Studies on Rearrangements in Derivatives of Grandiflorenic Acid. Part 1. Reaction of the Epoxides of Methyl (−)-Kaur-9(11)-en-19-oate and (−)-Kaur-9(11)-en-19-oic Acid with Boron Trifluoride–Diethyl Ether either in the Absence or in the Presence of *N*-Nitrosomethylurea. Formation of Two Diterpenes of a New Skeletal Type

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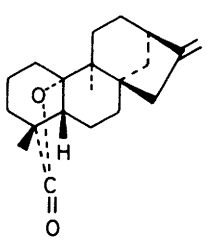
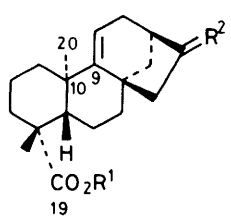
On treatment with boron trifluoride–diethyl ether in benzene the epoxide (**3b**) of methyl (−)-kaur-9(11)-en-19-oate (**2c**) yielded an aldehyde (**5a**). During the epoxidation of compound (**2c**) with *m*-chloroperbenzoic acid it was observed that in the presence of *N*-nitrosomethylurea the expected epoxide (**3b**) was not obtained, but instead compound (**4**) was isolated. Detailed studies showed that epoxide (**3b**) is an intermediate for the formation of compound (**4**) from compound (**2c**), and aldehyde (**5a**) is also involved in its mechanistic pathway. Epoxidation of aldehyde (**5a**), followed by acid treatment, led to compound (**4**). On rupture with boron trifluoride–diethyl ether in acetic anhydride epoxide (**3b**) afforded acylal (**5b**) in good yield.

(−)-Kaur-9(11)-en-19-oic acid (**2b**) behaved similarly. On rupture with boron trifluoride–diethyl ether its epoxide (**3a**) gave also an aldehyde, (**5c**), while on treatment with boron trifluoride–diethyl ether in acetic anhydride it yielded acylal (**5d**).

Some time ago, Caballero and Walls[1] isolated a new diterpene lactone which they named zoapatline from the roots of the native Mexican shrub 'Zoapatle' (*Montanoa tomentosa* Cerv.) and assigned to it the structure (**1**). This compound possesses a (−)-9α-kaurane skeleton in which the methyl group at C-10 migrates to C-9, with stereochemistry inverted from that of the natural (−)-kaurane skeleton, and the carboxyl group C-19 bridges the C-4 and C-10 positions. We assumed that this compound might be derived chemically from grandiflorenic acid[2] [(−)-kaura-9(11),16-dien-19-oic acid)] (**2a**) *via* the acid-catalysed rearrangement of its 9,11-epoxide, and considered it worthwhile to study it further. In order to simplify this approach, we first investigated the rearrangement of the epoxides of both methyl (−)-kaur-9(11)-en-19-oate[3] (**2c**) and (−)-kaur-9(11)-en-19-oic acid (**2b**),[4] which might lead to the formation of derivatives of compound (**1**).

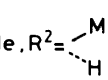


(**1**)



(**2**) a ; $R^1 = H, R^2 = CH_2$

b ; $R^1 = H, R^2 =$ 

c ; $R^1 = Me, R^2 =$ 

Results and Discussion

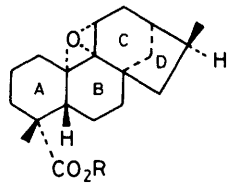
Epoxidation of compound (**2c**) with *m*-chloroperbenzoic acid (MCPBA) in chloroform occurred stereoselectively at the more accessible α-side[4] and yielded solely one epoxide† (**3b**), δ 0.65 (3 H, s, CH_3–C), 0.95 (3 H, d, *J* 6.5 Hz, CH_3–CH), 1.19 (3 H, s, CH_3–C), 3.00 (1 H, br s, 11-H), and 3.63 (3 H, s, CH_3O); *m/z* 332 (M^+).

