Aust. J. Chem., 1979, **32**, 823–32

Synthetic Plant Growth Regulators. IV* The Preparation of Hydroxylated Helminthosporic Acid Analogues

Lewis N. Mander[A] *and Lyndon T. Palmer*[B]

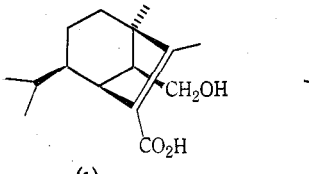
[A] Research School of Chemistry, Australian National University, P.O. Box 4, Canberra, A.C.T. 2600.
Author to whom correspondence should be addressed.
[B] Department of Organic Chemistry, University of Adelaide, P.O. Box 498, Adelaide, S.A. 5001.

Abstract

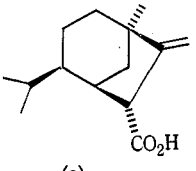
Sequential reduction (sodium borohydride, metal–ammonia, hydrogenation) of ketone (8) gave the hydroxy ketone (9) which was converted into olefin (10) (Wittig olefination) and thence to acid (14) by means of the [2,3] sigmatropic rearrangement of ylide (12) to (13). Acid (15) was similarly prepared from alcohol (11) which was obtained by deoxygenation of ketone (9). The tetrahydrocuminic acid (16) was hydroxylated (lithium diisopropylamine, oxygen); the new hydroxyl group was protected with a dichloroacetyl function and then converted into the diazoketone. Lewis-acid-induced cyclization of (17) gave the bicyclooctanone (18a) plus its Δ^3-isomer (18b), both of which were reduced and hydrolysed to hydroxy ketone (19). Wittig methylenation of (19) gave olefin (20) which was rearranged by acid to ketone (21). Both (20) and (21) were elaborated further to the acids (6) and (25), respectively, by the procedures used in the preparation of acids (14) and (15).

Introduction

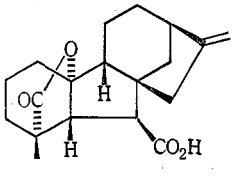
The acid (2), a synthetic analogue of the fungal metabolite helminthosporic acid (1), has been shown to be slightly more potent in the barley endosperm assay than gibberellin A_9 (3).[1] More active gibberellins such as GA_3 (4) are characterized by



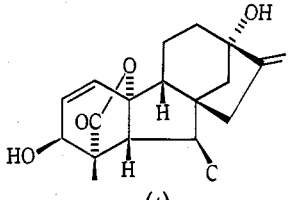
(1)



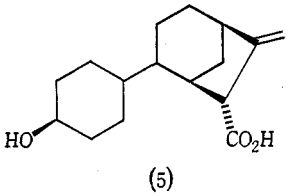
(2)



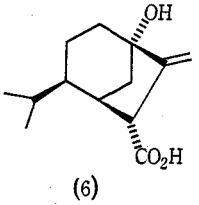
(3)



(4)



(5)

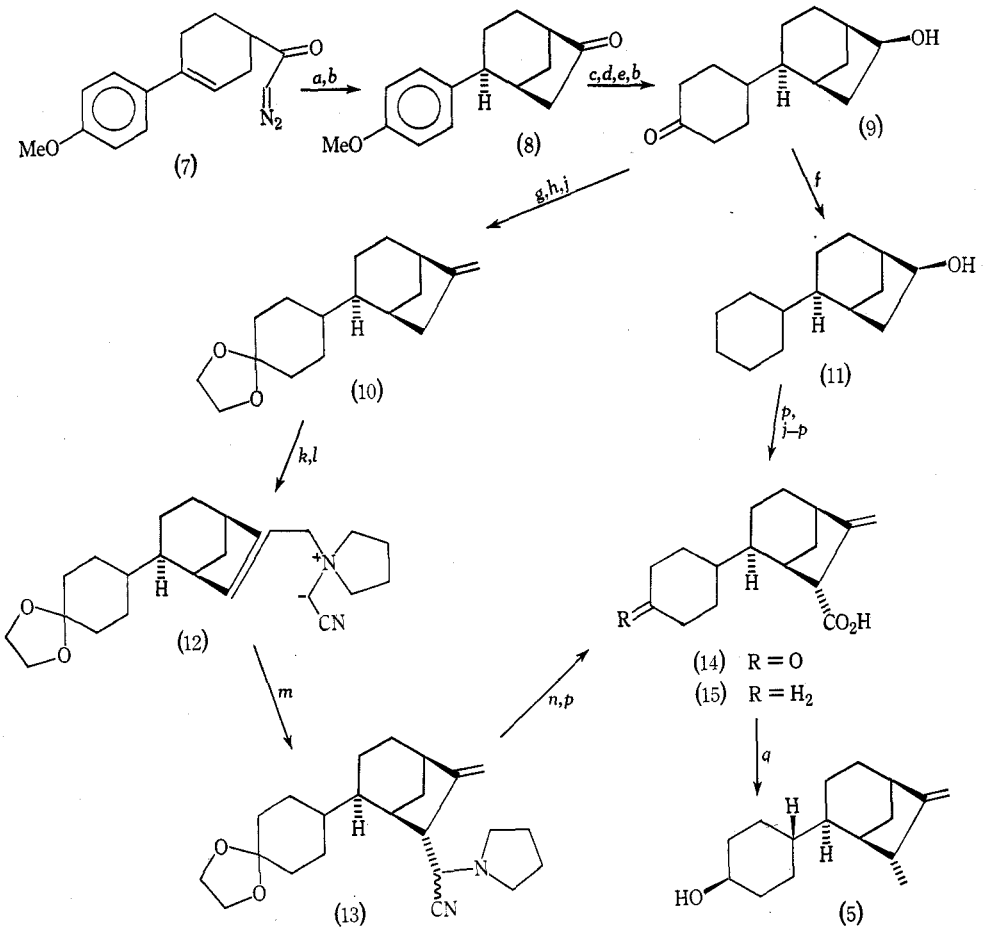


(6)

* Part III, *Aust. J. Chem.*, 1979, **32**, 817.

[1] Coombe, B. G., Mander, L. N., Paleg, L. G., and Turner, J. V., *Aust. J. Plant Physiol.*, 1974, **1**, 473.

hydroxylation at C3 and C13,[2] and it was therefore of considerable interest to assay analogues of (2) bearing hydroxyl groups in the same relative positions. To this end, we have undertaken the synthesis of hydroxy acids (5) and (6), among others.



