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DITERPENOID TOTAL SYNTHESIS—VIII*

(±)-KAUR-16-EN-19-OIC ACID, (±)-KAUR-16-EN-19-OL, (±)-MONOGYNOL AND SOME OXYGENATED KAURANES

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Abstract—The total synthesis of the title compounds, chemically and biologically interesting tetracyclic diterpenes, is described in detail.

(−)-KAUR-16-EN-19-OIC acid (I)† is one of the tetracyclic diterpenes isolated from an Australian shrub, *Ricinocarpus stylosus* Diels.[1] Recently its isolation from the mould *Gibberella fujikuroi*[2] as well as its detection in barley[3] has been reported. The discovery of the gibberellin-like biological activity of the acid and (−)-kaur-16-en-19-ol (II),[4] which is also found in barley,[3] aroused much interest among chemists and biochemists. Subsequent biochemical works indicated that the acid (I) and the alcohol (II) are intermediates in the biosynthesis of the gibberellins[5,6] and a partial synthesis of the acid (I) from 7β-hydroxykaurenolide (III) was accomplished.[7]

In view of recent successful achievements in the total synthesis of polycyclic diterpenes,[8–13] we decided to attempt the total synthesis of the acid (I). This paper describes the successful results of our efforts in this and related objectives which have been briefly reported in the preliminary communications.[14,15]

Our experience[16] with compounds derived from methyl (±)-13-methoxypodocarpa-8,11,13-trien-19-oate (IV)[17] suggested that a more promising starting point for the acid (I) was methyl (±)-14-methoxypodocarpa-8,11,13-trien-19-oate (V), although the ester (IV) is a promising intermediate for the synthesis of steviol (VI). Consequently, the first phase of this work was the synthesis of the ester (V).

Since the most popular approach to the aromatic resin acids is based on the A→C→B building principle, as exemplified in the synthesis of (±)-desoxypodocarpic acid (VII),[17,18] an attempt was made to cyclize an unsaturated ester (X). This, in turn, was prepared from ethyl 1,3-dimethylcyclohexan-2-one-1-carboxylate (VIII)[17] and β-(*o*-methoxyphenyl) ethyl bromide (IX)[19a,‡] by the Grignard reaction followed by dehydration. Treatment of the ester (X) with sulphuric acid in acetic acid afforded a crystalline acid. The structure XI was assigned to this acid, for the steric course of the ring-closure is known to give acids with podocarpic acid-type stereochemistry.[17]

* Part VII, K. Mori, M. Matsui, N. Ikekawa and Y. Sumiki, *Tetrahedron Letters* 3395 (1966).

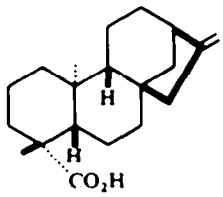
† The numbering system employed in this paper is that of R. McCrindle and K. H. Overton (*Adv. Org. Chem.* 5, 47 (1965)). Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate.

‡ This bromide was obtained by the bromination of the corresponding alcohol, which was prepared from anisole.[19b]

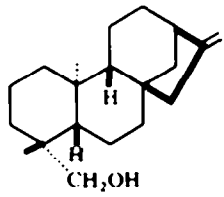
The yield, however, was disappointing (1·2% from VIII) and we decided to abandon this approach.

The next and successful attempt was based on the B, C → A building principle recently reported by Wenkert *et al.*[20] who condensed methyl acroylacetate (XIII)[21] with β-tetralones to give tricyclic esters. The starting materials for this route were methyl β-ethoxypropionyl acetate (XII)[20,21] and 1-methyl-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-one (XIV)[22], prepared by the enamine alkylation of 5-methoxy-β-tetralone. Condensation of the ketone (XIV) with methyl acroylacetate in the presence of sodium methoxide in methanol gave a crystalline keto ester (XV) in 32% yield. This was methylated with methyl iodide and potassium t-butoxide in benzene-tetrahydrofuran to give an oily ester (XVI). The assigned stereochemistry was supported by Wenkert's work[20] and was definitely proved by the conversion of the ester (XVI) to the ester (V) by the removal of the carbonyl oxygen and saturation of the non-conjugated double bond. For this purpose two different routes were explored. Firstly, the oily unsaturated ester (XVI) in acetic acid was hydrogenated by means of Pd-C to give a crystalline keto ester (XVII) in 44% yield. The observed low yield is analogous to that reported by Ireland and Schiess[22] in case of reduction of a tricyclic ketone (XVII; Me instead of CO_2Me). This may be ascribed to the lack of stereoselectivity during the hydrogenation due to the presence of the C-3 CO group which obscured the steric effect of the bulky, quasi-axial carbomethoxyl group and resulted in the formation of a stereoisomer (XVIII). The keto ester (XVII), upon Clemmensen reduction, gave a crystalline desoxo product. The identity of this with methyl (±)-14-methoxypodocarpa-8,11,13-trien-19-oate (V), prepared from the acid (XI) by treatment with diazomethane, was shown by mixture m.p. and comparison of IR spectra. Hydrolysis of the desoxo ester (V) by potassium t-butoxide in dimethyl sulfoxide[23] to the acid (XI) also confirmed the assigned structure. The second method was the desulphurization of a thioketal (XIX). This was prepared by mixing the oily keto ester (XVI) in chloroform with ethanedithiol and boron trifluoride etherate. Desulphurization of this thioketal in dioxan with W-7 Raney nickel[24] afforded an olefin (XX) which was hydrogenated over Pd-C to give the tricyclic ester (V) in 39% over-all yield from the ketone (XV). When a large excess of W-7 Raney nickel was employed for the desulfurization, concomitant saturation of the 5(6) double bond took place to give the ester (V) in one step.

Having obtained the desired tricyclic ester (V) in quantity, we started the second phase of the work, the elaboration of the D-ring, which was carried out without much difficulty according to the method developed by Ireland *et al.*[9] successfully applied in the total synthesis of garryine.[12] The first objective was the reduction of the aromatic C ring. In our hands Birch reduction of the ester (V) by the Dryden modification[25] or by the Johnson modification[26] failed completely and the only isolable crystalline product was the acid (XI). It is to be noted that the Dryden modification was successfully applied to the ester (IV).[17] We, therefore, turned our attention to the catalytic method for the reduction of the C ring. The methoxy ester (V) was converted to the corresponding hydroxy acid (XXI) by treatment with refluxing hydriodic acid in acetic acid. The methyl ester (XXII), obtained by esterification with diazomethene, was hydrogenated in the presence of T-1 Raney nickel[27] or rhodium-platinum oxides[28] to give an oily stereoisomeric mixture of saturated hydroxy esters (XXIII). Of the two catalysts employed, the former was found to be better, giving a



I



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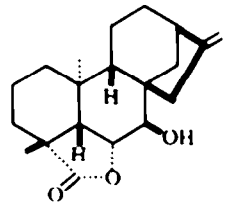

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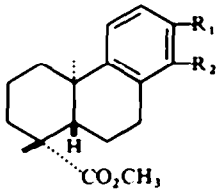
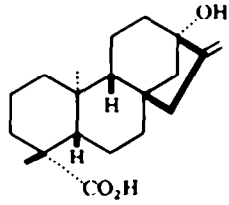


IV: R_1 = OMe, R_2 = H
V: R_1 = H, R_2 = OMe



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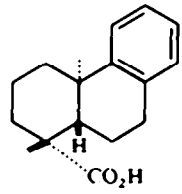

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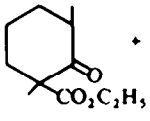
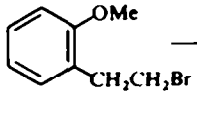


VIII



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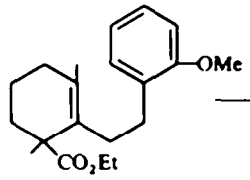

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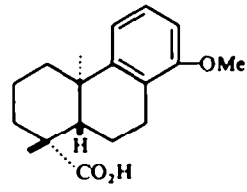

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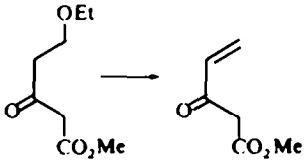
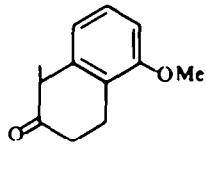


XII

XIII



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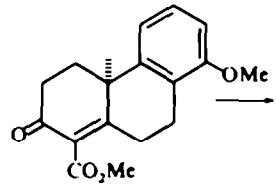

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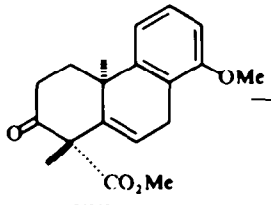

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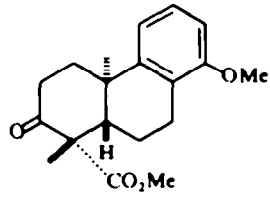

