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A Stereoselective Synthesis of the A,B,C-Ring System of a Triterpene, Pollinastanol

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The A,B,C-ring system of a triterpene, pollinastanol, was stereoselectively constructed by intramolecular γ-alkylation of the β,γ-unsaturated ketone prepared from the thermal cycloaddition product of a benzocyclobutene derivative as a key reaction.

Keywords——pollinastanol; β,γ-unsaturated ketone; intramolecular γ-alkylation; thermal cycloaddition; benzocyclobutene; cyclopropane ring formation; triterpene

Pollinastanol (**1**), a triterpenoid, has a characteristic carbon framework bearing a 9β,10β-cyclopropane ring with a B/C-*cis* ring juncture.[1] Although the synthesis of cycloartenol (**2**) from lanosterol by the use of photochemical transformation as a key reaction has been reported by Barton,[2] little work has been done on the synthesis of such triterpenoids having a cyclopropane ring.

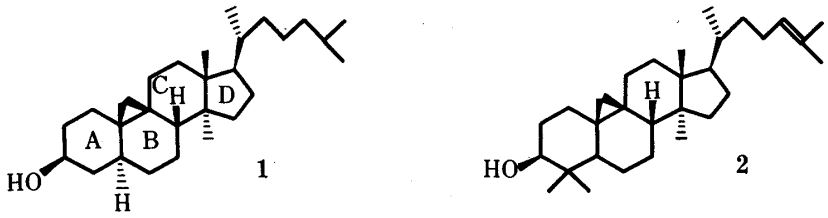

Chart 1

As a part of our continuing studies[3] on the synthesis of polycyclic natural products using benzocyclobutene derivatives as synthons, we have started to investigate a novel approach to pollinastanol-type triterpenoids and 11-oxygenated steroids from a common intermediate, based on the synthetic route shown in Chart 2, and we report here a stereoselective construction of the A,B,C-ring system of the triterpenoids. Our approach involved thermolysis of a benzocyclobutene derivative to control the stereochemistry of the B/C-*cis* ring juncture followed by efficient intramolecular γ-alkylation[4] of the β,γ-unsaturated ketone to obtain the cyclopropane ring.

Treatment of the benzocyclobutene (**3**)[5] with 1-bromo-6-chlorohexane in *N,N*-dimethylformamide (DMF) in the presence of sodium hydride afforded the chloride (**4**), and an elimination reaction with potassium *tert*-butoxide in dimethylsulfoxide gave the olefin (**5**) in 76.4% yield from **3**. Thermolysis of the benzocyclobutene derivative (**5**) in refluxing *o*-dichlorobenzene furnished a mixture of stereoisomers (**6** and **7**) in 92.2% yield, *via* the *o*-quinodimethane intermediate generated *in situ*. Reduction of the cycloadducts (**6** and **7**) with diisobutylaluminum hydride in benzene afforded the aldehydes **8** and **9** in 87.3% yield, in the ratio of *ca.* 3:2. These products were deduced to be stereoisomers based on their spectral

data, and the minor aldehyde (**9**) was confirmed by X-ray analysis to be the B/C-*trans*-isomer (Fig. 1). Hence the major product (**8**) was the desired B/C-*cis*-hydrophenanthrene derivative, as expected in the thermolysis of a 1-cyanobenzocyclobutene derivative, because this cycloaddition proceeds *via* the sterically favored *exo*-transition state.[6] Reduction of the aldehyde (**8**) with sodium borohydride gave the corresponding alcohol (**10**) in quantitative yield, and this was converted to the enone (**12**) under the Birch reduction conditions, followed by acid treatment. The enone (**12**) thus obtained was subjected to the intramolecular γ-alkylation reaction developed by Piers and Zbozny.[4] Reaction of **12** with mesyl chloride in methylene chloride in the presence of triethylamine gave the mesylate, which, without purification, was treated with potassium *tert*-butoxide in hexamethylphosphoric triamide to afford the desired cyclopropane derivative (**13**) in 67.8% yield from **12**. Similarly the *trans*-isomer (**11**) was also transformed to **15**, *via* the alcohol (**14**).

