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BRIDGED-RING PRODUCTS FROM THE ACYLOIN-LIKE CYCLIZATION OF DITERPENOID KETO-ESTERS

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Abstract—Bridged-ring structures are readily formed from acyloin-like cyclization of suitably constituted keto esters. Thus reaction of the keto ester *ent*-seco-kauranoid derivatives **1** and **2** with Na– liquid NH_3 affords mixtures of *ent*-kaurane, *ent*-beyerane and dimeric products.

The previous paper[1] described the synthesis of several *ent*-13-hydroxykaur-16-ene derivatives from 13,16-dioxygenated *ent*-17-norkauranes obtained via acyloin-like cyclization of seco-keto ester precursors. The cyclization afforded complex mixtures of products and in the course of identifying the desired 13,16-dioxygenated compounds and optimizing their yield a variety of reaction conditions were studied and the major associated products identified. This paper presents evidence for the assigned structures of the products from Na–NH_3 cyclization of the keto esters **1** and **2** and reports the influence of reaction conditions on product distribution.

The distribution of the identified products for the various reactions of **1** and **2** are summarized in Table 1. Under the reaction conditions used for **2**, the 19-ester functionality was almost completely hydrolysed but the acidic products were not readily separable: only **8** and **27** could be recovered from the acidic products of reaction conditions 4 whereas **6**, **7**, **12**, **13** and **25** were recovered from the residue after methylation. Consequently the analyses of the product compositions from the various conditions used with **2** were carried out by methylating the acidic product using ^{14}MeI and then submitting the labelled product to TLC radioassaying. Under the conditions used the esters **7** and **13** could not be distinguished.

The products from cyclization of the two keto esters (**1** and **2**) fall into three categories: (a) *ent*-17-norkauranes, (b) *ent*-17-norbeyeranes, (c) dimeric products.

ent-17-*Nor-kauranes*. This group includes 17-nor-13,16-dioxygenated compounds which were obtained from both **1** and **2** (**3** and **4** from the former and **6**, **7** and **8** from the latter) together with 17-nor-16-oxygenated compounds (**9** and **10**) which were only obtained from **1**.

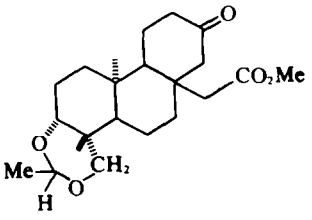
The chemical shifts of the 10-Me signals in the NMR spectra of the ethylidene compounds **3**, **4**, **9** and **10** (δ1·10, 1·07, 1·16, 1·06 respectively), the esters **6** and **7** (δ0·80, 0·80 respectively) and the acid **8** (δ1·20 in C_5D_5N) correlate with the corresponding signals for the known *ent*-kauranes **14**, **16** and **17** (δ1·10[3], 0·82[2], 1·22[5] respectively) thus demonstrating the *ent*-kaurane skeletons of the reaction products. These resonances occur at lower field than the 10-methyl resonances of the corresponding *ent*-beyerane products from the cyclizations (**11**, **12** and **13**; δ0·91, 0·70, 0·70 respectively) and of the known *ent*-beyerane **15** (δ0·93[4]) in accord with observations in other series.[2]

The mono-alcohol (**10**) showed a carbinol methine

Table 1. Product distribution from cyclization reactions[a]

Substrate	Reaction	Molar ratio (Na/keto ester)	Reaction time (Min)	Conc. of keto ester (mM)	Product (%)[b]
ethylidene keto ester (**1**)	1	200	30	1·3	**3**(20), **9**(19), **10**(29)
	2	30	30	0·8	**3**(14), **4**(5), **11**(16), **24**(5)
keto diester (**2**)	3	24	15[c]	3·1	**6**(22), **7** + **13**(tr), **12**(14), **25**(60)
	4	16	15[c]	3·1	**6**(27), **7** + **13**(3), **12**(10), **25**(54)[e]
	5	16	15[d]	3·1	**6**(26), **7** + **13**(tr), **12**(11), **25**(51)
	6	8	10[d]	3·1	**6**(11), **7** + **13**(tr), **12**(12), **25**(59)
	7	4	10[d]	3·1	**6**(14), **7** + **13**(tr), **12**(12), **25**(65)

[a] Reactions were conducted in NH_3/THF (1:2) and (3:4) for keto-esters (**1**) and (**2**) respectively.
[b] Yields are calculated from recovered products for the ethylidene keto ester (1) and from TLC radioscan of the ^{14}C-labelled esters derived from the product for **2**.
[c] Reaction terminated with t-BuOH.
[d] Reaction terminated with NH_4Cl.
[e] On a preparative scale, the acids **8** and **27** could be isolated prior to methylation.