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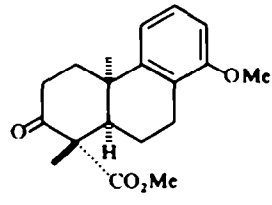
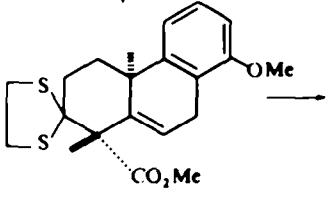


XVIII



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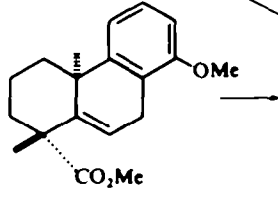
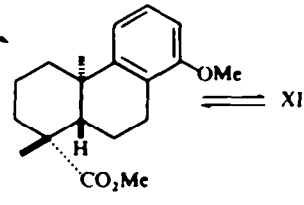
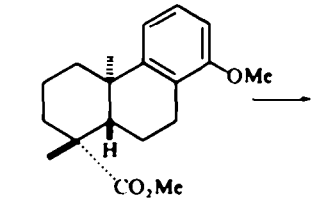


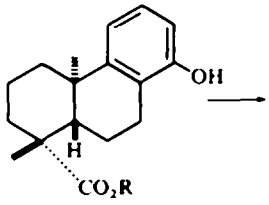
XX



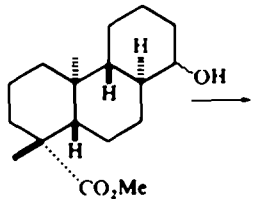
V ≡ XI



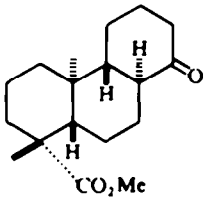
V



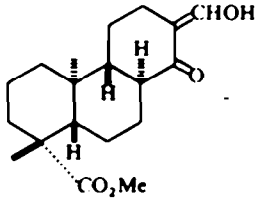
XXI: R = H
XXII: R = Me



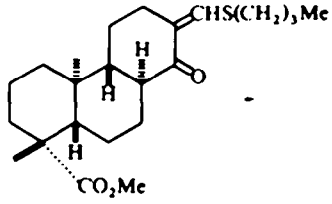
XXIIIa: β(ax.)-OH
XXIIIb: α(eq.)-OH



XXIV



XXV



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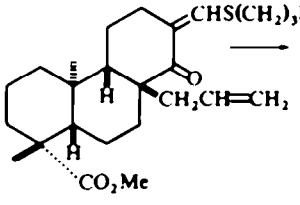
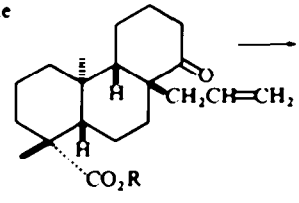
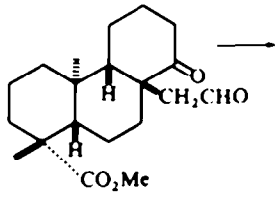


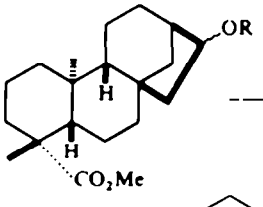
XXVII



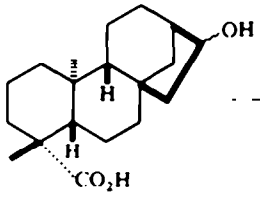
XXVIII: R = Me
XXIX: R = H



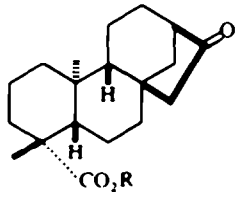
XXX



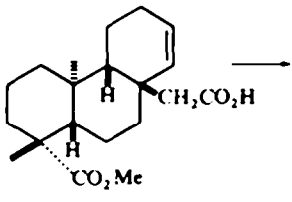
XXXVI: R = H
XXXVII: R =



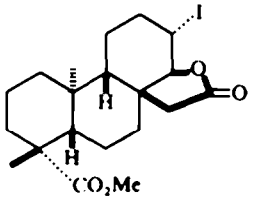
XXXVIII



XXXIX: R = H
XL: R = Me



XXXI



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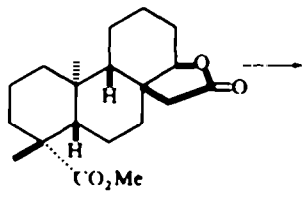
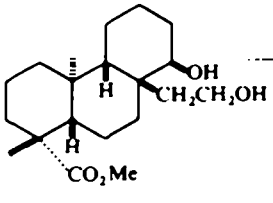
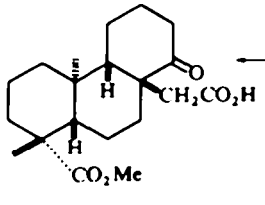


XXXIII



XXXIV



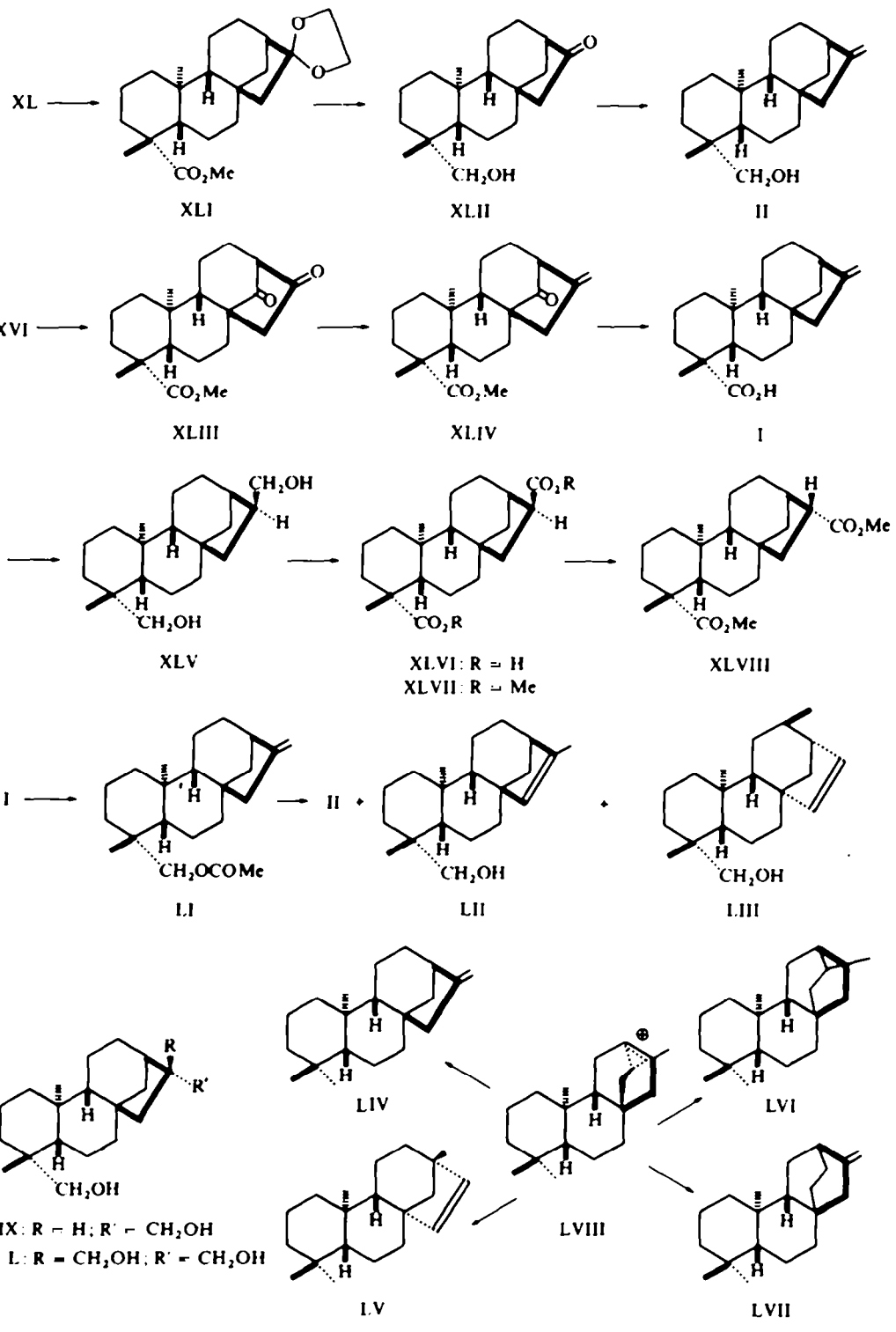
XXXV

XXX

smaller amount of hydrogenolysis (14-OH) products. The oily hydroxy esters were later separated into two crystalline isomers either by fractional crystallization or by chromatography on alumina. The isomer more easily eluted from alumina was assumed to be one with an axial hydroxyl group. By analogy with Turner's result,[8b] the structure XXIIIa was assigned to the axial epimer. Jones oxidation[29] of the crude mixture of hydroxy esters gave crystalline methyl (±)-14-oxopodocarpan-19-oate (XXIV). The B/C-*trans* stereochemistry of this ketone was proved by the fact that equilibration with methanolic sodium methoxide gave back the unchanged starting material.

