

Chemical Transformations of the Diterpene Lactones Momilactones A and B

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In order to confirm the structures of momilactones A (3-oxo-9 β -pimara-7,15-dien-19,6 β -olide) (I) and B (3,20-epoxy-3 α -hydroxy-9 β -pimara-7,15-dien-19,6 β -olide) (XIII), growth-inhibitors isolated from husk of rice, their chemical and physical properties were studied in detail. Momilactone B gives a rearrangement product (XVII) on treatment with alkali, whereas momilactone A affords a decarboxylation product (X).

In a previous paper¹ we described the isolation of several growth inhibitors, including momilactones A and B, (I) and (XIII), from rice husk. As reported in a preliminary communication,² the structure of momilactone A (MA) (I) was unequivocally determined by X-ray analysis, and that of momilactone B (MB) (XIII) was deduced from comparison of physical data with those of MA.†

This paper reports chemical and physical properties of the momilactones and their degradation products. Chemical degradation was undertaken to confirm the structures of the momilactones and to establish which functional groups are necessary for growth inhibition activity.

Momilactone A (I).—MA (I) showed three sharp H n.m.r. signals due to tertiary methyl groups (δ 0.90, 1.00, and 1.52); that at lowest field was assignable to the 4-Me (two adjacent carbonyl functions). For assignment of the other two signals, the effect of shift reagent Eu(fod)₃ was examined (Table 1). As expected,³ the

4-Me signal was influenced most strongly; the least shifted signal (δ 0.90) was attributed to the 13-Me, furthest from the two carbonyl functions, and the remaining signal (δ 1.00) to the 10-Me.

TABLE 1

	Chemical shifts of MA induced by Eu(fod) ₃					
	4-Me	10-Me	13-Me	5-H	6-H	7-H
δ (normal)	1.52	1.00	0.90	2.32	4.83	5.70
Δ_{Eu} ^a	8.91	4.22	1.12	5.76	5.05	2.21

^a Difference in chemical shift with Eu(fod)₃: MA 1.0:1.

In Table 2 are summarized the ¹³C chemical shifts of typical derivatives of the momilactones. Recently, Wenkert and his co-workers have observed the differences in ¹³C chemical shift of 13 α - and 13 β -methyl groups in pimaradiene-type compounds and concluded that ¹³C n.m.r. is an effective means of determining relative stereochemistry at C-13 of these diterpenoids.⁴ The

² T. Kato, C. Kabuto, N. Sasaki, M. Tsunakawa, H. Aizawa, K. Fujita, Y. Kato, Y. Kitahara, and N. Takahashi, *Tetrahedron Letters*, 1973, 3861.

³ (a) B. L. Shapiro, M. D. Johnston, and T. W. Psouls, *J. Amer. Chem. Soc.*, 1973, **95**, 520; (b) K. L. Servis and D. J. Bowler, *ibid.*, 1975, **97**, 80.

⁴ (a) E. Wenkert and B. L. Buckwalter, *J. Amer. Chem. Soc.*, 1972, **94**, 4367; (b) J. Polonsky, Z. Baskevitch, and E. Wenkert, *ibid.*, 1972, **94**, 4370.

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‡ The C-9 hydrogen atom of MA has the β -configuration, not α as erroneously shown in ref. 2.

¹ T. Kato, M. Tsunakawa, N. Sasaki, H. Aizawa, K. Fujita, Y. Ka, and N. Takahashi, *Phytochemistry*, in the press.

chemical shift of the 13-Me of MA (I) ² and its derivatives is 22 ± 1 p.p.m. This value corresponds to β -Me on the basis of Wenkert's findings, but this conclusion is opposite to that obtained from X-ray analysis. Thus ¹³C n.m.r. is not always a reliable method for determination of C-13 stereochemistry in this class of diterpenoids.

was involved in intramolecular hydrogen bonding with the lactone carbonyl group. The configuration at C-3 was deduced from the coupling H-3 [δ 3.71 (in CDCl₃-D₂O), doublet of doublets J 6.0 and 10.0 Hz].

