Synthesis of a Functionalized Carbocyclic Skeleton of Ptaquilosin, the Aglycone of a Bracken Carcinogen Ptaquiloside Based on an Intramolecular Diels-Alder Reaction

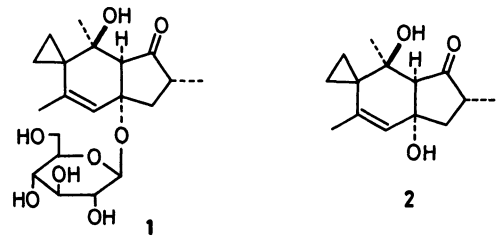
Hideo KIGOSHI, Akihiko SAWADA, Haruki NIWA, and Kiyoyuki YAMADA*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464
(Received December 10, 1988)

A tricyclic compound **13** possessing the carbocyclic skeleton of ptaquilosin (**2**), the aglycone of a bracken carcinogen ptaquiloside (**1**) has been synthesized by the intramolecular Diels-Alder reaction of trienes **12a** and **12b**.

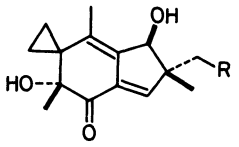
Since the carcinogenicity of bracken fern (*Pteridium aquilinum*: "warabi" in Japanese) was found in 1960,[1] studies in search for the carcinogen(s) have been carried out intensively: we isolated ptaquiloside (**1**) as a carcinogenic principle from bracken in 1983, determined the structure,[2] and proved its potent carcinogenicity.[3] Ptaquilosin (**2**),[4] the aglycone of **1** is a norsesquiterpene of the illudane-type. Illudin-S (**3**)[5] and -M (**4**)[5] are the representative members of the illudane-type sesquiterpenes and the total synthesis of **3** and **4** was reported.[6] Some synthetic studies on this class of sesquiterpenes have been reported.[7]

In connection with the synthesis of ptaquilosin (**2**), we have synthesized the functionalized carbocyclic skeleton of **2** based on the intramolecular Diels-Alder reaction. The Diels-Alder reaction of allylidenecyclopropane with various dienophiles to form spiro[2.5]-oct-4-enes was reported by Krief and Zutterman.[8] We attempted to utilize the Diels-Alder reaction of this type intramolecularly for a triene **11a** and for a stereoisomeric mixture of **12a** and **12b** toward the construction of the tricyclic carbon skeleton of **2**.

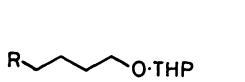
The triene **11a** was prepared as follows. Diethyl cyanomethylphosphonate[9] was alkylated with the iodide **5**[10] to afford the phosphonate **6** (91%), the reaction of which with the aldehyde **7**[11] provided the diene **8**[12,13] (54%, $Z:E=8:1$).[14] After removal of the tetrahydropyranyl protecting group in **8**, the resulting alcohol **9**[12,13] was oxidized to give the aldehyde **10**[12,13] (68% overall), which on reaction with diethyl (1-cyanoethyl)phosponate[9] furnished two stereoisomeric trienes **11a**[12,13] (42%) and **11b**[12,13] (29%). When **11a** was heated, the intramolecular Diels-Alder reaction did not occur, but a mixture of dimeric products resulted. Although the intramolecular Diels-Alder reaction of **11a** in the presence of $AlCl_3$ was examined, again a mixture of the dimers was obtained. The fail-



