Regioselective Hydroxylation in the B Ring of *ent*-Kaurene; Syntheses of *ent*-7β- and 9α-Hydroxykaur-16-enes

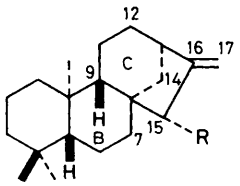
Manabu Node,*[a] Tetsuya Kajimoto,[a] Nozomu Ito,[b] Junto Tamada,[a] Eiichi Fujita,[c] and Kaoru Fuji[a]

[a] *Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan*
[b] *Research Laboratories, Nippon Shoji Kaisha Ltd., Sho 2-24-3, Ibaragi, Osaka 567, Japan*
[c] *Osaka College of Pharmacy, 10-65 Kawai 2-Chome, Matsubara 580, Japan*

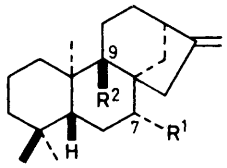
Regioselective hydroxylation at the C-7 and the C-9 position of *ent*-kaur-16-ene (**2**) was achieved *via* radical cyclization of a hydroxymethyl group introduced at the C-15 position followed by removal of the carbon atom at C-15.

Recently, we reported that *ent*-15β-hydroxykaur-16-ene (**1**) showed a potent stimulating effect on corticosterone production in isolated rat adrenal cells.[1] This finding stimulated our interest into investigating the steroidogenic effect of various monohydroxykaurenes. Hydroxylation of the unactivated carbon atom on the C ring in the kaurene skeleton has been published by Kato and Wada.[2] We also reported a more convenient hydroxylation at the C-12 and C-14 positions of *ent*-kaur-16-ene (**2**) through the regioselective C–O bond cleavage of cyclic ether intermediates with $AlCl_3$–NaI.[3] However, functionalization of the B ring of (**2**) has not been reported so far. Here, we report regioselective hydroxylation in the B ring of (**2**).

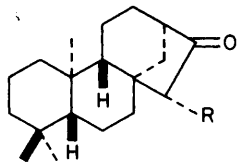
Our strategy involves the radical cyclization[4] of the newly introduced hydroxymethyl group at the C-15 position in the 17-norkaurane. From consideration of the molecular model, 15α- and 15β-hydroxymethyl groups were expected to cyclize to the C-7 and the C-9 positions, respectively, giving inter-



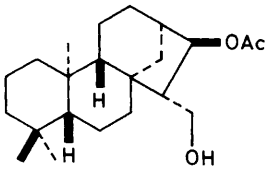
(1) R = OH
(2) R = H



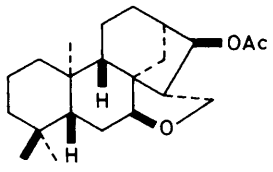
(3) R^1 = OH, R^2 = H
(4) R^1 = H, R^2 = OH



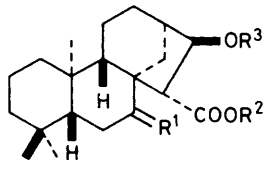
(5) R = H
(6) R = CH_2OH



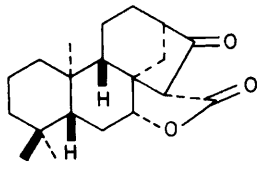
(7)



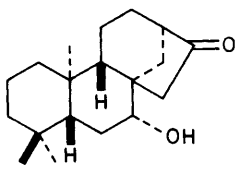
(10)



(11) R^1 = O, R^2 = H, R^3 = Ac
(12) R^1 = α-OH, β-H, R^2 = Me, R^3 = H

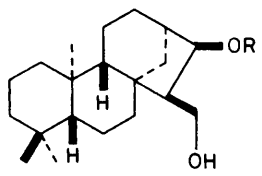


(13)

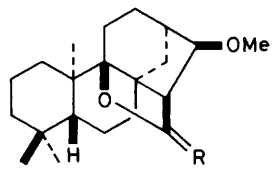


(14)