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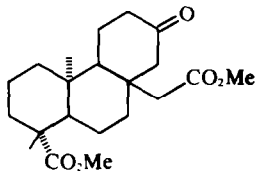

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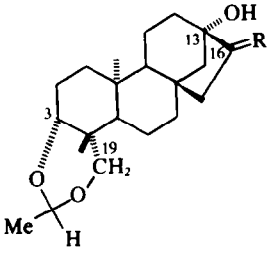
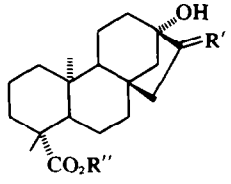




3: R= 

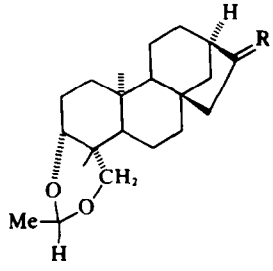
4: R= 

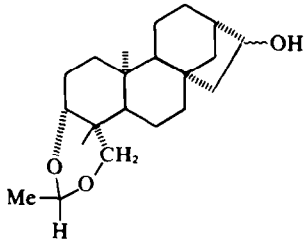
5: R = O

6: R′ =  , R″ = Me

7: R′ =  , R″ = Me

8: R′ =  , R″ = H





9: R = O

11

10: R = 

26: R = 

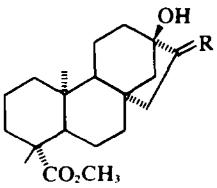
resonance at δ3·53 and IR absorption at 3590 cm^{-1} which is attributed to a secondary hydroxyl group. Oxidation of **10** with chromium trioxide-pyridine gave the known ketone **9**[3] which was also identified as a product from the reductive cyclization of the keto ester (**1**). This indicates that **10** is one of the epimeric *ent*-3β,19-ethylidenedioxy-17-nor-kauran-16-ols. Configurational assignment of the mono-alcohol (**10**) resulted from the reduction of the ketone (**9**) with $NaBH_4$, which gave an alcohol (**26**) possessing different physical properties to that of the mono-alcohol (**10**). Since this reagent is known to direct hydride attack from the less hindered α-face† to give the 16β (*endo*)-alcohol[9] the OH in **10** is assigned the 16α (*exo*)-configuration. Reduction of the ketone (**9**) with sodium-liquid ammonia gave a mixture from which the mono-alcohol (**10**) could be separated by column chromatography. This is consistent with the generally held view[10] that the more stable epimer is formed under these conditions.

The NMR spectra of the diols **3** and **4** showed carbinol methine resonances appearing as a doublet of doublets centered at δ4·50 and as a multiplet at δ3·64 respectively.

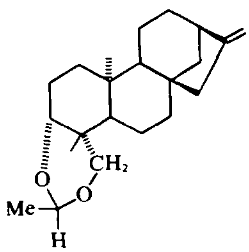
Separate oxidations of **3** and **4** with Jones reagent[11] gave the previously described ketol (**5**).[1] The structural identity of this compound has been established[1] by its conversion to the hydroxy-ene (**18**) and its subsequent rearrangement to the known ketone (**19**) via the steviol-isosteviol rearrangement.[12] This shows that the diols **3** and **4** are the epimeric *ent*-3β,19-ethylidenedioxy-17-nor-kauran-13,16-diols. Configurational assignment of these diols was based on their TLC mobility. The OH group of the less abundant, less polar diol **4** was assigned the 16α(*exo*)-configuration, since the intramolecular H-bonding expected between the *cis* (13α,16α)-OH groups would be expected to decrease the polarity of this compound.

The same polarity order was observed for the epimeric

†Although the systematic name of compounds in this paper follows the Rowe proposed system[6] in which an *ent* operator inverts the stereochemical designation of substituents we otherwise continue the recent practice[7,8] of specifying α- and β-stereochemistry according to the structural representations.



12: R = OH, H
13: R = O



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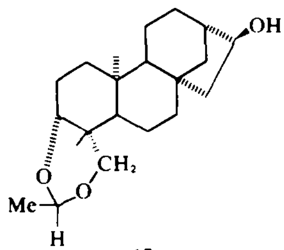

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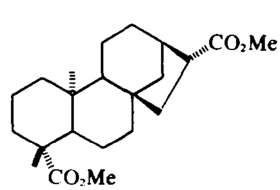

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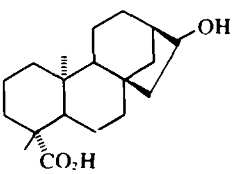

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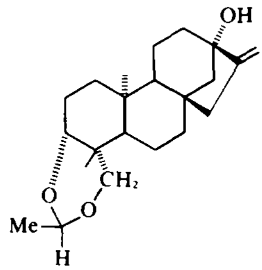

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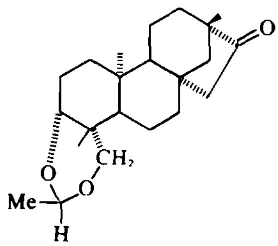

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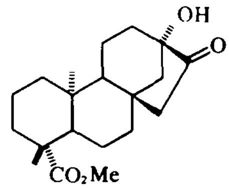

