

Bitter Principles of *Ailanthus altissima* SWINGLE. Conversion of Ailanthone into Shinjulactone C¹⁾

Masami ISHIBASHI, Takahiko TSUYUKI,* and Takeyoshi TAKAHASHI*

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

(Received April 13, 1985)

Ailanthone was converted into shinjulactone C with a hexacyclic 1 α ,12 α :5 α ,13 α -dicyclo-9 β H-picrasane skeleton. The key reaction consists of an intramolecular ionic [4+2] cycloaddition between a pentadienyl cation and an olefin.

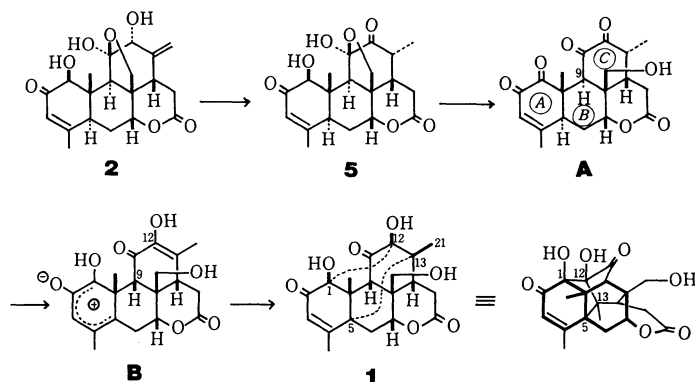
In the course of studies on the bitter principles of Simaroubaceous plants, we obtained three new compounds possessing modified picrasane skeletons, shinjudilactone,²⁾ shinjulactone B,³⁾ and shinjulactone C (**1**),²⁾ from *Ailanthus altissima* SWINGLE (Japanese name: Shinju or Niwaurushi). Structures of these new quassinoids were determined by single crystal X-ray diffraction analyses. These migrated picrasane skeletons are very interesting from the biogenetical view points and stimulated us to study on the backbone-rearrangement reactions leading to the modified picrasanes. Since it seems possible that these migrated quassinoids are biogenetically derived from ailanthone (**2**),⁴⁾ a main quassinoid of this plant, chemical conversions of ailanthone (**2**) into the migrated picrasanes were investigated. In previous papers^{2,5)} we have reported a transformation of ailanthone (**2**) into shinjudilactone through benzilic acid rearrangement. This paper deals with chemical conversion of ailanthone (**2**) into shinjulactone C (**1**) with a novel 1 α ,12 α :5 α ,13 α -dicyclo-9 β H-picrasane skeleton.

A conceivable biogenetic pathway from ailanthone (**2**) to shinjulactone C (**1**) via intermediates **A** and **B** is shown in Scheme 1. An inversion of a chiral center at C-9 position must occur prior to the cycloaddition of $\Delta^{12(13)}$ -double bond in ring C with a pentadienyl cation in ring A. If the inversion of 9 α -H into 9 β -H occurs and both B and C rings adopt boat forms, the rings A and C would be sterically very close to each other enough to overlap π -orbitals.

According to these considerations, chemical conversion of ailanthone (**2**) into shinjulactone C (**1**)

was investigated. Prior to the intramolecular cycloaddition, the compound which corresponds to the hypothetical intermediate **A** or **B** has to be prepared from ailanthone (**2**). For this purpose there seem to be three problems to be examined; i) an isomerization of $\Delta^{13(21)}$ -exocyclic double bond into $\Delta^{12(13)}$ endocyclic double bond, ii) a selective oxidation of the hydroxyl group at C-1 position, and iii) an inversion of the stereochemistry of the hydrogen atom at C-9 position.

