Tetrahedron. Vol. 32, pp 363 to 367 Pergamon Press 1976. Printed in Great Britain

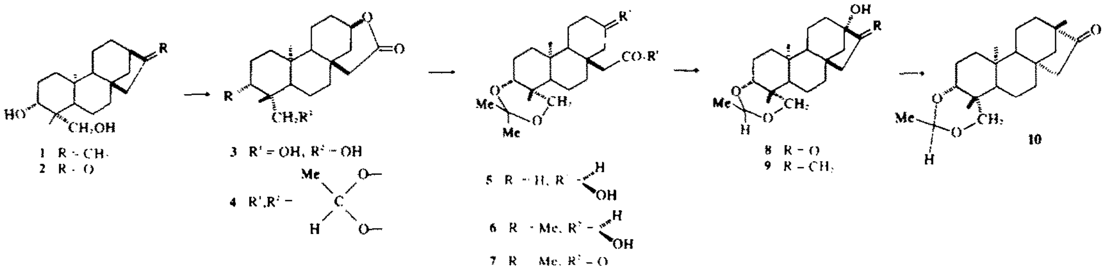
THE SYNTHESIS OF 13-HYDROXYLATED *ENT*-KAUR-16-ENE DERIVATIVES USING AN ACYLOIN-LIKE CYCLIZATION OF KETO ESTERS

I. F. COOK and J. R. KNOX
Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia, 6009

(*Received in UK* 17 *February* 1975; *Accepted for publication* 1 *July* 1975)

Abstract—The synthesis of steviol (**27**) and two A-ring modified analogues (**9** and **15**) is described. The synthetic sequences involve the preparation of suitably constituted 17-nor-13,16-seco-*ent*-kauranoid keto esters (**22**, **7** and **13**) which are then cyclized to 13,16-dioxygenated-17-nor-*ent*-kauranes (**23**, **8** and **14**).

Considerable interest has centered around the development of synthetic approaches leading to the 1 - hydroxy - 7 - methylenebicyclo[3.2.1]octane system,[1-8] as this grouping is a prominent feature of some gibberellins.[9] The sole naturally occurring *ent*-kaurene derivative of this type is steviol (**27**), the aglycone of stevioside obtained from *Stevia rebaudiana* Bertoni.[10] This paper deals with the synthesis of steviol (**27**) and of the related *ent*-kaurenes **9** and **15** using acyloin-like cyclizations. In this work model experiments were performed with the hydroxy-ene (**9**) which guided the subsequent synthesis of steviol (**27**) and of the diene-diol (**15**). This latter compound was of interest because it is the 13-hydroxylated analogue of the bioactive dienol (**17**) and it was considered likely to have gibberellin-like bioactivity. We have previously presented a brief communication on the synthesis of steviol.[11]



Scheme 1.

The scheme for the synthesis of the model compound **9** (Scheme 1) required the preparation of the seco-D-ring keto ester (**7**) which was then to be converted to the other key intermediate, the ketol (**7**). The naturally-occurring diol-ene (**1**)[12] was chosen as a suitable starting material for this synthesis. Lemieux-Johnson oxidation[13] of the diol-ene (**1**) gave the known *nor*-keto-diol (**2**) which, upon Baeyer-Villiger oxidation with perbenzoic acid and *p*-TsOH, formed the δ-lactone (**3**). The IR spectrum of this compound showed an absorption at 1725 cm^{-1} (δ-lactone).

Protection of the 1,3-diol system as a base-stable ethylidene group was achieved by treatment of the δ-lactone (**3**) with paraldehyde and conc. HCl. Alkaline hydrolysis of the product (**4**) followed by careful acidification and extraction then gave an ethereal solution of the hydroxy-acid (**5**) but concentration of this solution at room temperature induced relactonization. The hydroxy-acid was therefore treated *in situ* with diazomethane to yield the gummy hydroxy-ester (**6**). As attempts to purify this material also resulted in relactonization, it was directly converted to the keto-ester (**7**) by oxidation with chromium trioxide in pyridine. The IR spectrum of **7** showed absorptions at 1745 cm^{-1} (CO_2Me) and 1725 cm^{-1} (cyclohexanone).

Conditions for the cyclization of the keto-ester (**7**) were to some extent modelled on those used by Gutsche *et al.*,[14] as this work represents the only reported comprehensive study of the formation of fused ring structures via an acyloin-like cyclization.

