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Studies on the Syntheses of Heterocyclic Compounds and Natural Products. CMXCII.[1] Synthesis of an A-Homograyanotoxane and a Phyllocladane Ring System from a Common Precursor

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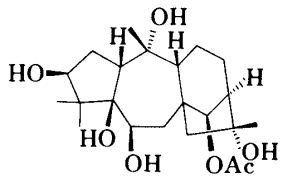
Thermolysis of 5-[(*n*-butylthio)methylene]-2-[2-(1-cyano-5-methoxybenzocyclobutenyl)-ethyl]-3-methylcyclopentanone(**16**) gave the tetracyclic compound (**18**) in excellent yield, and **18** was transformed into both the A-homograyanotoxane (**3**) and the phyllocladane (**4**) ring systems.

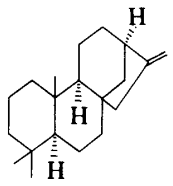
Keywords——A-homograyanotoxane ring system; phyllocladane ring system; thermolysis of benzocyclobutene; dissolving metal reduction; Wagner–Meerwein rearrangement

Of the many diterpenoids, grayanotoxins (**1**) and phyllocladenes (**2**) are two of the most important families[2] and have a bicyclo[3.2.1]octane ring system as a common structural feature.



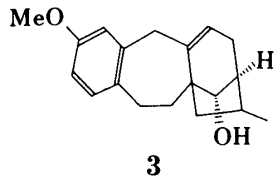
grayanotoxin I

1



phyllocladene

2



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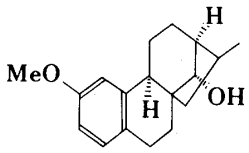

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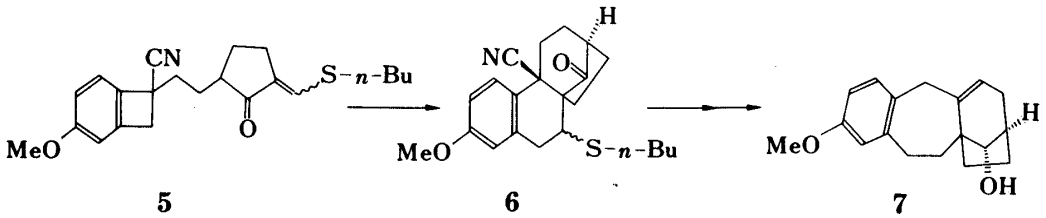

5 **6** **7**

Chart 1

The grayanotoxins[3] (**1**) are constituted of a perhydroazulene skeleton fused with a bicyclo[3.2.1]octane ring system. Not only do these structural features offer synthetic challenges, but also the characteristic biological activities are of considerable interest.

In the previous paper,[4] we described a new construction of the A-homograyanotoxane ring system (**7**) by thermolysis of the benzocyclobutene (**5**), followed by a Wagner–Meerwein rearrangement of the kauran-type compound. In this sequence, the formation of **6** by thermolysis of the benzocyclobutene (**5**) suggests that this type of reaction might provide a good method for constructing the bicyclo[3.2.1]octane ring system.[5] Now our attention has been focused on an efficient synthesis of the basic carbon framework of these two families from a readily preparable common precursor. Here we report a stereoselective and high yield synthesis of the tetracyclic precursor (**18**) and its conversion into the A-homograyanotoxane (**3**) and the phyllocladane (**4**) ring systems.

Condensation of 1-cyano-5-methoxybenzocyclobutene[6] (**8**) with 1-(5-methyl-2-furyl)-3-propyl iodide (**9**), prepared from 2-methylfuran according to the literature,[7] in the presence of sodium amide in liquid ammonia gave **10**[8] in 92.1% yield. The transformation of 2,5-disubstituted furan into 2,3-disubstituted cyclopentenone has been studied in the field of natural cyclopentenoids synthesis,[9] and thus, **10** was converted into the 1,4-diketone (**11**) by acid hydrolysis, then **11** was treated with 0.5 N sodium hydroxide in boiling ethanol to give a 1:25 mixture of **12** and **13** in 41.1% yield from **10**. These products are readily separable by column chromatography; **13** was then hydrogenated, followed by acetic anhydride treatment[10] to give the ketocyanide (**15**) in 74% yield from **13**. On the other hand, **12** was also converted into **15** by catalytic hydrogenation. The stereochemistry on the cyclopentanone ring of **15** is considered to be as shown in Chart 2 because this is the most thermodynamically stable structure.[11] Then the cyclopentanone (**15**) was condensed with ethyl formate in the presence

