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The Transformation of Epicandicandiol into a Gibberellin A_{12} Isomer

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Abstract: Favorskii rearrangement of a chloro-enol-lactone (**7**), obtained in two steps from the diterpene epicandicandiol (**1**), afforded **9**, which after hydrolysis led to the gibberellin A_{12} isomer **10** The stereochemistry of the affected centres has been established as 5α-H, 6β-H revising the previously assigned 5β-H, 6α-H. The structures of minor products obtained in the autoxidation of 7-oxo-ent-kaur-16-en-18-methyl ester and in the reduction of 7-oxo-ent-kaur-5,16-dien-18→6-olide have also been established.

The chemical transformation of naturally abundant diterpenes into gibberellins has been the objective of several research groups in order to obtain less readily available gibberellins or for the synthesis of more active analogues. We can name here the studies of Galt and Hanson[1] and Cross[2] on the transformation of kaurenolides in GA_{12} and the Japanese works on the synthesis of this same gibberellin.[3,4]

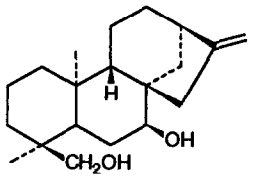
Our studies on the partial synthesis of compounds with a gibbane skeleton, using diterpenes isolated from Canary species of the *Sideritis* genus as starting material, can also be included in this objective. Thus we carried out a cyclo B reduction via a benzylic acid rearrangement starting with epicandicandiol.[5] Later and from this diterpene we also obtained a compound to which the structure of 4-*epi*-gibberellin A_{12} (**20**) was assigned in a previous communication.[6] Now in this full paper we revise this structure to the new one **10**, also giving the experimental data and the identification of other products formed when changes in the reaction conditions were introduced.

The oxidation of epicandicandiol (**1**) gave the ketoacid **2** as main product. When the crude product of the oxidation was methylated with diazomethane and chromatographed, a minor compound, the nor-ketone **4** was obtained together with the methyl ester **3**.

The reaction of the methyl 7-oxoester **3** with oxygen in potassium t-butoxide/t-butanol gave the enol-lactone **5** in good yield. When the reaction time was increased, two other secondary products were obtained and identified as compounds **11** and **12**. The structures of **11** and **12** were supported by their spectroscopic data and are also in accordance with the results obtained by Ourisson et al.[7] in the autoxidation of 3-keto-triterpenes. Analogous products have been obtained in 3-keto-steroids by treatment with potassium superoxide[8] and in aromatic diterpenes by chromic acid oxidation.[9]

Reduction of the 7-oxo-lactone **5** with sodium borohydride in methanol afforded the alcohol **6** The configuration assigned to the hydroxyl group in **6** was based on the fact that reduction of 7-oxo-kaurene derivatives gives the more stable equatorial alcohol.[1] The 6-oxo-7,18-diol **13** and the aldehyde **14** were also

formed as secondary products of the reduction. The *trans* stereochemistry of the join of the rings A and B in **13** and **14** was given in accordance with the ROESY spectrum of **13**, which showed interaction between the hydrogens at C-19 and C-20. To confirm this fact we reduced the 6-oxo derivative **13** with sodium borohydride in methanol giving the triol **15**, the ^{1}H NMR spectrum of which reveals that it must be a 7α,6α-diol and a 5β-H. The ^{1}H and ^{13}C NMR spectra of its triacetate **16** were assigned taking into consideration HMQC and HMBC experiments. The stereochemistry now assigned to H-5 in **13** indicates that that given by us to a similar compound of the trachylobane series must be corrected.[10]



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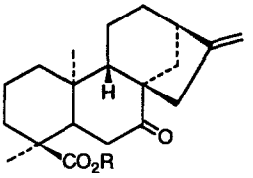
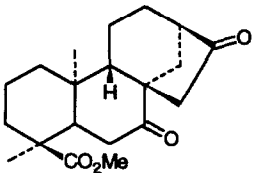


2 R = H
3 R = Me



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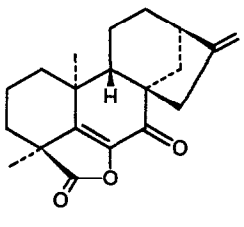
Treatment of the alcohol **6** with triphenylphosphine in carbon tetrachloride-pyridine (9:1) gave the chloro derivative **7**. The β-configuration of the chlorine atom was assumed because this reaction normally takes place with inversion of the configuration.[11]