Prior to the introduction of an allyl group at C-8 of the ketone (XXIV), the C-13 methylene had to be blocked by the n-butylthiomethylene protective group.[30] Thus the keto ester (XXIV) was converted to a formyl ketone (XXV) which in benzene was heated with n-butyl mercaptan and p-toluenesulfonic acid to yield a crystalline n-butylthiomethylene ketone (XXVI). This was alkylated with a large excess of allyl bromide in the presence of potassium t-butoxide to afford an oily keto ester (XXVII). The alkylation was expected to give B/C *cis* ketone because of the steric hindrance caused by the angular Me group.[12b, 31] The protective group was removed by heating with potassium hydroxide in aqueous ethanol to give an oily keto ester (XXVIII). The corresponding crystalline acid (XXIX) was obtained as a minor product. The oily keto ester (XXVIII), upon Johnson-Lemieux oxidation,[32] was converted to a crystalline keto aldehyde (XXX). The stereochemistry depicted for the aldehyde (XXX) was confirmed by comparing its Jones oxidation product with an authentic sample of methyl (±)-8β-carboxymethyl-14-oxopodocarpan-19-oate (XXXV). This was prepared from the previously reported acid (XXXI)[16] with established stereochemistry in the following way. The acid (XXXI) in aqueous sodium bicarbonate was treated with iodine and potassium iodide to give a crystalline iodolactone (XXXII).[cf. 33] The hydrogenolytic removal of the iodine at C-13 gave an oily γ-lactone. Compound XXXIII was reduced by excess sodium borohydride in ethanol to a crystalline diol (XXXIV). Jones oxidation of the diol gave the crystalline acid (XXXV), accompanied by a small amount of the γ-lactone (XXXIII). The keto acid (XXXV) obtained in this manner was identical (mixture m.p. and IR) with the acid derived from the aldehyde (XXX).

The aldol-type ring closure of the aldehyde (XXX) to the tetracyclic kaurane skeleton was effected by treatment with hot methanolic sodium methoxide. The resulting oily ketol (XXXVI), presumably an epimeric mixture at C-16, later solidified. No further attempt was made to separate the epimers at this stage. A benzene solution of this ketol was treated with dihydropyran and *p*-toluenesulfonic acid to give an epimeric mixture (at C-16) of the tetrahydropyranyl ethers (XXXVII), one of which crystallized. The Wolf-Kishner reduction of this crystalline isomer (XXXVII) under the forcing conditions developed by Barton, *et al.*[34] followed by acid-hydrolysis, yielded a crystalline hydroxy acid (XXXVIII). This, on oxidation with Jones reagent, gave a crystalline keto acid (XXXIX). The IR spectrum of its solution was identical in every detail with that of (−)-16-oxo-17-norkauran-19-oic acid (XXXIX) prepared from (−)-16,17,19-kauranetriol (L)[1] by oxidation. The corresponding racemic methyl ester (XL) also exhibited an IR spectrum identical with that of the (−)-ester (XL). Since the (−)-ester (XL) had been converted to (−)-kaur-16-en-19-ol (II),[5] which in turn had been transformed into (−)-kaur-16-en-19-oic acid (I),[1] this completed the formal total synthesis of both the racemic acid (I) and the alcohol (II).


XL
XLI
XLII
II
XXXVI
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XLIV
I
II
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XLVI: R = H
XLVII: R = Me
XLVIII
II
LI
II
LII
LIII
XLIX: R = H; R' = CH2OH
L: R = CH2OH; R' = CH2OH
LIV
LV
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LVII
LVIII

In order to test their biological activities, however, we felt it necessary to prepare the racemic acid (I) and the alcohol (II). The racemic alcohol (II) was obtained in a conventional manner from the ester (XL) as follows. The ester (XL) in boiling dichloroethane was treated with ethylene glycol and *p*-toluenesulfonic acid to give the corresponding crystalline ketal (XLI). Reduction of this in tetrahydrofuran with LAH in ether followed by acid-hydrolysis afforded crystalline (±)-16-oxo-17-norkauran-19-ol (XLII). Condensation of this ketone (XLII) with methylenetriphenylphosphorane[35] generated (±)-kaur-16-en-19-ol (II).

The starting point for the acid (I) was the ketol (XXXVI). This was oxidized with Jones reagent to give a crystalline diketone (XLIII). Treatment of this diketone with an excess of methylenetriphenylphosphorane yielded a monocondensation product (XLIV)[cf. 9]. Upon modified Wolff-Kishner reduction,[34] this methylene ketone gave (±)-kaur-16-en-19-oic acid (I), the NMR spectrum of which was identical with that of the (−)-acid.

The racemic acid (I), alcohol (II), methylene ketone (XLIV) and acetate (LI) were tested for biological activity employing d-5 dwarf mutants of *Zea mays* L. as the assay plants. With the exception of the methylene ketone (XLIV), they were found to be active.

After the completion of this major objective of synthesizing compounds with gibberellin-like activity, we next turned our attention to the conversion of (±)-kaur-16-en-19-ol (II) to other oxygenated kauranes isolated from *Ricinocarpus stylosus*.[1] Hydroboration–oxidation[36] of the alcohol (II) yielded a diol (XLV) as a crude oil which was oxidized with Jones reagent to give a crystalline diacid (XLVI). The IR spectrum of the corresponding dimethyl ester (XLVII) solution (CS_2) was different from that of methyl (−)-16α-kaurane-17,19-dioate (XLVIII) in the fingerprint regions. This suggested that the hydroboration proceeded stereoselectively on the less hindered α-side of the D-ring affording the 16β-alcohol (XLV) as the sole product which gave the 16β-acid (XLVI) after oxidation.* Inspection of a molecular model clearly indicated that the 16β-ester (XLVII) is less stable than the 16α-ester (XLVIII). Accordingly, the dimethyl ester (XLVII) was equilibrated with sodium methoxide in methanol to give a small amount of crystalline diester (XLVIII), the IR spectrum of a solution (CS_2) was identical with that of the optically active diester (XLVIII). Gas chromatographic analysis of the diester gave further evidence supporting the identity of the epimerized racemate (XLVIII) and the natural diester. The retention time of the former coincided with that of the latter, while that of the 16β-ester (XLVII) differed slightly. The parent diacid ((−)-16α-kaurane-17,19-dioic acid) of the diester (XLVIII) is one of the diterpenes isolated from *Ricinocarpus stylosus*.[1] Since both the conversion of the diester (XLVIII) into (−)-16α-kaurane-17,19-diol (XLIX) and that of (−)-kaur-16-en-19-ol (II) into (−)-16β-kaurane-16α,17,19-triol (L) has been reported by Henrick and Jefferies,[1] the present work constitutes the total synthesis of the two diterpenes from the Australian shrub.

The final work to be described in this paper is a transformation of (±)-kaur-16-en-19-ol (II) into (±)-monogynol (LIII) by a skeletal rearrangement. Monogynol[37]

* The steric course of the hydroboration reaction had also been studied by Professor Jefferies (Private communication to K.M. dated 11 March 1966). We thank him for kindly informing us of his result prior to publication.

or erythroxylol A[38] (LIII) is an alcohol isolated from *Erythroxylon monogynum* Roxb. by two groups of workers and belongs to the hibaene group of tetracyclic diterpenes. Recently its partial synthesis from steviol (VI) has been reported by Hanson.[39] According to Wenkert's scheme of diterpene biogenesis[40] which is now widely accepted, kaurene (LIV), hibaene (LV), atisirene (LVII) and trachylobane (LVI) all can be derived from a common intermediate such as a carbonium ion (LVIII). Several reports have appeared which describe the interconversion of diterpenes based on this scheme under laboratory conditions.[41 43] Our starting material was the acetate (LI) of (±)-kaur-16-en-19-ol (II). The acetate (LI) in xylene containing a small amount of iodine was heated under reflux for 9 hr.[43] After alkaline hydrolysis, the resulting mixture of alcohols was resolved by chromatography on silica gel impregnated with silver nitrate.[44] The alcohols obtained were, in the order of elution: an unidentified saturated alcohol, (±)-kaur-16-en-19-ol (II), (±)-kaur-15-en-19-ol (LII) (isokaurenol) and (±)-monogynol (LIII). The IR spectrum of the purified racemic monogynol solution (in CS_2) was superimposable on that of the natural product. The identity was further proved by gas chromatographic comparison. The ratio of kaurenol:isokaurenol:monogynol was 1:2:1.