The ring-opening of a cyclopropane derivative of a triterpenoid has been effectively achieved by treatment with hydrogen chloride to give the 19-methyl-$\Delta^{9(11)}$ compound as a major product.[7] This result suggested that similar treatment of **13** would also provide a similar product.

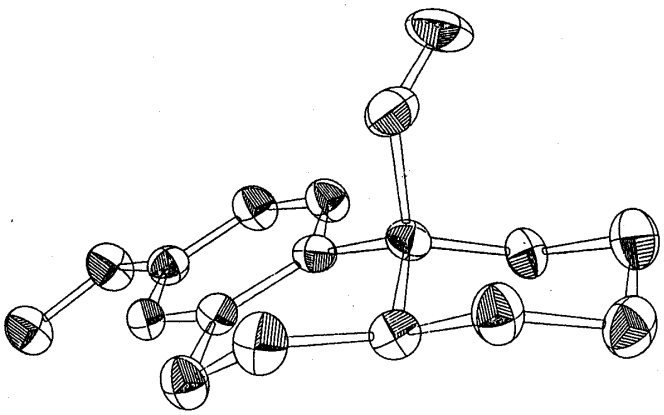

Fig. 1. ORTEP Drawing of Compound **9**

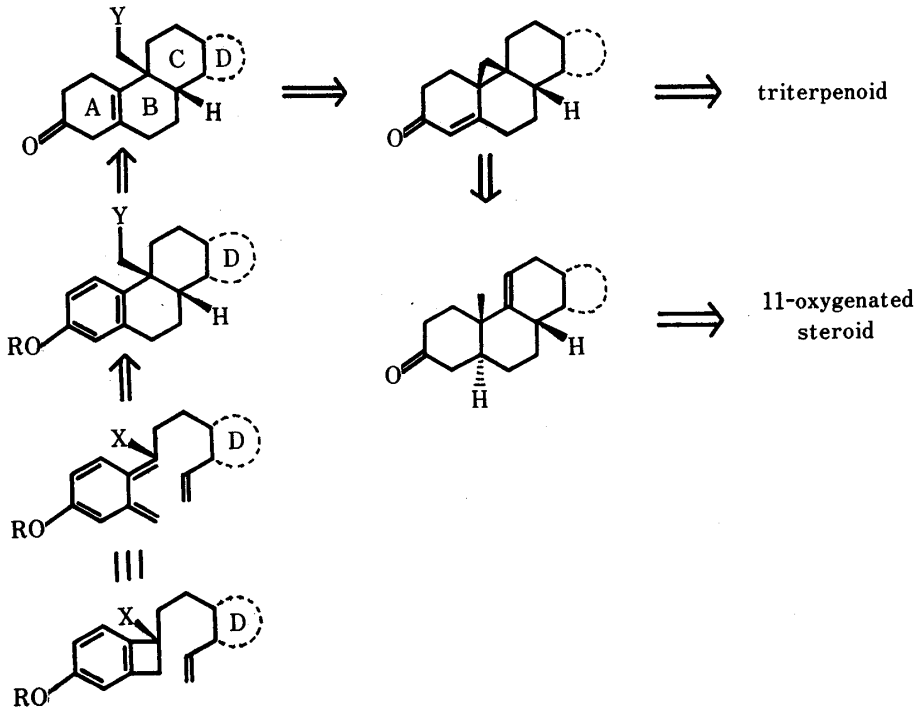

Chart 2

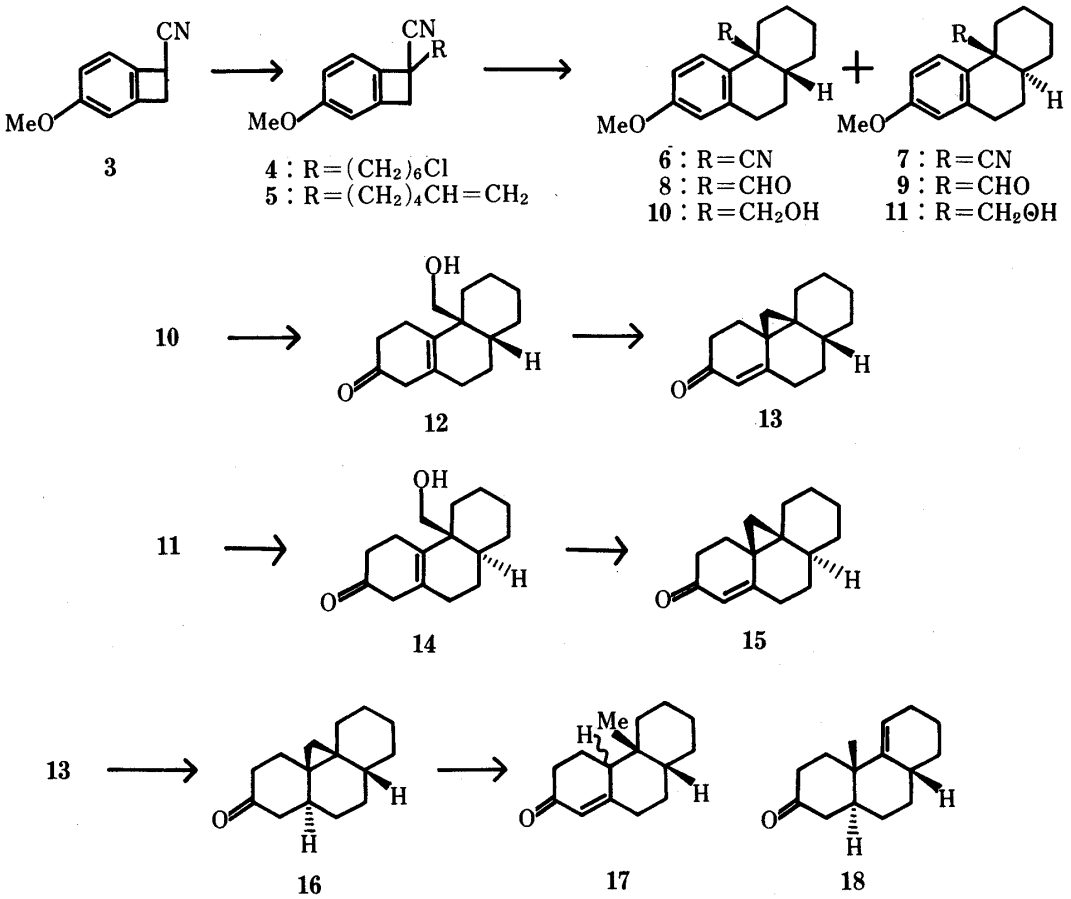

Chart 3

Thus, the ketone (**16**), prepared from **13** in two steps, was subjected to the ring-opening reaction. However, the isolated product was the enone (**17**) instead of the desired compound (**18**).

Further studies on the synthesis of pollinastanol and 11-oxygenated steroids are in progress.

Experimental

Infrared (IR) spectra were obtained with a Hitachi 260-10 spectrophotometer, nuclear magnetic resonance (NMR) spectra with JEOL PMX-60 and JEOL JNM FX-100 instruments (with tetramethylsilane as an internal standard), and mass spectra (MS) with a JEOL JMS D-300 spectrometer. Melting points were determined with a Yanagimoto micro melting point apparatus.