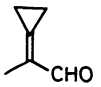
1 **2**



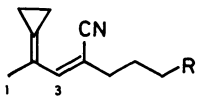
3 R = OH
4 R = H



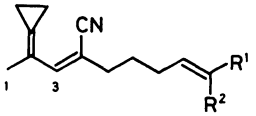
5 R = I
6 R = CH(CN)P(O)(OEt)$_2$



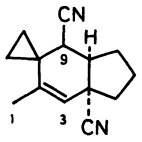
7



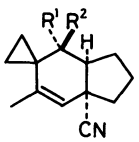
8 R = CH_2O·THP
9 R = CH_2OH
10 R = CHO



11a R^1=Me, R^2=CN
11b R^1=CN, R^2=Me
12a R^1=H, R^2=CN
12b R^1=CN, R^2=H



13



14a R^1=Me, R^2=CN
14b R^1=CN, R^2=Me

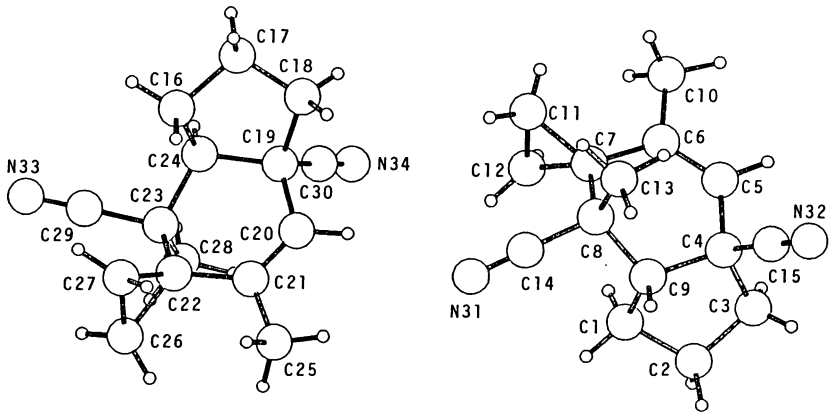


Fig. 1. Perspective drawing of the compound **14a**.

ure of the intramolecular Diels–Alder reaction of **11a** is presumably due to the steric hindrance in the transition state caused by the vinyl methyl group in the dienophilic part. Thus, the intramolecular Diels–Alder reaction of the trienes **12a** and **12b** was examined, the preparation of which follows: the reaction of **10** with diethyl cyanomethylphosphonate[9] afforded an inseparable 1:1 mixture of **12a**[12,13] and **12b**[12,13] (66%). On heating the trienes **12a** and **12b** in toluene (190—210 °C, 20 h) the tricyclic compound **13** was obtained as a single isomer (15%) together with a mixture of dimeric products (83%). The stereochemistry of **13** except for C-9 was established after conversion to the methylated derivative **14a**. The carbanion generated from **13** was methylated with methyl iodide to give two diastereomers, **14a** (mp 84—86 °C, 36%) and **14b** (mp 113—114 °C, 47%), and **14a** was subjected to X-ray crystallographic analysis. A perspective drawing of the final X-ray model of **14a** is shown in Fig. 1.[15] The result of the X-ray crystallographic analysis of **14a** reveals that the tricyclic compound **13** possesses the spirocyclopropane-containing *cis*-hexahydroindene skeleton desired for the synthesis of ptaquilosin (**2**). In summary, a functionalized tricyclic compound **13** potentially useful for the synthesis of ptaquilosin (**2**) has been synthesized, although in low yield, based on the intramolecular Diels–Alder reaction.

Experimental

Melting points are uncorrected. IR spectra were obtained in $CHCl_3$ with a JASCO IR-810 or a JASCO IR-S spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-90QE spectrometer in $CDCl_3$, unless otherwise stated: chemical shifts (δ) are reported in ppm downfield from internal Me_4Si, and coupling constants are given in herz. The low-resolution mass spectra were recorded on a Hitachi RMU-6C spectrometer. The high-resolution mass spectra (HRMS) were measured on a JEOL JMS-DX300 or a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820 MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, were used for thin-layer chromatography. Toluene was distilled from Na under nitrogen. Dichloromethane was distilled from CaH_2 under nitrogen. 1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from Na–benzophenone ketyl under nitrogen. Hexamethylphosphoric triamide (HMPT) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under reduced pressure. Organic solutions were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure by a rotary evaporator.

