# Partial Synthesis of Some Diterpenoids with Potential Antitumour Activity

**Mohammed Shaiq Ali, Mark K. Baynham, James R. Hanson * and Peter B. Hitchcock**
*The School of Molecular Sciences, University of Sussex, Brighton, Sussex, BN1 9QJ, UK*

The diterpenoid fungal metabolite, fujenal, has been converted into analogues of the *Rabdosia* diterpenoids, *ent*-7-hydroxy-15-oxo-6,7-secokaur-16-en-6,19-dioic acid 6,7-lactone 19-methyl ester and *ent*-7-acetoxy-19-hydroxy-15-oxo-6,7-secokaur-16-en-6-oic acid 6,19-lactone which possess moderate inhibitory activity against HeLa cells.

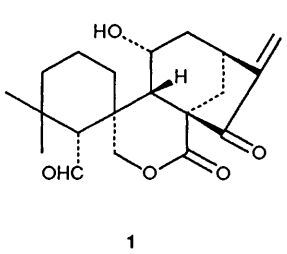
In recent years many *ent*-kaurenoid diterpenes have been isolated from Chinese and Japanese medicinal plants of the genus *Rabdosia* (*Labiatae*).[1] Particular interest has centred on the antitumour activity of these diterpenoids, *e.g.* trichorabdal A **1**.[2] A number of these compounds have structures in which ring **B** has been cleaved. Structure–activity relationships have revealed the importance of an α-methyleneketone on ring D and a synergistic increase in activity due to a second oxygen function in the molecule.

The fungal metabolite fujenal **2** is a kaurenoid diterpene in which ring **B** has been cleaved.[3] It is formed,[4] sometimes in significant amounts by *Gibberella fujikuroi*, which is used for the commercial production of gibberellic acid. It was the object of this work to introduce the unsaturated ketone onto ring D of fujenal derivatives and to evaluate the biological activity of the products. The conformation of fujenal has been examined[5] in the context of partial syntheses in this area.

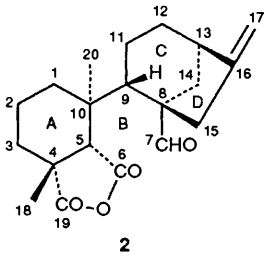
A well-established route for the introduction of oxygen functions at C-15 in the tetracyclic diterpenoids involves oxidation with selenium dioxide and hydrogen peroxide or *tert*-butyl hydroperoxide.[6–8] This reaction did not proceed cleanly with fujenal itself, presumably because of the ready oxidation of the aldehyde. However it was successful with a number of derivatives lacking the aldehyde group.

Fujenal **2** undergoes an internal aldol condensation with sodium hydride to form an alcohol **3**.[9] Allylic oxidation of this compound with selenium dioxide and hydrogen peroxide gave the 15α-alcohol **4**. The site of oxidation followed from changes in the $^{13}C$ NMR spectrum (see Table 1). In particular the signal assigned to C-15 had moved downfield to δ 83.2 whilst those assigned to C-8 and C-16 also showed smaller downfield shifts. The stereochemistry of the hydroxylation was established by $^{1}H$ NMR spectroscopic studies. Examination of molecular models reveals that the 15α-C–H bond in **3** is approximately 90° to the plane of the C-16=C-17 double bond and thus this proton should exhibit a significant allylic coupling to the 17-H protons.[10] Decoupling experiments based on irradiating the olefinic proton resonances established their coupling to a signal at δ 2.53 which was assigned to the 15α-H in **3**. There was no effect on the 15β-proton resonance which was located by irradiating the 15α-signal. There was however a long-range 'W' coupling from the 15β-H to that at δ 2.24 which was assigned to the 14α-proton. Further decoupling studies established the assignments, given in Fig. 1 for the 14β- and 13-protons. Decoupling studies with the hydroxylation product **4** starting from 13-H (δ 2.73) led to the identification of the 14β-proton resonance and thence the 14α-proton signal. There was a long-range coupling (*J* 1.3 Hz) between this signal and the 15-H resonance (δ 3.96). Hence this proton is a 15β-H and the hydroxy group has the α-orientation in accordance with oxidations observed previously in similar systems.[7,8]

