X-Ray Structure of a Fluoroguaianolide Derivative

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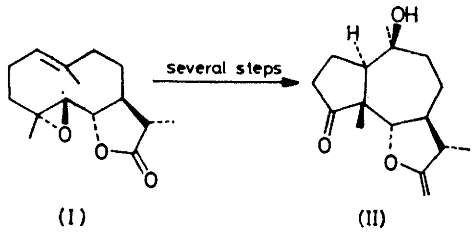
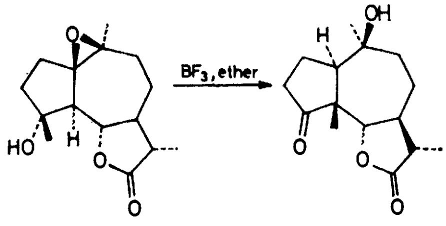
The molecular structure of a fluoro-derivative (IV) of a guaianolide has been established by single-crystal *X*-ray diffraction techniques. The compound is a product of the BF_3-catalyzed opening of an epoxide group in a 1,10-epoxyguaianolide (III) derived from the germacranolide sesquiterpene lactone dihydroparthenolide (I). Crystals of (IV) are orthorhombic, space group $P2_12_12_1$, with Z = 4 in a unit cell of dimensions a = 8.975(2), b = 11.174(2), c = 14.583(6) Å. The structure was refined to R 0.027 for 1 648 reflections. The molecule features a fully-saturated *cis*-fused guaianolide-type skeleton with idealized symmetry C_s, having the seven-membered ring in the chair and the five-membered ring in the envelope conformation. Substituents on this fused ring system are α-F at C(1), α-OH and β-Me at C(4), an α-methyl-γ-lactone *trans*-fused at C(6) and C(7), and α-Me and β-OH substituents at C(10). The stereochemistry of the precursor 1,10-epoxide is thus inferred to be β.

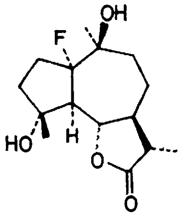
THE biogenetic pathway from *trans,trans*-farnesyl pyrophosphate to pseudoguaianolides presumably involves germacranolides and guaianolides at intermediate stages.[1,2] Wu and Fischer,[2] in order to give this postulate some indirect experimental verification, attempted the *in vitro* synthesis of a pseudoguaianolide, (II) from the germacrolide 4,5-epoxide, dihydroparthenolide, (I). As a crucial final step in this synthesis, the guaianolide epoxide (III) was treated with BF_3 in hopes of effecting the rearrangement to the pseudoguaianolide (II). The reaction mixture, after quenching with water, yielded two major products, one of which has been characterized by *X*-ray diffraction techniques to the guaianolide derivative (IV).



(I) (II)



(III) (II)



(IV)

EXPERIMENTAL

Crystals of the guaianolide derivative (IV) were obtained from ethyl acetate–ethyl ether solution as needles, which could be easily broken to yield approximately cubic fragments. One such fragment of size *ca.* 0.42 × 0.50 × 0.62 mm was glued to the tip of a glass fibre and mounted in a random orientation on an Enraf–Nonius CAD4 diffractometer. All measurements were made by use of graphite-monochromatized Mo-K_α radiation. Unit-cell dimensions and crystal orientation were determined from diffractometer co-ordinates of 60 accurately-centred reflections having $2\theta > 27°$.

Crystal Data.—$C_{15}H_{23}O_4F$, $M = 286.3$, orthorhombic, $a = 8.975(2)$, $b = 11.174(2)$, $c = 14.583(6)$ Å, $U = 1\ 462$ Å^3, $Z = 4$, $D_c = 1.30$ gcm^{-3}. Mo-K_α radiation, $\lambda = 0.7107$ Å; μ(Mo-K_α) = 1.09 cm^{-1}. Space group $P2_12_12_1$ from systematic absences.

