Tetrahedron. Vol. 23, pp. 4463 to 4468. Pergamon Press Ltd. 1967 Printed in Great Britain

19 → 20 LACTONES OF THE KAURANE SERIES

E. L. GHISALBERTI, P. R. JEFFERIES and W. A. MINCHAM

Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia

(*Received* 20 *January* 1967; *accepted for publication* 9 *February* 1967)

Abstract—Photolysis of N-iodoamides derived from kauran-19-oic acids gave reasonable yields of δ-lactones only. The method has provided a basis for preparation of the kaurene lactone XI.

THE gibberellin-like activity of steviol (I),[1] (−)-kaurene (II), (−)-kaur-16-ene-19-ol (III) and the kaurenoic acid (IV)[2] may be rationalized in terms of the intermediary role of (−)-kaurene[3] in gibberellin biosynthesis. Furthermore the formation[4] of (−)-kaurene (II) and the related alcohol III in cell-free homogenates of the endosperm nucellus of *Echinocystis macrocarpa* Greene, a rich source of gibberellins, and the incorporation of ^{14}C-(−)-kaurene and the alcohol III into gibberellic acid (V) by the culture *Fusarium monoliforme* points to these two compounds as intermediates in gibberellin biosynthesis both in the fungus and in the higher plants.[4]

The interest aroused by the activity of II, III and IV in biological assays has resulted in the total synthesis of III and IV on the one hand[5] and the partial synthesis of IV from 7-hydroxykaurenolide VI on the other.[6] As part of a survey of kaurene derivatives for gibberellin-like activity we decided to prepare the lactone XI, bearing in mind that the kaurenolides, e.g. VI, which occur[7] together with the gibberellins in *Gibberella fujikuroi*, indicate that XI is a less likely intermediate between the kaurenol (III) and gibberellic acid (V). This view is strongly supported by recent reports of the new C_{20}-gibberellins; GA_{12}[8] VII, GA_{13}[9] VIII, GA_{14}[9] VIIIa, the Bamboo gibberellin[10] (IX) and the Lupinus-gibberellin—I[11] (X). Qualitative results[9] indicate that the kaurenol (III) is incorporated into GA_{13} VIII and Cross and Norton [12] have

[1] M. Ruddat, A. Lang, and E. Mossettig, *Naturwissenschaften* **50**, 23 (1963).
[2] M. Katsumi, B. O. Phinney, P. R. Jefferies and C. A. Henrick, *Science* **144**, 849 (1964); M. Katsumi, B. O. Phinney, P. R. Jefferies and C. A. Henrick, *Plant Physiol.* **39** (suppl.), XXVII (1964).
[3] A. J. Birch, R. W. Richards, and H. Smith, *Pro. Chem. Soc.* 192 (1958); A. J. Birch, R. W. Richards, H. Smith, A. Harris and W. B. Whalley, *Tetrahedron* **7**, 241 (1959); B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 295 (1964).
[4] J. E. Graebe, D. T. Dennis, C. D. Upper and C. A. West, *J. Biol. Chem.* **20**, 1847 (1965).
[5] K. Mori and M. Matsui, *Tetrahedron Letters* No. 2, 175 (1966).
[6] R. H. B. Galt and J. R. Hanson, *Tetrahedron* **22**, 3185 (1966).
[7] B. E. Cross, R. H. B. Galt, J. R. Hanson, and (in part) P. J. Curtis, J. F. Grove and A. Morrison, *J. Chem. Soc.* 2937 (1963).
[8] B. E. Cross and K. Norton, *J. Chem. Soc.* 1570 (1965).
[9] R. H. B. Galt, *J. Chem. Soc.* 3143 (1965); B. E. Cross, *Ibid.*, *C, Org.* 501 (1966).
[10] S. Tamura, N. Takahashi, N. Murofushi, S. Iriuchyima, J. Kato, Y. Wada, E. Watanabe and T. Aoyama, *Tetrahedron Letters* No. 22, 2465 (1966).
[11] K. Koshimizu, H. Fukui, T. Kusaki, T. Mitsui and Y. Ogawa, *Tetrahedron Letters* No. 22, 2459 (1966).
[12] B. E. Cross and K. Norton, *Chem. Comm.* 535 (1965); *Tetrahedron Letters* No. 48, 6003 (1966).

reported that GA_{12} VII is incorporated into gibberellic acid (V) as also is GA_{14} VIIIa.