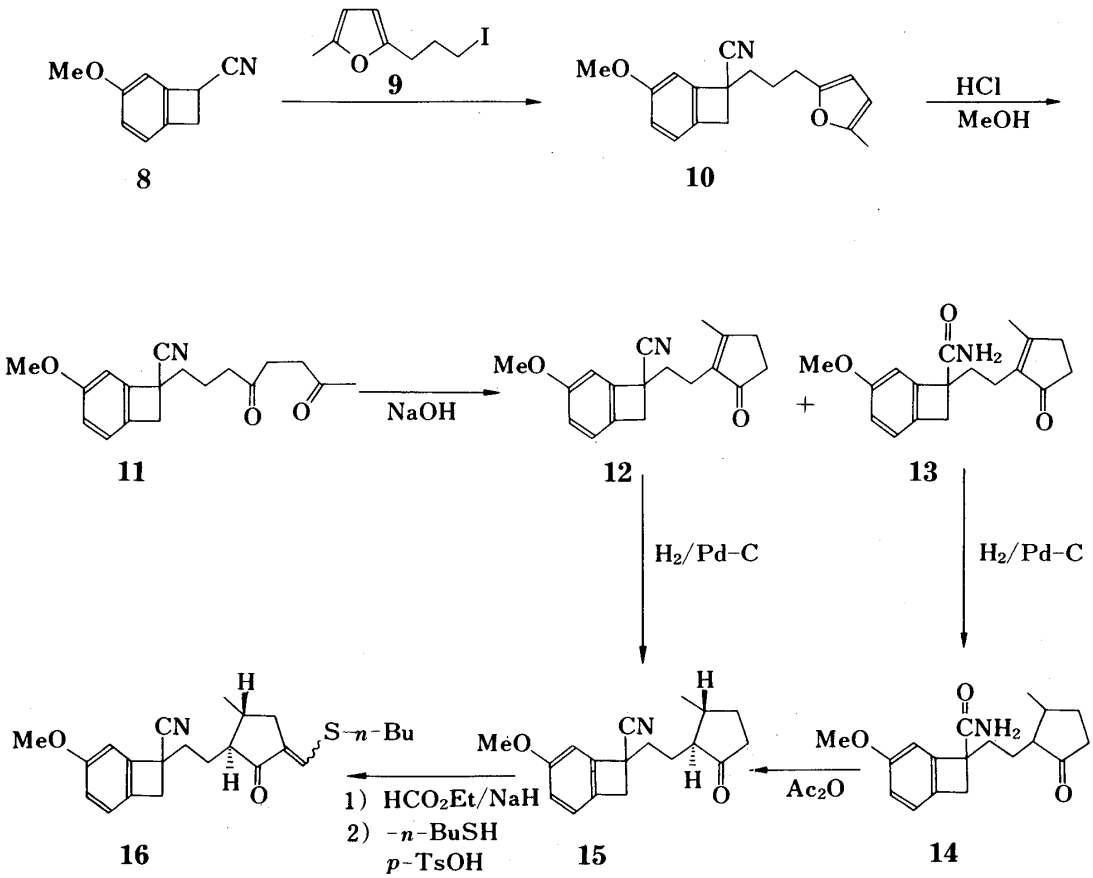

Chart 2

of sodium hydride in benzene at room temperature and the resulting crude 5-hydroxymethylenecyclopentanone was treated with *n*-butyl mercaptan and *p*-toluenesulfonic acid in boiling benzene to give the 5-*n*-butylthiomethylenecyclopentanone (**16**) in 72.9 % overall yield.