Scheme 1. Reagents: *a*, BF_3,Et_2O, CH_3NO_2; *b*, H_2, 5% Pd/C, MeOH; *c*, $NaBH_4$, EtOH; *d*, Li, liq. NH_3, thf, Bu^tOH; *e*, oxalic acid, H_2O, MeOH; *f*, $HSCH_2CH_2SH$, BF_3,Et_2O, AcOH; Raney Ni, EtOH; *g*, $HOCH_2CH_2OH$, TsOH, PhH; *h*, CrO_3,2py, CH_2Cl_2; *j*, $Ph_3P{=}CH_2$, Me_2SO; *k*, *N*-bromosuccinimide, CCl_4; *l*, pyrrolidinylacetonitrile, Me_2SO; *m*, $KOBu^t$, Me_2SO; *n*, oxalic acid, H_2O, thf; *p*, CrO_3, H_2SO_4, H_2O, Me_2CO; *q*, $LiAl(OBu^t)_3H$, thf.

Apart from the obvious structural differences between the helminthosporane and gibberellin derivatives, acid (2) diverges from the gibberellins by having the C4 hydrogen *anti* to the two-carbon bridge. The spatial changes which might have arisen from this difference are minimal, since the C-ring in gibberellins adopts a boat-like conformation.[3] Nevertheless, the examination of the 4-epimer of acid (2) warrants attention and it was hoped that the envisaged precursor (20) of acid (6) would provide us with an opportunity to prepare such a compound, i.e. (25).

[2] Reeve, D. R., and Crozier, A., *J. Exp. Biol.*, 1974, **25**, 431.
[3] Hartsuck, J. A., and Lipscombe, W. N., *J. Am. Chem. Soc.*, 1963, **85**, 3414.

Results and Discussion

The syntheses of acid (5) and its deoxy analogue (15) (for a reference standard in the bioassay) are outlined in Scheme 1. The assembly of the basic carbon skeleton [(7) → (8)] was based on our earlier studies.[4,5] An independent synthesis has been reported[6] since the completion of this phase of the work by an essentially identical sequence, and so no further details are recorded here. Ketone (8) was converted by a series of basic functional group manipulations into hydroxy ketone (9) and thence to the methylene derivative (10). This was then transformed to acid (14) by a standard procedure,[4] in which the critical step was the [2,3] sigmatropic rearrangement of the allylic ammonium ylide (12). The pyrrolidinylacetonitrile moiety in (13) served as a latent formyl group which was readily oxidized to the desired carboxyl function. Selective reduction of the 4′-carbonyl group with lithium tri-(t-butoxy)aluminium hydride gave mainly the expected equatorial isomer[7] so the product can be assigned structure (5). Although this compound differs from the gibberellins at two chiral centres, the overall shapes are similar. Alcohol (11), from the desulfurization (with W2 Raney nickel) of the dithioacetal derivative from ketone (9), was converted into the reference acid (14) in an equivalent sequence.

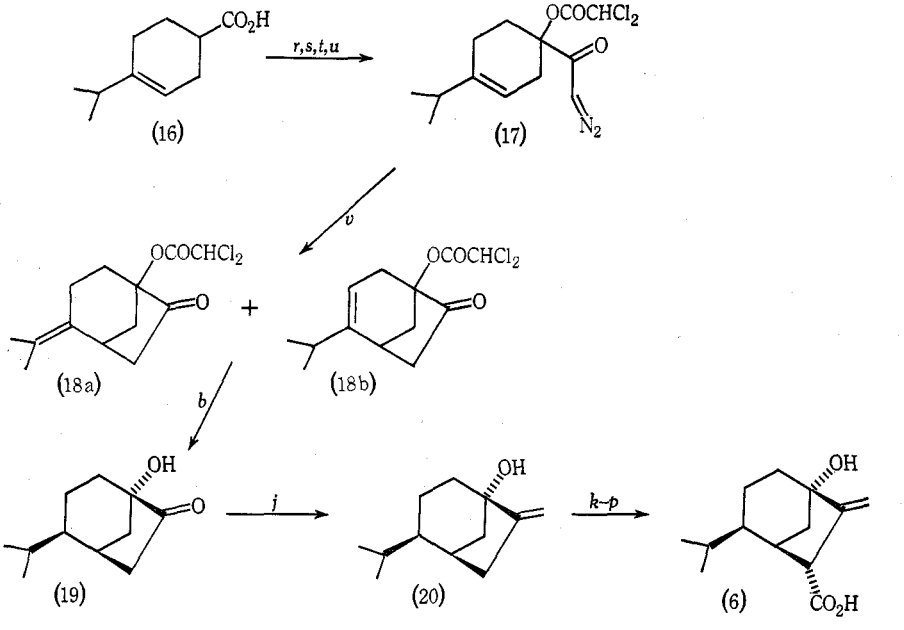
With the benefit of earlier synthetic studies, the preparation (Scheme 2) of acid (6) was also very straightforward. The tetrahydrocuminic acid (16)[8]* was hydroxylated through oxygenation of its derived dianion[9] and the hydroxyl function then masked by a dichloroacetyl group in preparation for the acid-catalysed cyclization of the diazoketone (17). (The dichloroacetoxy group does not compete effectively with the olefinic bond for the electrophilic diazonium intermediate.[10]) The exocyclic olefin (18a) dominated in a mixture with its endocyclic isomer and a sample crystallized selectively from a purified fraction. Hydrogenation of the mixture in methanol was accompanied by methanolysis of the ester function and hydroxy ketone (19) was thus obtained. Its stereochemistry was assigned through analogy with comparable reductions[4] and confirmed by later events.

Although protection of the hydroxyl function through the remainder of the planned sequence seemed to be advisable, it proved to be unneccessary. Isomerization during the Wittig olefination of similar hydroxy ketones has been observed,[11] but in the present case it was expected that the isopropyl group would provide a 'thermodynamic lock'. In fact, in the product of an acyloin rearrangement either the isopropyl group must occupy an axial conformation as in (ii) or the six-membered ring must take up the twist-boat conformation (i) (Scheme 3) to avoid the very unfavourable diaxial interactions in (ii). This analysis was confirmed by subjecting hydroxy ketone (19) to a variety of bases, which returned the starting material unchanged.