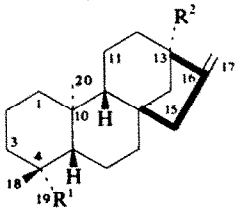
Functionalization of C–20 in diterpenes had been achieved photolytically[15,20] and similar procedures were envisaged for the preparation of XI. Preliminary experiments were carried out using the kauranes XII and XIII, both readily available from *Ricinocarpus stylosus*.[13] Efforts to functionalize C–20 following the methods of Heusler[14] or Edwards,[15] using the methyl ester of XIII or the azide derived from XIV respectively, were unpromising and so we were attracted by the appearance of a direct process for the preparation of lactones[16] based on the photolysis of saturated N-iodoamides. Application of this method to the amide XV, obtained in the normal way from XIV, and isolation of the product as the methyl ester gave the lactone XVI in 15% yield. The structure assigned XVI follows from the IR absorption in the carbonyl region which is restricted to ν_{max} 1740 cm^{-1} and the NMR spectrum which shows resonances due to one Me group attached to quaternary carbon at 8·80 τ as well as a pattern due to two protons at 5·88 and 4·85 τ, chemical shifts expected for the C–20 protons of XVI.

This experiment was used as a guide for the preparation of XI. The lability of the vinylidene group in the kaurenes requires that this function be introduced at a late stage, and for simplicity XXII was chosen for the photolytic procedure. The triol XVII and (−)-kaur-16-en-19-oic acid (IV) were available in reasonable quantities from two sources.[13,17] Prolonged oxidation of XVII with the Jones reagent or osmium tetroxide-periodate oxidation[18] of IV gave the keto acid XVIII in good yields. Reduction of XVIII with sodium borohydride gave mainly the 16β-epimer XIX together with a small amount of the isomer XX more readily available from XVIII by reduction with sodium-butanol. The alcohol XIX was acetylated and converted to the amide XXII in the usual way. After photolysis and alkaline hydrolysis of the product, the lactone XXIII was recovered in 40% yield, based on recovered XXII. Oxidation of XXIII with the Jones reagent gave the keto lactone XXIV which was then treated with a 1·5 molar proportion of triphenylphosphine methylide under Wittig reaction conditions, providing the required lactone XI.

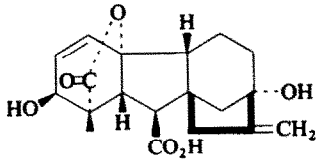
Although both γ- and δ-lactones are obtained by the photolytic method described by Barton *et al.*,[16] the usual feature is for a large predominance of the former. Using this method, on the tricyclic system of (±) desoxypodocarpamide, Mori and Matsui[19] obtained γ- and δ-lactones in the proportions of 12% and 2–3% respectively. No γ-lactones were isolated from the photolysis of either of the kaurane derivatives although the mother liquors possessed IR absorption at 1770 cm^{-1} indicating their formation in trace quantities. This quantitative variation in products may be attributed to the comparative steric congestion of the C-10-methyl group in the kauranes favouring a 7-membered transition state.

[13] C. A. Henrick and P. R. Jefferies, *Austral. J. Chem.* **17**, 915 (1964).
[14] G. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Experientia* **17**, 475 (1961); *Helv. Chim. Acta* **45**, 1317 (1962).
[15] J. W. Apsimon and O. E. Edwards, *Canad. J. Chem.* **40**, 896 (1962).
[16] D. H. R. Barton, A. L. J. Beckwith and A. Goosen, *J. Chem. Soc.* 181 (1965).
[17] P. R. Jefferies and T. G. Payne, *Austral. J. Chem.* **18**, 1441 (1965).
[18] R. Pappo, D. S. Allen, Jr., R.U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).
[19] K. Mori and M. Matsui, *Tetrahedron Letters* No. 15, 1633 (1966).
[20] D. H. R. Barton and J. R. Hanson, *Chem. Comm.* No. 7, 117 (1965).

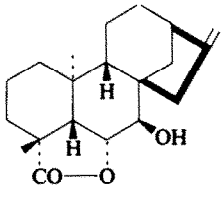
The NMR spectra of the δ-lactones all show quartets for the C-10 methylene protons where the downfield half of each quartet exhibits long range coupling of the order $J = 2$ c/s. If this coupling is through 4 σ bonds[21] and is a necessary consequence of a "W" relation between the protons concerned then it may be used to indicate a boat conformation for ring A in the lactones. Although it has been shown that δ-lactones prefer conformations in which C-2, C-5 and the O—C=O atoms are coplanar such arrangements are severely strained in the 19 → 20 lactones. Of those conformations which seem likely on general grounds[22–24] that in which the A ring and the lactone are boat and chair respectively provides a "W" arrangement for only one of the C-20 protons.