In regard to the third problem J. Polonsky *et al.* described that when glaucanol (**3**) was heated in pyridine, the inversion of 9 α -H occurred to afford a 9 β -H derivative (**4**).⁶⁾ According to this procedure, an isomerization of ailanthone (**2**) was examined. But on heating in pyridine under reflux for 10 h, **2** produced isoailanthone (**5**) in 67% yield.²⁾ Though it was shown that the isomerization proceeded without an inversion of the C-9 position, this experiment corresponds to giving a solution to the problem i discussed above. However the heating of ailanthone (**2**) in pyridine was continued for longer time to furnish a complex mixture, from which shinjulactone C (**1**) was obtained in 5–8% yield together with isoailanthone (**5**; 30–40% yield) and many unidentified by-products. Since the reaction was carried out in atmosphere, isoailanthone (**5**) or other intermediates must suffer autoxidation, which was supported by the following experiment; neither ailanthone (**2**) nor isoailanthone (**5**), on heating in argon atmosphere, yielded shinjulactone C (**1**). The reaction carried out in atmosphere was shown to yield so many by-products by HPLC examination and the separation of them was



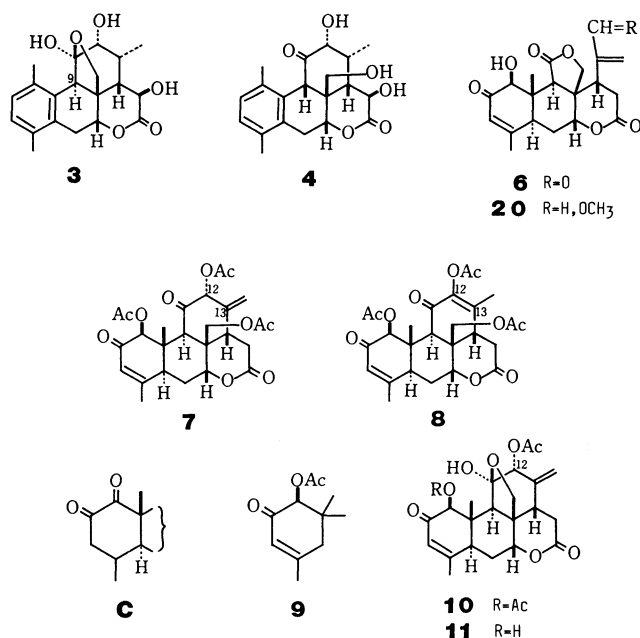
Scheme 1.

found to be so difficult that any attempts to isolate intermediates corresponding to **A** or **B** were not successful.

Instead of the isolation of intermediates, a stepwise conversion from aianthone (**2**) into shinjulactone C (**1**) was then investigated. First examination concerned a direct oxidation of the hydroxyl group at C-1 of aianthone (**2**). But oxidation of **2** with Jones reagent afforded unidentified polar products, while oxidation of aianthone (**2**) with lead tetraacetate or manganese dioxide gave an 11,12-seco aldehyde (**6**);⁴ this suggested that the protection of hydroxyl groups in C ring was required.

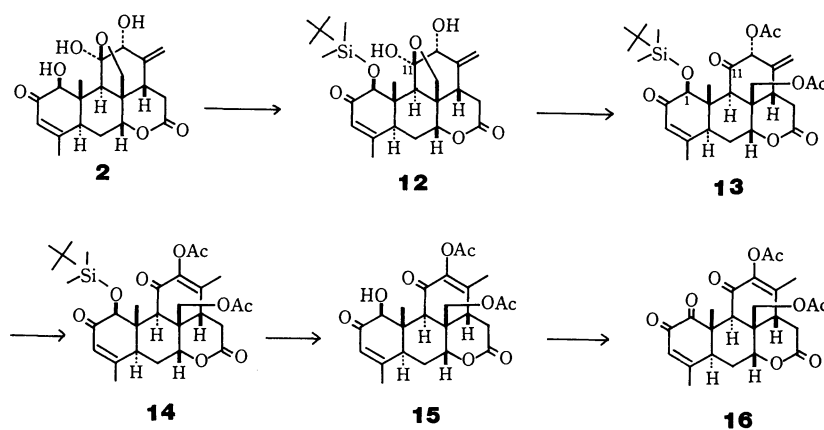
On heating in pyridine aianthone triacetate (**7**)⁷ isomerized to enol acetate (**8**), which was also obtained by acetylation of isoaiianthone (**5**). Partial hydrolysis of the acetates (**7** and **8**) was examined under several conditions, but it was found that the selective removal of the acetyl group at C-1 was not easy. Under alkaline conditions (NaHCO_3 , NH_3 , etc.) the hydrolysis reactions did not proceed cleanly, probably owing to the opening of δ -lactone in D ring and an isomerization to α -diketone (C-type) in A ring, the latter being proposed in the case of 6-acetoxyisophorone (**9**).⁸ Heating might cause a backbone rearrangement in C ring.^{2,5} Acidic hydrolysis of the triacetate (**7**) afforded 1,12-di-*O*-acetylaiianthone (**10**) and 12-*O*-acetylaiianthone (**11**), but the 1-hydroxy-12,20-di-*O*-acetyl derivative was not obtained.