During this epoxidation, we observed that when compound (**2c**) contained *N*-nitrosomethylurea‡ as an impurity, the expected epoxide (**3b**) was not obtained. In this case, the reaction took a different course and a compound, $C_{21}H_{32}O_4$, was isolated; δ 0.86 (3 H, d, *J* 6 Hz, CH_3–CH), 0.95 (3 H, s, CH_3–C), 1.23 (3 H, s, CH_3–C), 3.87 (3 H, s, CH_3O), 5.01 (1 H, ddd, *J* 6.5, 6, and 3 Hz, O–CH=CH), and 6.86 (1 H, d, *J* 6.5 Hz, O–CH=CH); $\nu_{max.}$ 3 550 (OH), 1 740 (ester CO), 1 650 (CH=CH), and 1 247 cm^{-1} (C–O); *m/z* 348 (M^+). This compound was formulated as (**4**), and its structure and stereochemistry were further confirmed by a single-crystal *X*-ray analysis.[5]

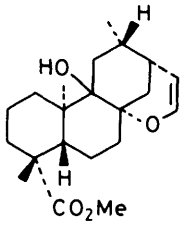
We postulated that an intermediate for the formation of compound (**4**) from compound (**2c**) in the above reaction is epoxide (**3b**) and we studied in detail how the reaction

† The stereochemistries of this epoxide and the 16β-methyl group were determined unequivocally by a single-crystal *X*-ray analysis (unpublished results by A. T. McPhail and K. D. Onan).

‡ Compound (**2c**) was prepared by the methylation of compound (**2b**) with ethereal diazomethane. Diazomethane was generated in ether solution from *N*-nitrosomethylurea and aqueous potassium hydroxide, and was used directly without purification by distillation. In this case, a small amount of *N*-nitrosomethylurea inevitably contaminated the product (**2c**), as demonstrated by t.l.c. on silica gel, and was not readily removed by recrystallisation. The best way to eliminate the *N*-nitrosomethylurea contaminant is to filter the methylated product in benzene solution through silica gel.

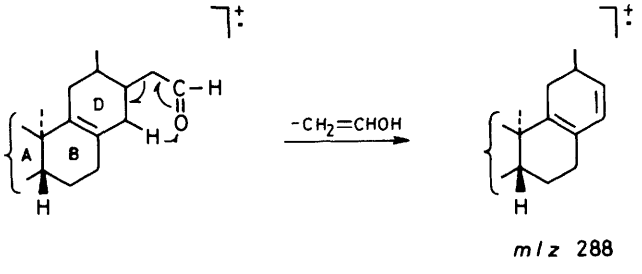


(3) a ; R = H
b ; R = Me



(4)

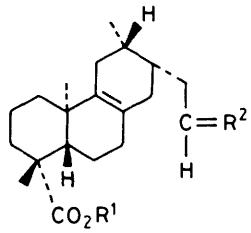
proceeded. Immediately after compound (**2c**) (1 mol equiv.) was mixed in chloroform with *N*-nitrosomethylurea (1 mol equiv.) and MCPBA (2 mol equiv.), the reaction was monitored by t.l.c. on silica gel (solvent 5% ether in benzene). After 1 h, almost all of compound (**2c**) had disappeared, and a product (*ca.* 90%) of polarity identical with that of compound (**3b**) appeared. The reaction was discontinued at this point and, when the reaction mixture was filtered through Merck standardised alumina II—III, compound (**3b**) was isolated. However, when the above reaction was allowed to continue for an additional 3 h, compound (**3b**) disappeared and two products, both of which are more polar than compound (**3b**), appeared on t.l.c. The more polar of these proved to be identical with compound (**4**), while the other was obtained as an oil, $C_{21}H_{32}O_3$, *m/z* 332 (M^+). The n.m.r. spectrum in carbon tetrachloride exhibited two tertiary methyl groups (δ 0.76 and 1.18, s), a secondary methyl group (δ 0.78, d, *J* 6 Hz), a methoxy group (δ 3.60, s), and an aldehyde proton (δ 9.75, t, *J* 1.8 Hz). The presence of an aldehyde function was also confirmed by the i.r. spectrum [$\nu_{max.}$ (liquid film) 2 720 (aldehyde CH) and 1 736 cm^{-1} (CO of ester and aldehyde)]. It is apparent that an aldehyde group must have been generated from the rupture of ring C bearing an epoxide ring, and so this compound must be tricyclic with a tetrasubstituted double bond in its molecule. The base peak in its mass spectrum occurs at *m/z* 288 ($M - CH_2$=CHOH) and this ion must have been formed by the transfer of a γ-hydrogen atom to the carbonyl oxygen with concomitant β-fission through a six-membered cyclic transition state,[6] as shown in Scheme 1.



