New Sesquiterpene Esters from *Euonymus verrucosus*: The 'Ever' Series. *X*-Ray Molecular Structure of Ever-1

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Seven new sesquiterpenoid esters (Ever-1, -2, -4, -6, -7, -8, and -10) have been isolated from *Euonymus verrucosus*. Structure (3) was determined for Ever-1 by *X*-ray (direct methods) analysis: the structure incorporates the pentahydroxydihydroagarofuran 3,4-dideoxymaytol. The same core is found in Ever-4, Ever-8, and Ever-10. However, Ever-2, -6, and 7 are esters of the hexahydroxydihydroagarofuran, 3,4,12-trideoxyeuonyminol (alatol).

The sesquiterpene dihydroagarofuran (**1**) is found in Nature in various oxygenated forms, bearing as many as nine hydroxy groups, as in euonyminol (**2**). These polyols mostly occur in members of the Celastraceae as esters. Esterifying acids include
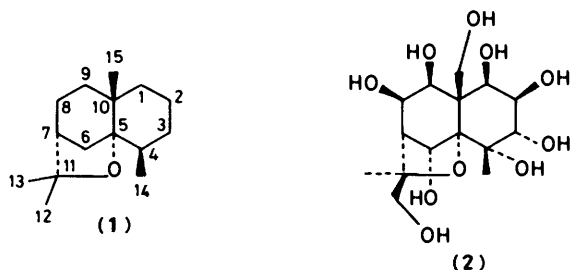
aliphatic (acetic, 2-methylbutyric, hydroxyisobutyric, etc.) and aromatic (benzoic, furoic, nicotinic, etc.) acids, as well as nitrogen-containing diacids (*e.g.* evoninic, wilfordic, and cathic acids) which form macrolide bridges. Despite their sesquiterpene core, many of these compounds are nitrogeneous bases through esterification: they are legitimately described as alkaloids and have been reviewed as such.[1] Recent literature is collected in ref. 2.

In continuation of previous interests in this area [3] we describe here a group of esters isolated from the fruits of *Euonymus verrucosus*. These were isolated by repeated chromatography of the light petroleum–soluble fraction of a methanol extract, using normal-pressure silica, polyamide, and Sephadex columns. Seven pure esters, Ever-1, -2, -4, -6, -7, -8 and -10, were characterised and their structures are discussed in this paper. Preliminary m.s. and n.m.r. examination indicated that the compounds fell into two sets, each set with a different sesquiterpene core.

The most abundant product, Ever-1, $C_{32}H_{43}NO_{11}$, *M* 617, afforded crystals with m.p. 189—192 °C (from aqueous methanol). The structure was solved by direct methods using diffractometer data and refined to $R = 6.05\%$ over 2 501 independent observed reflections. Figure 1 shows the conformation of the molecule in the crystal and verifies the structure and stereochemistry shown in structure (**3**). The *X*-ray numbering is displayed in Figure 2. Bond lengths and angles are listed in Tables 1 and 2 respectively, together with their standard deviations. These adopt expected values with the exception of the 2-methylbutyryl side-chain at C(17) where the bond lengths are associated with large thermal motion in this region of the molecule. The neighbouring acetyl group at C(18), C(19), is also vibrating more than the remainder of the molecule.
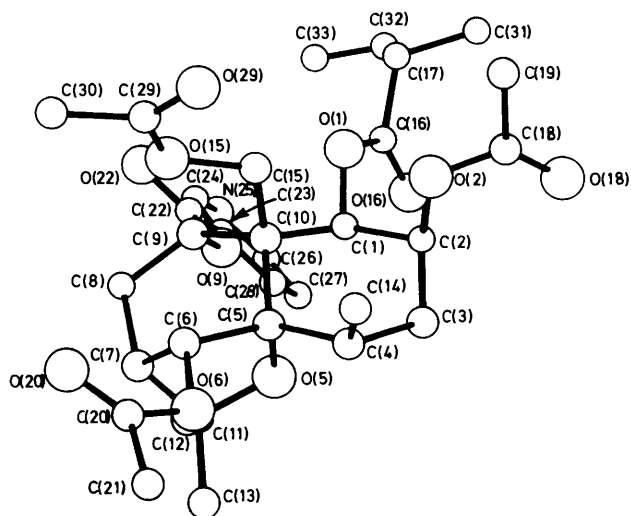

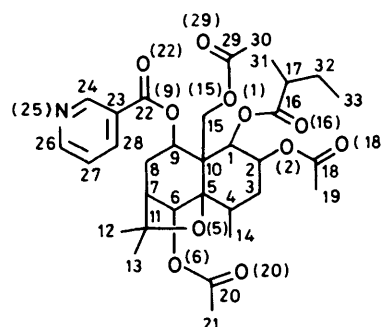**Figure 1.** Single-crystal *X*-ray molecular structure of Ever-1 (**3**)

Figure 2. *X*-Ray numbering scheme for Ever-1 (**3**)