Thermolysis of **16** was carried out by heating in *o*-dichlorobenzene at 180°C for 13 h under an atmosphere of argon to afford, *via* *o*-quinodimethane (**17**), the tetracyclic ketone (**18**) in 91.6% yield as a mixture of two diastereomers, whose infrared (IR) spectrum showed the presence of a five-membered cyclic ketone moiety at 1740 cm^{-1}. Reduction of **18** with sodium borohydride afforded the alcohol (**19**),[5] which was then treated with deactivated Raney nickel catalyst (W-2) in boiling ethanol to give the desulfurized product (**20**) in 10.1% yield accompanied by **21**[4a,b] and **22**[12] in 20.4% and 20.7% yields, respectively. The mass spectrum (MS) of **22** showed the molecular ion peak at *m/e* 270, and the methyl resonance at C-10 was observed at δ 0.47 in the ^{1}H-nuclear magnetic resonance (NMR) spectrum because of the shielding effect of the naphthalene ring. The ultraviolet (UV) spectrum showed characteristic bands for naphthalene[13] at 317 and 332 nm. The olefinic product (**21**) was converted into **20** by catalytic hydrogenation. At this stage, since the ^{1}H-NMR (100 MHz) and ^{13}C-NMR of **20** indicated the presence of a single compound, it was concluded that the thermolysis product (**18**) was a mixture of diastereomers at the C-7 position. The relative configuration of the cyano group and the C-13 hydrogen in **19** was determined as *trans* by the fact that the ^{1}H-NMR spectrum of the corresponding acetate (**23**) showed the methyl resonance of the