Scheme 1.

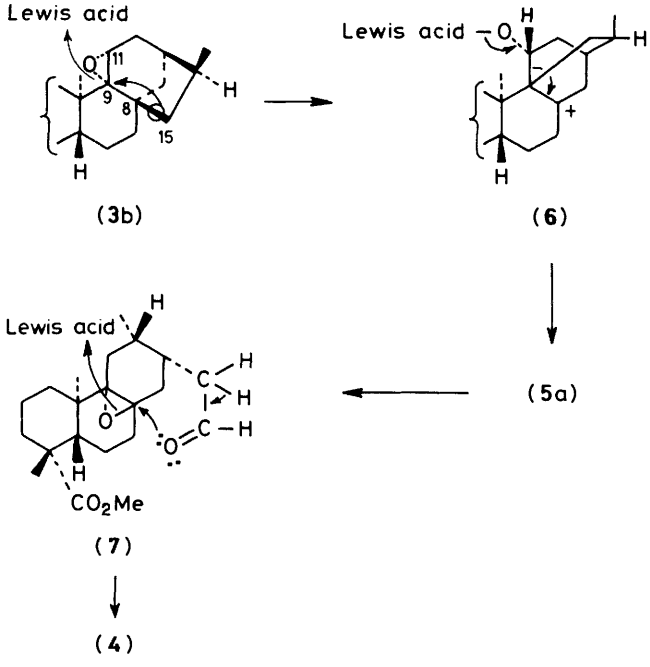
This aldehyde forms a crystalline oxime, $C_{21}H_{33}NO_3$, and in its mass spectrum a similar type of McLafferty rearrangement is observed, and the same peak (*m/z* 288) occurs *via* ($M - CH_2$=CHNHOH) with the relative intensity of 76%. The structure (**5c**) was assigned to this aldehyde, and the structure was supported by a possible mechanistic pathway for the formation of compound (**4**) from compound (**2c**).

That epoxide (**3b**) is indeed an intermediate was further supported by a separate experiment in which compound (**4**) was obtained after 4 h when compound (**3b**) was treated with *N*-nitrosomethylurea (1 mol equiv.) and MCPBA (2 mol equiv.) under the same conditions as above. Epoxide (**3b**) is stable in chloroform solution towards either *N*-nitrosomethylurea or a



(5) a ; R^1 = Me , R^2 = O
b ; R^1 = Me , R^2 = OCOMe / OCOMe
c ; R^1 = H, R^2 = O
d ; R^1 = H, R^2 = OCOMe / OCOMe

mixture of MCPBA and *m*-chlorobenzoic acid. One reasonable guess, therefore, would be that *N*-nitrosomethylurea in the presence of MCPBA may generate some nitric acid (from oxidation and cleavage of the nitroso group), but when epoxide (**3b**) was treated with MCPBA and one drop of either 65% or 10% aqueous nitric acid, compound (**4**) was not obtained, and instead the reaction yielded a mixture of unidentifiable products. However, on treatment with MCPBA and one drop of nitric acid in the presence of urea, epoxide (**3b**) yielded compound (**4**) in small yield. Therefore, it is likely that when nitric acid is generated, the amides such as *N*-nitrosomethylurea or urea may act as a buffer so as not to allow the medium of the reaction mixture to be too acidic. We consider a plausible mechanism for the formation of compound (**4**) to be as depicted in Scheme 2. The initially formed epoxide (**3b**) undergoes ring opening by the mixture of *N*-nitrosomethylurea and MCPBA which then acts as a Lewis acid to cause rupture of the epoxide ring. As illustrated by arrows, the cleavage of the epoxide ring

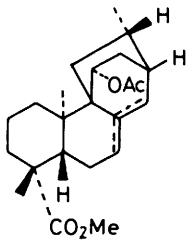


Scheme 2.

