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An Intramolecular Hydride Shift in Derivatives of Kamebakaurin and Kamebacetal A

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Derivatives of kamebakaurin and kamebacetal A with an aldehyde function at C-20 undergo an intramolecular hydride rearrangement (crossed Cannizzaro reaction) under mild basic conditions. The mechanism is discussed.

Keywords——kamebakaurin; kamebacetal A; *ent*-kaurenoid; intramolecular hydride rearrangement; crossed Cannizzaro reaction

In the previous paper,[2)] we have reported the isolation and structure elucidation of four new diterpenoids, kamebakaurin (**1**), kamebakaurinin (**2**), and kamebacetals A (**3**) and B (**4**), from *Rabdosia umbrosa* var. *leucantha* f. *Kameba*. During the course of the structure elucidation, we found that a hydride shift occurred under mild basic conditions in the *ent*-kaurene derivatives. This paper describes the results and presents a plausible mechanism.

Dihydrokamebakaurin aldehyde triacetate (**5**),[2)] obtained from kamebakaurin (**1**) by successive catalytic hydrogenation, acetylation and Jones oxidation, was treated with 5% methanolic potassium carbonate at room temperature to give compound I (**6**), mp 274—276 °C, as a major product and compound II (**7**), mp 261—263 °C, as a minor compound. Compound I (**6**) has the molecular formula $C_{20}H_{30}O_5$, on the basis of elemental analysis. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, **6** showed signals at δ 4.70 and 4.04 (each 1H, d, $J=12$ Hz) assigned to methylene protons located between an oxygen atom and a quaternary carbon and those at δ 4.63 (1H, dd, $J=10$ and 6 Hz) and 3.88 (1H, m, $W_{1/2}=8$ Hz) assigned to protons on a carbon having a secondary hydroxy group, in addition to the signals at δ 1.12 (3H, d, $J=7$ Hz), and at δ 1.02 and 0.92 (each 3H, s) assigned to one secondary and two tertiary methyl groups. On the other hand, the ^{1}H-NMR spectrum of **6** did not show any signal due to an aldehyde group or C-14α-H, which were observed in that of the starting material (**5**). The above-mentioned spectral data clearly exclude the structure (**8**) for compound I, in which a cyclic hemiacetal exists between the aldehyde group at C-20 and the α-hydroxy group at C-7. Acetylation of **6** with a mixture of acetic anhydride and pyridine gave the diacetate (**9**), mp 243—246 °C, in the ^{1}H-NMR spectrum of which a signal (δ 5.25, dd, $J=11$ and 6 Hz) assigned to 7β-H was observed, as in the case of the starting material (**5**), suggesting the presence of the 7α-hydroxy group intact. The diacetate (**9**) contained a tertiary unacetylated hydroxy group as judged from the infrared (IR) spectrum (ν_{max} 3500 and 3400 cm^{-1}). Considering the structure of the starting material, these findings led to the structure **6** for compound I. The stereochemistry of the hydroxy group at C-1 was determined as β by analyzing the coupling pattern of the ^{1}H-NMR signal assigned to C-1-H (δ 3.88, 1H, m, $W_{1/2}=8$ Hz).

A minor product, compound II (**7**), has the same molecular formula as **6** and showed a very similar ^{1}H-NMR spectrum to that of **6** except for the coupling pattern of the signal