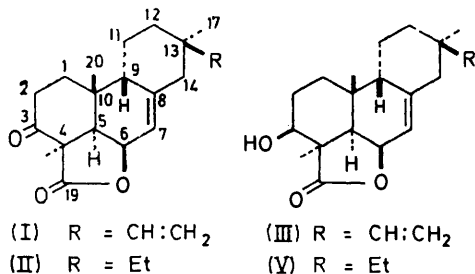
Catalytic reduction of the mono-ol gave the dihydro-mono-ol (V), also obtainable from dihydro-MA (II)

TABLE 2

¹³C N.m.r. spectra of typical momilactone derivatives (p.p.m. from Me₄Si)

C	Dihydro-MA (II)	Mono-ol (III)	Acetylmono-ol (VII)	Dihydro-MB (XIV)	Dilactone (XVII)
1	34.9	33.1	33.1	28.9	25.4
2	31.3	31.8	31.8	26.5	34.8
3	205.0	74.7	74.8	96.9	178.0
4	53.6	44.6	45.2	50.4	35.8
5	46.5	47.0	47.0	43.4	27.7
6	73.4	74.5	72.9	73.9	73.4
7	113.3	114.4	114.6	113.3	120.2
8	149.0	149.1	148.6	147.6	139.5
9	50.6	51.4	51.3	44.8	45.7
10	32.5	30.9	29.7	30.8	37.0
11	24.2	23.6	23.9	25.1	31.9
12	37.4	37.1	37.1	37.4	38.3
13	37.6	40.2	40.1	37.6	37.2
14	48.0	47.4	47.3	47.9	47.5
15	37.6	149.6	149.1	37.6	148.4
16	7.9	110.1	110.0	7.9	110.5
17	21.8	23.0	23.1	21.4	21.7
18	21.5	22.8	22.6	19.1	16.6
19	174.0	176.0	177.0	168.0	182.0
20	21.8	22.0	22.0	72.8	71.8
			172.1,		
			21.1 (Ac)		

By catalytic reduction of MA(I), the vinyl group at C-13 was selectively reduced to give dihydro-MA (II).



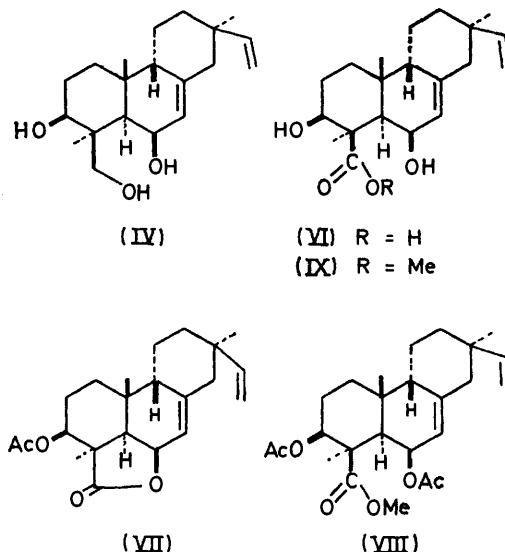
As anticipated from a Dreiding model, the remaining double bond in ring B was sterically hindered, resisting catalytic reduction under the usual conditions. The ¹H n.m.r. signal at δ 0.90 p.p.m. due to the 13-Me of MA (I) was shifted to δ 0.71 p.p.m. in dihydro-MA (II), supporting the assignment of the tertiary methyl signals of MA determined with the aid of the shift reagent.

By treatment of MA (I) with lithium aluminium hydride, the mono-ol (III) was obtained predominantly under controlled conditions; the triol (IV) was formed with an excess of hydride. The mono-ol (III) showed i.r. absorption at 3520 cm^{-1} in CHCl₃ due to the hydroxy-group, the frequency of which remained unchanged when the concentration was altered between 0.05M and 0.017M.* This evidence as well as a clear ¹H n.m.r. doublet (10.0 Hz) at δ 3.91 (OH) indicated that the hydroxy-proton

* Similar intramolecular hydrogen bonding was also observed in MB and other natural products having a similar partial structure.⁵

by reduction with lithium aluminium hydride under controlled conditions.

Treatment of the mono-ol (III) with potassium hydroxide in t-butyl alcohol afforded the corresponding diol acid (VI). Relactonization of (VI) required treatment with acetic anhydride. Refluxing with acetic anhydride converted the diol acid into the acetyl mono-ol (VII), also derived by acetylation of the mono-ol



(III). The diol acid (VI) was converted into the diol ester (IX) with diazomethane. Acetylation of (VI)

⁵ S. Ito, M. Kodama, M. Sunagawa, T. Takahashi, H. Imamura, and O. Honda, *Tetrahedron Letters*, 1968, 2065.