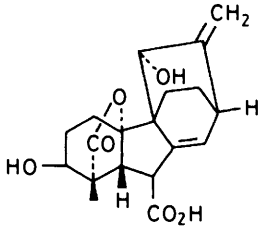
would be followed by the migration of the C-8–C-15 bond to C-9. Rupture of the C-9–C-11 bond in compound (**6**) and concurrent formation of the aldehyde group would then give

compound (**5a**), which would further react with MCPBA to form epoxide (**7**). Subsequent nucleophilic attack from the α-side at C-8 by the aldehyde carbonyl oxygen, followed by rupture of the epoxide ring, would then lead to compound (**4**).

On treatment with boron trifluoride–diethyl ether in benzene, epoxide (**3b**) yielded intractable mixtures. After chromatography over silica gel, aldehyde (**5a**) was isolated in small amount as the only identifiable product. We assumed that the complexity of the reaction might be avoided in the presence of acetic anhydride, *viz.*, if any alcohol (**6**) were formed, it might be esterified *in situ* and the resultant product might be compound (**8**)* rather than aldehyde (**5a**). Rupture of epoxide (**3b**) with boron trifluoride–diethyl ether in acetic anhydride gave only one product, as demonstrated by t.l.c. After work-up, it was



(**8**)

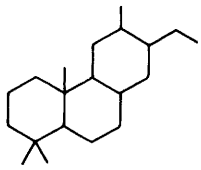


(**9**)

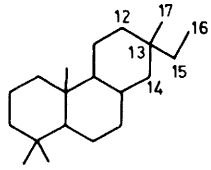
obtained in *ca.* 50% yield as a crystalline compound, $C_{25}H_{38}O_6$, *m/z* 434 (M^+). Contrary to our expectation, however, this compound showed three separate carbonyl bands ($\nu_{max.}$ 1 770, 1 750, and 1 725 cm^{-1}) in its i.r. spectrum. The n.m.r. spectrum revealed two tertiary methyls (δ 0.70 and 1.14, each s), a secondary methyl (δ 0.75, d, *J* 6 Hz), two acetoxy groups (δ 2.00, s), a CO_2CH_3 group (δ 3.56, s), and a $CH_2CH\langle^{O-}_{O-}$ grouping (δ 6.65, 5, t, *J* 5.4 Hz). The structure and stereochemistry of this compound were unequivocally determined as (**5b**) by a single-crystal *X*-ray analysis.[5]

Epoxidation of compound (**2b**) with MCPBA in chloroform gave α-epoxide† (**3a**) as the sole product. Epoxide (**3a**) is also very reactive and when set aside in benzene solution over silica gel, it undergoes cleavage of the epoxide ring to yield aldehyde (**5c**). The same aldehyde was also obtained by the rupture of epoxide (**3a**) with boron trifluoride–diethyl ether in benzene. On treatment with boron trifluoride–diethyl ether in acetic anhydride, aldehyde (**5c**) afforded acylal (**5d**), which on methylation with ethereal diazomethane led to compound (**5b**), obtained previously by the rupture of epoxide (**3b**) with boron trifluoride–diethyl ether in acetic anhydride. We then attempted to verify the previously postulated mechanistic pathway (see Scheme 2) by converting compound (**5a**) into compound (**4**). Epoxidation of compound (**5a**) with MCPBA in chloroform yielded epoxide (**7**) which, on treatment with one drop of conc. hydrochloric acid in chloroform, cyclised to a product identical with compound (**4**).