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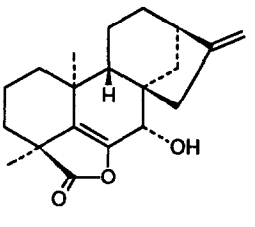

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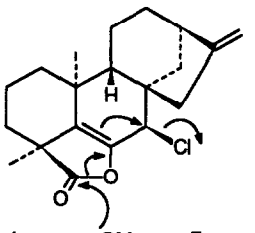

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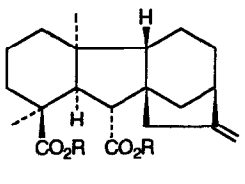
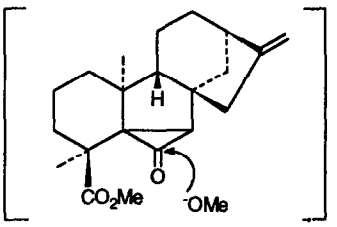


9 R = Me
10 R = H



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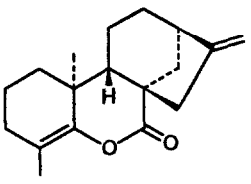
The chloro-enol-lactone **7** was treated with sodium methoxide in dimethoxyethane, yielding the analogue of gibberellin A_{12} dimethyl ester (**9**) by a Favorskii rearrangement. In the literature there are no other applications of these rearrangement conditions to a chloro-enol-lactone. The dimethyl ester **9** was treated with potassium t-butoxide in dimethyl sulphoxide giving the gibberellin A_{12} isomer **10.**



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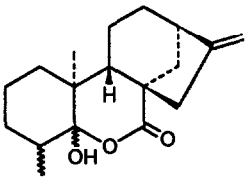
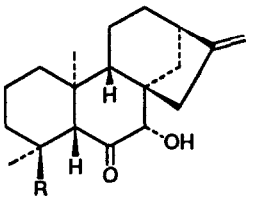
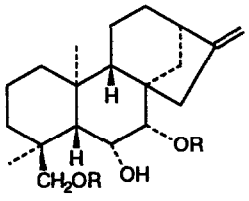


12



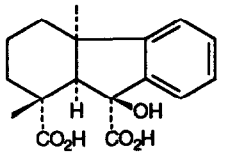
13 R = CH_2OH

14 R = CHO



15 R = H

16 R = Ac



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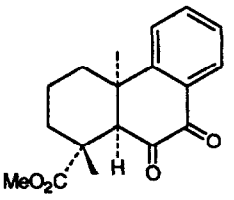

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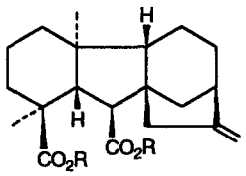
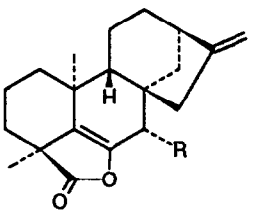


19 R = Me

20 R = H



21 R = OTs

22 R = Cl

In our previous communication the structure **19**, with an erroneous stereochemistry, was assigned to the compound obtained in the above rearrangement on the basis of the spin coupling constant observed in the ^{1}H-NMR spectrum, between the hydrogens at C-5 and C-6 (J = 12 Hz), but this coupling constant can also be explained by a 5α-H and a 6β- H as in **9**. Nakata et al.[12] determined unequivocally the stereochemistry 5α-H, 6β-OH of the hydroxy-diacid **17** obtained from the benzylic acid rearrangement of methyl 6,7-dioxo-5α,10α-

podocarpa-8,11,13-trien-15-oate (**18**). Since in this reaction the rearrangement proceeds via a keto-enol intermediate and later the hydrogen at C-5 enters by the α-face, it is logical that the same should occur in our reaction to form compound **9**. This structure was indirectly confirmed by the X-ray analysis of a trachyloba-gibberellin analogue, obtained from trachinodiol by the same reaction sequence, which showed unequivocally a 5α-H, 6β-H configuration.[10]

We also thought of preparing the tosylate **21** to produce the rearrangement with a 7α-departing group, but when the alcohol **6** was treated with tosyl chloride in pyridine, a mixture of two chlorine derivatives was obtained. Chromatography of the mixture gave the pure 7β-chloroderivative **7**. All attempts to obtain the pure α-compound **22** were unsuccessful. When the mixture was submitted to the rearrangement conditions given above only the gibberellin analogue **9** was again formed. The β-isomer at C-6 was not detected.

