Structure and Conformation of a Stoicheiometric Adduct of 4-Epimatricin† with 3β-Hydroxydihydrocostunolide‡ and of 4-Epimatricin Alone

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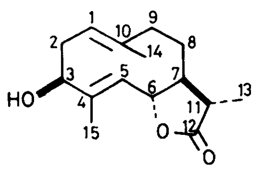
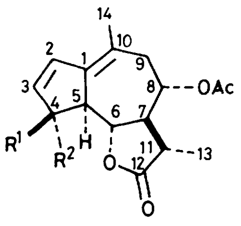
The guaianolide 4-epimatricin (**2**) and the germacrolide 3β-hydroxydihydrocostunolide (**3**) form in the solid state a stoicheiometric non-covalent adduct through a complex chain of hydrogen bonds involving their hydroxy groups and one water molecule. In this adduct, 3β-hydroxydihydrocostunolide exists as a $[^{15}D_{5',1}D^{14}]$ double-chair rotamer, whereas the cycloheptene ring system of 4-epimatricin adopts a C_s conformation. The crystal structure of 4-epimatricin alone has also been investigated. Comparison of the results for the latter compound alone and in the adduct reveals a somewhat different conformation of the γ-lactone rings and a larger deviation from the ideal C_s symmetry of the cycloheptene ring in the adduct.

Recent work on *Artemisia arborescens* L., a plant believed to have contraceptive properties by the ancient Greeks, Romans, and Arabs,[1] led to the isolation and stereochemical elucidation of the epimeric proazulene sesquiterpene lactones matricin (**1**) and 4-epimatricin (**2**).[2] Investigation of a new chemotype lacking matricin has given as a major constituent a crystalline material which, according to spectral analysis (^1H n.m.r., ^{13}C n.m.r.), is a stoicheiometric mixture of 4-epimatricin and another sesquiterpene lactone. To establish the nature of the unidentified compound and to shed light on its interaction with 4-epimatricin in the solid state, a crystallographic investigation was undertaken. The crystal structure of 4-epimatricin alone has also been investigated for reference and is reported here.



(3)



(1) $R^1 = CH_3$, $R^2 = OH$
(2) $R^1 = OH$, $R^2 = CH_3$

Results and Discussion

The *X*-ray analysis showed that the above crystalline material is a stoicheiometric non-covalent adduct of 4-epimatricin with the germacrolide 3β-hydroxydihydrocostunolide (**3**) § and that an unforeseen water molecule is also present in the asymmetric unit (see Experimental section).

Tables 3 and 4 list the bond distances and angles of 4-epimatricin alone and of the adduct respectively, using the numbering of Figures 1 and 2 which are ORTEP II drawings.[3]

3β-*Hydroxydihydrocostunolide* (**3**) *in the Adduct*.—In the present adduct, the *trans,trans*-cyclodeca-1,5-diene system of molecule (**3**) adopts the crossed double-chair $[^{15}D_{5},{}_{1}D^{14}]$ conformation already observed in costunolide[4] and typical of C(6) *trans*-fused germacrolides.[5] The carbon–carbon torsion angles ¶ around the endocyclic double bonds show the differential distortion already found in several other germacrolides[4] (Table 5). The OH function at C(3′) (Figure 2) is β-orientated and has little influence on the conformation of the cyclodecadiene ring since it can be accommodated in equatorial position. The bond lengths (Table 4) are consistently longer than in costunolide,[4] but not unusual $[<C_{sp^3}–C_{sp^3}> 1.539(2)$ Å, $<C_{sp^2}–C_{sp^2}> 1.510(2)$ Å], whilst the corresponding valence angles are very similar. The γ-lactone ring of the present molecule (**3**) is *trans*-fused at C(6′) and adopts an envelope conformation with puckering parameters[6] $\varphi_2 = 3.4(7)°$, $Q = 0.308(3)$ Å and asymmetry parameter[7] $\Delta C_s = 0.015(2)$ through the C(7′) atom. The C(13′) methyl group (Figure 2) is in α-pseudo-equatorial position. Molecule (**3**) is connected to (**2**) by a fairly strong hydrogen bond involving the hydroxy groups of the two molecules (Figure 3, Table 6).

4-*Epimatricin Alone*.—The present investigation has confirmed the stereochemistry of (**2**) established by spectroscopic analysis.[2] The cycloheptene ring shows the C_s chair conformation[8] (Table 5) with a mirror plane through C(7) and the middle point of the double bond C(1)=C(10). Despite the marked asymmetry of the substitution pattern of the cycloheptene ring, the deviation from the ideal C_s symmetry is small as measured by the parameter[8] $\Sigma_s = 8.4°$, and by the asymmetry parameters[6,7] $\Delta C_s[C(7)] = 0.009(1)$. The total puckering amplitude is $Q = 0.672(3)$ Å. Atom C(7) is 0.73 Å above the plane through the moiety C(9)–C(10)=C(1)–C(5), whereas C(6) and C(8) are both 1.02 Å above that plane. The torsion angles around the bonds involved in the fusion with the two five-membered rings deviate significantly from the

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† (3*S**,3a*R**,4*S**,9*S*,9a*S**,9b*S**)-4-Acetoxy-3a,4,5,9,9a,9b-hexahydro-9-hydroxy-3,6,9-trimethylazuleno[4,5-*b*]furan-2(3*H*)-one.