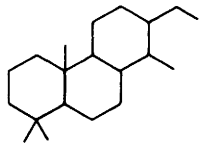
The rearrangement products (**4**) and (**5a** and **c**) represent new types of diterpene skeleton (**10**). So far, similar types of diterpenes, *viz.*, a pimarane (**11**), a cassane[7] (**12**), and a cleistanthane[8] (**13**), are known to occur in nature. The carbon



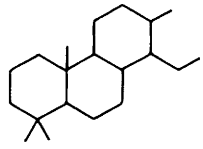
(**10**)



(**11**)



(**12**)



(**13**)

skeletons for cassane (**12**) and cleistanthane (**13**) may be derived biogenetically[9] from a pimarane (**11**) *via* a 1,2-migration of the C-13 methyl [in (**12**)] or C-13 ethyl group [in (**13**)] to C-14. The carbon skeletons for compounds (**5a** and **c**) and (**4**) may provide the fourth example of such rearrangement diterpenes, in which the C-13 methyl group in pimarane (**11**) migrates to C-12. Although our initial objective has not been achieved, the present work suggests the possibility of the future occurrence in Nature of new diterpenes typified by compounds (**5a** and **c**) and (**4**). Furthermore, it is also likely that they may be formed *in vivo* from the parent olefinic precursors such as (**2b** and **c**) by a similar sequence of oxidation and cyclisation reactions (see Scheme 2) under biogenetic conditions.

Experimental

M.p.s. were taken with a Kofler hot-stage apparatus. Unless otherwise specified, i.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 spectrophotometer and n.m.r. spectra with a Varian EM 3940 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Rotations were measured at 23—25 °C with a Zeiss polarimeter '0.01°' for solutions in chloroform. Mass spectra were determined with a DuPont 21-492B mass spectrometer at 70 eV using a direct inlet system. Only relevant ions in the mass spectra are listed and their relative intensities are indicated in parentheses as a percentage of the base peak. For column chromatography, Merck silica gel 60 (35—70 mesh ASTM) was used. T.l.c. was performed on Merck silica gel GF_{254} (Type 60) and the spots were observed either by exposure to iodine vapour or by u.v. light. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure below 60 °C. MCPBA was purchased from the Aldrich Chemical Company and purified before use according to the literature method.[10] Microanalyses were carried out by the A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

Epoxidation of Methyl (−)-Kaur-9(11)-en-19-oate (**2c**).—Compound (**2c**) (0.386 g) was dissolved in chloroform (20 ml), followed by MCPBA (0.344 g). The solution was stirred at 21 °C. The reaction was monitored by t.l.c. (silica gel; benzene). After 1 h, the reaction was complete and the solution was filtered through Merck standardised alumina (activity II—III). Elution was effected by hexane–benzene (1:1), benzene, and benzene–ether (9:1). The eluates were combined and evaporated. The *epoxide* (**3b**) was crystallised from ether–hexane (0.19 g), m.p. 114—116 °C; $[\alpha]_D$ +28° (*c* 1.0) (Found: C, 75.6; H, 9.55. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%).

* Note that this compound is a ring C/D-analogue of antheridiogen, A_{An} (**9**), the antheridium-inducing factor from *Anemia phyllitidis* (see K. Nakanishi, M. Endo, U. Näf, and L. F. Johnson, *J. Am. Chem. Soc.*, 1971, **93**, 5579).

† The stereochemistry of this compound was determined by a single-crystal *X*-ray analysis (unpublished results by A. T. McPhail and K. D. Onan).

Reaction of Methyl (−)-Kaur-9(11)-en-19-oate (**2c**) *with MCPBA and* N-*Nitrosomethylurea for* 4 h.—*N*-Nitrosomethylurea was purified before use. Its ethereal solution was washed with distilled water and dried over anhydrous sodium sulphate. After evaporation of the filtered solution under reduced pressure, the compound was crystallised from ether–hexane. A solution of compound (**2c**) (0.319 g) in chloroform (20 ml) was treated with *N*-nitrosomethylurea (0.103 g), followed by MCPBA (0.345 g). The solution was stirred at 21 °C for 4 h. Then, solid sodium sulphite (1 g) was added and the mixture was stirred for an additional 1 h. The solution was washed with 5% aqueous sodium hydrogen carbonate, dried, and evaporated, to yield an oil (0.41 g). This was chromatographed over silica gel; elution with benzene and subsequent crystallisation from ether–hexane gave *compound* (**4**) (30 mg), m.p. 182—184 °C; $[\alpha]_D$ +15° (*c*. 1.0); $\nu_{max.}$ 1 735 cm^{-1} (CO_2CH_3) (Found: C, 72.15; H, 9.1. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26%).

