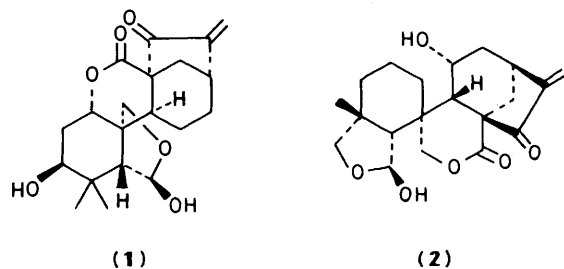


The Conformation of Fujenal, a Seco-ring B *ent*-Kaurenoid Diterpene

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X-Ray crystallographic and n.m.r. studies have shown that the seco-ring B diterpenoid, fujenal, adopts a conformation in which rotation about the C(9)–C(10) bond away from a kaurenoid conformation has occurred.

The tetracyclic diterpenoids are a widespread group of natural products.¹ In contrast to the steroids not only are there a number of different carbon skeletons but also these possess more pendant groups whose interactions may provide the driving force for various skeletal deformations making the conformational analysis of their reactions more complex. Amongst the *ent*-kaurenoid diterpenes are about 40 natural products in which ring B has been cleaved between C-6 and C-7. Most of these compounds have been obtained from medicinal herbs of the genus *Rabdosia* (*Isodon*) (*Labiatae*).² These plants are widely used in folk medicine in the Far East. Their diterpenoid constituents have attracted attention for their biological activity which includes anti-tumour, antibacterial, insect antifeedant, and plant growth inhibitory activity. Many of the compounds possess either a 7,1 [*e.g.* enmein, (1)] or a 7,20 lactone ring [*e.g.* shikodonin (2)] representing various rotamers



about the C(9)–C(10) bond. Fujenal (3), from *Gibberella fujikuroi*, was the first of these 6,7-seco-kaurenoid compounds to be isolated.^{3,4} The corresponding dicarboxylic acid has been detected both in the fungus and in higher plants such as *Cucurbita maxima*.⁵ It was of interest to examine the conformation of fujenal (3) about the C(9)–C(10) bond in the context of possible synthetic transformations. In some earlier work⁶ we had presented two pieces of evidence which suggested that the lactone (4) derived from fujenal retained the conformation approximating to (4) rather than existing as the enmein-like rotamer (5). The i.r. spectrum of the hydroxy lactone (4) showed some evidence of hydrogen bonding whilst the position of the 5-H resonance in the ¹H n.m.r. spectra of a series of derivatives, was sensitive to the oxidation level of C-7—both effects requiring the proximity of C-5, C-6, and C-7 in contrast to the enmein conformation.

The *X*-ray crystal structure of fujenal (3) was obtained and is shown in the Figure. Ring A of the diterpenoid adopts a chair conformation which is somewhat flattened by the 6,19-anhydride ring. Ring C possesses a chair conformation and ring D an envelope conformation. However the two portions of the molecule have clearly rotated away from an overall kaurene-like conformation. Thus the torsion angle C(11)–C(9)–C(10)–C(5) is -76° compared with *ent*-7 α -hydroxykaurenoic acid methyl ester (6) in which it is -179.7° .⁷ A comparable situation exists