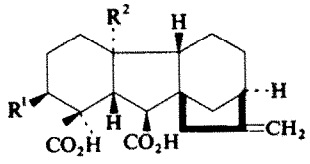
	R^1	R^2
I	COOH	OH
II	Me	H
III	CH_2OH	H
IV	COOH	H



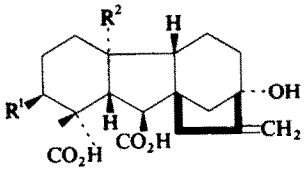
V



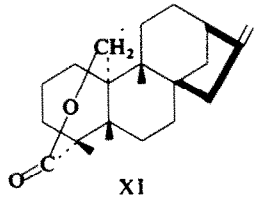
VI



	R^1	R^2
VII	H	Me
VIII	OH	CO_2H
VIIIa	OH	Me



	R^1	R^2
IX	H	CHO
X	OH	Me



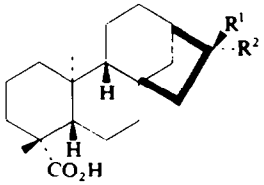
XI

[21] Bhacca and Williams, *Application of NMR in Organic Chemistry* p. 115. Holden–Day. San Francisco (1964).

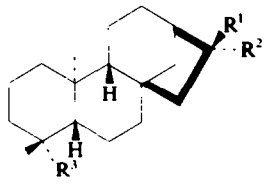
[22] J. F. McConnell, A. McL. Mathieson and B. P. Schoenborn, *Tetrahedron Letters* No. 10. 445 (1962); A. McL. Mathieson, *Ibid.* No. 2. 81 (1963).

[23] K. K. Cheung. K. H. Overton and G. A. Sim, *Chem. Comm.* 634 (1965).

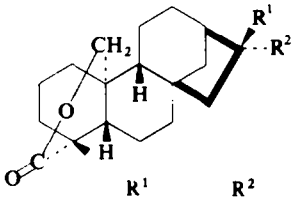
[24] W. A. C. Brown, G. Eglinton. J. Martin, W. Parker and G. A. Sim. *Pro. Chem. Soc.* 57 (1964); M. Dobler and J. D. Dunitz, *Helv. Chim. Acta* 47, 695 (1964).



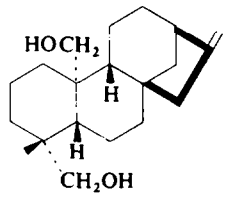
	R^1	R^2
XII	H	CO_2H
XIV	H	CO_2Me
XVIII	=O	
XIX	OH	H
XX	H	OH
XXI	OAc	H



	R^1	R^2	R^3
XIII	H	CO_2H	CH_2OH
XV	H	CO_2Me	$CONH_2$
XVII	CH_2OH	OH	CH_2OH
XXII	OAc	H	$CONH_2$



	R^1	R^2
XVI	H	CO_2Me
XXIII	OH	H
XXIV	=O	



XXV

EXPERIMENTAL

Analyses were carried out by the Australian Microanalytical Service, Melbourne. Rotations were determined for $CHCl_3$ solns unless otherwise stated, and at room temp (20–25°). IR spectra were measured with a Perkin-Elmer 337 spectrophotometer for CS_2 solns unless otherwise stated. The NMR spectra were measured with a Varian A-60 spectrometer (60 Mc) for $CDCl_3$ or $CHCl_3$ solns containing TMS as internal reference. $CHCl_3$ used in photolysis was EtOH free, dried and distilled. Irradiations were conducted in a quartz flask under N_2 using a Hanovia Photochemical Reactor with a medium press arc tube (125 watts). *Preparation and photolysis of the* N-*iodoamide from* XV. The 17-monomethyl ester of 16α-(−)-kauran-17,19-dioic acid[13] (600 mg), $SOCl_2$ (50 ml) and pyridine (1 ml) were heated under reflux for 2 hr. Excess $SOCl_2$ was removed *in vacuo* and the residue (300 mg) extracted with light petroleum (2 × 100 ml) was recrystallized from light petroleum to give the acid chloride as needles, m.p. 104–105°, ν_{max} 1800 cm^{-1} (acid chloride) and 1745 cm^{-1} (ester carbonyl). The acid chloride (200 mg) in dry benzene (50 ml) was treated with ammonia for 0·5 hr. Evaporation of the solvent, extraction with ether and recrystallization of the recovered product (100 mg) from EtOH gave needles of the *amide* XV, m.p. 211–213°, $[\alpha]_D$-108° (*c*, 1·1). (Found: C, 72·5; H, 9·4; N, 4·3. $C_{21}H_{33}O_3N$ requires: C, 72·6; H, 9·6; N, 4·0%.) ν_{max} 1695 (amide) and 1745 cm^{-1} (methyl ester). The NMR spectrum showed resonances at 9·06 and 8·76 τ (C_{10} and C_4 tertiary methyls respectively), 6·34 τ (3H; OMe) and a broad multiplet at 3·96 τ (2H; NH_2).

