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Terpenoids. XLIX. Reactions of Shikoccin: Oxidation, Catalytic Reduction, and Conversion into the Abietane Skeleton

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The Jones oxidation of shikoccin (**1**), the major diterpenoid of *Rabdosia shikokiana* var. *occidentalis*, unexpectedly provided products **3** and **4**. Tetrahydroshikoccin (**6**) afforded the abietane-type compound **11** upon Jones oxidation.

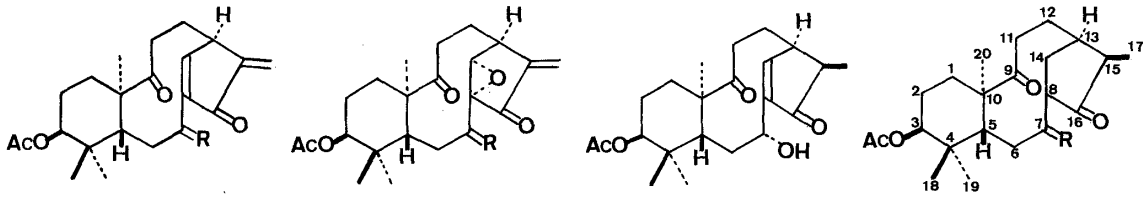
Keywords——shikoccin; Jones oxidation; *ent*-kaurane; abietane; *Rabdosia shikokiana*; Labiatae; epoxidation; diterpenoid

In the preceding paper,[1] we described the structures of five new diterpenoids isolated from *Rabdosia shikokiana* (MAKINO) HARA var. *occidentalis* (MURATA) HARA (Labiatae). Here, we report the chemical reactions of shikoccin (**1**), the major diterpenoid from *R. shikokiana* var. *occidentalis*.

The Jones oxidation of shikoccin (**1**) furnished the corresponding ketone **2**, epoxyshikoccin (**3**) which was identical with the natural product, and an epoxyketone **4** in 6.4%, 5.3%, and 13.2% yields, respectively. Though the oxidation of a secondary allylic alcohol with the Jones reagent to the corresponding ketone accompanied with epoxidation of the double bond is known in diterpenoid[2] and steroid[3] chemistry, the formation of an epoxide while the hydroxyl group remains intact is unprecedented.[4] The structure of the epoxyketone **4** was supported by the following spectral characteristics: i) the absence of a hydroxy absorption in the infared (IR) spectrum, ii) disappearance of the proton nuclear magnetic resonance (^{1}H-NMR) signal at δ 4.64 (dd, J=11.5 Hz) due to the hydrogen at C-7 in shikoccin (**1**), iii) a remarkable upfield shift of H-14 (from 7.23 in **1** to 3.70 in **4**). On hydrogenation over the Adams catalyst, shikoccin (**1**) afforded dihydroshikoccin (**5**) and tetrahydroshikoccin (**6**), which gave an acetate **7** on acetylation. On the other hand, hydrogenolysis occurred with palladium carbon to provide the deoxy derivative **8** together with **6**.

The molecular structure of shikoccin acetate (**9**) in the crystalline state has been determined to be as shown in the Fig.[5] In this structure, one face of the cyclopentene ring is blocked by the 10-membered ring, while the other is relatively unhindered. A similar environment might be present in solution, if the conformation of this molecule does not change much on going from the crystalline state to the solution state. The conformation of shikoccin (**1**) might be similar to that of shikoccin acetate (**9**), because the ^{1}H-NMR pattern of the characteristic signals of both compounds closely resembled each other.[1] The only notable difference was the downfield shift (from δ 4.64 in **1** to δ 5.50) of the H-7 signal in the acetate **9**. The same coupling pattern (dd, J=11.5 Hz), however, was observed for the H-7 signal in both

compounds, again supporting the above assumption. Thus, hydrogenation from the less hindered α side of the cyclopentene ring in **1** would occur preferentially to provide the dihydroshikoccin (**5**) and tetrahydro derivatives **6** and **8**.