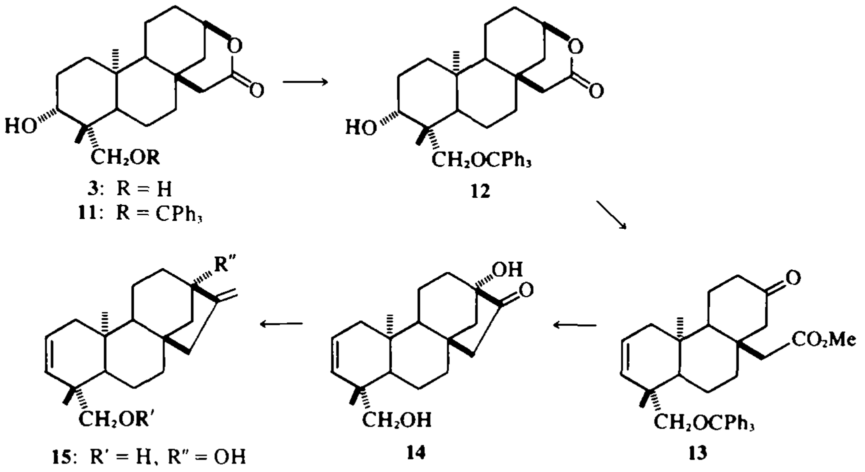
A full report of the conditions used and the major products obtained from the reaction of **7** and of **22** is presented in the following publication.[15] It was found that treatment of the keto-ester (**7**) with sodium naphthalenide in THF gave a complex mixture from which the desired ketol (**8**) could be isolated by chromatography. The IR spectrum of **8** showed absorptions at 3520 cm^{-1} (OH) and 1745 cm^{-1} (cyclopentanone).

Treatment of this compound with triphenylmethylene phosphorane under Wittig conditions gave a mixture from which the hydroxy-ene (**9**) was isolated in crystalline form. Although not isolated in pure form, a minor component from this reaction was considered, by analogy with previous work,[2] to be the 8,13-epimer of **9**, formed by the base-catalysed rearrangement of the ketol (**8**) under the Wittig conditions. The NMR spectrum of **9** showed one proton multiplets at δ 4·76 and 4·93 attributed to the C-17 vinylic protons. The IR spectrum showed absorptions at 3580 cm^{-1} (–OH) and 3080, 1660 and 890 cm^{-1} ($\rangle C{=}CH_2$).

The identity of the hydroxy-ene (**9**) was confirmed by steviol-isosteviol rearrangement[16] to the known ketone (**10**).

The key intermediate in the synthesis of the diene-diol (**15**) (Scheme 2) was seen to be the trityl ether (**13**). The trityl ether functionality was chosen because a base-stable protective group was required for the formation of the keto-ester grouping and because this group could be removed under the conditions of the reductive cyclization. The latter point was demonstrated by the quantitative conversion of the trityl ether (**16**) to the dienol (**17**) with sodium naphthalenide.

The starting material for the synthesis of **15** was the previously described δ-lactone (**3**). Attention was initially directed to the introduction of the Δ^2-double bond. For this purpose, the δ-lactone (**3**) was treated with triphenylmethyl chloride to give the monotrityl ether (**11**). The NMR spectrum of **11** showed a three proton singlet at δ 0·53 attributed to the 10-methyl group. The abnormally high field position of this resonance is due to a net shielding of the 10-Me group by the 19-trityl ether grouping.[17]



3: R = H
11: R = CPh₃
12
15: R′ = H, R″ = OH
16: R′ = CPh₃, R″ = H
17: R′ = H, R″ = H
14
13

Scheme 2.

Treatment of the monotrityl ether (**11**) with phosphorus oxychloride gave the alkene (**12**). The NMR spectrum of this compound showed a multiplet between 5·41 and 6·08 $\delta\ (\underset{H}{\diagup}C{=}C\underset{H}{\diagdown})$. This product was then converted by saponification, methylation and oxidation to the corresponding keto-ester (**13**).

The reductive cyclization of this compound was carried out with sodium naphthalenide under the conditions which had proved successful with **7**. A complex mixture was obtained from which the ketol (**14**) was isolated in poor yield. This compound was assigned an *ent*-norkaurane nucleus rather than the alternative *ent*-norbeyerane nucleus as the chemical shift of the 10-Me group was similar to that of the dienol (**17**) (Table 1).

Although no direct comparison could be made with *ent*-nor-beyerane compounds possessing the same A-ring substitution pattern, it is known that the 10-Me signal of *ent*-beyerane compounds occur at higher field than those of the corresponding *ent*-kaurane compounds.[18–21]

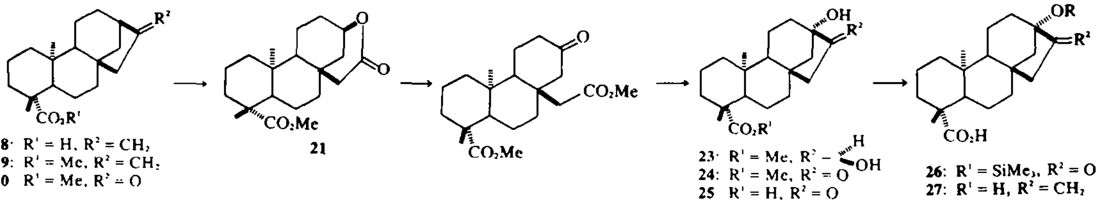
Table 1. Chemical shift of 10-methyl group (δ)

