 (Me, C-4'), 15.3 (Me, C-19), 16.5 (Me, C-5'), 17.2 (Me, C-16), 18.0, 20.5, 20.7, 20.9 and 21.1 (Me, acetate), 23.1 (C_q, C-10), 26.7 (CH, C-11), 26.7 (CH_2, C-3'), 28.7 (Me, C-18), 29.3 (CH, C-2), 30.2 (CH, C-9), 38.5 (CH_2, C-1), 41.2 (CH, C-2'), 61.1 (2 × CH_2, C-20 and C-17), 71.4 (2 × CH, C-7 and C-14), 72.5 (CH, C-8), 76.8 (CH, C-3), 76.9 and 77.2 (C_q, C-4 and C-15), 124.3 and 133.8 (C_q, C-6 and C-13), 131.3 (2 × CH, C-5 and C-12), 169.7, 169.8, 170.7, 170.8 and 174.9 (C_q, 6 × ester carbonyl, two coincident); *m/z* 677 ([M + 1]$^+$, 2%), 617 (100), 575 (4), 557 (8), 515 (12), 497 (6), 455 (14), 437 (2), 395 (12), 377 (2), 335 (15) and 275 (9).

Crystallographic Analysis of 3,8,14,20-*Tetraacetyl*-7-(2-*methylbutanoyl*)-*synadenol* **3**.—*Crystal data.* $C_{33}H_{46}O_{12}$, M = 634.7; orthorhombic, a = 11.514(4), b = 16.521(7), c = 17.695(5) Å, V = 3366.0 Å^3; Mo-$K\alpha$ radiation, λ = 0.710 69 Å; space group $P2_12_12_1$, Z = 4, D_c = 1.25 g cm^{-3}; μ = 0.58 cm^{-1}; F(000) = 1360. A colourless prism of approximate dimensions 0.5 × 0.4 × 0.45 mm was used for data collection at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 < \theta < 22°$. 2377 Reflections were

collected of which 1988 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarisation but not for absorption. The structure was solved by direct methods using the SHELX suite of programs.[17] In the final least-squares cycles, carbon atoms labelled 73, 74 and 75 were allowed to vibrate anisotropically because of their large thermal parameters, but all other atoms were refined isotropically. Hydrogen atoms were included at calculated positions for the appropriate saturated carbon centres. Final residuals after 11 cycles of full-matrix least-squares refinement were $R = R_w = 0.0866$ for unit weights. The maximum shift/esd was 0.019. The maximum and minimum residual densities were 0.19 and -0.13 e Å^{-3} respectively. The oxygen atom at C-17 was disordered, occurring at two positions, and satisfactory convergence was achieved for 50% occupancy of each site (O-171 and O-172). No assignment of the hydrogen atom attached to O-17 was attempted due to the disorder.*

* *Supplementary data:* Tables of calculated hydrogen positions and anisotropic temperature factors are available from the Cambridge Crystallographic Data Centre.

Acknowledgements

The authors are grateful to Mrs. S. Holmes of the Royal Botanic Gardens, Kew, Richmond, Surrey for the identification of the plant material.

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Paper 2/00467D
Received 29*th January* 1992
Accepted 13*th April* 1992