under mild conditions followed by treatment with diazomethane gave the diacetyl ester (VIII). As anticipated from the structure of MA (I), decarboxylation occurred easily on refluxing with methanolic potassium hydroxide, giving nor-MA (X) in moderate yield. The ^1H n.m.r. spectra of nor-MA (X), the triol (IV), and the diol ester (IX) all showed a marked downfield shift (*ca.* 0.3 p.p.m.) of the 10-Me signal as compared with MA (I). This is attributable to the 1,3-diaxial relation between the 10-Me and 6-OH groups.⁶

Figure 1 shows the change in chemical shift of the 10-Me caused by the addition of various concentrations of shift reagent. There is only a small difference amongst the three compounds (I), (III), and (X) when the $\text{Eu}(\text{fod})_3$ -substrate ratio is below 1.0 : 1. When the ratio

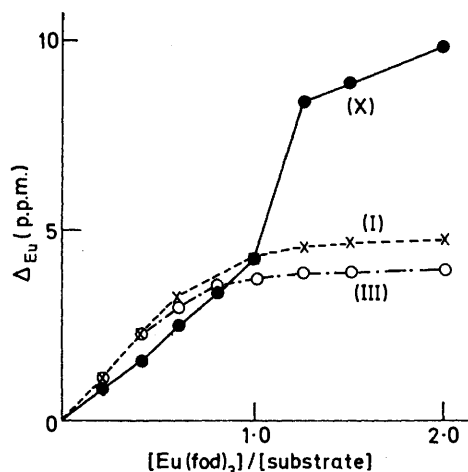


FIGURE 1 Effect of $\text{Eu}(\text{fod})_3$ on the chemical shift of the 10-Me of MA and derivatives

is more than 1.0 : 1, however, nor-MA (X) displays a marked shift in comparison with the other two compounds. This may be due to the fact that the added shift reagent first interacts predominantly with the 3-oxo-group and then with the sterically more hindered axial 6-OH.

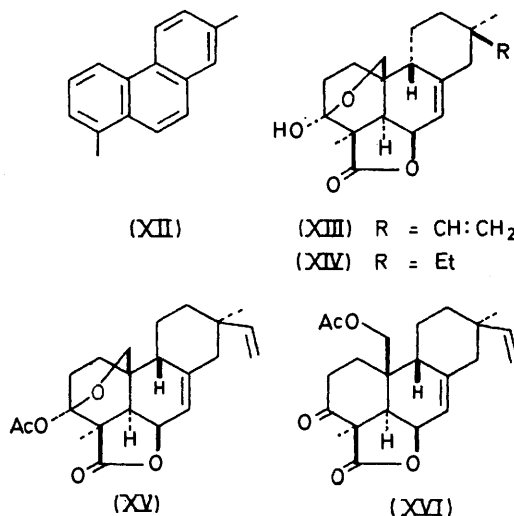
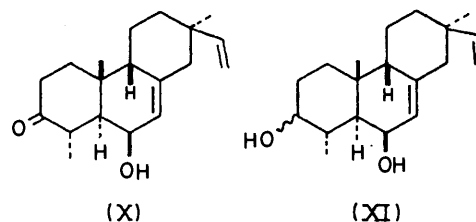
O.r.d. and c.d. curves of nor-MA (X) are shown in Figure 2. Both exhibit a positive Cotton effect although that in the o.r.d. spectrum is very weak. The absolute configuration of MA (I) was established from these Cotton effects, which revealed the absolute configuration of nor-MA (X).

By reduction with lithium aluminium hydride, nor-MA was converted into nor-MA diol (XI), which dehydrogenated with selenium to give 1,7-dimethylphenanthrene (XII) in 30% yield.

Momilactone B (XIII).—As in the case of MA (I), catalytic reduction of MB (XIII) proceeded selectively to give dihydro-MB (XIV). The sterically hindered hemiacetal nature of the 3-OH was revealed by acetylation experiments. MB (XIII) was unchanged when treated with refluxing acetic anhydride or acetic anhydride in pyridine at room temperature. Under reflux

⁶ M. Fetizon and P. Mourgues, *Tetrahedron*, 1975, **30**, 327, and references therein.

conditions in acetic anhydride-pyridine, however, the acetate (XV) was formed in high yield. When MB



(XIII) was treated with acetic anhydride in the presence of perchloric acid with cooling,⁷ a 2 : 3 mixture of the acetate (XV) and the oxo-acetate (XVI) was obtained; these were easily separated by column chromatography