The amide XV (3·2 g), $CHCl_3$ (60 ml) and lead tetracetate (7·0 g) were stirred for 1 hr under N_2 and I_2 (3·2 g) added slowly. The ppt formed was filtered off, washed with $CHCl_3$ but could not be characterized as I_2 was liberated on storing. The ppt was redissolved in $CHCl_3$ (900 ml) and after condition of lead tetracetate (10 g) and I_2 (5·0 g) the soln was photolysed for 18 hr under N_2. The inorganic ppt was removed by filtration, and the excess I_2 by washing the $CHCl_3$ soln with 10% $Na_2S_2O_3$ aq and then water. The soln was dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue thus isolated was heated under reflux for 2 hr with 10% methanolic KOH. The recovered product was dissolved in benzene–ether and adsorbed on a silicic acid column. Elution with ether yielded a fraction which was methylated with diazomethane and crystallized from ether to give needles of the *lactone methyl ester* (XVI), m.p. 189–191°, $[\alpha]_D$ −72° (*c*, 1·2). (Found: C, 72·9; H, 8·7. $C_{21}H_{30}O_4$ requires: C, 72·8; H, 8·7%.) ν_{max} 1740 cm^{-1} (ester

and lactone groups). The NMR spectrum showed resonances at 8·80 τ (C_4 tertiary Me) at 6·35 τ (MeO) and an AB pattern 5·88 τ (1H) and 4·85 τ (1H; J_{AB} = 12 c/s) with the downfield proton further coupled (J = 2 c/s).

16β-*Acetoxy*-17-*nor*-(−)-*kauran*-19-*oic acid* (XXI). Kaur-16-en-19-oic acid (IV; 10 g), dioxan (400 ml) and water (130 ml) were treated with OSO_4 (40 mg) and after stirring for 1 hr sodium periodate (25 g) was added and the soln left overnight. Addition of sodium metabisulphite, concentration (1/4 volume) dilution with water and extraction with ether gave the nor-keto acid XVIII (8·9 g) also available by the Jones oxidation of XVII.[13] The nor-keto acid XVIII (3·5 g) in MeOH (200 ml) was reduced with $NaBH_4$ (3·5 g) for 24 hr at room temp. The excess reagent was destroyed with 10% aq. AcOH, the soln diluted with water and the product (3·4 g) recovered with ether. The crude product was treated with hot $CHCl_3$ and the less soluble component crystallized from $CHCl_3$ as needles of 16β-*hydroxy*-17-*nor*-(−)-*kauran*-19-*oic acid* (XIX), m.p. 217–218°, $[\alpha]_D$ −91° (EtOH) (*c*, 0·6). (Found: C, 74·3; H, 10·2. $C_{19}H_{30}O_3$ requires: C, 74·5; H, 9·9%.) The NMR spectrum (pyridine), showed signals at 8·78 and 8·63 τ (tertiary Me's) and a multiplet at 5·43 τ (16α—H). A small amount of the more soluble component was recovered from the mother liquor of XIX and shown to be the 16α-epimer (see (d) below). The hydroxy-acid XIX (3·0 g) was acetylated with Ac_2O-pyridine and the product (2·90 g) crystallized from benzene–light petroleum to give the 16-β-*acetoxy acid* XXI as needles, m.p. 176–178°, $[\alpha]_D$ −83° (*c*, 1·2). (Found: C, 72·1; H, 9·3. $C_{21}H_{32}O_4$ requires: C, 72·4; H, 9·3%.) ν_{max} 1730 cm^{-1} (acetate), 1760, 1690 cm^{-1} (carboxylic acid). The NMR spectrum showed resonances as singlets at 9·04 and 8·77 τ (C_{10} and C_4 tertiary Me's respectively), 7·96 τ (acetoxyl Me) and a multiplet at 4·98 τ (1H; $W_{\frac{1}{2}}$ 20 c/s, 16 α—H).

