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# Synthetic Plant Growth Regulators. I The Synthesis of (±)-14-Norhelminthosporic Acid and Related Compounds

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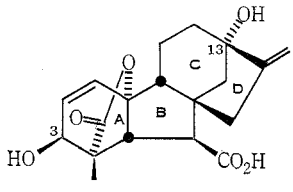
*Abstract*

Cuminic acid (9) was converted by reductive methylation into 1,2,3,6-tetrahydro-4-isopropyl-1-methylbenzoic acid (12). Acid-catalysed cyclization of the diazomethyl ketone (8) derived from (12), followed by hydrogenation, gave the bicyclo[3,2,1]octanone derivative (7), which was then converted through the allylic bromide mixture of (18) and (19) into the *p*-toluenesulphonyldithiocarbazone (21) and the allylic ammonium bromide (25). The [2,3]-sigmatropic rearrangement of the dithiocarbene derived from (21) and the ylid derived from (25) afforded the dithioester (22) and pyrrolidine (26), respectively, from which the alcohol (24), aldehydes (27) and (28), and acids (5) and (6) were prepared. Bioassay of (5), (6), (27) and (28) indicated gibberellin-like properties for all these compounds with potency comparable with that of helminthosporic acid (2).

## Introduction

Unlike that of their animal counterparts, the fundamental cellular function of the principal plant growth regulators[1]—the auxins, the cytokinins, and the gibberellins[2]—is poorly understood. It is ironical that the gibberellins, e.g. gibberellic acid (1) whose primary effect is least defined, have so far found greatest use in agriculture and horticulture by increasing the height of plants or the number and size of leaves, by improving the set of fruit and yield from a tree, by offsetting frost damage, by delaying senescence and by effecting other spectacular changes in plant physiology.[3]



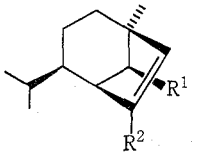
(1)

Nevertheless, despite prolific information on the chemistry and biosynthesis of gibberellins,[4] the precise mode of physiological action in the cell remains obscure.[4,5] Much effort on the problem of structure–activity relationships has been expended in testing the relative biological activities of gibberellins and structurally related molecules, usually derived through chemical modification of the gibberellins themselves. These approaches, however, are confused by a diverse array of functional groups, the general lability of this type of molecule and, therefore, the difficulties implicit in undertaking a systematic modification of the skeleton and substituents.

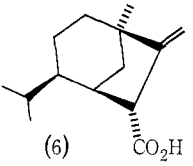
[1] Fleming, W. J., and Howden, H. E. H., *Rev. Pure Appl. Chem.*, 1972, **22**, 67.
[2] Jones, R. L., *Annu. Rev. Plant Physiol.*, 1973, **24**, 571.
[3] Cathey, H. M., and Stuart, N. W., *Annu. Rev. Plant Physiol.*, 1961, **12**, 369; Briggs, D. E., *J. Inst. Brew.*, 1963, **69**, 244; Turner, J. N., *Outlook Agr.*, 1972, **7**, 14.
[4] Lang, A., *Annu. Rev. Plant Physiol.*, 1970, **21**, 537.
[5] Paleg, L. G., *Annu. Rev. Plant Physiol.*, 1965, **16**, 291.

So far, the only functional group found to be essential for activity is the B-ring $\beta$-carboxyl group,[6] although the more active gibberellins also possess a $\gamma$-lactone function fused to the A-ring which, in the most active compounds, usually bears *inter alia* a 3$\beta$-hydroxyl group.[7,8] The problem is further confused by the possibility of rapid biological modification of the test substance.

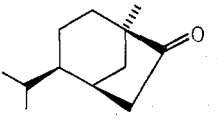
Flexible syntheses of gibberellins, which could incorporate isotopic labels,[9] could be invaluable in unravelling the structure–function enigma and, although efforts along these lines are proceeding in this and other laboratories,[10] such an approach appears to be limited severely by molecular complexity. The problem would be simplified enormously if the moiety essential for growth activity (the 'effector' part) could be delineated and synthesized; then, a systematic elaboration of substituent groups about this basis structure should enable the systematic evaluation of the growth-promoting effects of each added substituent.



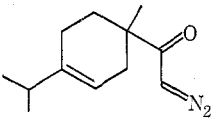

| | $R^1$ | $R^2$ |
|---|---|---|
| (2) | $CH_2OH$ | $CO_2H$ |
| (3) | $CH_2OH$ | CHO |
| (4) | CHO | CHO |
| (5) | H | $CO_2H$ |




(6)



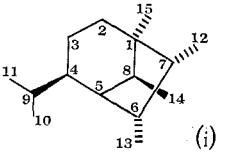

(7)




(8)

A clue to the nature of the effector might lie in the known gibberellin-like activity of the sesquiterpenes helminthosporic acid (2) and helminthosporol (3),[11] which have been related chemically[12] to the plant toxin helminthosporal (4),[13] whose structure and absolute configuration[14] corresponds to the C/D-ring structure of gibberellins. Briggs has postulated[11] that helminthosporins* may possess the minimum growth-effector requirement and a number of derivatives have been prepared and subjected

* 'Helminthosporin' is the family name suggested for these compounds and 'helminthosporane'[15] proposed for the carbon network (i), which has been numbered for consistency with the literature.[16] For instance, helminthosporic acid becomes 14-hydroxyhelminthospor-6-en-13-oic acid.




(i)

[6] Brian, P. W., Grove, J. F., and Mulholland, T. P. C., *Phytochemistry*, 1967, **6**, 1475.
[7] Crozier, A., Durley, R. C., Pharis, R. P., and Kuo, C. C., *Can. J. Bot.*, 1970, **48**, 867.
[8] Coombe, B. G., *Science*, 1971, **172**, 856.
[9] Kende, H., *Plant Physiol.*, 1967, **42**, 1612; Hanson, J. R., and Hawker, J., *Tetrahedron Lett.*, 1972, 4299.
[10] Johnson, D. W., and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1277; Klose, T. R., and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1287, and references cited therein.
[11] Briggs, D. E., *Nature*, 1966, **210**, 418.
[12] Kainuma, K., Sakurai, A., Takai, M., and Tamura, S., *Agr. Biol. Chem.*, 1965, **29**, 216.
[13] DeMayo, P., Spencer, E. Y., and White, R. W., *Can. J. Chem.*, 1965, **43**, 1357; 1963, **41**, 2996.
[14] Corey, E. J., and Nozoe, S., *J. Amer. Chem. Soc.*, 1965, **87**, 5728.
[15] Herout, V., in 'Aspects of Terpenoid Chemistry and Biochemistry' (Ed. T. W. Goodwin) p. 60 (Academic Press: London 1970).
[16] Aldridge, D. C., and Turner, W. B., *J. Chem. Soc. C*, 1970, 686.

to bioassay.[17,18] Nevertheless, these investigations are also limited by the availability of the natural products and by their structures.

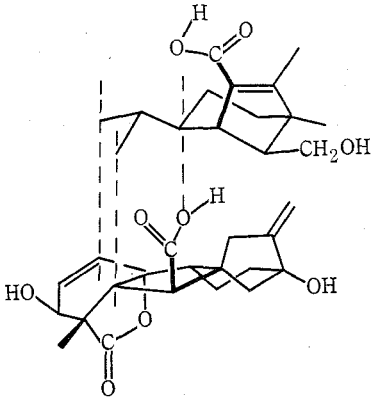



**Fig. 1.** Structural resemblance between helminthosporic acid (2) and gibberellic acid (1).

A comparison of models of the 'right hand' portion of a gibberellin molecule and of heminthosporic acid (Fig. 1), indeed, reveals a striking similarity. In particular, the all-important carboxyl group occupies approximately the same relative position in space, and there is the same bicyclo[3,2,1]octane structure in both compounds. The obvious differences are the hydroxymethyl residue in the latter molecule and the exocyclic methylene substituent in the former. Briggs has suggested[11] that this second difference may be accommodated by the *in vivo* deconjugation of the $\alpha,\beta$-unsaturated double bond in helminthosporic acid, but there appears to be no function for the hydroxymethyl appendage in this compound.*

We have, accordingly, undertaken syntheses of helminthosporin analogues lacking the hydroxymethyl group and which possess a double bond in both the endocyclic and exocyclic positions, e.g. acids (5) and (6).† The successful outcome of this effort is described in this paper and the preparation of further analogues with structures resembling helminthosporins and gibberellins will be described in future publications.

## Discussion

In designing syntheses of the nor-helminthosporins such as (5) and (6), we sought a route to a common intermediate, relatively late in the synthetic sequence, which would permit the greatest flexibility in the preparation of substrates for biological testing.‡ The bicyclic ketone (7) appeared to be suitable for our purposes and we envisaged that it would be readily available from the olefinic diazoketone (8) in

* The alcoholic hydroxyl substituent in helminthosporic acid occupies a position in space approximating (relatively) to that of the C13 hydroxyl group in 13-hydroxy gibberellins; but, since the presence or absence of this hydroxyl residue has no apparent effect on biological potency,[6] there would also appear to be no role (in terms of Briggs's hypothesis) for the hydroxyl group in helminthosporic acid.