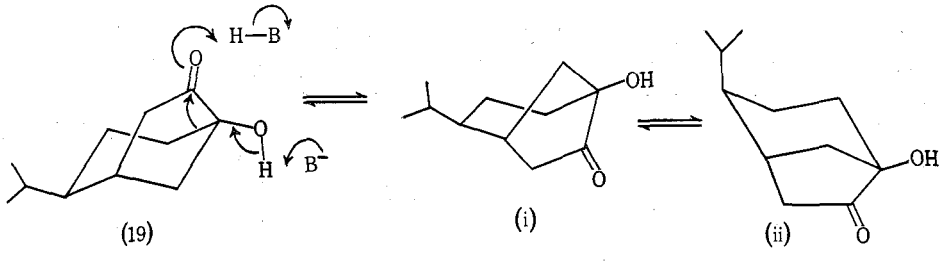
* A new preparation was devised for this compound; see Experimental.

[4] Mander, L. N., Turner, J. V., and Coombe, B. G., *Aust. J. Chem.*, 1974, **27**, 1985.
[5] Klose, T. R., and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1287.
[6] Ghatak, U. R., Alam, S. K., Chakraborti, P. C., and Ranu, B. C., *J. Chem. Soc., Perkin Trans. 1*, 1976, 1669.
[7] Eliel, E. L., and Rerick, M. N., *J. Am. Chem. Soc.*, 1960, **82**, 1367.
[8] Nazarov, I. N., Titov, Yu. A., and Kuznetsova, A. I., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1959, 1595 (*Chem. Abstr.*, 1960, **54**, 8714).
[9] Konen, D. A., Silbert, L. S., and Pfeffer, P. E., *J. Org. Chem.*, 1975, **40**, 3253.
[10] Blair, I. A., Ellis, A., Johnson, D. W., and Mander, L. N., *Aust. J. Chem.*, 1978, **31**, 405.
[11] Bell, R. A., Ireland, R. E., and Mander, L. N., *J. Org. Chem.*, 1966, **31**, 2536.

The addition of a carboxyl group to (20) was achieved smoothly, even though Wagner–Meerwein rearrangement during the bromination (adventitious HBr) and hydrolysis (hot aqueous oxalic acid) stages presented a potential hazard.[12]



Scheme 2. Reagents: *r*, $LiNPr^i_2$, O_2; *s*, $Cl_2CHCOCl$, PhH; *t*, ClCOCOCl; *u*, CH_2N_2; *v*, BF_3,-Et_2O, CH_2Cl_2; *b*, *j*–*p* as in Scheme 1.

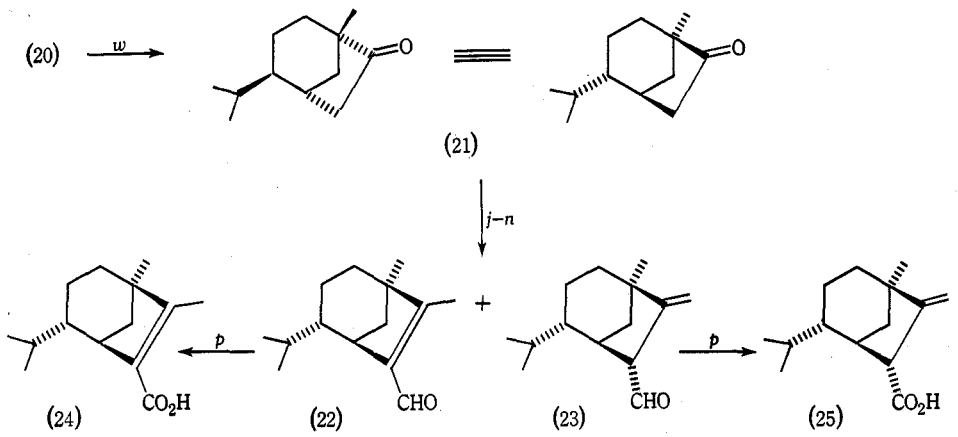


Scheme 3

Access to the C4 epimer of acid (2) was gained through acid-catalysed rearrangement[11–13] of hydroxy olefin (20) to ketone (21), which was transformed by the standard procedure[4] to give the usual mixture of α,β- and β,γ-unsaturated aldehydes (22) and (23) (Scheme 4). These were conveniently separated by selective oxidation of the latter aldehyde (23) to acid (25). Aerial oxidation of the conjugated isomer gave acid (24). In all these compounds the isopropyl group gave rise to a simple doublet in ^1H n.m.r. spectra, indicating a twist-boat conformation [cf. structure (i), Scheme 3].

[12] Cross, B. E., *J. Chem. Soc.*, 1954, 4670.
[13] Dolder, F., Lichti, H., Mosettig, E., and Quitt, P., *J. Am. Chem. Soc.*, 1960, **82**, 256.

Acids (24) and (25) are therefore stereochemically more precise analogues of the gibberellins.



Scheme 4. Reagents: *w*, HCl, MeOH; *j–p* as in Scheme 1.

Acids (5), (14) and (15) have been shown to have gibberellin-like activity. Although (15) is as potent as (2), the oxygenated derivatives (5) and (14) are less active. A rationalization of this trend has been presented.[14] Preliminary bioassays indicate that acids (6), (24) and (25) are also active, but are significantly less potent than (2).

Experimental

For general directions relating to compounds (7)–(15) see Part I[4] of this Series. For the remaining compounds see Part III.

endo-*2-(4'-Methoxyphenyl)bicyclo[3,2,1]octan*-endo-*6-ol*

A solution of ketone (8)[6] (9·5 g, 0·041 mol) in absolute ethanol (200 ml) was treated with a solution of $NaBH_4$ (2·36 g, 0·062 mol) in absolute ethanol (50 ml) and stirred overnight. Water (150 ml) was added, and the solution extracted with methylene chloride (2 × 250 ml). The extracts were washed with water (2 × 60 ml), dried (Na_2SO_4) and evaporated to a white crystalline solid (9·49 g, 99%) which was used without further purification. A small sample was recrystallized from ether/X4 to give white *crystals*, m.p. 85·5–87° (Found: C, 77·7; H, 8·5. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7%). ν_{max} (Nujol) 3400, 1610 cm^{-1}. N.m.r. δ 3·8, s, OMe; 4·4, e, $W_{h/2}$ 10 Hz; 6·9, 7·15, ABq, ArH.