Intensity data were collected by the ω—2θ scan technique. Diffracted *X*-rays were detected by a scintillation counter equipped with pulse-height analyser. All reflections in one octant for which $6° < 2\theta < 60°$ were measured at least once. The 2θ scan width was computed for each reflection as $(0.9° + 0.35 \tan\theta)$ to account for α_1–α_2 splitting. The scan was then extended on both ends by 25% with the counts collected during these extensions taken as measurements of backgrounds. The width of the receiving aperture was also varied as a function of angle, being computed as $(3.0 + 1.0 \tan\theta)$ mm. A rapid (3 1/3° min^{-1}) prescan was made for each reflection. A prescan intensity of $>10^3$ counts was accepted as the final measurement, one of <35 counts, was considered unobserved; for an intermediate value, the reflection was remeasured at a scan speed appropriate to yield a net intensity of 1 000 counts. An upper limit of 180 s was set for the scan time spent on any reflection. During data collection, three reflections periodically remeasured every 50 reflections exhibited no significant decrease.

Of 2 430 independent intensities thus measured 953 were considered as observed, having $I > 3\sigma(I)$. The variances $\sigma^2(I)$ were estimated from counting statistics, including a term $[0.02\ (\text{counts})]^2$. Lorentz and polarization corrections were applied to the data, but owing to the low linear absorption coefficient and equant shape of the crystal, errors due to absorption were judged to be insignificant.

Structure Solution and Refinement.—Space group $P2_12_12_1$, and $Z = 4$ requires one molecule per asymmetric unit. The structure was solved by routine application of the multiple-solution direct phasing method[3] using program

MULTAN 74. Phasing of the 300 reflections with highest E values by means of 1 900 Σ_2 relationships led to 32 phase sets; the set with highest overall figure of merit proving correct. An E map phased with this set revealed the locations of all 20 non-hydrogen atoms of the structure among the top 22 peaks.

This model was refined by full-matrix least-squares techniques. After some anisotropic refinement, methyl and hydroxy hydrogen atoms were found by calculating a difference Fourier synthesis using data with $\sin\theta/\lambda < 0.5$. Hydrogen atom positions were indicated by well-defined peaks of density 0.2—0.4 e Å^{-3}; other hydrogen atoms were placed in calculated positions. At this point in the refinement, the fluorine atom F(1) was thought to be an oxygen atom, and was treated as such. However, no electron density >0.1 e Å^{-3} was found in its vicinity, and the hydroxy-hydrogen atom was thought to be disordered.

Refinement was continued on an IBM 360/65 using programs of ref. 4 (primarily *X*-Ray '73), and adjusting anisotropic temperature factors for non-hydrogen atoms and isotropic temperature factors for hydrogen atoms. Scattering factors for non-hydrogen atoms were taken from ref. 5 and for hydrogen from ref. 6. The function minimized in the least-squares procedure was $\Sigma w\ (|F_o| - |F_c|)^2$, where the weights are $w = \sigma^{-2}(F_o)$. This model was refined in two blocks, one containing all positional parameters (129), and the other containing all temperature factors (143) and the scale factor. The strongest reflection (120) suffered from extinction or difficulty in measurement, and thus was assigned zero weight in the refinement. Refinement was terminated when all shifts were small with respect to the standard deviation of the refined value of the variable. The refined model produced discrepancy indices of R 0.035 and R' 0.033 based upon observed reflections $[R' = \Sigma w(|F_o| - |F_c|)^2/\Sigma F_o^2]$.

Careful consideration of this model (a guaianolide triol) revealed several disturbing features about the substituent atom on C(1), which at that point was thought to be a hydroxy-group: the hydrogen atom was not located although all other hydroxy and methyl hydrogen atoms showed up clearly on difference maps, the anisotropic thermal parameters for this atom were smaller than would be expected based upon other thermal parameters (particularly for genuine hydroxy-oxygen atoms) in the structure, and the C–O distance for this atom [1.424(3) Å] was significantly shorter than the identical values of 1.443(3) and 1.441(3) Å for hydroxy-substituents O(3) and O(4). Also the hydrogen analysis for the compound was slightly low [2] (8.24% experimental *vs.* 8.45% calc. for $C_{15}H_{24}O_5$).