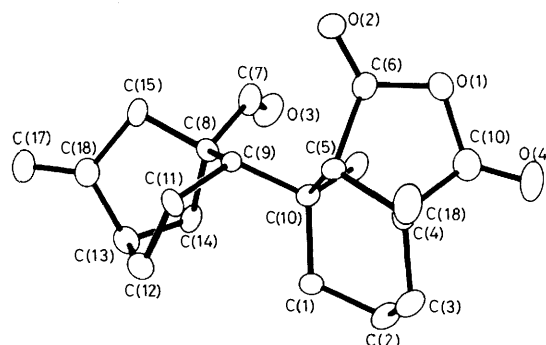
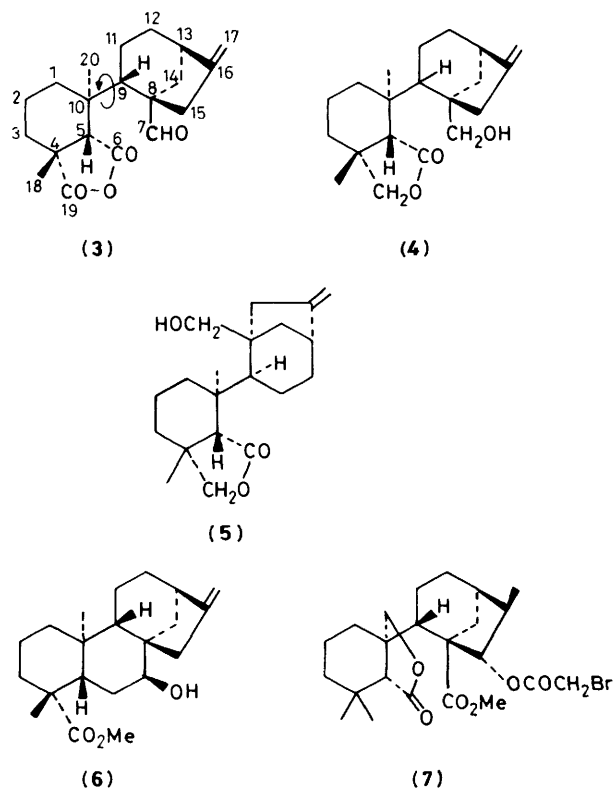


Figure. The molecular structure of fujenal



in the bromo acetate (7)⁸ derived from enmein in which the molecule has rotated around the C(9)–C(10) bond away from an enmein-like rotamer towards the conformation adopted by fujenal. This is reflected in the C(1)–C(10)–C(9)–C(11) torsion angles which are -63.2° in *ent*-7 α -hydroxykaurenoic acid methyl ester, 35° in the bromo acetate (7), and 44.3° in fujenal (3).

The conformation of fujenal (3) in solution was examined by

Table 1. ^{13}C and ^1H N.m.r. signals in fujenal (3) (determined in deuteriochloroform)

Carbon atom	^{13}C Signal	^1H Signal
1	33.30	1.8 and 1.6
2	17.86	1.6 and 1.4
3	28.83	2.35 and 1.21
4	44.60	
5	56.25	2.61
6	172.42	
7	203.74	9.70
8	58.98	
9	46.49	2.67
10	41.91	
11	19.62	1.92 and 1.7
12	32.06	2.0 and 1.5
13	44.00	2.85
14	32.44	1.7 and 1.6
15	42.84	2.46 and 2.20
16	150.97	
17	105.07	4.96 and 4.83
18	29.81	1.37
19	175.89	
20	22.68	0.87

Table 2. Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

	x	y	z
O(1)	4 754(4)	1 565(4)	910(2)
O(2)	5 895(4)	2 841(4)	1 313(2)
O(3)	8 828(6)	-72(5)	2 057(2)
O(4)	4 072(5)	230(5)	367(2)
C(1)	8 109(7)	377(7)	308(2)
C(2)	7 155(7)	-290(7)	25(3)
C(3)	6 299(8)	542(7)	-216(2)
C(4)	5 782(6)	1 437(6)	149(2)
C(5)	6 627(6)	1 949(6)	553(2)
C(6)	5 767(6)	2 212(6)	963(2)
C(7)	8 656(7)	879(7)	1 861(2)
C(8)	9 346(6)	1 341(6)	1 427(2)
C(9)	8 538(6)	1 892(5)	1 021(2)
C(10)	7 598(6)	1 087(6)	746(2)
C(11)	9 342(6)	2 576(6)	661(3)
C(12)	10 484(7)	1 941(7)	522(3)
C(13)	11 117(7)	1 420(7)	967(3)
C(14)	10 299(6)	526(6)	1 218(3)
C(15)	10 126(7)	2 351(6)	1 661(3)
C(16)	11 240(6)	2 367(6)	1 356(3)
C(17)	12 159(7)	3 045(8)	1 424(3)
C(18)	5 227(8)	2 482(7)	-135(3)
C(19)	4 801(7)	962(7)	460(2)
C(20)	7 063(6)	186(6)	1 118(2)

difference n.O.e. spectroscopy. If fujenal retains a conformation comparable with that revealed by the X-ray analysis, n.O.e. effects should exist between 9-H and 5-H and between 7-H and 20-H. If, however, rotation to an enmein-like conformation has occurred, n.O.e. effects should exist between 9-H and 20-H and not with 5-H. This entailed an analysis of the 360 ^1H n.m.r. spectrum and in turn the ^{13}C n.m.r. spectrum of fujenal which was determined at 90.5 MHz.