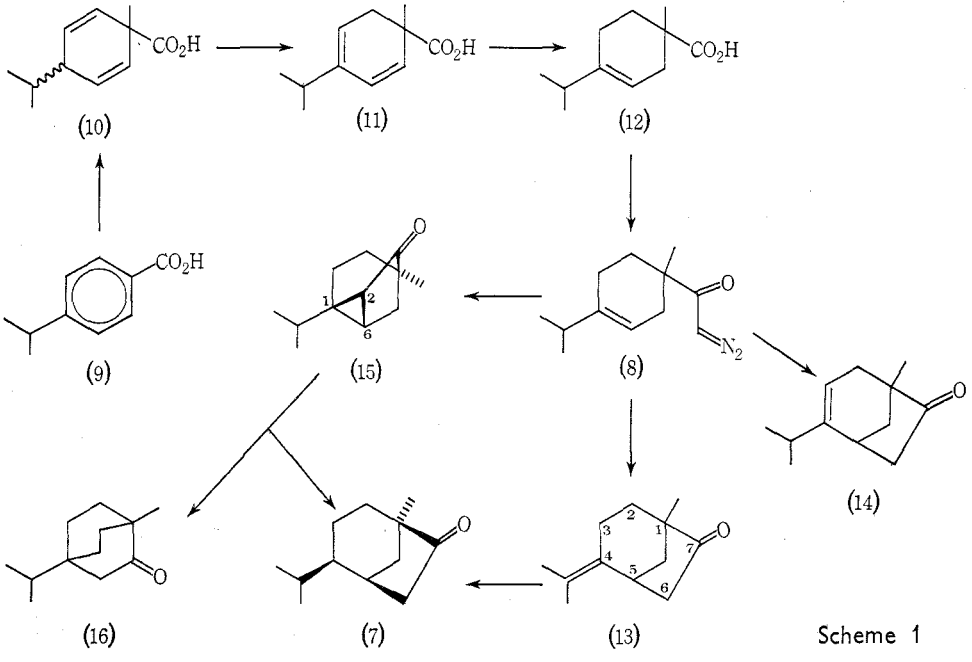
† Only one enantiomer is drawn for the racemates (5)–(8) and (10)–(28).

‡ The short and elegant synthetic route from (−)-carvomenthone to helminthosporal described by Corey and Nozoe[14] is not, unfortunately, compatible with these aims.

[17] Sakurai, A., and Tamura, S., *Agr. Biol. Chem.*, 1965, **29**, 407; 1966, **30**, 793.

[18] Kato, J., Katsumi, M., Tamura, S., and Sakurai, A., in 'Biochemistry and Physiology of Plant Growth Substances' (Ed. F. Wightman) pp. 347–59 (Ringe Press: Ottawa 1968).

view of our experience with related compounds.[10,19] The isopropyl substituent on the olefinic bond was expected to activate it towards electrophilic attack[20] and to ensure formation of the bicyclo[3,2,1]octanone isomer, by virtue of the intermediacy of the more stable, incipient, tertiary carbenium ion. In choosing a preparation of the logical diazoketone (8) precursor, acid (12), we again sought maximum flexibility and based our approach on the reductive alkylation[21] of *p*-cuminic acid (9). This route is applicable to other aromatic acids and allows the incorporation of a variety of (future) bridgehead substituents.




Scheme 1

The end result of the above considerations was a short and efficient synthesis of ketone (7) (Scheme 1) which serves also as a model for the preparation of similar compounds. Jones oxidation[22] of commercially available cuminic aldehyde provided a more satisfactory and convenient preparation of acid (9) than the reported procedure.[23] The acid was then simply reduced by lithium in liquid ammonia and the presumed di-anionic intermediate methylated *in situ* at $-70°$ [21] to furnish an epimeric mixture of diene acids (10). Conjugation of the double bonds in preparation for further reduction proved unexpectedly troublesome. Methods based on acidic catalysts[24] failed, as did treatment with tris(triphenylphosphine)rhodium chloride.[25]

[19] Beames, D. J., Halleday, J. A., and Mander, L. N., *Aust. J. Chem.*, 1972, **25**, 137.
[20] Malherbe, R., Tam, N. T. T., and Dahn, H., *Helv. Chim. Acta*, 1972, **55**, 245; Erman, W. F., and Stone, L. C., *J. Amer. Chem. Soc.*, 1971, **93**, 2821.
[21] Camps, F., Coll, J., and Pascual, J., *J. Org. Chem.*, 1967, **32**, 2563; Bachi, M. D., Epstein, J. W., Herzberg-Minzly, Y., and Loewenthall, H. J. E., *J. Org. Chem.*, 1969, **34**, 126.
[22] Bowens, A., Halsall, T. G., Jones, E. R. H., and Lemin, A. J., *J. Chem. Soc.*, 1953, 2548.
[23] Cooke, R. G., and Macbeth, A. K., *J. Chem. Soc.*, 1939, 1245.
[24] Laffer, M. H., Ph.D. Thesis, University of Adelaide, 1971, p. 116; Goldberg, M. W., and Scott, W. E., U.S. Pat., 2,894,958, 1959; Powell, J. W., and Whiting, M. C., *Proc. Chem. Soc.*, 1960, 412.
[25] Birch, A. J., and Subba Rao, G. S. R., *Tetrahedron Lett.*, 1968, 3797.

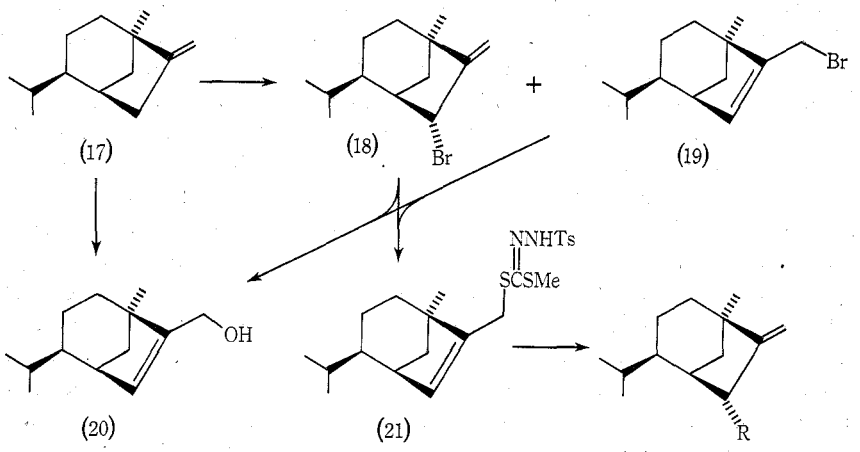
Lithium amide in liquid ammonia[26] or lithium ethylamide in tetrahydrofuran[27] gave some encouragement, but the most satisfactory solution was one based on the action of a strong solution of potassium hydroxide in boiling ethanediol.[28] Reduction of the conjugated diene acid (11)[29] proceeded without incident and the olefinic acid (12) became available in 86% overall yield from cuminic acid.

The conversion of acid (12) via its chloride and diazomethyl derivative (8) into the mixture of olefins (13) and (14) was then achieved smoothly in excellent yield, by procedures previously documented by us.[10] Initially, a 4 : 1 mixture of exocyclic olefin (13) with its $\Delta^3$ endocyclic isomer (14) was obtained, which was slowly equilibrated to one with a 9 : 11 ratio (exocyclic : endocyclic) after 24 h in the reaction mixture. This result suggested concerted proton loss during the cyclization:[30] the isopropyl methine-hydrogen bond may align with the C 3, C 4 $\pi$-bond orbital, whereas the C 5 carbon–hydrogen bonds are restricted to an angle of *c.* 45°. Catalytic hydrogenation of the olefinic mixture then gave ketone (7) in 91% overall yield from diazoketone (8). The stereochemistry of the isopropyl group follows, not only from analogous hydrogenations,[16,31] but also from its identity with the minor product derived by Birch reduction[29] of cyclopropyl ketone (15), which was expected to proceed with stereochemical inversion at the $\beta$-carbon.[32] We had originally hoped to prepare ketone (7) from this latter procedure, since the work of Dauben and coworkers[33] indicated that the C 1–C 2 bond of (15) should cleave; models indicated that better overlap between the breaking bond and the carbonyl $\pi$-system would be maintained during the transition state leading to the bicyclo[3,2,1]octyl isomer. Apparently, in the transition state, the greater stability of the incipient secondary carbanion at C 2 outweighs the energy gain associated with the marginally better overlap of the C 1–C 2 bond, which on fission leads to an incipient tertiary carbanion. The bicyclo[2,2,2]octane derivative [ultimately (16)] thus becomes the major isomer, and the synthesis of ketones with this ring system by this type of approach may, in some circumstances, offer advantages over the established routes based on the Diels–Alder reaction.[34]

We addressed ourselves next to the problem of converting the ketone (7) into the olefinic acid (5) and its isomer (6). Procedures based on the [2,3]-sigmatropic rearrangements of allylic sulphonium ylids, from the laboratories of Baldwin,[35] Lythgoe[36] and Evans[37] appeared to be appropriate, and we initiated a sequence based on the first approach, which is summarized in Scheme 2.