Dienol 17	1·05 (C_5D_5N) 1·08 ($CDCl_3$)
Ketol 14	1·13 (C_5D_5N)
Diene-diol 15	1·08 ($CDCl_3$)

From the model compound series it was known that some rearrangement of the ketol (**8**) took place during the Wittig reaction. To prevent this transformation the ketol (**14**) was reacted with trimethylsilyl chloride and hexamethyldisilazane. The resulting silyl ether derivative was then treated with triphenylmethylenephosphorane under Wittig conditions and the product heated with ethanol to give the diene-diol (**15**). The NMR spectrum of **15** showed multiplets at δ 4·86 and 5·03 ($>C{=}CH_2$) and the IR spectrum showed absorptions at 3550, 3480 cm^{-1} (OH) and 3080, 1660 and 890 cm^{-1} ($>C{=}CH_2$).

Bioassay of the diene-diol (**15**) in d − 1 maize showed that unlike the dienol (**17**), this material induced no growth response. This result is unexpected as steviol (**27**) and the corresponding 13-deoxy compound (*ent*-kaur-16-en-19-oic acid) have a similar level of bioactivity in mutant maize systems.[22,23]

For the synthesis of steviol (**27**) (Scheme 3), *ent*-kaur-

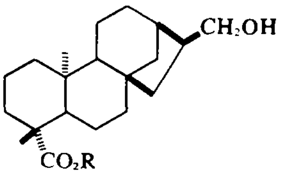


18: R′ = H, R² = CH₂
19: R′ = Me, R² = CH₂
20 R′ = Me, R² = O
21
23: R′ = Me, R² –
24: R′ = Me, R² = O
25 R′ = H, R² = O
26: R′ = SiMe₃, R² = O
27: R′ = H, R² = CH₂

Scheme 3.

16-en-19-oic acid (**18**) was chosen as starting material. Treatment of its methyl ester derivative (**19**) with ozone at −70° and oxidative work up with Jones reagent gave the known keto-ester (**20**).[19] Baeyer-Villiger oxidation of this compound gave the δ-lactone (**21**) which was converted by hydrolysis, methylation and oxidation to the known keto-diester (**22**).[24]

In view of the previous successful cyclizations and the fact that the hindered 19-methyl ester of **28** can be hydrolysed by treatment with sodium naphthalenide, it was expected that treatment of **22** under these cyclizing conditions would lead to the ketol-acid (**24**). However, treatment of the keto-diester (**22**) with sodium naphthalenide gave complex acidic and neutral fractions showing no detectable amounts of the required ketols (**24** or **25**) (NMR and TLC analysis). The failure of this approach prompted an investigation of the products resulting from the reductive cyclization of the keto-diester (**22**) with sodium-liquid ammonia. The full analysis of this reaction appears in the following publication.[15]



28: R = Me
29: R = H

It was found that, under controlled conditions, cyclization of the keto-diester (**22**) with sodium-liquid ammonia gave a 26% yield of the diol-acid (**23**). Careful oxidation of this compound with Jones reagent gave the ketol-acid (**24**). The IR spectrum of this compound showed absorptions at 3540 and 3350 cm^{-1} (OH), 1740 cm^{-1} (cyclopentanone) and 1695 cm^{-1} (CO_2H). The ketol-acid (**24**) was converted to the silyl ether (**26**) and then treated with triphenylmethylenephosphorane under Wittig conditions. Careful work up of the reaction product with dilute, ice-cold acid gave a product shown by comparison with an authentic sample to be steviol (**27**).

EXPERIMENTAL

For general experimental details see Ref. 25. Mass spectra were measured with a Varian MAT CH-7 using a direct insertion probe at the minimum temperature necessary to obtain a measurable spectrum.

Synthesis of ent-3β,19-*ethylidenedioxy*-13-*hydroxykaur*-16-*ene* (9)

ent-3β,19-*dihydroxy*-17-*nor*-*kauran*-16-*one* (2). To an aqueous dioxan (1:3, 1 l) soln of **1** (16·2 g) was added OsO_4 (150 mg) and $NaIO_4$ (26 g). The soln was stirred at r.t. for 16 hr and then worked up with ether to give a residue (15·7 g). Chromatography of this residue on Al_2O_3 (150 g) and elution with ether gave **2** (13·5 g), which crystallized from aqueous MeOH as plates, m.p. 202–204°, $[\alpha]_D$ −24° (*c*, 1·5), m.m.p. 203–204° (lit.[12] 203–204°, $[\alpha]_D$ −21°).