‡ (3*S**,3a*S**,9*S**,11a*S**)-3a,4,5,8,9,11a-Hexahydro-3,6,10-trimethylcyclodeca[*b*]furan-2(3*H*)-one.

§ 3β-Hydroxydihydrocostunolide was found in minute amounts in *Picris echioides* L., but it was isolated as its acetate owing to separation problems (F. Bohlmann, Ch. Zdero, H. Robinson, and M. R. King, *Phytochemistry*, 1981, **20**, 2029).

¶ The calculation of the torsion value τ (F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **53**, 169) seems of little meaning in the present case since the hydrogen atoms were placed in calculated positions.

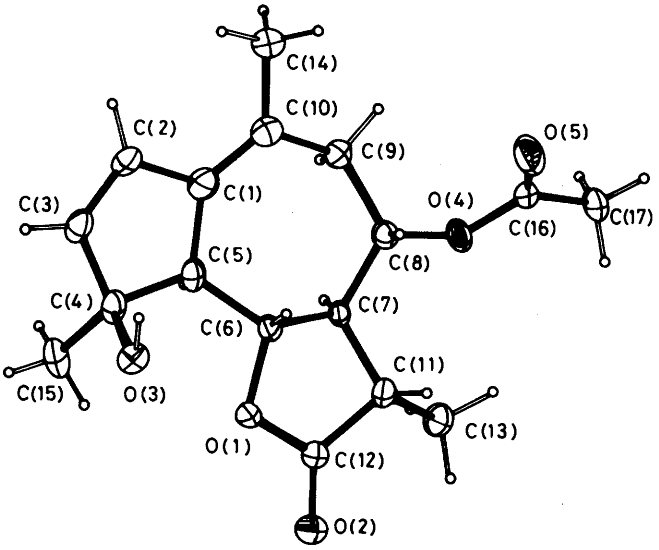

Figure 1. ORTEP II drawing of the molecule of 4-epimatricin (**2**) with the thermal ellipsoids at the 20% probability level

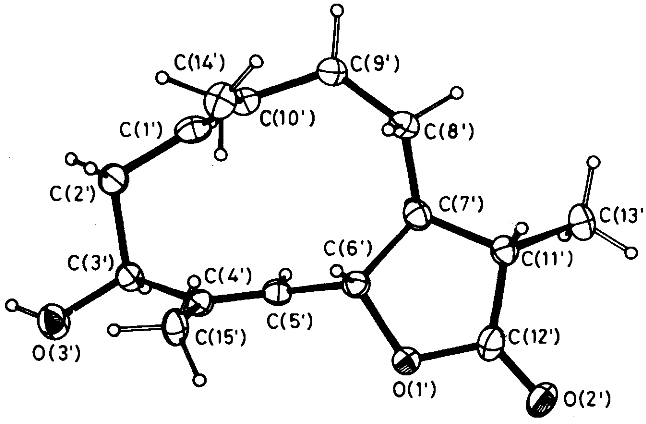

Figure 2. ORTEP II drawing of the molecule of 3β-hydroxydihydrocostunolide (**3**) with the thermal ellipsoids at the 20% probability level

theoretical values.[9] The bond angles within the cycloheptene ring are all larger than the ideal tetrahedral or trigonal values [mean values 114.5(2)° and 126.7(2)°, respectively] as expected with a ring of this size;[10] the bond lengths are, *vice versa*, shorter than the ideal: $< C_{sp^3}\text{–}C_{sp^3} > = 1.514(2)$ Å.

For the cyclopentene ring, both the deviation from 90° of $\varphi_2[=83(1)°]$ and the value of $\Delta C_2[C(2)]$ [=0.029(1)] indicate a deviation from the ideal twist. The overall puckering, Q = 0.126(3) Å, is not marked; C(4) and C(5) are at −0.071(3) and 0.076(3) Å, respectively, from the mean plane through the ring. The hydroxy group at C(4) is in a β-pseudo-axial orientation, *trans* to the α-pseudo-axial H(5).