From the mother liquor of the crystallisation of compound (**4**), *aldehyde* (**5a**) was obtained as an oil (0.2 g), *m/z* 332 (M^+, 38%), 317 ($M^+ - CH_3$, 7), 288 ($M^+ - CH_2{=}CHOH$, 100), 273 ($M^+ - CO_2CH_3$, 76), 257 ($M^+ - CH_2{=}CHOH - CH_3$, 33), and 229 ($M^+ - CH_2{=}CHOH - CO_2CH_3$, 30). It formed an oxime, m.p. 90 °C (from aqueous ethanol), *m/z* 347 (M^+, 6%), 332 ($M^+ - CH_3$, 16), 330 ($M^+ - OH$, 34), 289 ($M^+ - CH_2CH{=}NOH$, 20), 288 ($M^+ - CH_2{=}CHNHOH$, 76), 273 ($M^+ - CH_2{=}CHNHOH - CH_3$, 44), 299 ($M^+ - CH_2{=}CHNHOH - CO_2CH_3$, 15), 59 ($CH_2{=}CHNHOH$, 38), and 41 ($CH_2{=}C{=}NH$, 100) (Found: C, 72.3; H, 9.4; N, 3.9. $C_{21}H_{33}NO_3$ requires C, 72.58; H, 9.57; N, 4.03%).

Elution with 10% ether in benzene yielded a small amount of an oily fraction, which could not be identified, and *N*-nitrosomethylurea (5 mg).

Reaction of Methyl (−)-Kaur-9(11)-en-19-oate (**2c**) *with MCPBA and* N-*Nitrosomethylurea for* 1 h.—A solution of compound (**2c**) (0.236 g) in chloroform (6 ml) was stirred with MCPBA (0.258 g) and *N*-nitrosomethylurea (0.103 g) at 21 °C for 1 h. The formation of epoxide (**3b**) was demonstrated by t.l.c. (silica gel; 5% ether in benzene). The solution was then filtered through Merck standardised alumina (activity II—III). Elution with benzene yielded epoxide (**3b**) (0.155 g) after crystallisation from ether–hexane (by i.r. and m.p. comparisons).

In another experiment, a mixture of compound (**2c**) (0.305 g), MCPBA (0.331 g), and *N*-nitrosomethylurea (0.105 g) in chloroform (20 ml) was stirred at 21 °C for 1 h. Solid sodium sulphite (1 g) was then added and the mixture was stirred for an additional 1 h. The solution was filtered, washed with 5% aqueous sodium hydrogen carbonate, dried, and evaporated. An oily product (0.37 g) was obtained, which was chromatographed over silica gel. Elution with benzene yielded an oil (0.1 g) whose i.r. and n.m.r. spectra were identical with those of aldehyde (**5a**). The product formed an oxime, m.p. 90 °C (from aqueous ethanol), and a 2,4-dinitrophenylhydrazone, m.p. 106—108 °C (from chloroform–ethanol). Elution with 10% ether in benzene gave a small amount of an oily fraction, which could not be identified, and *N*-nitrosomethylurea (5 mg).

Reaction of Epoxide (**3b**) *with MCPBA and* N-*Nitrosomethylurea.*—A mixture of epoxide (**3b**) (40 mg), MCPBA (43 mg), and *N*-nitrosomethylurea (12 mg) in chloroform (4 ml) was stirred at 21 °C for 3 h. The solution was then filtered through Merck standardised alumina (activity II—III) and elution with benzene gave compound (**4**) (5 mg) (by t.l.c., i.r., and m.p. comparisons).