Table 3 shows some selected torsion angles about the central ring system. Both six-membered rings adopt the expected chair conformation but the ring with the ether bridge has been sharpened at C(6) and flattened at C(9) to accommodate the bridge. The 5-membered ring adopts the envelope conformation with C(7) out of the plane containing the other 4 atoms. Structure (**3**) shows that the three acetates occupy positions 2, 6, and 15 of the sesquiterpene. Position 9 is occupied by the nicotinate ester, whilst the (*S*)-2-methylbutyrate residue is at C-1. The C(5)–C(6)–C(7)–C(8) torsion angle ($-76.2°$) implies

Table 1. Bond lengths (Å) for Ever-1 (3)

C(1)–C(2)	1.527(8)		C(16)–O(1)	1.328(9)
C(1)–C(10)	1.544(7)		C(16)–O(16)	1.231(11)
C(1)–O(1)	1.458(6)		C(17)–C(31)	1.508(24)
C(2)–C(3)	1.500(9)		C(17)–C(32)	1.305(19)
C(2)–O(2)	1.459(8)		C(18)–C(19)	1.524(15)
C(3)–C(4)	1.529(9)		C(18)–O(2)	1.306(9)
C(4)–C(5)	1.550(7)		C(18)–O(18)	1.186(13)
C(4)–C(14)	1.540(9)		C(20)–C(21)	1.483(9)
C(5)–C(6)	1.526(7)		C(20)–O(6)	1.360(7)
C(5)–C(10)	1.581(7)		C(20)–O(20)	1.186(7)
C(5)–O(5)	1.451(6)		C(22)–C(23)	1.478(8)
C(6)–C(7)	1.512(7)		C(22)–O(9)	1.332(7)
C(6)–O(6)	1.439(6)		C(22)–O(22)	1.206(8)
C(7)–C(8)	1.557(7)		C(23)–C(24)	1.401(9)
C(7)–C(11)	1.536(8)		C(23)–C(28)	1.373(9)
C(8)–C(9)	1.515(8)		C(24)–N(25)	1.332(10)
C(9)–C(10)	1.553(8)		N(25)–C(26)	1.326(11)
C(9)–O(9)	1.466(6)		C(26)–C(27)	1.359(11)
C(10)–C(15)	1.555(7)		C(27)–C(28)	1.397(9)
C(11)–C(12)	1.512(8)		C(29)–C(30)	1.472(11)
C(11)–C(13)	1.508(8)		C(29)–O(15)	1.320(8)
C(11)–O(5)	1.478(6)		C(29)–O(29)	1.173(9)
C(15)–O(15)	1.459(7)		C(32)–C(33)	1.322(21)
C(16)–C(17)	1.540(13)			

Table 2. Bond angles (°) for Ever-1 (3)

C(2)–C(1)–C(10)	115.3(5)		C(12)–C(11)–O(5)	109.2(4)
C(2)–C(1)–O(1)	109.1(5)		C(13)–C(11)–O(5)	107.3(4)
C(10)–C(1)–O(1)	108.1(4)		C(10)–C(15)–O(15)	109.5(4)
C(1)–C(2)–C(3)	111.5(5)		C(17)–C(16)–O(1)	111.0(8)
C(1)–C(2)–O(2)	108.0(5)		C(17)–C(16)–O(16)	126.7(7)
C(3)–C(2)–O(2)	110.9(6)		O(1)–C(16)–O(16)	121.9(7)
C(2)–C(3)–C(4)	114.5(5)		C(16)–C(17)–C(31)	113.2(13)
C(3)–C(4)–C(5)	110.2(5)		C(16)–C(17)–C(32)	108.3(9)
C(3)–C(4)–C(14)	112.5(5)		C(31)–C(17)–C(32)	106.4(8)
C(5)–C(4)–C(14)	117.5(5)		C(19)–C(18)–O(2)	108.9(10)
C(4)–C(5)–C(6)	116.7(4)		C(19)–C(18)–O(18)	128.7(9)
C(4)–C(5)–C(10)	114.8(4)		O(2)–C(18)–O(18)	122.4(10)
C(4)–C(5)–O(5)	105.2(4)		C(21)–C(20)–O(6)	110.5(6)
C(6)–C(5)–C(10)	107.8(4)		C(21)–C(20)–O(20)	127.0(6)
C(6)–C(5)–O(5)	106.3(4)		O(6)–C(20)–O(20)	122.5(5)
C(10)–C(5)–O(5)	105.0(4)		C(23)–C(22)–O(9)	111.8(5)
C(5)–C(6)–C(7)	99.8(4)		C(23)–C(22)–O(22)	123.8(6)
C(5)–C(6)–O(6)	110.1(4)		O(9)–C(22)–O(22)	124.4(6)
C(7)–C(6)–O(6)	114.7(4)		C(22)–C(23)–C(24)	118.2(6)
C(6)–C(7)–C(8)	104.3(4)		C(22)–C(23)–C(28)	124.2(6)
C(6)–C(7)–C(11)	103.5(4)		C(24)–C(23)–C(28)	117.5(6)
C(8)–C(7)–C(11)	114.0(4)		C(23)–C(24)–N(25)	123.9(8)
C(7)–C(8)–C(9)	116.8(4)		C(24)–N(25)–C(26)	116.0(7)
C(8)–C(9)–C(10)	116.3(4)		N(25)–C(26)–C(27)	125.8(7)
C(8)–C(9)–O(9)	109.8(4)		C(26)–C(27)–C(28)	117.4(7)
C(10)–C(9)–O(9)	108.6(4)		C(23)–C(28)–C(27)	119.4(6)
C(1)–C(10)–C(5)	106.2(4)		C(30)–C(29)–O(15)	111.6(7)
C(1)–C(10)–C(9)	110.5(4)		C(30)–C(29)–O(29)	126.3(8)
C(1)–C(10)–C(15)	109.2(4)		O(15)–C(29)–O(29)	122.1(8)
C(5)–C(10)–C(9)	109.6(4)		C(17)–C(32)–C(33)	107.9(10)
C(5)–C(10)–C(15)	114.0(4)		C(1)–O(1)–C(16)	116.9(5)
C(9)–C(10)–C(15)	107.3(4)		C(2)–O(2)–C(18)	117.5(7)
C(7)–C(11)–C(12)	114.4(5)		C(5)–O(5)–C(11)	110.1(4)
C(7)–C(11)–C(13)	116.9(5)		C(6)–O(6)–C(20)	115.7(4)
C(7)–C(11)–O(5)	100.8(4)		C(9)–O(9)–C(22)	116.8(4)
C(12)–C(11)–C(13)	107.6(5)		C(15)–O(15)–C(29)	117.8(5)