The γ-lactone ring adopts an envelope conformation with φ_2 = 4.0(4)°, Q = 0.383(2) Å, and with a C_s plane through C(7), $\Delta C_s[C(7)]$ = 0.024(1). The acetate group adopts the *Z* conformation with the carbonyl group and H(8) *syn* [H(8)–C(8)–O(4)–C(16) = −33(2)°]; this is the most stable conformation according to both dipole moment[11] and *X*-ray analysis.[12]

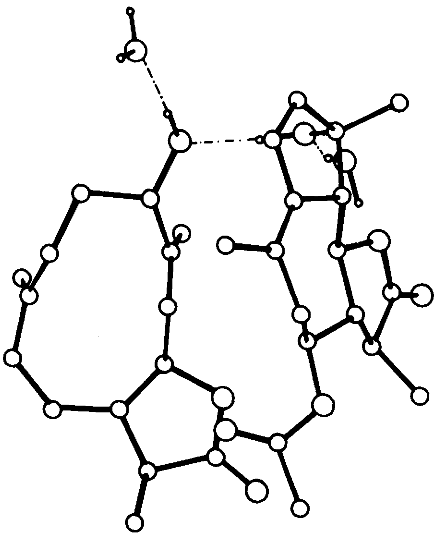

Figure 3. Hydrogen bonding in the structure of the adduct.

Table 1. Atom co-ordinates (× 10^4) and temperature factors (Å^2, × 10^3) of 4-epimatricin alone; e.s.d.s in parentheses

Atom	x	y	z	U*
C(1)	1 969(2)	4 397(4)	3 458(2)	47(1)
C(2)	3 412(3)	4 167(5)	3 616(2)	62(1)
C(3)	3 508(3)	2 806(6)	2 901(2)	68(1)
C(4)	2 139(2)	1 915(4)	2 068(2)	51(1)
C(5)	1 141(2)	2 789(4)	2 591(2)	44(1)
C(6)	−259(2)	3 390(3)	1 588(2)	41(1)
C(7)	−1 368(2)	3 847(3)	2 034(2)	41(1)
C(8)	−1 144(2)	5 758(4)	2 654(2)	45(1)
C(9)	75(2)	5 788(4)	3 945(2)	55(1)
C(10)	1 541(2)	5 691(4)	4 038(2)	47(1)
C(11)	−2 712(2)	3 454(4)	823(2)	47(1)
C(12)	−2 285(2)	1 928(4)	237(2)	49(1)
C(13)	−4 059(2)	3 094(5)	934(3)	62(1)
C(14)	2 502(3)	7 130(4)	4 934(2)	63(1)
C(15)	2 108(3)	−223(5)	2 083(3)	72(1)
C(16)	−2 757(2)	7 887(4)	2 873(2)	58(1)
C(17)	−4 059(3)	7 994(6)	3 039(3)	88(2)
O(1)	−886(2)	1 820	715(2)	51(1)
O(2)	−3 021(2)	825(3)	−540(2)	66(1)
O(3)	1 768(2)	2 415(3)	797(1)	54(1)
O(4)	−2 398(2)	6 115(3)	2 829(2)	56(1)
O(5)	−2 087(2)	9 221(3)	2 811(2)	85(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Hydrogen Bonding System in the Adduct of (**2**), (**3**), *and Water*.—In the adduct, molecules (**2**) and (**3**) interact through hydrogen bonding (Figure 3, Table 6) between their hydroxy groups with the tertiary O–H groups of (**2**) acting as donor. Also the water molecule is involved in the hydrogen bonding, acting as donor towards O(3) of (**2**) and as acceptor from atom O(3′) of (**3**), which belongs to another asymmetric unit (Table 6). In this way a chain of hydrogen bonds develops along a two-fold axis. It is worth noting that each hydroxy group of (**2**) and (**3**) acts both as donor and as acceptor of hydrogen bonds whilst one of the hydrogen atoms of the water molecule approaches both O(1) and O(2), without forming true hydrogen bonds (Table 6). This net of hydrogen bonds, involving water molecules, provides an explanation for the preferential formation of the adduct over the crystallization of (**2**) and (**3**) separately. In fact, compound (**2**) could be obtained in crystal form only after the removal of (**3**) through formation of the adduct. Compound (**3**) does not crystallize alone, it is an

Table 2. Atom co-ordinates (× 10^4) and temperature factors (Å^2, × 10^3) of the adduct; e.s.d.s in parentheses