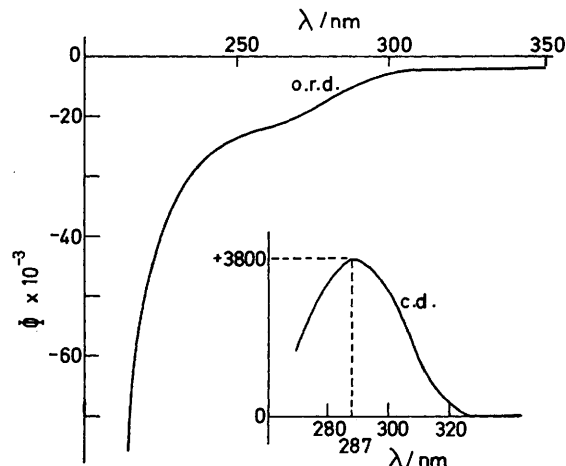
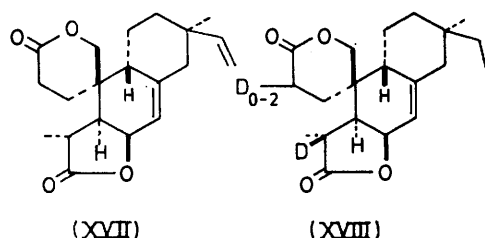


FIGURE 2 O.r.d. and c.d. curves of nor-MA

on silica gel. The structure of the latter (XVI) was deduced from physical evidence: ν_{max} , 1 775, 1 740, and 1 710 cm^{-1} ; δ 3.95 and 4.22 (ABq, J 12.0 Hz, CH_2OAc).

⁷ K. Fuji, S. Nakano, and E. Fujita, 18th Symposium on the Chemistry of Natural Products, 1974, paper P39.

The formation of the oxo-acetate (XVI) demonstrates the presence of a hemiacetal structure in MB (XIII). When MB (XIII) was treated with methanolic potassium hydroxide, the rearrangement product (XVII) was produced [δ 1.35 (d, J 7.0 Hz, 18-H₃)]. The ¹³C n.m.r. spectra (Table 2) indicated the change of C-3 from a hemiacetal in (XIV) to a carbonyl function in (XVII). Similar treatment of dihydro-MB (XIV) with potassium deuterioxide in tetradeuteriomethanol afforded a mixture of deuteriated products. The mass spectrum demonstrated the presence of products containing three, two, and



one deuterium atoms (XVIII) (²H₃:²H₂:²H₁ 2:4:5). In the ¹H n.m.r. spectrum, the doublet at δ 1.35 due to the secondary methyl in (XVII) had become singlet at δ 1.37. The easy cleavage of the 3,4-bond of MB (XIII) suggests that the AB ring system is highly strained.

All the foregoing evidence confirms the deduced structure of MB (XIII). The absolute configuration was deduced from the o.r.d. curve, the shape and sign of which were similar to those of MA (Figure 3).

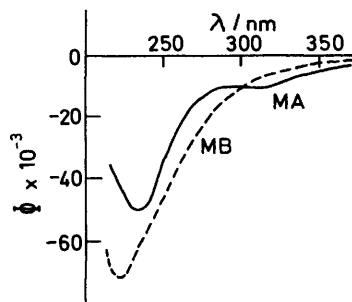


FIGURE 3 O.r.d. curves of MA and MB

The growth inhibition activity of all the derivatives described was examined: the mono-ol (III) and the acetate (XV) were more active than MA (I) and MB (XIII), respectively. Detailed results will be given elsewhere.

EXPERIMENTAL

Details of preparation and properties of compounds (II), (V), (VII)—(IX), (XI), (XII), and (XIV) are available as Supplementary Publication No. SUP 21934 (11 pp., 1 microfiche).*

Reduction of Momilactone with Lithium Aluminium Hydride.—(A) To a stirred mixture of MA (I) (50 mg) and anhydrous ether (10 ml) was added lithium aluminium hydride (10 mg), and stirring was continued for 15 min at

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

room temperature. After addition of water, the ether layer was separated and the aqueous layer extracted with ether. The combined ether solutions were washed with water, dried (Na₂SO₄), and evaporated to leave a white solid (50 mg), which was eluted through a silica gel (2 g) column [C₆H₆-AcOEt (3:1)] to yield 3 β -hydroxy-9 β -pimara-7,15-dien-19,6 β -olide (III) (40 mg), m.p. 148°, m/e 316 (M^+), $[\alpha]_D$ (CHCl₃) -225°, ν_{max} (CHCl₃) 3 520 and 1 740 cm⁻¹, δ (CDCl₃) 3.59 (dd, J 6.0 and 10.0 Hz, 3-H), 4.89 (t, J , 5.0 Hz, 6-H), 5.62 (d, J 5.0 Hz, 7-H), 5.82 (15-H), 4.87 and 4.89 (16-H₂), 0.81 (s, 17-H₃), 1.49 (s, 18-H₂), 1.01 (s, 20-H₃), and 3.91 (d, J 10.0 Hz, OH) (Found: C, 75.9; H, 8.9. C₂₀H₂₈O₃ requires C, 75.9; H, 8.9%).