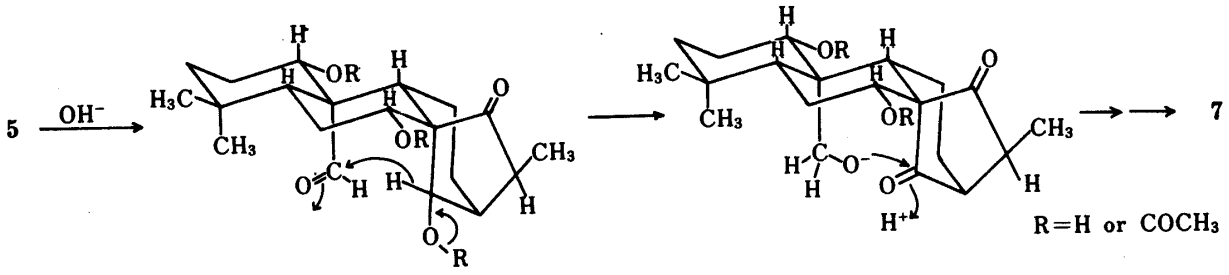


Chart 1

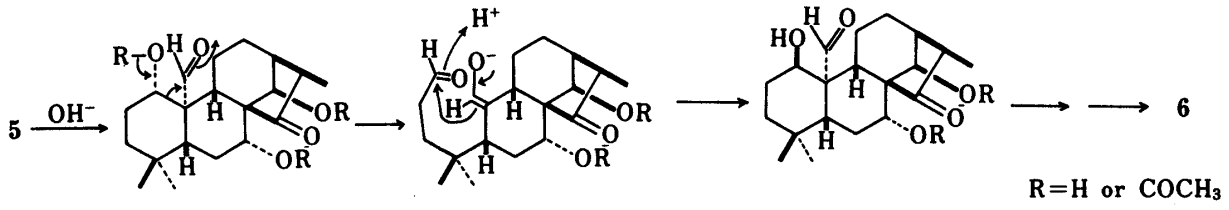
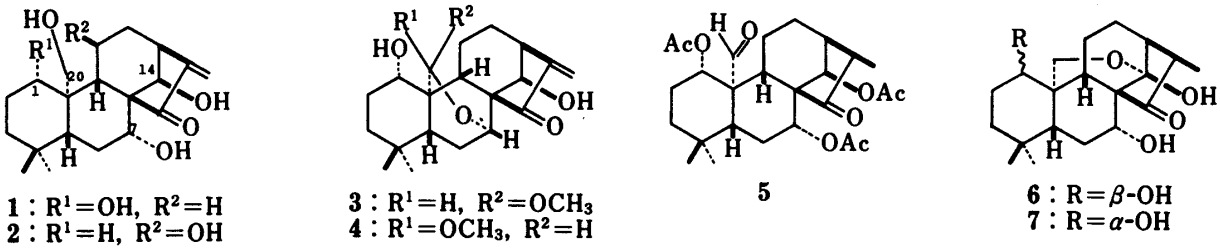
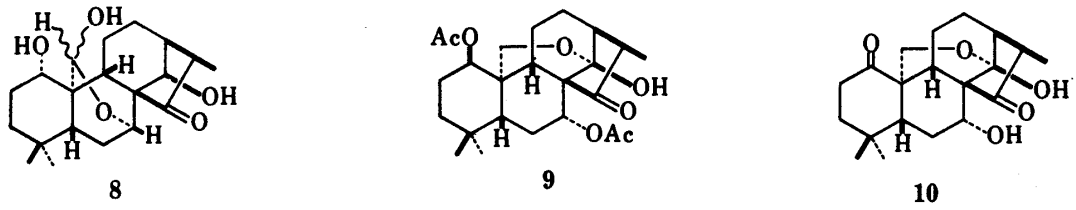


Chart 2





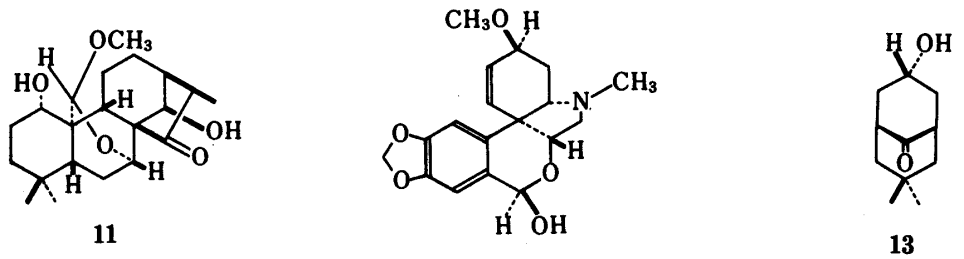


Fig. 1

assigned to C-1-H (δ 3.50, dd, J=9 and 6 Hz). These findings suggest that compound II is the epimer at C-1 of compound I (**6**), and the structure could be represented as **7**. This assignment was supported by the fact that the AB doublets due to the protons at C-20 in **7** resonated at lower field (δ 4.62 and 5.12) compared to those in **6** and was established by the fact that compounds I (**6**) and II (**7**) gave the same ketone (**10**) [IR ν_{max} 1700 cm^{-1}] on Jones oxidation.

The mechanism of the conversion from **5** to **7** was presumed to proceed according to the route shown in chart 1, involving a hydride shift from C-14α to C-20. On the other hand, the mechanism of the conversion from **5** to **6** may follow the route shown in Chart 2. Namely, ring

A undergoes ring opening by retro-Aldol reaction and then cyclizes again. In the cyclization stage, the C-1β-hydroxy compound is formed through kinetic control as the consequence of maximum overlapping of π-orbitals in the anti-periplanar arrangement of the double bonds of $-C_1=O$ and C_{10}-enolate.[3,4] After that, the hydride rearrangement from C-14α to C-20 gives **6**.