[26] Birch, A. J., Shoukry, E. M. A., and Stanfield, F., *J. Chem. Soc.*, 1961, 5376.
[27] Benkeser, R. A., Burrows, M. L., Hazdra, J. J., and Kaiser, E. M., *J. Org. Chem.*, 1963, **28**, 1094.
[28] Burgstahler, A. W., and Worden, L. R., *J. Amer. Chem. Soc.*, 1964, **86**, 96.
[29] Birch, A. J., and Subba Rao, G. S. R., *Advan. Org. Chem.*, 1972, **8**, 1.
[30] Cf. Corey, E. J., and Sneen, R. A., *J. Amer. Chem. Soc.*, 1956, **78**, 6269.
[31] Berkoff, C. E., and Crombie, L., *J. Chem. Soc.*, 1960, 3734; De Mayo, P., and Williams, R. E., *J. Amer. Chem. Soc.*, 1965, **87**, 3275.
[32] Mander, L. N., Prager, R. H., and Turner, J. V., unpublished data.
[33] Dauben, W. G., and Deviny, E. J., *J. Org. Chem.*, 1966, **31**, 3794; Dauben, W. G., and Wolf, R. E., *J. Org. Chem.*, 1970, **35**, 374, 2361.
[34] Evans, D. A., Scott, W. L., and Truesdale, L. K., *Tetrahedron Lett.*, 1972, 121; Quaseem, M. A., Rogers, N. A., and Othman, A. A., *Tetrahedron*, 1968, **24**, 4535.
[35] Baldwin, J. E., and Walker, J. A., *Chem. Commun.*, 1972, 354.
[36] Hunt, E., and Lythgoe, B., *Chem. Commun.*, 1972, 757.
[37] Andrews, G., and Evans, D. A., *Tetrahedron Lett.*, 1972, 8932.

The carbonyl group of ketone (7), presumably because of its crowded environment, proved to be poorly electrophilic; it was recovered unchanged from treatment by a range of nucleophiles, e.g. methyllithium and methylenetriphenylphosphorane, at ambient temperatures. It appeared that the ketone was forming the enolate anion instead. By working at $-70°$, however, the Wittig reaction[38] afforded olefin (17) in nearly quantitative yield.




(22) R = $CS_2Me$
(23) R = COSMe
(24) R = $CH_2OH$

Scheme 2

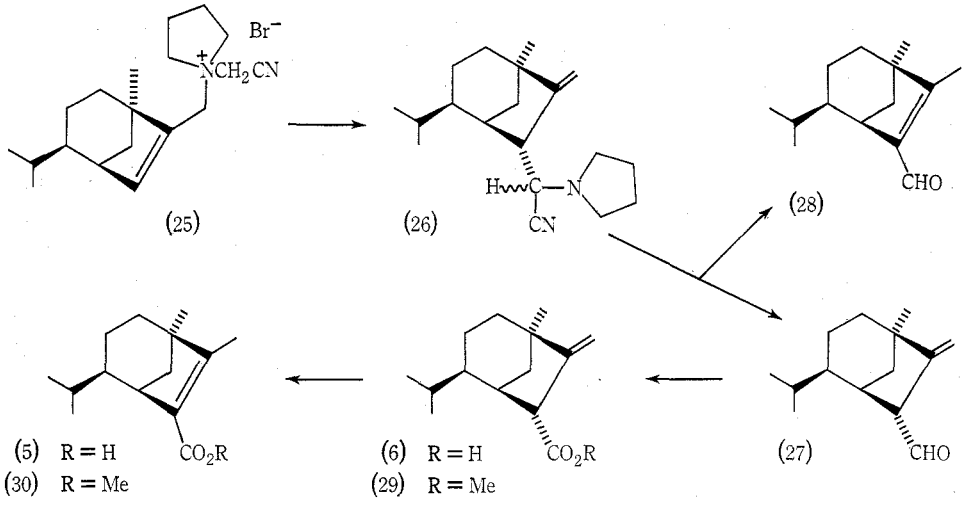
In constrast to similar examples,[39] free-radical bromination of the olefin gave a 3·5 : 1 mixture of allylic bromides (18) and (19) in which the secondary bromide was dominant, due, no doubt, to crowding of the primary terminus of the allylic radical by the angular methyl group. The bromide mixture proved to be too labile for other than spectral characterization, and was converted by basic alumina into mainly the primary allylic alcohol (20) which was also prepared by photo-oxygenation of olefin (17).[40,41] The mixture of bromides was similarly converted into only the carbonohydrazonodithioate (21) by the action of methyl *p*-toluenesulphonyldithiocarbazate[42] and potassium hydroxide. Thermolysis in tetrahydrofuran of the sodium salt, derived (NaH) from (21) according to the directions of Baldwin and Walker,[35] gave a complex mixture of products. By carrying out the reaction in a less polar solvent (cyclohexane), however, the 6-*exo*-dithioester (22) was formed cleanly and in excellent yield. The stereochemical assignment was based on the expectation of rearrangement occurring on the less hindered *exo*-face of the molecule, and was confirmed by the observation that $J_{5,6} < 2$ Hz in the n.m.r. spectrum of the product. Full details of this and other stereochemical determinations by n.m.r. methods are recorded in the Experimental section.

Unexpectedly, all attempts to hydrolyse the dithioester (22) to the corresponding acid (6) by the use of aqueous base,[35] or by methods based on mercuric, cadmium

[38] Maercker, A., *Org. React.*, 1965, **14**, 270.
[39] Briggs, L. H., Cambie, R. C., Rutledge, P. S., and Stanton, D. W., *J. Chem. Soc.*, 1965, 6212.
[40] Bell, R. A., Ireland, R. E., and Mander, L. N., *J. Org. Chem.*, 1966, **31**, 2536.
[41] Gollnick, K., *Advan. Photochem.*, 1968, **6**, 1.
[42] Schöllkopf, U., and Wiskott, E., *Justus Liebigs Ann. Chem.*, 1966, **694**, 44.

and lead salts, were unsuccessful.[43] Eventually, a procedure employing copper(II) chloride and copper(II) oxide[44] gave the thioester (23) as the major component (60% by n.m.r.) of a complex mixture, obtained in 75% yield. Reduction of the mixture by lithium aluminium hydride then gave alcohol (24), but in only 39% overall yield from the bromides.

A preliminary examination of the alternative literature procedures was not encouraging and we therefore sought a novel solution. The [2,3]-sigmatropic rearrangement of allylic ylids was clearly appropriate to the problem in hand, and was just as clearly amenable to extensive variation. We eventually arrived at a proposal based on the rearrangement of an allylic ammonium ylid and the successful execution of the plan, culminating in the formation of aldehyde (27), is outlined in Scheme 3.*




Scheme 3

Thus, a solution of pyrrolidin-1-ylacetonitrile[46] in dimethyl sulphoxide was alkylated by the mixture of allylic bromides (18) and (19), the solution of the resulting salt (25) diluted with tetrahydrofuran, cooled, and treated with potassium t-butoxide. Ylid formation and concomitant rearrangement[47] proceeded smoothly to afford a crystalline diastereomeric (at C 13) mixture of the 6-*exo* pyrrolidinyl nitriles (26). Hydrolysis with 30% aqueous oxalic acid was complete within 15 min at 65° and a 17 : 3 mixture of the $\beta,\gamma$-unsaturated aldehyde (27) with its conjugated isomer (28) was obtained in 90% overall yield from the bromides. A sample of (27) was reduced to the alcohol (24), identical in all respects with the sample prepared previously from dithioester (22).

* The preparation of this and other $\beta,\gamma$-unsaturated aldehydes has been described briefly by us, elsewhere.[45] Further details of the scope and utility of the sequence will be published soon.

[43] Corey, E. J., and Erickson, B. W., *J. Org. Chem.*, 1971, **36**, 3553; Demuynck, C., and Thuillier, A., *Bull. Soc. Chim. Fr.*, 1969, 2434; Mori, K., and Matsui, M., *Agr. Biol. Chem.*, 1970, **34**, 1198.
[44] Mukaiyama, T. T., Narasaka, K., and Sakashita, T., *Bull. Chem. Soc. Jap.*, 1972, **45**, 3724.
[45] Mander, L. N., and Turner, J. V., *J. Org. Chem.*, 1973, **38**, 2915.
[46] Cuinget, E., Debaert, M., and Lespagnol, A., *Bull. Soc. Chim. Fr.*, 1960, 383.
[47] Pine, S. H., *Org. React.*, 1970, **18**, 403.

The acid (6) was simply obtained by Jones oxidation[22] of aldehyde (27) and the $\alpha,\beta$-unsaturated acid (5) by base-catalysed conjugation of the methyl ester (29), derived from acid (6), to ester (30). Basic hydrolysis of this last compound gave a 4 : 1 mixture of the conjugated and non-conjugated acids, (5) and (6), respectively. Presumably, the $\beta,\gamma$-unsaturated ester (29) is produced in low concentration in the basic mixture and undergoes more rapid hydrolysis than its isomer (30).

The modified barley endosperm bioassay[8] was used to measure gibberellin-like activity in all the synthetic compounds. Details of the tests, which are based on the ability of gibberellins to trigger, in embryoless barley endosperm, the production of $\alpha$-amylase,[4] will be published elsewhere.[48] In summary, however, acids (5) and (6) and aldehydes (27) and (28) show activity at the same level as helminthosporic acid (2). Although *c.* $10^3$ times higher concentrations are required to elicit a response comparable with that from gibberellic acid (1), the level of activity still exceeds that of all but the most potent gibberellins.[7] No other compounds, e.g. ketone (7), alcohol (24), and ester (29), gave any indication of activity and the activity of the aldehydes (27) and (28) may well be due to *in situ* oxidation to the acids.

The results may be interpreted in terms of support for Briggs's hypothesis;[11] certainly, the hydroxymethyl group in helminthosporic acid has been demonstrated to be superfluous. The finer details of the tests indicate, however, that the conjugated acid (5) is significantly more active than the isomer (6), which, superficially, appears to be more gibberellin-like.

We propose, therefore, to prepare and test compounds which resemble gibberellic acid more closely, as well as even more simplified analogues of helminthosporic acid. We hope that these efforts will help to delineate the structural essentials from which the characteristic physiological properties of gibberellins arise.

## Experimental

Melting points were determined by means of a Kofler hot-stage apparatus or with a heated Gallenkamp apparatus where sealed tube capillaries have been used. Melting points and boiling points are uncorrected.