EXPERIMENTAL

M.ps and b.ps are uncorrected.

Ethyl 1,3-dimethyl-2-β-(o-methoxyphenyl)ethylcyclohex-2-en-1-carboxylate (X)

To the Grignard reagent prepared from Mg (3 g) and IX (25 g) in ether (150 ml), compound VIII (21·5 g) in ether (50 ml) was added with stirring at 0 5°. The mixture was left to stand overnight at room temp and then treated with ice and sat NH_4Cl aq. The ether layer was separated, dried over Na_2SO_4 and concentrated. The residue dissolved in toluene (50 ml) was heated under reflux for 2 hr in the presence of $KHSO_4$ (5 g). After removal of $KHSO_4$ by filtration the toluene soln was concentrated *in vacuo*. Distillation of the residual oil gave the product (8 g) in 24% yield; b.p. 160 170°/0·4 mm n_D^{26} 1·5260; ν_{max} (film) 1735, 1608, 1592, 755 cm^{-1}. (Found: C, 76·33; H, 9·02. $C_{20}H_{28}O_3$ requires C, 75·91; H, 8·92%).

(±)-14-*Methoxy*-5β,10α-*podocarpa*-8,11,13-*trien*-19-*oic acid* (XI)

The ester X (4 g) dissolved in AcOH (20 ml) containing conc H_2SO_4 (1·5 ml) was heated under reflux for 5 hr. After dilution with water the mixture was extracted with ether. The ether soln was washed with water followed by brine, dried over Na_2SO_4, and concentrated to give crystalline XI (50 mg, 1·5% yield) and an oil (2·5 g). The oil exhibited an absorption at 1780 cm^{-1} due to a lactonic CO group. The crystalline acid was recrystallized from EtOAc as elongated prisms, m.p. 243 244°; ν_{max} (Nujol) 1695, 1600, 1590, 782, 725 cm^{-1}. (Found: C, 74·84; H, 8·16. $C_{18}H_{24}O_3$ requires: C, 74·97; H, 8·39%).

Methyl β-ethoxypropionylacetate (XII)

Methyl acetoacetate (210 g) was added dropwise to a suspension of powdered Na (44 g) in dry ether (1·4 l) with cooling and stirring during 2–3 hr. To the solidified sodioacetoacetate was added β-ethoxypropionyl chloride (219 g) in dry ether (240 ml) with stirring at 5 10°. After the exothermic reaction had ceased, the mixture was stirred for an additional hr and then left to stand overnight at room temp. Dry ammonia gas was passed into the well-cooled mixture for 1 hr at 5 10° until the ether soln was saturated with ammonia. Then the mixture was poured into ice water and the ether layer separated. The aqueous layer was extracted with ether. The combined ether soln was successively washed with water, ice-cooled 5% HCl, $NaHCO_3$ aq and brine. The dried ($MgSO_4$) extract was concentrated and the residue was distilled *in vacuo*, b.p. 86°/0·2 mm, to give 81 g (29%) of the product; ν_{max} (film) 1745, 1715, 1120 cm^{-1}.

Methyl acroylacetate (XIII)

The ester XII (200 g) was pyrolysed at 120 130° (bath temp) under reduced press (15 20 mm) in the

presence of hydroquinone (0·5 g) and *p*-toluenesulfonic acid (5 g). The distillate was redistilled to give 100 g (68%) b.p. 60–70° 15 mm; ν_{max} (film) 1750, 1730 (sh), 1700 (sh), 1670, 1620, 1590, 1250, 1150, 830 cm^{-1}.

1-*Methyl*-5-*methoxy*-1,2,3,4-*tetrahydronaphthalen*-2-*one* (XIV)

5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-one (400 g) and pyrrolidine (250 g) were mixed with benzene (2·5 l.) and heated under reflux for 2 hr with removal of water (36 ml). Subsequent removal of benzene and pyrrolidine gave an oily crude enamine; ν_{max} (film) 1615, 1595, 1560, 1470, 1400, 1365, 1265, 1205, 1100, 790 cm^{-1}. This was dissolved in dry dioxan and mixed with MeI (1·2 kg). When the initial exothermic reaction ceased, the mixture was heated under reflux on an oil bath and kept refluxing for 20 hr. Then conc HCl (8 ml) and water (1·05 l.) were added and the mixture was again refluxed for 2 hr. About ¾ of the solvent was removed *in vacuo* and the residue was diluted with water. The separated oily ketone was taken in ether. The ether soln was washed with $NaHSO_3$ aq and dried (Na_2SO_4). The product (XIV, 361 g, 84% from the tetralone) distilled at 150–160°/5 mm; ν_{max} (film) 1722, 1590, 1270, 1100, 1055, 780 cm^{-1}.

Methyl (±)-3-*oxo*-14-*methoxy*-18-*nor*-10α-*podocarpa*-4,8,11,13-*tetraen*-19-*oate* (XV)

The tetralone XIV (361 g) dissolved in dry benzene (600 ml) was added to NaOMe (from 46 g of Na) in MeOH (1·2 l.) at 5–10° with stirring; XIII (317 g) in dry benzene (550 ml) was then added dropwise to the stirred and well-cooled (−3–3°) soln of the enolized ketone. The mixture was left to stand overnight at room temp and then heated under relux for 40 min with stirring. After cooling, conc HCl (200 ml) and ice–water (2 l.) were added and the benzene layer spearated. The aqueous layer was extracted with EtOAc. The combined extract was washed with water, $NaHCO_3$ aq and brine. The dried ($MgSO_4$) extract was concentrated *in vacuo*. Trituration of the residue with ether gave crystalline XV (138 g). The mother liquor was concentrated *in vacuo* to remove low-boiling impurities up to b.p. 150°/4 mm. Trituration of the residue with ether gave a second crop of XV (45 g) giving a total of 183 g (32% yield). It was recrystallized from EtOAc–petrol as elongated prisms, m.p. 185–186°; ν_{max} (Nujol) 1745, 1680, 1638, 1608, 1590, 1270, 1055, 796, 777 cm^{-1}. (Found: C, 71·63; H, 6·61. $C_{18}H_{20}O_4$ requires: C, 71·98; H, 6·71%).

Methyl (±)-3-*oxo*-14-*methoxy*-10α-*podocarpa*-5,8,11,13-*tetraen*-19-*oate* (XVI)

The ester XV (183 g) suspended in dry THF (1 l.) was added to a soln of t-BuOK (from 26·5 g K) in t-BuOH (1·2 l.) with stirring. The mixture was stirred and heated to remove the solvents in 2 hr. To the residue was added dry benzene (800 ml) which was also distilled off with stirring. Dry benzene (1·2 l.) and MeI (400 g) were added to the solid potassium enolate. The mixture was heated under reflux for 6 hr. The operations were all carried out under N_2 atm. After cooling, the benzene soln was washed with water, dried over $MgSO_4$ and concentrated to give an oil (ca. 190 g). This resisted crystallization and was employed for the next step without further purification; ν_{max} (film) 1742, 1720, 1670, 1605, 1590, 1055, 790, 720 cm^{-1}.

Methyl (±)-3-*oxo*-14-*methoxy*-5β,10α-*podocarpa*-8,11,13-*trien*-19-*oate* (XVII)

The oily XVI obtained from 45 g of XV was dissolved in AcOH (200 ml) and hydrogenated over 10% Pd-C (20 g) under atm press at 70° for 30 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give crystalline XVII (20 g, 44% yield). The residual oil probably containing the stereoisomer XVIII crystallized after standing for 1½ years. This was not studied further. The desired XVII crystallized from EtOAc–petrol as rods, m.p. 155–156°; ν_{max} (Nujol) 1736, 1718, 1602, 1585, 1260, 1055, 785, 780, 720 cm^{-1}. (Found: C, 72·41; H, 7·58. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%).

Methyl (±)-14-*methoxy*-5β,10α-*podocarpa*-8,11,13-*trien*-19-*oate* (V)

(a) The ester XVII (19 g) suspended in 20% HCl (400 ml) was heated under reflux for 48 hr in the presence of amalgmated mossy Zn [390 g, shaken for 15 min with $HgCl_2$ soln (300 ml containing 25 g $HgCl_2$ and 20 ml conc HCl)]. During the heating, seven 30 ml portions of conc HCl were added in 6 hr intervals. After cooling, the mixture was extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give V (16 g, 88% yield) which was recrystallized from EtOAc–petrol as rods, m.p. 124–125; ν_{max} (Nujol) 1730, 1600, 1580, 1260, 1190, 1152, 1060, 785, 724 cm^{-1}. (Found: C, 74·90; H, 8·28. $C_{19}H_{26}O_3$ requires: C, 75·46; H, 8·67%).

(b) The unsaturated XX (13·5 g) in AcOH (150 ml) was hydrogenated over 10% Pd-C (3·5 g) at 80° under atm press for 5 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give 13·5 g (99%) of the crystalline saturated ester which showed the same IR spectrum as V prepared above.