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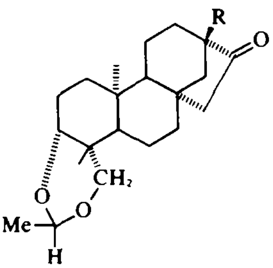
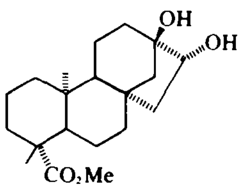


21: R = H
22: R = CO_2H



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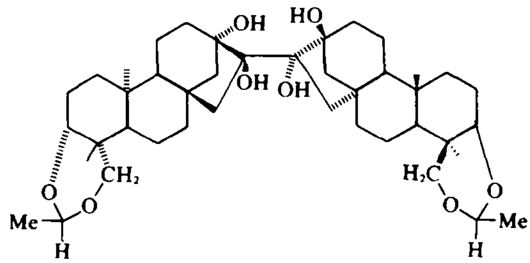

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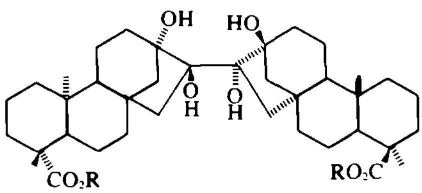
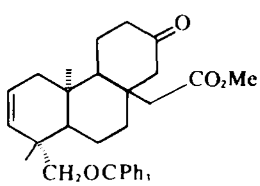


25: R = Me
27: R = H



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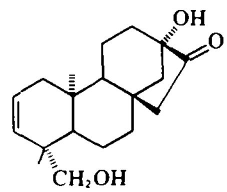

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diols **6** and **7** obtained in the 19-ester series. Furthermore, the more polar diol (**6**) in this latter series was the more abundant product from the cyclization reaction as was the case in the ethylidene series. Evidence for the structure of the diols **6** and **7** derives from their conversion to a common crystalline ketol ester (**20**) with Jones reagent. The physical constants of this compound closely matched those reported for **20**, obtained from ozonolysis of methyl steviate.[13]

Sodium borohydride reduction of **20** gave a diol-ester possessing identical physical properties to those of the more polar diol-ester (**6**), isolated from the cyclization of **2**. Since an inspection of molecular models of **20** suggested that borohydride complexing with the 13-OH should not reverse its preference for directing hydride attack from the less hindered α-face, the diol-ester (**6**) was assigned the 13,16β-configuration.

Treatment of the diol-acid (**8**) with CH_2N_2 gave the diol-ester (**6**), thus demonstrating its precursor relationship.

ent-17-*Nor-beyeranes.* The three members of this group (**11**, **12** and **13**) were assigned nor-beyerane skeletons on the basis of the chemical shift of their 10-Me groups which have already been discussed.

The mono-alcohol (**11**) was the sole *ent*-17-nor-beyerane derivative isolated from the ethylidene series. This compound showed a carbinol methine resonance at δ3·68 and IR absorption at 3620 cm^{-1} attributed to a secondary OH group. Oxidation of **11** with chromium trioxide-pyridine gave a ketone (**21**) which showed IR absorption at 1745 cm^{-1} (cyclopentanone). This ketone (**21**) was shown to be identical with the product from decarboxylation of the known[3] keto-acid (**22**). The decarboxylation of this bridgehead carboxylic acid proceeded smoothly and in good yield in the presence of barium hydroxide at 310°. These conditions were

suggested from a consideration of the recently demonstrated[14] linear dependence of the temperature of decarboxylation on the angular separation of the interacting carbonyl and carboxylic acid groups.

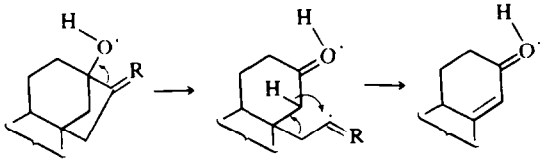
The mono-alcohol (**11**) is thus formulated as one of the epimeric *ent*-3β,19-ethylidenedioxy-17-nor-beyeran-16-ols.

Two *ent*-17-nor-13,16-dioxygenated beyerane derivatives (**12** and **13**) were obtained from the 19-ester series. The ketol-ester (**13**) has physical constants similar to those published for the product from base treatment of the ketol-ester (**20**)[13] and the structural assignment (**13**) is based on this observation.

An interesting feature in the NMR spectrum of **13** is a doublet of doublets centered at δ2·73 with splittings that are consistent with J = 20, 3Hz. A similar signal occurs in the 13-deoxy compound **19**.[4] The most reasonable assignment for this signal is H-15β with the large and small coupling attributed respectively to the geminal coupling and to a "W" coupling to H-14.[15]

Oxidation of the other beyerane derivative (**12**) with Jones reagent gave the ketol-ester (**13**) showing that **12** is one of the epimeric 16-alcohols. Sodium borohydride reduction of the ketol-ester (**13**) gave a gummy product showing a molecular ion in the MS at *m/e* 336 and IR absorption at 3450 cm^{-1}. This product showed a greater TLC polarity than **12** and is considered to be the epimeric diol-ester **23**. A parallel argument to that used with the 13,16-dihydroxy-nor-kauranes, based on the preferred direction of hydride attack, led to **23** being assigned the 16α-configuration. This requires the diol-ester (**12**) obtained from the cyclization reaction to have the 13,16β-configuration.