Atom	*x*	*y*	*z*	*U**
O(1)	6 295(2)	3 923	4 595(2)	50(1)
O(2)	5 159(2)	2 297(2)	3 931(2)	66(1)
O(3)	8 798(2)	4 544(2)	5 339(2)	55(1)
O(4)	3 708(2)	6 685(2)	2 266(2)	53(1)
O(5)	4 272(2)	7 642(2)	1 018(2)	60(1)
C(1)	7 373(3)	7 236(3)	4 898(2)	56(1)
C(2)	8 626(3)	7 470(3)	5 570(3)	68(1)
C(3)	9 125(3)	6 523(4)	6 152(3)	69(1)
C(4)	8 316(3)	5 410(3)	5 904(2)	55(1)
C(5)	7 063(3)	5 954(3)	5 203(2)	47(1)
C(6)	6 381(2)	5 182(2)	4 249(2)	41(1)
C(7)	5 061(3)	5 521(3)	3 660(2)	42(1)
C(8)	4 973(2)	6 614(3)	2 948(2)	43(1)
C(9)	5 318(3)	7 808(3)	3 563(2)	57(1)
C(10)	6 644(3)	8 014(3)	4 184(3)	60(1)
C(11)	4 543(3)	4 313(3)	3 128(2)	50(1)
C(12)	5 307(3)	3 379(3)	3 886(2)	49(1)
C(13)	3 174(3)	4 081(4)	2 902(3)	73(1)
C(14)	7 094(5)	9 258(4)	3 970(4)	105(2)
C(15)	8 221(4)	4 735(4)	6 868(3)	75(1)
C(16)	3 495(3)	7 204(3)	1 315(2)	50(1)
C(17)	2 173(3)	7 134(4)	678(3)	76(1)
O(1′)	5 310(2)	4 807(2)	839(2)	54(1)
O(2′)	3 348(2)	4 710(3)	−109(2)	81(1)
O(3′)	9 933(2)	5 538(2)	4 006(2)	62(1)
C(1′)	9 330(3)	7 035(3)	1 339(3)	60(1)
C(2′)	10 070(3)	6 525(4)	2 404(3)	64(1)
C(3′)	9 223(3)	6 114(3)	3 034(2)	53(1)
C(4′)	8 287(3)	5 238(3)	2 355(2)	45(1)
C(5′)	7 293(3)	5 727(3)	1 667(2)	46(1)
C(6′)	6 458(2)	5 165(3)	674(2)	45(1)
C(7′)	6 057(2)	6 036(3)	−279(2)	48(1)
C(8′)	6 891(3)	6 134(4)	−961(2)	61(1)
C(9′)	8 032(3)	6 936(4)	−542(3)	65(1)
C(10′)	9 011(3)	6 449(3)	422(3)	56(1)
C(11′)	4 788(3)	5 553(3)	−904(2)	50(1)
C(12′)	4 353(3)	4 995(3)	−61(3)	56(1)
C(13′)	3 891(3)	6 478(4)	−1 585(3)	66(1)
C(14′)	9 528(3)	5 233(4)	271(3)	75(2)
C(15′)	8 645(3)	3 918(3)	2 405(3)	62(1)
W	8 262(2)	2 084(2)	4 857(2)	86(1)

* Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor.

unstable oil. Other cases of co-crystallization of different sesquiterpene lactones can be found in the literature. However, in two cases studied by *X*-ray analysis,[13,14] the molecules are very similar and form solid solutions. In the present instance, where the molecules are quite different, we have an ordered crystalline form instead.

Comparison of Molecule (**2**) *Alone and in the Adduct.*—Comparison of the results for (**2**) in the crystal structure of 4-epimatricin alone and in the adduct (Tables 3 and 4) reveals that most of the bond distances and angles are equal within their standard deviations. The differences regard the bonds involving atoms engaged in hydrogen bonding. Thus, C(12)–O(2) is equal in the two structures since O(2) is involved in hydrogen bonds in both structures, whilst C(4)–O(3) and C(12)–O(1) are significantly longer in the adduct where O(3) and O(1) form hydrogen bonds (Tables 3 and 4). This stretching can be attributed, in part, to the perturbation induced by atom H(2W) which approaches both O(1) and O(2); the perturbation seems to influence the torsion angles within the lactone ring as well (Table 5).

Table 3. Bond lengths (Å) and bond angles (°) in 4-epimatricin alone; e.s.d.s in parentheses