(c) The acid XI was methylated with an excess of ethereal diazomethane to give V, the identity of which was proved by m.m.p. and IR comparison.

Dithioethyleneketal of methyl (±)-3-oxo-14-methoxy-10α-podocarpa-5,8,11,13-tetraen-19-oate (XIX)

The oily XVI (ca. 190 g) dissolved in $CHCl_3$ (1 l.) was mixed with ethanedithiol (90 ml) and BF_3–Et_2O (90 ml). The mixture was left to stand at room temp for 3 days and then poured into water. The $CHCl_3$ layer was washed with brine, dried ($MgSO_4$) and concentrated. Trituration of the residue with ether–petrol afforded a crystalline mass of the thioketal. This was collected on a Buchner funnel and washed with ether–petrol to give 98 g (40% from XV) of prisms. Recrystallization from THF–EtOAc gave prisms, m.p. 193–194°; ν_{max} (Nujol) 1732, 1672, 1604, 1582, 1234, 1055, 784, 720 cm^{-1}. (Found: C, 64·36; H, 6·86; S, 16·33. $C_{21}H_{26}O_3S_2$ requires: C, 64·60; H, 6·71; S, 16·40%).

Methyl (±)-14-methoxy-10α-podocarpa-5,8,11,13-tetraen-19-oate (XX)

The thioketal XIX (6·5 g) dissolved in dioxan (250 ml) was stirred with Raney Ni W-7 (35 g) for 3 hr on a boiling water bath. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 4·0 g (81%) of XX, which crystallized from EtOAc–petrol as prisms, m.p. 153–154°; ν_{max} (Nujol) 1735, 1680, 1600, 1588, 1255, 1150, 1135, 1060, 784 cm^{-1}; δ_{ppm}^{TMS} ($CDCl_3$) 1·15 (3H, s), 1·35 (3H, s), 3·32 (2H, t), 3·60 (3H, s), 3·78 (3H, s), 5·94 (1H, t, J = 7 c/s), 6·5–7·2 (3H). (Found: C, 75·91; H, 8·15. $C_{19}H_{24}O_3$ requires: C, 75·97; H, 8·05%).

Use of a larger amount of Raney Ni resulted in the saturation of the 5(6)-double bond. The thioketal XIX (50 g) in dioxan (2 l.) was stirred with Raney Ni W-7 (500 g) under reflux for 4 hr. Subsequent work-up gave 38 g (98%) of XVIII.

(±)-14-Hydroxy-5β,10α-podocarpa-8,11,13-trien-19-oic acid (XXI)

The ester V (24 g) dissolved in AcOH (320 ml) was mixed with 48% HBr (280 ml) and 60% HI (66 g). The mixture was heated under reflux for 8 hr, diluted with water and extracted with ether. The ether extract was washed with water, $NaHSO_3$ aq, water and brine. The dried ($MgSO_4$) and decolorized (charcoal) soln was concentrated *in vacuo* to give 16 g (74%) of XXI which recrystallized from EtOAc–petrol as needles, m.p. 223–224°; ν_{max} (Nujol) 3530, 1680, 1610, 1580, 1272, 782, 725 cm^{-1}. (Found: C, 74·45; H, 8·06. $C_{19}H_{22}O_3$ requires: C, 74·42; H, 8·08%).

The acid XI from the ester V by saponification

Solid t-BuOH obtained by evaporation *in vacuo* of the solvent from a soln of K (3·9 g) in t-BuOH (200 ml) was dissolved in redistilled DMSO (100 ml) by gentle heating. To the soln XVIII (2·0 g) was added at 65°. After heating at 60–65° for 2 hr, the mixture was poured into water, acidified with HCl and extracted with ether–EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1·6 g (84%) of XI, m.p. 240–243°. The identity was proved by IR and m.m.p.

Methyl (±)-14-hydroxy-5β,10α-podocarpa-8,11,13-trien-19-oate (XXII)

The acid XXI suspended in EtOAc was treated with an excess of ethereal diazomethane. Removal of the solvent gave the ester. Recrystallization from MeOH afforded needles, m.p. 191–192°; ν_{max} (Nujol) 3380, 1702, 1582, 787, 728 cm^{-1}. (Found: C, 74·90; H, 8·28. $C_{18}H_{24}O_3$ requires: C, 74·97; H, 8·39%).

Methyl (±)-14β-hydroxy-5β,8α,9β,10α-podocarpan-19-oate (XXIIIa) *and its 14α-hydroxy epimer* (XXIIIb)

(a) *With rhodium–platinum oxide catalyst.* The ester XXII (4 g) dissolved in EtOAc (60 ml) and AcOH (40 ml) was hydrogenated over Rh–PtO_2 (prepared from 0·35 g $RhCl_3$ and 0·05 g H_2PtCl_6) at 70–110° and an initial press of 100 kg/cm^2 for 2·5 hr. Removal of the catalyst and the solvents gave 3·8 g of an oily mixture of XXIIIa, XXIIIb and the hydrogenolysis product; ν_{max} (film) 3440, 1732, 1155 cm^{-1}. This was employed for the next step without further purification.

(b) *With Raney nickel T-1.* The ester XXII (12 g) suspended in 99% EtOH (150 ml) was hydrogenated over Raney Ni T-1 (15 g) at 180° and an initial press of 110 kg/cm^2 for 3 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residual oil was triturated with ether–petrol to give 5·4 g (45%) of XXIIIa which was more easily eluted when chromatographed on alumina. Recrystallization from EtOAc–petrol gave prisms, m.p. 153–154°; ν_{max} (Nujol) 3585, 1712, 1240, 1200, 1158, 1062, 1010, 973 cm^{-1}; ($CHCl_3$) ca. 3640, ~3440, 1714, 1153, 1090, 1052, 1005, 970, 842 cm^{-1}. (Found: C, 73·43; H, 10·08. $C_{18}H_{30}O_3$ requires: C, 73·43; H, 10·27%). The mother liquor deposited the needles (1·5 g, 12%) of XXIIIb.

Recrystallization from EtOAc–petrol gave needles, m.p. 139–140°; ν_{max} (Nujol) ~3250, 1734, 1238, 1228, 1214, 1185, 1162, 1152, 1094, 1050, 1044, 1035, 1031, 934 cm^{-1}; ($CHCl_3$) ca. 3640, ~3440, 1716, 1149, 1025, 1015, 936 cm^{-1}. (Found: C, 73·77; H, 10·20. $C_{18}H_{30}O_3$ requires: C, 73·43; H, 10·27%). In the same manner 10 g of XXII was hydrogenated to give 4·3 g of XXIIIa and 1·2 g of XXIIIb. The combined mother liquors of the two experiments deposited 1·2 g XXIIIa. The total yield of the crystalline alcohols was 13·6 g (62%). Since the Jones oxidation of the mother liquor gave 1·5 g of XXIV, the attained yield of the alcohols was 15·1 g (68%).

Methyl (±)-14-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (XXIV)

An oily mixture of XXIIIa and XXIIIb (12 g) in acetone (150 ml) was treated with the Jones reagent (12 ml). The mixture was cooled in an ice-bath at 0–5° during the addition of the reagent (5 min) and kept at 5° for 30 min. The excess reagent was decomposed by MeOH and the mixture was concentrated *in vacuo*. To the residue, water and EtOAc was added. The EtOAc layer was separated, washed with water, $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 4·3 g (36% from XXII) of the ketone. The mother liquor was chromatographed on alumina to give 0·3 g of the ketone. The total yield was thus 4·6 g (38% from XXII). When the crystalline alcohols were employed, the yield was almost quantitative. For the purpose of purification, 8·6 g of crude ketone dissolved in EtOAc (200 ml) was chromatographed on alumina (14 × 5 cm) in n-hexane–EtOAc (3:2). Elution with n-hexane–EtOAc (3:2, 1·2 l.) gave 7·6 g of pure crystals. This showed the identical IR spectrum with that of the crude material eliminating the possibility of isomerization on alumina. Recrystallization from EtOAc–petrol gave plates, m.p. 155–156°; ν_{max} (Nujol) 1728, 1708, 1166 cm^{-1}. (Found: C, 74·40; H, 9·72. $C_{18}H_{28}O_3$ requires: C, 73·93; H, 9·65%).

Attempted equilibration of the keto ester XXIV

The ester XXIV (50 mg) was heated under reflux with methanolic NaOMe (100 mg of Na and 10 ml MeOH) for 1 hr. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether–EtOAc. The extract was washed with water and brine and concentrated to give back the starting keto ester (40 mg), identified by IR and m.m.p.