A feature of the mass spectra of *ent*-17-nor-13,16-dioxygenated kauranes and beyeranes (**3**, **8**, **12**, **13**) is a common base peak, attributed to an ion resulting from the fragmentation of the D-ring with transfer or loss of hydrogen (Scheme 1).



Scheme 1. MS Fragmentation of *ent*-17-nor-13,16-Dioxygenated Kauranes and Beyeranes.

A similar D-ring fragmentation has recently been suggested for some gibberellin derivatives.[16]

Dimeric compounds. The major products from the sodium-liquid ammonia reactions were dimeric substances. The dimer **27** was the only acidic product, apart from the diol acid **8**, to be isolated from the cyclization of **1**; it was also recovered in the form of the dimethyl ester **25**. A dimeric substance (**24**) isolated from the cyclization of **2** has not been fully characterized but the close correlation of the spectral data points to analogous structures for the dimers from the two sources.

The structures for these compounds are tentatively assigned on the basis of their spectral data.

The mass spectrum of **24**, not unexpectedly, failed to show a molecular ion, but peaks were observed at *m/e* 680 due to the loss of H_2O and at *m/e* 348 due to cleavage of the C-16, C-16′ bond with transfer or loss of hydrogen. A peak at *m/e* 305 is considered to be due to the same type of fragmentation as shown in Scheme 1 for the fragmentation of the D-ring of the *ent*-13,16-dioxygenated nor-kaurane and nor-beyerane derivatives and an ion at *m/e* 393 is considered to result from retention of charge on the complementary fragment. Loss of H_2O from this complementary fragment accounts for an ion at *m/e* 375.

These ions indicate that the dimer **24** is composed of two 13,16-dioxygenated monomeric units coupled through the 16- and 16′-positions. A similar pinacolic dimer was isolated by Fried *et al.*[17] from the metal-liquid ammonia reduction of estrone methyl ether.

The monomeric units of the dimer **24** are assigned nor-kaurane structures on the basis of the chemical shift of their 10-Me groups (δ1·10). Bearing in mind the preference for bulky groups to approach *ent*-17-nor-kauran-16-ones from the less hindered α-face,[9] it is reasonable to expect the monomeric units to be coupled at the 16-position from their less hindered side thus indicating β,β'-linkage in the dimer **24**.

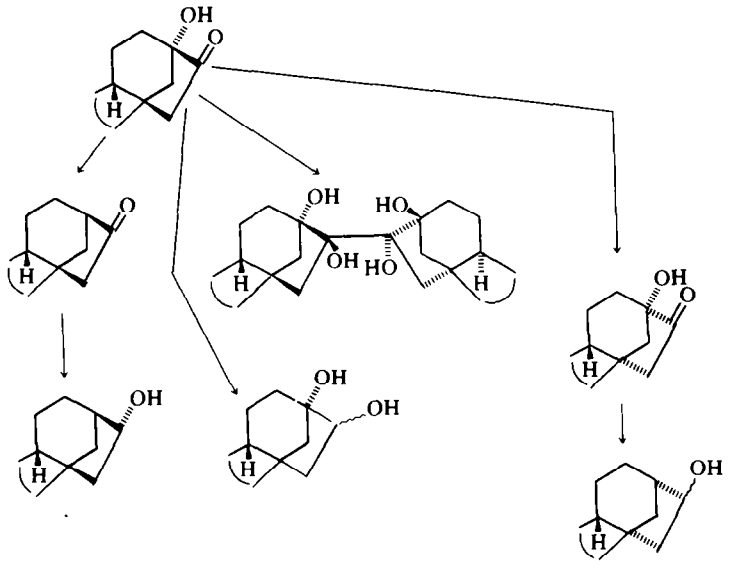
Entirely analogous observations were made with the dimer (**25**) obtained from the reductive cyclization of the keto diester **2**. The tetrol formulation of **25** was confirmed by the spectral properties of the product derived from treatment of **25** with trimethylsilyl chloride and hexamethyldisilazane. The NMR spectrum of the product showed it to be a disilyl ether. A two proton singlet at δ5·01 slowly disappeared when the NMR solution was shaken for 2 hr with deuterated water, indicating the presence of two unreacted OH groups. This was supported by IR absorption at 3450 cm^{-1}. Attempts to cleave the C-16, C-16′ bond of **25** with sodium metaperiodate proved unsuccessful, presumably due to the highly hindered nature of the bridging 1,2-diol system.

Although the products described in this paper were the major compounds formed in the various reductions, the complexity of the product mixtures prevented their complete analysis and undoubtedly other products were also formed.