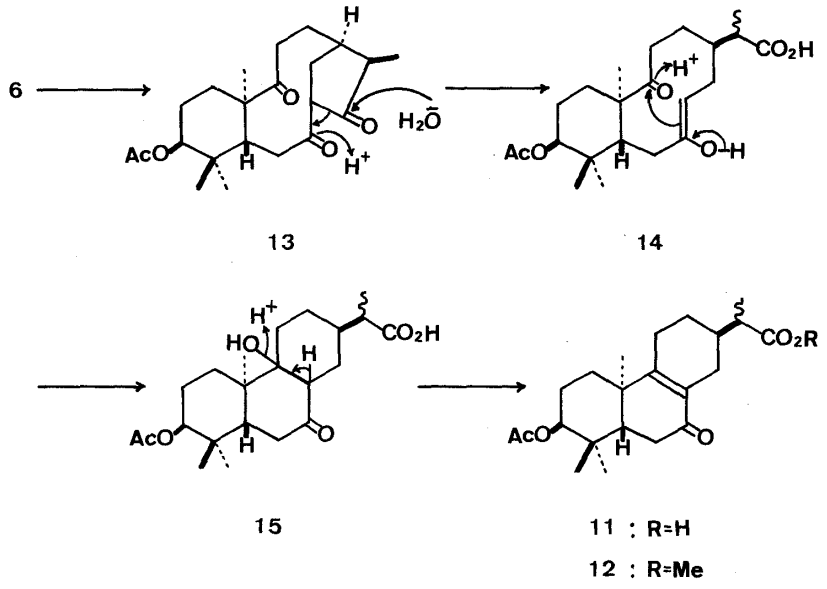


1: R=α-OH, β-H
2: R=O
9: R=α-OAc, β-H

3: R=α-OH, β-H
4: R=O

5

6: R=α-OH, β-H
7: R=α-OAc, β-H
8: R=H_2
10: R=O



13 **14**

15

11 : R=H
12 : R=Me

Chart 1

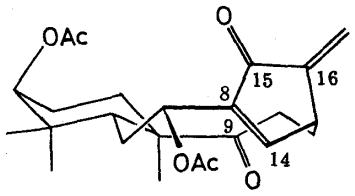


Fig. Molecular Structure of Shikoccin Acetate (**9**)

The Jones oxidation of tetrahydroshikoccin (**6**) did not afford the expected ketone **10** but gave an unexpected product **11**, $C_{22}H_{32}O_5$, in 95.6% yield. The carboxyl group was confirmed by esterification with diazomethane. The remaining three oxygen atoms in the ester **12** could be assigned to a secondary acetoxyl group at C-3 [$\nu_{max}^{CHCl_3}$ 1725 cm^{-1}, δ 2.06 ppm (3H, s), 4.73 ppm (1H, br t, J=3 Hz)] and an α,β-unsaturated carbonyl group ($\nu_{max}^{CHCl_3}$ 1650, 1615 cm^{-1}, λ_{max}^{MeOH} 250.5 nm). Singlet signals at δ 165.7 and 129.2 ppm in the carbon 13 nuclear magnetic resonance (^{13}C-NMR) spectrum indicated that no hydrogen atom was attached to the carbon atoms in the conjugated double bond system. These spectral data together with the ^{13}C-NMR spectral data (see Experimental) support the structure **11** for the oxidation product. A possible pathway for the formation of abietane-type skeleton from **6** is shown in Chart 1.

Thus, the retro-aldol type cleavage of 1,3-diketone **13** should provide **14** followed by aldol condensation to give **11** as a final product.

Antitumor activities of the epoxyketone **4** and the natural products have been tested. The results will be the subject of the following paper.

Experimental

^{1}H-NMR spectra were recorded on a Varian T-60 NMR spectrometer or a JEOL JNM-FX100 spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were obtained with a JEOL JNM-FX100 spectrometer in $CDCl_3$ solution with TMS as an internal standard. Chemical shifts are given in δ value (ppm). IR spectra were measured on a EPI-S_2 spectrophotometer. Ultraviolet (UV) spectra were measured on a Hitachi EPS-3 spectrometer. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-O1SG double-focusing mass spectrometer. Preparative thin layer chromatography (PTLC) was performed on plates of silica gel (Kieselgel 60 F_{254}, Merck).

The Jones Oxidation of Shikoccin (1)——The Jones reagent (6 drops) was added to a solution of shikoccin (**1**) (102 mg) in acetone (15 ml) under ice-cooling, and the mixture was stirred for 3 h. After addition of methanol, the reaction mixture was neutralized with 5% aq. Na_2CO_3, concentrated under reduced pressure, and extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to give a residue. PTLC of the residue with chloroform–acetone (9 : 1) afforded the unstable oily ketone **2** (6.5 mg, 6.4%), epoxyshikoccin (**3**) (57 mg, 53.6%), and the epoxyketone **4** (14 mg, 13.2%).

The Ketone 2——IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1690, 1650, 1610, 1248. ^{1}H-NMR: 0.89 (3H, s, $-CH_3$), 1.02 (3H, s, $-CH_3$), 1.06 (3H, s, $-CH_3$), 2.05 (3H, s, $-OCOCH_3$), 3.73 (1H, m, H-13), 4.79 (1H, t, J=3 Hz, H-3), 5.57, 6.28 (each 1H, br s, H_2-17), 7.12 (1H, d, J=2 Hz, H-14). HRMS *m/e*: 372.194 (Calcd for $C_{22}H_{28}O_5$, 372.194).

The Epoxyketone 4——mp 199—202 °C (from ethyl acetate–hexane). *Anal.* Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found C, 68.00; H, 7.34. UV λ_{max}^{MeOH} nm (ε): 232.5 (5850). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1715, 1700 (sh), 1640, 1250. ^{1}H-NMR: 0.94 (3H, s, $-CH_3$), 0.98 (3H, s, $-CH_3$), 1.03 (3H, s, $-CH_3$), 2.08 (3H, s, $-OCOCH_3$), 3.26 (1H, br s, H-13), 3.70 (1H, s, H-14), 4.76 (1H, br t, J=3 Hz, H-3), 5.57, 6.27 (each 1H, s, H_2-17).