C(1)–C(2)	1.488(4)	C(1)–C(5)	1.533(3)
C(1)–C(10)	1.345(4)	C(2)–C(3)	1.321(5)
C(3)–C(4)	1.499(3)	C(4)–C(5)	1.579(4)
C(4)–C(15)	1.524(5)	C(4)–O(3)	1.425(3)
C(5)–C(6)	1.507(3)	C(6)–C(7)	1.531(4)
C(6)–O(1)	1.470(2)	C(7)–C(8)	1.515(3)
C(7)–C(11)	1.536(3)	C(8)–C(9)	1.512(3)
C(8)–O(4)	1.466(3)	C(9)–C(10)	1.524(4)
C(10)–C(14)	1.508(3)	C(11)–C(12)	1.515(4)
C(11)–C(13)	1.536(4)	C(12)–O(1)	1.349(3)
C(12)–O(2)	1.203(3)	C(16)–C(17)	1.490(5)
C(16)–O(4)	1.327(4)	C(16)–O(5)	1.212(4)
C(2)–C(1)–C(5)	105.3(2)	C(2)–C(1)–C(10)	125.6(2)
C(5)–C(1)–C(10)	129.0(2)	C(1)–C(2)–C(3)	111.8(2)
C(2)–C(3)–C(4)	113.9(3)	C(3)–C(4)–C(5)	101.9(2)
C(3)–C(4)–C(15)	115.8(2)	C(5)–C(4)–C(15)	111.6(3)
C(3)–C(4)–O(3)	109.2(2)	C(5)–C(4)–O(3)	113.3(2)
C(15)–C(4)–O(3)	105.4(2)	C(1)–C(5)–C(4)	105.5(2)
C(1)–C(5)–C(6)	113.4(2)	C(4)–C(5)–C(6)	114.2(2)
C(5)–C(6)–C(7)	116.0(2)	C(5)–C(6)–O(1)	109.1(2)
C(7)–C(6)–O(1)	102.8(2)	C(6)–C(7)–C(8)	112.2(2)
C(6)–C(7)–C(11)	101.3(2)	C(8)–C(7)–C(11)	117.6(2)
C(7)–C(8)–C(9)	112.7(2)	C(7)–C(8)–O(4)	105.4(2)
C(9)–C(8)–O(4)	106.8(2)	C(8)–C(9)–C(10)	118.2(2)
C(1)–C(10)–C(9)	124.4(2)	C(1)–C(10)–C(14)	123.1(2)
C(9)–C(10)–C(14)	112.4(2)	C(7)–C(11)–C(12)	100.9(2)
C(7)–C(11)–C(13)	118.4(2)	C(12)–C(11)–C(13)	111.3(2)
C(11)–C(12)–O(1)	110.7(2)	C(11)–C(12)–O(2)	128.3(2)
O(1)–C(12)–O(2)	121.0(2)	C(17)–C(16)–O(4)	110.9(3)
C(17)–C(16)–O(5)	125.4(3)	O(4)–C(16)–O(5)	123.7(3)
C(6)–O(1)–C(12)	109.3(2)	C(8)–O(4)–C(16)	118.0(2)

The cycloheptene ring of (**2**) in the adduct has less marked C_s symmetry than in (**2**) alone; $\Sigma_s = 16.2°$, ΔC_s[C(7)] = 0.044(2), with a slightly smaller total puckering amplitude $Q = 0.614(5)$ Å. For the γ-lactone ring of (**2**) $\varphi_2 = 86.0(7)°$ indicates that the conformation of this ring can be described as twisted. However, the value of ΔC_s[C(12)] = 0.086(1) indicates a significant deviation from the ideal twist towards the envelope form adopted by the lactone ring in 4-epimatricin alone.

Experimental

Crystal Data.—4-Epimatricin (**2**), $C_{17}H_{22}O_5$, m.p. 147 °C, $[\alpha]_D^{25}$ −80° ($CHCl_3$, *c* 0.52 g dm^{-3}), monoclinic, space group $P2_1$, $a = 10.689(2)$, $b = 7.123(1)$, $c = 11.858(2)$ Å, $\beta = 116.08(1)°$, $V_c = 810.8(2)$ Å^3, $Z = 2$, $D_c = 1.25$ mg m^{-3}; graphite-monochromatized Mo-K_α radiation, $\lambda = 0.710\,69$ Å, μ(Mo-K_α) = 0.08 mm^{-1}, *F*(000) = 328.

Adduct of 4-epimatricin, H_2O, and 3β-hydroxydihydrocostunolide (1:1:1), $C_{32}H_{44}O_9$, m.p. 96—98 °C, monoclinic, space group $P2_1$, $a = 11.645(2)$, $b = 10.981(5)$, $c = 13.419(5)$ Å, $\beta = 109.4(1)°$, $V_c = 1\,619(1)$ Å^3, $Z = 2$, $D_c = 1.25$ mg m^{-3}, graphite-monochromatized Mo-K_α radiation, $\lambda = 0.710\,69$ Å, μ(Mo-K_α) = 0.09 mm^{-1}, *F*(000) = 616.

Data Collection.—The measurements for both compounds were done on a Nicolet R3 diffractometer at room temperature; the cell parameters were obtained and refined from 25 reflections, 30° ≤ 2θ ≤ 40° in the case of (**2**), 13° ≤ 2θ ≤ 37° in the case of the adduct. The intensities were collected using the ω-scan technique at variable speed; the backgrounds were measured in stationary mode for 0.8 times the peak scan time; periodic remeasurements of standard reflections did not show significant intensity variations for either compound.