In the next step, we treated demethyldihydrokamebacetal A (**8**), obtained from kamebacetal A (**3**) by catalytic hydrogenation followed by hydrolysis with oxalic acid, under the same conditions. In this case, we obtained only compound II (**7**) as the product. The difference between the reactions of **5** and **8** could be explained by considering the possibility that the oxygen functional group (OAc or OH) at C-1 is attacked more easily than that at C-14 in **5** compared with the case of **8**. Inspection of a Dreiding model revealed that the 14β-OAc (or OH) group is actually hindered by the 7α-OAc (or OH) group *via* 1,3-diaxial interaction.

This type of intramolecular hydride rearrangement, *i.e.* crossed Cannizzaro reaction, also occurs when pretazettine (**12**)[5] and *endo*-7,7-dimethylbicyclo[3.3.1]-nonan-3-ol-9-one (**13**)[6] are treated with base. These reactions suggest that hydride rearrangement occurs between a spatially closely located carbonyl group and carbinyl functional group on treatment with base. The fact that a nuclear Overhauser effect (16%) was observed for 20-H, on irradiation at the frequency of 14α-H in the ^{1}H-NMR spectrum of **5**, supports the proposed reaction mechanism.

Experimental

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-510 spectrometer for KBr disks. ^{1}H-NMR spectra were taken on a JEOL PS 100 spectrometer with tetramethylsilane as an internal standard; chemical shifts are given in δ (ppm) values. Mass spectra were determined with a JEOL 01SG or JMS D-300 spectrometer. Kieselgel 60 (0.063—0.200 mm, Merck) was used for chromatography and precoated Silica gel plates F_{254} (0.25 and 0.5 mm in thickness) were used for thin layer chromatography. Extracts were dried over anhydrous sodium sulfate or magnesium sulfate.

Treatment of Dihydrokamebakaurin Aldehyde Triacetate (5) with Potassium Carbonate——Dihydrokamebakaurin aldehyde triacetate (**5**) (37 mg) dissolved in 5% aqueous methanolic potassium carbonate (5 ml) was kept for 18 h at room temperature. Water (25 ml) was added to the mixture and the whole was extracted with AcOEt (25 ml × 3). The AcOEt extract was washed with H_2O, dried and evaporated *in vacuo* to give a residue (20 mg), which was separated by preparative layer chromatography ($CHCl_3$–MeOH, 19 : 1, developed three times, and then $CHCl_3$–MeOH, 7 : 1) to give compound I (**6**) (11 mg) and compound II (**7**) (6 mg), each as colorless needles.

Compound I (**6**): mp 274—276 °C. IR ν_{max}: 3350, 1730, 1105 cm^{-1}. ^{1}H-NMR (C_5D_5N) δ: 4.70 (1H, d, J=12 Hz, 20-H_1), 4.63 (1H, dd, J=10, 6 Hz, 7-H), 4.04 (1H, d, J=12 Hz, 20-H_1), 3.88 (1H, m, $W_{1/2}$=8 Hz, 1-H), 3.18 (1H, m, 16-H), 1.12 (3H, d, J=7 Hz, 16-Me), 1.02, 0.92 (each 3H, s, 4-Me_2). MS *m/z*: 350 (M^+). *Anal.* Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.64.

Compound II (**7**): mp 261—263 °C. IR ν_{max}: 3400, 3250, 1740 cm^{-1}. ^{1}H-NMR (C_5D_5N) δ: 8.24 (1H, br s, OH), 7.46 (1H, m, OH), 6.23 (1H, br d, J=4 Hz, OH), 5.12, 4.62 (each 1H, d, J=11 Hz, 20-H_2), 4.55 (1H, dd, J=11, 6 Hz, 7-H), 3.50 (1H, dd, J=9, 6 Hz, 1-H), 3.17 (1H, m, 16-H), 1.13 (3H, d, J=7 Hz, 16-Me), 0.92, 0.81 (each 3H, s, 4-Me_2). MS *m/z*: 350.2126 $(M)^+$. Calcd for $C_{20}H_{30}O_5$: 350.2094.