Catalytic Reduction of Shikoccin (1) over the Adams Catalyst——Shikoccin (**1**) (79 mg) was hydrogenated in methanol with PtO_2 (4 mg) for 7 h under atmospheric pressure. The oily product was separated by PTLC with chloroform–acetone (4 : 1) to afford oily dihydroshikoccin (**5**) (10 mg, 12.6%) and tetrahydroshikoccin (**6**) (36 mg, 45.1%).

Dihydroshikoccin (5)——IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1725, 1695, 1625, 1250. ^{1}H-NMR: 1.02 (6H, s, $-CH_3 \times 2$), 1.05 (3H, s, $-CH_3$), 1.09 (3H, d, J=8 Hz, $-CH_3$), 2.21 (3H, s, $-OCOCH_3$), 3.24 (1H, m, H-13), 4.58 (1H, dd, J=11.5 Hz, H-7), 4.78 (1H, t, J=3 Hz, H-3), 7.34 (1H, d, J=3 Hz, H-14). HRMS *m/e*: 376.224 (Calcd for $C_{22}H_{32}O_5$, 376.222).

Tetrahydroshikoccin (6)——mp 219—221 °C (from ethyl acetate). *Anal.* Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.01; H, 9.29. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490, 1720, 1260. ^{1}H-NMR: 0.91 (6H, s, $-CH_3 \times 2$), 1.02 (3H, s, $-CH_3$), 1.12 (3H, d, J=8 Hz, $-CH_3$), 2.05 (3H, s, $-OCOCH_3$), 4.35 (1H, dd, J=11.5 Hz, H-7), 4.62 (1H, t, J=3 Hz, H-3).

The Acetate 7——Tetrahydroshikoccin (**6**) (28 mg) was acetylated with 1 ml of a 1 : 1 mixture of acetic anhydride and pyridine overnight. Usual work-up followed by recrystallization from methanol afforded the acetate **7** (19 mg, 61.1%), mp 191—193 °C. *Anal.* Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1250. ^{1}H-NMR: 0.91 (6H, s, $-CH_3 \times 2$), 1.22 (3H, s, $-CH_3$), 1.10 (3H, d, J=8 Hz, $-CH_3$), 1.96 (3H, s, $-OCOCH_3$), 2.07 (3H, s, $-OCOCH_3$), 4.63 (1H, t, J=3 Hz, H-3), 5.42 (1H, dd, J=11.5 Hz, H-7).

The Jones Oxidation of Tetrahydroshikoccin (6)——The Jones reagent (0.6 ml) was added to a solution of tetrahydroshikoccin (**6**, 305 mg) in acetone (50 ml) under ice-cooling, and the mixture was stirred for 2 h. After addition of methanol, the solvent was evaporated off under reduced pressure. The residue was taken up in water and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave **11** (290 mg, 95.6%), mp 186—191 °C (dec.) (from ethyl acetate). *Anal.* Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.42; H, 8.87. UV λ_{max}^{EtOH} nm (ε): 248.5 (9500). IR ν_{max}^{KBr} cm^{-1}: 3250, 2700—2300, 1734, 1710, 1658, 1618, 1600, 1256. ^{1}H-NMR: 0.89 (3H, s, $-CH_3$), 1.02 (3H, s, $-CH_3$), 1.14 (3H, s, $-CH_3$), 1.21 (3H, d, J=8 Hz, $-CH_3$), 2.08 (3H, s, $-OCOCH_3$), 4.75 (1H, br t, J=3 Hz, H-3), 8.65 (1H, br, $-COOH$).

Methylation of 11——An ethereal solution of diazomethane was added to a solution of **11** (203 mg) in methanol (15 ml), and the mixture was left overnight. After addition of acetic acid, the solvent was removed under reduced pressure to leave a residue, which was chromatographed over silica gel (10 g) with chloroform to give the ester **12** as a colorless oil (118 mg, 56.1%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1650, 1615, 1255. ^{1}H-NMR: 0.87 (3H, s, $-CH_3$), 1.02 (3H, s, $-CH_3$), 1.13 (3H, s, $-CH_3$), 1.19 (3H, d, J=8 Hz, $-CH_3$), 2.06 (3H, s, $-OCOCH_3$), 3.68 (3H, s, $-COOCH_3$), 4.73 (1H, br t, J=3 Hz, H-3). ^{13}C-NMR: 14.7 (q), 18.8 (q), 21.1 (q), 21.3 × 2 (d, q), 22.8 (t), 24.0 (t), 25.5 (t), 26.5 (t), 26.9 (q), 29.8 (t), 34.7 (t), 35.7 (d), 36.6 (s), 39.1 (s), 43.9 (d), 51.3 (q), 76.6 (d), 129.2 (s), 165.7 (s), 170.0 (s), 176.1 (s), 198.7 (s). HRMS *m/e*: 390.243 (Calcd for $C_{23}H_{34}O_5$, 390.241).

References and Notes

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