Reaction of Epoxide (**3b**) *with MCPBA, Urea, and one Drop of 65% Aqueous Nitric Acid.*—A mixture of epoxide (**3b**) (25 mg), MCPBA (25 mg), and urea (5 mg) in chloroform (3 ml) was treated with one drop of 65% aqueous nitric acid. The solution was stirred at 21 °C for 1 h and then filtered through Merck standardised alumina (activity II—III). Elution with benzene and crystallisation from ether–hexane gave compound (**4**) (3 mg) (by t.l.c., i.r., and m.p. comparisons).

Reaction of Epoxide (**3b**) *with Boron Trifluoride–Diethyl Ether.*—Epoxide (**3b**) (0.2 g) was dissolved in benzene (12 ml), followed by boron trifluoride–diethyl ether (1 ml). The solution was stirred at 21 °C for 1 h, and then poured onto water and the product was extracted with ether. The extract was washed with water, dried, and evaporated to yield an oil. This was chromatographed over silica gel; elution with benzene gave aldehyde (**5a**) (50 mg) (by i.r. and n.m.r. comparisons). Elution with benzene–ether yielded polar fractions (70 mg) which could not be identified.

Reaction of Epoxide (**3b**) *with Boron Trifluoride–Diethyl Ether in Acetic Anhydride.*—Epoxide (**3b**) (0.11 g) was dissolved in acetic anhydride (6 ml) and treated with boron trifluoride–diethyl ether (0.5 ml). The solution was stirred at 21 °C for 10 min. Water was then added and the product was extracted with ether. The extract was washed with 5% aqueous sodium hydrogen carbonate, dried, and evaporated. The crystalline residue was dissolved in hexane–benzene (1:1) and filtered through Merck standardised alumina (activity II—III). *Compound* (**5b**) (50 mg), m.p. 113—115 °C, was obtained after crystallisation from ether–hexane; $[\alpha]_D$ −198° (*c* 1.1) (Found: C, 68.75; H, 8.6. $C_{25}H_{38}O_6$ requires C, 69.09; H, 8.81).

Epoxidation of (−)-Kaur-9(11)-en-19-oic Acid (**2b**).—Compound (**2b**) (0.20 g) and MCPBA (0.22 g) were dissolved in chloroform (10 ml) and the solution was stirred at 21 °C for 3 h. Then, solid sodium sulphite was added and the mixture was stirred for 1 h. The solution was filtered and then washed with 5% aqueous sodium hydrogen carbonate, dried, and evaporated. The product was isolated in the usual way. Upon crystallisation from ether–hexane, *epoxide* (**3a**) was obtained (0.12 g), m.p. 169—171 °C; $[\alpha]_D$ +38° (*c* 0.4); $\nu_{max.}$ 1 700 cm^{-1} (CO_2H); *m/z* 318 (M^+) (Found: C, 75.2; H, 9.3. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%).

Rupture of Epoxide (**3a**) *during Chromatography over Silica Gel.*—Compound (**2b**) (0.90 g) in chloroform (20 ml) was treated with MCPBA (0.77 g) and the solution was stirred at 21 °C. The formation of epoxide (**3a**) was monitored by t.l.c. (silica gel; 20% ether in benzene). After 2 h, the reaction was complete. The solution was filtered through silica gel, and elution with chloroform yielded a mixture of epoxide (**3a**) and some *m*-chlorobenzoic acid. This mixture was rechromatographed over silica gel. Elution with 5% ether in benzene gave *aldehyde* (**5c**) as an oil (0.6 g); *m/z* 318 (M^+); $\nu_{max.}$ (liquid film) 2 700 (aldehyde CH), 1 725 (CHO), and 1 680 cm^{-1} (CO_2H); δ 0.73 (3 H, d, *J* 6 Hz, 12-Me), 0.83 (3 H, s, CH_3–C), 1.24 (3 H, s, CH_3–C), and 9.79 (1 H, t, *J* 1.9 Hz, CHO) (Found: C, 75.7; H, 9.8. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%).

Further elution with 10% ether in benzene yielded oily fractions (0.1 g) which could not be identified.