Table 4. Bond lengths (Å) and bond angles (°) in the adduct; e.s.d.s in parentheses

O(1)–C(6)	1.472(3)	O(1)–C(12)	1.363(3)
O(2)–C(12)	1.205(4)	O(3)–C(4)	1.441(4)
O(4)–C(8)	1.455(3)	O(4)–C(16)	1.343(4)
O(5)–C(16)	1.204(4)	C(1)–C(2)	1.460(4)
C(1)–C(5)	1.542(4)	C(1)–C(10)	1.353(4)
C(2)–C(3)	1.314(5)	C(3)–C(4)	1.511(5)
C(4)–C(5)	1.568(4)	C(4)–C(15)	1.526(5)
C(5)–C(6)	1.520(4)	C(6)–C(7)	1.523(4)
C(7)–C(8)	1.516(4)	C(7)–C(11)	1.532(4)
C(8)–C(9)	1.530(4)	C(9)–C(10)	1.508(5)
C(10)–C(14)	1.524(6)	C(11)–C(12)	1.509(4)
C(11)–C(13)	1.542(5)	C(16)–C(17)	1.495(4)
O(1′)–C(6′)	1.479(4)	O(1′)–C(12′)	1.360(3)
O(2′)–C(12′)	1.193(4)	O(3′)–C(3′)	1.438(3)
C(1′)–C(2′)	1.511(4)	C(1′)–C(10′)	1.328(5)
C(2′)–C(3′)	1.564(5)	C(3′)–C(4′)	1.511(4)
C(4′)–C(5′)	1.332(3)	C(4′)–C(15′)	1.503(5)
C(5′)–C(6′)	1.497(3)	C(6′)–C(7′)	1.540(4)
C(7′)–C(8′)	1.543(5)	C(7′)–C(11′)	1.531(4)
C(8′)–C(9′)	1.537(5)	C(9′)–C(10′)	1.509(4)
C(10′)–C(14′)	1.505(6)	C(11′)–C(12′)	1.514(5)
C(11′)–C(13′)	1.525(4)		

C(6)–O(1)–C(12)	108.8(2)	C(8)–O(4)–C(16)	116.7(2)
C(2)–C(1)–C(5)	105.7(2)	C(2)–C(1)–C(10)	126.1(3)
C(5)–C(1)–C(10)	128.1(3)	C(1)–C(2)–C(3)	112.4(3)
C(2)–C(3)–C(4)	112.9(3)	O(3)–C(4)–C(3)	109.0(3)
O(3)–C(4)–C(5)	112.5(2)	C(3)–C(4)–C(5)	102.2(2)
O(3)–C(4)–C(15)	106.0(3)	C(3)–C(4)–C(15)	114.9(3)
C(5)–C(4)–C(15)	112.3(3)	C(1)–C(5)–C(4)	104.7(2)
C(1)–C(5)–C(6)	112.9(2)	C(4)–C(5)–C(6)	114.5(2)
O(1)–C(6)–C(5)	109.2(2)	O(1)–C(6)–C(7)	103.3(2)
C(5)–C(6)–C(7)	117.1(2)	C(6)–C(7)–C(8)	111.5(2)
C(6)–C(7)–C(11)	101.7(2)	C(8)–C(7)–C(11)	117.3(2)
O(4)–C(8)–C(7)	106.3(2)	O(4)–C(8)–C(9)	108.8(2)
C(7)–C(8)–C(9)	112.8(2)	C(8)–C(9)–C(10)	117.7(3)
C(1)–C(10)–C(9)	125.7(3)	C(1)–C(10)–C(14)	121.7(3)
C(9)–C(10)–C(14)	112.6(3)	C(7)–C(11)–C(12)	102.8(2)
C(7)–C(11)–C(13)	117.1(3)	C(12)–C(11)–C(13)	111.1(3)
O(1)–C(12)–O(2)	119.9(2)	O(1)–C(12)–C(11)	110.1(2)
O(2)–C(12)–C(11)	129.9(2)	O(4)–C(16)–O(5)	124.2(2)
O(4)–C(16)–C(17)	110.6(3)	O(5)–C(16)–C(17)	125.2(3)
C(6′)–O(1′)–C(12′)	110.0(2)	C(2′)–C(1′)–C(10′)	126.4(3)
C(1′)–C(2′)–C(3′)	110.8(3)	O(3′)–C(3′)–C(2′)	110.0(2)
O(3′)–C(3′)–C(4′)	110.4(3)	C(2′)–C(3′)–C(4′)	108.4(3)
C(3′)–C(4′)–C(5′)	116.7(3)	C(3′)–C(4′)–C(15′)	116.9(2)
C(5′)–C(4′)–C(15′)	125.8(2)	C(4′)–C(5′)–C(6′)	127.5(3)
O(1′)–C(6′)–C(5′)	109.2(2)	O(1′)–C(6′)–C(7′)	104.4(2)
C(5′)–C(6′)–C(7′)	114.3(2)	C(6′)–C(7′)–C(8′)	117.3(3)
C(6′)–C(7′)–C(11′)	102.2(2)	C(8′)–C(7′)–C(11′)	112.5(2)
C(7′)–C(8′)–C(9′)	117.4(3)	C(8′)–C(9′)–C(10′)	115.2(3)
C(1′)–C(10′)–C(9′)	121.4(3)	C(1′)–C(10′)–C(14′)	123.6(3)
C(9′)–C(10′)–C(14′)	114.9(3)	C(7′)–C(11′)–C(12′)	103.5(2)
C(7′)–C(11′)–C(13′)	116.2(3)	C(12′)–C(11′)–C(13′)	112.6(3)
O(1′)–C(12′)–O(2′)	120.5(3)	O(1′)–C(12′)–C(11′)	110.2(3)
O(2′)–C(12′)–C(11′)	129.2(3)		