ent - 3β,13α,19 - *Trihydroxy* - 17 - *nor* - 13,16 - *seco*-*kauran* - 16-*oic acid* 16→13 - *lactone* (3). The keto-diol **2** (12·2 g) in a 1·85 M soln of $PhCO_3H$ in $CHCl_3$ (650 ml), containing *p*-TsOH (150 mg) was set aside at 0° for 3 days. Work up with $CHCl_3$ gave a residue (11·9 g) which was filtered through Al_2O_3 (100 g) in ether. The *δ-lactone* (3, 9·2 g) thus obtained crystallized from aqueous-MeOH as needles, m.p. 189–190°, $[\alpha]_D$ −52° (*c*, 0·9). (Found: C, 66·8; H, 9·4. $C_{19}H_{30}O_4$. H_2O requires: C, 67·0; H, 9·5%), ν_{max} ($CHCl_3$) 1725 cm^{-1}.

ent - 3β,19 - *Ethylidenedioxy* - 13α - *hydroxy* - 17 - *nor* - 13,16 - *seco*-*kauran* - 16 - *oic acid* 16→13-*lactone* (4). The δ-lactone **3** (8·3 g) was suspended in dry ether (250 ml) and treated for 1 hr with paraldehyde (15 ml) and conc. HCl (1 ml). Work up of the mixture gave a residue which crystallized from benzene-light petroleum to give **4** (7·4 g) as needles, m.p. 192–193°, $[\alpha]_D$ −32° (*c*, 0·83) (Found: C, 72·2; H, 9·3. $C_{21}H_{32}O_4$ requires: C, 72·4; H, 9·3%). ν_{max} 1730 cm^{-1} NMR (δ): 1·16, 1·38 (3° Me); 1·29 (d, J = 7 Hz, 2°Me); an AB pattern, 3·42, 4·12, (J = 11 Hz, $-\underline{CH_2}-O-$), 4·96 (1H, q, J = 7 Hz, $\left.\begin{matrix}-O\\ \\-O\end{matrix}\right\rangle CH\underline{Me}$).

Methyl - ent - 3β,19 - *ethylidenedioxy* - 13 - *oxo* - 17 - *nor* - 13,16 *seco*-*kauran* - 16 - *oate* (7). The δ-lactone **10** (6·1 g) was dissolved in a soln of MeOH (200 ml) and KOH (14·0 g) and heated under reflux for 16 hr. The mixture was diluted with water and extracted with ether. The aqueous fraction was carefully acidified with ice cold 2 N HCl (125 ml) and extracted with ether. The dried organic phase (Na_2SO_4) was treated with an ethereal soln of diazomethane. Work up in the usual way gave **12** (5·9 g) which was dissolved in dry pyridine (65 ml) and added to a suspension of CrO_3 (3·9 g) in cold pyridine (42 ml). After 14 hr at r.t. the mixture was worked up with ether and the residue crystallized from benzene-light petroleum to give the *keto-ester* (7, 4·3 g) as rosettes of needles, m.p. 201–202°, $[\alpha]_D$ −32° (*c*, 1·4) (Found: C, 70·2; H, 9·2. $C_{22}H_{34}O_5$ requires: C, 69·8; H, 9·1%) ν_{max} 1745, 1725 cm^{-1} NMR (δ): 1·08, 1·38 (3°Me), 1·29 (J = 7 Hz, 2°Me), 3·73 ($CO_2\underline{CH_3}$), an AB quartet 3·42, 4·12, (J = 11 Hz, $-CH_2O-$), 4·96 (1H, q, J = 7 Hz, $\left.\begin{matrix}-O\\ \\-O\end{matrix}\right\rangle CHMe$).

ent - 3β,19 - *Ethylidenedioxy* - 13 - *hydroxy* - 17 - *nor*-*kauran* - 16 - *one* (**8**). The keto-ester 7 (1·1 g) in dry THF (100 ml) was added to a mixture of Na (400 mg), naphthalene (2·4 g) and THF (300 ml) which had been stirred for 1 hr, under N_2. After 14 hr the reaction was terminated with CH_3CO_2H (15 ml) and worked up with ether to give a residue (3·3 g). Chromatography of this on Al_2O_3 (105 g) and elution with ether gave a brown gum which crystallized from benzene-light petroleum to give **8** (191 mg) as rosettes of needles, m.p. 180–181°, $[\alpha]_D$ −51° (*c*, 1·1) (Found: C, 72·2; H, 9·3. $C_{21}H_{32}O_4$ requires: C, 72·4; H, 9·3%), ν_{max} 3520, 1745 cm^{-1}. NMR (δ): 1·16, 1·35 (3°Me), 2·05 (s, $-C\underline{H}_2\underset{|}{C}{=}O$) MS: *m*/*e* 348 (48, M$^+$), 333 (32), 305 (100), 304 (84), 287 (19), 261 (42).