Phosphonate 6. To a solution of diethyl cyanomethylphosphonate[9] (378 mg, 2.14 mmol) in DME (4 ml) was added KH (35% dispersion in mineral oil, 0.24 g, 2.10 mmol) under nitrogen. The suspension was stirred at room temperature for 1.5 h and then a solution of **5**[10] (582 mg, 2.05 mmol) in DME (2 ml) was added. The reaction mixture was stirred at room temperature for 2 h, diluted with the 0.25 M phosphate buffer solution (pH 7.0, 15 ml) (1 M=1 mol dm^{-3}), and extracted with EtOAc (3×20 ml). The combined extracts were washed with saturated NaCl solution, dried, and concentrated. The crude product was purified by chromatography on silica gel (15 g, EtOAc) to give **6** (644 mg, 91%) as a colorless oil: IR 2250, 1265, and 1025 cm^{-1}; ^1H NMR (90 MHz) δ=1.20—2.10 (12H, m), 1.39 (6H, t, J=7.0 Hz), 2.92 (1H, m), 3.20—4.00 (4H, m), 4.24 (4H, m), and 4.59 (1H, m); MS m/z (rel intensity) 333 (M^+; 2), 304 (2), 278 (3), 250 (40), 249 (40), 233 (60), 232 (60), 219 (30), 204 (50), 176 (75), and 165 (100). HRMS Found: m/z 333.1692. Calcd for $C_{15}H_{28}NO_5P$: M, 333.1705.

Diene 8. To a solution of **6** (2.17 g, 6.52 mmol) in DME (22 ml) was added KH (35% dispersion in mineral oil, 0.76 g, 6.65 mmol) under nitrogen. The mixture was stirred at room temperature for 1.5 h and then a solution of **7**[11] (0.99 g, 10.3 mmol) in DME (4 ml) was added. After being stirred at room temperature for 1 h, the reaction mixture was poured into the 0.25 M phosphate buffer solution (pH 7.0, 50 ml) containing hydroquinone (40 mg). The mixture was extracted with EtOAc (3×50 ml) and the combined extracts were washed with saturated NaCl solution, dried, and concentrated. The residue was separated by chromatography on silica gel (30 g, hexane/EtOAc=10:1) to afford an 8:1 mixture of (*Z*)-**8**[12] and (*E*)-**8**[12] (974 mg, 54%) as a colorless oil: IR 3010, 2210, 1735, and 1605 cm^{-1}; MS m/z (rel intensity) 275 (M^+; 2), 191 (20), 118 (20), and 85 (100). HRMS Found: m/z 275.1886. Calcd for $C_{17}H_{25}NO_2$: M, 275.1885.

^{1}H NMR (90 MHz) of (*Z*)-**8**:[16] δ=1.22 (4H, m), 1.35—1.90 (10H, m), 2.25 (3H, m), 2.10—2.50 (2H, m), 3.20—4.00 (4H, m), 4.56 (1H, m), and 6.71 (1H, br s). The *Z*/*E* ratio of **8** was determined by ^{1}H NMR spectral analysis.

Alcohol 9. A solution of **8**[13] (974 mg, 3.54 mmol) and hydroquinone (9 mg) in AcOH (30 ml)–H_2O (10 ml) was stirred at 45 °C for 1 h under nitrogen and then concentrated. The residue was dissolved in toluene (10 ml) and the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (20 g, hexane/EtOAc=2:1) to provide **9**[12,13] (513 mg, 76%) as a colorless oil: IR 3620, 3450 (broad), 3010, 2210, 1735, and 1605 cm^{-1}; MS *m*/*z* (rel intensity) 191 (M^+; 15), 176 (4), and 118 (100). HRMS Found: *m*/*z* 191.1289. Calcd for $C_{12}H_{17}NO$: M, 191.1310. ^{1}H NMR (90 MHz) of (*Z*)-**9**:[16] δ=1.23 (4H, m), 1.45—1.85 (5H, m), 2.25 (3H, m), 2.10—2.50 (2H, m), 3.67 (2H, br t, *J*=6.5 Hz), and 6.71 (1H, br s).