an H–C(6)–C(7)–H dihedral angle closer to 90° than in an undistorted chair ring: this is reflected in the near zero coupling constant for 6-H and 7-H. Similarly the relatively large $J_{8,9}$ value is congruent with the C(7)–C(8)–C(9)–C(10) torsion angle (−29.3°).

Table 3. Selected torsion angles (°) for Ever-1 (3)

|	
C(10)–C(1)–C(2)–C(3)	+54.9
C(1)–C(2)–C(3)–C(4)	−51.8
C(2)–C(3)–C(4)–C(5)	+50.9
C(3)–C(4)–C(5)–C(10)	−52.8
C(4)–C(5)–C(10)–C(1)	+53.2
C(5)–C(10)–C(1)–C(2)	−53.8
C(10)–C(5)–C(6)–C(7)	+81.2
C(5)–C(6)–C(7)–C(8)	−76.2
C(6)–C(7)–C(8)–C(9)	+53.2
C(7)–C(8)–C(9)–C(10)	−29.3
C(8)–C(9)–C(10)–C(5)	+28.8
C(9)–C(10)–C(5)–C(6)	−55.4
O(5)–C(5)–C(6)–C(7)	−30.9
C(5)–C(6)–C(7)–C(11)	+43.4
C(6)–C(7)–C(11)–O(5)	−39.7
C(7)–C(11)–O(5)–C(5)	+20.1
C(11)–O(5)–C(5)–C(6)	+6.7

(3)   (4)
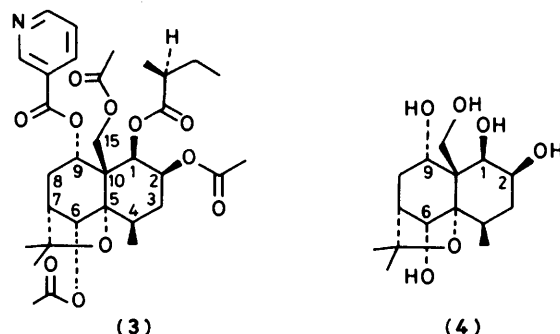
The core sesquiterpene is 1R,2S,6R,9S,15-pentahydroxy-dihydroagarofuran (4) (3,4-dideoxymaytol), on the assumption that the absolute configuration of the sesquiterpene framework is the same as for other members of the group. This pentaol was not known in Nature when our work was completed. Very recently, however, Baudouin et al.[4] have determined the structures of maymyrsine (5a) and acetylmaymyrsine, from *Maytenus myrsinoides* Reiss., using X-ray methods; these compounds are also based on core structure (4). With the constitution of Ever-1 secure, significant n.m.r. comparisons within the group became possible, using the data collated in Table 4. Further structural information is revealed: thus, the homologous set Ever-4 ($C_{34}H_{39}NO_{11}$), Ever-10 ($C_{35}H_{41}NO_{11}$), and Ever-8 ($C_{36}H_{43}NO_{11}$) have ^{1}H n.m.r. spectra very similar to each other and to Ever-1. The close correspondence of both chemical shifts and coupling constants for the characteristic sesquiterpene protons, (1-, 2-, 6-, 9-, and 14-H, and 15-H$_2$) strongly suggests that Ever-4, -10, and -8 are also based on 3,4-dideoxymaytol (4). All three compounds contain one nicotinate unit [m/z 78, 106, 124; four characteristic signals, δ_H 7—9 (Experimental section)], and one benzoate residue [m/z 77, 105; characteristic 2- and 3-proton signals, δ_H 7—8 (Experimental section)]. Ever-4 has in addition three acetate residues [M − 42; δ_H 1.93, 1.69, and 1.66 (C_6D_6)], whilst Ever-10 has two acetate [M − 42; δ_H 2.13 and 2.30 (CDCl$_3$)] and one propionate [m/z 57; δ_H 1.08 (3 H, t) and 1.8—2.7 (2 H, m)] units, and Ever-8 contains two acetates [M − 42; δ_H 2.12 and 2.29] and one butyrate [m/z 71; δ_H 1.12 (3 H, t) and 1.8—2.7 (4 H, m)]. Ever-4, -10, and -8 thus form the set (5b), (5c), and (5d) respectively, though it is not possible at present to solve the problem of siting the ester residues. Ever-4 is isomeric with acetylmaymyrsine,[4] the ^{1}H n.m.r. data showing clearly that the two compounds are not identical. More material is required for ester-site investigation than is at present available.