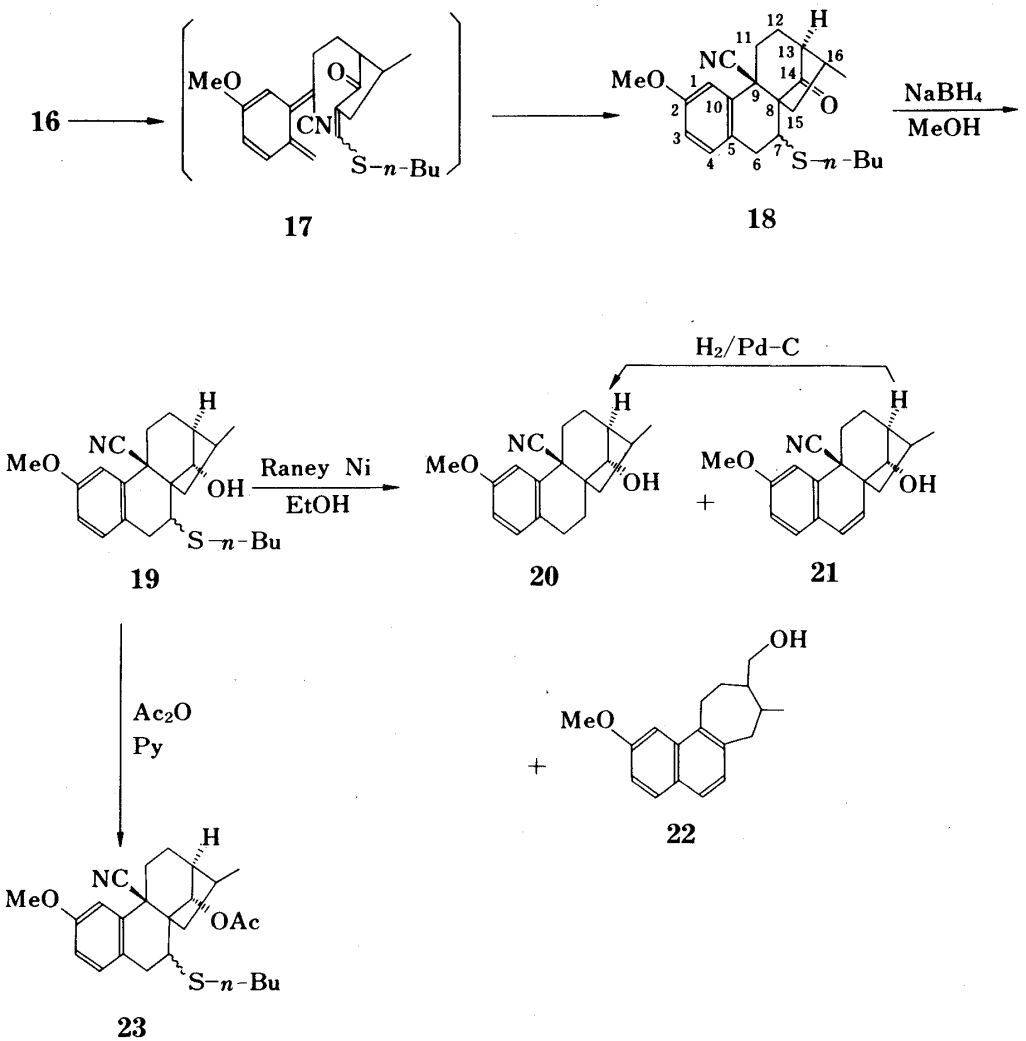

Chart 3

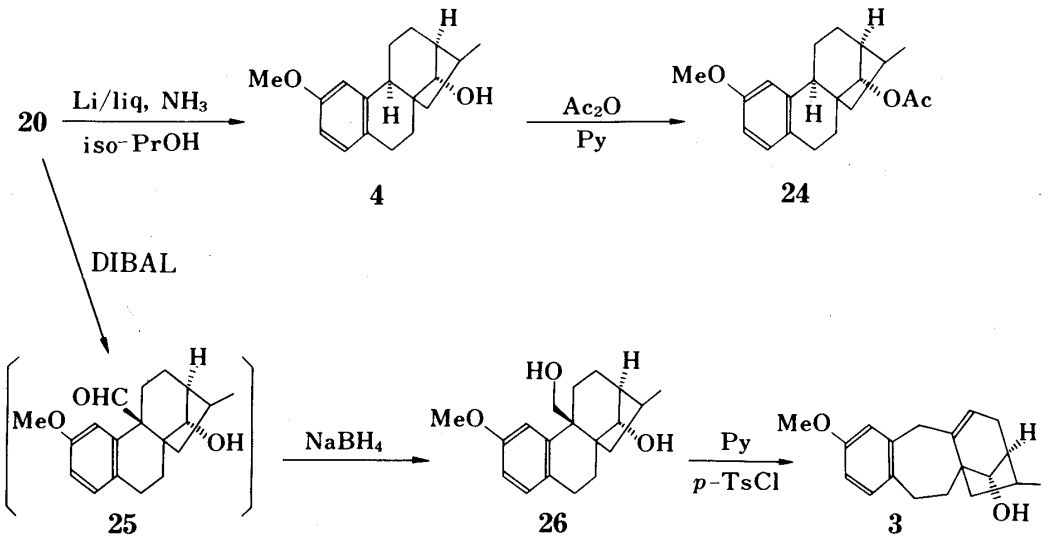

Chart 4

acetoxyl group at an abnormally high field[4b] (δ 1.39) and the methine proton of C-14 at δ 5.23 as a doublet.[5]

Dissolving metal reduction[14] of the cyanide (**20**) using lithium in liquid ammonia in the presence of isopropanol afforded **4** in 45.5% yield. The stereochemistry of C-9 was confirmed by the same method as in the case of **19**. The ^{1}H-NMR spectrum of the acetate (**24**) showed the methyl resonance of the acetoxyl group at a normal field (2.08). This shows that the configuration of C-9 hydrogen is α, as shown in **4**.

On the other hand, treatment of the alcohol (**20**) with diisobutylaluminum hydride in toluene at −78°C followed by sodium borohydride reduction of the resulting aldehyde (**25**) yielded the diol (**26**) in 30.7% yield from **20**. Wagner–Meerwein type rearrangement of (**26**) by treatment with *p*-toluenesulfonyl chloride in pyridine at room temperature for 28 h provided the olefinic alcohol (**3**) in 53.2% yield; its ^{1}H-NMR showed an olefinic proton at δ 5.42 as a broad signal, and a satisfactory ^{13}C-NMR spectrum was obtained.

Thus, we were able to develop an efficient route to synthesize both the A-homograyanotoxane (**3**) and phyllocladane (**4**) ring systems from a readily obtainable single precursor.

Experimental

Melting points were determined on a Yanagimoto MP-22 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 125 grating spectrophotometer and NMR spectra on a JEOL-PMX-60 or JEOL-PS-100 spectrometer using tetramethylsilane as an internal standard. Ordinary mass spectra were measured with a Hitachi M-52G while accurate mass spectra were taken with a JEOL JMS-01SG-2 spectrometer.