Aldehyde 10. To a solution of oxalyl dichloride (0.31 ml, 3.56 mmol) in CH_2Cl_2 (7 ml) was added a solution of DMSO (0.50 ml, 7.18 mmol) in CH_2Cl_2 (1.5 ml) at −65 °C under nitrogen. The mixture was stirred at −65 °C for 2 min, and then a solution of **9**[13] (0.34 g, 1.78 mmol) and hydroquinone (4 mg) in CH_2Cl_2 (4 ml) was added. The mixture was stirred at −60 °C for 15 min and Et_3N (2.5 ml, 18.0 mmol) was added. After stirring at −50 °C for 5 min, the reaction mixture was allowed to warm to room temperature and was kept for 1 h. Water (20 ml) was added to the mixture and the resulting mixture was extracted with CH_2Cl_2 (3×20 ml). The combined extracts were washed with saturated NaCl solution, dried, and concentrated. The residue was separated by chromatography on silica gel (10 g, hexane/EtOAc=6:1) to give **10**[12,13] (0.30 g, 89%) as a colorless oil: IR 3020, 2210, 1725, and 1625 cm^{-1}; MS *m*/*z* (rel intensity) 189 (M^+; 5), 174 (1), 160 (5), and 118 (100). HRMS Found: *m*/*z* 189.1147. Calcd for $C_{12}H_{15}NO$: M, 189.1154. ^{1}H NMR (90 MHz) of (*Z*)-**10**:[16] δ=1.25 (4H, m), 1.50—2.10 (2H, m), 2.27 (3H, m), 2.15—2.65 (4H, m), 6.71 (1H, br s), and 9.79 (1H, t, *J*=1.5 Hz).

Trienes 11a and 11b. To a solution of diethyl (1-cyanoethyl)phosphonate[9] (151 mg, 0.791 mmol) in DME (3 ml) was added KH (35% dispersion in mineral oil, 86 mg, 0.753 mmol) under nitrogen. The suspension was stirred at room temperature for 1.5 h and then a solution of **10**[13] (113 mg, 0.592 mmol) and hydroquinone (2 mg) in DME (1 ml) was added. The mixture was stirred at room temperature for 2.5 h and then to this mixture was further added the carbanion solution, prepared from diethyl (1-cyanoethyl)phosphonate (54 mg, 0.28 mmol) and KH (35% dispersion in mineral oil, 33 mg, 0.29 mmol) in DME (0.5 ml) as described above. After stirring at room temperature for further 30 min, the mixture was diluted with H_2O (5 ml) and extracted with EtOAc (4×5 ml). The combined extracts were washed with saturated NaCl solution and dried. Hydroquinone (23 mg) was added to the EtOAc solution, which was concentrated. The oily residue was purified by chromatography on silica gel (10 g, hexane/ether=8:1) to provide **11a**[12,13] (colorless oil, 56.9 mg, 42%) and **11b**[12,13] (colorless oil, 37.5 mg, 29%), respectively.

11a: IR 3020, 2220, 1735, 1645, and 1605 cm^{-1}; MS *m*/*z* (rel intensity) 226 (M^+; 10), 211 (8), and 118 (100). HRMS Found: *m*/*z* 226.1477. Calcd for $C_{15}H_{18}N_2$: M, 226.1470. ^{1}H NMR (90 MHz) of (3*Z*)-**11a**:[16] δ=1.26 (4H, m), 1.50—2.00 (2H, m), 1.94 (3H, d, *J*=1.5 Hz), 2.20—2.55 (4H, m), 2.27 (3H, m), 6.13 (1H, tq, *J*=7.5, 1.5 Hz), and 6.54 (1H, br s).

11b: IR 3020, 2220, 1735, 1640, and 1605 cm^{-1}; MS *m*/*z* (rel intensity) 226 (M^+; 10), 211 (15), and 118 (100). HRMS Found: *m*/*z* 226.1490. Calcd for $C_{15}H_{18}N_2$: M, 226.1470. ^{1}H NMR (90 MHz) of (3*Z*)-**11b**:[16] δ=1.25 (4H, m), 1.40—2.00 (2H, m), 1.88 (3H, d, *J*=1.5 Hz), 2.00—2.55 (4H, m), 2.27 (3H, m), 6.34 (1H, tq, *J*=7.5, 1.5 Hz), and 6.72 (1H, br s).