These considerations indicated that the substituent at C(1) was possibly fluorine. To test this hypothesis, this identity was assigned, and a new refinement carried out leading to significant improvement of the fit of the data, and to more reasonable values for thermal parameters for the fluorine atom. In the last cycles of refinement, 688 reflections considered unobserved, but calculating greater than their measured values, were used in the calculation, in addition to the observed reflections. This model produced discrepancy indices of R 0.027 and R' 0.026 based upon observed reflections, and a goodness-of-fit value $\{= [\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)]^{\frac{1}{2}}$, where N_o = no. of observations and N_v = no. of refined variables$\}$ of 0.827 for 1 640 measurements and 273 refined variables. This low value is apparently due to an overestimation of the standard deviations of the measurements. Since the method of data collection leads to approximately equal weights for all reflections, this overestimation introduces no systematic error, but merely leads to underestimation of the precision of the final results. A three-dimensional Fourier map computed at the conclusion of refinement exhibited no residuals $> \pm 0.15$ eÅ^{-3}. Observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 22361 (19 pp., 1 microfiche).*

RESULTS AND DISCUSSION

One of the products of the BF_3-catalyzed opening of the epoxide ring in the epoxyguaianolide (III) has been shown by this study to be the *trans*-1-fluoro-10-hydroxyguaianolide (IV), apparently formed by backside nucleophilic attack at C(1) by fluoride ion or a fluorine-containing nucleophile derived from BF_3. The details of this reaction are not clear. It is clearly quite unusual, as BF_3 normally does not act as a fluorinating agent towards organic molecules, but typically merely catalyzes a variety of reactions. One possible explanation for this unusual product is that commercial BF_3–ether was used undistilled in the reaction. If it were contaminated with HF, a simple acid-catalyzed opening of the epoxide ring by HF would lead to the observed product.

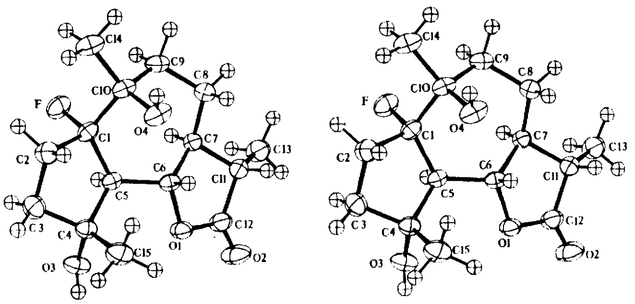


FIGURE 1 Stereoview of fluoroguaianolide molecule $C_{15}H_{23}O_4F$. Thermal ellipsoids for nonhydrogen atoms are drawn at the 40% probability level. Hydrogen atoms are represented by spheres of arbitrary radius

TABLE 1

Non-hydrogen atom positional (× 10^5) parameters

Atom	x	y	z
F(1)	39 709(15)	77 898(13)	12 894(8)
O(1)	75 832(17)	77 948(15)	35 267(9)
O(2)	95 551(20)	67 260(16)	39 838(11)
O(3)	44 466(21)	77 092(15)	41 327(10)
O(4)	61 688(23)	104 552(14)	15 524(11)
C(1)	45 845(28)	87 899(21)	17 782(14)
C(2)	32 475(32)	94 752(26)	21 691(17)
C(3)	29 575(29)	89 111(27)	31 017(18)
C(4)	45 134(27)	86 895(20)	34 943(15)
C(5)	53 926(27)	82 511(21)	26 322(15)
C(6)	70 689(26)	83 923(21)	26 738(15)
C(7)	79 646(25)	77 762(23)	19 185(14)
C(8)	81 288(27)	85 312(24)	10 542(16)
C(9)	66 671(31)	87 491(25)	5 543(16)
C(10)	54 674(28)	94 991(20)	10 496(15)
C(11)	94 350(25)	74 896(22)	24 088(15)
C(12)	89 183(28)	72 823(24)	33 874(15)
C(13)	103 815(35)	64 678(27)	20 402(19)
C(14)	43 896(36)	100 003(26)	3 239(17)
C(15)	51 778(36)	97 829(24)	39 510(19)