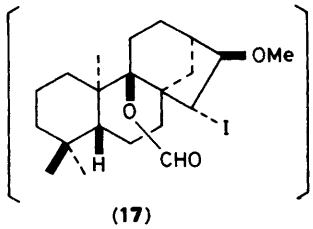
(3)



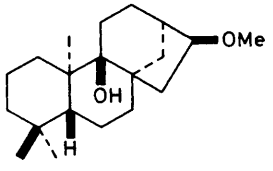
(8) R = H
(9) R = Me



(15) R = H_2
(16) R = O



(17)



(18)

(4)

mediates which can be transformed into hydroxykaurenes (**3**)† and (**4**)† by the removal of the extra carbon atom at C-15.

The reaction of the zinc enolate of ketone (**5**)[5] with formaldehyde in diethyl ether at −30 °C yielded the 15α-hydroxymethyl ketone (**6**) in 85% yield resulting from attack at the less hindered side. Since the presence of the C-16 carbonyl group effected elimination of the hydroxymethyl moiety during the radical cyclization with lead tetra-acetate, the carbonyl group in (**6**) was converted into the acetoxy group by successive treatment with NaH–MeI in dimethylformamide, $NaBH_4$ in MeOH, Ac_2O–pyridine, and $AlCl_3$–NaI in $MeCN–CH_2Cl_2$ to give (**7**) in 80% overall yield. On the other hand, the 15β-hydroxymethyl derivative (**8**) was produced in 75% yield by dehydration of (**6**) with p-$MeC_6H_4SO_3H$ in benzene with azeotropic removal of water followed by hydroboration–oxidation of the resulting α,β-unsaturated ketone. The diol (**8**) was transformed into the methoxyalcohol (**9**) in 73% overall yield by dimethylation with NaH—MeI followed by partial demethylation with $AlCl_3$–NaI.[6]

Treatment of (**7**) with lead tetra-acetate in refluxing cyclohexane for 5 h produced the cyclic ether (**10**) in 72% yield. The oxidation of (**10**) with ruthenium tetroxide[7] proceeded smoothly to give the keto-acid (**11**). Sodium borohydride reduction of (**11**) followed by acid treatment in methanol led to diol (**12**) which was converted *via* lactonization with NCS–Me_2S and oxidation into (**13**)† in 65% overall yield from (**10**). Removal of the lactone-carbonyl group was readily carried out in refluxing ethanol in the presence of potassium hydroxide to generate hydroxyketone (**14**). The desired *ent*-7β-hydroxykaur-16-ene (**3**)[8] was obtained by the Wittig reaction of the acetate of (**14**) followed by alkaline hydrolysis in 63% overall yield from (**13**).

Radical cyclization of (**9**) with lead tetra-acetate in refluxing cyclohexane yielded cyclic ether (**15**) as a major product in 47% yield. The removal of the extra carbon atom at C-15 was carried out by a radical cleavage reaction of the hemiacetal derived from the cyclic ether (**15**).[9] Namely, the lactone (**16**)† which was obtained in 68% yield by the careful oxidation of (**15**) with ruthenium tetroxide was converted into (**17**) by the di-isobutyl aluminium hydride reduction and by the hypoiodite reaction of resulting hemiacetal with lead tetra-acetate and iodine. The unstable iodoformate (**17**) was immediately reduced with Bu_3SnH in the presence of $NaBH_4$ in ethanol to give the alcohol (**18**) in 73% overall yield from (**16**). Oxidation of the methoxy group in (**18**) with ruthenium tetroxide and introduction of the *exo*-methylene group by Lombardo's procedure[10] yielded the desired *ent*-9α-hydroxy-kaur-16-ene (**4**) in 85% overall yield from (**18**).

The synthesis of 15-oxokaurenes from hydroxykaurenes is in progress since hydroxy and acyloxy groups in the antitumour active kaurenoids which have an α-methylene cyclopentanone system as the active site in the D ring appear to play an important role in enhancing the antitumour activity.[11]

Support from the Ministry of Education, Science, and Culture, Japan is gratefully acknowledged.