(B) A mixture of MA (I) (83 mg), lithium aluminium hydride (40 mg), and anhydrous ether (20 ml) was stirred at room temperature for 15 min, then treated as in (A). The crude product was chromatographed on a silica gel (4 g) column [C₆H₆-AcOEt (4:1) then AcOEt]. From the latter eluate was obtained 9 β -pimara-7,15-diene-3 β ,6 β ,19-triol (IV) (66 mg) as white needles, m.p. 204—205° (from AcOEt), m/e 320 (M^+), $[\alpha]_D$ (CHCl₃) -230°, ν_{max} (KBr) 3 220 cm⁻¹, δ [CDCl₃-(CD₃)₂SO] 4.73 (dd, J 4.0 and 5.0 Hz, 6-H), 5.51 (d, J 5.0 Hz, 7-H), 5.83 (15-H), 4.87 and 4.90 (16-H₂), 0.85 (s, 17-H₃), 1.19 (s, 18-H₃), 1.28 (s, 20-H₂), 3.89 and 4.73 (each 1 H, ABq, 11.0 Hz, 19-H₂) (Found: C, 75.4; H, 10.15. C₂₀H₃₂O₃ requires C, 74.95; H, 10.05%).

Hydrolysis of the Mono-ol (III).—A mixture of the mono-ol (III) (59 mg), aqueous *N*-potassium hydroxide (2 ml), and *t*-butyl alcohol (3 ml) was refluxed for 24 h, then diluted with water and washed with ethyl acetate. The aqueous layer, cooled in ice, was acidified with hydrochloric acid. The mixture was extracted with ethyl acetate and the organic layer was washed with water, dried (Na₂SO₄), and evaporated to give pale yellow crystals (63 mg). Column chromatography [SiO₂ (3 g); C₆H₆-MeOH (5:1)] of the crude product yielded 3 β ,6 β -dihydroxy-9 β -pimara-7,15-dien-19-oic acid (VI) (50 mg), m.p. 154—156°, m/e 316 (M - 18), 301 (M - 33), and 298 (M - 36), $[\alpha]_D$ (CHCl₃) 0°, ν_{max} (CHCl₃) 3 600—2 400 cm⁻¹, δ (CDCl₃-CD₃OD) 3.10 (m, 3-H), 4.57 (t, J 5.0 Hz, 6-H), 5.49 (d, J 5.0 Hz, 7-H), 5.87 (15-H), 4.90 and 4.95 (16-H₂), 0.88 (s, 17-H₃), 1.57 (s, 18-H₃), and 1.13 (s, 20-H₃) (Found: C, 71.6; H, 9.1. C₂₀H₃₀O₄ requires C, 71.8; H, 9.05%).

Decarboxylation of Momilactone A. MA (I) (30 mg) was dissolved in 2*N*-potassium hydroxide (2 ml) and methanol (10 ml). After the mixture had been kept at room temperature for a week, it was poured into hydrochloric acid and extracted with ethyl acetate. From the organic layer was obtained 19-nor-MA (X) (20 mg). 19-Nor-MA (X) (75 mg) was also obtained by refluxing MA (I) (100 mg) in *N*-potassium hydroxide (3 ml) and methanol (5 ml) for 2.5 h; the product (X) had m.p. 146°, m/e 288 (M^+) and 270 (M - 18) (Found: C, 79.05; H, 9.8. C₁₉H₂₈O₂ requires C, 79.1; H, 9.8%).