The structures and yields of the identified products demonstrate that cyclization of the keto esters **1** and **2** to the ketols **5** and **20** (or the corresponding 19-acid) proceeds readily but over-reduction occurs through several pathways as summarized in Scheme 2. The mildest reducing conditions appear to be with sodium naphthalenide,[1] as these conditions afforded the desired ketol (**5**) in 17% yield. An analogous transformation was also observed with **28** but only a very small quantity of the product **29** was obtained in this case.[1] No other products could be identified from the complex mixtures obtained from these reactions.[1] When the keto-diester (**2**) was subjected to the same conditions no ketols or other identifiable products could be recovered.

The sodium-liquid ammonia cyclization conditions were the more vigorous as only over-reduced products were isolated from these reactions. These conditions were synthetically useful for the preparation of 1-hydroxy-7-methylenebicyclo[3.2.1]octanes[1] as moderate yields of 13,16-dioxygenated-nor-kauranes were produced.

Attempts to prevent over-reduction with the sodium-liquid ammonia reactions by using a lower molar ratio of sodium : keto-ester and short reaction times did not afford observable quantities of the ketols. In fact only marginal differences in product distribution were found with the variations used for keto ester **2** (Table 1). A small increase



Scheme 2. Reduction pathways from ketol intermediates.

in the yield of the 13,16β-diol (**6**) was obtained with the higher Na:keto ester ratios. It also appears that lower concentrations of the keto-ester makes formation of the dimeric products less favoured. The formation of isomerized nor-beyerane derivatives appears to be favoured by lower sodium:keto-ester ratios.

The results obtained with the mildest cyclization conditions in this work (sodium naphthalenide) were similar to those obtained by Gutsche *et al.*[18] in that only ketol derivatives were isolated. In contrast, sodium-liquid NH_3 gave only over-reduced products in this work with dimeric compounds forming a major part of the products in the diester series whereas Gutsche *et al.*[18] observed significant proportions of a ketol product along with over-reduced products. These authors did not observe dimeric products from the reductions but their method of analysis (g.c.) probably precluded this observation.

EXPERIMENTAL

For general details see Ref. 1.

Na–NH_3 *Treatment of methyl*-ent-3β,19-*ethylidenedioxy*-13-*oxo*-17-*nor*-13,16-*seco*-*kauran*-16-*oate* (**1**). (*Reaction* 1, *Table* 1). The keto-ester (**1**, 202 mg) in THF (50 ml) was added to a mixture of Na (2·5 g), THF (100 ml) and liquid NH_3 (250 ml) which had been stirred under N_2 for 1 hr. After 30 min the reaction was terminated (t-BuOH) and worked up to give a neutral fraction (190 mg) which was chromatographed on Al_2O_3 (25 g). Elution with ether-benzene mixtures (1:19–1:9) gave **9** (39 mg) which crystallized from benzene-light petroleum as needles, m.p. 197–198° m.m.p. 197–198° [lit.[3] m.p. 197–198°]. Elution with 1:9 ether-benzene gave ent-3β,19-*ethylidenedioxy*-17-*nor*-*kauran*-16β-*ol* (**10**, 59 mg), which crystallized from benzene as needles, m.p. 319–320° (dec) $[\alpha]_D$ −16° (*c*, 1·0) (Found: C, 75·6; H, 10·1; $C_{21}H_{34}O_3$ requires: C, 75·4; 10·3%), ν_{max} 3590 cm^{-1}; NMR (δ): 1·06, 1 33 (3°Me), 3·53 (1H, m, >CHOH). Elution with 1:9 MeOH-ether gave ent-3β,19-*ethylidenedioxy*-17-*nor*-*kauran*-13,16β-*diol* (**3**, 41 mg), which crystallized from benzene as needles m.p. 278–280 (dec), $[\alpha]_D$ −6° (*c*, 0·92) (Found: C, 71·8; H, 9·5; $C_{21}H_{34}O_4$ requires: C, 72·0; H, 9·8%), NMR (δ): 1·07, 1·42 (3°Me), 4·50 (dd, $J_{15\alpha,16\alpha}$ = 12Hz, $J_{15\beta,16\alpha}$ = 5 Hz, >CHOH); MS: *m/e* 350 (30, M^+), 332 (7), 306 (78), 305 (100), 288 (18), 261 (58).

Oxidation of ent-3β,19-*ethylidenedioxy*-17-*nor*-*kauran*-16β-*ol* (**10**). The mono-alcohol (**10**, 31 mg) was dissolved in pyridine (5 ml), added to CrO_3 (52 mg) in pyridine (7 ml), and the mixture left at r.t. for 14 hr. Work-up gave **9** (21 mg), which crystallized from benzene-light petroleum as needles, m.p. 196–199° [lit.[3] m.p. 197–198°].