Discrimination of the hydroxyl group at C-1 from those in C ring was accomplished as follows (Scheme 2). Treatment of aianthone (**2**) with *t*-butyldimethylsilyl chloride in the presence of imidazole in *N,N*-dimethylformamide⁹ afforded a monosilyl derivative (**12**; 91% yield), which underwent acetylation to give a monosilyl diacetate (**13**; 92% yield). On heating in pyridine, **13** isomerized to a monosilyl enol acetate (**14**; 95% yield). ^1H NMR spectrum of **14** showed a signal due to vinyl methyl protons (δ 1.79, 3H, s; $\text{C}_{(13)}\text{-CH}_3$) instead of signals due to *exo*-methylene (δ 5.14 and 5.20, each 1H, s; $\text{C}_{(21)}\text{-H}$) and a proton (δ 5.45, 1H, s; $\text{C}_{(12)}\text{-H}$) attached to a carbon atom with an acetoxyl



group for **13**. Signals due to a proton attached to a carbon atom with a silyl group appeared at δ 3.97 (1H, s; $\text{C}_{(1)}\text{-H}$) in ^1H NMR spectra of both **13** and **14**. ^{13}C NMR spectrum of **13** showed a signal at δ 198.9 due to a carbonyl carbon atom at C-11 position, while a signal due to a hemiacetal carbon atom was observed at δ 108.5 for **12**. From these results the structure of the monosilyl diacetate (**13**) was firmly established. Then the deprotection of the monosilyl enol acetate (**14**) was carried out by a treatment with $\text{AcOH-H}_2\text{O-THF}$ (2:1:1) at room temperature to afford 1-hydroxy enol acetate (**15**; 85% yield based on the consumed **14**). Jones oxidation of **15** gave an α -diketone (**16**; 80% yield). This compound corresponds to a diacetate of the intermediate **A** shown in Scheme 1.

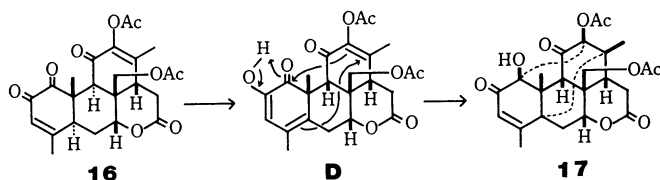
Now the α -diketone (**16**) in hand was transformed into 12,20-di-*O*-acetylshinjulactone C (**17**) by heating in pyridine under reflux for 9 h in 22% yield, which was shown to be completely identical with a specimen (**17**) derived from natural shinjulactone C (**1**). Alkaline hydrolysis of **17** afforded shinjulactone C (**1**) in *ca.*



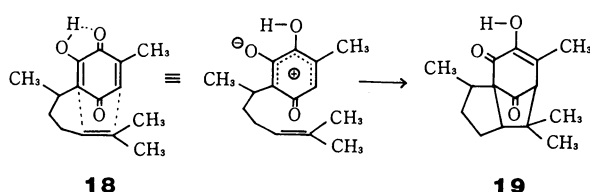
Scheme 2.

90% yield.

The reaction from the α -diketone (**16**) to the diacetate (**17**) could be explained by an inionic [4+2] cycloaddition of class B,¹⁰ which was proposed for a transformation from perezon (**18**) to pipitzol (**19**).¹¹ The reaction process from **16** to **17** through an intermediate **D** is depicted in Scheme 3.