8-(6-Chloro-*n*-hexyl)-8-cyano-4-methoxybicyclo[4.2.0]octa-1,3,5-triene (4)——Sodium hydride (60% in oil) (5.02 g, 125.6 mmol) was added slowly to a stirred solution of benzocyclobutene (**3**) (5 g, 31.4 mmol) in dry DMF (400 ml) at 0 °C, and the reaction mixture was stirred for 30 min. After the above mixture had warmed to room temperature, 1-bromo-6-chlorohexane (9.4 g, 47.1 mmol) was added dropwise and the resulting mixture was stirred at 60 °C for 2 h. The mixture was poured into ice-cold water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (95 : 5, v/v) as the eluant, to give **4** (7.54 g, 86.5%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, d, J=14 Hz, ArCHH), 3.56 (2H, t, J=5 Hz, CH_2Cl), 3.72 (1H, d, J=14 Hz, ArCHH), 3.80 (3H, s, OCH_3), 6.82 (1H, d, J=2 Hz, C_3H), 6.86 (1H, dd, J=2, 7 Hz, C_5H), 7.18 (1H, d, J=7 Hz, (C_6H). MS *m/z*: 277 (M^+). *Anal.* Calcd for $C_{16}H_{20}ClNO \cdot 1H_2O$: C, 68.73; H, 7.28; N, 5.01. Found: C, 68.44; H, 7.26; N, 4.96.