Methyl (±)-13-*hydroxymethylene*-14-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (XXV)

The ester XXIV (1·6 g) in dry THF (40 ml) was added to a stirred suspension of powdered NaOMe (1·5 g) in dry benzene (25 ml). To the ice-cooled mixture redistilled ethyl formate (4 ml) was added with stirring. Within 5 min the mixture solidified and was left to stand overnight at room temp. It was poured into ice water (25 ml) and the aqueous layer was separated. The organic layer was diluted with ether and extracted with 5% NaOHaq (15 ml × 3). The combined aqueous soln was acidified with HCl at 0–5° and rapidly extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$) and concentrated to give 1·7 g (96%) of the crystalline product. Recrystallization from MeOH afforded prisms, m.p. 122–123°; ν_{max} (Nujol) 1718, 1645, 1590 cm^{-1}. (Found: C, 71·35; H, 8·76. $C_{19}H_{28}O_4$ requires: C, 71·22; H, 8·81%).

Methyl (+)-13-n-*butylthiomethylene*-14-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (XXVI)

The ester XXV (1·5 g) dissolved in dry benzene (50 ml) was mixed with n-butyl mercaptan (0·5 ml) and *p*-toluenesulfonic acid (20 mg). The mixture was heated under reflux for 4 hr and poured into water. The benzene layer was separated and the aqueous layer was extracted with ether. The combined extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1·8 g (98%) which recrystallized from MeOH as needles, m.p. 86–87°; ν_{max} (Nujol) 1728, 1670, 1554 cm^{-1}. (Found: C, 70·65; H, 8·79; S, 8·17. $C_{23}H_{36}O_3S$ requires: C, 70·37; H, 9·24; S, 8·15%).

Methyl (+)-13-*n-butylthiomethylene*-14-*oxo*-8β-*allyl*-5β,9β,10α-*podocarpan*-19-*oate* (XXVII)

To a stirred and ice-cooled soln of t-BuOK (from 4·5 g K) in t-BuOH (150 ml), XXVI (9·5 g) dissolved in dry benzene (130 ml) was added under N_2 atm. After 6 min stirring, redistilled allyl bromide (25 ml) was added at once with stirring. Ice-cooling was continued for 10 min after the addition. Then the mixture was heated under reflux for 2 hr. During this period an additional amount of allyl bromide (10 ml) was added. After cooling, the mixture was poured into water and extracted with ether. The extract was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (10 g, 95%); ν_{max} (film) 1730, 1674, 1642, 1550, 915 cm^{-1}. This was employed for the next reaction without further purification.

Methyl (+)-14-oxo-8β-allyl-5β,9β,10α-podocarpan-19-oate (XXVIII)

The oily XXVII (2·1 g) dissolved in 95% EtOH (20 ml) was mixed with KOH (2 g) in water (10 ml). The mixture was heated under reflux for 32 hr under N_2 atm. EtOH was removed *in vacuo* and the residue was extracted with ether. The extract was washed with water followed by brine, dried ($MgSO_4$) and concentrated to give 1·5 g (92%) of an oil; ν_{max} (film) 1730, 1712, 1648, 915 cm^{-1}. This was employed for the next step without further purification. The alkaline aqueous layer was acidified with HCl and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 50 mg of XXIX. Recrystallization from EtOAc gave prisms, m.p. 226–227°; ν_{max} (Nujol) 3200, ~2400, 1704, 1648, 934, 915 cm^{-1}. (Found: C, 75·27; H, 9·25. $C_{20}H_{30}O_3$ requires: C, 75·43; H, 9·50%). This afforded XXVIII upon treatment with ethereal diazomethane.

Methyl (+)-14-oxo-8β-formylmethyl-5β,9β,10α-podocarpan-19-oate (XXX)

OsO_4 (31 mg) was added to a stirred soln of XXX (1·5 g) in THF (30 ml) and water (10 ml) under N_2 atm. The color of the soln turned dark brown after stirring for 5 min. Then powdered sodium metaperiodate (3·0 g) was added and the stirring was continued for 4 hr. The mixture was left to stand overnight at room temp and then diluted with ether. The ether soln was dried ($MgSO_4$) and evaporated to give 1·4 g (93%) of XXX. It crystallized from petrol as rosettes of needles, m.p. 110–111°; ν_{max} (film) 2740, 1730, 1708 cm^{-1}. (Found: C, 70·91; H, 8·49. $C_{19}H_{28}O_4$ requires: C, 71·22; H, 8·81%).

Methyl (+)-8β-carboxymethyl-13α-iodo-14β-hydroxy-5β,9β,10α-podocarpan-19-oate-lactone (XXXII)

Compound XXXI (800 mg) was dissolved in 0·5N $NaHCO_3$ (30 ml) by heating. A soln of I_2 (1·7 g) in KI (3·3 g in 10 ml) was added portionwise. Within 10 min the iododlactone precipitated. The reaction mixture was left to stand overnight at room temp and then extracted with EtOAc. The extract was washed with $Na_2S_2O_3$ aq, $NaHCO_3$ aq and brine, successively. Concentration of the soln after drying (Na_2SO_4) gave 1·05 g (95%) of the lactone. Recrystallization from EtOAc–petrol gave prisms, m.p. 200–201° (dec); ν_{max} (Nujol) 1788 (1772 sh), 1720, 1156, 1000 cm^{-1}. (Found: C, 52·81; H, 6·59. $C_{20}H_{29}O_4I$ requires: C, 52·18; H, 6·35%).

Methyl (±)-8β-carboxymethyl-14β-hydroxy-5β,9β,10α-podocarpan-19-oate γ-lactone (XXXIII)

Compound XXXII (2·0 g) in dioxan (80 ml) was hydrogenolyzed over Raney Ni W-7 (14 g) in the presence of $NaHCO_3$ (1 g) at room temp for 3 hr under atm press. After filtration, the solvent was removed *in vacuo* to give an oil (1·1 g, 76%); ν_{max} (film) 1770, 1718 cm^{-1}. This was employed for the next step without further purification.

Methyl (±)-8β-β-hydroxyethyl-14β-hydroxy-5β,9β,10α-podocarpan-19-oate (XXXIV)

$NaBH_4$ (4 g) was added to an ice-cooled soln of the oily XXXIII (1·0 g) in 99% EtOH (40 ml). After standing overnight at room temp the excess borohydride was destroyed by dil HCl, and the product was taken into EtOAc. The extract was washed with dil KOH aq, dried (K_2CO_3) and concentrated to give XXXIV (800 mg, 80%). It crystallized from EtOAc as rods, m.p. 190–191°; ν_{max} (Nujol) 3250 (broad), 1725 cm^{-1}. (Found: C, 71·09; H, 10·18. $C_{20}H_{34}O_4$ requires: C, 70·97; H, 10·13%).

Methyl (±)-8β-carboxymethyl-14-oxo-5β,9β,10α-podocarpan-19-oate (XXXV)

(a) Compound XXX (21 mg) in acetone (3 ml) was treated with the Jones reagent (0·05 ml) for 10 min at room temp. The mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$) and concentrated to give 15 mg of XXXV. Recrystallization from EtOAc–petrol gave leaflets, m.p. 201–202°; ν_{max} (Nujol) ~2700, 1725, 1705, 1695 (sh) cm^{-1}. (Found: C, 68·63; H, 8·59. $C_{20}H_{30}O_5$ requires: C, 68·54; H, 8·63%).

(b) The diol XXXIV (800 mg) in acetone (150 ml) was treated with the Jones reagent (2 ml) at 0–5°. After 40 min MeOH was added to the reaction mixture which was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was extracted with dil NaOH aq. The aqueous layer was acidified with HCl and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and evaporated to give 750 mg (90%) of XXXV. The identity was proved by IR comparison and m.m.p. As the neutral part, 50 mg of XXXIII was recovered.

(c) A soln of XXXIV (250 mg) in pyridine (3 ml) was added to the Sarett reagent prepared from CrO_3 (500 mg) and pyridine (6 ml) at 0–5°. The mixture was left to stand at room temp for 20 hr. Then it was diluted with ice–water and ether and filtered through a small column of Celite. The ether layer was

separated, washed with water and 10% Na_2CO_3 aq, dried (Na_2SO_4) and concentrated to give XXXIII (150 mg). Acidification of the sodium carbonate soln gave XXXV (70 mg).

Methyl (±)-14-*oxo*-16ξ-*hydroxy*-17-*norkauran*-19-*oate* (XXXVI)

Compound XXX (1·3 g) dissolved in THF (30 ml) was added to a soln of NaOMe (from 1·0 g Na) in MeOH (40 ml). The mixture was refluxed for 2 hr under N_2. After concentration *in vacuo*, the residue was diluted with water and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1·25 g (96%) of an oil; ν_{max} (film) 3420, 1745, 1732 cm^{-1}. On one occasion, this crystallized after a long period of storage. Recrystallization from EtOAc-petrol gave rosettes of needles, m.p. 188–190°. (Found: C, 71·80; H, 8·86. $C_{20}H_{30}O_4$ requires: C, 71·82; H, 9·04%).