1-(1-Cyano-5-methoxybenzocyclobutenyl)-3-(5-methyl-2-furyl)propane (10)——1-(5-Methyl-2-furyl)-3-propyl iodide[5] (**9**) was added dropwise to a stirred solution of 1-cyano-5-methoxybenzocyclobutene[5] (**8**) (51.0 g) and $NaNH_2$ [prepared from Na (8.3 g)] in liquid NH_3 (3 l) at −78°C, and the mixture was stirred for 0.5 h at −78°C. After addition of excess solid NH_4Cl, the solvent was evaporated off to give a gray residue which was treated with 10% aqueous NH_4Cl solution. The resulting mixture was extracted with $CHCl_3$ and the extract was washed with water, dried over Na_2SO_4 and concentrated to afford a brown oil, which was subjected to silica gel chromatography using hexane–dichloromethane (v/v 2:1) as an eluent to give the cyanide (**10**) (83.0 g, 92.1%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N). NMR ($CDCl_3$) δ: 2.26 (3H, s, $-CH_3$), 3.78 (3H, s, $-OCH_3$), 5.85 (2H, br s, C=CH–CH=C). MS *m/e*: 281 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.85; H, 7.03; N, 5.00.

8-(1-Cyano-5-methoxybenzocyclobutenyl)octane-2,5-dione (11)——A mixture of the cyanide (**10**) (17.9 g), conc. HCl (90 ml) and MeOH (300 ml) was stirred at room temperature for 24 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution and concentrated to give a residue,which was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated to give the diketone

(**11**) (17.5 g, 92.1%) as pale yellow prisms, mp 57—58°C after recrystallization from MeOH. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220 (C≡N), 1710 (C=O). NMR ($CDCl_3$) δ: 2.16 (3H, s, $-CH_3$), 2.66 (4H, s, $-OCH_2CH_2O-$), 3.76 (3H, s, $-OCH_3$). MS *m/e*: 299 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 71.81; H, 6.99; N, 4.55.

Aldol Condensation of the 1,4-Diketone (11)———A mixture of the diketone (**11**) (17.5 g), 0.5 N aqueous NaOH solution (420 ml) and EtOH (160 ml) was refluxed for 6 h. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated to give a brown oil, which was chromatographed on silica gel using $CHCl_3$–MeOH (v/v 95:5) as an eluent to give the cyanide (**12**) (0.29 g, 1.6% from **10**) as a pale yellow oil and the amide (**13**) (7.53 g, 39.5% from **10**) as colorless prisms, mp 150—152°C, after recrystallization from MeOH. **12**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡N), 1680 (C=O). NMR ($CDCl_3$) δ: 2.07 (3H, s,$-CH_3$), 3.37 (3H, s, $-OCH_3$). MS *m/e*: 281 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_2 \cdot 1/4H_2O$: C, 75.63; H, 6.88; N, 4.90. Found: C, 75.38; H, 6.78; N, 4.92. **13**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3400 ($-\overset{O}{\overset{\|}{C}}-NH_2$), 1670 (C=O), 1640 ($H_2N-\overset{O}{\overset{\|}{C}}-$). NMR ($CDCl_3$) δ:2.60 (3H, s, $-CH_3$), 3.80 (3H, s, $-OCH_3$), 5.81 (2H, br s, $-\overset{O}{\overset{\|}{C}}-NH_2$, disappeared with D_2O). MS *m/e*: 299 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.46; H, 7.22; N, 4.62.

Catalytic Hydrogenation of the Amide (13)———A solution of **13** (1.8 g) in EtOH (100 ml) was hydrogenated over 10% Pd–C (600 mg) at a pressure of 4.5 kg/cm^2 at room temperature for 48 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give **14** (1.87 g) as a brown oil, which was used for the next reaction without further purification. Silica gel chromatography to obtian an analytical sample using $CHCl_3$ as an eluent gave pure **14** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3400 ($-\overset{O}{\overset{\|}{C}}-NH_2$), 1720 (C=O), 1670 ($-\overset{O}{\overset{\|}{C}}-NH_2$). NMR ($CDCl_3$) δ: 3.83(3H, s, $-OCH_3$), 5.85 (2H, br s, $-\overset{O}{\overset{\|}{C}}-NH_2$, disappeared with D_2O). MS *m/e*: 301 (M^+). *Anal.* Calcd for $C_{18}H_{23}NO_3 \cdot 1/2H_2O$): C, 69.65; H, 7.79; N, 4.51. Found: C, 69.95; H, 7.91; N, 4.58.