4-(endo-*6-Hydroxybicyclo[3,2,1]oct*-endo-*2-yl)cyclohexanone* (*9*)

Liquid NH_3 (300 ml) was decanted into a solution of the aromatic alcohol (9·0 g, 0·039 mol) in dry tetrahydrofuran (100 ml, dried over CaH_2) and t-butyl alcohol (26·8 g, 0·35 mol) in a 500-ml three-necked flask fitted with a dry ice/acetone condenser. Lithium wire (1·95 g, 0·24 g-atom) was added over 15 min to the stirred solution at −60° under nitrogen. After dissolution of the lithium and disappearance of the blue colour (2 h), ethanol (40 ml) was added slowly, then NH_4Cl (10·6 g, 0·200 mol) was added. The NH_3 was allowed to evaporate overnight under nitrogen to leave a white cake which was dissolved in water (80 ml). The solution was extracted with chloroform (2 × 250 ml), dried (Na_2SO_4) and evaporated to a white solid (9·0 g, 99%), ν_{max} 3300, 1685, 1650 cm^{-1}. The crude product was dissolved in ethanol (150 ml), treated with a solution of oxalic acid (5·0 g, 0·055 mol) in water (70 ml) and stirred for 30 min. This solution was diluted with water, extracted with benzene (2 × 150 ml), dried (Na_2SO_4) and evaporated to give a yellow liquid (8·45 g, 100%), ν_{max} (film) 3400, 1705 cm^{-1}. N.m.r. δ 2·9, m, $C{=}CCH_2CO$: 4·4, e, $W_{h/2}$ 10 Hz, CHOH; 5·46, t, *J* 6 Hz, C=CH.

[14] Turner, J. V., Coombe, B. G., and Mander, L. N., *Aust. J. Plant Physiol.*, 1978, **5**, 347.

This crude product was dissolved in absolute ethanol (200 ml) and stirred with 5% palladium/carbon (1·64 g) under hydrogen (*c.* 1 atm) at ambient temperature. This was continued until the uptake of hydrogen had ceased for 1 h (*c.* 5 h). The filtered (Celite) solution was concentrated under reduced pressure to a slightly yellow liquid which gave a white solid on standing overnight (7·9 g, 95%). Chromatography on Sorbsil (240 g) in X4 and elution with benzene/ether (20 : 1) gave *hydroxy ketone* (9) (5·21 g, 63%). A small sample crystallized from ether had m.p. 111–115° (Found: C, 75·7; H, 9·9. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). ν_{max} 3400, 1710 cm^{-1}. N.m.r. δ 4·4, e, CHOH.

endo-2-(*4′-Ethylenedioxycyclohexyl*)*bicyclo*[*3,2,1*]*octan*-endo-*6-ol*

A mixture of the hydroxy ketone (5·21 g, 0·023 mol), ethylene glycol (2·88 g, 0·046 mol) and toluene-*p*-sulfonic acid (10 mg) in benzene (200 ml) was heated overnight in a Dean–Stark water separator. The reaction mixture was cooled and washed with NaOH (10%, 2 × 30 ml) and brine (2 × 60 ml), then dried (Na_2SO_4) and evaporated to a white crystalline *product* (5·97 g, 95·5%). A small sample was recrystallized from ether/X4 before analysis, m.p. 90·5–92° (Found: C, 72·1; H, 9·8. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%). ν_{max} 3300 cm^{-1}. N.m.r. δ 3·94, s, OCH_2CH_2O; 4·33, e, $W_{h/2}$ 10 Hz, CHOH.

endo-2-(*4′-Ethylenedioxycyclohexyl*)*bicyclo*[*3,2,1*]*octan-6-one*

Chromic anhydride (13·25 g, 0·13 mol) was added to a stirred solution of pyridine (21·0 g, 0·26 mol) in dry methylene chloride (200 ml). The mixture was protected by a drying tube and the burgundy solution stirred for 15 min at room temperature. A solution of the hydroxy acetal (5·5 g, 0·02 mol) in methylene chloride (50 ml) was then added; a black precipitate formed. After stirring for 15 min at room temperature the reaction mixture was decanted and the residue washed with ether (200 ml). The organic layer was washed with NaOH (5%, 3 × 100 ml), briefly with HCl (1%, made from conc. HCl and brine), then with saturated NaCl (100 ml), then dried ($MgSO_4$) and evaporated to give a whitish *solid* (5·08 g, 93%). A sample was recrystallized from ether before analysis, m.p. 129–131° (Found: C, 72·8; H, 9·1. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·2%). ν_{max} 1730 cm^{-1}.

endo-2-(*4′-Ethylenedioxycyclohexyl*)-*6-methylenebicyclo*[*3,2,1*]*octane* (*10*)

Dry dimethyl sulfoxide (50 ml) was added to NaH (1·79 g, 0·075 mol) and the suspension was stirred under nitrogen at 72° until the NaH dissolved (*c.* 20 min). The reaction mixture was cooled to room temperature and methyl triphenylphosphonium iodide (30 g, 0·075 mol) was added. After stirring for 10 min the ketone (10) (4·9 g, 0·018 mol) in dry tetrahydrofuran (30 ml) was added and the reaction mixture stirred for 30 h at room temperature. Ice (100 g) was then added and the mixture extracted with X4 (3 × 150 ml). The extracts were washed with methanol/water (1 : 1) (2 × 100 ml), dried (Na_2SO_4) and evaporated to give a yellow oil (4·9 g, > 100%). This was chromatographed on Sorbsil (150 g) in X4. Elution with benzene gave the product *olefin* as a colourless oil (2·55 g, 52·5%). A small sample was distilled before analysis, b.p. 100–102°/0·6 Torr (Found: C, 77·6; H, 9·9. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%). ν_{max} (film) 3020, 1650 cm^{-1}. N.m.r. δ 3·93, s, OCH_2CH_2O; 4·8, m, $C{=}CH_2$.