Engel et al. have shown[13] that in certain steroid cases, the Favorskii rearrangement in the aprotic and mildly polar medium sodium methoxide-dimethoxyethane process via a concerted cyclopropanone formation and that the stereochemistry of this cyclopropanone depends on the molecular environment. This appears to be our case, where only the α-CO_2Me at C-7 is formed stereospecifically.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-plate apparatus and are uncorrected. IR spectra were run on a Perkin Elmer 257. The NMR spectra were run on a Perkin Elmer R-32, Bruker WP200 SY and Bruker AMX 400, for solutions in $CDCl_3$. MS were taken on a Hewlett-Packard 5930A and a Shimadzu QP 2000, and HRMS on a VG-Micromass ZAB-2F. Silica gel Merck (0.05-0.2 mm) was used for column chromatography.

Treatment of epicandicandiol (1) with Jones' reagent.- Epicandicandiol (**1**) (6.8 g) in acetone (240 ml) was magnetically stirred at room temperature and Jones' reagent was added dropwise over 5 hrs.. After this time the reaction was completed (TLC). The reagent excess was destroyed with methanol. The acetone solution was filtered and the chromic salts were washed with acetone (3 x 50 ml). The combined acetonic extracts were evaporated *in vacuo* until the volume was about 50 ml, then poured into water (500ml) and extracted with ether. The usual work-up gave a gum, which was not purified. This material was disolved in dried ether and treated with a freshly prepared solution of diazomethane, and was left standing overnight in a refrigerator. The solvent was evaporated *in vacuo* giving a crude material which showed two spots on TLC (silica gel / Ag NO_3 20 %). The mixture was chromatographed over 20 % $AgNO_3$ / silica gel with 40 % ethyl acetate-light petroleum as eluent to give: **7-oxo-ent-kaur-16-ene 18-methyl ester (3)** (3.4 g as a gum which did not crystallize, ^{1}H NMR (90 MHz) δ: 1.20 (6 H, s, 2 Me), 3.60 (3 H, s, -COOMe), 4.80 (2 H, br s, $W_{1/2}$ = 6 Hz , H-17); EIMS m/z 330 $[M]^+$. Further elution afforded **17-nor-7,16-dioxo-ent-kaur-16-ene 18-methyl ester (4)** (426 mg); m.p 109-110° C (from methanol), (Found: $[M]^+$ 332.1969, calc. for $C_{20}H_{28}O_4$: $[M]^+$, 332.1987); IR ν_{max} ($CHCl_3$): 2940, 1700, 1720, 1450, 1220, and 1110 cm^{-1}; ^{1}H NMR (90 MHz) δ: 1.20 and 1.25 (each 3H, s, Me), 2.55 and 2.93 (each 1H, d, J= 11 Hz, H-15); EIMS m/z 332 $[M]^+$, 290, 272, 168, 165, 136. 109.

Auto-oxidation of 7-oxo-ent-kaur-16-ene 18-methyl ester (3).- The methyl 7-oxoester **3** (3.4 g) and potassium t-butoxide (2.3 g) were disolved in t-butanol (200 ml) and the mixture was magnetically stirred at room temperature in oxygen atmosphere for 18 hrs. Then the reaction mixture was poured into water (1000 ml) and acidified with hydrochloric acid to pH 6. A precipitated formed which was extracted with chloroform. The solvent was evaporated at vacuum to give a light brown material which showed three spots on TLC. The mixture was chromatographed over silica gel with 12 % ethyl acetate-light petroleum to yield in increasing order of polarity: **6,18-di-nor-ent-kaur-4,16-dien-7→5-olide (11)** (300 mg), m.p. 85-87° C (from MeOH / H_2O), (Found $[M]^+$ 272.1761, calc. for $C_{18}H_{24}O_2$: $[M]^+$ 272.1731); IR ν_{max} (KBr): 3080, 3020, 2930, 1740, 1660, 1690, 1450, 1300, 1250, 1230, 1180, 1120 and 890 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.07 (3H, s, H-20), 1.67 (3H, s, H-19), 4.86 and 4.98 (each 1H, br s, H-17), 2.35 and 2.66 (each ^{1}H, d, J = 15 Hz, H-15), 2.73 (1H, br s, H-13); ^{1}H NMR (50.3 MHz) δ : 35.7 (C-1), 16.9 (C-2), 30.4 (C-3), 112.9 (C-4), 147.8 (C-5), 175.0