Infrared spectra were recorded on either a Unicam SP200 or a Perkin–Elmer 237 spectrophotometer. The $^1$H nuclear magnetic resonance spectra were determined with Varian DA-60IL or T-60 spectrometers operating at 60 MHz, using tetramethylsilane as an internal standard. Data are given in the following order: solvent; chemical shift ($\delta$); multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), d of d (doublet of doublets), m (multiplet), e (envelope), exch. means that the signal disappears on shaking the sample with $D_2O$]; first-order coupling constant ($J$) expressed in Hz ($W_{h/2}$ means peak width at half-height); relative intensity as number of protons (H); assignment. Ultraviolet spectra were determined with a Unicam SP 800 spectrophotometer. Mass spectra were measured with an Hitachi Perkin–Elmer RMU-7D spectrometer. The data are recorded in the following order: operating voltage; *m/e* value; assignment with metastable peak (where observed); relative intensity to base peak (100).

Gas chromatographic analyses (g.l.c.) were performed on Perkin–Elmer 880 and 881 instruments, with nitrogen as carrier gas. The columns, constructed of stainless steel, were: (1) NPGS: Silicone GE XE-60 (NPX), 1 : 1, 3%, 3 m by 1·6 mm, flow rate 30 cm$^3$/min; (2) FFAP, 3–4%, 6 m by 1·6 mm, 25 cm$^3$/min (unless stated otherwise); (3) Apiezon M 5%, 3 m by 1·6 mm, 30 cm$^3$/min; (4) SE30 Silicone Golay, 46 m by 0·25 mm, 2 cm$^3$/min. It has been assumed that compounds with similar structures evoke the same response from the recorder. The relative areas of peaks have been determined by triangulation. Data are recorded in the order: column; temperature; retention time (min/s); relative percentage of product in crude reaction mixture (where relevant). The conversion

[48] Coombe, B. G., Mander, L. N., Paleg, L. G., and Turner, J. V., unpublished data.

of carboxylic acids with ethereal diazomethane to methyl esters for g.l.c. analysis has been assumed to be quantitative.

Chromatographic adsorbents used were Spence grade H alumina, Sorbsil silica gel, and Florisil. Analytical and preparative thin-layer chromatography (t.l.c.) was effected with layers containing equal mixtures of Merck Kieselgel G and HF254.

Tetrahydrofuran, diethyl ether (ether), dimethoxyethane were dried by distillation from lithium aluminium hydride. Dimethyl formamide, dimethyl sulphoxide, and hexamethylphosphoriotriamide were distilled under reduced pressure from calcium hydride. Nitromethane was distilled from $P_2O_5$ and stored over 4 Å molecular sieves. X4 refers to light petroleum, b.p. 45–60°.

All organic solvent extracts were dried over anhydrous sodium sulphate unless specified otherwise.

Distilled ethereal diazomethane was prepared from *N*-nitroso-*N*-methylurea or from *p*-tolylsulphonylmethylnitrosoamide ('Diazald') by normal procedures.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

*Cuminic Acid* (*9*)

A solution of cuminic aldehyde (71 g, 0·5 mol) in acetone (200 ml) was treated dropwise with Jones reagent (over 4 h) at such a rate as to maintain the temperature of the reaction mixture at 30°. When t.l.c. indicated the absence of starting material, sufficient isopropyl alcohol was added to turn the solution green, then enough water was added to generate a heavy green precipitate. The organic layer was decanted and extracted with methylene chloride (3 × 250 ml). The pooled extract was washed with sodium carbonate (20%, 3 × 200 ml), then the combined aqueous material cooled to 0° and cautiously acidified (conc. HCl). The precipitate was collected (78 g, 99%) and recrystallized from X4 to yield (63 g, 80%) pure cuminic acid (9); m.p. 117–118° (lit.[23] 117–118°); g.l.c. FFAP (methyl ester) (175°) 06/21.

cis- *and* trans-*1,4-Dihydro-4-isopropyl-1-methylbenzoic Acid* (*10*)

Dry ammonia (500 ml) was distilled onto cuminic acid (9) (24 g, 147 mmol) suspended in dry ether (168 ml) at −40° under nitrogen. The resulting solution was stirred, and pieces (*c.* 100 mg) of lithium (3·15 g, 450 mg-atom) added over 20 min until the solution remained blue for 25 min. The solution was cooled to −70° and dry methyl iodide (208·5 g, 91·8 ml, 1·47 mol), previously cooled to −50°, added dropwise initially, until the blue faded (this avoids a violent reaction with an induction period of *c.* 3 min), then, with care, rapidly. After 15 min the colourless solution was treated cautiously with solid ammonium chloride (42 g) and the solvent allowed to evaporate overnight to leave a pale solid. This was dissolved in water (300 ml) and successively extracted with methylene chloride (2 × 150 ml), acidified to pH 3 (conc. HCl), and extracted with more methylene chloride (6 × 150 ml). The total final extract was washed with water (2 × 150 ml), dried, and evaporated to a pale viscous liquid (24·07 g, 92%), which had two major components (g.l.c., methyl esters) and was characterized spectrally. $\nu_{max}$ (film) 3300–2650 (broad, OH), 3020 (=CH), 1700 (C=O), 1640 (C=C), 1295, 1260, 1115, 940 (broad), 840, 760 and 720 $cm^{-1}$ (=CH); n.m.r. ($CDCl_3$) $\delta$ 0·9 (broad d, *J* 7 Hz, 6H, isopropyl $CH_3$), 1·3 (s, 3H, $\mathbf{H}_3CCCO_2H$), 1·9 (m, 1H, isopropyl CH), 2·6 (e, 1H, =CHCH), 5·8 (broad d of d as t, *J* 10 Hz, 4H, HC=HC), 12·0 (broad s, 1H, $CO_2H$). The methyl esters showed: $\nu_{max}$ (film) 3020 (=CH), 1730 (C=O), 1635 (C=C), 1395 and 1375 (isopropyl), 1245 and 1120 (C–O), 840, 795, 720 $cm^{-1}$ (=CH); mass spectrum (70 eV) *m/e* 194 ($M^+$, $C_{12}H_{18}O_2$ requires $M^+$ 194) (3), 135 ($M^+ - CO_2CH_3$) (27), 93 (100), 91 (50); g.l.c. FFAP (methyl ester) (120°) 09/30 (45·5%) and 11/42 (51·5%).

*1,2-Dihydro-4-isopropyl-1-methylbenzoic Acid* (*11*)

Potassium hydroxide (240 g, 4·2 mol) was added, with stirring, to ethylene glycol (1·5 l.), followed by the 2,5-diene acid (10) (24 g, 134 mmol). The resulting solution was heated under reflux for 20 h in an atmosphere of nitrogen, cooled, and poured slowly onto water (1·5 l.). The solution was cooled to 0°, acidified to pH 3 (conc. HCl), then extracted with methylene chloride (6 × 300 ml). The pooled extract was washed with water (2 × 300 ml), dried, and evaporated under vacuum to leave a pale mobile *oil* (24 g, quantitative). A sample was distilled before analysis: b.p. 88° (block), 0·1 mm (Found: C, 73·6; H, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). $\nu_{max}$ (film) 3300–2650 (broad, OH), 1700 (C=O), 1650sh and 1600w (C=C), 1420, 1395 and 1375 (isopropyl $CH_3$), 1300 (OH),

1135 (C–O), 950 (broad), 800 and 765 $cm^{-1}$ (=CH); n.m.r. ($CDCl_3$) $\delta$ 1·1 (d, $J$ 7 Hz, 6H, isopropyl $CH_3$), 1·3 (s, 3H, $CH_3$), 2·0–3·0 (m, 3H, $H_2CHC{=}C$ and isopropyl CH), 5·4 (e, 1H, $H_2CHC{=}C$), 5·9 (broad d of d as t, $J$ 9 Hz, 2H, HC=CH), 12·1 (broad s, 1H, $CO_2H$); g.l.c. FFAP (methyl ester) (120°) 09/34 (92·5%), (115°) 11/18.

*1,2,3,6-Tetrahydro-4-isopropyl-1-methylbenzoic Acid (12)*

Onto the 3,5-diene acid (11) (24 g, 133 mmol), dissolved in dry ether (165 ml) and t-butyl alcohol (40 g, 51·5 ml, 540 mmol), was distilled ammonia (500 ml) under nitrogen. Pieces (*c.* 100 mg) of lithium (2·87 g, 410 mg-atom) were added over *c.* 20 min and the blue colour allowed to persist for 15 min. Ethanol (50 ml) was added and the colourless solution allowed to evaporate overnight. The residue was dissolved in water (200 ml), cooled to 0°, acidified (conc. HCl) to pH 3, and finally extracted with more methylene chloride (3 × 200 ml). The total latter extract was washed with water (2 × 150 ml), dried and concentrated to a pale mobile oil (23 g, 95%). This crystallized from methanol : water (2 : 1) at −50° as colourless *plates* (14·5 g, 60%, m.p. 44–46°). The analytical sample, obtained after a further recrystallization from the same solvent pair, had m.p. 44–46° (Found: C, 72·1; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%). $\nu_{max}$ (Nujol) 3200–2650 (OH), 1700 (C=O), 1240, 1130 (C–O), 950 (broad) 820 $cm^{-1}$ (=CH); n.m.r. ($CDCl_3$) $\delta$ 1·0 (d, $J$ 7 Hz, 6H, isopropyl $CH_3$), 1·2 (s, 3H, $CH_3$), 1·4–2·8 (broad m, 7H), 5·4 (e, 1H, C=CH), 12·0 (e, 1H, exch., $CO_2H$); g.l.c. FFAP (methyl ester) (115°) 10/15 (87%).