8-Cyano-8-(*n*-hex-5-enyl)-4-methoxybicyclo[4.2.0]octa-1,3,5-triene (5)——A solution of **4** (7.0 g, 25.2 mmol) in dry dimethyl sulfoxide (DMSO) (50 ml) was added dropwise to a suspension of potassium *tert*-butoxide (3.96 g, 35.3 mmol) in dry DMSO (50 ml). After being stirred for 1 h at room temperature, the mixture was poured into ice-

cold water, and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent afforded a pale yellow oil, which was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (96:4, v/v) as the eluant to give **5** (5.37 g, 88.4%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 3.13 (1H, d, J=4 Hz, ArCH$\underline{H}$H), 3.65 (1H, d, J=4 Hz, ArCH$\underline{H}$), 3.72 (3H, s, OCH_3), 4.72—5.26 (2H, m, CH=C$\underline{H}_2$), 5.43—6.26 (1H, m, –C$\underline{H}$=CH_2), 6.70 (1H, d, J=2 Hz, C_3H), 6.77 (1H, dd, J=2, 7 Hz, C_5H), 7.08 (1H, d, J=7 Hz, C_6H). MS *m/z*: 241 (M^+). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.17; H, 8.02; N, 5.58.

4a-Cyano-1,2,3,4,4a,9,10,10a-octahydro-7-methoxyphenanthrene (6 and 7)——A solution of the hexenylbenzocyclobutene (**5**) (1 g, 3.6 mmol) in *o*-dichlorobenzene (250 ml) was refluxed for 5 h under an atmosphere of nitrogen. After evaporation of the solvent, the residue was recrystallized from *n*-hexane to give the adduct (**6** and **7**) as an inseparable mixture (0.922 g, 92.2%), colorless needles, mp 149.5—150.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, OCH_3), 6.73 (1H, br s, C_8H), 6.78 (1H, dd, J=3, 8 Hz, C_6H), 7.55 (1H, d, J=8 Hz, C_5H). MS *m/z*: 241 (M^+). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.69; H, 7.97; N, 5.79.

4aβ-Formyl-1,2,3,4,4a,9,10,10a-octahydro-7-methoxyphenanthrene (8 and 9)——Diisobutylaluminum hydride (1 M, 66.51 ml, 66.51 mmol) was added dropwise to a stirred solution of the above mixture (**6** and **7**) (10.7 g, 44.34 mmol) in dry benzene (300 ml), and the resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched by addition of 10% aqueous NH_4Cl solution and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel using *n*-hexane–benzene (1:1, v/v) as the eluant to give a mixture (**8** and **9**) (9.55 g, 87.25%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CHO). ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 6.55 (1H, br s, C_8H), 6.62 (1H, dd, J=2, 8 Hz, C_6H), 7.00 (1H, d, J=8 Hz, C_5H), 9.39 (1H, s, CHO for **8**), 9.65 (1H, s, CHO for **9**). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.84; H, 8.37.

Compound **9** was obtained from an *n*-hexane solution of the mixture as colorless prisms, mp 84—84.5 °C (from *n*-hexane).

This product was subject to X-ray analysis. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CHO). ^{1}H-NMR ($CDCl_3$) δ: 3.73 (3H, s, –OCH_3), 6.62 (1H, br s, C_8H), 6.70 (1H, dd, J=3, 8 Hz, C_6H), 7.16 (1H, d, J=8 Hz, C_5H), 9.62 (1H, s, –CHO). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.79; H, 8.41. Since the separation of the stereoisomers could be easily carried out in the next stage, the mixture (**8** and **9**) was used in the next reaction without separation.

Crystallographic Measurements——A single crystals of **9** was grown in *n*-hexane as a colorless prism with dimensions of 0.5 × 0.5 × 0.1 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphitemonochromated MoK_α radiation. The unit cell dimensions were determined by least-squares calculation from 20 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $5° < 2\theta < 50°$ with an average scan rate of 4°/min. In total, 2307 independent reflections were collected, and 1288 satisfying the condition $F_o < 3\sigma(F)$ were used for calculation.