**Table 4.** ^1H N.m.r. data (δ, J/Hz) for sesquiterpene protons

	1-H	2-H	6-H	9-H	3-H₂, 4-H, 7-H, 8-H₂	15-Hₐ	15-H_b	12-H₃, 13-H₃	14-H₃
Ever-1 (3)ᵃ	5.78 (d, J 3.5)	5.52 (m)	5.97 (s)	5.32 (br d, J_ax,ax 6.8)	2.5—1.8	5.07 (d, J 13)	4.41 (d, J 13)	1.42 (s), 1.36 (s)	1.18 (d, J 7.8)
Ever-4 (5b)ᵇ	6.31 (d, J 3.5)	6.15 (m)	6.18 (s)	5.90 (br d, J_ax,ax 7.2)	2.7—1.6	5.51 (d, J 12.5)	4.9 (d, J 12.5)	1.37(s), 1.39 (s)	1.13 (d, J 4.5)
Ever-8 (5d)ᵃ	5.98 (d, J 4.0)	5.74 (m)	6.07 (s)	5.48 (br d, J_ax,ax 6.8)	2.7—1.8	5.24 (d, J 13)	4.58 (d, J 13)	1.45 (s), 1.46 (s)	1.21 (d, J 8.1)
Ever-10 (5c)ᵃ	5.95 (d, J 4.5)	5.72 (m)	6.04 (s)	5.47 (br d, J_ax,ax 6.1)	2.7—1.8	5.21 (d, J 12.5)	4.58 (d, J 12.5)	1.46 (s, 6 H)	1.21 (d, J 8.1)

ᵃ CDCl₃. ᵇ C₆D₆

Table 5. ^1H N.m.r. data (CDCl₃; δ, J/Hz) for sesquiterpene protons

	1-H	2-H	3-H₂, 4-H	6-H	7-H	8-H	9-H	15-Hₐ	15-H_b	13-H₃, 12-H₃	14-H₃
Ever-2 (7)	5.83 (d, J 4.0)	5.52 (m)	2.6—1.8	6.89 (br s)	2.59 (d, J 3.9)	5.65 (dd, J 3.9, 5.6)	5.52	5.52 (d, J 14.3)	4.60 (d, J 14.3)	1.59 (s), 1.47 (s)	1.13 (d, J 7.7)
Ever-6 (10)	5.61 (d, J 3.9)	5.41 (m)	2.5—1.8	6.9 (d, J 1)	2.64 (d)	5.77ᵃ	5.78ᵇ	5.26 (d, J 13.5)	4.61 (d, J 13.5)	1.62 (s), 1.57 (s)	1.18 (d, J 7.6)
Ever-7 (9)	5.93 (d, J 4.0)	5.50 (m)	2.6—1.9	6.90 (br s)	2.66 (d, J 4.0)	5.75 (dd, J 4.0, 5.8)	5.88 (d, J 5.8)	5.38 (d, J 13.5)	4.90 (d, J 13.5)	1.65 (s), 1.51 (s)	1.24 (d, J 7.6)

ᵃ δ 5.91 (dd, $J_{7,8}$ 3.9, $J_{8,9}$ 6.1 Hz in C₆D₆). ᵇ δ 6.15 (d, $J_{8,9}$ 6.1 Hz in C₆D₆).

(5)
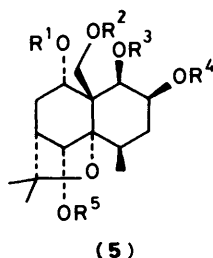
a; R¹ = nicotinoyl, R² = H, R³ = R⁵ = MeCO, R⁴ = PhCO
b; R¹⁻⁵ = 3 × MeCO, PhCO, nicotinoyl
c; R¹⁻⁵ = 2 × MeCO, EtCO, PhCO, nicotinoyl
d; R¹⁻⁵ = 2 × MeCO, n-PrCO, PhCO, nicotinoyl

Ever-2, -6, and -7 form a second related set of extractives. Ever-2 ($C_{37}H_{42}O_{13}$) contains four acetate fragments (M − 42; δ_H 2.14, 2.09, 1.98, and 1.42) and two benzoates [m/z 77, 105; δ_H 7.3—7.6 (6 H) and 7.9—8.2 (4 H)]. A hexaol framework is thus implied, and the ^1H n.m.r. resonances (Table 5) suggest that this is 3,4,12-trideoxyeuonyminol (6). The stereochemistry is supported by the observed coupling constants[3]: $J_{1,2}$ 4.0 Hz is typical for 1-Hₐₓ-2-H_eq: $J_{6,7}$ ca. 0 Hz suggests 6-Hₐₓ-7-H_eq; $J_{7,8}$ 3.9 Hz is appropriate for 7-H_eq–8-H_eq(cf. 7-H_eq–8-Hₐₓ 2.6 Hz), and $J_{8,9}$ 5.6 Hz is in the range observed for 8-H_eq–9-Hₐₓ. The ^1H n.m.r. data measured for Ever-2 (7) are closely similar to those