*Diazomethyl 4-Isopropyl-1-methylcyclohex-3-en-1-yl Ketone (8)*

The acid (12) (10 g, 55 mmol) was dissolved in dry benzene (250 ml) containing pyridine (5·04 g, 65 mmol), and added over 30 min to a stirred solution of oxalyl chloride (46·5 ml, 69 g, 550 mmol) and benzene (65 ml) under nitrogen. The reaction mixture was stirred for a further 45 min (evolution of $CO_2$ and CO had ceased); the filtered (Celite) solution was then evaporated under reduced pressure and a slow stream of nitrogen. The residue was dissolved in dry benzene (50 ml) and the solvent removed as before. The latter step was repeated twice to furnish the acid chloride as a pale oil (11 g, quantitative) which was used directly: $\nu_{max}$ (film) 1785 (C=O), 1670w (C=C), 1395 and 1375 (isopropyl), 925, 900, 820, 770 $cm^{-1}$.

The crude acid chloride (11 g, 55 mmol), dissolved in dry ether (75 ml), was dropped over 30 min onto a stirred, ice-cold solution of diazomethane (*c.* 310 mmol from 108 g Diazald) in dry ether (700 ml). The reaction mixture was allowed to warm to room temperature during 18 h, then heated to 40° to remove the excess of diazomethane. Concentration of the solution under reduced pressure revealed a pale yellow *oil* (11·2 g, 99%) which was used without purification. A small sample was distilled before analysis: b.p. 56° (block), 0·005 mm (Found: C, 69·9; H, 8·9; N, 13·8. $C_{12}H_{18}N_2O$ requires C, 69·9; H, 8·8; N, 13·6%). $\nu_{max}$ (film) 3100 ($HCN_2$), 2140 and 1635 ($COCHN_2$), 1360 (broad), 1160, 1050, 820 $cm^{-1}$ (C=CH); crude material showed also 1740–1730vw $cm^{-1}$ ($COCH_2Cl$); n.m.r. ($CDCl_3$) $\delta$ 1·0 (d, $J$ 7 Hz, 6H, isopropyl $CH_3$), 1·2 (s, 3H, $CH_3$), 1·6–2·8 (m, 7H), 5·4 (e, 1H, C=CH), 5·5 (s, 1H, $COCHN_2$).

*Olefinic Ketones (13) and (14)*

A stirred solution of diazoketone (8) (10 g, 49·6 mmol) in dry nitromethane (200 ml) was cooled to between −10° and 0° and treated dropwise with $BF_3$ etherate (2 g, 14 mmol). After 10 min, sodium carbonate (sat., 2 ml) was added, and after a further 10 min the solution was poured onto brine (sat., 200 ml) and diluted with methylene chloride (200 ml). The lower layer was washed with brine (200 ml), water (200 ml), dried and concentrated under vacuum to a pale oil. The remaining traces of nitromethane were removed as an azeotropic mixture, first with ethanol, and then benzene. The olefinic ketones (13) and (14) were obtained as a pale, mobile oil (8·6 g, quantitative); $\nu_{max}$ (film) 3050 (=CH), 1738 (C=O), 1645 (C=C), 1410, 1380, 1055, 825, 795 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 1·0 (1 major s in m, 4·2H, $CH_3CR^1R^2R^3$, (14) and (13); isopropyl $CH_3$, (14)), 1·7 (broad 2s, 4·8H, $(CH_3)_2C{=}C$), 2·1 (m, 2H, $H_2CCO$), 3·4 [e, 0·8H, $W_{h/2}$ 16 Hz reduced to $W_{h/2}$ 10 Hz on double irradiation at 2·1; HCC=C, (13)], 5·1 [e, 0·12OH, HC=C, (14)]; g.l.c. FFAP (140°) 08/03 [20%, (14)], 10/43 [80%, (13)]; mass spectrum (70 eV) *m/e* 178 ($M^+$, $C_{12}H_{18}O$ requires $M^+$ 178) (47), 93 (100), 91 (34).

*Equilibration Study of Olefinic Ketones (13) and (14)*

Boron trifluoride etherate (26·5 mg, 0·188 mmol) was added to a solution of diazoketone (8) (120 mg, 0·593 mmol) in dry nitromethane (1·2 ml) at 18°. Aliquots (100 μl each) were removed at the time indicated, and immediately quenched by addition to separate tubes, containing a mixture of sodium carbonate (sat., 84·5 mg) and ether (37·5 mg). The ethereal layer of each sample was analysed by g.l.c. (FFAP, 140°), standard injections (0·4 μl) being used. The absolute concentration of the isomers combined was virtually constant (>98%); their relative proportions are tabulated:

| Removal time | 1 min | 20 min | 1 h | 2 h | 3 h | 9 h | 24 h | 48 h |
|---|---|---|---|---|---|---|---|---|
| 08/03 (percentage of (14)) | 20 | 22 | 25 | 27 | 31 | 37·5 | 45 | 45 |
| 10/43 (percentage of (13)) | 80 | 78 | 75 | 73 | 69 | 62·5 | 55 | 55 |

The combined products after 3 h reaction were isolated in the normal manner and showed: n.m.r. ($CDCl_3$) $\delta$ 1·0 [4s, 5H, isopropyl $CH_3$, (14), and $CH_3CO$ (13) and (14)], 1·7 [broad 2s, 4H, $(CH_3)_2C=$ (13)], 5·1 [e, 0·33H, HC=C, (14)], ratio (13) : (14) = 2·1.

(±)-*12,13,14-Trinorhelminthosporan-7-one* (*7*)

The mixture of olefinic ketones (13) and (14) (8·6 g, 48 mmol) was dissolved in methanol (150 ml) and shaken with palladium-on-carbon (5%, 860 mg), under hydrogen (4 atm) at room temperature, until the reaction was complete (g.l.c. analysis, *c.* 12 h). The filtered (Celite) solution was concentrated under reduced pressure to an oil which was chromatographed on a column of Sorbsil (250 g) in X4. Elution with benzene : ether (5 : 1) gave the *ketone* (7) as a colourless oil (8·6 g, 99%). A small sample was distilled before analysis: b.p. 60° (block), 0·01 mm (Found: C, 80·1; H, 11·0. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). $\nu_{max}$ (film) 1738 (C=O), 1415, 1395 and 1375 (isopropyl $CH_3$), 1145, 1055, 880, 850, 790 $cm^{-1}$ (weak bands); n.m.r. ($CDCl_3$) $\delta$ 0·9–1·0 (m, isopropyl $CH_3$), 1·0 (broad s, $CH_3CR^1R^2R^3$) (9H under 0·9–1·0), 2·0 (m, 2H, $H_2CC$)). Mass spectrum (70 eV) *m/e* 180 ($M^+$, $C_{12}H_{20}O$ requires $M^+$ 180) (25), 93 (99), 81 (100); g.l.c. FFAP (140°) 09/09 (91%).

*1-Isopropyl-4-methyltricyclo[2,2,2,0$^{2,6}$]octan-3-one* (*15*)

The diazoketone (8) (1·5 g, 7·3 mmol) in cyclohexane (50 ml, spectroscopic grade) was added over 1·5 h to a suspension of copper powder (Merck, 4 g, previously dried at 80° for 15 min) in boiling cyclohexane (150 ml) under nitrogen. After a further 2 h, the cooled mixture was filtered (Celite) and concentrated under reduced pressure to afford a pale oil which crystallized on standing at 0° (1·3 g, quantitative); a sample (1·03 g) was chromatographed on Sorbsil (30 g in X4). Elution with X4 : ether (17 : 3, then 4 : 1) gave crystals of the *cyclopropyl ketone* (1 g, 97%). The remainder (270 mg) was distilled before analysis and formed prisms on cooling; m.p. 40–42°, b.p. 74° (block)/0·005 mm (Found: C, 80·5; H, 10·1. $C_{12}H_{18}O$ requires C, 80·8; H, 10·2%). $\nu_{max}$ (Nujol) 3010 (cyclopropyl H), 1720 (C=O), 1275, 1205, 1165, 1130, 1100, 915 and 880 $cm^{-1}$ (cyclopropyl H); n.m.r. ($CDCl_3$) $\delta$ 0·9–1·0 (m, 9H, $CH_3$ and isopropyl $CH_3$), 1·7–2·3 (m, 9H, remainder); g.l.c. FFAP (145°) 10/57 (98%), (130°) 11/50.

(±)-*12,13,14-Trinorhelminthosporan-7-one* (*7*) *and the 4-Isopropyl-1-methylbicyclo[2,2,2]octan-2-one* (*16*)

The cyclopropyl ketone (15) (700 mg, 3·9 mmol), dissolved in dry tetrahydrofuran (5 ml) containing t-butyl alcohol (1·98 g, 2·52 ml, 26·8 mmol), was added to dry ammonia (100 ml). The solution was cooled to −70° and pieces of lithium added (109 mg, 15·6 mg-atom) under a stream of nitrogen, until the blue colour had persisted for 25 min. Ethanol (5 ml) was added cautiously and the ammonia allowed to evaporate. The residue was treated with water (20 ml), the pH adjusted to *c.* 6 (conc. HCl), then the solution extracted with methylene chloride (3 × 20 ml). The pooled extract was washed with water (2 × 100 ml), dried, and reduced under vacuum to afford a mixture of bicyclic alcohols as a pale viscous oil (700 mg, 98%); i.r. (film) 3450 (OH), 1395 and 1375 (isopropyl), 1050 (C–O), 955, 920, 865, 820 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 9H, $CH_3$ and isopropyl $CH_3$), 3·6 (e, 1H, HCOH); g.l.c. FFAP (145°) 11/20 (12%), 11/44 (86%)—partial resolution.