Tetrahydropyranyl ether of methyl (±)-14-*oxo*-16ξ-*hydroxy*-17-*norkauran*-19-*oate* (XXXVII)

A soln of XXXVI (1·229 g) in dry benzene (50 ml) was mixed with dihydropyran (4 ml) and *p*-toluenesulfonic acid (50 mg) and stirred overnight at room temp. Then the soln was washed with K_2CO_3 aq, dried (K_2CO_3) and concentrated *in vacuo*. Trituration of the residue with petrol afforded 452 mg (30%) of crystals. Recrystallization from MeOH gave rods, m.p. 165–166°; ν_{max} (Nujol) 1745, 1725, 1242, 1198, 1140, 1026, 1015 cm^{-1}. (Found: C, 71·68; H, 9·12. $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%).

(±)-16ξ-*Hydroxy*-17-*norkauran*-19-*oic acid* (XXXVIII)

To a soln of Na (1·1 g) in anhyd diethylene glycol (90 ml), anhyd hydrazine (25 ml) and XXXVII (1·318 g) was added and the mixture heated under reflux for 18 hr at 180° (bath temp). Then the bath temp was raised to 210–220° to distill off the excess of hydrazine. The mixture was kept at this temp for 24 hr. After cooling, water and conc HCl (20 ml) was added and the mixture was heated on a boiling water bath for 5 min. The crystalline acid thus formed was extracted with a large volume of EtOAc. The extract was concentrated *in vacuo* to give 699 mg (74%) of XXVIII. Recrystallization from EtOAc gave prisms, m.p. 281–282°; ν_{max} (Nujol) 3390, ~3200–~2400, 1708, 1270, 1260, 1030, 1020 cm^{-1}. (Found: C, 74·42; H, 9·58. $C_{19}H_{30}O_3$ requires: C, 74·47; H, 9·87%).

(+)-16-*Oxo*-17-*norkauran*-19-*oic acid* (XXXIX)

Jones chromic acid reagent (1·2 ml) was added to an ice-cooled soln of XXXVII (620 mg) in acetone (400 ml) and the mixture left to stand at room temp for 10 min. MeOH was added to destroy the excess of the oxidant. After the removal of the solvents *in vacuo*, the residue was diluted with water and the ppt was collected (603 mg; 97%). Recrystallization from THF-petrol gave fine rosettes of needles, m.p. 247–248°; ν_{max} (Nujol) ~3200–~2400, 1743, 1700; ($CHCl_3$) ~3200–~2400, 1740, 1698 cm^{-1}. The authentic (−)-acid exhibited an entirely identical IR spectrum (in $CHCl_3$). (Found: C, 74·60; H, 9·22. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%).

Methyl (±)-16-*oxo*-17-*norkauran*-19-*oate* (XL)

The acid XXXIX (143 mg) suspended in EtOAc was treated with ethereal diazomethane and the mixture left for 30 min at room temp. A small amount of AcOH was added to destroy the remaining diazomethane. Then the soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give XL (150 mg, 99%) which recrystallized from MeOH as needles, m.p. 127–128°; ν_{max} (Nujol) 1745, 1728; ($CHCl_3$) 1738, 1726 cm^{-1}. The IR spectrum (in $CHCl_3$) was superimposable on that of the authentic (−)-ester. (Found: C, 75·81; H, 9·59. $C_{20}H_{30}O_3$ requires: C, 75·43; H, 9·50%).

Methyl (±)-16-*ethylenedioxy*-17-*norkauran*-19-*oate* (XLI)

To a soln of XL (617 mg) in anhyd dichloroethane (100 ml) ethylene glycol (5 ml) and *p*-toluenesulphonic acid (50 mg) was added and the mixture stirred and heated under reflux for 2 hr. During that period anhyd dichloroethane (about 300 ml) was gradually added while an equal amount of the water-containing solvent was distilled off from it. After cooling, the soln was washed with K_2CO_3 aq, dried over K_2CO_3 and concentrated *in vacuo* to give XLI (610 mg, 90%) which recrystallized from EtOAc-petrol as elongated prisms, m.p. 133–134°; ν_{max} (Nujol) 1736, 1153, 1110, 1025 cm^{-1}. (Found: C, 72·78; H, 9·30. $C_{22}H_{34}O_4$ requires: C, 72·89; H, 9·45%).

(±)-16-*Oxo*-17-*norkauran*-19-*ol* (XLII)

A soln of XLI (600 mg) in dry THF (30 ml) was added to a soln of LAH (300 mg) in dry ether (50 ml).

The mixture was stirred and heated under reflux for 1·5 hr. After cooling, the excess hydride was destroyed by the addition of EtOAc. Dilute HCl (3 ml conc HCl in 30 ml H_2O) added while heating at 100° for 10 min with concommitant removal of ether. THF resulted in the removal of the ethylene ketal protective group. After cooling, the product was taken into EtOAc. The extract was washed with brine, dried over K_2CO_3 and concentrated *in vacuo* to give 470 mg (98%) which recrystallized from benzene–petrol as needles, m.p. 155–156°; ν_{max} (Nujol) 3460, 1735, 1038, 1008; (CS_2) ca. 3650, 1747, 1028, 1007 cm^{-1}. (Found: C, 78·82; H, 10·19. $C_{19}H_{30}O_2$ requires: C, 78·57; H, 10·41%).

(±)-*Kaur*-16-*en*-19-*ol* (II)

To a stirred suspension of triphenylmethylphosphonium bromide (5·8 g) in dry THF (120 ml) an ethereal soln of n-BuLi (prepared from 0·42 g Li and 3·4 g n-BuBr in 15 ml ether) was added and the stirring continued for 1 hr. The ketol XLII (450 mg) in dry THF (30 ml) was added to the stirred soln of the orange-colored phosphorane at room temp. The mixture was stirred and heated under reflux for 8 hr. Subsequently acetone was added to destory the excess phosphorane and the heating and stirring was continued for a further 0·5 hr. All the operations were carried out under N_2 atm. The solvents were removed from the mixture *in vacuo*. Ether and water were added to the residue. The ether layer was washed with water followed by brine, dried over K_2CO_3 and concentrated *in vacuo* to give a semi-solid mass. This was chromatographed on alumina (2·5 × 18 cm) in benzene to give the following fractions (200 ml each). No. 1–3 (benzene): triphenylphosphine oxide (2·3 g). No. 4–7 (benzene): a mixture of triphenylphosphine oxide and the kaurenol. No. 8–10 (benzene:ether 3:1): a mixture of triphenylphosphine oxide and the kaurenol. No. 11 (benzene:ether 3:1): gum. The semi-solid mixture obtained from No. 4–10 was recrystallized from MeOH–water to give 219 mg (47%) of the product. Recrystallization from MeOH–water afforded needles, m.p. 144–145°; ν_{max} (Nujol) ca. 3320 broad, 3060, 1662, 1023, 1014, 1005, 870; (CS_2) ca. 3650, 3060, 1658, 1026, 1014, 1006, 874 cm^{-1}. (Found: C, 83·51; H, 10·93. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%).

Methyl (+)-14,16-*dioxo*-17-*norkauran*-19-*oate* (XLIII)

To a soln of oily XXXVI (2 g) in acetone (200 ml) Jones chromic acid reagent (5 ml) was added dropwise at 3–5°. The mixture was kept at this temp for 10 min after the addition. Then MeOH was added to destroy the remaining oxidant and the mixture was concentrated *in vacuo*. Water was added to the residue and the product was extracted with EtOAc–ether. The extract was washed with water, $NaHCO_3$ aq and sat brine. The dried ($MgSO_4$) soln was concentrated *in vacuo*. Trituration of the residue with ether gave 1·4 g (70%) of the product. Recrystallization from EtOAc gave needles, m.p. 218–219°; ν_{max} (Nujol) 1758, 1730, 1722 (sh), 1240, 1190, 1152 cm^{-1}. (Found: C, 72·15; H, 8·20. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49%).

Methyl (±)-14-*oxokaur*-16-*en*-19-*oate* (XLIV)

Triphenylmethylphosphonium bromide (10·5 g) was added to a soln of t-BuOK (from 1 g of K) in t-BuOH (40 ml) and dry THF (40 ml). The mixture was stirred and heated under reflux for 1 hr and then cooled to room temp. A soln of the XLIII (1·0 g) in dry THF (40 ml) was added to the stirred phosphorane soln. The stirring was continued for 2 hr at 60–80°. All the operations were carried out under N_2 atm. After cooling, the reaction mixture was diluted with water (50 ml) and concentrated *in vacuo*. To the residue were added n-hexane (150 ml) and 80% MeOH (32 ml MeOH and 8 ml water). The n-hexane layer was separated and washed with 80% MeOH (30 ml), water and sat brine. The dried ($MgSO_4$) extract was concentrated *in vacuo*. Trituration of the residue with MeOH gave 224 mg (22%) of the desired olefin which recrystallized from MeOH as needles, m.p. 138–140°; ν_{max} (Nujol) 1730, 1660, 1145, 1138, 894 cm^{-1}; δ ($CDCl_3$), TMS as internal standard at 100 Mc) 0·70 (3H, s), 1·19 (3H, s), 3·64 (3H, s), 4·90 (2H, broad) ppm. (Found: C, 75·94; H, 9·00. $C_{21}H_{30}O_3$ requires: C, 76·32; H, 9·15%).