Acetylation of Momilactone B.—(A) A mixture of MB (XIII) (15 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was refluxed for 1 h, then poured into water, and extracted with ethyl acetate. The extract was successively washed with hydrochloric acid and water, dried (Na₂SO₄), and evaporated to give a solid (13 mg). The solid was eluted through a silica gel (3 g) column [C₆H₆-AcOEt (5:1)] to give *MB acetate* (XV), m.p. 210°, m/e 372 (M^+), $[\alpha]_D$ (CHCl₃) -180°, ν_{max} (CHCl₃) 1 775 and 1 750 cm⁻¹, δ (CDCl₃) 4.89 (t, J 5.0 Hz, 6-H), 5.69 (d, J 5.0 Hz, 7-H), 5.88 (15-H), 4.91 and 4.94 (16-H₂), 0.88 (s, 17-H₃), 1.45

(s, 18-H₃), 3.69 (dd, *J* 2.0 and 12.0 Hz, 20-H), 4.13br (d, *J* 12 Hz, 20-H), and 2.12 (s, OAc) (Found: C, 71.1; H, 7.5. C₂₂H₂₆O₅ requires C, 70.95; H, 7.6%).

(B) To a stirred solution of MB (20 mg) in chloroform (10 ml) cooled in ice were added, 70% perchloric acid (2 drops) and acetic anhydride (2 drops), and stirring was continued for 30 min. After addition of ice-water, the chloroform layer was separated and the aqueous solution was extracted with chloroform. The combined chloroform solutions were washed with water, dried (Na₂SO₄) and evaporated to afford a gum (22 mg), which was passed through a silica gel (3 g) column [C₆H₆-AcOEt (5 : 1)]. MB acetate (XV) (8 mg) and then the oxo-acetate (XVI) (12 mg) were eluted successively. 12-Acetoxy-3-oxo-9β-pimara-7,15-dien-19,6β-olide (XVI) had m.p. 207–209°, *m/e* 372 (*M*⁺), [α]_D (CHCl₃) –240°, *v*_{max.}(CHCl₃) 1 775, 1 740, and 1 710 cm⁻¹, δ(CDCl₃) 4.85 (t, *J* 5.0 Hz, 6-H), 5.73 (d, *J* 5.0 Hz, 7-H), 5.89 (15-H), 4.94 and 4.97 (16-H₂), 0.90 (s, 17-H₃), 1.54 (s, 18-H₃), 3.95 and 4.22 (ABq, *J* 12 Hz, 20-H₂), and 1.99 (s, OAc) (Found: C, 70.9; H, 7.65. C₂₂H₂₆O₅ requires C, 70.95; H, 7.6%).

Reaction of Momilactone B with Methanolic Potassium Hydroxide.—A mixture of MB (XIII) (30 mg), 2*N*-potassium hydroxide (2 ml), and methanol (10 ml) was stirred at room temperature overnight, then poured into hydrochloric acid

and extracted with ethyl acetate. The extract was washed with water, dried (Na₂SO₄), and evaporated to afford an oil (30 mg), which was passed through a silica gel (20 g) column [C₆H₆-AcOEt (2 : 1)] to yield the dilactone (XVII) (14 mg), m.p. 50–55°, *m/e* 330 (*M*⁺), 312 (*M* – 18), 301, 284, and 257, [α]_D (CHCl₃) –120°, *v*_{max.}(CHCl₃) 1 760 and 1 720sh cm⁻¹, δ(CDCl₃-C₆D₆) *ca.* 4.6br (d, 6-H), 5.29br (s, 7-H), 5.78 (15-H), 4.92 and 4.87 (16-H₂), 0.87 (s, 17-H₃), 1.35 (d, *J* 7.0 Hz, 18-H₃), and 3.73 and 3.97 (2 H, ABq, *J* 12 Hz, 20-H₂) (Found: C, 72.85; H, 7.85. C₂₀H₂₆O₄ requires C, 72.7; H, 7.95%).

Rearrangement of Dihydro-MB (XIV) with Potassium Deuterioxide in Tetradeuteriomethanol.—A mixture of dihydro-MB (XIV) (15 mg), 40% potassium deuterioxide (5 ml), tetradeuteriomethanol (2 ml), and deuterium oxide (4 ml) was stirred at room temperature overnight, neutralized with 12*N*-hydrochloric acid, and then quickly extracted with chloroform. The extract was washed with water, dried (Na₂SO₄), and evaporated to give oily products. Preparative t.l.c. [SiO₂; C₆H₆-AcOEt (3 : 1)] gave the rearrangement product (XVIII), *m/e* 333, 334, and 335 (5 : 4 : 2) δ(CDCl₃) 4.93br (d, *J* 7 Hz, 6-H), 5.37br (s, 7-H), 0.84 (t, *J* 7.0 Hz, 16-H₃), 0.73 (s, 17-H₃), 1.37 (s, 18-H₃), and 4.12 and 4.30 (ABq, *J* 12.0 Hz, 20-H₂).

[6/1058 Received, 3rd June, 1976]