Bromination of Olefin (*10*)

To the olefin (10) (1·7 g, 6·5 mol) dissolved in carbon tetrachloride (100 ml) was added *N*-bromosuccinimide (1·2 g, 6·75 mmol) and a few crystals of benzoyl peroxide. The mixture was heated under reflux for 30 min, during which time the heavy precipitate of *N*-bromosuccinimide gave way to a light precipitate of succinimide. The cooled solution was filtered and evaporated under reduced pressure. The residue was chromatographed on a short column of Sorbsil (30 g) in X4. Elution with X4/benzene (5 : 1) gave a mixture of bromides as a colourless oil (1·92 g, 87%). ν_{max} (film) 1650, 1630 cm^{-1}. N.m.r. δ 3·93, s, OCH_2CH_2O; 4·1, s, 0·58H, CH_2Br; 5·91, m, 0·29H, C=CH; 4·96, m, 0·71H, CHBr; 5·2, d, 0·71H, *J* 1·5 Hz, $C{=}CH_2$. Ratio primary/secondary bromide 29 : 71.

2-[endo-*4′*-(*4″-Ethylenedioxycyclohexyl*)-*7′-methylenebicyclo*[*3,2,1*]*oct*-exo-*6′-yl*]-2-(*pyrrolidin-1‴-yl*)*acetonitrile* (*13*)

The allylic bromides (1·2 g, 3·52 mmol) were added to a stirred solution of pyrrolidin-1-yl-acetonitrile (0·41 g, 3·73 mmol) in dry Me_2SO (5 ml) under nitrogen, and the reaction mixture stirred

at 45° for 18 h. The solution of the resulting salt was diluted with dry tetrahydrofuran (25 ml), cooled to −10°, and treated with solid potassium t-butoxide (0·52 g, 4·65 mmol). The reaction mixture was stirred for 3 h, extracted with benzene/ether (9 : 1, 2 × 100 ml), washed with brine (3 × 50 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil (1·3 g, 100%) which crystallized on standing, and was used without further purification. ν_{max} (film) 2200, 1645 cm^{-1}. N.m.r. δ 3·5, m, epimeric NCHCN; 3·92, s, OCH_2CH_2O; 5·08, m, $C{=}CH_2$.

7-Methylene-endo-*4-(4'-oxocyclohexyl)bicyclo[3,2,1]octane*-exo-*6-carbaldehyde*

The acetonitrile (13) mixture (1·0 g, 2·7 mmol) was dissolved in tetrahydrofuran (35 ml) and treated with a warm solution of oxalic acid (35 ml, 30%). This mixture was heated under reflux for 30 min, cooled and then extracted with benzene (2 × 100 ml). The fractions were washed with brine (2 × 40 ml) and water to neutrality, then dried (Na_2SO_4) and evaporated to a pale yellow oil (0·67 g, >100%). ν_{max} (film) 1715s, 1660w (C=CCHO) cm^{-1}. N.m.r. δ 9·57, d, J 2 Hz, 0·89H, CHCHO; 10·11, s, 0·11H, C=CCHO. Chromatography on Sorbsil (60 g, in X4) and elution with benzene/ether (20 : 1) gave unconjugated aldehyde (520 mg, 78·5%) as white crystals. Further elution with benzene/ether (5 : 1) gave the conjugated aldehyde (64 mg, 9·6%). A sample of the β,γ-unsaturated aldehyde was recrystallized from ether/X4 to give white crystals, m.p. 87–89° (Found: C, 77·7; H, 8·9. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%). ν_{max} 3040, 2700, 1705, 1650 cm^{-1}. N.m.r. δ 3·15, m, H6; 5·07, 5·23, 2 × m, $C{=}CH_2$; 9·57, d, J 2 Hz, CHO.

7-Methylene-endo-*4-(4'-oxocyclohexyl)bicyclo[3,2,1]octane*-exo-*6-carboxylic Acid* (*14*)

The unconjugated aldehyde prepared above (400 mg, 1·63 mmol) was dissolved in acetone (20 ml) and the solution cooled to −10°. Jones reagent[15] was cooled to −10° and added dropwise up to an orange end point. After 20 min, sufficient propan-2-ol was added to quench excessive reagent and the mixture diluted with benzene (50 ml) and water (40 ml). The aqueous layer was extracted with benzene (50 ml), the benzene fractions washed with brine (2 × 40 ml) and water until colourless, dried (Na_2SO_4), and evaporated to give the acid as a white solid (430 mg, >100%). Chromatography on Sorbsil (25 g in X4) and elution with benzene/ether (10 : 1) gave the *acid* (14) as white crystals (332 mg, 78%). A sample was recrystallized from ether/X4 to give clear flakes, m.p. 148–149° (Found: C, 73·5; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·5%). ν_{max} 3200–2700, 1710, 1660 cm^{-1}. N.m.r. δ 3·27, m, H6; 5·12, 5·20, 2 × m, $C{=}CH_2$; 9·11, br s, CO_2H.

endo-*4-(4'*-trans-*Hydroxycyclohexyl)-7-methylenebicyclo[3,2,1]octane*-exo-*6-carboxylic Acid* (*5*)

A solution of acid (14) (262 mg, 1·0 mmol) in dry tetrahydrofuran (10 ml) at 0° under nitrogen was treated with lithium tri(t-butoxy)aluminium hydride (0·75 g, 3 mmol) and the solution stirred for 3 h at 0°, then at 24° for 16 h. Addition of water, 1 N HCl (5 ml), and extraction with methylene chloride afforded *acid* (5) (220 mg, 83%). Recrystallization from acetone/X4 gave prisms, m.p. 168–170° (Found: C, 72·4; H, 9·5. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·2%). ν_{max} 3390, 3200–2400, 1715, 1660w cm^{-1}. N.m.r. (methyl ester) δ 3·42, e, $W_{h/2}$ 35 Hz, CHOH; 3·67, s, OMe; 5·02, m, $C{=}CH_2$.

endo-*2-Cyclohexylbicyclo[3,2,1]octan*-endo-*6-ol* (*11*)

Hydroxy ketone (9) (450 mg, 2 mmol) was dissolved in a mixture of ethanedithiol (285 mg, 3·0 mmol) and acetic acid (10 ml), treated with freshly distilled boron trifluoride–diethyl ether complex (280 mg, 2 mmol); the mixture was stirred for 16 h. Dilution with ether (100 ml) and X4 (10 ml), thorough washing with NaOH (5 × 10 ml, 10%), drying (Na_2SO_4) and removal of solvent gave a colourless gum. This was immediately dissolved in ethanol (25 ml), W2 Raney nickel (3 g) added and the suspension heated under reflux for 0·5 h. Filtration and removal of solvent gave a mixture of alcohol (11) and its derived ketone (ν_{max} 1730 cm^{-1}). The mixture was therefore treated with sodium borohydride as for ketone (8), affording pure *alcohol* (11) as a colourless gum (420 mg, 100%). A sample crystallized from ether/X4 had m.p. 111–111·5° (Found: C, 80·8; H, 11·6. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%). ν_{max} 3300 cm^{-1}. m/z 208 (M, 9%) 190 (37), 125 (25), 107 (91), 81 (68), 79 (100).