Scheme 3.



Experimental¹²

Reaction of Ailanthone (2) with Pyridine. Ailanthone (**2**; 60 mg) was heated in pyridine (5 ml) under reflux for 19 h. After evaporation under reduced pressure, the reaction mixture was separated by preparative TLC developed with 10% methanol-chloroform to give isoailanthone (**5**; 30–40%) and shinjulacone C (**1**; 5–8%) together with many unidentified by-products. After recrystallization from acetone, **1** was identified with a natural specimen by mp, TLC, HPLC, ¹H NMR, and IR. The yields were estimated by HPLC examination (column: Nucleosil 10-CN; solvent system: hexane-THF, 3:2; flow rate: 0.8 ml/min; retention times were 11.5, 13.2, and 23.1 min for **1**, **2**, and **5**, respectively).

Oxidation of Ailanthone (2) with Manganese Dioxide. A solution of ailanthone (**2**; 19 mg) in ethyl acetate (20 ml) was treated with manganese dioxide (120 mg) for 3 d at room temperature. After the usual work-up, the reaction mixture was subjected to a separation by preparative TLC developed with methanol-chloroform (1:19) to afford a mixture (13 mg) of an aldehyde (**6**) and a hemiacetal (**20**) in ca. 1:1 ratio.⁴⁾

1β,12,20-Triacetoxypicrasa-3,12-diene-2,11,16-trione (8).

i) Ailanthone triacetate (**7**; 497 mg) in pyridine (10 ml) was heated under reflux for 10 h. After evaporation of the solvent under reduced pressure, the reaction mixture was purified by a column chromatography eluted with 3% methanol-chloroform to give an enol acetate (**8**; 369 mg). ii) Ailanthone (**2**; 26 mg) in pyridine (5 ml) was heated under reflux for 11 h. After cooling, acetic anhydride (5 ml) and a catalytic amount of 4-dimethylaminopyridine were added to the reaction mixture. Standing at room temperature for 6 d followed by the usual work-up afforded the enol acetate (**8**; 23 mg), mp 153–156°C (acetone-hexane); IR (Nujol) 1745, 1705, 1685, 1230, and 1140 cm⁻¹; UV (EtOH) 240 nm (ϵ 17000); ¹H NMR (400 MHz; CDCl₃) δ =1.33 (3H, s; C₁₀-CH₃), 1.82 (3H, s; C₁₃-CH₃), 1.98 (3H, br s; C₄-CH₃), 2.07, 2.09, and 2.23 (each

3H, s; CH₃CO-), 3.25 (1H, s; C₉-H), 4.13, and 4.59 (each 1H, d, J =12.5 Hz; C₂₀-H), 4.61 (1H, br s; C₇-H), 5.25 (1H, s; C₁₁-H), and 6.08 (1H, br s; C₃-H); MS m/z (%) 502 (M⁺; 2), 460 (30), 418 (100), and 400 (20); Found: m/z 502.1807. Calcd for C₂₆H₃₀O₁₀: M, 502.1837.