The mixture of alcohols (670 mg, 3·68 mmol) was dissolved in acetone (60 ml) and treated with Jones reagent in excess. After 5 min, the red solution was turned to green by the addition of isopropyl

alcohol. Water was added and a mixture of ketones (7) and (16) (665 mg, quantitative) isolated from a methylene chloride extract in the normal manner: $\nu_{max}$ (film) 1738s and 1718s $cm^{-1}$ (C=O); g.l.c. FFAP (145°) 08/07 [12%, spiked with authentic bicyclo[3,2,1] ketone (7)], 09/47 (86%).

Chromatography on Sorbsil (30 g in X4) gave, on elution with X4 : ether (100 : 3 then 20 : 1) sequentially: a mixture of ketones (7) and (16) (40 mg); mainly [2,2,2] ketone (16) (400 mg, 60%); [2,2,2] ketone (16) (80 mg, 12%). Rechromatographing the major fraction, as above, afforded a mixture of ketones (50 mg), then *[2,2,2] ketone* (16) (350 mg, 53%) as a colourless oil. A sample was distilled before analysis, b.p. 45° (block), 0·005 mm (Found: C, 79·6; H, 11·1. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). *Semicarbazone* (aq. ethanol), m.p. 192–194° (Found: C, 66·0; H, 9·9; N, 18·0. $C_{13}H_{23}N_3O$ requires C, 65·8; H, 9·8; N, 17·7%). $\nu_{max}$ (film) 1718 (six-membered ring C=O), 1410 ($CH_3CR^1R^2R^3$), 1395 and 1375 (isopropyl), 1210, 1100 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·9–1·0 (3s, 9H, $CH_3$ and isopropyl $CH_3$), 1·6 (e, 9H, $CH_2CH_2$ and isopropyl CH), 2·1 (s, 2H, $H_2CC{=}O$); g.l.c. FFAP (145°) 09/47.

### (±)-*13,14-Dinorhelminthospor-7(12)-ene* (*17*)

A mixture of methyltriphenylphosphonium iodide (34·4 g, 85 mmol) and potassium t-butoxide (10·1 g, 84 mmol) in dry ether (200 ml) was stirred under reflux for 1·5 h, then cooled to −70°. The ketone (7) (5 g, 27·8 mmol), in ether (20 ml), was added over 0·25 h to the stirred yellow mixture, which was allowed to warm to room temperature during 6 h, then stirred for a further 12 h. The mixture was heated under reflux for 0·5 h, cooled to 0°, and treated cautiously with methanol (80%, 40 ml). Ether was removed by distillation under reduced pressure, more methanol added (80%, 10 ml), and the mixture extracted with X4 (3 × 120 ml). The combined extract was washed with aqueous methanol (80%, 200 ml), water (200 ml), dried and evaporated to a pale oil (5·5 g). Distillation under reduced pressure furnished the *olefin* (17) as a colourless liquid (4·8 g, 97%): b.p. 100° (block), 13 mm; 112–115°, 23 mm (Found: C, 87·9; H, 12·5. $C_{13}H_{22}$ requires C, 87·6; H, 12·4%). $\nu_{max}$ (film) 3050 (=$CH_2$), 1655 (C=C), 1395 and 1380 (isopropyl), 890 and 880 $cm^{-1}$ (=$CH_2$); n.m.r. ($CCl_4$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (s, 3H, $CH_3$), 2·2 (broad s, 2H, $H_2CC{=}CH_2$), 4·7 (m, 2H, $C{=}CH_2$); g.l.c. FFAP (130°) 4/45; (100°) 6/57.

### *The Bicyclic Allylic Bromides* (*18*) *and* (*19*)

To the olefin (17) (1 g, 5·6 mmol) dissolved in carbon tetrachloride (60 ml) was added pure *N*-bromosuccinimide (1·04 g, 5·84 mmol) and five 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 (Celite) and evaporated under reduced pressure. The residue was chromatographed on a short column of Sorbsil (10 g) in X4. Elution with X4 gave a mixture of the bromides (18) and (19), a colourless oil (1·29 g, 89%), which was analysed spectrally. The bromides afforded a single *S*-methyl-*p*-tosyldithiocarbazone derivative (21) (see below): $\nu_{max}$ (film) 1650 and 1630 (C=C), 1395 and 1375 (isopropyl), 905 (=$CH_2$), 770 $cm^{-1}$ (C–Br); n.m.r. ($CCl_4$) $\delta$ 0·9 (t, *J* 6 Hz, 6H, isopropyl $CH_3$), 1·1 (broad 2s, 3H, $CH_3$), 4·0 [s, 0·44H, $CH_2Br$, (19)], 5·9 [m, 0·22H, C=CH, (19)], 4·7 [m, 0·77H, CHBr, (18)], 5·0 (d, *J* 1·8 Hz) and 5·3 [d, *J* 1·6 Hz, 1·55H, $C{=}CH_2$, (18)], i.e. ratio (18) : (19) = 3·5 : 1. Mass spectrum (70 eV) *m/e* 256, ($M^+$, $C_{13}H_{21}Br$ requires $M^+$ 256, 258) (14), 255, 257 ($M^+ - H$) (46); 177 ($M^+ - Br$) (100).

### (±)-*13,14-Dinorhelminthospor-6-en-12-ol* (*20*)

(i) *By photo-oxygenation of the olefin* (*17*).—To the olefin (17) (1·0 g, 5·6 mmol) in methanol (130 ml), containing t-butyl alcohol (10 ml) as a co-solvent, and pyridine (1 ml), was added haematoporphyrin (15 mg). A stream of oxygen (51 $cm^3$/min) was passed through the water-cooled solution, which was irradiated for 6 days with a Philips 'Argaphoto' lamp (250 V, 500 W) placed 60 cm from the apparatus. The volume was reduced to 10 ml under reduced pressure, then the solution treated with methanol (10% aqueous, 10 ml) containing $NaBH_4$ (2 g, 52·5 mmol); after 15 min, water (3 ml) was added. When no more hydrogen was evolved, the solution was filtered (Celite), diluted with water (17 ml), and extracted with methylene chloride (3 × 40 ml). The total extract was washed with water (60 ml), dried and evaporated to a pale oil. Chromatography on neutral alumina (8 g, in X4) gave on elution with X4, olefin (17) (500 mg, 50%) then, with X4 : ether (4 : 1), allylic alcohol

(20) (400 mg, 37%) as a colourless viscous oil. The 3,5-dinitrobenzoate derivative crystallized as faint yellow prisms from X4 and ether, m.p. 74–76° (Found: C, 61·8; H, 6·3; N, 7·4. $C_{20}H_{24}N_2O_6$ requires C, 61·8; H, 6·2; N, 7·2%). $\nu_{max}$ (film) 3350 (OH), 1635 (C=C), 1395 and 1375 (isopropyl), 1080, 1025, 995, 830 $cm^{-1}$ (HC=); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·0 (s, 3H, $CH_3$), 1·6 (e, partly exchangeable with $D_2O$, OH amongst other resonances), 2·6 (e, 1H, HCCH=C), 4·1 (broad s, 2H, $H_2COH$), 5·6 (e, 1H, HC=C); g.l.c. FFAP (170°) 09/19. The 3,5-dinitrobenzoate showed $\nu_{max}$ (Nujol) 3100 (H–Ar), 1730 (C=O), 1650 ($NO_2$), 1360 (C–$NO_2$) 1280, 1170, 1080, 860 and 840 (Ar), 780 $cm^{-1}$ (C=CH); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·2 (s, 3H, $CH_3$), 2·7 (e, 1H, C5–H), 5·0 (broad s, 2H, $H_2COCOAr$), 6·0 (e, 1H, HC=C), 9·2 (m, 3H, Ar).

(ii) *From allylic bromides (18) and (19).*—The mixture of the bromides (18) and (19) (70 mg, 0·27 mmol) was left on a column of alumina (Spence, 14 g, in X4) for 18 h; elution with X4 gave bromides (14 mg, 20%), then with ether, the primary allylic alcohol (20) (42 mg, 80%) contaminated (*c.* 14%, g.l.c., n.m.r.) by, presumably, the less polar, secondary allylic alcohol. T.l.c. showed low $R_F$ major, high $R_F$ minor spots (benzene : ether 20 : 1); g.l.c. FFAP (170°) 07/100 (14%), 09/16 (86%, spiked with authentic primary allylic alcohol); $\nu_{max}$ (film) indistinguishable from the authentic primary alcohol (20) above; n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·0 (s, 3H, $CH_3$), 2·6 (e, 1H, C5–H), 4·1 (broad s, 1·72H, C=C$CH_2$OH), 4·75, 4·9, 5·1 (3m, 0·42H, HOCHC=$CH_2$), 5·6 (e, 0·8H, HC=C).