[15] Bowers, A., Halsall, T. G., Jones, E. R. H., and Lemin, A. J., *J. Chem. Soc.*, 1953, 2548.

endo-*2-Cyclohexylbicyclo[3,2,1]octan-6-one*

Alcohol (11) (400 mg, 1·9 mmol) in acetone (20 ml) at 0° was treated with Jones reagent[15] (0·62 ml, 2·5 mmol). The mixture was stirred for 10 min, quenched (propan-2-ol), diluted with ether (50 ml) and X4 (20 ml), and washed with brine. Drying and removal of solvent gave a colourless oil. Crystallization from X4 gave the desired *ketone*, m.p. 24–26° (Found: C, 81·2; H, 11·0. $C_{14}H_{22}O$ requires C, 81·5; H, 10·8%). ν_{max} 1730 cm^{-1}.

endo-*4-Cyclohexyl-7-methylenebicyclo[3,2,1]octane*-exo-*6-carboxylic Acid (15)*

This acid was obtained in 45% overall yield by the sequence described for acids (2) and (14). Spectroscopic constants (i.r., n.m.r., m.s.) of intermediates were comparable to those described for those leading to (2). The final *product* crystallized from hexane and had m.p. 153–155° (Found: C, 77·4; H, 9·9. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). ν_{max} 3200–2700, 1710, 1660 cm^{-1}. δ 2·66, e, $W_{h/2}$ 9 Hz, H1+H4; 3·20, m, $W_{h/2}$ 7 Hz, H6; 5·05, 5·12, br s, C=CH_2; 9·30, e, $W_{h/2}$ 25 Hz, CO_2H.

1,2,5,6-Tetrahydrocuminic Acid (16)

A solution of 3,6-dihydrocuminic aldehyde[16] (3·0 g, 0·02 mmol) in dry ether (30 ml) was added dropwise to a stirred solution of lithium (0·7 g, 0·10 mol) in liquid ammonia (150 ml) and t-butyl alcohol (7·4 g, 0·10 mol). After 15 min methanol (5 ml) was added, the ammonia removed (water bath) and the residue dissolved in water (100 ml). This mixture was extracted with ether/X4 (2 × 50 ml, 4 : 1); the organic layer was washed with brine (2 × 20 ml), dried and reduced to a colourless liquid (3·1 g, quantative). This was dissolved in acetone (60 ml); the solution was cooled to 5° and treated dropwise with Jones reagent[15] (6 ml) over a 10-min period. After a further 10 min propan-2-ol (0·5 ml) was added, then water (100 ml); the mixture was extracted with ether/benzene (2 × 50 ml, 3 : 1). These extracts were combined and washed with sat. $NaHCO_3$ (3 × 50 ml). The aqueous fractions were acidified to pH 4 and extracted with ether/X4 (2 × 70 ml, 5 : 1). The dried extracts were reduced to a semicrystalline gum (2·8 g, 84%). Crystallization from hexane gave colourless crystals, m.p. 62–64°, lit. 65–66°.[8]

1-Hydroxy-4-isopropylcyclohex-3-enecarboxylic Acid

Butyllithium (4·8 ml, 1·6 M in hexane, 0·007 mol) was added dropwise to a stirred mixture of diisopropylamine (1·0 ml, 0·077 mol) and tetrahydrofuran (15 ml) at −30° under nitrogen, followed by acid (16) (0·59 g, 0·035 mol). The reaction mixture was warmed to 50° for 30 min (completion of dianion formation) then cooled to 25°. Oxygen was bubbled through this solution for 30 min, then ice and 1 N hydrochloric acid were added and the mixture was extracted with ether/X4 (2 × 50 ml, 4 : 1). The washed (brine) and dried extracts were reduced to a semicrystalline gum which was triturated with dichloromethane and hexane to give colourless *crystals* (0·36 g, 56%), m.p. 100–102° (Found: C, 65·5; H, 8·7. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·8%). ν_{max} 3400, 3200–2700, 1700 cm^{-1}. N.m.r. δ 1·04, d, J 6·5 Hz, Pr^i; 5·37, e, $W_{h/2}$ 11 Hz, H3; 7·10, e, $W_{h/2}$ 25 Hz, OH+CO_2H.

1-Dichloroacetoxy-4-isopropylcyclohex-3-enecarboxylic Acid

A mixture of hydroxy acid (0·92 g, 5 mmol), CH_2Cl_2 (10 ml) and dichloroacetyl chloride (2·2 g, 15 mmol) was heated under reflux for 0·5 h, reduced to a gum, then dissolved in acetone/water (9 : 1, 10 ml). After 1 h this solution was diluted with water, extracted with CH_2Cl_2 (3 × 30 ml) and the combined extracts washed with water (2 × 10 ml). The dried solution was reduced to dryness and the residue crystallized from CH_2Cl_2/hexane to give *prisms* (1·31 g, 90%), m.p. 90–92° (Found: C, 48·6; H, 5·6. $C_{12}H_{16}Cl_2O_4$ requires C, 48·8; H, 5·5%). ν_{max} (film) 3400–2300, 1760, 1710 cm^{-1}. N.m.r. δ 0·99, d, 6H, J 6·5 Hz, Pr^i; 5·28, m, $W_{h/2}$ 10 Hz, H3; 5·92, s, $COCHCl_2$.