Trienes 12a and 12b. To a solution of diethyl cyanomethylphosphonate[9] (434 mg, 2.45 mmol) in DME (5 ml) was added KH (35% dispersion in mineral oil, 0.27 g, 2.36 mmol) under nitrogen. The suspension was stirred at room temperature for 50 min, and then a solution of **10**[13] (300 mg, 1.59 mmol) and hydroquinone (3 mg) in DME (4 ml) was added. The mixture was stirred at room temperature for 1 h, diluted with H_2O (20 ml), and extracted with EtOAc (4×10 ml). The combined extracts were washed with saturated NaCl solution, dried, and concentrated. The oily residue was separated by chromatography on silica gel (10 g, hexane/EtOAc=6:1) to afford an inseparable 1:1 mixture[14] of **12a**[12,13] and **12b**[12,13] (268 mg, 66%) as a colorless oil: IR 3030, 3020, 2230, 2210, 1735, 1635, and 1605 cm^{-1}; MS *m*/*z* (rel intensity) 212 (M^+; 5), 197 (3), and 118 (100). HRMS Found: *m*/*z* 212.1300. Calcd for $C_{14}H_{16}N_2$: M, 212.1313. ^{1}H NMR (90 MHz) of (3*Z*)-**12a**[16] and (3*Z*)-**12b**:[16] δ=1.26 (4H, m), 1.50—2.00 (2H, m), 2.00—2.65 (4H, m), 2.27 (3H, m), 5.37 (1H, m), and 6.35—6.90 (2H, m).

Tricyclic Compound 13. A solution of the 1:1 mixture of **12a**[13] and **12b**[13] (23 mg, 0.11 mmol) and hydroquinone (1 mg) in toluene (1 ml) in a Pyrex sealed tube under nitrogen was heated at 190—210 °C for 20 h. The solution was concentrated and the residue was separated by chromatography on silica gel (2 g, hexane/EtOAc=6:1) to give **13** (3.4 mg, 15%) and a mixture of dimeric products (19 mg, 83%).

13: colorless oil; IR 3020, 2230, 1655, and 1450 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.75—1.25 (4H, m), 1.50 (3H, d, *J*=1.5 Hz), 1.70—2.40 (6H, m), 2.76 (1H, m), 3.34 (1H, d, *J*=4.0 Hz), and 5.33 (1H, br s); ^{13}C NMR (22.5 MHz, C_6D_6) δ=8.2 (t), 10.6 (t), 18.1 (s), 18.2 (q), 22.8 (t), 26.4 (t), 35.8 (d), 38.9 (t), 41.8 (s), 45.7 (d), 118.5 (s), 121.8 (d), 122.6 (s), and 137.7 (s); MS *m*/*z* (rel intensity) 212 (M^+; 65), 197 (30), 185 (35), 170 (100), and 155 (75). HRMS Found: *m*/*z* 212.1283. Calcd for $C_{14}H_{16}N_2$: M, 212.1313. The mixture of dimeric products: colorless oil; IR 3020, 2220, and 1635 cm^{-1}; ^{1}H NMR (90 MHz) δ=−0.10—1.00 (8H, m), 1.30—1.90 (6H, m), 1.50 (6H, br s), 2.10—2.65 (6H, m), 5.25—5.50 (3H, m), and 6.25—6.90 (3H, m); MS *m*/*z* (rel intensity) 424 (M^+; 35), 409 (30), 358 (20), 344 (30), and 330 (100).

Methylation of 13. To a stirred solution of diisopropylamine (0.35 ml, 2.50 mmol) in THF (8.35 ml) at 0 °C was added dropwise a 1.64 M solution of *n*-BuLi in hexane (1.3 ml, 2.1 mmol) under nitrogen, and the solution was stirred for 10 min. The 0.2 M solution of LDA described above (1.0 ml, 0.2 mmol) was added to a solution of **13** (11 mg, 0.052 mmol) in THF (0.06 ml) at 0 °C and the mixture was stirred at 0 °C for 40 min under nitrogen. To this mixture was added a solution of MeI (13 μl, 0.21 mmol) and HMPT (18 μl, 0.10 mmol) in THF (0.17 ml). The mixture was stirred at 0 °C for 1 h, diluted with 1 M HCl (2 ml), and extracted with ether (3×5 ml). The combined extracts were washed with saturated $NaHCO_3$ solution and saturated NaCl solution successively, dried, and concentrated. The

residue was separated by chromatography on silica gel (2 g, hexane/EtOAc=10:1 to 4:1) to afford **14a** (4.2 mg, 36%) and **14b** (5.5 mg, 47%).