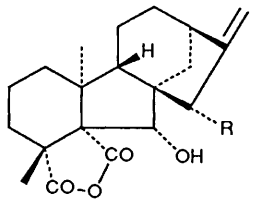
An alternative way of blocking the aldehyde of fujenal **2** is to reduce it with sodium borohydride.[11,12] The anhydride is also reduced and a major product is the 7-hydroxy 6,19-lactone **5**. The alcohol was then converted into its acetate **6** which was oxidized with selenium dioxide and hydrogen peroxide to give the corresponding 15α-alcohol **7**. Alternatively methanolysis of



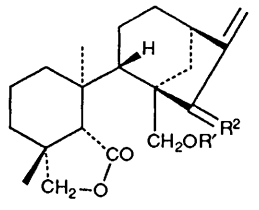

**1**



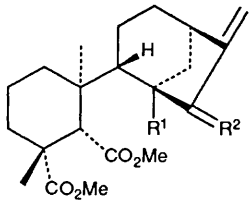

**2**



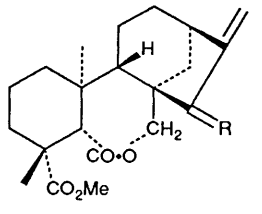

**3**; R = H
**4**; R = OH



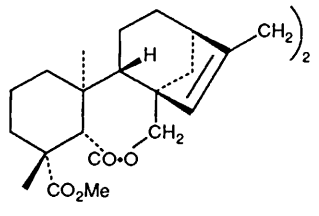

**5**; $R^1$ = H, $R^2$ = $H_2$
**6**; $R^1$ = Ac, $R^2$ = $H_2$
**7**; $R^1$ = Ac, $R^2$ = α-OH, β-H
**8**; $R^1$ = Ac, $R^2$ = O




**9**; $R^1$ = CHO, $R^2$ = $H_2$
**10**; $R^1$ = $CH_2OH$, $R^2$ = $H_2$
**11**; $R^1$ = $CH_2OH$, $R^2$ = α-OH, β-H




**12**; R = $H_2$
**13**; R = α-OH, β-H
**14**; R = O




**15**

**Table 1** $^{13}C$ NMR spectroscopic data (determined in $CDCl_3$)

| | δ | | | | | | |
|---|---|---|---|---|---|---|---|
| Carbon atom | **3** | **4** | **7** | **8** | **13** | **14** | **15**[a] |
| 1 | 38.9 | 39.1 | 33.5 | 32.2 | 34.2 | 36.3 | 41.0 |
| 2 | 18.2 | 18.5 | 17.6 | 17.6 | 19.3 | 17.5 | 18.3 |
| 3 | 28.4 | 28.6 | 32.5 | 31.7 | 36.2 | 33.8 | 27.8 |
| 4 | 43.9 | 44.2 | 42.8 | 42.4 | 44.2 | 44.2 | 44.7 |
| 5 | 66.6 | 66.3 | 53.4 | 52.8 | 58.4 | 57.0 | 57.6 |
| 6 | 175.3 | 175.6 | 178.5 | 178.0 | 174.7 | 173.7 | 174.8 |
| 7 | 76.0 | 73.8 | 66.0 | 66.3 | 72.4 | 71.3 | 75.0 |
| 8 | 51.1 | 55.4 | 61.6 | 54.9 | 51.2 | 54.9 | 52.8 |
| 9 | 56.4 | 54.4 | 44.0 | 46.4 | 56.7 | 56.2 | 52.9 |
| 10 | 47.8 | 47.6 | 38.4 | 38.6 | 40.3 | 40.3 | 40.3 |
| 11 | 19.3 | 19.5 | 20.8 | 21.1 | 17.8 | 19.6 | 20.7 |
| 12 | 32.5 | 32.0 | 31.6 | 31.6 | 31.7 | 31.5 | 25.4 |
| 13 | 38.2 | 36.3 | 42.9 | 38.5 | 42.2 | 38.2 | 43.4 |
| 14 | 29.5 | 25.8 | 35.6 | 35.4 | 40.8 | 40.1 | 41.1 |
| 15 | 47.9 | 83.2 | 79.6 | 207.5 | 80.8 | 207.8 | 127.9 |
| 16 | 157.3 | 162.0 | 158.6 | 149.1 | 159.9 | 148.3 | 149.0 |
| 17 | 106.7 | 111.4 | 108.1 | 114.0 | 108.3 | 115.7 | 36.8 |
| 18 | 26.1 | 26.3 | 31.2 | 30.8 | 29.7 | 29.3 | 29.6 |
| 19 | 173.3 | 172.7 | 75.7 | 75.7 | 175.9 | 175.5 | 175.9 |
| 20 | 19.5 | 19.2 | 22.7 | 23.7 | 18.9 | 18.6 | 18.9 |
| OMe/OAc | | | 20.9 | 20.7 | 51.5 | 51.4 | 51.5 |
| | | | 171.6 | 170.7 | | | |