(6)
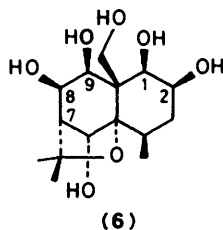
reported [2e,f] for ester-A2 isolated from *Euonymus europaeus*, which has been assigned as the tetra-acetyldibenzoyl-3,4,12-trideoxyeuonyminol (8). The ester-A2 is reported to have m.p.

188—192 °C, whereas Ever-2 has m.p. 81—86 °C but the possible identity of the two esters cannot be discounted at present. The ester functions cannot be placed with certainty; the positive shielding of one acetate methyl (δ_H 1.42) is probably ascribable to an adjacent aryl ring as in maytoline[5] and cathedulin-E2.[3b]. However, with two benzoates present such shielding is possible in several arrangements.

Ever-7 ($C_{41}H_{43} NO_{13}$) has sesquiterpene resonances close to those of Ever-2 (Table 5). Six ester functions are present, involving three acetate residues [M − 42; δ_H 1.97, 2.06, and 2.18], two benzoates [m/z 77, 105; δ_H 6.9—7.5 (6 H) and 7.9—8.1 (4 H)] and a nicotinate [m/z 78, 106; characteristic four protons δ_H 7—9 (Experimental section)]. Structure (9) is thus assigned to Ever-7.
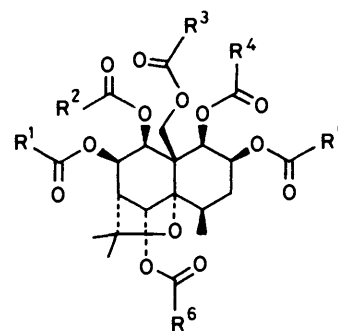
(7); R¹⁻⁶ = 4 × Me, 2 × Ph
(8); R²·³·⁵·⁶ = Me, R¹·⁴ = Ph
(9); R¹⁻⁶ = 3 × Me, 2 × Ph, 3-pyridyl
(10); R¹⁻⁶ = 4 × Me, 1 × Ph, 3-pyridyl

Finally Ever-6 ($C_{36}H_{41}NO_{13}$) is allocated structure (10). Four acetate moieties (δ_H 2.17, 2.06, 1.94, and 1.48) were demonstrated, with one benzoate (m/z 77, 105) and one nicotinate (m/z 78, 106), both with appropriate proton resonances (Experimental section). The sesquiterpene protons (Table 5) give a similar n.m.r. pattern to those of Ever-2 and -7.

The 8-H and 9-H signals were almost coincident in deuterio-chloroform, but were well resolved in deuteriobenzene, thus revealing the essential coupling constants.

Experimental

$R_F(A)$ and $R_F(B)$ Refer respectively to 100 R_F measured on Kieselgel 60F$_{254}$, with cyclohexane–ethyl acetate–ethanol (60:30:1), and on alumina 60F$_{254}$, neutral (type E), with cyclohexane–ethyl acetate–ethanol (60:30:0.1). Unless stated otherwise, ^{1}H chemical shifts were measured at 250 MHz using deuteriochloroform solutions; in assignments given below nicotinoyl and benzoyl residues are numbered with single and double primes respectively. Light petroleum refers to the fraction boiling over the range 40—60 °C.

Extraction of Euonymus verrucosus.—Fresh fruits (5 kg) of *E. verrucosus* were extracted at ambient temperature with methanol (25 dm^3). The extract was evaporated to 5 dm^3 and diluted with water (5 cm^3). The solution was then extracted with light petroleum (5 × 10 dm^3). Evaporation of the organic phase gave a residue (260 g) which was absorbed onto silica (400 g) and chromatographed on silica (1 250 g). Elution commenced with light petroleum, and 500 cm^3 fractions were collected. After 14 fractions, elution with cyclohexane–ethyl acetate (19:1) (23 fractions), cyclohexane–ethyl acetate (9:1) (8 fractions), and cyclohexane–ethyl acetate (8:2) (30 fractions) followed. Elution with cyclohexane–ethyl acetate (7:3) then gave 36 fractions (Nos. 76—111) containing the sesquiterpene esters described herein. Fractions 86 and 87 were rechromatographed on a polyamide column, with methanol–water (1:1) elution, to yield Ever-1 (3) (2 g) as the major crystalline ester, m.p. 188.5—192 °C (from aq. methanol); $R_F(A)$ 37, $R_F(B)$ 61 (Found: M^+, 617.284. C$_{32}$H$_{43}$NO$_{11}$ requires M, 617.284); δ_H 9.23 (1 H, d, J 2 Hz, 2'-H), 8.78 (1 H, dd, J 2 and 5 Hz, 6'-H), 8.30 (1 H, ddd, J 2, 2, and 8 Hz, 4'-H), 7.40 (1 H, dd, J 5 and 8 Hz, 5'-H), 2.26, 2.11, and 2.07 (each 3 H, s, COMe), 0.81 (3 H, d, J 7 Hz, CH_3CH), and 0.57 (3 H, t, J 7.4 Hz, CH_3CH$_2$).