A number of resonances in the ^1H n.m.r. spectrum were readily assigned on the basis of their chemical shift (e.g. 7-H, δ_{H} 9.70; 17-H δ_{H} 4.83 and 4.96). The signal assigned to 5-H (δ_{H} 2.61) was a clean singlet whilst a decoupling experiment revealed a long-range coupling (J 1.1 Hz) between the aldehydic 7-H and 13-H (δ_{H} 2.85). The two methyl group resonances (δ_{H} 0.87, 20-H

Table 3. Intramolecular distances (\AA) and angles ($^\circ$) with estimated standard deviations in parentheses

(a) Bonds			
O(1)-C(6)	1.371(8)	O(1)-C(19)	1.398(8)
O(2)-C(6)	1.192(8)	O(3)-C(7)	1.217(9)
O(4)-C(19)	1.198(9)	C(1)-C(2)	1.526(11)
C(1)-C(10)	1.546(9)	C(2)-C(3)	1.501(11)
C(3)-C(4)	1.532(10)	C(4)-C(5)	1.564(9)
C(4)-C(18)	1.546(10)	C(4)-C(19)	1.494(10)
C(5)-C(6)	1.506(9)	C(5)-C(10)	1.562(10)
C(7)-C(8)	1.504(9)	C(8)-C(9)	1.561(9)
C(8)-C(14)	1.529(10)	C(8)-C(15)	1.579(10)
C(9)-C(10)	1.587(9)	C(9)-C(11)	1.542(9)
C(10)-C(20)	1.557(9)	C(11)-C(12)	1.529(10)
C(12)-C(13)	1.521(11)	C(13)-C(14)	1.532(11)
C(13)-C(16)	1.510(11)	C(15)-C(16)	1.509(10)
C(16)-C(17)	1.308(11)		
(b) Angles			
C(6)-O(1)-C(19)	108.8(5)	C(2)-C(1)-C(10)	112.1(6)
C(1)-C(2)-C(3)	111.4(7)	C(2)-C(3)-C(4)	112.6(5)
C(3)-C(4)-C(5)	117.5(6)	C(3)-C(4)-C(18)	110.1(5)
C(3)-C(4)-C(19)	114.1(6)	C(5)-C(4)-C(18)	108.1(6)
C(5)-C(4)-C(19)	101.4(5)	C(18)-C(4)-C(19)	104.6(6)
C(4)-C(5)-C(6)	101.0(5)	C(4)-C(5)-C(10)	115.7(6)
C(6)-C(5)-C(10)	109.5(5)	O(1)-C(6)-O(2)	120.4(6)
O(1)-C(6)-C(5)	111.0(5)	O(2)-C(6)-C(5)	128.5(6)
O(3)-C(7)-C(8)	124.4(7)	C(7)-C(8)-C(9)	112.5(6)
C(7)-C(8)-C(14)	116.4(6)	C(7)-C(8)-C(15)	103.4(5)
C(9)-C(8)-C(14)	113.4(5)	C(9)-C(8)-C(15)	108.7(5)
C(14)-C(8)-C(15)	101.0(5)	C(8)-C(9)-C(10)	119.6(5)
C(8)-C(9)-C(11)	107.4(5)	C(10)-C(9)-C(11)	113.0(5)
C(1)-C(10)-C(5)	109.5(5)	C(1)-C(10)-C(9)	114.0(5)
C(1)-C(10)-C(20)	107.4(5)	C(5)-C(10)-C(9)	105.7(5)
C(5)-C(10)-C(20)	110.6(5)	C(9)-C(10)-C(20)	109.7(5)
C(9)-C(11)-C(12)	114.7(6)	C(11)-C(12)-C(13)	112.9(6)
C(12)-C(13)-C(14)	108.8(6)	C(12)-C(13)-C(16)	108.6(6)
C(14)-C(13)-C(16)	102.6(6)	C(8)-C(14)-C(15)	101.0(5)
C(8)-C(15)-C(16)	105.0(5)	C(13)-C(16)-C(15)	107.1(6)
C(13)-C(16)-C(17)	126.1(7)	C(15)-C(16)-C(17)	126.7(7)
O(1)-C(19)-O(4)	119.6(6)	O(1)-C(19)-C(4)	110.0(6)
O(4)-C(19)-C(4)	130.3(6)		