Sodium-butanol reduction of XVIII. The nor-keto acid XVIII (2·5 g) in n-butanol (100 ml) was heated under reflux and Na (10 g) was added over a period of 1·5 hr. After dissolution of the Na the soln was poured into water, acidified and extracted with ether. Recovery of the acidic product gave a residue (2·3 g) which crystallized from light petroleum–benzene to give 16α-*hydroxy*-17-*nor*-(−)-*kauran*-19-*oic acid* (XX) as prisms, m.p. 206–206·5°, $[\alpha]_D$ −88° (EtOH) (C, 0·6). (Found: C, 74·4; H, 9·8. $C_{19}H_{30}O_3$ requires: C, 74·5; H, 9·9%). ν_{max} 3625 cm^{-1} (OH) and 1760, 1690 cm^{-1} (carboxylic acid). The NMR spectrum showed resonances as singlets at 9·01 and 8·76 τ (C_{10} and C_4 tertiary Me's) and a broad multiplet at 5·65 τ (1H, $W_{\frac{1}{2}}$ 20 c/s, 16β—H).

The 16β-ol in pyridine was treated with tosyl chloride for 18 hr at room temp. Isolation of the product in the normal way and methylation with diazomethane gave a residue which was adsorbed on neutral alumina (Act III). Elution with light petroleum–benzene gave a fraction which cystallized from light petroleum as prisms of the *methyl ester tosylate*, m.p. 131–132°, $[\alpha]_D$ −13° (*c*, 1·1). Found: C, 68·4; H, 7·6; S, 6·9. $C_{27}H_{38}O_5S$ requires: C, 68·3; H, 8·1; S, 6·8%.) ν_{max} 1720 cm^{-1} (methyl ester), 1350 and 1155 cm^{-1} (sulphonate ester). The NMR showed resonances at 9·20 τ (C_{10} Me), 8·75 τ (C_4 Me), 7·53 τ (aromatic Me), 6·52 τ (3H, MeO) and a multiplet at 5·20 τ (1H; 16β—H).

Amide of 16β-*acetoxy*-17-*nor*-(−)-*kauran*-19-*oic acid* (XXII). The acetoxy-acid XXI (3·0 g), $SOCl_2$ (50 ml) and pyridine (1 ml) were heated under reflux for 2 hr. Evaporation of the excess $SOCl_2$ *in vacuo* and extraction of the residue with light petroleum (200 ml) gave the acid chloride, m.p. 144–147°. ν_{max} 1795 (acid chloride) and 1745 cm^{-1} (acetate). Ammonia gas was passed through a soln of the acid chloride in benzene for 0·5 hr, the solvent removed and the residue extracted with ether. The crude product was adsorbed on a column of neutral alumina (Act II: 100 g) and elution with $CHCl_3$ yielded the *amide* XXII (1·8 g) which crystallized from aqueous EtOH as needles, m.p. 126–128°, $[\alpha]_D$ −70° (*c*, 0·6). (Found: C, 72·7; H, 9·6; N, 3·7. $C_{21}H_{33}O_3N$ requires: C, 72·6; H, 9·6; N, 4·0%.) ν_{max} 1740 and 1660 cm^{-1}. The NMR spectrum showed resonances at 9·01 and 8·82 τ (C_{10} and C_4 Me's), 7·96 τ (acetoxy Me) a multiplet (2H) at 4·15 τ ($-NH_2$) and one at 4·97 τ (16α H, $W_{\frac{1}{2}}$ 20 c/s).