Fraction 83 was rechromatographed on a polyamide column, with methanol–water (1:1), and Ever-2 (7) (100 mg) was finally obtained after preparative t.l.c. (p.l.c.) (silica) with cyclohexane–ethyl acetate–ethanol (60:30:1). Ever-2 had m.p. 81—86 °C (from methanol), $R_F(A)$ 59, $R_F(B)$ 69 (Found: M^+, 694 (FAB), m/z 652.247. C$_{37}$H$_{42}$O$_{13}$ requires M, 694; M − 42 requires m/z, 652.252); δ_H 8.1 and 7.9 (both 2 H, m, 2 × 2''- and 6''-H), 7.6—7.3 (6 H, m, 2 × 3''-H, 4''-H, 5''-H), and 2.14, 2.09, 1.98, and 1.42 (each 3 H, s, COMe).

The mother liquors obtained after crystallisation of Ever-1 from fraction 87 were chromatographed on a silica column with cyclohexane–ethyl acetate (3:1). Fractions rich in Ever-4 (5b) were rechromatographed on a Sephadex LH 20 column, in methanol, and Ever-4 (150 mg) was finally purified by p.l.c. on silica [cyclohexane–ethyl acetate–ethanol (60:30:1)]. It had m.p. 102—110 °C (from methanol), $R_F(A)$ 27, $R_F(B)$ 44 (Found: M^+, 637.251. C$_{34}$H$_{39}$NO$_{11}$ requires M, 637.252); δ_H(C$_6$D$_6$) 9.31 (1 H, br d, J 2 Hz, 2'-H), 8.42 (1 H, dd, J 2 and 5 Hz, 6'-H), 8.05 (1 H, ddd, J 2, 2, and 8 Hz, 4'-H), 7.75 (2 H, dd, J 1 and 8 Hz, 2''- and 6''-H), 6.87 (3 H, m, 3''-, 4''-, and 5''-H), 6.59 (1 H, dd, J 5 and 8 Hz, 5'-H), and 1.93, 1.69, and 1.66 (each 3 H, s, COMe).

Fractions 91—96 were combined and rechromatographed on a polyamide column employing methanol–water (1:1) as eluant, and fractions containing Ever-6 and Ever-7 were further chromatographed, first on a Sephadex LH-20 column in methanol, then on alumina plates with cyclohexane–ethyl acetate–ethanol (60:30:0.1), and then dichloromethane–benzene (7:3) as developer. Final purification on silica plates with cyclohexane–ethyl acetate–ethanol (60:30:1.5) provided Ever-6 (10) (66 mg), $R_F(A)$ 16, $R_F(B)$ 37; m.p. 89—96 °C (from

methanol, and Ever-7 (9) (17 mg), $R_F(A)$ 16, $R_F(B)$ 36; m.p. 83—95 °C (from methanol). Ever-6 (Found: M^+, 695.252. C$_{36}$H$_{41}$NO$_{13}$ requires M, 695.258) had δ_H 9.09 (1 H, d, J 2 Hz, 2'-H), 8.77 (1 H, dd, J 2 and 5 Hz, 6'-H), 8.19 (1 H, ddd, J 2, 2, and 8 Hz, 4'-H), 7.99 (2 H, m, 2''- and 6''-H), 7.6—7.3 (4 H, m, 5'-, 3''-, 4''-, and 5''-H), and 2.17, 2.06, 1.94, and 1.48 (each 3 H, s, COMe). Ever-7 (Found: M^+, 757.268. C$_{41}$H$_{43}$NO$_{13}$ requires M, 757.273) had δ_H 8.68 (1 H, d, J 2.5 Hz, 2'-H), 8.64 (1 H, dd, J 2 and 7 Hz, 6'-H), 8.03 and 7.98 (both 2 H, m, 2 × 2''- and 6''-H), 7.89 (1 H, d, J 7 Hz, 4'-H), 7.7—7.2 (1 H, m, 5'-H), 7.5—6.9 (6 H, m, 2 × 3''-, 4''-, and 5''-H), and 2.18, 2.06, and 1.97 (each 3 H, s, COMe).