Reduction of ent-3β,19-*ethylidenedioxy*-17-*nor*-*kauran*-16-*one* (**9**)

(i) The nor-ketone (**9**, 104 mg) in MeOH (10 ml) was added to a solution of $NaBH_4$ (150 mg) in MeOH (15 ml) and the mixture left at r.t. for 14 hr. Work up gave ent-3β,19-*ethylidenedioxy*-17-*nor*-*kauran*-16β-*ol* (**26**, 72 mg) which crystallized from benzene-light petroleum as needles, m.p. 224–225°, $[\alpha]_D$ −42° (*c*, 1·6) (Found: C, 75·7; H, 10·2. $C_{21}H_{34}O_3$ requires: C, 75·4; H, 10·3%).

(ii) The ketone (**9**, 242 mg) in THF (30 ml) was added to a mixture of Na (1·0 g), THF (100 ml) and liquid ammonia (100 ml) which had been stirred for 1 hr under N_2. After 30 min the reaction was terminated (t-BuOH) and worked up to give a neutral fraction (245 mg) which was chromatographed on Al_2O_3 (5 g). Elution with ether-benzene mixtures (1:19 – 1:9) gave **9** (75 mg) while elution with ether-benzene gave **10** (105 mg) m.p. and m.m.p. 319–320° (dec).

Oxidation of ent-3β,19-*ethylidenedioxy*-13,16α-*dihydroxy*-17-*nor*-*kaurane* (**3**) *and the* 16-*epimer* (**4**). The diol (**3**, 50 mg) in dry acetone (100 ml) was treated with Jones reagent (0·1 ml) for 3 min at −24°. The reaction was terminated (EtOH) and worked up to give **5** (31 mg), m.p. and m.m.p. 180–181° (lit.[1] m.p. 180–1°). The ketol (**5**) was similarly obtained from oxidation of the epimeric diol (**4**).

Na-*liquid* NH_3 *treatment of methyl*-ent-3β,19-*ethylidenedioxy*-13-*oxo*-17-*nor*-13,16-*seco*-*kauran*-16-*oate* (*Reaction* 2, *Table* 1). The keto-ester (**1**, 586 mg) in THF (150 ml) was added to a mixture of Na (1·0 g), THF (600 ml) and liquid NH_3 (1 l) which had been stirred for 1 hr under N_2. After 30 min the reaction was terminated (t-BuOH) and worked up to give a neutral fraction (210 mg). A second experiment using the same conditions gave a further neutral fraction (295 mg). Chromatography of the combined neutrals (505 mg) on Al_2O_3 (12 g) and elution with ether-benzene mixtures (1:4 – 2:3) gave ent-3β,19-*ethylidenedioxy*-17-*nor*-*beyeran*-16ξ-*ol* (**11**, 86 mg) which crystallized from benzene-light petroleum as needles, m.p. 195–196°; $[\alpha]_D$ +12° (*c*, 1·1). ν_{max} 3620 cm^{-1}; NMR (δ): 0·91, 1·33 (3°Me), 3·58 (1H, m, >CHOH).

Elution with ether benzene (1:1 – 3:1) gave a two component mixture (105 mg). Fractional crystallization of this mixture from benzene-light petroleum gave the less polar component, the *dimer* (**24**, 28 mg) as platelets, m.p. 295–297° (dec.), $[\alpha]$ −56° (*c*, 1·2) Found: M^+-18:680·46; $C_{42}H_{64}O_7$ requires: 680·465. ν_{max} 3510, 3350 cm $^{-1}$; NMR (δ): 1·10, 1·33 (2 × 3°Me) MS: *m/e* 680 (9, M-18), 662 (42), 618 (7), 589 (4), 393 (61), 375 (38), 348 (21), 305 (100).

The more polar component was purified by preparative TLC using benzene-acetone (1:1) and crystallized from benzene-light petroleum to give **4**, (28 mg) as needles, m.p. 184–185°, $[\alpha]_D$ −47° (*c*, 0·51); ν_{max} ($CHCl_3$) 3370 cm^{-1}; NMR (δ): 1·10, 1·33 (3°Me), 3·66 (1H, m, >CHOH); MS: *m/e* 350 (15, M^-), 335 (25), 332 (5), 306 (65), 305 (100), 288 (19), 261 (54).

Elution with ether-benzene (9:1) and MeOH–ether (1:9) gave **3** (75 mg) m.p. and m.m.p. 278–80°.

Oxidation of ent-3β,19-*ethylidenedioxy*-17-*nor*-*beyeran*-16ξ *ol* (**11**). The mono-alcohol (**11**, 21 mg) was dissolved in pyridine (3 ml), added to CrO_3 (45 mg) in cold pyridine (5 ml) and the mixture left at r.t. for 14 hr. Work up gave **21** (6·2 mg) which crystallized from benzene-light petroleum as needles, m.p. 170–171°; ν_{max} 1745 cm^{-1}.

Decarboxylation of ent-3β,19-*ethylidenedioxy*-16-*oxo*-*beyeran*-19-*oic acid* (**22**). The keto-acid[3] (**22**, 10·1 mg) was ground with $Ba(OH)_2$ (6 mg), placed in a sealed tube and heated in a Wood's metal bath at 310–320° for 30 min. Normal work up and preparative TLC in benzene-chloroform (6:1) gave **21** (3·2 mg) which crystallized from benzene-light petroleum as needles, m.p. and m.m.p. 169–171°.