2-[2-(1-Cyano-5-methoxybenzocyclobutenyl)ethyl-3-methylcyclopentanone (15)———A mixture of the amide (**14**) (1.87 g) and acetic anhydride (18.7 ml) was refluxed for 3 h. After removal of excess acetic anhydride, the residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give the cyanide (**15**) (1.26 g, 74.0% from **13**) as pale yellow prisms, mp 84—87°C, after recrystallization from hexane–MeOH. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡N) 1720 (C=O). NMR ($CDCl_3$) δ: 3.82 (3H, s, $-OCH_3$). MS *m/e*: 283 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_2 \cdot H_2O$; C, 75.10; H, 7.53; N, 4.87. Found: C, 75.23; H, 7.58; N, 4.80.

Catalytic Hydrogenation of the Cyanide (12)———A solution of **12** (120 mg) in EtOH–AcOH (5 ml, 4/1) was hydrogenated over 5% Pd–C (20 mg) at atmospheric pressure and room temperature for 3 h. The catalyt was removed by filtration and the filtrate was concentrated *in vacuo* to give **15** (110 mg, 90.9%),which was identical with an authentic sample.

5-[(*n*-Butylthio)methylene]-2-[2-(1-cyano-5-methoxybenzocyclobutenyl)ethyl]-3-methylcyclopentanone (16)———A solution of ethyl formate (1.57 g) in dry benzene (7 ml) was added to a solution of (1.50 g) and NaH (50% in oil, 1.02 g) in dry benzene (17 ml), stirring at room temperature. Stirring was continued at room temperature for 1 h, then water (20 ml) was added to the reaction mixture. The resulting aqueous layer was acidified with 10% H_2SO_4 and extracted with benzene. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent afforded the crude formyl derivative (1.52 g), which was used for the next reaction without further purification. A solution of the formyl derivative (1.52 g), *n*-butyl mercaptan (1.32 g), a catalytic amount of *p*-toluenesulfonic acid and dry benzene (24 ml) was refluxed for 2 h in a current of argon. After the reactant had been cooled to room temperature, saturated aqueous $NaHCO_3$ solution (3 ml) was added to it. The resulting mixture was extracted with benzene and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent left a reddish oil, which was chromatographed on silica gel using $CHCl_3$ as an eluent to give the thiomethylene derivative (**16**) (1.48 g, 72.9% from **15**) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡N), 1680 (C=O). NMR ($CDCl_3$) δ:3.75 (3H, s, $-OCH_3$), 7.35 (1H, br s, C=C<u>H</u>-S-*n*-Bu). MS *m/e*: 383 (M^+). *Anal.* Calcd for $C_{23}H_{29}NO_2S$: C, 72.02; H, 7.62; N, 3.65; S, 8.36. Found: C, 71.78; H, 7.79; N, 3.59; S, 8.12.

Thermolysis of 16———A solution of **16** (813 mg) in dry *o*-dichlorobenzene (65 ml) was heated with stirring under a stream of argon for 13 h at 180°C. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give the tetracyclic compound (**18**) (745 mg, 91.6%) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡N), 1740 (C=O). NMR ($CDCl_3$) δ: 3.75 (3H, s, $-OCH_3$). MS *m/e*: 383 (M^+), 197 (base peak). High resolution MS *m/e*: Calcd for $C_{23}H_{29}NO_2S$: 383.1888. Found: 383.1903.