Fractions 88—90 were combined and rechromatographed on a polyamide column with methanol–water (1:1) as eluant. Material obtained from fraction 87 after the removal of Ever-1 and Ever-4 was added, and the mixture was rechromatographed twice on silica columns, with cyclohexane–ethyl acetate (3:1). Ever-1 (3) crystallised out of early fractions, and the mother liquors were finally separated by p.l.c. on alumina with n-hexane–tetrahydrofuran–acetonitrile (6:1:0.3), to give Ever-8 (5d) (12 mg), $R_F(A)$ 31, $R_F(B)$ 48; m.p. 69—74 °C (from methanol). Later column fractions were similarly plated on alumina to yield Ever-10 (5c) (12 mg), $R_F(A)$ 30, $R_F(B)$ 42; m.p. 81—87 °C (from methanol). Ever-8 (Found: M^+, 665.286. C$_{36}$H$_{43}$NO$_{11}$ requires M, 665.284) had δ_H 8.84 (1 H, d, J 2 Hz, 2'-H), 8.71 (1 H, dd, J 2 and 4 Hz, 6'-H), 8.05 (1 H, ddd, J 2, 2, and 7 Hz, 4'-H), 7.7—7.2 (6 H, m, 5'-, 2''-, 3''-, 4''-, 5''-, and 6''-H), 2.7—1.8 (4 H, m, CH$_3$CH_2CH_2CO), 1.12 (3 H, t, CH_3CH$_2$CH$_2$CO), and 2.29 and 2.12 (both 3 H, s, COMe).

Ever-10 (Found: M^+, 651.266. C$_{35}$H$_{41}$NO$_{11}$ requires M, 651.268) had 8.86 (1 H, br, 2'-H), 8.71 (1 H, dd, J 2 and 5 Hz, 6'-H), 8.07 (1 H, br ddd, 4'-H), 7.6—7.1 (6 H, m, 5'-, 2''-, 3''-, 4''-, 5''-, and 6''-H), 2.7—1.8 (2 H, m, CH$_3$CH_2CO); 1.08 (3 H, t, CH_3CH$_2$CO), and 2.30 and 2.13 (both 3 H, s, COMe).

Crystallographic Analysis of Ever-1.—The space group and preliminary cell parameters for Ever-1 (3) were determined photographically. For intensity measurement a crystal of approximate dimensions 0.7 × 0.5 × 0.35 mm was mounted on an Enraf-Nonius CAD 4 diffractometer. Accurate lattice parameters were obtained by least-squares refinement of the positions of 25 reflections with θ *ca.* 30°. Intensity data were collected with Cu-K_α radiation using an $\omega/\frac{2}{3}\theta$ scan for 1° < θ < 76°. A total of 3 895 independent reflections was measured of which 2 501 had $I > 3\sigma$ (I) and were considered observed and used in the subsequent refinement. The data were collected for Lorentz and polarisation factors but no absorption corrections were applied. Data reduction and subsequent crystallographic calculations were performed using the CRYSTALS system of programs.[6]

Crystal data. C$_{32}$H$_{43}$NO$_{11}$, $M = 617.7$, orthorhombic, $a = 10.321(1)$, $b = 15.190(1)$, $c = 21.275(1)$ Å, $V = 3 335.28$ Å^3, $Z = 4$, $D_c = 1.23$ g cm^{-3}, $F(000) = 1 320$. Space group $P2_12_12_1$ uniquely from systematic absences. Cu-K_α radiation $\lambda = 1.541 78$ Å, μ(CuK_α) = 7.79 cm^{-1}.

Structure solution and refinement. The structure was solved by direct methods using the MULTAN program:[7] 38 of the 44 non-hydrogen atoms were located in this way and the remaining atoms were found in subsequent difference Fourier calculations. Atomic positions were refined using full-matrix least-squares procedures initially isotropically and subsequently with anisotropic thermal parameters. The approximate positions of many hydrogen atoms were revealed in difference maps but accurate positions were calculated using geometric considerations. The hydrogen atoms were then included in the structure factor calculations but without refinement. In the latter stages of refinement a weighting scheme based on a Chebyshev poly-nominal was used. Refinement finally converged with the largest

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Table 6. Atomic co-ordinates for Ever-1 (3)