Table 5. Relevant torsion angles (°); e.s.d.s 0.2—0.3° unless given in parentheses

	(2) Alone	**(2)** In the adduct
C(1)–C(5)–C(6)–C(7)	−71.7	−72.0
C(5)–C(6)–C(7)–C(8)	77.2	78.1
C(6)–C(7)–C(8)–C(9)	−73.2	−73.0
C(7)–C(8)–C(9)–C(10)	72.0	72.1
C(8)–C(9)–C(10)–C(1)	−50.8	−52.4
C(9)–C(10)–C(1)–C(5)	0.7	3.5
C(10)–C(1)–C(5)–C(6)	47.4	44.9
Σ_s	8.4	16.2
C(6)–O(1)–C(12)–C(11)	−3.4	−10.2
O(1)–C(12)–C(11)–C(7)	−20.6	−13.2
C(12)–C(11)–C(7)–C(6)	34.7	29.8
C(11)–C(7)–C(6)–O(1)	−37.5	−36.0
O(2)–C(12)–C(11)–C(13)	32.4	41.0
C(1)–C(2)–C(3)–C(4)	3.2	5.1
C(2)–C(3)–C(4)–C(5)	−9.9	−12.2
C(3)–C(4)–C(5)–C(1)	12.3	13.9
C(4)–C(5)–C(1)–C(2)	−11.1	−11.8

	(3) In the adduct
C(1′)–C(2′)–C(3′)–C(4′)	54.3
C(3′)–C(4′)–C(5′)–C(6′)	156.7
C(5′)–C(6′)–C(7′)–C(8′)	87.1
C(7′)–C(8′)–C(9′)–C(10′)	69.3
C(9′)–C(10′)–C(1′)–C(2′)	165.2
C(14′)–C(10′)–C(1′)–H(1′)	174(2)
C(2′)–C(3′)–C(4′)–C(5′)	−85.0
C(4′)–C(5′)–C(6′)–C(7′)	−137.2
C(6′)–C(7′)–C(8′)–C(9′)	−79.3
C(8′)–C(9′)–C(10′)–C(1′)	−115.9
C(10′)–C(1′)–C(2′)–C(3′)	−99.0
C(15′)–C(4′)–C(5′)–H(5′)	−179(2)

Table 6. Hydrogen bonding in compound **(2)** and in the adduct with some relevant O–H distances; e.s.d.s in parentheses

Compound **(2)**			
O(3) ··· O(2$^{\mathrm{I}}$)	2.854(3)	H(3O) ··· O(2$^{\mathrm{I}}$)	1.86(2)
Adduct			
O(3) ··· O(3′)	2.775(2)	O(3)–H(3O)	0.98(3)
H(3O) ··· O(3′)	1.80(2)	O(3′)–H(3′O)	0.96(2)
O(3) ··· W	2.800(3)	W–H(1W)	0.97(2)
O(3) ··· H(1W)	1.85(2)	W–H(2W)	0.95(3)
W ··· O(3′$^{\mathrm{II}}$)	2.738(2)	W ··· H(3′O$^{\mathrm{II}}$)	1.80(2)
O(1) ··· W	2.986(3)	O(1) ··· H(1W)	2.55(2)
O(2) ··· W	3.417(2)	O(1) ··· H(2W)	2.67(2)
		O(2) ··· H(2W)	2.59(2)

Superscripts refer to the following positions: I, $\bar{x}$, $0.5 + y$, $\bar{z}$; II, $2 - x$, $y - 0.5$, $1 - z$.

Compound **(2)**. A colourless prismatic elongated crystal (0.22 × 0.29 × 0.93 mm), crystallized from ethyl acetate, was mounted. The scan speed was from 1.5° min^{-1} for the weakest to 10.0° min^{-1} for the strongest reflections; the scan range was 1.0°. Two independent octants of the reciprocal lattice sphere were explored up to $2\theta = 50°$; 1 580 independent reflections were measured; 1 427 with $I \leq 2\sigma(I)$ were considered as observed and corrected for background and Lorentz-polarization effect[15] (h −11, 10; k 0, 8; l 0, 14). Seven reflections, exceeding 60 000 counts s^{-1} on pre-scan, were measured with the insertion of a copper attenuator, but two of them had to be discarded in the course of the refinement because of too poor agreement between F_o and F_c. An empirical absorption correction, based on the ψ-scan method,[16] was applied using six reflections over the range $14 \leq 2\theta \leq 41°$.