and δ_{H} 1.37 18-H) were distinguished firstly on chemical shift grounds—the equatorial 18-H at lower field influenced by the C-19 carbonyl group—and secondly because irradiation of the signal at δ_{H} 1.37 (18-H) produced an n.O.e. enhancement of the signal for 5-H. The remaining proton resonances were assigned *via* their associated ^{13}C resonances.

Broad-band decoupled, coupled and JMOD ^{13}C n.m.r. spectra were obtained. A number of ^{13}C resonances (e.g. C-7, C-16, and C-17) were immediately assigned on chemical shift grounds. The anhydride carbonyl signals (C-6 and C-19) were readily distinguished since the former was a doublet in the coupled spectrum and showed a 2J coupling to 5-H (5.3 Hz) whilst the latter was a multiplet. A 2J coupling of 23 Hz existed between C-8 and 7-H and was conformed by a selective decoupling of 7-H. A ^1H : ^{13}C two-dimensional chemical shift correlation as then made. Since C-5, C-7, and C-13 could be assigned *via* their proton resonances, the remaining methine carbon signal (δ_{C} 46.49) must belong to C-9. The signal (δ_{H} 2.67) from 9-H was then identified from the ^1H : ^{13}C shift correlation. A further ^1H : ^1H decoupling experiment then revealed the signals for 11-H_a and 12-H leading *via* the 2-D spectrum to the assignment of C-11 and C-12 and the remaining 11 β -H and 12-H signals.

At this stage we had identified 13 out of the 20 carbon signals.

Table 4. Table of torsional angles (°)