ent - 3β,19 - *Ethylidenedioxy* - 13 - *hydroxy-kaur* - 16 - *ene* (9). The ketol **8** (105 mg) was added in dry THF (20 ml) to a mixture of t-BuO^-K^+ (225 mg), triphenylmethylphosphonium iodide (800 mg) t-BuOH (4 ml) and THF (70 ml) which had been stirred for 1 hr under N_2. After 15 hr the mixture was worked up with ether to give a residue (210 mg). Preparative TLC of the residue gave a gum (75 mg) which crystallized from benzene-light petroleum to give the *hydroxy-ene* (9, 37 mg) as plates, m.p. 146–148°, $[\alpha]_D$ −31° (*c*, 1·2). (Found: C, 76·0; H, 9·8. $C_{22}H_{34}O_3$ requires: C, 76·3; H, 9·9%), ν_{max} 3580, 3080, 1660, 890 cm^{-1}. NMR (δ): 1·08, 1·33 (3°Me) 4·76, 4·93 (1H, $W_{h/2}$ = 3 Hz, $\rangle C{=}CH_2$). MS: *m*/*e* 346 (28, M$^+$), 331 (32), 302 (100), 284 (21), 272 (14).

ent - 3β,19 - *Ethylidenedioxy-beyeran* - 16 - *one* (**10**). The hydroxy-ene **9** (13 mg) was dissolved in MeOH (3 ml) and 2 N HCl (1 ml), and the mixture heated under reflux for 4 hr. The product (12 mg) was reacted with paraldehyde (1 ml) and conc. HCl (3 drops) in dry ether (3 ml) for 1 hr. Preparative TLC of the product with benzene–EtOAc (4:1) gave a gum which crystallized from MeOH aq to give **10** (3 mg) as plates, m.p. and m.m.p. 183–185° [lit.[26] m.p. 183–185°].

Synthesis of ent - *kaura* - 2,16 - *diene* - 13,19 - *diol* (15)

ent - *Trityloxy* - 3β,13α - *dihydroxy* - 17 - *nor* - 13,16 - *seco*-*kauran* - 16 - *oic acid* 16→13-*lactone* (**11**). The δ-lactone **3** (12·1 g) was dissolved in dry pyridine (100 ml) Ph_3CCl (14 g) added and the mixture heated on a steam bath for 8 hr. The mixture was worked up in the usual way to give a residue (25·2 g) which was chromatographed on Al_2O_3 (250 g). Elution with 1:1 benzene–light petroleum gave **11** (12·6 g) which crystallized from benzene-petrol as cubes, m.p. 241–242°, $[\alpha]_D$ −124° (*c*, 0·93) (Found: C, 80·7; H, 7·7. $C_{38}H_{44}O_4$ requires: C, 80·8; H, 7·9%), ν_{max} 3510, 3090, 3015, 1730, 770, 760, 740, 700 cm^{-1}; NMR (δ): 0·53, 1·56 (3°Me), an AB quartet 3·11, 3·45 (J = 11 Hz, $\underline{CH}_2O$–), 3·25 (1H, m, $W_{h/2}$ = 10 Hz, $>$C$\underline{H}$OH), 7·35 (15H, m, Ph$\underline{H}$).

ent - 19 - *Trityloxy* - 13α - *hydroxy* - 17 - *nor* - 13,16 - *seco-kaur* - 2 - *en* - 16 - *oic acid* 16→13-*lactone* (**12**). The ether **11** (8·1 g) was dissolved in dry pyridine (55 ml) and $POCl_3$ (9·7 g), and left for 12 hr at r.t. The mixture was then heated for 1 hr at 95°, cooled and poured into cold 8% $NaHCO_3$ aq. Work up with ether gave a residue (6·51 g) which was filtered through Al_2O_3 in ether to give the *alkene* (**12**, 5·92 g) which crystallized from benzene–light petroleum as clumps, m.p. 239–240°, [α] −100° (*c*, 1·15) (Found: C, 83·5; H, 7·5. $C_{38}H_{42}O_3$ requires: C, 83·5; H, 7·7%), ν_{max} 3090, 3060, 3015, 1730, 770, 760, 740, 700 cm^{-1}, NMR (δ): 0·70, 1·20 (3°Me), an AB quartet 2·83, 3·25 (J = 11 Hz, $-\underline{CH}_2$–OR) 5·41–6·08 (2H, m, H-2, H-3), 7·35 (15H, Ph$\underline{H}$).

