Bitter Principles of *Ailanthus altissima* Swingle. Conversion of Ailanthone into Shinjulactone C[1)]

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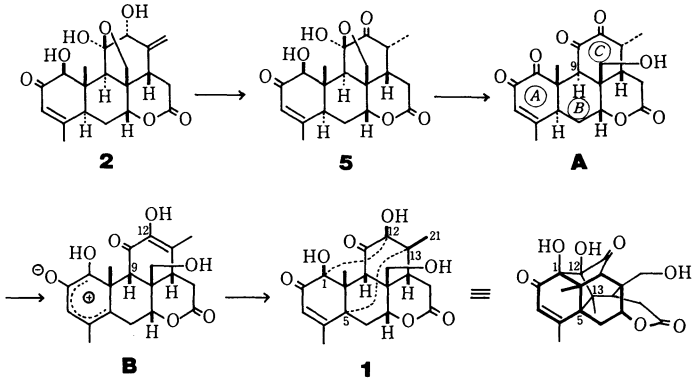
Ailanthone was converted into shinjulactone C with a hexacyclic 1α,12α:5α,13α-dicyclo-9β*H*-picrasane skeleton. The key reaction consists of an intramolecular ionic [4+2] cycloaddition between a pentadienyl cation and an olefin.

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 1α,12α:5α,13α-dicyclo-9β*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 9α-H into 9β-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 9α-H occurred to afford a 9β-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.

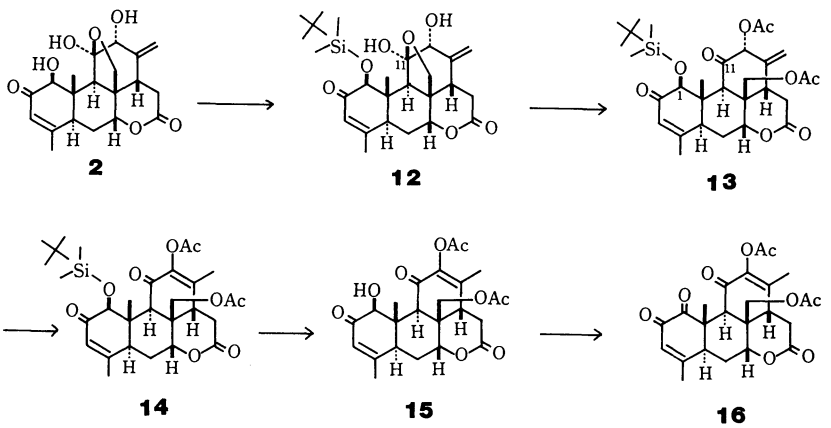
found to be so difficult that any attempts to isolate intermediates corresponding to **A** or **B** were not successful.

Instead of the isolation of intermediates, a stepwise conversion from ailanthone (**2**) into shinjulactone C (**1**) was then investigated. First examination concerned a direct oxidation of the hydroxyl group at C-1 of ailanthone (**2**). But oxidation of **2** with Jones reagent afforded unidentified polar products, while oxidation of ailanthone (**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 ailanthone triacetate (**7**)[7] isomerized to enol acetate (**8**), which was also obtained by acetylation of isoailanthone (**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*-acetylailanthone (**10**) and 12-*O*-acetylailanthone (**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 ailanthone (**2**) with *t*-butyldimethylsilyl chloride in the presence of imidazole in *N*,*N*-dimethylformamide[9] 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). ^{1}H NMR spectrum of **14** showed a signal due to vinyl methyl protons (δ 1.79, 3H, s; $C_{(13)}$-CH_3) instead of signals due to *exo*-methylene (δ 5.14 and 5.20, each 1H, s; $C_{(21)}$-H) and a proton (δ 5.45, 1H, s; $C_{(12)}$-H) attached to a carbon atom with an acetoxyl group for **13**. Signals due to a proton attached to a carbon atom with a siloxyl group appeared at δ 3.97 (1H, s; $C_{(1)}$-H) in ^{1}H 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 AcOH–H_2O–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.

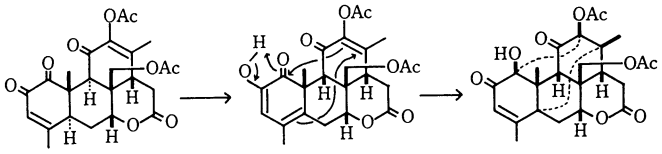
Now the α-diketone (**16**) in hand was transformed into 12,20-di-*O*-acetylshinjulactone C (**17**) by heating in pyridine under reflux for 9 h in 22% yield, which was shown to be completely identical with a specimen (**17**) derived from natural shinjulactone C (**1**). Alkaline hydrolysis of **17**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



Scheme 2.

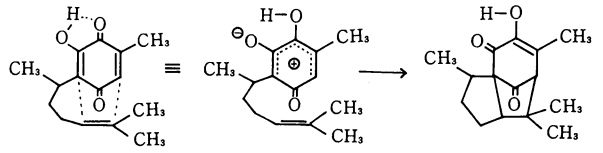
90% yield.

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.



16 **D** **17**

Scheme 3.



18 **19**

Experimental[12]

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 shinjulactone 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, ^{1}H 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); ^{1}H NMR (400 MHz; $CDCl_3$) δ=1.33 (3H, s; $C_{(10)}$-CH_3), 1.82 (3H, s; $C_{(13)}$-CH_3), 1.98 (3H, br s; $C_{(4)}$-CH_3), 2.07, 2.09, and 2.23 (each 3H, s; CH_3CO-), 3.25 (1H, s; $C_{(9)}$-H), 4.13, and 4.59 (each 1H, d, *J*=12.5 Hz; $C_{(20)}$-H), 4.61 (1H, br s; $C_{(7)}$-H), 5.25 (1H, s; $C_{(1)}$-H), and 6.08 (1H, br s; $C_{(3)}$-H); MS *m/z* (%) 502 (M^+; 2), 460 (30), 418 (100), and 400 (20); Found: *m/z* 502.1807. Calcd for $C_{26}H_{30}O_{10}$: 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}; ^{1}H NMR ($CDCl_3$) 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 $C_{24}H_{28}O_9$: M, 460.1733. **11**: Mp 221—224 °C (acetone); IR (Nujol) 3200, 1730, 1670, and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{22}H_{26}O_8$: 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}. ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{38}O_7Si$: 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}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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.

1β-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-1β-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).

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12) General procedures are the same as described in the preceding papers.[4,13]

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