Acidic Hydrolysis of Ailanthone Triacetate (7). A solution of the triacetate (**7**; 590 mg) in 1.5 M (1 M=1 mol dm⁻³) sulfuric acid-THF (each 10 ml) was refluxed for 5 h. After extraction with dichloromethane, the organic layer was dried over magnesium sulfate and evaporated to give a residue. Purification by a silica-gel column chromatography eluted 3% methanol-chloroform afforded 1,12-di-*O*-acetylailanthone (**10**; ca. 120 mg), 12-*O*-acetylailanthone (**11**; ca. 120 mg), and ailanthone (**2**; 155 mg) in succession. **10**: Mp 266–268°C (chloroform-acetone); IR (Nujol) 3420, 1735, 1705, and 1675 cm⁻¹; ¹H NMR (CDCl₃) δ =1.35 (3H, s), 2.04 (6H, s), 2.24 (3H, s), 3.55 and 3.93 (each 1H, d, J =8 Hz), 4.49 (1H, t, J =3 Hz), 5.25 (1H, s), 5.32 (1H, s), 5.38 (1H, s), 5.49 (1H, s), and 6.10 (1H, m); MS m/z (%) 460 (M⁺; 2), 418 (88), 358 (94), 247 (63), 151 (100), and 60 (86); Found: m/z 460.1768. Calcd for C₂₄H₂₈O₉: M, 460.1733. **11**: Mp 221–224°C (acetone); IR (Nujol) 3200, 1730, 1670, and 1240 cm⁻¹; ¹H NMR (CDCl₃) δ =1.20 (3H, s), 2.03 (3H, br s), 2.07 (3H, s), 3.56 and 3.94 (each 1H, d, J =8 Hz), 4.07 (1H, br s), 4.52 (1H, t, J =3 Hz), 5.10 (1H, br s), 5.30 (2H, s), 5.51 (1H, s), 6.15 (1H, m), and 7.66 (1H, s); MS m/z (%) 418 (M⁺; 24), 358 (14), 328 (23), 313 (18), 247 (22), 151 (32), and 60 (100); Found: m/z 418.1632. Calcd for C₂₂H₂₆O₈: M, 418.1627.

1-*O*-*t*-Butyldimethylsilylailanthone (12). Ailanthone (**2**; 402 mg) was treated with *t*-butyldimethylsilyl chloride (806 mg; 5.0 equiv) in the presence of imidazole (950 mg; 13 equiv) in DMF (12 ml) at room temperature for 18 h. After addition of water, the reaction mixture was extracted with dichloromethane. The organic layer was washed with 2 M hydrochloric acid and then with a saturated solution of sodium hydrogencarbonate, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was subjected to separation by a silica-gel column chromatography eluted with 15–30% ethyl acetate-ether to give the starting ailanthone (**2**; 12 mg) and a monosilyl derivative (**12**; 480 mg), mp 234–236°C; IR (KBr) 3450, 3250, 1730, 1685, 1660, and 840 cm⁻¹; ¹H NMR (CDCl₃) δ =0.15 and 0.16 (each 3H, s), 1.05 (9H, s), 1.25 (3H, s), 1.95 (3H, br s), 3.52 and 3.90 (each 1H, d, J =8 Hz), 4.01 (1H, s), 4.26 (1H, s), 4.50 (1H, t, J =2.5 Hz), 5.22 and 5.31 (each 1H, br s), 5.99 (1H, m); ¹³C NMR (CDCl₃) δ =-4.1q, -2.5q, 10.1q, 19.1s, 22.4q, 25.7t, 26.7q, 26.7q, 26.7q, 34.5t, 43.0d, 43.5d, 45.2s, 45.6s, 47.2d, 71.6t, 78.0d, 79.3d, 86.0d, 108.5s, 120.7t, 126.3d, 143.4s, 159.4s, 169.3s, and 195.1s; MS m/z (%) 490 (M⁺; 3), 475 (3), 433 (55), and 57 (100); Found: m/z 490.2383. Calcd for C₂₆H₃₈O₇Si: M, 490.2385.

1β-*t*-Butyldimethylsiloxy-12α,20-diacetoxypicrasa-3,13(21)-diene-2,11,16-trione (13). The monosilyl derivative (**12**; 480 mg) was acetylated with acetic anhydride (5 ml) and pyridine (15 ml) at 70°C for 18 h. After the usual work-up, purification with a silica-gel column chromatography eluted with ethyl acetate-ether (1:3) afforded a monosilyl diacetate (**13**; 519 mg), mp 182–184°C (ether-hexane); IR (Nujol) 1750, 1690, 1230, and 845 cm⁻¹; ¹H NMR (CDCl₃) δ =-0.14, -0.10 (each 3H, s), 0.84 (9H, s), 1.14 (3H, s), 1.83 (3H, br s), 2.00 and 2.07 (each 3H, s), 3.97 (1H, s), 3.80 and 4.31 (each 1H, d, J =12 Hz), 4.57 (1H, br s), 5.14 and 5.20 (each 1H, s), 5.45 (1H, s), and 5.85 (1H, br s); ¹³C NMR (CDCl₃) δ =-3.7, -3.3,