(C-7), 48.2 (C-8), 49.4 (C-9), 36.4 (C-10), 18.7 (C-11), 31.6 (C-12), 39.1 (C-13), 36.5 (C-14), 48.7 (C-15), 155.3 (C-16), 106.7 (C-17), 15.6 (C-19), 19.5 (C-20); EIMS m/z 272 $[M]^+$ (100%), 257, 229, 148, 133, 119, 105; **6,18-di-nor-5-hydroxy-ent-kaur-16-en-7→5-olide (12)** (250 mg); m.p. 166-167° C (from MeOH); (Found: $[M]^+$ 290.1885, calc. for $C_{18}H_{26}O_3$, $[M]^+$, 290.1882); IR ν_{max} (KBr): 3490, 3030, 2940, 1710, 1650, 1450, 1300, 1210, 1050, 1000 and 890 cm^{-1}; ^1H NMR (90 MHz) δ: 0.98 (3H, s, H-20), 1.06 (3H, d, J=6 Hz, H-19), 3.70 (1 H, br s. OH), 4.80 and 4.94 (each 1H, br s, H-17); EIMS m/z 290 $[M]^+$, 272 $[M - H_2O]^+$, 147, 126 (100 %); and **7-oxo-ent-kaur-5,16-dien-18→6-olide (5)** (2.4 g), m.p. 251-253° C (from MeOH); $[\alpha]_D$ = -25° (c, 1.18, $CHCl_3$); IR ν_{max} (KBr): 2920, 1792, 1675, 1210, 1000, 950 and 890 cm^{-1}; UV λ_{max} (EtOH): 265 nm ; ^1H NMR (90 MHz) δ: 1,46 and 1.55 (each 3 H, s, Me), 4.92 (2 H, br s, $W_{1/2}$ = 12 Hz, H-17); EIMS m/z : 312 $[M]^+$, 284, 269, 242, 191.

Reduction of 7-oxo-ent-kaur-5,16-dien-18→6-olide (5).- The 7-oxo-enol-lactone **5** (2.5 g) in methanol was treated at room temperature and with magnetic stirring with sodium borohydride (200 mg) in nitrogen atmosphere. After 1/4 h. the reaction was completed, showing two spots on TLC. The mixture was poured into water (600 ml), acidified with acetic acid and extracted with ether (4 x 100 ml). The solvent was evaporated under vacuum and the crude product chromatographed over silica gel (100 g) with 20% ethyl acetate-light petroleum to yield in increasing order of polarity, **7α-hydroxy-ent-kaur-5,16-dien-18→6-olide (6)** (1.6 g) m.p. 199-201°C (from light petroleum-acetone); $[\alpha]_D$= -53° (c, 0.077, $CHCl_3$) (Found: C, 76.52 %; H, 8.60 %; $C_{20}H_{26}O_3$ requires C, 76.4 %; H, 8.33 %); IR ν_{max} (KBr) 3450, 2030, 1800, 1450, 1200, 1070, 1000, 950 and 880 cm^{-1}; ^1H NMR (90 MHz) δ: 1.30 and 1.45 (each 3H, s, Me), 4.34 (1H, s, H-7), 4.83 and 4.91 (each 1H, br s, H-17); EIMS m/z 314 $[M]^+$, 270 $[M - CO_2]^+$, 255 $[M - CO_2Me]^+$, **7α-hydroxy-6-oxo-ent-kaur-16-en-18-al (14)** (250 mg), m.p. 147-149°C (from MeOH), $[\alpha]_D$ = -83.4° (c, 0.26, $CHCl_3$), (Found: C, 75.75; H, 8.94; $C_{20}H_{28}O_3$ require C, 75.91; H, 8.92), IR ν_{max} (KBr) 3460, 3060, 2910, 2730, 1705, 1650, 1382, 1130, 1010 and 870 cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 and 1.51 (each 3H, s), 2.65 (1H, br s, H-5), 4.17 (1H, br s, H-7), 4.77 and 4.80 (each 1H, s, H-17), and 9.25 (1H, s, H-18); ^{13}C NMR (25.1 MHz) δ: 39.7 (C-1), 16.8 (C-2), 30.5 (C-3), 54.7 (C-4), 53.8 (C-5), 210.8 (C-6), 78.4 (C-7), 47.3 (C-8), 56.6 (C-9), 44.9 (C-10), 17.9 (C-11), 33.0 (C-12), 42.9 (C-13), 33.4 (C-14), 44.8 (C-15), 153.4 (C-16), 104.1 (C-17), 205.3 (C-18), 16.4 (C-19), 19.3 (C-20); and **7α,18-dihydroxy-6-oxo-ent-kaur-16-ene (13)** (500 mg), m.p. 143-145°C (from light petroleum); IR ν_{max} (KBr) 3620, 3460, 2920, 1700, 1650, 1050 and 880 cm^{-1}; ^1H NMR (200 MHz) δ: 1.06 and 1.22 (each 3H, s, 2Me), 2.61 (1H, s, H-5), 3.14 and 3.50 (each 1H, d, J= 11 Hz, H-18), 4.13 (1H, s, H-7), 4.81 and 4.85 (each 1H, br s, H-17); EIMS m/z 318 $[M]^+$.