[a] Determined in $C_5D_5N$.

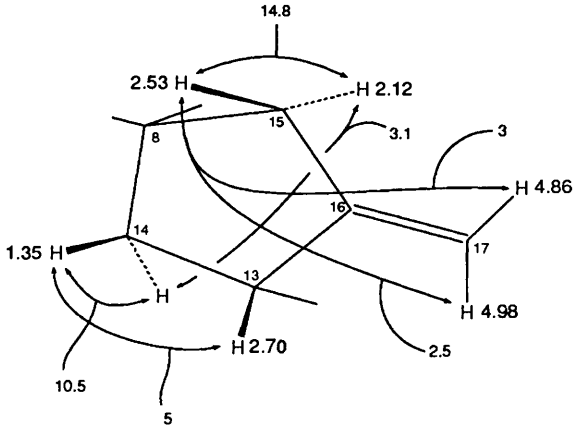



**Fig. 1** Coupling constants and assignments for ring D of **3**

fujenal **2** with sodium methoxide and methylation of the resultant hemi-methyl ester with diazomethane gave the dimethyl ester **9**.[12] Reduction of the aldehyde with sodium borohydride gave a separable mixture of the 6,7-lactone **12** and the 7-alcohol **10**. Oxidation of the lactone **12** with selenium dioxide and hydrogen peroxide in dioxane gave two products. The first possessed a trisubstituted double bond [$\delta_H$ 5.60; $\delta_C$ 127.93(CH), 149.05(C)] and an additional methylene signal ($\delta_C$ 36.76) rather than a methyl signal. An X-ray crystal structure showed that the compound was the dimer **15** (see Fig. 2). The formation of a symmetrical dimer is of interest since oxidations with selenium dioxide have been regarded as being ionic in character.[13] The second product was assigned the 15α-hydroxy structure **13** from its spectral data. Oxidation of the 7-alcohol **10** with selenium dioxide and hydrogen peroxide gave a similar 15α-alcohol **11**.

Oxidation of the 15α-alcohols **7** and **13** to the corresponding 15-ketones **8** and **14** was achieved using chromium trioxide in pyridine, a procedure which has been successful in previous work.[14] The unsaturated ketones possessed the anticipated spectral characteristics (*e.g.* $\delta_C$ 207.82, 148.30, 115.72 for C-15, C-16 and C-17 in **14**).

When tested* at concentrations of 3 and 7.5 $cm^{-3}$, the compounds **8** and **14** reduced the growth of HeLa cells by about 50% over a period of 4 days. They are thus fairly potent inhibitors of cell growth. Thus fujenal **2**, a by-product of the gibberellin fermentation, may be transformed on the one-hand to compounds with potential plant-growth regulatory activity[9,15] and on the other to compounds with potential tumour inhibitory activity.