4-Isopropylidene-7-oxobicyclo[3,2,1]oct-1-yl Dichloroacetate (18a)

A solution of acid (1·28 g, 4·5 mmol) in CH_2Cl_2 (20 ml) and oxalyl chloride (2·54 g, 20 mmol) at 0° was treated with pyridine (0·35 g, 4·5 mmol) and the mixture stirred under a nitrogen

[16] Birch, A. J., and Dastur, K. P., *Aust. J. Chem.*, 1973, **26**, 2547.

atmosphere for 40 h. The CH_2Cl_2 was removed, the residue extracted with dry benzene (2 × 20 ml) and the extracts filtered. Solvent was removed again, the residue redissolved in benzene (10 ml) and added dropwise to a stirred ethereal solution of diazomethane (0·6 g, 15 mmol) at −25°. The solution was allowed to warm to 0°, stirred for a further 2 h and then evaporated to dryness (care!). The crude diazoketone showed ν_{max} 2130, 1640 ($COCHN_2$), 1760 cm^{-1} ($OCOCHCl_2$); n.m.r. δ 1·03, d, 6H, J 6·5 Hz, Pr^i; 5·35, e, $W_{h/2}$ 10 Hz, H3; 5·52, s, $COCHN_2$; 5·95, s, Cl_2CHCO. A stirred solution of diazoketone in CH_2Cl_2 (50 ml) at 0° was treated dropwise with BF_3,Et_2O (0·7 g, 5 mmol) and stirring continued for 40 min (nitrogen evolution ceased after 30 min). The reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with water (2 × 20 ml) and dried. Removal of solvent gave a dark gum (1·3 g), a 100 mg sample of which was purified by preparative layer chromatography (CH_2Cl_2) to give 75 mg of a mixture of olefin isomers (endocyclic/exocyclic, 1 : 3). The minor isomer had δ 0·96, m, Pr^i; 5·96, e, C=CH. Crystallization from hexane gave the *major isomer* (18a) (50 mg), m.p. 98–100° (Found: C, 53·8; H, 5·6. $C_{13}H_{16}Cl_2O_3$ requires C, 53·6; H, 5·5%). ν_{max} 1760 cm^{-1}. N.m.r. δ 1·66, s, Me; 1·73, s, Me; 3·60, t, J 6 Hz, H5; 5·97, s, Cl_2CHCO. m/z 294 (6%), 292 (32), 290 (M, 48), 247* (12), 234* (19), 163 (16), 162 (21), 147 (13), 137 (44), 135 (35), 134 (100), 124 (37), 123 (30), 121 (20), 120 (31), 119 (36), 109 (23), 105 (67), 95 (73), 93 (35), 91 (36).

5-Hydroxy-endo-*2-isopropylbicyclo[3,2,1]octan-6-one* (*19*)

The crude product obtained from cyclization of the diazoketone (1·2 g) was hydrogenated (4 atm) in methanol over 5% palladium/carbon for 20 h (concomitant methanolysis of dichloroacetate). Solvent was removed from the filtered solution and the residue chromatographed on silica gel (30 g). Elution with ether/X4 (1 : 4) gave *hydroxy ketone* (19) (0·42 g, 70%). A sample crystallized from acetone/hexane had m.p. 90–92° (Found: C, 72·6; H, 9·8. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%). ν_{max} 3400, 1755 cm^{-1}. N.m.r. δ 0·88, 0·92, 2 × d, J 6·5 Hz, Pr^i; 3·25, s, exch. D_2O. m/z 182 (M, 98%), 154 (16), 139 (34), 136 (17), 126 (38), 121 (18), 112 (16), 111 (18), 96 (25), 84 (40), 83 (100).

endo-*4-Isopropyl-7-methylenebicyclo[3,2,1]octan-1-ol* (*20*)

A mixture of hydroxy ketone (19) (0·41 g, 2·2 mmol), methyltriphenylphosphonium bromide (3·6 g, 10 mmol) and $KOBu^t$ (1·1 g, 10 mmol) in tetrahydrofuran (20 ml) was stirred under a nitrogen atmosphere for 20 h. Solvent was removed, the residue was extracted with hexane (4 × 20 ml) and the combined extracts were washed with methanol/water (1 : 1, 2 × 10 ml). Removal of solvent and sublimation of the residue (80°/1 atm) gave fine *needles* (0·36 g, 90%), m.p. 49–51° (Found: C, 79·6; H, 10·9. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). ν_{max} 3300 (OH), 3080, 1662, 886 cm^{-1} (C=CH_2). N.m.r. δ 0·81, 0·85, 2 × d, J 6·5 Hz, Pr^i; 2·05, s, exch. D_2O, OH; 2·22; br s, $W_{h/2}$ 6 Hz, (H6)$_2$; 4·80, br s, $W_{h/2}$ 4 Hz, C=CH_2; 4·90, d, J 3 Hz, C=CH_2. The sample kept for mass spectrometry was lost through sublimation from a stoppered vial.

1-Hydroxy-endo-*4-isopropyl-7-methylenebicyclo[3,2,1]octane*-exo-*6-carboxylic Acid* (*6*)

A suspension of *N*-bromosuccinimide (174 mg, 1·0 mmol) in a CCl_4 (10 ml) solution of hydroxy olefin (20) (162 mg, 0·9 mmol) and benzoyl peroxide (0·1 mg) was heated under reflux for 50 min. The usual isolation and purification procedure gave a 1 : 1 mixture of bromides (230 mg), δ 4·0 (CH_2Br), 5·92 (=CH), 4·75 (=CCHBr), 5·3 (=CH_2), to which was added Me_2SO (5 ml) and pyrrolidin-1-ylacetonitrile (0·11 g). The mixture was stirred at 50° for 40 h under a nitrogen atmosphere. Tetrahydrofuran (5 ml) was then added, the solution cooled to −20° and $KOBu^t$ (0·11 g) added. After 3 h, the usual isolation procedure followed by hydrolysis with oxalic acid (aq., 30%) gave a 3 : 1 mixture of aldehydes (150 mg), ν_{max} 3450, 1730, 1670 cm^{-1}. N.m.r. δ 0·90, m, 6H, Pr^i; 2·95, e, 0·75H, $W_{h/2}$ 6 Hz, H5; 3·37, s, exch. D_2O, OH; 4·95, d, 0·75H, J 2 Hz, =CH_2; 5·20, d 0·75H, J 2 Hz, =CH_2; 9·47, d, 0·75H, J 3 Hz, CHO; 9·88, s, 0·25H, CHO.