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

Figure 1 shows the fluoroguaianolide molecule. Positional parameters arising from the refinement are tabulated in Tables 1 and 2, bonded interatomic distances in Table 3, important angles in Table 4, and torsion angles involving atoms of the ten-membered ring in Table 5.

TABLE 2

Hydrogen atom positional ($\times 10^4$) parameters

Atom	x	y	z
H(21)	3 509(23)	10 346(20)	2 240(13)
H(22)	2 426(28)	9 467(19)	1 708(14)
H(31)	2 368(30)	9 476(21)	3 514(15)
H(32)	2 463(23)	8 146(19)	3 002(13)
H(5)	5 176(18)	7 437(15)	2 583(11)
H(6)	7 359(23)	9 280(17)	2 713(13)
H(7)	7 546(20)	6 988(16)	1 769(11)
H(81)	8 521(24)	9 288(20)	1 217(13)
H(82)	8 946(25)	8 115(20)	640(14)
H(91)	6 907(23)	9 252(19)	−18(14)
H(92)	6 240(22)	7 984(18)	346(12)
H(11)	10 034(22)	8 275(16)	2 465(13)
H(131)	9 809(29)	5 684(25)	1 963(17)
H(132)	10 775(31)	6 718(24)	1 430(20)
H(133)	11 174(29)	6 253(21)	2 431(16)
H(141)	3 883(28)	9 250(24)	15(15)
H(142)	3 647(31)	10 538(21)	576(16)
H(143)	5 004(22)	10 388(19)	−139(14)
H(151)	4 497(26)	10 030(19)	4 411(16)
H(152)	5 381(29)	10 044(24)	3 470(18)
H(153)	6 226(31)	9 670(20)	4 245(16)
H(30)	4 442(27)	7 876(22)	4 621(13)
H(40)	5 981(29)	11 066(21)	1 266(15)

TABLE 3

Bond distances (Å)

C(1)–C(2)	1.533(4)	C(8)–H(82)	1.06(2)
C(1)–C(5)	1.562(3)	C(9)–C(10)	1.544(4)
C(1)–C(10)	1.544(3)	C(9)–H(91)	1.03(2)
C(1)–F(1)	1.435(3)	C(9)–H(92)	0.98(2)
C(2)–C(3)	1.521(4)	C(10)–C(14)	1.539(4)
C(2)–H(21)	1.01(2)	C(10)–O(4)	1.440(3)
C(2)–H(22)	1.00(2)	C(11)–C(13)	1.521(4)
C(3)–C(4)	1.529(4)	C(11)–C(12)	1.518(3)
C(3)–H(31)	1.02(2)	C(11)–H(11)	1.03(2)
C(3)–H(32)	0.97(2)	C(12)–O(1)	1.344(3)
C(4)–C(5)	1.563(3)	C(12)–O(2)	1.212(3)
C(4)–C(15)	1.514(4)	C(13)–H(131)	1.02(3)
C(4)–O(3)	1.439(3)	C(13)–H(132)	1.00(3)
C(5)–C(6)	1.514(3)	C(13)–H(133)	0.94(2)
C(5)–H(5)	0.93(2)	C(14)–H(141)	1.06(3)
C(6)–C(7)	1.528(3)	C(14)–H(142)	0.97(3)
C(6)–O(1)	1.485(3)	C(14)–H(143)	0.97(2)
C(6)–H(6)	1.03(2)	C(15)–H(151)	0.95(2)
C(7)–C(8)	1.524(3)	C(15)–H(152)	1.03(3)
C(7)–C(11)	1.535(3)	C(15)–H(153)	1.04(3)
C(7)–H(7)	0.98(2)	O(3)–H(30)	0.74(2)
C(8)–C(9)	1.520(4)	O(4)–H(40)	0.82(2)
C(8)–H(81)	0.95(2)		