## Experimental

*General Experimental Details.*—$^1H$ and $^{13}C$ NMR spectra were determined at 360 and 90.56 MHz respectively on a Bruker WM 360 spectrometer for solutions in deuteriochloroform except where otherwise stated; *J* values are given in Hz. IR spectra were determined as Nujol mulls. Solutions were dried over sodium sulphate. Light petroleum refers to the fraction b.p. 60–80 °C. Silica for chromatography was Merck 9385.

*Hydroxylation of the Anhydride* **3**.—*ent*-6β-Hydroxy-7-nor-5β-gibberell-16-ene-5β,19-dioic acid anhydride **3**[9] (500 mg) and selenium dioxide (200 mg) in dioxane (8 $cm^3$) were treated with 30% hydrogen peroxide (4 $cm^3$) dropwise at room temperature for 1 h. The mixture was cooled in ice and poured into aqueous sodium hydrogen carbonate. The solution was extracted with dichloromethane. The extract was dried, the solvent was evaporated and the residue was chromatographed on silica. Elution with ethyl acetate–light petroleum (1:4) gave the starting material (290 mg) followed by ent-6β,15β-*dihydroxy*-7-*nor*-5β-*gibberell*-16-*ene*-5β,19-*dioic acid anhydride* **4** (145 mg) which crystallized from ethyl acetate–light petroleum as prisms, m.p. 200–201 °C (Found: C, 69.2; H, 7.3. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.6%), $\nu_{max}/cm^{-1}$ 3440br, 1840, 1780 and 1660; δ 0.95 (3 H, s, 20-H), 1.49 (3 H, s, 18-H), 1.85 (1 H, dd, *J* 5.1 and 11.8, 14-H), 2.33 (1 H, dd, *J* 11.8 and 1.3, 14-H), 2.73 (1 H, dd, *J* 5.1 and 8.8, 13-H), 3.96 (1 H, d, *J* 1.3, 15-H), 4.55 (1 H, s, 7-H) and 5.19 and 5.24 (each 1 H, s, 17-H).

*Hydroxylation of the Ester* **10**.—*ent*-7-Hydroxy-6,7-secokaur-16-ene-6,19-dioic acid 6,19-dimethyl ester[12] **10** (1.5 g) in dioxane (24 $cm^3$) was treated with selenium dioxide (600 mg) and hydrogen peroxide (30%, 12 $cm^3$) at room temperature for 1 h. The products were recovered as above to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (2:3) gave ent-7,15β-*dihydroxy*-6,7-*secokaur*-16-*ene*-6,19-*dioic acid* 6,19-*dimethyl ester* **11** (530 mg) as a gum, (Found: C, 67.1; H, 8.6. $C_{22}H_{34}O_6$ requires C, 67.0; H, 8.7%), $\nu_{max}/cm^{-1}$ 3481, 1733, 1719 and 1654; δ 1.16 (3 H, s, 20-H), 1.49 (3 H, s, 18-H), 3.61 and 3.62 (each 3 H, s, OMe), 3.76 and 4.28 (each 1 H, d, *J* 11, 7-H), 4.20 (1 H, br s, 15-H) and 5.08 and 5.20 (each 1 H, br s, 17-H). On one occasion a 7,16,17-*triol* was isolated as a gum, (Found: C, 64.4; H, 8.6. $C_{22}H_{36}O_7$ requires C, 64.1; H, 8.8%), $\nu_{max}/cm^{-1}$ 3400, 1730 and 1710; δ 1.30 (3 H, s, 20-H), 1.37 (3 H, s, 18-H), 3.53 (1 H, d, *J* 11.7, 7-H) 3.63 and 3.69 (each 3 H, s, OMe), 3.77 (1 H, d, *J* 12.8, 17-H), 4.09 (1 H, d, *J* 11.7, 7-H) and 4.80 (1 H, d, *J* 12.8, 17-H).