10.6, 18.8, 20.6, 21.0, 21.9, 25.9, 26.5, 26.5, 26.5, 30.7, 40.1, 41.6, 42.6, 46.4, 51.1, 65.0, 76.0, 77.9, 86.9, 114.5, 126.9, 140.5, 158.3, 168.9, 169.9, 170.1, 196.5, 198.9; MS m/z (%) 574 (M^+ ; 0.3), 559 (5), 517 (100), 475 (10), 457 (10), 415 (15), and 207 (8); Found: m/z 574.2618. Calcd for $C_{30}H_{42}O_9Si$: M , 574.2598.

1 β -t-Butyldimethylsiloxy-12,20-diacetoxypicrasa-3,12-diene-2,11,16-trione (14). The monosilyl diacetate (**13**; 75 mg) was heated in pyridine (5 ml) under reflux for 11 h. After evaporation under reduced pressure, the reaction mixture was purified by a silica-gel column chromatography eluted with ethyl acetate–ether (1:3) to give a monosilyl enol acetate (**14**; 71.5 mg), mp 210–213°C (ether–hexane); IR (Nujol) 1740, 1710, 1690, 1240, and 845 cm^{-1} ; 1H NMR ($CDCl_3$) δ = –0.12 and 0.07 (each 3H, s), 0.90 (9H, s), 1.24 (3H, s), 1.79 (3H, s), 1.93 (3H, br s), 2.08 and 2.20 (each 3H, s), 3.97 (1H, s), 4.60 (1H, t, J = 2.5 Hz), 4.19 and 4.68 (each 1H, d, J = 12 Hz), and 5.98 (1H, m); MS m/z (%) 574 (M^+ ; 0.1), 559 (3), 517 (100), 475 (10), 457 (18), and 207 (18); Found: m/z 574.2648. Calcd for $C_{30}H_{42}O_9Si$: M , 574.2598.

12,20-Diacetoxy-1 β -hydroxypicrasa-3,12-diene-2,11,16-trione (15). The monosilyl enol acetate (**14**; 457 mg) was treated with AcOH (10 ml), H_2O (5 ml), and THF (5 ml) at room temperature for 22 h. The reaction mixture was evaporated and separated by a silica-gel column chromatography eluted with 30–80% ethyl acetate–ether to give the starting monosilyl enol acetate (**14**; 147 mg) and 1-hydroxy enol acetate (**15**; 210 mg), mp 173–175°C (acetone); IR (KBr) 3430, 1740, 1675, 1220, and 1030 cm^{-1} ; 1H NMR ($CDCl_3$) δ = 1.16 (3H, s), 1.86 (3H, s), 1.97 (3H, br s), 2.11 and 2.26 (each 3H, s), 3.30 (1H, s), 3.97 (1H, d, J = 3.5 Hz), 4.47 (1H, d, J = 3.5 Hz), 4.21 and 4.61 (each 1H, d, J = 12 Hz), 4.59 (1H, br s), and 6.07 (1H, br s); MS m/z (%) 460 (M^+ ; 3), 418 (18), 400 (23), 358 (40), 151 (90), and 60 (100); Found: m/z 460.1741. Calcd for $C_{24}H_{28}O_9$: M , 460.1734.