Examination of the torsion angles in Table 5 indicates that the ten-membered fused ring system of this compound closely approximates ideal C_s symmetry. The seven-membered ring is essentially in the chair conformation; the largest deviation from an ideal angle for the chair conformation[7] is only 13°, presumably reflecting the conformational constraints placed upon the ring by the fusion of the lactone at C(6)–C(7). Deviations of the five-membered ring from torsion angles expected for the ideal envelope formation[8] with $\phi_{\text{max.}}$ 42° are also small.

Distances between bonded tetrahedral carbon atoms in this molecule range from 1.514(3) to 1.563(3) Å, mean 1.532(4) Å. The two C–O(hydroxy) distances are statistically identical [1.439(3) and 1.440(3) Å]. The mean of the twenty one C–H distances is 0.999(8) Å, and of the two O–H distances 0.78(4) Å. The C–F bond distance [1.435(3) Å] is somewhat longer than expected. Standards for comparison are rare, as only a few measure-

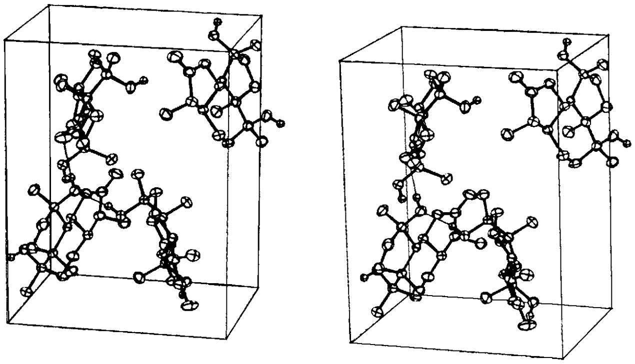

FIGURE 2 Unit-cell contents viewed oblique to a axis. The origin of the crystal co-ordinate system is in the lower right corner (foreground). The b axis runs horizontally, and the c axis vertically. All hydrogen atoms except those of hydroxy-groups have been omitted for clarity

TABLE 4

Bond angles (°)

C(2)–C(1)–C(5)	105.0(2)	C(6)–C(7)–C(8)	113.4(2)
C(2)–C(1)–C(10)	113.6(2)	C(6)–C(7)–C(11)	102.2(2)
C(2)–C(1)–F(1)	105.9(2)	C(8)–C(7)–C(11)	114.7(2)
C(5)–C(1)–C(10)	120.5(2)	C(7)–C(8)–C(9)	113.7(2)
C(5)–C(1)–F(1)	105.9(2)	C(8)–C(9)–C(10)	117.7(2)
C(10)–C(1)–F(1)	104.8(2)	C(9)–C(10)–C(1)	113.7(2)
C(1)–C(2)–C(3)	105.0(2)	C(9)–C(10)–C(14)	108.3(2)
C(2)–C(3)–C(4)	104.2(2)	C(9)–C(10)–O(4)	109.6(2)
C(3)–C(4)–C(5)	102.2(2)	C(1)–C(10)–C(14)	109.7(2)
C(3)–C(4)–C(15)	113.2(2)	C(1)–C(10)–O(4)	104.7(2)
C(3)–C(4)–O(3)	109.1(2)	C(14)–C(10)–O(4)	110.8(2)
C(5)–C(4)–C(15)	114.1(2)	C(7)–C(11)–C(12)	102.0(2)
C(5)–C(4)–O(3)	107.6(2)	C(7)–C(11)–C(13)	118.2(2)
C(15)–C(4)–O(3)	110.3(2)	C(12)–C(11)–C(13)	112.8(2)
C(1)–C(5)–C(4)	106.6(2)	C(11)–C(12)–O(1)	110.5(2)
C(1)–C(5)–C(6)	117.0(2)	C(11)–C(12)–O(2)	127.5(2)
C(4)–C(5)–C(6)	115.9(2)	O(1)–C(12)–O(2)	122.0(2)
C(5)–C(6)–C(7)	116.6(2)	C(4)–O(3)–H(30)	116(2)
C(5)–C(6)–O(1)	107.2(2)	C(10)–O(4)–H(40)	106(2)
C(7)–C(6)–O(1)	103.8(2)		