*Hydroxylation of the Ester* **12**.—*ent*-7-Hydroxy-6,7-seco-kaur-16-ene-6,19-dioic acid 6,7-lactone 19-methyl ester[12] **12** (1 g) in dioxane (30 $cm^3$) was treated with selenium dioxide (450 mg) and hydrogen peroxide (30%; 8 $cm^3$) at room temperature for 1 h. The products were recovered as above to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (3:7) gave the 17,17′-*dimer* of *ent*-7-

* We thank Dr. E. A. Hamilton (ICI Pharmaceuticals) for carrying out these determinations.

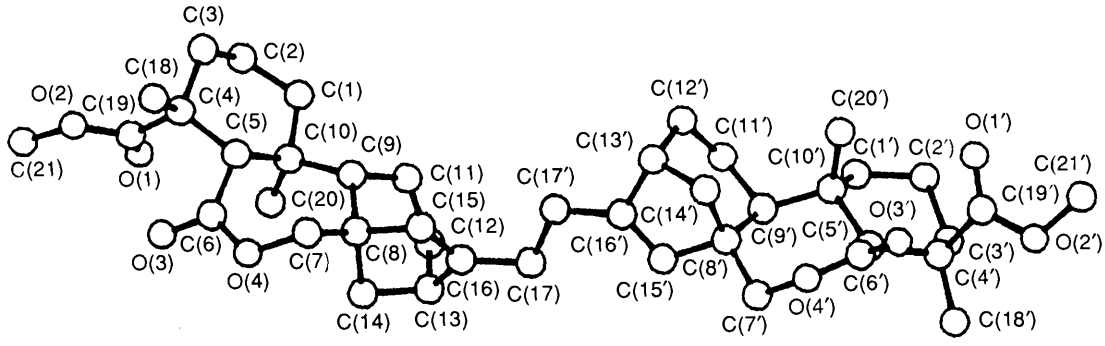



**Fig. 2** X-Ray molecular structure of the 17,17'-dimer (15)

**Table 2** Crystal data and structure refinement details for the X-ray structure **15**

| | |
|---|---|
| Formula | $C_{42}H_{52}O_8$ |
| *M* | 684.9 |
| Crystal size (mm) | 0.20 × 0.15 × 0.10 |
| Crystal system | monoclinic |
| Space group | $P2_1$ (no. 4) |
| *a*, *b*, *c*, (Å), β ° | 11.759(9), 7.618(2), 21.409(7), 105.83(4) |
| *V* (Å)$^3$ | 1845.1 |
| *Z*, $D_c$ (g.cm$^{-3}$), *F*(000) | 2, 1.23, 736 |
| μ Mo-$K\alpha$ (cm$^{-1}$) | 0.8 |
| Total unique reflections | 3497 |
| Significant reflections [$I > \sigma(I)$] | 2319 |
| *R* | 0.039 |
| *R'* | 0.048 |