Crystal Data——$C_{16}H_{20}O_2$. M_r=244.3. Orthorhombic a=15.416 (5), b=13.415 (3), c=12.604 (5) Å, D_c=1.25 g cm^{-3}, Z=8. μ(MoK_α)=0.7 cm^{-1}. Space group *Pbca*.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[8] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The R factor was finally reduced to 0.075.

4aβ-Hydroxymethyl-1,2,3,4,4a,9,10,10a-octahydro-7-methoxyphenanthrene (10 and 11)——Sodium borohydride (0.81 g, 21.3 mmol) was added to a stirred solution of the aldehyde (**8** and **9**) (2.60 g, 10.64 mmol) in methanol (200 ml) and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was treated with water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated to dryness *in vacuo*. The residue was purified by high performance liquid chromatography (HPLC) using *n*-hexane–ethyl acetate (85:15, v/v) as the eluant to give **10** (1.54 g, 58.8%) and **11** (1.03 g, 39.2%) as oils. **10**: ^{1}H-NMR ($CDCl_3$) δ: 3.43 (2H, s, –CH_2–OH), 3.72 (3H, s, OCH_3), 6.50 (1H, br s, C_8H), 6.58 (1H, dd, J=3, 8 Hz, C_6H), 7.09 (1H, d, J=8 Hz, C_5H). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.19; H, 9.10. **11**: ^{1}H-NMR ($CDCl_3$) δ: 3.53 (2H, br s, –CH_2–OH), 6.43 (1H, br s, C_8H), 6.50 (1H, dd, J=3, 8 Hz, C_6H), 7.03 (1H, d, J=8 Hz, C_5H). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.75; H, 9.13.

4bβ-Hydroxymethyl-1,4,4b,5,6,7,8,8aβ,9,10-decahydro-2(1*H*)-oxophenanthrene (12)——Small pieces of sodium (0.45 g, 20 mmol) were added to a stirred solution of **10** (500 mg, 2.03 mmol) in liquid ammonia (80 ml) containing dry tetrahydrofuran (10 ml) and *tert*-butanol (10 ml) at −78 °C over a period of 1 h. The mixture was stirred for 2 h at the same temperature, the reaction was quenched by addition of methanol, and most of the solvent was evaporated off. The residue was treated with water and extracted with ethyl acetate. The extract was washed with brine and concentrated to leave the residue, which was taken up with methanol (50 ml) and water (5 ml) containing oxalic acid (183 mg, 2.03 mmol). The resulting mixture was stirred at 0 °C for 1 h, then neutralized by addition of solid sodium bicarbonate. The solvent was evaporated off and the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent

gave the residue, which was subjected to column chromatography. Elution with *n*-hexane–ethyl acetate (4:1, v/v) afforded **12** (284.1 mg, 59.7%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR (CCl_4) δ: 2.01 (2H, br s, $C_{10}H_2$), 2.42 (4H, br s, C_3H_2 and C_4H_2), 2.75 (2H, br s, C_1H_2), 3.53 (2H, s, $-C\underline{H}_2-OH$). High-resolution MS *m/z*: Calcd for $C_{15}H_{22}O_2$: 234.1618. Found: 234.1611.

4bβ-Hydroxymethyl-1,4,4b,5,6,7,8,8aα,9,10-decahydro-2(1*H*)-oxophenanthrene (14)——By the same procedure as described above for the preparation of **12**, compound **14** was obtained by reaction of **11** (500 mg, 2.03 mmol) with sodium (0.45 g, 20 mmol) and oxalic acid (183 mg, 2.03 mmol) in 71.5% yield (340 mg) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR (CCl_4) δ: 1.98 (2H, br s, $C_{10}H_2$), 2.33 (2H, br s, C_4H_2), 2.42 (2H, br s, C_3H_2), 2.70 (2H, br s, C_1H_2), 3.70 (2H, s, $-C\underline{H}_2-OH$). MS *m/z*: 234 (M^+). High-resolution MS *m/z*: Calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1633.