Received, 15th April 1986; Com. 496

† Compound (**3**): colourless powder from CH_2Cl_2 and MeOH, m.p. 116.5—117.3 °C; *m/z* 288 (M^+); $\delta_H(CDCl_3)$ 0.82, 0.88, 1.04 (each 3H, s), 3.50 (1H, dd, *J* 4 and 11 Hz, 7-H), 4.74 and 4.80 (each 1H, br. s, 17-H). This compound was identified by direct comparison with an authentic sample of (**3**).[8] (**4**): colourless needles from MeOH, m.p. 98.5—99.2 °C; *m/z* 288 (M^+); $\nu_{max.}$ ($CHCl_3$) 3600 and 1660 cm^{-1}; δ_H ($CDCl_3$) 0.82, 0.86, 1.14 (each 3H, s), 4.76 (2H, s, 17-H), $\delta_C(CDCl_3)$ 18.6, 19.3, 20.1, 21.9, 29.3, 32.4, 33.3, 33.8, 34.7, 36.5, 40.5, 41.7, 42.4, 43.9, 48.1, 49.1, 77.6 (s, C-9), 103.0 (t, C-17), and 155.3 (s, C-16). (**13**): colourless plates from MeOH, m.p. 186.5—187.2 °C; *m/z* 316 (M^+); $\nu_{max.}$ ($CHCl_3$) 1785, 1740, and 1120 cm^{-1}; $\delta_H(CDCl_3)$ 0.92, 0.94, 1.18 (each 3H, s), 2.60 (1H, t, *J* 4 Hz), 2.94 [1H, d, *J* 4 Hz (long-range coupling between 15-H and 14α-H), 15-H], and 4.16 (1H, dd, *J* 4 and 12 Hz, 7-H). (**16**): colourless plates from MeOH, m.p. 170.5—171.0 °C; *m/z* 332 (M^+); $\nu_{max.}$ ($CHCl_3$) 1750 and 1120 cm^{-1}; $\delta_H(CDCl_3)$ 0.82, 0.92, 1.08 (each 3H, s), 2.78 (1H, d, *J* 10 Hz, 15-H), 3.44 (3H, s, −OMe), and 3.94 (1H, dd, *J* 5 and 10 Hz, 16-H). The structures of all new compounds were confirmed by elemental analyses and spectroscopic data.

References

1 K. Moriwaki, M. Gomi, Y. Itoh, S. Iida, M. Tsugawa, S. Tarui, K. Fuji, M. Node, and T. Kajimoto, *Life Science*, 1986, **38**, 453.
2 N. Fukuzawa, M. Funamizu, Y. Kitahara, and T. Kato, *Chem. Lett.*, 1976, 1253; K. Wada and H. Yamashita, *Agric. Biol. Chem.*, 1980, **44**, 2249.
3 M. Node, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Tetrahedron Lett.*, 1984, **25**, 219.
4 J. Kalvoda and K. Heusler, *Synthesis*, 1971, 501; K. Heusler and T. Kalvoda, *Angew. Chem.*, 1964, **76**, 518, and references therein.
5 H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.
6 M. Node, K. Ohta, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Chem. Pharm. Bull.*, 1983, **31**, 4178.
7 P. H. J. Carlsen, T. Katzuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
8 T. Fujita, S. Takao, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2468.
9 M. Node, H. Hori, and E. Fujita, *Chem. Pharm. Bull.*, 1976, **24**, 2149; E. Fujita, I. Uchida, and T. Fujita, *ibid.*, 1974, **32**, 1656.
10 L. Lombardo, *Tetrahedron Lett.*, 1982, **23**, 4293.
11 E. Fujita, Y. Nagao, T. Kohno, M. Matsuda, and M. Ozaki, *Chem. Pharm. Bull.*, 1981, **29**, 3208; E. Fujita, Y. Nagao, M. Node, K. Kaneko, S. Nakazawa, and H. Kuroda, *Experientia*, 1976, **32**, 203.