Acetylation of Compound I (6)——Compound I (**6**) (14 mg) dissolved in a mixture of acetic anhydride and pyridine (1 : 1, v/v; 2 ml) was kept for 48 h at room temperature. Excess MeOH was added to the mixture and the solvent was evaporated off *in vacuo* to give a residue (22 mg), which was recrystallized from MeOH to give the diacetate (**9**) (3.2 mg) as colorless needles, mp 243—246 °C. IR ν_{max}: 3500, 3400, 1740, 1250, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.25 (1H, dd, J=11, 6 Hz, 7-H), 4.60 (1H, d, J=12 Hz, 20-H_1), 4.51 (1H, m, $W_{1/2}$=8 Hz, 1-H), 4.36 (1H, d, J=12 Hz, 20-H_1), 2.81 (1H, m, 16-H), 1.98, 2.00 (each 3H, s, Ac_2), 1.07 (3H, d, J=7 Hz, 16-Me), 0.97, 0.92 (each 3H, s, 4-Me_2). MS *m/z*: 434.2292 $(M)^+$. Calcd for $C_{24}H_{34}O_7$: 434.2305.

Jones Oxidation of Compound I (6)——Jones reagent (1 drop) was added to a solution of compound I (**6**) (5 mg) in anhydrous Me_2CO (2 ml) and the mixture was stirred for 5 min at 0 °C. MeOH was added to the reaction mixture to decompose the excess reagent and the solvent was evaporated off *in vacuo* to give a residue which was extracted with AcOEt (10 ml × 3) after addition of H_2O (10 ml). The AcOEt extract was washed with H_2O, dried and evaporated *in vacuo* to give a residue (3 mg), which was recrystallized from MeOH to give the ketone (**10**) as colorless needles, mp 208—210 °C. IR ν_{max}: 3550, 3460, 3270, 1725, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.88 (1H, s, OH), 4.72, 4.16 (each 1H, d, J=12 Hz, 20-H_2), 4.10 (1H, ddd, J=12, 6, 5 Hz, changed to dd on addition of D_2O, J=12, 6 Hz, 7-

H), 3.06 (1H, d, $J=5$ Hz, OH), 2.19 (1H, m, 16-H), 1.23 (3H, s, 4-Me), 1.06 (3H, d, $J=7$ Hz, 16-Me), 0.99 (3H, s, 4-Me). MS *m/z*: 348.1931 $(M)^+$. Calcd for $C_{20}H_{28}O_5$: 348.1937.

Jones Oxidation of Compound II (7)——Jones reagent (1 drop) was added to a solution of compound II (7) (5 mg) in anhydrous Me_2CO (2 ml) and the mixture was stirred for 5 min at 0 °C. Work-up as before gave a residue which was recrystallized from MeOH to give the ketone (**10**) as colorless needles, mp 209—210 °C. This compound was identical with an authentic sample of the ketone (**10**) on the basis of mixed melting point determination and comparison of IR spectra.

Demethylation of Dihydrokamebacetal A (11)——Oxalic acid (10 mg) was added to a solution of dihydrokamebacetal A (**11**) (26 mg) in a mixture of tetrahydrofuran and H_2O (2 : 1, v/v) (3 ml) and the mixture was refluxed for 2 h. The solvent was removed *in vacuo* to give a residue, which was extracted with AcOEt (20 ml × 3) after addition of H_2O (20 ml). The AcOEt extract was washed with H_2O, dried and evaporated *in vacuo* to give a residue (20 mg), which was purified by preparative layer chromatography (CH_2Cl_2–Me_2CO, 7 : 3) to give demethyldihydrokamebacetal A (**8**) (10 mg) as an amorphous powder. IR ν_{max}: 3450, 3200, 1730, 1680, and 1095 cm^{-1}. ^{1}H-NMR (C_5D_5N–$CDCl_3$) δ: 10.59 (*ca.* 0.2H, br s, 20-H), 6.00 (*ca.* 0.8H, br s, 20-H), 5.40 (1H, d, $J=2$ Hz, 14-H), 4.41 (*Ca.* 1H, m, 7-H), 3.55 (1H, dd, $J=10$, 6 Hz, 1-H), 1.17 (3H, d, $J=7$ Hz, 16-Me), 0.93, 0.82 (each 3H, s, 4-Me_2). MS *m/z*: 350.2046. Calcd for $C_{20}H_{30}O_5$: 350.2094.

Treatment of Demethyldihydrokamebacetal A (8) with Potassium Carbonate——Demethyldihydrokamebacetal A (**8**) (40 mg) dissolved in 5% aqueous methanolic potassium carbonate (12 ml) was kept for 40 h at room temperature. Work-up as before gave a residue (36 mg), which was recrystallized from MeOH to give compound II (**7**) (20 mg) as colorless needles, mp 266—268 °C. This compound was identical with compound II (**7**) derived from **5** on the basis of mixed melting point determination and comparison of IR spectra.

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References and Notes

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