Atom 1	Atom 2	Atom 3	Atom 4	Angle	Atom 1	Atom 2	Atom 3	Atom 4	Angle
C(19)	O(1)	C(6)	O(2)	176.7	O(3)	C(7)	C(8)	C(9)	135.0
C(19)	O(1)	C(6)	C(5)	-6.3	O(3)	C(7)	C(8)	C(14)	1.8
C(6)	O(1)	C(19)	O(4)	170.8	O(3)	C(7)	C(8)	C(15)	-107.9
C(6)	O(1)	C(19)	C(4)	-12.8	C(7)	C(8)	C(9)	C(10)	-62.2
C(10)	C(1)	C(2)	C(3)	64.2	C(7)	C(8)	C(9)	C(11)	167.3
C(2)	C(1)	C(10)	C(5)	-56.4	C(14)	C(8)	C(9)	C(10)	72.4
C(2)	C(1)	C(10)	C(9)	-174.5	C(14)	C(8)	C(9)	C(11)	-58.0
C(2)	C(1)	C(10)	C(20)	63.7	C(15)	C(8)	C(9)	C(10)	-176.1
C(1)	C(2)	C(3)	C(4)	-52.8	C(15)	C(8)	C(9)	C(11)	53.4
C(2)	C(3)	C(4)	C(5)	38.4	C(7)	C(8)	C(14)	C(13)	-156.4
C(2)	C(3)	C(4)	C(18)	162.7	C(9)	C(8)	C(14)	C(13)	70.8
C-2	C(3)	C(4)	C(19)	-80.1	C(15)	C(8)	C(14)	C(13)	-45.3
C-3	C(4)	C(5)	C(6)	-151.4	C(7)	C(8)	C(15)	C(16)	149.0
C(3)	C(4)	C(5)	C(10)	-33.3	C(9)	C(8)	C(15)	C(16)	-91.2
C(18)	C(4)	C(5)	C(6)	83.3	C(14)	C(8)	C(15)	C(16)	28.3
C(18)	C(4)	C(5)	C(10)	-158.6	C(8)	C(9)	C(10)	C(1)	-83.6
C(19)	C(4)	C(5)	C(6)	-26.4	C(8)	C(9)	C(10)	C(5)	156.1
C(19)	C(4)	C(5)	C(10)	91.7	C(8)	C(9)	C(10)	C(20)	36.9
C(3)	C(4)	C(19)	O(1)	152.4	C(11)	C(9)	C(10)	C(1)	44.3
C(3)	C(4)	C(19)	O(4)	-31.6	C(11)	C(9)	C(10)	C(5)	-76.0
C(5)	C(4)	C(19)	O(1)	25.2	C(11)	C(9)	C(10)	C(20)	164.8
C(5)	C(4)	C(19)	O(4)	-158.9	C(8)	C(9)	C(11)	C(12)	42.6
C(18)	C(4)	C(19)	O(1)	-87.2	C(10)	C(9)	C(11)	C(12)	-91.4
C(18)	C(4)	C(19)	O(4)	88.7	C(9)	C(11)	C(12)	C(13)	-46.3
C(4)	C(5)	C(6)	O(1)	21.3	C(11)	C(12)	C(13)	C(14)	60.1
C(4)	C(5)	C(6)	O(2)	-162.0	C(11)	C(12)	C(13)	C(16)	-50.8
C(10)	C(5)	C(6)	O(1)	-101.2	C(12)	C(13)	C(14)	C(8)	-68.7
C(10)	C(5)	C(6)	O(2)	75.5	C(16)	C(13)	C(14)	C(8)	46.2
C(4)	C(5)	C(10)	C(1)	40.8	C(12)	C(13)	C(16)	C(15)	86.7
C(4)	C(5)	C(10)	C(9)	163.9	C(12)	C(13)	C(16)	C(17)	-95.3
C(4)	C(5)	C(10)	C(20)	-77.4	C(14)	C(13)	C(16)	C(15)	-28.3
C(6)	C(5)	C(10)	C(1)	154.1	C(14)	C(13)	C(16)	C(17)	149.7
C(6)	C(5)	C(10)	C(9)	-82.8	C(8)	C(15)	C(16)	C(13)	-0.1
C(6)	C(5)	C(10)	C(20)	35.9	C(8)	C(15)	C(16)	C(17)	-178.0

The unassigned resonances were two quaternary carbons (C-4 and C-10) and five methylenes (C-1, C-2, C-3, C-14, and C-15). We then performed a modified heteronuclear shift correlation experiment in which longer delay times were chosen to permit the transfer of magnetization *via* geminal ($^1\text{H}-\text{C}-^{13}\text{C}$) and vicinal ($^1\text{H}-\text{C}-\text{C}-^{13}\text{C}$) couplings rather than the usual $^1\text{H}-^{13}\text{C}$ couplings. This reveals the long range couplings. In particular, one of the quaternary peaks (δ_{C} 44.6) showed coupling to 18-H and was therefore assigned to C-4 whilst the higher field quaternary carbon showed coupling to 20-H and was therefore assigned to C-10. The C-19 carbonyl showed a long range coupling to 5-H, 18-H and to a multiplet at δ_{H} 1.21 which was therefore assigned to $3\beta\text{-H}$. Using the one-bond $^1\text{H}:^{13}\text{C}$ two dimensional shift correlation, we then assigned C-3 and $3\alpha\text{-H}$. The 20-H resonance showed a coupling to C-5, C-9, and C-10 and to a ^{13}C signal at 33.3 p.p.m. which was therefore assigned to C-1. The one bond $^1\text{H}:^{13}\text{C}$ shift correlation then revealed the 1-H signals. Of the remaining methylene carbons (δ_{C} 17.83, 32.44, and 42.84), the latter showed a long-range coupling to 17-H and was therefore assigned to C-15. The signal at δ_{C} 32.44 showed a long-range correlation with 9-H and was therefore assigned to C-14. The remaining signal (δ_{C} 17.83) was therefore C-2. The one-bond $^1\text{H}:^{13}\text{C}$ then permitted the assignment of the remaining proton signals.