Adduct. A fragment (0.85 × 0.85 × 1.25 mm), cut from large yellowish squat prisms crystallizing from ethyl acetate, was mounted.

The scan speed was from 2° to 15° min^{-1}; the scan range was 1.2°. Two independent octants were explored up to $2\theta = 58°$; 4 138 independent reflections were measured and 3 252 with $I \leq 2\sigma(I)$ were considered as observed and treated as for **(2)**.

Nine reflections, measured with the attenuator, were discarded together with six other low-angle reflections because they were probably affected by the secondary extinction effect (*h* –15, 13; *k* 0, 14; *l* 0, 17).

Structure Solution and Refinement.—For all the subsequent computations use was made of the SHELXTL system.[17]

Compound (**2**). The solution was attained by the RANTAN program,[18] assigning random phases to the 202 $|E|$ values ≥ 1.60 (1 509 triple-phase relationships). The E-map from the solution with the best figures of merit showed all the 22 non-hydrogen atoms. The refinement was by standard least-squares procedure.[17] All H atoms were located on difference Fourier maps at an advanced stage of the anisotropic refinement. However, only the co-ordinates of the H atoms at O(3), C(2), and C(3) (Figure 1) were allowed to refine under the constraints[17] C–H, O–H = 0.98 ± 0.02 Å whilst the other hydrogens were placed in calculated positions and treated as rigid groups. Three different isotropic thermal parameters were refined for the H atoms: the first was assigned to the hydrogens of the C–H and O–H groups, the second to the hydrogens of the methyl groups, and the third to the two hydrogens at C(9). These parameters converged to 0.058(2), 0.095(3), and 0.086(6) Å^2, respectively. The weighting scheme introduced in the final cycles was: $w = 1/[\sigma^2(F_o) + GF_o{}^2]$ where σ is the standard deviation of F_o based on counting statistics and G is a variable to be refined.[17] Convergence (average ratio of shifts to errors *ca.* 0.04) was attained at $R = 0.039$, $wR = 0.044$, $G = 0.001\,07$, goodness of fit = 1.447 for 1 475 reflections and 222 least-squares parameters.

Adduct. In the case of the adduct, analysed for $C_{32}H_{44}O_9$, the value of the density calculated assuming $Z = 2$ led us to surmise, initially, that the asymmetric unit was here formed by two molecules of similar formula. The presence of two molecules of 4-epimatricin in the asymmetric unit was excluded by the spectroscopic analysis that had revealed the presence of 32 carbon atoms: the ^{1}H n.m.r. spectrum showed two sets of signals in an equimolar ratio and the ^{13}C n.m.r. spectrum had shown that besides the 17 lines of 4-epimatricin, 15 additional lines were present. The solution was attempted with the RANTAN program[18] assigning random phases to the 318 $|E|$ values ≥ 1.78 (2 202 triple-phase relationships). The E-map calculated from the best solution showed only 26 atoms belonging to two molecular fragments. Several cycles of difference Fourier maps and least-squares refinement were necessary to locate the remaining atoms of the asymmetric unit consisting, in fact, of one molecule of 4-epimatricin joined, through hydrogen bonding, to one molecule of 3β-hydroxydihydrocostunolide and to one molecule of water. The refinement was as for compound (**2**); all H atoms were successfully located on difference Fourier maps, but only the co-ordinates of hydrogens at C(2), C(3), O(3), C(1′), C(5′), O(3′), and W (Figures 2 and 3) were allowed to refine under the constraints C–H, O–H = 0.98 ± 0.02 Å; to the two hydrogen atoms of the water molecule a further constraint $H \cdots H = 1.55 \pm 0.02$ Å was applied. The other hydrogens were treated as for (**2**). Three isotropic temperature factors were allotted to the H atoms: the first to the hydrogens of the C–H and O–H groups and of the water molecule, the second to the hydrogens of the methyl groups, and the third to the hydrogens at C(9), C(2′), C(8′), and C(9′). These parameters converged to 0.056(2), 0.147(4), and 0.060(3) Å^2, respectively. At convergence (average ratio of shifts to errors *ca.* 0.10) the agreement parameters were: $R = 0.049$, $wR = 0.053$, $G = 0.000\,87$, goodness of fit = 1.424 for 3 237 reflections and 417 least-squares parameters.

Tables of anisotropic thermal parameters of the non-hydrogen atoms and hydrogen atom parameters have been deposited as Supplementary Publication No. SUP 56101 (5 pp.).* Tables 1 and 2 list the final parameters of compound (**2**) and of the adduct respectively, using the numbering scheme of Figures 2 and 3.[3]

Acknowledgements

We are greatly indebted to Professor T. Sacco for providing the plant material and to Professor P. Gariboldi for the preliminary spectroscopic analysis of the adduct.

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Received 12*th March* 1984; *Paper* 4/396

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* For details of the Supplementary Publications, see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1.