**Table 3** Fractional atomic co-ordinates ( × $10^4$)

| | *x* | *y* | *z* |
|---|---|---|---|
| O(1) | 4 233(2) | 5 099(5) | 3 673(1) |
| O(2) | 5 556(2) | 5 128(5) | 4 632(1) |
| O(3) | 5 851(2) | 2 085(4) | 3 680(1) |
| O(4) | 6 834(2) | 1 442 | 2 989(1) |
| C(1) | 5 371(3) | 6 977(6) | 2 350(2) |
| C(2) | 5 149(4) | 7 925(6) | 2 927(2) |
| C(3) | 6 145(3) | 7 605(6) | 3 526(2) |
| C(4) | 6 295(3) | 5 661(5) | 3 719(2) |
| C(5) | 6 354(3) | 4 539(5) | 3 114(2) |
| C(6) | 6 316(3) | 2 635(5) | 3 288(2) |
| C(7) | 7 493(3) | 1 971(6) | 2 541(2) |
| C(8) | 6 693(3) | 2 544(6) | 1 892(2) |
| C(9) | 6 159(3) | 4 414(5) | 1 887(1) |
| C(10) | 5 522(3) | 4 952(5) | 2 415(2) |
| C(11) | 5 409(3) | 4 852(6) | 1 178(2) |
| C(12) | 4 776(3) | 3 318(7) | 758(2) |
| C(13) | 5 524(3) | 1 654(6) | 860(2) |
| C(14) | 5 785(3) | 1 158(6) | 1 579(2) |
| C(15) | 7 404(3) | 2 608(6) | 1 386(2) |
| C(16) | 6 766(3) | 2 098(6) | 817(2) |
| C(17) | 7 052(3) | 2 142(7) | 168(2) |
| C(18) | 7 469(3) | 5 412(7) | 4 232(2) |
| C(19) | 5 236(3) | 5 202(6) | 3 979(2) |
| C(20) | 4 309(3) | 4 099(6) | 2 310(2) |
| C(21) | 4 612(3) | 4 873(8) | 4 935(2) |
| O(1') | 10 134(3) | 5 631(5) | −3 599(1) |
| O(2') | 9 991(2) | 3 510(5) | −4 325(1) |
| O(3') | 10 974(2) | 2 457(5) | −2 751(1) |
| O(4') | 10 273(2) | 1 351(4) | −2 000(1) |
| C(1') | 7 568(3) | 5 736(6) | −2 924(2) |
| C(2') | 7 528(4) | 5 924(7) | −3 634(2) |
| C(3') | 7 607(4) | 4 139(7) | −3 929(2) |
| C(4') | 8 769(3) | 3 199(6) | −3 616(2) |
| C(5') | 8 938(3) | 3 107(6) | −2 860(2) |
| C(6') | 10 123(3) | 2 301(6) | −2 546(2) |
| C(7') | 9 304(4) | 1 085(6) | −1 711(2) |
| C(8') | 8 998(3) | 2 716(6) | −1 399(2) |
| C(9') | 8 223(3) | 4 087(5) | −1 889(2) |
| C(10') | 8 653(3) | 4 736(5) | −2 482(2) |
| C(11') | 7 877(3) | 5 615(6) | −1 495(2) |
| C(12') | 8 798(4) | 6 168(6) | −866(2) |
| C(13') | 9 460(3) | 4 590(6) | −482(2) |
| C(14') | 10 058(3) | 3 610(6) | −925(2) |
| C(15') | 8 279(3) | 2 230(6) | −922(2) |
| C(16') | 8 557(3) | 3 239(6) | −407(2) |
| C(17') | 8 085(4) | 3 335(7) | 182(2) |
| C(18') | 8 686(4) | 1 306(8) | −3 865(2) |
| C(19') | 9 719(3) | 4 243(7) | −3 817(2) |
| C(20') | 9 676(3) | 6 034(6) | −2 298(2) |
| C(21') | 10 745(4) | 4 558(9) | −4 609(2) |

hydroxy-6,7-secokaur-15-ene-6,19-dioic acid 6,7-lactone 19-methyl ester **15** which crystallized from pyridine as prisms, m.p. 250 °C (Found: C, 72.7; H, 8.5. $C_{42}H_{58}O_8$ requires C, 73.0; H, 8.5%), $\nu_{max}$/cm$^{-1}$ 1729; δ($C_5D_5N$) 1.34 (3 H, s, 20-H), 1.47 (3 H, s, 18-H), 2.97 (1 H, s, 5-H), 3.69 (3 H, s, OMe), 3.80 and 4.68 (each 1 H, d, *J* 12, 7-H) and 5.60 (1 H, br s, 15-H). Further elution with ethyl acetate–light petroleum (2:3) gave ent-7,15β-*dihydroxy*-6,7-*secokaur*-16-*ene*-6,19-*dioic acid* 6,7-*lactone* 19-*methyl ester* **13** (560 mg) which crystallized from ethyl acetate as needles, m.p. 248–250 °C (Found: C, 69.6; H, 8.4. $C_{21}H_{30}O_5$ requires C, 69.6; H, 8.3%), $\nu_{max}$/cm$^{-1}$ 3459 and 1724; δ 1.24 (3 H, s, 20-H), 1.34 (3 H, s, 18-H), 2.86 (1 H, s, 5-H), 3.69 (3 H, s, OMe), 4.03 (1 H, br s, 15-H), 4.37 and 4.43 (each 1 H, d, *J* 13, 7-H) and 5.12 and 5.23 (each 1 H, s, 17-H).