Methyl ent-19-*trityloxy*-13-*oxo*-17-*nor*-13,16-*seco-kaur*-2 - *en* - 16 - *oate* (**13**). The alkene **12** (5·81 g) was dissolved in methanolic NaOH (5% w/v, 200 ml) and heated under reflux for 12 hr. The mixture was worked up as previously described and methylated with diazomethane. The product (5·6 g) was dissolved in pyridine (50 ml) and added to a suspension of CrO_3 (3·2 g) in pyridine (40 ml). After 14 hr the mixture was worked up in the usual way to give a residue (4·2 g) which was filtered through Al_2O_3 in benzene to give the *keto-ester* (**13**, 3·6 g) as a non-crystallizable gum. (Found: C, 81·0; H, 7·5. $C_{39}H_{44}O_4$ requires: C, 81·2; H, 7·7%), ν_{max} 1740, 1725 cm^{-1}. NMR (δ): 0·70, 1·19 (3°Me), 3·53 ($CO_2\underline{CH}_3$) 7·35 (15H, Ph$\underline{H}$).

Reductive hydrolysis of a model 19-*trityl ether* (**16**). The dienol **17** (1·2 g) was converted to **16** (1·8 g) by treatment with Ph_3CCl (2·1 g) by the previously discussed method. The ether **16** was a noncrystallizable gum; ν_{max} 3075, 3060, 3015, 1665, 770, 760, 740, 700 cm^{-1}, NMR (δ): AB quartet 2·80, 3·25 (J = 11 Hz, $-\underline{CH}_2$–OR); 7·35 (15H, $\underline{ArH}$).

The tritylether in THF (100 ml) was added to a mixture of Na (1·7 g), naphthalene (10·3 g) and THF (100 ml) which had been stirred for 1 hr under N_2. After 15 hr the mixture was worked up in the usual way to give a residue (11·2 g) which was chromatographed on Al_2O_3 (150 g). Elution with benzene gave **17** (365 mg), m.p. and m.m.p. 73–74° [lit.[27] m.p. 73–75°].

ent - 13,19 - *Dihydroxy* - 17 - *nor-kaur* - 2 - *en* - 16 - *one* (**14**). The keto-ester **13** (800 mg) was reacted with a mixture of Na (25 g), naphthalene (15 g) and THF (150 ml) as previously described for **7**. The product (153 g) obtained was chromatographed on Al_2O_3 (150 g). Elution with ether–MeOH (4 : 1 to 1 : 1) gave crude fractions containing **14**. Preparative TLC of these fractions gave **14** (19 mg) which crystallized from aqueous MeOH as needles, m.p. 219–221°, $[\alpha]_D$ −62° (*c*, 0·92); (Found: C, 74·8; H, 9·2. $C_{19}H_{28}O_3$ requires: C, 75·0; H, 9·3%), ν_{max} ($CHCl_3$) 3540, 3500, 1740 cm^{-1}; NMR (δ, C_5D_5N): 1·13, 1·30 (3°Me), 2·05 (2H, s, $-\underline{CH}_2C{=}O$), and AB quartet at 3·66 and 4·00 (J = 11 Hz, $-\underline{CH}_2$–OR), 5·16→6·16 (2H, m, H-2, H-3) MS: *m/e* 304 (9, M$^+$), 289 (2), 286 (5), 273 (100), 261 (12), 206 (31), 205 (63).

ent-*Kaura* - 2,16 - *dien* - 13,19 - *diol* (**15**). The ketol **14** (38 mg) was converted to its silyl ether derivative by reaction with hexamethyldisilazane (1 ml) and trimethylsilyl chloride (1 ml) in pyridine (10 ml) for 25 min. The mixture was concentrated and the product filtered through glass wool in dry benzene. Evaporation of the solvent gave the silyl ether derivative which was added in THF (10 ml) to $Ph_3P{=}CH_2$ prepared from K^+tBuO^- (100 mg), tBuOH (1·5 ml) and $Ph_3\overset{+}{P}CH_3\overset{-}{I}$ (400 mg) in THF (20 ml). Work up in the usual way gave a residue (75 mg) which was dissolved in EtOH (10 ml) and heated under reflux for 12 hr. The product was purified by preparative TLC (ether solvent) and then crystallized from MeOH aq to give **15** (12 mg) as needles, m.p. 159–161°, $[\alpha]_D$ −41°, (*c*, 0·42) (Found: 302·225; $C_{20}H_{30}O_2$ requires: 302·225), ν_{max} 3550, 3480, 890, 740 cm^{-1}. NMR: 1·08 (2 × 3°Me), an AB quartet 3·60, 3·95 (J = 11 Hz, $-\underline{CH}_2OR$), 4·86, 5·03 ($>$C=CH$_2$), 5·63 (2H, m, $w_{h/2}$ = 7 Hz, H-2, H-3). The *diene-diol* (**15**) was bioassayed in d − 1 maize using the method of Phinney;[28] it showed no leaf extension compared with the control whereas **17** showed a 20% increase at the same dose level (100 μg/plant).