Na-*liquid* NH_3 *treatment of dimethyl* ent-13-*oxo*-17-*nor*-13,16-*seco*-*kauran*-16,19-*dioate* (**2**). The various conditions and the yields of products obtained from a series of experiments with **2** are tabulated in Table 1. The general method employed in this study involved the addition of Na to a soln of liquid NH_3 (150 ml) and dry THF (150 ml). The keto-diester (**2**, 400 mg) in dry THF (50 ml) was added to this soln and the reaction terminated after varying times with NH_4Cl or t-BuOH. Work-up in the usual way gave an acidic and a neutral fraction. One-tenth of the acidic fraction was converted to ^{14}C-methyl esters by treatment with ^{14}MeI (200 mg, 1·0 μc) and K_2CO_3 (50 mg) in acetone (50 ml), under reflux for 4 hr. The product was applied to a TLC plate, developed in ether and analysed for radioactivity by scanning. The procedure was slightly varied in condition 5 (Table 1), in that **2** was added to a soln of liquid NH_3 (150 ml) and dry THF (150 ml). Na was then added and, 10 min after the development of the radical (blue colour), the reaction was terminated with NH_4Cl.

The chromatographic separation of **8** from the acidic fraction obtained by the treatment of **2** (6·8 g) from reaction 4 (Table 1) is described in the previous paper.[1] The earliest fraction eluted from this column, with ether-benzene mixtures (1:9–1:4) crystallized from aqueous MeOH to give the *dimer* (**27**, 1·95 g) as an amorphous powder, m.p. 285–287° (dec.) $[\alpha]_D$ −116°. (Found: C, 68·9, H, 9·1, $C_{38}H_{58}O_8$. H_2O requires: C, 69·1; H, 9·2%) ν_{max} (Nujol) 3520, 3400–3150, 1695 cm^{-1}. Elution with ether-benzene mixtures (2:3–4:1) gave a complex mixture (2·3 g) which was methylated with CH_2N_2 and combined with the neutral product (0·75 g) from the cyclizations, for the purpose of the chromatographic separation described later.

Reactions of the dimer (**27**)

(i) Treatment of **27** (242 mg) with CH_2N_2 in the usual way gave **25** (239 mg) which crystallized from MeOH as a powder, m.p. 291–292° (dec.), $[\alpha]_D$ −74° (*c*, 1·2). Found: M^+ −18: 652·426; $C_{40}H_{60}O_8$ requires: 652·434 ν_{max} 3480, 3400–3250, 1725 cm^{-1}; NMR (δ): 0·80, 1·13 (3°Me), 3·60 ($CO_2\underline{CH}_3$) MS: *m/e* 652 (5, M-18), 634 (4), 379 (18), 361 (47), 343 (15), 334 (37), 291 (100).

(ii) The dimer **25** (160 mg) was treated with bexamethyldisilazane (1 ml) and trimethylsilyl chloride (1 ml) in dry pyridine (5 ml) for 25 min. The mixture was concentrated, dissolved in dry benzene and filtered. Evaporation of the benzene gave a gum (81 mg); ν_{max} 3450, 1725 cm^{-1}; NMR (δ): 0·19 (2 × ($\underline{CH}_3$)$_3$Si–), 0·80, 1·13 (2 × 3°Me), 3·60 (2 × $CO_2\underline{CH}_3$), 5·01 (2H, $W_{h/2}$ = 10 Hz, 2 × $\underline{OH}$).