*13,14-Dinorhelminthospor-6-en-12-yl Methyl* N′-p-*Toluenesulphonylcarbonohydrazonodithioate (21)*

To methyl *p*-tosyldithiocarbazate[42] (1·37 g, 4·96 mmol), suspended in absolute ethanol (36 ml) at ambient temperature under nitrogen, was added a solution of KOH (328 mg, purity 86%, 4·96 mmol) in ethanol (12 ml) over 3 min; during the addition, the solid dissolved. The bromides (18) and (19) (1·21 g, 4·7 mmol) in ethanol (12 ml) were added over 3 min, and the stirred solution kept at 40° for 20 h. Water (60 ml) was added, followed by two drops of 5N HCl, and the solution extracted with methylene chloride (3 × 60 ml). The total extract was washed with water (60 ml), dried, and evaporated to a pale oil (2·07 g), which crystallized on standing. Chromatography on Sorbsil (30 g) in X4 gave, on elution with X4, unchanged bromides (150 mg, 12%); on elution with benzene : X4 : ether (25 : 24 : 1), the *dithioate* (21) (1·73 g, 81%, 92% based on consumed bromides) as a colourless solid. A small amount was recrystallized from X4–ether before analysis: m.p. 93–95° (Found: C, 58·3; H, 7·2; N, 6·3; S, 20·9. $C_{22}H_{32}N_2O_2S_3$ requires C, 58·4; H, 7·1; N, 6·2; S, 21·2%). $\nu_{max}$ (Nujol) 3150 (NH), 1625 (C=C), 1600 (Ar), 1390 and 1350 and 1170 ($SO_2$), 865, 820, 705 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (s, 3H, C1–$CH_3$), 2·3 (s, 3H, $CH_3$Ar), 2·4 (s, 3H, $CH_2S$), 2·5 (m, 1H, C5–H), 3·6 (s, 2H, $SCH_2C$=), 5·7 (m, 1H, C=CH), 7·3 (broad d, *J* 8 Hz, each peak m, 2H, *o*-Ar), 7·8 (broad d, *J* 8 Hz, each band m, 2H, *m*-Ar), 7·9 (s, superimposed on low field band of d, 7·8; 1H, NH).

(±)-*Methyl 14-Norhelminthospor-7(12)-ene-13-dithioate (22)*

The carbonodithioate (21) (250 mg, 0·59 ml) in cyclohexane (20 ml, spectroscopic grade) was added under nitrogen to a stirred suspension of NaH (56·6 mg, 2·36 mmol) in cyclohexane (4 ml) at 7°. After 4 h the supernatant was removed with a syringe and transferred to a flask containing nitrogen, then heated under reflux for 2 h. The yellow mixture was cooled, filtered (Celite), and concentrated under reduced pressure and a stream of nitrogen, to reveal the dithioester (22) as an orange oil (136 mg, 92%), which showed n.m.r. (film) $\delta$ 0·9 (2d, *J* 3·5 Hz, 6H, isopropyl $CH_3$), 1·1 (s, 3H, 1-$CH_3$), 2·6 (s, 3H, $CH_3S$), 4·1 (m, $W_{h/2}$ 6 Hz, collapses to broad s, $W_{h/2}$ 4 Hz on double irradiation of 2d, 5·0; 1H, C6–H), 5·0 (2d, both *J* 2 Hz, collapses to 2s, 3 Hz apart on double irradiation of m, 4·1; 2H, =$CH_2$), thus $J_{5,6} \leqslant 2$ Hz. Calc. for epimer: d, $J_{5,6}$ 6–7 Hz, cf. data for ester (28). G.l.c. FFAP (160°, prog. to 200° 14/00) 25/00.

(±)-*Methyl 14-Norhelminthospor-7(12)-ene-13-thioate (23)*

To the dithioester (22) (48 mg, 0·179 mmol) under nitrogen was added $CuCl_2,2H_2O$ (122 mg, 0·174 mmol) and CuO (128 mg, 1·431 mmol) in acetone (8 ml, 3% water). The solution was heated under reflux for 10 h, then cooled, diluted with water (10 ml), dried and concentrated to a yellow oil (34 mg, 75%), which contained *c.* 60% thioester (23) (n.m.r. analysis): $\nu_{max}$ (film) 3050 (=$CH_2$), 1695 (broad, C=O), 1395 and 1375 (isopropyl), 1035 (broad), 900 (=$CH_2$), 835 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (broad s, 3H, 1-$CH_3$), 2·3 (s, 1·8H, $CH_3S$), 5·1 (m, 1·2H, C=$CH_2$).

(±)-*14-Norhelminthospor-7(12)-en-13-ol* (*24*)

The crude thioester (23) (34 mg, 0·135 mmol) was dissolved in dry ether (2 ml) and added to $LiAlH_4$ (38 mg, 1 mmol) in ether (4 ml). The mixture was stirred under reflux overnight in an atmosphere of nitrogen, then cooled to −10° and, in the hood (stench), treated cautiously with water until the grey precipitate became white. Ether was decanted and the precipitate washed with benzene (6 ml). The pooled ether and benzene solutions were washed to neutrality with water, dried and evaporated to a colourless oil (17 mg, 61%). This had spectral and g.l.c. characteristic sindistinguishable from the alcohol (24) derived through the pyrrolidinium ylid sequence.

(±)-N-*Cyanomethyl*-N-(*13,14-dinorhelminthospor-6-en-12-yl*)*pyrrolidinium Bromide* (*25*)

The allylic bromides (18) and (19) (1·29 g, 5 mmol) were added dropwise to a stirred solution of pyrrolidin-1-ylacetonitrile (0·59 g, 5·3 mmol) in dry $Me_2SO$ (5 ml) under nitrogen, and the reaction mixture was stirred at 45° for 18 h. The progress of salt formation, in a parallel experiment (0·1× scale) using $Me_2SO$-$d_6$, was monitored by n.m.r. spectroscopy: $\delta$ 0·9 (t, $J$ 5 Hz, isopropyl $CH_3$, amongst other resonances), 1·1 (s, $CH_3$, amongst other resonances), 2·2 (m, 4H, $^+N(CH_2CH_2)_2$), 3·8 (m, 4H, $^+N(CH_2CH_2)_2$), 4·3 (s, 2H, $^+NCH_2CN$), 5·1 (s, 2H, $^+NCH_2C{=}CH$), 6·3 (m, 1H, $^+NCH_2C{=}CH$).

(±)-N-(*13-Cyano-14-norhelminthospor-7(12)-en-13-yl*)*pyrrolidines* (*C 13 Epimers*) (*26*)

The solution of the salt (25) (5 mmol) in $Me_2SO$ (5 ml) was diluted with dry tetrahydrofuran (25 ml), cooled to −10°, and treated with solid potassium t-butoxide (0·74, 6·6 mmol). The reaction mixture was stirred for 3 h, diluted with benzene : ether (9 : 1, 50 ml), washed with brine (3 × 20 ml), dried and finally concentrated to a pale oil (1·44 g, quantitative) which crystallized on standing. A small sample was chromatographed on a short column of neutral alumina (in X4, eluting with X4 : benzene, 4 : 1), and recrystallized from X4 at −70° before elementary analysis: m.p. (epimeric mixture) 55–86° (Found: C, 79·9; H, 10·6. $C_{19}H_{30}N_2$ requires C, 79·7; H, 10·6%). $\nu_{max}$ (Nujol) 2250 (wk, C≡N), 1645 (C=C), 1140, 1120, 1100, 925 and 900 $cm^{-1}$ (=$CH_2$); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (s, 3H, $CH_3$), 1·8 (m, 4H, $CH_2CH_2)_2$), 2·7 (m, 4H, N $(CH_2CH_2)_2$), 3·5 (m, 1H, epimeric $CHCNN(CH_2CH_2)_2$), 5·2 (m, 2H, $C{=}CH_2$).

(±)-*14-Norhelminthospor-7(12)-en-13-al* (*27*) *and* (±)-*14-Norhelminthospor-6-en-13-al* (*28*)

The pyrrolidinyl nitriles (26) (1·32 g, 4·62 mmol) were dissolved in tetrahydrofuran (36 ml) and treated with a warm solution of oxalic acid (36 ml, 30% w/v). The two-phase mixture was heated under reflux for 15 min, cooled, then extracted with X4 (2 × 50 ml). The combined fractions were washed with brine (2 × 30 ml), then water to neutrality, dried and evaporated to a pale oil (1·05 g, quantitative), $\nu_{max}$ (film) 1720s (unconj. HC=O), 1660w $cm^{-1}$ (conj. HC=O); n.m.r. ($CDCl_3$) $\delta$ 9·6 (d, $J$ 2 Hz, coupled with C 6–H, 0·85H, HCCHO), 10·1 (s, 0·15H, C=CCHO). Chromatography on Sorbsil (75 g in X4) gave sequentially, on elution with X4: unchanged secondary allylic bromide (18) (55 mg, 5%); the oily unconjugated aldehyde (27) (705 mg, 67%); an oily mixture of aldehydes (27) and (28) (240 mg, 23%) which was treated with base (see below). The unconjugated aldehyde (27) afforded a *semicarbazone* as colourless small needles from aq. ethanol, m.p. 177–179° (Found: C, 68·7; H, 9·7; N, 16·3. $C_{15}H_{25}N_3O$ requires C, 68·4; H, 9·6; N, 16·0%). The aldehyde had $\nu_{max}$ (film) 3050 (=$CH_2$), 2700 (CHO), 1700 (HC=O), 1650 (C=C), 1395 and 1380 (isopropyl $CH_3$), 900 $cm^{-1}$ (=$CH_2$); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (s, 3H, $CH_3$), 2·7 (broad d, $J$ 7 Hz, 1H, C 5–H), 3·1 (m, $W_{h/2}$ 6 Hz, coupled with $C{=}CH_2$ and CHO, 1H, HCCHO), 5·0 (d, $J$ 2 Hz, coupled with C 6–H 2H, $C{=}CH_2$), 9·6 (d, $J$ 2 Hz, coupled with C 6–H, 1H, CHO), thus $J_{5,6} < 2$ Hz; mass spectrum (70 eV) $m/e$ 206 ($M^+$, $C_{14}H_{22}O$ requires $M^+$ 206) (43), 177 ($M^+ - HCO$) (54), 93 (100), 91 (94); g.l.c. FFAP (150°) 07/48 [some isomerization to aldehyde (27)].