*Hydroxylation of the Lactone* **6**.—*ent*-7-Acetoxy-19-hydroxy-6,7-secokaur-16-en-6-oic acid 6,19-lactone **6**[12] (1.03 g) in dioxane (30 cm$^3$) was treated with selenium dioxide (400 mg) and hydrogen peroxide (30%; 8 cm$^3$) for 1 h. The products were recovered as above to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (3:7) gave ent-7-*acetoxy*-15β,19-*dihydroxy*-6,7-*secokaur*-16-*en*-6-*oic acid* 6,19-*lactone* **7** (913 mg) which crystallized from light petroleum as needles, m.p. 162 °C (Found: C, 70.1; H, 8.6. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.6%), $\nu_{max}$/cm$^{-1}$ 3472, 1765 and 1741; δ 1.12 (3 H, s, 20-H), 1.27 (3 H, s, 18-H), 2.16 (3 H, s, OAc), 3.75 and 4.04 (each 1 H, d, *J* 9, 19-H), 4.25 (1 H, br s, 15-H), 4.28 and 4.41 (each 1 H, d, *J* 12, 7-H) and 5.11 and 5.23 (each 1 H, s, 17-H).

*Oxidation of the Hydroxy Lactone* **13** *with Chromium Trioxide*.—The above lactone **13** (520 mg) was treated with a solution of chromium trioxide (5 g) in a mixture of pyridine (9 cm$^3$) and dichloromethane (125 cm$^3$) for 30 min at room temperature. Aqueous sodium hydroxide was added and the product was isolated with dichloromethane. The extract was washed with aqueous copper sulphate and water and dried. The solvent was evaporated to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (3:7) gave ent-7-*hydroxy*-15-*oxo*-6,7-*secokaur*-16-*ene*-6,19-*dioic acid* 6,7-*lactone* 19-*methyl ester* **14** (450 mg) which crystallized

from ethyl acetate as plates, m.p. 160 °C (Found: C, 69.7; H, 7.9. $C_{21}H_{28}O_5$ requires C, 67.0; H, 7.8%), $\nu_{max}/cm^{-1}$ 1723 and 1646; $\delta$ 1.24 (3 H, s, 20-H), 1.40 (3 H, s, 18-H), 2.85 (1 H, s, 5-H), 3.16 (1 H, br s, 13-H), 3.69 (3 H, s, OMe), 3.80 and 4.60 (each 1 H, d, *J* 13, 7-H) and 5.37 and 5.97 (each 1 H, s, 17-H).

*Oxidation of the Hydroxy Lactone* **7** *with Chromium Trioxide.*—The above hydroxy lactone **7** (600 mg) was treated with a solution of chromium trioxide (6 g) in pyridine (10 $cm^3$) and dichloromethane (200 $cm^3$) for 30 min at room temperature. Aqueous sodium hydroxide was added and the product was recovered in dichloromethane. The organic layer was washed with aqueous copper sulphate, water and dried. The solvent was evaporated to give a residue which was chromatographed on silica. Elution with ethyl acetate–light petroleum (1:3) gave ent-7-*acetoxy*-19-*hydroxy*-15-*oxo*-6,7-*secokaur*-16-*en*-6-*oic acid* 6,19-*lactone* **8** (475 mg) as a foam (Found: C, 67.7; H, 8.2. $C_{22}H_{30}O_5 \cdot H_2O$ requires C, 67.3; H, 8.2%), $\nu_{max}/cm^{-1}$ 1734br and 1652; $\delta$ 1.13 (3 H, s, 20-H), 1.20 (3 H, s, 18-H), 3.11 (1 H, br s, 13-H), 3.77 and 4.03 (each 1 H, d, *J* 9, 19-H), 4.23 and 4.58 (each 1 H, d, *J* 11, 7-H) and 5.27 and 5.92 (each 1 H, br s, 17-H).