Reaction of Epoxide (**3a**) *with Boron Trifluoride–Diethyl Ether in Acetic Anhydride.*—Epoxide (**3a**) (80 mg) was dissolved in acetic anhydride (6 ml) and treated with boron trifluoride–diethyl ether (0.5 ml). The solution was stirred at 21 °C for 15 min, poured onto water, and extracted with ether. The extract was washed with 5% aqueous sodium hydrogen carbonate until the extract reached pH 7.0, dried, and evaporated. The product was chromatographed over silica gel; elution with 5% ether in

benzene *compound* (**5d**), (30 mg), m.p. 169—171 °C (from ether–hexane); $[\alpha]_D$ −249° (*c* 1.3); *m/z* 420 (M^+); $\nu_{max.}$ 1 770 (OAc), 1 750 (OAc), and 1 700 cm^{-1} (CO_2H) (Found: C, 68.25; H, 8.4. $C_{24}H_{36}O_6$ requires C, 68.54; H, 8.63%).

Reaction of Aldehyde (**5c**) *with Boron Trifluoride–Diethyl Ether in Acetic Anhydride.*—Aldehyde (**5c**) (0.2 g) was dissolved in acetic anhydride (10 ml), followed by boron trifluoride-diethyl ether (1 ml). The solution was stirred at 21 °C for 20 min and then poured onto water, and the product was extracted with ether. The extract was washed with 5% aqueous sodium hydrogen carbonate until pH 7.0, dried, and evaporated. Filtration of the crude product through silica gel and elution with 10% ether in benzene yielded compound (**5d**) (80 mg) (by m.p. and i.r. comparisons).

Methylation of Compound (**5d**) *with Diazomethane.*—Diazomethane was prepared in ether solution from *N*-nitrosomethylurea and aqueous potassium hydroxide and distilled before use. A solution of compound (**5d**) (30 mg) in ether was treated with the above ethereal diazomethane. Evaporation of the solution and crystallisation of the product from ether–hexane gave compound (**5b**) (20 mg) (by m.p. and i.r. comparisons).

Methylation of Aldehyde (**5c**) *with Diazomethane.*—A solution of aldehyde (**5c**) (0.2 g) in ether was treated with ethereal diazomethane. Filtration of the product in benzene solution through Merck standardised alumina (activity II—III) gave aldehyde (**5a**) (0.15 g) (by i.r. comparison).

Conversion of Aldehyde (**5a**) *into Compound* (**4**).—A solution of aldehyde (**5a**) (0.15 g) in chloroform (10 ml) was treated with MCPBA (0.1 g) at 21 °C for 1 h. Solid sodium sulphite was then added and the mixture was stirred for an additional 1 h. The solution was filtered, washed with 5% aqueous sodium hydrogen carbonate, dried, and evaporated. *Compound* (**7**) was obtained as an oil (0.1 g); $\nu_{max.}$ (liquid film) 2 720 (aldehyde CH) and 1 735 cm^{-1} (CO of ester and aldehyde); δ 0.79 (3 H, d, *J* 6 Hz, CH_3–CH), 0.81 (3 H, s, CH_3–C), 1.16 (3 H, s, CH_3–C), 3.63 (3 H, s, CO_2CH_3), and 9.74 (1 H, br s, CHO) (Found: C, 72.05; H, 9.0. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26%).

Compound (**7**) (80 mg) was dissolved in chloroform (5 ml) and the solution was treated with one drop of conc. hydrochloric acid. The solution was stirred at 21 °C for 1 h and then filtered through Merck standardised alumina (activity II—III). Elution with benzene yielded compound (**4**) (20 mg) (by m.p. and i.r. comparisons).

Acknowledgements

We thank Dr. H. O. House of Georgia Institute of Technology for helpful discussions, and Mr. J. Bermudez, Mrs. C. Cabello de Dazon and I. Romero de Gosen, and Miss M. L. Tasayso of the Chemistry Centre of this Institute for determination of the i.r., mass, and n.m.r. spectra.

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Received 26*th November* 1984; *Paper* 4/2001