4aβ,4bβ-Methano-4,4a,4b,5,6,7,8,8aβ,9,10-decahydro-2(3*H*)-oxophenanthrene (13)——Mesyl chloride (0.26 ml, 3.3 mmol) was added dropwise to a stirred solution of **12** (700 mg, 2.99 mmol) in dry dichloromethane (50 ml) and triethylamine (0.51 ml, 4.5 mmol) at −78 °C, then poured onto water and extracted with dichloromethane. The extract was washed with saturated aqueous sodium bicarbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the keto mesylate, which was used in the next step without purification. A solution of the crude keto mesylate in dry hexamethylphosphoramide (HMPA) (5 ml) was added dropwise to a stirred solution of *tert*-butoxide (722 mg, 6.9 mmol) in dry HMPA (5 ml), under an atmosphere of nitrogen, at room temperature. After the addition was completed, the reaction mixture was stirred for an additional 30 min and then poured into ice-cold water. The resulting mixture was extracted with benzene. The extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (95:5, v/v) as the eluant to give **13** (439 mg, 67.8%) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (–CH=CH–C–). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (1H, d, J=4.8 Hz, $C_{11}H_\alpha$), 1.25 (1H, d, J=4.8 Hz, $C_{11}H_\beta$), 5.86 (1H, br s, C_1H). MS *m/z*: 216 (M^+). High-resolution MS *m/z*: Calcd for $C_{15}H_{20}O$: 216.1515. Found: 216.1517.

4aβ,4bβ-Methano-4,4a,4b,5,6,7,8,8aα,9,10-decahydro-2(3*H*)-oxophenanthrene (15)——By the same procedure as described above for the preparation of **13**, compound **15** was obtained by the reaction of **14** (700 mg, 2.99 mmol) with mesyl chloride (0.26 ml, 3.3 mmol) and *tert*-butoxide (722 mg, 6.9 mmol) in 61.3% yield (396.5 mg) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (–CH=CH–C–). ^{1}H-NMR ($CDCl_3$) δ: 0.062 (1H, d, J=4.6 Hz, $C_{11}H_\alpha$), 1.03 (1H, d, J=4.6 Hz, $C_{11}H_\beta$), 5.82 (1H, br s, C_4H). MS *m/z*: 216 (M^+). High-resolution MS *m/z*: Calcd for $C_{15}H_{20}O$: 216.1513. Found: 216.1505.

4aβ,4bβ-Methano-perhydro-2-oxophenanthrene (16)——$NiCl_2 \cdot 6H_2O$ (374 mg, 1.57 mmol) was added to a stirred solution of **13** (170 mg, 0.79 mmol) in methanol (10 ml) at 0 °C, and the reaction mixture was stirred for 10 min. Sodium borohydride (90 mg, 2.37 mmol) was then added. The mixture was stirred for 30 min at ambient temperature, insoluble material was filtered off, and the filtrate was concentrated to give the residue, which was extracted with benzene. The benzene layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in acetone (20 ml), and 8 N Jones reagent (0.12 ml, 0.94 mmol) was added dropwise to this solution at 0 °C. The resulting mixture was further stirred for 10 min at 0 °C. After addition of an excess of isopropyl alcohol, the reaction mixture was extracted with benzene and the organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (98:2, v/v) afforded **16** (147 mg, 85.6%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.15 (1H, d, J=2 Hz, $C_{11\alpha}$), 0.62 (1H, d, J=2 Hz, $C_{11\beta}$). MS *m/z*: 218 (M^+). High-resolution MS *m/z*: Calcd for $C_{15}H_{22}O$: 218.1670. Found: 218.1688.

4bβ-Methyl-4,4a,4b,5,6,7,8,8aβ,9,10-decahydro-2-oxophenanthrene (17)——HCl gas was bubbled through a solution of **16** (100 mg, 0.459 mmol) in chloroform (5 ml) at 0 °C. After being stirred for 1.5 h, the reaction mixture was basified with saturated aqueous sodium bicarbonate solution and extracted with chloroform. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (95:5, v/v) as the eluant, to give an inseparable epimeric mixture of **17** (56.3 mg, 56.3%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (–CH=CH–C–). ^{1}H-NMR ($CDCl_3$) δ: 0.76, 0.89 (3H, each s (3:5)), 5.85 (1H, s, C_1H). MS *m/z*: 218 (M^+). High resolution MS *m/z*: Calcd for $C_{15}H_{22}O$: 218.1670. Found: 218.1645.

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