Treatment of the aldehyde mixture with Jones reagent and isolation of the acidic fraction in the usual manner gave *acid* (6) (70 mg). Recrystallization from acetone/hexane gave prisms, m.p. 118–120° (Found: C, 69·5; H, 9·1. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%). ν_{max} 3320 (OH), 3200–2400, 1710 (CO_2H), 1642, 890 cm^{-1} (C=CH_2). N.m.r. (CD_3COCD_3) δ 0·90, 2 × d, 6H, J 6·5 Hz, Pr^i; 2·50, d, 6 Hz, H5; 3·10, e, J 5 Hz, H6; 5·08, t, J 2 Hz, C=CH_2; 6·5, e, $W_{h/2}$ 30 Hz, exch. D_2O, OH. m/z 224 (M, 19%), 181 (26), 140 (26), 139 (100), 137 (12), 135 (10), 95 (22).

* $^{37}Cl_2$ and ^{37}Cl, ^{35}Cl peaks observed also.

exo-*2-Isopropyl-5-methylbicyclo[3,2,1]octan-6-one* [(±)-*4-Epi-12,13,14-trinorhelminthosporan-7-one*] (*21*)

A solution of the methylene alcohol (20) (200 mg) in methanol (20 ml) and 3 M HCl (5 ml) was heated under reflux for 1·5 h. Dilution by water and extraction with hexane gave *ketone* (21) (185 mg) as a homogeneous (t.l.c.) colourless oil, ν_{max} (film) 1740 cm^{-1}. N.m.r. δ 0·94, d, J 6·5 Hz, Pr^i; 0·96, s, Me. *Semicarbazone*, m.p. 185–187° (Found: C, 65·8; H, 9·7; N, 17·6. $C_{13}H_{23}N_3O$ requires C, 65·8; H, 9·8; N, 17·7%).

exo-*2-Isopropyl-5-methyl-6-methylenebicyclo[3,2,1]octane* [(±)-*4-Epi-13,14-dinorhelminthospor-7(12)-ene*]

Ketone (21) (150 mg) was added to a stirred mixture of methyltriphenylphosphonium bromide (1·06 g, 3 mmol) and $KOBu^t$ (0·336 g, 3 mmol) in ether (20 ml) under a blanket of nitrogen. After 48 h the ether was removed under reduced pressure and the residue fractionated between X4 and methanol/water (4 : 1). The hydrocarbon extract was filtered through silica gel and reduced (care!) to a colourless oil (120 mg, 75%), ν_{max} 3082, 1670, 890 cm^{-1}. N.m.r. δ 0·99, d, J 6·5 Hz, Pr^i; 1·10, s, 3H, Me; 4·64, e, $W_{h/2}$ 7 Hz, and 4·76, e, $W_{h/2}$ 5 Hz, methylene protons.

exo-*4-Isopropyl-1-methyl-7-methylenebicyclo[3,2,1]octane*-exo-*6-carboxylic Acid* [(±)-*4-Epi-14-norhelminthospor-7(12)-en-13-oic Acid*] (*25*)

Application of the standard sequence to the above olefin (120 mg) described for (10) gave a crude mixture of aldehydes (89 mg) which were dissolved in acetone (5 ml) at 5° and treated with Jones reagent (0·2 ml). After 10 min propan-2-ol (0·2 ml) was added (quench) followed by ether (50 ml) and benzene (10 ml). After washing with water (2 × 10 ml) the *acid* (25) (60 mg) was separated by extraction with 10% $NaHCO_3$ in the usual way. Crystallization from pentane at −20° gave colourless prisms (25 mg), m.p. 138–140° (Found: C, 75·9; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). ν_{max} 3500–2200, 1710 (CO_2H), 1650, 895 cm^{-1} (C=CH_2). N.m.r. (CCl_4) δ 0·90, d, J 6·5 Hz, Pr^i; 1·06, s, Me; 2·55, m, $W_{h/2}$ 10 Hz, H5; 3·14, e, $W_{h/2}$ 7 Hz, H6; 4·84, d, J 2 Hz, 5·19, s, methylene protons; 11·1, e, $W_{h/2}$ 20 Hz, CO_2H. m/z 222 (M, 34%) 179 (100), 177 (42), 152 (16), 139 (20), 138 (76), 137 (26), 135 (16), 133 (20), 121 (16), 119 (20), 107 (40), 95 (25), 93 (47), 91 (35).

exo-*4-Isopropyl-1,7-dimethylbicyclo[3,2,1]oct-6-ene-6-carbaldehyde* [(±)-*4-Epi-14-norhelminthospor-6-en-13-al*] (*22*)

Preparative layer chromatography (ether/X4, 1 : 4) of the neutral material obtained from the previous experiment gave *aldehyde* (22) (15 mg) as an unstable (aerial oxidation) gum, λ_{max} 254 nm (ε 2800). ν_{max} 2840, 2740, 1680 (CHO), 1635 cm^{-1} (C=C). N.m.r. δ 0·94, d, J 6·5 Hz, Pr^i; 1·03, s, Me; 1·97, s, Me; 2·94, m, $W_{h/2}$ 6 Hz, H5; 9·93, s, 1H, CHO. m/z 206 (M, 23%), 205 (100), 137 (15), 109 (12), 107 (10), 95 (17), 93 (10).

exo-*4-Isopropyl-1,7-dimethylbicyclo[3,2,1]oct-6-ene-6-carboxylic Acid* [(±)-*4-Epi-14-norhelminthospor-6-en-13-oic Acid*] (*24*)

A solution of aldehyde (22) (15 mg) in CCl_4 (10 ml) open to the air was stirred for 48 h. Preparative layer chromatography (ether/X4 1 : 1) of the concentrate and crystallization from pentane gave *acid* (24) (12 mg), m.p. 119–122° (Found: C, 75·2; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). λ_{max} 241 nm (ε 4100). ν_{max} (film) 3400–2500, 1665 (CO_2H), 1618 cm^{-1} (C=C). N.m.r. δ 0·94, d, J 6·5 Hz, Pr^i; 1·01, s, Me; 2·0, s, Me; 2·9, e, $W_{h/2}$ 8 Hz, H5. m/z 222 (M, 62%), 179 (72), 177 (89), 152 (33), 151 (21), 139 (63), 138 (100), 121 (13), 107 (54), 95 (20), 93 (32), 91 (32).

Acknowledgment

Part of this work was supported by a grant from the Australian Research Grants Committee.

Manuscript received 30 October 1978