Reduction of 13.- The 6-oxo-derivative **13** (100 mg) in methanol (10 ml) was treated with sodium borohydride (50 mg) for 3 h. The work-up was as above for **7** to give **15** (55 mg) (Found: $[M - H_2O]^+$ 302.2246, calc. for $C_{20}H_{30}O_4$: $[M - H_2O]^+$, 332.2245), ^1H NMR (200 MHz) δ: 1.15 and 1.39 (each 3H, s), 3.18 and 3.59 (each 1H, d, J = 11 Hz, H-18), 3.40 (1H, d, J = 3 Hz, H-7), 4.24 (1H, br s, H-6), 4.78 and 4.83 (each 1H, br s, H-17); EIMS m/z 302 $[M - H_2O]^+$ (100%), 289, 287, 284, 269, 253. **7,18-Diacetate (16).**- Obtained in the usual way at room temperature, (Found: $[M - AcOH]^+$ 344.2553, calc. for $C_{22}H_{32}O_3$, $[M - AcOH]^+$, 344.2351), ^1H NMR (400 MHz) δ: 0.76 and 1.78 (each 1H, td, J = 13 and 4 Hz, H-14), 1.19 and 1.42 (each 3H, s), 1.25 (1H, br s, H-9), 1.30 (1H, br s, H-5), 2.03 (1H, d, J = 16 Hz, H-15), 2.07 and 2.10 (each 3H, s), 2.25 (1H, dt, J = 16 and 3 Hz, H-15), 2.67 (1H, br s, H-13), 3.62 and 3.98 (each 1H, d, J = 11 Hz, H-18), 4.07 (1H, br s, H-6), 4.70 (1H, d, J = 3 Hz, H-7), 4.77 and 4.84 (H-17); ^{13}C NMR (50.3 MHz) δ: 37.3 (C-1), 17.9 (C-2), 33.5 (C-3), 37.0 (C-4), 48.4 (C-5), 69.3 (C-6), 77.9 (C-7), 46.4 (C-8), 55.2 (C-9), 39.1 (C-10), 18.0 (C-11), 33.3 (C-12), 43.5 (C-13), 42.2 (C-14), 44.0 (C-15), 153.9 (C-16), 103.5 (C-17), 72.1 (C-18), 19.6 (C-19), 19.2 (C-20); EIMS m/z 344 $[M - AcOH]^+$, 326, 311, 284, 269, 255, 253, 241, 213, 185.