Synthesis of ent - 13 - *hydroxy-kaur* - 16 - *en* - 19 - *oic acid* (27)

Methyl ent - 16 - *oxo* - 17 - *nor-kauran* - 19 - *oate* (**20**). The acid **18** (10·5 g) was methylated with CH_2N_2 to give **19** (10·7 g).[20] The ester in acetone (150 ml) was ozonized in batches (2·1 g) at −70°. After complete ozonolysis the mixture was warmed to r.t. and treated with Jones reagent (2·5 ml). After 1 hr the oxidation was terminated with EtOH and the product isolated with ether giving **20** (8·9 g) which crystallized from light–petroleum as plates m.p. and m.m.p. 142–143° [lit.[20] m.p. 142–143°].

ent - 13α - *Hydroxy* - 17 - *nor* - 13,16 - *seco-kauran* - 16,19 - *dioic acid* **16**→13-*lactone* 19-*methyl ester* (**21**). The nor-ketone **20** (8·9 g) was converted to **21** as for **2**→**3** using a 1·2 M soln of $PhCO_3H$ in $CHCl_3$ (420 ml) together with *p*-TsOH (120 mg). The δ-lactone (**21**, 7·1 g) thus obtained crystallized from benzene-light petroleum as needles m.p. 152–153° $[\alpha]_D$ −88° (*c*, 1·2) (Found: C, 71·5; H, 9·0. $C_{20}H_{30}O_4$ requires: C, 71·8; H, 9·0%), ν_{max} 1730, 1725 cm^{-1}. NMR (δ): 4·78 (1H, m, $w_{h/2}$ = 10 Hz, H-13).

Dimethyl ent - 13 - *oxo* - 17 - *nor* - 13,16 - *seco-kauran*-16,19 - *oate* (**22**). The δ-lactone **21** (6·3 g) was dissolved in methanolic KOH (10% w/v, 150 ml) and heated under reflux for 15 hr. The hydrolysis product was methylated and oxidized as previously described for **7** to give **22** (3·2 g) which crystallized from benzene-light petroleum as plates m.p. 117–119° $[\alpha]_D$ −49° (*c*, 1·0) (Found: C, 69·2; H, 8·7. $C_{21}H_{32}O_5$ requires: C, 69·2; H, 8·9%), ν_{max} 1745, 1725 cm^{-1}, NMR (δ): 0·95, 1·20 (3°Me), 3·62 (2 × $CO_2\underline{CH}_3$).

Model reductive hydrolysis of methyl ent-17-*hydroxy-kauran*-19 - *oate* (**28**). The ester[18] **28** (350 mg) was added to a mixture of Na (1·1 g), naphthalene (6·6 g) and dry THF (75 ml) which had been stirred for 1 hr under N_2. After 15 hr the mixture was worked up to a NaOH-soluble fraction (365 mg) which crystallized from MeOH to give **29** (205 mg) as needles, m.p. and m.m.p. 270–722° [lit.[18] m.p. 271–272°].

ent - 13,16α - *Dihydroxy* - 17 - *nor-kauran* - 19 - *oic acid* (**23**). The keto-diester **22** (400 mg) in dry THF (50 ml) was added to a mixture of Na (400 mg), liquid-NH_3 (150 ml) and THF (150 ml) which had been stirred for 15 min, under N_2. After 5 min the reaction was terminated with *t*-BuOH. The acidic fraction (6·01 g) from a number of such reactions (using a total of 6·8 g of **22**) was chromatographed on SiO_2 (200 g). Elution with benzene–ether gave the *diol-acid* (**23**, 0·85 g) which crystallized from benzene as needles, m.p. 265–267° $[\alpha]_D$ −82 (*c*, 1·32) (Found: C, 70·6; H, 9·3. $C_{19}H_{30}O_4$ requires: C, 70·8; H, 9·4%).

ent - 13 - *Hydroxy* - 16 - *oxo* - 17 - *nor-kauran* - 19 - *oic acid* (**24**). The diol-acid **23** (200 mg) in dry acetone (150 ml) was treated with Jones reagent[29] (0·4 ml) at −24° for 3 min. Propan-2-ol (2 ml) was then added and the reaction worked up in the normal way to give the *ketol-acid* (**24**, 180 mg) which crystallized from benzene as needles, m.p. 221–222°, $[\alpha]_D$ −96° (*c*, 0·93) (Found: C, 71·2; H, 8·6. $C_{19}H_{28}O_4$ requires: C, 71·2; H, 8·8%), ν_{max} (Nujol) 3540, 3350, 1740, 1695 cm^{-1}.

ent - 13 - *Hydroxykaur* - 16 - *en* - 19 - *oic acid* (**27**). The ketol acid **24** (160 mg) was converted to **26** as described for **14** using hexamethyldisilazane (2 ml), trimethylsilyl chloride (2 ml) and pyridine (20 ml). The product was a homogeneous (TLC) gum. ν_{max} 1740, 1700 cm^{-1}; NMR (δ): 0·18 (Me_3Si–).