14a: mp 84—86 °C (hexane); IR 3020, 2230, 1650, and 1450 cm^{-1}; ^1H NMR (90 MHz) δ=0.55—1.20 (4H, m), 1.20—2.50 (6H, m), 1.50 (3H, d, J=1.5 Hz), 1.65 (3H, s), 2.73 (1H, br t, J=8.5 Hz), and 5.33 (1H, br s); MS m/z (rel intensity) 226 (M^+; 80), 211 (70), 199 (35), 197 (35), and 184 (100). HRMS Found: m/z 226.1488. Calcd for $C_{15}H_{18}N_2$: M, 226.1470.

14b: mp 113—114 °C (hexane-benzene); IR 3020, 2230, 1650, and 1450 cm^{-1}; ^1H NMR (90 MHz) δ=0.75—1.10 (4H, m), 1.21 (3H, s), 1.54 (3H, d, J=1.5 Hz), 1.60—2.50 (6H, m), 2.77 (1H, br t, J=8.5 Hz), and 5.45 (1H, br s); MS m/z (rel intensity) 226 (M^+; 90), 211 (85), 199 (80), and 184 (100). HRMS Found: m/z 226.1481. Calcd for $C_{15}H_{18}N_2$: M, 226.1470.

X-Ray Crystallographic Analysis of 14a. Crystals of **14a** were obtained by slow crystallization from hexane. D_m was measured by floatation. Crystal data of **14a** were as follows: $C_{15}H_{18}N_2$, M=226.32; monoclinic, space group $P2_1/n$, a=16.770(2) Å, b=11.076(1) Å, c=15.745(1) Å, β=117.91(1)°, V=2584.6(4) Å^3; D_c=1.163 g cm^{-3}, D_m=1.163 g cm^{-3}; Z=8; μ=4.565 cm^{-1}; crystal size 0.30×0.25×0.20 mm. Total 4764 reflections with $2\theta \leqq 126°$ were collected on a RIGAKU ARC-5R automated four-circle diffractometer using graphite monochromated Cu $K\alpha$ radiation (1.54178 Å). Structure was solved by Monte-Carlo direct method[17] with the aid of MULTAN 78 program system[18] using 4097 unique reflections with $|F_o| \geqq \sigma(|F_o|)$ and refined by full-matrix least-square program. Non-H atoms were assigned with anisotropic thermal parameters. All H atoms were located in a difference Fourier map and refined with the equivalent isotropic thermal parameters to those for the bonded atoms. The final unweighted R factor was 0.09 after minimizing $\sum\omega(|F_o|^2-|F_c|^2)^2$ with $\omega=1/\sigma^2(F_o^2)$; R_w=0.13, S=3.8. Atomic scattering factors were from Ref. 19. PLUTO 78 program[20] was employed in drawing the computer-generated molecular structure. All crystallographic calculations were performed on a FACOM M-382 computer, operated by Computation Center of Nagoya University, using the library program of CRYSTAN system.

References

1) I. A. Evans, "Chemical Carcinogens, Second Edition," ed by C. E. Searle, American Chemical Society, Washington, D.C. (1984), Vol. 2, Chap. 18. I. Hirono and K. Yamada, "Naturally Occurring Carcinogens of Plant Origin," ed by I. Hirono, Kodansha-Elsevier, Tokyo-Amsterdam (1987), Chap. 4.