Atom	x	y	z
C(1)	0.253 6(6)	0.250 4(4)	0.151 5(2)
C(2)	0.307 6(6)	0.344 0(4)	0.149 5(3)
C(3)	0.369 1(6)	0.369 1(4)	0.210 8(3)
C(4)	0.283 4(6)	0.354 2(3)	0.268 5(3)
C(5)	0.228 5(5)	0.259 3(3)	0.268 2(2)
C(6)	0.141 2(5)	0.233 7(3)	0.323 1(2)
C(7)	0.174 2(5)	0.137 0(3)	0.328 3(2)
C(8)	0.100 3(5)	0.093 5(3)	0.272 6(3)
C(9)	0.123 3(5)	0.132 1(4)	0.207 9(2)
C(10)	0.157 3(5)	0.231 6(3)	0.205 4(2)
C(11)	0.322 2(6)	0.135 3(4)	0.321 4(3)
C(12)	0.395 2(6)	0.162 9(4)	0.379 8(3)
C(13)	0.382 0(6)	0.050 7(4)	0.298 1(3)
C(14)	0.187 0(8)	0.430 1(4)	0.279 2(4)
C(15)	0.029 2(5)	0.282 5(4)	0.193 0(3)
C(16)	0.263 1(9)	0.209 1(8)	0.043 9(3)
C(17)	0.188 8(11)	0.217 1(11)	−0.018 6(4)
C(18)	0.228 5(12)	0.471 8(7)	0.099 0(4)
C(19)	0.103 4(14)	0.521 2(8)	0.084 8(4)
C(20)	0.078 4(6)	0.292 5(4)	0.421 8(3)
C(21)	0.116 6(8)	0.356 0(5)	0.471 3(3)
C(22)	0.189 3(7)	0.012 0(4)	0.143 1(3)
C(23)	0.301 2(6)	−0.033 5(4)	0.114 5(3)
C(24)	0.277 2(8)	−0.107 2(5)	0.076 6(5)
N(25)	0.369 4(9)	−0.153 2(4)	0.047 7(4)
C(26)	0.489 7(9)	−0.124 3(5)	0.055 4(4)
C(27)	0.525 4(7)	−0.052 9(5)	0.089 7(3)
C(28)	0.427 4(6)	−0.006 1(5)	0.120 2(3)
C(29)	−0.181 0(7)	0.288 0(5)	0.238 9(4)
C(30)	−0.277 6(8)	0.237 7(7)	0.274 9(6)
C(31)	0.226 4(19)	0.297 3(16)	−0.056 2(5)
C(32)	0.217 2(21)	0.149 0(15)	−0.053 3(7)
C(33)	0.170 2(31)	0.078 2(13)	−0.025 3(10)
O(1)	0.188 5(4)	0.231 6(3)	0.092 2(2)
O(2)	0.201 5(5)	0.403 5(3)	0.134 0(2)
O(5)	0.341 1(3)	0.202 3(2)	0.271 8(2)
O(6)	0.173 3(4)	0.285 2(2)	0.377 8(2)
O(9)	0.225 7(4)	0.082 7(3)	0.175 7(2)
O(15)	−0.076 5(3)	0.240 6(3)	0.227 4(2)
O(16)	0.379 5(7)	0.193 7(6)	0.050 4(3)
O(18)	0.335 3(10)	0.487 9(6)	0.082 0(5)
O(20)	−0.021 4(4)	0.254 1(3)	0.417 8(2)
O(22)	0.078 6(5)	−0.012 1(4)	0.137 3(3)
O(29)	−0.191 3(7)	0.361 0(4)	0.221 7(5)

parameter shifts 0.05σ giving a final R value of 6.05% with R_w 0.0805. A final difference map showed no peaks or depressions greater than 0.22 e $Å^{-3}$. Final atomic co-ordinates are listed in Table 6; temperature factors and H-atom co-ordinates are listed as Supplementary Publication [SUP 56448 (5 pp.)].*

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1. Structure factors are available from the editorial office on request.

References

1 R. M. Smith in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, London, 1977, vol. 16, 213.
2 *Inter alia* (a) K. Sugiura, Y. Shizuri, K. Yamada, and Y. Hirata, *Chem. Lett.*, 1975, 471; *Tetrahedron*, 1982, **38**, 3465; (b) C. R. Smith, R. W. Miller, D. Weisleder, W. K. Rohwedder, N. Eickman, and J. Clardy, *J. Org. Chem.*, 1976, **41**, 3264; (c) A. Römer, H. Thomas, and H. Budzikiewicz, *Z. Naturforsch, Teil B*, 1976, **31**, 607; (d) H. Budzikiewicz and A. Römer, *Tetrahedron*, 1975, **31**, 1761, 2638; (e) H. Wagner, R. Brüning, H. Lotter, and A. Jones, *Tetrahedron Lett.*, 1977, 125; (f) H. Lotter, R. Brüning, and H. Wagner, *ibid.*, 1978, 3243; (g) H. Ishiwata, Y. Shizuri, and K. Yamada, *Phytochemistry*, 1983, **22**, 2839; (h) K. Yamada, Y. Shizuri, and Y. Hirata, *Tetrahedron Lett.*, 1973, 741; *Tetrahedron*, 1978, **34**, 1915; (i) R. Brüning and H. Wagner, *Phytochemistry*, 1978, **17**, 1821; (j) L. Dúbravková, L. Dolejuš, and Z. Voticky, *ibid.*, 1979, **18**, 1740.
3 (a) R. L. Baxter, L. Crombie, D. J. Simmonds, D. A. Whiting, O. J. Braenden, and K. Szendrei, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2965; (b) R. L. Baxter, L. Crombie, D. J. Simmonds, and D. A. Whiting, *ibid.*, 1979, 2972; (c) L. Crombie, W. M. L. Crombie, D. A. Whiting, and K. Szendrei, *ibid.*, 1979, 2976; (d) R. L. Baxter, W. M. L. Crombie, L. Crombie, D. J. Simmonds, D. A. Whiting, and K. Szendrei, *ibid.*, 1979, 2982; (e) L. Crombie, P. J. Ham, and D. A. Whiting, *Phytochemistry*, 1973, **12**, 703.
4 G. Baudouin, F. Tillequin, M. Koch, M.-E. Tran Huu Dau, J. Guilhem, and H. Jacquemin, *Heterocycles*, 1984, **22**, 221.
5 S. M. Kupchan, R. M. Smith, and R. F. Bryan, *J. Am. Chem. Soc.*, 1970, **92**, 666.
6 J. R. Carruthers, CRYSTALS User Manual, Oxford University Laboratory, 1975.
7 P. Main, S. L. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, MULTAN, a System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, Universities of York, England and Louvain, Belgium, 1980.