The silyl ether **26** (171 mg) was added in THF (10 ml) to $Ph_3P{=}CH_2$ prepared from $tBuO^-K^+$ (300 mg), tBuOH (4 ml) and $Ph_3\overset{+}{P}CH_3\overset{-}{I}$ (1 g) in THF (50 ml). After 15 hr the mixture was worked up with ether and ice cold NHCl to give **27** (75 mg) which crystallized from MeOH aq as needles, 209–210°, $[\alpha]_D$ −91° (*c*, 1·2), m.m.p. 209–210° [lit.[10] m.p. 212–213°, [α] −93·6°]; ν_{max} (Nujol) 3450, 3270, 1695 cm^{-1} NMR (δ): 0·95, 1·21 (3°Me), 4·81, 5·00 (1H, m, H-17), 6·10 (2H, broad m, $CO_2\underline{H}$, O$\underline{H}$).

Acknowledgements—We are grateful to Dr. A. Duffield for precise mass measurements, Dr. A. McComb for bioassays and Dr. M. Ruddat for a sample of steviol.

REFERENCES

[1]G. Stork, S. Malhotra, H. Thompson and M. Uchibayashi, *J. Am. Chem. Soc.* **87**, 1148 (1965).

[2]R. A. Bell, R. E. Ireland and L. N. Mander, *J. Org. Chem.* **31**, 2536 (1966).

[3]E. J. Corey, M. Narisada, T. Kiraoka and R. A. Ellison, *J. Am. Chem. Soc.* **92**, 396 (1970).

[4]F. E. Ziegler and M. E. Condon, *J. Org. Chem.* **36**, 3707 (1971).

[5]F. E. Ziegler and J. A. Kloek, *Tetrahedron Letters* 2201 (1971).

[6]L. J. Dolby, S. Esfandiari, A. A. Elliger and K. S. Marshall, *J. Org. Chem.* **36**, 1277 (1971).

[7]K. Mori, Y. Nakahara and M. Matsui, *Tetrahedron* **28**, 3217 (1972).

[8]H. O. House, D. G. Melillo and F. J. Sauter, *J. Org. Chem.* **38**, 741 (1973).

[9]A. Lang, *Ann. Rev. Plant Physiol.* **21**, 537 (1970).

[10]E. Mosettig and W. R. Nes, *J. Org. Chem.* **20**, 884 (1955).

[11]I. F. Cook and J. R. Knox, *Tetrahedron Letters* 4091 (1970).

[12]G. V. Baddeley, P. R. Jefferies and R. W. Retallack, *Tetrahedron* **20**, 1983 (1964).

[13]R. Pappo, D. S. Allen, Jr., R. V. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).

[14]C. D. Gutsche, I. Y. C. Tao and J. Kocma, *J. Org. Chem.* **32**, 1782 (1967).

[15]I. F. Cook and J. R. Knox, *Tetrahedron* **32**, 369 (1976).

[16]J. F. King and P. de Mayo, *Molecular Rearrangements* (Edited by P. de Mayo), p. 830. Interscience, New York (1964).

[17]D. W. Mathieson, *Nuclear Magnetic Resonance for Organic Chemists*, p. 34. Academic Press, New York (1967).

[18]C. A. Henrick and P. R. Jefferies, *Austral. J. Chem.* **17**, 915 (1964).

[19]C. A. Henrick and P. R. Jefferies, *Tetrahedron Letters* 1507 (1964).

[20]P. R. Jefferies and T. G. Payne, *Austral. J. Chem.* **18**, 1441 (1965).

[21]G. V. Baddeley, M. W. Jarvis, P. R. Jefferies and R. S. Rosich, *Ibid.* **17**, 578 (1964).

[22]M. Ruddat, A. Lang and E. Mosettig, *Naturwissenschaften* **50**, 23 (1963).

[23]M. Katsumi, B. O. Phinney, P. R. Jefferies and C. A. Henrick, *Science* **144**, 849 (1964).

[24]E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt and J. A. Waters, *J. Am. Chem. Soc.* **85**, 2305 (1963).

[25]P. Coates, A. K. Goh, P. R. Jefferies, J. R. Knox and T. G. Payne, *Tetrahedron* **24**, 795 (1968).

[26]E. L. Ghisalberti and P. R. Jefferies, *Austral. J. Chem.* **19**, 1759 (1966).

[27]E. L. Ghisalberti, P. R. Jefferies and E. J. Middleton, *Ibid.* **22**, 455 (1969).

[28]B. O. Phinney, *Plant Growth Regulation*, p. 489. Iowa State Press, Ames, Iowa (1961).

[29]P. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953).