12,20-Diacetoxypicrasa-3,12-diene-1,2,11,16-tetrone (16). 1-Hydroxy enol acetate (**15**; 210 mg) was treated with Jones reagent (in excess) in acetone (30 ml) at 0°C for 30 min. After addition of 2-propanol (ca. 3 ml) and sodium hydrogencarbonate (ca. 1 g), the reaction mixture was filtered through Florisil (Wako, 100–200 mesh; ca. 5 g) and evaporated to a concentrated solution, to which brine and dichloromethane were added. After extraction with dichloromethane, the organic layer was subjected to purification by a silica-gel column chromatography eluted with 3% methanol–chloroform to afford an α -diketone (**16**; 167 mg), mp 160–164°C (dichloromethane–hexane); IR (KBr) 2910, 1740, 1695, 1220, and 1040 cm^{-1} ; UV (EtOH) 245 nm (ϵ 9100); 1H NMR ($CDCl_3$) δ = 1.41 (3H, s), 1.89 (3H, s), 2.04 (3H, br s), 2.11 and 2.25 (each 3H, s), 3.52 (1H, s), 4.25 and 4.65 (each 1H, d, J = 12 Hz), 4.56 (1H, t, J = 2.5 Hz), and 6.23 (1H, m); ^{13}C NMR ($CDCl_3$) δ = 14.2, 16.0, 20.0, 20.6, 22.4, 25.6, 30.3, 38.5, 41.0, 43.1, 44.8, 51.5, 61.9, 76.9, 129.0, 141.4, 143.2, 164.1, 167.9, 168.5, 170.2, 185.5, 187.5, and 198.5; MS m/z (%) 458 (M^+ ; 60), 430 (12), 416 (100), 398 (30), 356 (45), 151 (70); Found: m/z 458.1586. Calcd for $C_{24}H_{26}O_9$: M , 458.1576.

12,20-Di-O-acetylshinjulactone C (17). The α -diketone (**16**; 51 mg) was heated in pyridine (5 ml) under reflux for 9 h. After evaporation, the reaction mixture was separated by preparative TLC developed with ethyl acetate–ether (1:1) to give 12,20-diacetylshinjulactone C (**17**; 11 mg), whose 1H NMR, IR, and mass spectra and optical rotation were completely identical with those of a specimen (**17**) obtained by acetylation of natural shinjulactone C (**1**).

Hydrolysis of 12,20-Di-O-acetylshinjulactone C (17). To a solution of the diacetate (**17**; 2.8 mg) in methanol (2 ml), 0.24 M potassium methoxide–methanol solution (0.1 ml) was added and the reaction mixture was stirred at room temperature for 1 h. After addition of 2 M hydrochloric acid (ca. 1 ml), the reaction mixture was evaporated to give a residue, which was subjected to purification by preparative TLC developed by 10% methanol–chloroform to afford shinjulactone C (**1**; 2.1 mg).

The authors wish to thank Mr. Kazuhiro Matsushita of JEOL Co., Ltd. for measurement of 1H NMR spectrum at 400 MHz.

References

- 1) A preliminary account of this report: M. Ishibashi, T. Tsuyuki, T. Takahashi, *Tetrahedron Lett.*, **24**, 4843 (1983).
- 2) M. Ishibashi, T. Tsuyuki, T. Murae, H. Hirota, T. Takahashi, A. Itai, and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, **56**, 3683 (1983).
- 3) T. Furuno, M. Ishibashi, H. Naora, T. Murae, H. Hirota, T. Tsuyuki, T. Takahashi, A. Itai, and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, **57**, 2484 (1984).
- 4) H. Naora, M. Ishibashi, T. Furuno, T. Tsuyuki, T. Murae, H. Hirota, T. Takahashi, A. Itai, and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, **56**, 3694 (1983).
- 5) M. Ishibashi, T. Tsuyuki, T. Murae, and T. Takahashi, *Chem. Pharm. Bull.*, **30**, 1917 (1982).
- 6) J. Polonsky, CL. Fouquey, and A. Gaudemer, *Bull. Soc. Chim. Fr.*, **1964**, 1818.
- 7) J. Polonsky and J.-L. Fourrey, *Tetrahedron Lett.*, **1964**, 3983.
- 8) A. W. Fort, *J. Org. Chem.*, **26**, 332 (1961).
- 9) A. J. Caruso, J. Polonsky, and B. S. Rodriguez, *Tetrahedron Lett.*, **23**, 2567 (1982).
- 10) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York (1970), p. 86.
- 11) P. Joseph-Nathan, V. Mendoza, and E. Garcia, *Tetrahedron*, **33**, 1573 (1977) and references cited therein.
- 12) General procedures are the same as described in the preceding papers.^{4,13)}
- 13) M. Ishibashi, S. Yoshimura, T. Tsuyuki, T. Takahashi, A. Itai, and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, **57**, 2885 (1984).