2) H. Niwa, M. Ojika, K. Wakamatsu, K. Yamada, I. Hirono, and K. Matsushita, *Tetrahedron Lett.*, **24**, 4117 (1983). H. Niwa, M. Ojika, K. Wakamatsu, K. Yamada, S. Ohba, Y. Saito, I. Hirono, and K. Matsushita, *ibid.*, **24**, 5371 (1983). S. Ohba, Y. Saito, I. Hirono, H. Niwa, M. Ojika, K. Wakamatsu, and K. Yamada, *Acta Crystallogr., Sect. C*, **40**, 1877 (1984). M. Ojika, K. Wakamatsu, H. Niwa, and K. Yamada, *Tetrahedron*, **43**, 5261 (1987).

3) I. Hirono, K. Yamada, H. Niwa, Y. Shizuri, M. Ojika, S. Hosaka, T. Yamaji, K. Wakamatsu, H. Kigoshi, K. Niiyama, and Y. Uosaki, *Cancer Lett.*, **21**, 239 (1984). I. Hirono, S. Aiso, T. Yamaji, H. Mori, K. Yamada, H. Niwa, M. Ojika, K. Wakamatsu, H. Kigoshi, K. Niiyama, and Y. Uosaki, *Gann*, **75**, 833 (1984). I. Hirono, H. Ogino, M. Fujimoto, K. Yamada, Y. Yoshida, M. Ikagawa, and M. Okumura, *J. Natl. Cancer Inst.*, **79**, 1143 (1987).

4) Natural ptaquilosin (**2**) was prepared from natural **1** by chemical transformation: H. Kigoshi, A. Sawada, Y. Imamura, H. Niwa, and K. Yamada, unpublished result.

5) T. C. McMorris and M. Anchel, *J. Am. Chem. Soc.*, **87**, 1594 (1965). K. Nakanishi, M. Ohashi, M. Tada, and Y. Yamada, *Tetrahedron*, **21**, 1231 (1965). T. Matsumoto, H. Shirahama, A. Ichihara, Y. Fukuoka, Y. Takahashi, Y. Mori, and M. Watanabe, *Tetrahedron*, **21**, 2671 (1965). A. Furusaki, H. Shirahama, and T. Matsumoto, *Chem. Lett.*, **1973**, 1293.

6) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, and S. Nishida, *J. Am. Chem. Soc.*, **90**, 3280 (1968). T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, and F. Sakan, *Tetrahedron Lett.*, **1970**, 1171. T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, and K. Miyano, *ibid.*, **1971**, 2049.

7) Y. Ohfune, S. Misumi, A. Furusaki, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, **1977**, 279. J. Furukawa, N. Morisaki, H. Kobayashi, S. Iwasaki, S. Nozoe, and S. Okuda, *Chem. Pharm. Bull.*, **33**, 440 (1985). N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, A. Itai, S. Nozoe, and S. Okuda, *ibid.*, **33**, 2783 (1985).

8) F. Zutterman and A. Krief, *J. Org. Chem.*, **48**, 1135 (1983).

9) B. Deschamps, G. Lefebvre, and J. Seyden-Penne, *Tetrahedron*, **28**, 4209 (1972).

10) K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2693 (1973).

11) F. Huet, A. Lechevallier, and J. M. Conia, *Tetrahedron Lett.*, **1977**, 2521.

12) This compound is air-sensitive and must be stored under argon in the presence of 5 percent of hydroquinone at −20 °C.

13) This material is an 8:1 mixture of (3*Z*)- and (3*E*)-isomers. Depicted is the structural formula corresponding to the major (3*Z*)-isomer.

14) The ratio was determined by ^1H NMR spectral analysis.

15) The tables of the atomic parameters and bond distances and angles and F_o-F_c table are deposited at the Chemical Society of Japan (Document No. 8873).

16) Signals due to the minor (3*E*)-isomer are omitted.

17) A. Furusaki, *Acta Crystallogr., Sect. A*, **35**, 220 (1979).

18) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, MULTAN 78, (1978). Univ. of York, England, and Louvain, Belgium.

19) "International Tables for X-ray Crystallography," Kynoch Press, Birmingham (1974), Vol. IV.

20) W. D. S. Motherwell, PLUTO 78, (1978). Univ. of Cambridge, England.