Chromatography of the neutral and methylated acid products from reduction of dimethyl ent-13-*oxo*-17-*nor*-13,16-*seco*-*kauran*-16,19-*dioate* (**2**). The previously mentioned combined ester fraction (3·05 g) was chromatographed on Al_2O_3 (150 g). Elution with ether-benzene (1:9) gave **25** (475 mg) m.p. and m.m.p. 291–293° (dec.). Elution with ether-benzene (3:7) gave **13** (65 mg) which crystallized from benzene-light petroleum as needles, m.p. 196–198°, $[\alpha]_D$ −61° (*c*, 1·51) [lit.[13] m.p. 197–199°, $[\alpha]_D$ −62·5° (*c*, 1·03)]. ν_{max} 3525, 1745, 1725 cm^{-1}; NMR (δ): 0·70, 1·20 (3°Me), 3·63 ($CO_2\underline{CH}_3$), 2·73 (d of d, $J_{15\alpha,15\beta}$ = 20 Hz, $J_{14\alpha,15\beta}$ = 3 Hz, H −15β); MS: *m/e* 334 (41, M^+), 316 (7), 306 (27), 291 (100), 231 (43). Elution with ether-benzene (1:4) gave *methyl* ent-13,16α-*dihydroxy*-17-*nor*-*beyeran*-19-*oate* (**12**, 725 mg), which crystallized from benzene-light petroleum as rhombs, m.p. 136–137°, $[\alpha]_D$ −77° (*c*, 0·77) (Found: C, 71·2; H, 9·5. $C_{20}H_{32}O_4$ requires: C, 71·4; H, 9·6%) ν_{max} 3450, 3320, 1725 cm^{-1}; NMR (δ): 0·70, 1·18 (3°Me), 3·63 ($CO_2\underline{CH}_3$), 3·95 (1H, m, $W_{h/2}$ = 14 Hz, >CHOH) MS: *m/e* 336 (1, M^+) 334 (3), 318 (15), 300 (2), 291 (100), 274 (62). Elution with ether-benzene (3:7) to ether gave a complex mixture (425 mg) from which *methyl* ent-13,16β-*dihydroxy*-17-*nor*-*kauran*-19-*oate* (**7**, 85 mg) was isolated as a gum. Found M^+: 336·230; $C_{20}H_{32}O_4$ requires: 336·230 ν_{max} (Nujol) 3350, 1725 cm^{-1}; NMR (δ): 0·80, 1·18 (3°Me), 3·63 ($CO_2\underline{CH}_3$), 3·53 (3H, m, 2 × $\underline{OH}$, >$\underline{CH}$OH); MS: *m/e* 336 (27, M^+), 318 (1), 291 (100), 259 (14), 231 (31). Elution with ether afforded *methyl*-ent-13,16α-*dihydroxy*-17-*nor*-*kauran*-19-*oate* (**6**, 950 mg) which crystallized from benzene-light petroleum as cubes, m.p. 185–187°, $[\alpha]_D$ −85° (*c*, 0·56) (Found: C, 71·1; H, 9·5. $C_{20}H_{32}O_4$ requires: C, 71·4; H, 9·6%) ν_{max} (Nujol) 3350, 1725 cm^{-1}; NMR (δ): 0·80, 1·18 (3°Me), 3·63 ($CO_2\underline{CH}_3$), 4·03 (d of d, $J_{15\alpha,16\alpha}$ = 12 Hz, $J_{15\beta,16\alpha}$ = 5 Hz, >$\underline{CH}$OH); MS: *m/e* 336 (10, M^-), 291 (100), 259 (11), 231 (26). This compound was identical with the product of CH_2N_2 methylation of **8**.

Oxidation of the diol-esters **6** *and* **7**. The diol-ester (**6**, 60 mg) in anhydrous acetone (50 ml), at −24° was treated with Jones reagent (0·08 ml) for 3 min. The reaction was terminated (EtOH) and worked up in the normal way to yield *methyl*-ent-13-*hydroxy*-16-*oxo*-17-*nor*-*kauran*-19-*oate* (**20**, 42 mg) which crystallized from benzene-light petroleum as needles, m.p. 224–226°, $[\alpha]_D$ −100° (*c*, 1·2) [lit.[10] m.p. 224–227°, $[\alpha]_D$ −102·5° (*c*, 0·77)]. (Found: C, 71·8; H, 9·0, $C_{20}H_{30}O_4$ requires: C, 71·8; H, 9·0%). MS: *m/e* 334 (42, m^-), 316 (12), 306 (4), 291 (100), 275 (14), 274 (17), 231 (34); NMR (δ): 0·88, 1·20 (3°Me) 2·06 (2H, s, C-15H$_2$), 3·63 ($CO_2\underline{CH}_3$). Oxidation of **7** under identical conditions gave the ketol-ester (**20**).

$NaBH_4$ *reduction of methyl* ent-13-*hydroxy*-16-*oxo*-17-*nor*-*kauran*-19-*oate* (**20**). The ketol-ester **20** (65 mg) was treated with a soln of $NaBH_4$ (120 mg) in MeOH (15 ml) for 16 hr. Work up in the normal way gave **6**, (49 mg) m.p. and m.m.p. 185–187°.

Methyl ent-13-*hydroxy*-16-*oxo*-17-*nor*-*beyeran*-19-*oate* (**13**). The diol-ester **12** (132 mg) in dry acetone (75 ml) was oxidised as previously described for **6** and **7**, using Jones reagent (0·2 ml). The product was **13** (105 mg) m.p. 196–198°, m.m.p. with material isolated from cyclization, 196–198°.

The ketol-ester **13** (61 mg) was treated with a soln of $NaBH_4$ (120 mg) in MeOH (15 ml) for 16 hr. Normal work up gave *methyl* ent-13,16β-*dihydroxy*-17-*nor*-*beyeran*-19-*oate* (**23**, 47 mg) as a gum; ν_{max} 3450, 3320, 1725 cm^{-1}; MS: *m/e* 336 (3, M^+), 334 (1), 318 (5), 291 (100), 274 (49); NMR (δ): 0·70, 1·18 (3°Me), 3·63 (CO_2CH_3), 4·00 (3H, m, $W_{h/2}$ = 20 Hz, 2 × OH, >$\underline{CH}$OH).

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