Treatment of 7α-hydroxy-ent-kaur-5,16-dien-18→16-olide (6) with triphenylphosphine in carbon tetrachloride.- The 7α-hydroxy-enol-lactone **8** (750 mg) dissolved in carbon tetrachloride (85 ml) was treated with pyridine (9 ml) and triphenylphosphine (900 mg) and the reaction mixture was heated at reflux in a water bath for 5 h. Then the solvent was distilled at vacuum and the pyridine was removed by repeated vacuum distillations with benzene. The reaction mixture was chromatographed over silica gel (20 g) with 5% ethyl acetate-light petroleum. Fractions of 20 ml were colected. Fractions 3-5 afforded pure **7β-chloro-ent-kaur-5,16-dien-18→6-olide (7)** (520 mg), which crystallized from methanol as colourless prisms, m.p. 200-

202°C (from MeOH) (found: C, 71.96 % ; H, 7.72 % ; $C_{20}H_{25}O_2$ Cl requires: C, 72.02 % ; H, 7.53 %); IR ν_{max} (KBr) 3060, 2920, 2870, 1790, 1650, 1450, 1360, 1240, 1000, 880, 725 and 660 cm^{-1}; ^1H NMR (200 MHz) δ: 1.24 and 1.40 (each 3H, s, Me), 4.36 (1H, s, H-7), 4.85 (2H, br s, H-17); EIMS m/z 332 $[M]^+$, 298, 290, 270, 253, 187.

Favorskii rearrangement of the 7β-cloro-enol lactone 7.- The 7β-chloro-enol-lactone (7) (200 mg) dissolved in DME (20 ml) was treated with sodium methoxide (100 mg) and refluxed under inert atmosphere for 16 h. After this time the reaction was completed (one spot on TLC). The reaction mixture was poured into water and extracted with ether. The solvent was evaporated at vacuum to give a gum, which was chromatographed over silica gel with 10% ethyl acetate-light petroleum to give the **dimethyl ester of the gibberellin isomer GA_{12}** (9) (150 mg) as a gum which did not crystallize.; ^1H NMR (90 MHz) δ: 1.13 and 1.32 (each 3H, s, Me), 2.33 and 3.52 (each 1H, d, J= 12 Hz, H-5 and H-6), 3.58 and 3.63 (each 3H, s, OMe), 4.86 (2H, br s , 17-H); EIMS m/z 360 $[M]^+$, 301 $[M - CO_2Me]^+$, 285 $[M - AcOH - Me]^+$.

Gibberellin A_{12} isomer 10.- The dimethyl ester 9 (420 mg) dissolved in DMSO (65 ml) was treated with potassium t-butoxide (420 mg) and refluxed under inert atmosphere for 3.5 h. Then the reaction mixture was poured into water, acidified with 5% hydrochloric acid and extracted with ethyl ether. The solvent was evaporated at vacuum to give **10,** an amorphus solid which crystallized from ethyl acetate-chloroform as prisms (300 mg): m.p. 233-235°C; ^1H NMR (90 MHz) δ: 1.14 and 1.42 (each 3H, s, Me), 2.36 and 3.19 (each 1 H, d, J= 12 Hz, H-5 and H-6), 4.82 and 4.90 (each 1H, br s, H-17), 9.70 (2H, broad signal, 2 CO_2H); EIMS m/z 332 $[M]^+$, 314 $[M - H_2O]^+$, 286 $[M - HCO_2H]^+$, 271, 256.

Treatment of 7α-hydroxy-ent-kaur-5,16-dien-18→16-olide (6) with tosyl chloride.- The 7α-hydroxy-enol-lactone **6** (1.2 g) dissolved in dry pyridine was treated with tosyl chloride (1.5 g) and left to stand at room temperature for 24 h. After this time the reaction was completed, showing two spots on TLC with very nearly Rf. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with satured solution of copper sulfate (3 x 50 ml) to eliminate pyridine and then with water and dried over sodium sulfate. The solvent was evaporated at vacuum and the brute product cromatographied over silica gel, using 20% ethyl acetate-light petroleum as eluent to yield: **7β-chloro-ent-kaur-5,16-dien-18→6-olide (7)** (see above). Further elution afforded a mixture of (7) and (22) (NMR, MS).

Favorskii rearrangement of the 7-chloro-enol-lactones 7 and 22.- A mixture of two epimeric 7-chloro-enol-lactones 7 and 22 (500 mg) dissolved in DME (40 ml) was treated with sodium methoxide (524 mg) and refluxed under inert atmosphere for 16 h. The reaction mixture was poured into water and extracted with ether. The solvent was evaporated at vacuum to give a gum, which was cromatographied over silica gel with 10% ethyl acetate-light petroleum to give pure 9 (420 mg) (see above).

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