The mixture of aldehydes (240 mg, 1·16 mmol) was dissolved, under nitrogen, in methanol (25 ml) containing sodium methoxide (5·4 mg, 0·1 mmol). The solution was stirred for 20 h at room temperature, poured onto water (25 ml), then extracted with X4 (2 × 40 ml). The combined X4 extract was washed with brine (40 ml), water (40 ml), dried and concentrated to furnish the conjugated aldehyde (28) as a colourless viscous oil (240 mg, quantitative); this gave a *semicarbazone* as colourless prisms from aqueous ethanol, m.p. 204–207° (Found: C, 68·5; H, 9·5; N, 15·7.

$C_{15}H_{25}N_3O$ requires C, 68·4; H, 9·6; N, 16·0%). The aldehyde had $\nu_{max}$ (film) 2700 (CHO), 1660 (HC=O), 1615 (C=C), 1380, 1370 (isopropyl), 1170, 1040, 785, 670 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, isopropyl $CH_3$, amongst other resonances), 1·1 (s, C1–$CH_3$ amongst other resonances), 2·0 (s, 3H, $CH_3C$=C), 3·2 (broad d, $J$ 6 Hz, 1H, C5–H), 10·1 (s, 1H, CHO); g.l.c. FFAP (150°) 11/28.

*(±)-14-Norhelminthospor-7(12)-en-13-oic Acid (6) and its Methyl Ester (29)*

The unconjugated aldehyde (27) (250 mg, 1·22 mmol) was dissolved in acetone (20 ml) and the solution cooled to −10°. Jones reagent was cooled to −10° and added dropwise up to an orange end-point. After 15 min, sufficient isopropyl alcohol was added to turn the colour to green, then the mixture diluted with benzene (30 ml) and water (20 ml). The aqueous layer was extracted with benzene (30 ml) and the total benzene fractions washed with brine (2 × 40 ml) and water until colourless, then dried and evaporated to afford the acid (6) as a colourless solid (270 mg, quantitative, m.p. 90–100°). Two recrystallizations from X4 gave regular colourless *prisms* (105 mg, 39%, m.p. 106–107°); the combined mother liquors contained *c.* 2% starting material, *c.* 98% acid (6) (n.m.r.) (Found: C, 75·4; H, 9·9. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). $\nu_{max}$ (Nujol) 3200–2700 (broad, OH), (=$CH_2$), 1700 (C=O), 1650 (C=C), 1375 (isopropyl), 1300, 1240 (C–O), 955, 900 $cm^{-1}$ (=$CH_2$); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl $CH_3$), 1·1 (s, 3H, $CH_3$), 2·5 (broad d, $J$ 5 Hz, 1H, C5–H), 3·2 (m, $W_{h/2}$ 8 Hz, collapses to broad s, $W_{h/2}$ 6 Hz, upon double irradiation at 4·8 or 5·1, 1H, $HCCO_2H$), 4·8 and 5·1 (2m, 2H, C=$CH_2$), 7·8 (broad s, 1H, exch., OH), thus $J_{5,6} \leqslant 4$ Hz.

The methyl ester (29) was prepared by treating the acid (6) (222 mg, 1·0 mmol) with excessive ethereal diazomethane in the normal way. Evaporation of solvent gave the ester (29) (236 mg, quantitative) as a colourless oil, $\nu_{max}$ (film) 3050 (=$CH_2$), 1730 (C=O), 1650 (C=C), 1390 and 1375 (isopropyl), 1155 (broad, C–O), 900 $cm^{-1}$ (=$CH_2$); n.m.r. ($CDCl_3$) $\delta$ 0·9 (2d, 6H, isopropyl $CH_3$), 1·1 (s, 3H, $CH_3$), 2·6 (broad d, $J$ 5 Hz), 3·3 (m, $W_{h/2}$ 6 Hz, collapses to m, $W_{h/2}$ 4 Hz on double irradiation at 4·9 or 5·1, 1H, $HCCO_2CH_3$), 3·7 (s, 3H, $OCH_3$), 4·9 and 5·1 (2d, both $J$ 2 Hz, allylic coupling to C6–H,2H, C=$CH_2$), thus $J_{5,6} \leqslant 2$ Hz; g.l.c. FFAP (150°) 09/30; (160°) 07/57.

The n.m.r. data above, together with those from the aldehyde (29) and acid (6), are consistent only with a C6 *exo*-isomer.[17]

*(±)-14-Norhelminthospor-6-en-13-oic Acid (5) and its Methyl Ester (30)*

Unconjugated ester (29) (236 mg, 1·0 mmol) was boiled in methanol (40 ml), containing sodium methoxide (40 mg, 0·74 mmol), for 48 h in an atmosphere of nitrogen. The solution was concentrated to 1 ml, then poured onto X4 : ether (4 : 1) and washed with water to neutrality. The solution was dried, then evaporated under vacuum to reveal the conjugated ester (30) as a homogeneous (g.l.c.), colourless oil (233 mg, 99%) which had the following properties: $\nu_{max}$ (film) 1705 (C=O), 1630 (C=C), 1200 (C–O), 1070, 1050, 795 $cm^{-1}$; n.m.r. ($CDCl_3$) $\delta$ 0·8–1·0 (m, isopropyl $CH_3$), 1·0 (broad s, $CH_3Cl$) (9H under 0·8–1·0 e), 2·0 (s, 3H, $CH_3C$=C), 3·1 (broad d, $J$ 6 Hz, C=CCH), 3·7 (s, 3H, $OCH_3$), no resonances in olefinic region; mass spectrum (70 eV) *m/e* 236 ($M^+$, $C_{15}H_{24}O_2$ requires $M^+$ 236) (12), 177 ($M^+ - CO_2CH_3$) (16), 93 (58), 91 (53), 55 (100); g.l.c. FFAP (160°) 11/52.

The ester (30) (230 mg, 0·97 mmol) was dissolved in methanol (20 ml) containing water (2 ml) and NaOH (100 g, 2·5 mmol). The solution was heated under reflux in a nitrogen atmosphere for 20 h, cooled, diluted with water (30 ml), acidified to pH 3 (conc. HCl), and finally extracted with X4 : ether (4 : 1, 3 × 40 ml). The entire extract was washed with water (50 ml), dried, and evaporated under vacuum to a colourless solid (200 mg, 92%): n.m.r. ($CDCl_3$) 2·0 (s, 2·4H, $CH_3C$=C), 3·1 (m, 1H, C5–H), 4·8 and 5·0 (2m, 0·4H, C=$CH_2$), i.e. 80% conjugated acid (5). Recrystallization from X4 gave crystals, m.p. 126–128°; one more recrystallization from X4 afforded colourless *prisms*; m.p. 127–129° (Found: C, 75·8; H, 10·1; $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). $\nu_{max}$ (Nujol) 3200–2600 (broad, OH), 1665 (C=O), 1615 (C=C), 1305, 1295, 1275, 1165, 1140, 945 $cm^{-1}$ (broad, C–O); n.m.r. ($CDCl_3$) $\delta$ 0·9 (d, isopropyl $CH_3$, amongst other resonances), 1·1 (broad s, $CH_3Cl$, and isopropyl $CH_3$, amongst other resonances), 2·0 (s, 3H, $CH_3C$=C), 3·1 (broad d, $J$ 5 Hz, 1H, C=CCH), 11·1 (e, 1H, $CO_2H$).

*Reduction of the Aldehyde (27) to (±)-14-Norhelminthospor-7(12)-en-13-ol (24)*

A solution of aldehyde (27) (60 mg, 0·29 mmol) in dry ether (1 ml) was dropped onto $LiAlH_4$ (11 mg, 0·29 mmol) in ether (4 ml) at 0°, under nitrogen. The mixture was stirred for 18 h at room temperature, cooled to 0°, and treated cautiously with drops of water until the grey precipitate

turned white. Ether was decanted and the precipitate washed with benzene (3 × 5 ml). The total benzene–ether solution was washed with water to neutrality, dried, and concentrated to a colourless viscous oil (60 mg, 99%), homogeneous by g.l.c. A *3,5-dinitrobenzene derivative* was prepared in the normal manner; this crystallized from X4 : ether (×2) as faint yellow plates, m.p. 99–102° (Found: C, 61·7; H, 6·6; N, 7·0. $C_{21}H_{26}N_2O_6$ requires C, 61·5; H, 6·7; N, 7·2%). The alcohol had $\nu_{max}$ (film) 3350 (OH), 3050 (=$CH_2$), 1650 (C=C), 1395 and 1380 (isopropyl), 1030 (C–O), 895 $cm^{-1}$ (=$CH_2$); n.m.r. ($CDCl_3$) $\delta$ 0·9 (m, 6H, isopropyl), 1·1 (s, 3H, $CH_3$), 2·5 (broad t, $J$ 7 Hz, $HOCH_2CH$), 3·5 (d, $J$ 7 Hz, collapses to broad s on double irradiation at 2·5; 2H, $HOCH_2CH$), 5·9 (2d, both $J$ 2 Hz, collapses to 2s, 5 Hz apart on double irradiation at 2·5; 2H, =$CH_2$); mass spectrum (70 eV) *m/e* 208 ($M^+$, $C_{14}H_{24}O$ requires 208) (19), 177 ($M^+ - CH_2OH$, m* 150·6) (41), 93 (99), 91 (100); g.l.c. FFAP (185°) 07/29 [spiked with alcohol derived from thioester (23)].

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