(±)-*Kaur*-16-*en*-19-*oic acid* (I)

To a soln of Na (200 mg) in freshly distilled diethylene glycol (15 ml) anhyd hydrazine (5 ml) and XLIV (183 mg) was added. The bath temp was maintained at 160° for 18 hr, and then raised to 210° to remove the excess hydrazine. The mixture was heated at 210° for 24 hr. After cooling, the mixture was acidified with dil AcOH and extracted with EtOAc. The extract was washed with water and sat brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with MeOH to give 58 mg (33%) which recrystallized from MeOH as prisms, m.p. 232–234° (dec) with previous softening; ν_{max} (Nujol) 1690, 1660, 871 cm^{-1}; δ ($CDCl_3$, TMS as internal standard at 100 Mc) 0·96 (3H, s), 1·24 (3H, s), 2·04 (2H, s C-15 CH_2), 2·60 (1H,

broad, C-13 CH), 4·71 (2H, broad, $=CH_2$) ppm. The NMR spectrum was identical with that of the natural product. (Found: C, 79·24; H, 9·46. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

(±)-16β-*Kaurane*-17,19-*diol* (XLV)

To a soln of II (35 mg) in dry THF (15 ml) $NaBH_4$ (50 mg) and BF_3-Et_2O (0·2 ml) was added. The mixture was left at room temp for 2 hr and then heated at 50–60° for 1 hr after the addition of 10% NaOH aq (1 ml) and 30% H_2O_2 (0·5 ml). Ether and brine were added to the mixture and the ether layer was separated. The ether extract was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (35 mg); ν_{max} (film) ~3300, 1035, 1010 cm^{-1}. No absorption was observed at 875 cm^{-1} (=CH_2). This was employed for the next reaction without further purification.

(±)-16β-*Kaurane*-17,19-*dioic acid* (XLVI)

To a soln of oily XLV (34 mg) in acetone (150 ml) Jones chromic acid reagent (0·3 ml) was added and the mixture left to stand at room temp for 18 hr. The solvent was removed *in vacuo* and the residue was diluted with water and EtOAc. The EtOAc layer was separated, washed with sat brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 20 mg which recrystallized from MeOH as fine prisms, m.p. 279–280°; ν_{max} (Nujol) ~3200–~2600, 1705, ~940 cm^{-1}. (Found: C, 71·91; H, 8·75. $C_{20}H_{30}O_4$ requires: C, 71·82; H, 9·04%).

Methyl (±)-16β-*kaurane*-17,19-*dioate* (XLVII)

The diacid XLVI (10 mg) suspended in EtOAc (3 ml) was treated with ethereal diazomethane. The solvent was removed *in vacuo* and the residue was recrystallized from petrol as needles, m.p. 165–166°; ν_{max} (Nujol) 1740, 1722, 1190, 1160, 1154; (CS_2) 1734, 1235, 1214, 1190, 1175, 1160, 1152 cm^{-1}.

Methyl (±)-16α-*kaurane*-17,19-*dioate* (XLVIII)

The diester XLVII (6 mg) dissolved in MeOH (2 ml) containing NaOMe (from ca. 30 mg Na) was heated under reflux for 15 min and MeOH removed *in vacuo*. Dil HCl was added to the residue and the mixture was extracted with ether. The extract was dried ($MgSO_4$), treated with ethereal diazomethane and evaporated. The residue was recrystallized from petrol to give crude XLVIII (4 mg), m.p. 79–83°; ν_{max} (CS_2) 1734, 1236, 1193, 1176 (sh), 1168 (sh), 1152, 1026 cm^{-1}. This spectrum was superimposable on that of the (−)-diester.

(±)-*Kaur*-16-*en*-19-*ol acetate* (LI)

To a soln of II (110 mg) in dry pyridine (10 ml) Ac_2O (10 ml) was added. The mixture was left to stand overnight at room temp. The solvents were removed *in vacuo*. The residue was recrystallized from MeOH to give 112 mg (92%) which recrystallized from MeOH as rosettes of needles, m.p. 89–90°; ν_{max} (Nujol) 1742, 1662, 1252, 1035, 870 cm^{-1}. (Found: C, 79·74; H, 10·44. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%).

(±)-*Kaur*-15-*en*-19-*ol* (LII) *and* (±)-*monogynol* (LIII)

The acetate LI (150 mg) and I_2 (ca. 30 mg) were dissolved in xylene (30 ml) and the soln was heated under reflux for 9 hr. After the removal of the solvent, the residue was dissolved in MeOH (10 ml) containing KOH (1 g). The soln was heated under reflux for 4 hr. Then MeOH was removed *in vacuo* and the residue was mixed with water and ether. The ether layer was dried over $MgSO_4$ and evaporated to give a crystalline mass. This was chromatographed on silica gel impregnated with $AgNO_3$[44] (1·5 × 27 cm) in petrol. The eluant was saturated with Ag ion by shaking with $AgNO_3$ aq in a separatory funnel prior to use. All fractions were 100 ml. Fractions No. 1–4: benzene:petrol = 1:2. Fraction 3 contained an unidentified substance (33 mg) which crystallized from MeOH as needles, m.p. 153–156°; ν_{max} (Nujol) 3300, 1022, 1015; (CS_2) ca. 3640, 1028, 1015 cm^{-1}. (Found: C, 83·48; H, 11·68. $C_{20}H_{34}O$ requires: C, 82·69; H, 11·80%). Fractions No. 5, 6: benzene:petrol = 5:3. Fraction 6 contained II (24 mg) which crystallized from MeOH as needles, m.p. 142–144°. This was identified by IR and m.m.p. Fractions No. 7, 8: benzene. Fractions No. 9–11: benzene:ether = 9:1. Fractions 9 and 10 crystallized from MeOH as needles of LII (49 mg), m.p. 162–163°; ν_{max} (Nujol) ~3300, ca. 3020, 1655, 1022, 1007, 815; (CS_2) ca. 3640, ca. 3020, 1655, 1025, 1007, 816 cm^{-1}. (Found: C, 83·22; H, 10·92. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%). Fraction 11 gave LIII (23 mg) as needles from MeOH, m.p. 123–124°; m.p. 123–124°; ν_{max} (Nujol) ~3280, ca. 3035, 1580, 1025, 749; (CS_2) ca. ~3640, ca. 3020, 1580, 1022, 750 cm^{-1}. This IR spectrum was identical with that of the natural product. (Found: C, 83·05; H, 10·87. $C_{20}H_{32}O$ requires: C, 83·27; H, 11·18%).

Gas chromatographic analysis

Compound		Retention times (min) 1·0% SE-30*	1·5% XE-60*	1% XE-61†	1·5% SE-30‡
XL	synthetic	10·4[a]			
	natural	10·4[a]			
XLVII	synthetic		23·6[b]	30·35[c]	48·3[d]
XLVIII	synthetic		23·4[b]	29·7[c]	47·8[d]
	natural		23·4[b]	29·7[c]	47·7[d]
LII	synthetic		24·8[e]	16·25[f]	
	natural		24·8[e]	16·25[f]	

All retention times were determined on Shimadzu Seidakusho model GCIC hydrogen flame detectors, stainless steel columns, * 180 cm × 4 mm i.d., † 400 cm × 3 mm i.d., ‡ 300 cm × 3 mm i.d. Column temp: [a] 192°; [b] 180°; [c] 190°; [d] 197°; [e] 160°; [f] 170°. Carrier gas: N_2. Flow rate of N_2 (ml/min): [a] 70; [b] 35; [c] 20; [d] 17·5; [e] 40; [f] 25. Press (kg/cm²): [b] 0·9; [c] 2·75; [d] 0·45; [e] 0·8; [f] 2·8.

Bioassay

Assay plants: dwarf maize (*Zea mays* L.) d_5 mutants.

Treatment: as a 10 μl drop of 90% ethanolic soln applied to the first leaf blade.

Measurement: 10 days after application. Lengths of the first and the second leaf sheath (average of 9 plants).

	(−)-Kaurenol		(±)-Kaurenol	(±)-Kaurenol acetate	Gibberellin C
Control	50 μg/plant	100 μg	100 μg	100 μg	100 μg
45·9 mm	70·6	84·1	69·4	84·8	115·6

	(−)-Kaurenoic acid	(±)-Kaurenoic acid	Compound XLIV	Gibberellic acid
Control	100 μg/plant	100 μg	100 μg	1 μg
29·2 mm	38·5	39·2	28·0	68·9

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