Having assigned the ^1H n.m.r. spectrum, it was possible to use n.o.e. difference spectroscopy to determine the conformation around the C(9)-C(10) bond in solution. A significant n.o.e. (16%) was observed at the aldehydic C-H on irradiation of the 20-H resonance. Irradiation of the 5-H signal produced a 7% n.o.e. at 9-H and a 6.5% effect on the downfield methyl (18-H)

and a 9% effect on $3\beta\text{-H}$. Irradiation of the aldehydic proton (7-H) produced a 4% effect on the 9-H signal. However, the most significant effect was obtained on irradiation of 9-H in which a 36% effect was observed on 5-H and a 5% effect on the aldehydic C-H. These n.o.e.'s are only compatible with the conformation shown in the Figure being maintained in solution.

A variable temperature (^{13}C) study in deuteriomethylene chloride over the temperature range 183-303 K showed only small changes in the positions of the resonances (± 1.0 p.p.m.) indicating that fujenal retained its conformation over this temperature range.

In conclusion, the conformation which fujenal adopts involves rotation about the C(9)-C(10) bond away from a kaurene-like structure. This rotation relieves interactions between C-1 and C-11 and between C-20 and C-14. The juxtaposition of the C-7 oxygen functions and C-20 suggests routes to the formation of the 7,20 spiro lactones.

Experimental

Crystal Data.— $\text{C}_{20}\text{H}_{26}\text{O}_4$, $M = 330.4$, tetragonal, space group $P4_12_12$, $a = b = 11.340(2)$, $c = 27.037(3)$ Å, $U = 3476.6$ Å³, $Z = 8$, $D_c = 1.26$ g cm⁻³, Mo- K_{α} radiation (monochromated), $\lambda = 0.71069$ Å, $\mu = 0.8$ cm⁻¹.

Data were collected on an Enraf-Nonius CAD4 diffractometer using a crystal *ca.* $0.2 \times 0.2 \times 0.2$ mm. Reflections from the positive octant with $2 < \theta < 25^\circ$ were measured by an $\omega - 2\theta$ scan with a maximum time of 1 min. No correction was made for absorption. Out of 3469 reflections measured, 691 unique

reflections with $\sigma|F^2| > \sigma(F^2)$ were used in the structure refinement where $\sigma(F^2) = [\sigma^2(I) + (0.04 I)^2]^{1/2}/Lp$.

The structure was solved by direct methods using MULTAN and non-H atoms refined anisotropically by full matrix least squares. H Atoms were placed at calculated positions (C-H 1.08 Å) and held fixed with a common B_{iso} of 6.0 Å². Refinement converged at $R = 0.037$, $R' = 0.037$ with a weighting scheme of $w = 1/\sigma^2(F)$. A final difference map was featureless. All calculations were done on a PDP 11/34 computer using the Enraf-Nonius SDP-Plus program package. Final atom co-ordinates are shown in Table 2, bond lengths and angles in Table 3, and torsion angles in Table 4. Tables of H atom co-ordinates and temperature factors are included in the Supplementary Publication [SUP No. 56345 (4 pp.)].* The structural factors are available on request from the Editorial Office.

N.m.r. Experiments.—All experiments were performed on a Bruker WM 360 spectrometer using standard 2D software. The sample was 200 mg fujenal in deuteriochloroform in a 5 mm

* For details of the Supplementary publications scheme, see 'Instructions for Authors (1985),' *Chem. Soc., Perkin Trans. 1* 1985, Issue 1.

tube. The one bond shift correlation experiment concentrated on the aliphatic region (δ_{C} 10–70, 5 500 Hz; δ_{H} 0.5–3.5, 1 080 Hz) and used 128 time increments and a ¹³C FID size of 1 K. The long range shift correlation covered the whole spectrum in both dimensions (δ_{C} 10–210, 18 000 Hz; δ_{H} 0.5–10.5, 3 600 Hz) and used 256 time increments and an FID size of 2 K. Both experiments were 15 h overnight runs although a satisfactory S/N could have been obtained in a shorter period.

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Received 26th April 1985; Paper 5/686