TABLE 5

Important torsion angles (°) involving the fused ring system

	Found	Calc.*
C(10)–C(1)–C(5)–C(6)	−4	0
C(1)–C(5)–C(6)–C(7)	−63	−71
C(5)–C(6)–C(7)–C(8)	86	92
C(6)–C(7)–C(8)–C(9)	−66	−70
C(7)–C(8)–C(9)–C(10)	65	70
C(8)–C(9)–C(10)–C(1)	−79	−92
C(9)–C(10)–C(1)–C(5)	63	71
C(5)–C(1)–C(2)–C(3)	−23	−25
C(1)–C(2)–C(3)–C(4)	40	40
C(2)–C(3)–C(4)–C(5)	−40	−40
C(3)–C(4)–C(5)–C(1)	25	25
C(4)–C(5)–C(1)–C(2)	−2	0

* Calc. values are for ideal angles for the chair conformation of the seven-membered ring and for the envelope conformation of the five-membered ring, both having ideal symmetry C_s.

ments exist for such bond lengths involving tertiary carbon atoms. The most closely related compound containing a tertiary C–F bond appears to be a steroid, in which the fluoro-substituent is also at a carbon atom involved in ring fusion. The C–F distance there[9] is 1.424(4) Å, which differs from the present value by only 0.011 Å, or *ca.* 2σ.

The molecular packing is seen in Figure 2.* The arrangement of molecules in the crystal appears to be determined by hydrogen bonding as the dominant intermolecular interaction. Each molecule donates two hydrogen bonds *via* its two hydroxy-substituents and accepts two hydrogen bonds *via* a hydroxy- and a carbonyl function. The fluorine atoms is not involved in the hydrogen-bonding network. The hydroxy-group O(3)–H(30) donates [a hydrogen bond to the lactone carbonyl oxygen atom of a molecule related by a two-fold screw operation along the *x* direction, and simultaneously accepts a hydrogen bond from the hydroxy-substituent O(4)–H(40) of a molecule symmetrically related by a two-fold screw operation along the *y* direction. Both hydrogen bonds are essentially linear and of lengths indicating moderately strong interactions. [O(3) $\cdots$ O(2) 2.82 and O(4) $\cdots$ O(3) 2.77 Å]. There are no other unusually close intermolecular contacts. Of particular interest is the fact that the fluorine atom F(1) has no intermolecular contacts closer than 4 Å.

Fluorination of the 1,10-epoxy-compound (III) at C(1) *via* BF_4-catalyzed opening of the epoxide is certainly unusual chemistry, but fortuitous, in that it reveals the stereochemistry of the parent epoxide. Since the hydroxy-group O(4) is β-oriented and carbon atom C(10) has not been inverted in the epoxide opening, the epoxy-substituent must also have been β-oriented. As no other stereochemical changes occurred during the reaction, the parent epoxide must have the stereochemistry shown in the formula.

Note that the absolute configuration of the fluoro-compound has not been experimentally determined, but rather has been assumed. The *trans*-fusion of the lactone at C(6)–C(7) is assumed to have absolute stereochemistry with H(6) on the β-face of the molecule and H(7) on the α-face. This enantiomer is consistent with all sesquiterpene lactones of known absolute configuration.[10]

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* The unit-cell contents viewed oblique to the *b* axis are illustrated in the Supplementary Publication. See earlier.

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