*Crystal Structure Determination.*—A summary of the crystal data and structure refinement details are given in Table 2. The data were collected from a crystal mounted on an Enraf-Nonius CAD4 diffractometer operating in the $\theta$–$2\theta$ mode with $\Delta\theta = (0.8 + 0.35 \tan\theta)°$ and a maximum scan time of one minute and with monochromated Mo-$K\alpha$ radiation ($\lambda$ = 0.710 69 Å). Unique reflections were measured for $2 < \theta < 25°$ and those reflections with $|F^2| > 3\sigma(F^2)$ were used in the refinement where $\sigma(F^2) = \{\sigma^2(I) + (0.04I)^2\}^{\frac{1}{2}}/L_p$. The structure was solved by direct methods using SHELXS-86.[16] Refinement was by full matrix least squares with non-hydrogen atoms anisotropic and weights of $w = 1/\sigma^2(F)$. Hydrogen atoms were held fixed at calculated positions with $U_{iso} = 1.3U_{eq}$ for the parent carbon atom. Programs from the Enraf-Nonius SDP-Plus package were run on a Micro-Vax computer. Fractional atomic co-ordinates are shown in Table 3. The remaining crystallographic data has been deposited at the Cambridge Crystallographic Data Centre.*

* For full details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

## Acknowledgements

We thank the AFRC and the British Council for financial support and ICI Pharmaceuticals for a gift of fujenal. Part of this work was carried out under the HEJ Institute, University of Karachi–University of Sussex Link Scheme. We thank Professor Atta-ur-Rahman and Dr. D. R. M. Walton for establishing this link. We thank Dr. N. F. Elmore (ICI Pharmaceuticals) for arranging the bio-assay.

## References

1 E. Fujita and M. Node in *Progress in the Chemistry of Organic Natural Products*, 1984, **46**, 78.
2 K. Fuji, M. Node, M. Sai, E. Fujita, S. Takeda and N. Unemi, *Chem. Pharm. Bull.*, 1989, **37**, 1472 and refs. therein.
3 B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1963, 5052.
4 B. E. Cross, R. H. B. Galt, J. R. Hanson, P. J. Curtis, J. F. Grove and A. Morrison, *J. Chem. Soc.*, 1963, 2937.
5 A. G. Avent, C. Chamberlain, J. R. Hanson and P. B. Hitchcock, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2493.
6 A. Carcia-Granados, A. Parra-Sanchez and A. Y. Pena Carrillo, *Anales de Quim.*, 1980, **76**, 85.
7 S. C. Dolan and J. MacMillan, *J. Chem. Soc. Perkin Trans. 1*, 1985, 2741.
8 A. G. Avent, J. R. Hanson, P. B. Hitchcock and B. H. de Oliveira, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2661.
9 J. R. Hanson, C. L. Willis and K. P. Parry, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3020.
10 S. Sternhell, *Pure Appl. Chem.*, 1964, **14**, 15.
11 R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1965, 1565.
12 M. K. Baynham, J. M. Dickinson, J. R. Hanson and P. B. Hitchcock, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1987.
13 E. N. Trachtenberg in *Oxidation*, ed. R. L. Augustine, Marcel Decker, New York, 1970, vol. 1, ch. 3, p. 119.
14 J. R. Cannon, P. W. Chow, P. R. Jefferies and G. V. Meehan, *Aust. J. Chem.*, 1966, **19**, 861.
15 M. K. Baynham, J. M. Dickinson and J. R. Hanson, *Phytochemistry*, 1988, **27**, 761 and refs. therein.
16 G. M. Sheldrick in *Crystallographic Computing 3*, eds. G. M. Sheldrick, C. Kruger and R. Goddard, Oxford University Press, 1985, pp. 175–189.

*Paper* 1/03258E
*Received* 1*st July* 1991
*Accepted* 15*th July* 1991