Photolysis of the amide XXII. The amide XXII (7·0 g) in dry $CHCl_3$ (200 ml), lead tetra-acetate (20 g) and I_2 (7·0 g) was photolysed under N_2 for 18 hr. No attempt was made to isolate the intermediate N-iodoamide. The soln was washed with 10% $Na_2S_2O_3$ aq. dried and the solvent removed *in vacuo*. The residue was hydrolysed with KOH (15 g) in water (75 ml) and EtOH (75 ml) for 2 hr. The soln was diluted with water and the neutral fraction recovered with ether to give unchanged amide XXII (2 g). Acidification of the aqueous solution with 2N HCl, extraction with ether, washing of the organic layer with 5% Na_2CO_3 aq. drying over Na_2SO_4 and removal of the solvent gave a crystalline residue (1·9 g). The residue was dissolved in benzene and adsorbed on a column of alumina (neutral; Act. II, 60 g). Elution with 50% benzene ether gave a fraction which crystallized from benzene–light petroleum as needles of the *hydroxy-lactone* (XXIII), m.p. 188–190°, $[\alpha]_D$ −58° (*c*, 0·7). (Found: C, 75·0; H, 9·4. $C_{19}H_{28}O_3$ requires: C, 75·0; H, 9·3%.) ν_{max} 3665 cm^{-1} (OH) and 1740 cm^{-1} (δ-lactone).

The mother liquor showed weak IR absorption at 1770 cm^{-1}.

Jones oxidation of the hydroxy-lactone XXIII. The hydroxy-lactone XXIII (600 mg) in acetone (30 ml) was treated with excess Jones reagent for 0·5 hr. Working up the usual way gave a crystalline residue (500 mg) which recrystallized from $CHCl_3$ light petroleum as needles of the *keto-lactone* (XXIV), m.p. 183–185°, $[\alpha]_D$ −34° (*c*, 1·8). (Found: C, 75·2; H, 8·4. $C_{19}H_{26}O_3$ requires: C, 75·5; H, 8·7%.) ν_{max} 1736 and 1747 cm^{-1} The NMR spectra showed resonances as a singlet at 8·77 τ (C_4 Me), a quartet at 5·79 τ and 4·76 τ (J_{AB} 12 c/s).

Wittig reaction on the keto-lactone XXIV. Triphenylmethylphosponium iodide (2·4 g; 1·5 mmoles) was suspended and stirred in dry THF (15 ml) and n-butyl-lithium in light petroleum (12 ml; 0·5M) was added over a period of 10 min under N_2. After 1 hr the soln gave a negative test for excess base (Michler's ketone) and the keto-lactone XXIV (500 mg) in THF (20 ml) was added dropwise. The soln was stirred for 16 hr at room temp and then THF (50 ml) was added and the light petroleum co-distilled from the reaction mixture. The soln was heated for 6 hr, acidified with 2N HCl and extracted with ether.

The recovered product was then refluxed with 1N NaOH and EtOH for 1 hr. Dilution with water, removal of the phosphine oxide with ether and recovery of the lactonic component from the aqueous layer gave a crystalline residue (350 mg) which was adsorbed on a column of neutral alumina (Act II: 30 g). Elution with benzene gave the *unsaturated lactone* XI (130 mg), recrystallized from light petroleum as needles, m.p. 177–178°, $[\alpha]_D$ −86° (*c*, 0·8). (Found: C, 79·6; H, 9·3. $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%.) ν_{max} 3057, 1653, 877 cm^{-1} (=CH_2) and 1743 cm^{-1} (δ-lactone). Resonances in the NMR spectrum appeared at 8·79 τ (C_4 Me), 5·85 and 4·79 τ (C_{10} methylene) and at 5·16 τ (exocyclic double bond). Elution with 20% ether–benzene gave XXIV (200 mg). TLC of the unsaturated lactone on silica gel or alumina showed only one spot.

Lithium aluminium hydride reduction of XI. The lactone XI (50 mg), ether (20 ml) and LAH (50 mg) were heated under reflux for 2 hr. Recovery of the product in the normal way gave a crystalline residue (40 mg) which recrystallized from benzene–light petroleum as needles of the *diol* (XXV), m.p. 147–148°, $[\alpha]_D$ −67° (*c*, 0·4). (Found: C, 79·3; H, 10·9. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.) ν_{max} 3057, 1650, 871 cm^{-1} (=CH_2) and 3599 (OH). The NMR spectrum showed resonances as singlets at 8·98 τ (3H, C_4 Me) and 3·97 τ (2H, —CH_2—OH) as well as an AB quartet centred at 3·46 and 3·95 τ (*J* 12 c/s; 2H, —CH_2—OH) and a broad signal at 4·79 τ (=CH_2).

Acknowledgement—This work was supported by Public Health Service Research Grant No. CA07810-02 from the National Cancer Institute (U.S.A.).