$NaBH_4$ Reduction of 18———A solution of **18** (1.36 g) in MeOH (20 ml) was treated with $NaBH_4$ (400 mg) at 0°C. The mixture was stirred at room temperature for 2 h, then the solvent was evaporated off to leave the residure, which was extracted with CH_2Cl_2 and the extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave the crude alcohol, which was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give the alcohol (**19**) (1.13 g, 82.4%) as a yllow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500

(OH), 2210 (C≡N). NMR ($CDCl_3$) δ: 3.75 (3H, s, $-OCH_3$). MS *m/e*: 385 (M^+). High resolution MS *m/e*: Calcd for $C_{23}H_{31}NO_2S$: 385.2054. Found: 385.2064.

Desulfurization of 19———A mixture of the alcohol (**19**) (640 mg), deactivated W-2 Raney Ni (treating with refluxing acetone for 2 h) and EtOH (40 ml) was refluxed for 24 h. The reaction mixture was filtered with the aid of celite and the filtrate was concentrated to leave the residue, which was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give **20** (50 mg, 10.1%) as colorless prisms, mp 156—160°C, after recrystallization from MeOH, and **21** (100 mg, 20.4%) as colorless prisms, mp 165—168°C, after recrystallization from MeOH and **22** (93 mg, 20.7%) as a colorless oil. **20**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 2210 (C≡N). NMR ($CDCl_3$), δ: 1.01 (3H, d, *J*=7 Hz, >CH-C<u>H</u>$_3$), 3.71 (3H, s, $-OCH_3$), 6.70 (1H, dd, *J*=8 and 3 Hz, arom.-H), 6.88 (1H, d, *J*=3 Hz, 3 Hz, arom.-H), 7.00 (1H, d, *J*=8 Hz, arom.-H). ^{13}C-NMR ($CDCl_3$) δ: 20.417, 23.390, 25.875, 26.460, 30.554, 31.285, 42.687,43.418, 45.562, 45.905, 55.114, 77.578, 110.13, 113.199, 122.411, 130.207, 130.543, 133.764, 158.417. MS *m/e*: 297 (M^+). High resolution MS *m/e*: Calcd for $C_{19}H_{23}NO_2$: 297.1725. Found: 297.1726. **21**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2210 (C≡N). NMR ($CDCl_3$) δ: 1.10 (3H, d, *J*=7 Hz, CH-C<u>H</u>$_3$), 3.79 (3H, s, $-OCH_3$), 5.63 (1H, d, *J*=10 Hz, olefinic-H), 6.53—7.30 (4H, m, arom. and olefinic-H). MS *m/e*: 295 (M^+). High resolution MS (*m/e*): Calcd for $C_{19}H_{21}NO_2$: 295.1549. Found: 295.1560. **22**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). NMR ($CDCl_3$) δ: 0.47 (3H, d, *J*=7 Hz, >CH-C<u>H</u>$_3$), 3.86 (3H, s, $-OC\underline{H}_3$), 6.94—7.68 (5H, m, arom.-H). UV λ_{max}^{MeOH} nm: 317, 332. MS *m/e*: 270 (M^+). High resolution MS *m/e*: Calcd for $C_{18}H_{22}NO_2$: 270.1602. Found: 270.1610.

Catalytic Hydrogenation of 21———A solution of **21** (30 mg) in EtOH (2 ml) was hydrogenated over 10% Pd–C (60 mg) at atmospheric pressure at room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **20** (29 mg, 96.7%), which was identical with an authentic sample.

Acetylation of 19———A mixture of the alcohol (**19**) (55 mg), acetic anhydride (0.5 ml), pyridine (0.5 ml) and a catalytic amount of 4-dimethylaminopyridine was stirred under a stream of argon at room temperature for 16 h. After removal of the excess reagents, the residue was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give the acetate (**23**) (30 mg, 49.2%) as a colorlss oil. NMR ($CDCl_3$) δ: 1.39 (3H, s, $-\underset{\underset{O}{\|}}{C}-C\underline{H}_3$), 3.80 (3H, s, $-OCH_3$), 5.22 (1H, d, *J*=5 Hz, $\underset{\underline{H}}{\overset{OAc}{C}}$). MS *m/e*: 427 ($M^+$). High resolution MS *m/e*: Calcd for $C_{25}H_{33}NO_3S$: 427.2090. Found: 427.2135.

Birch Reduction 20———Lithium (14 mg) was added in small portions to a stirred solution of **20** (60 mg) in a mixture of THF (0.75 ml), isopropanol (0.03 ml), and liquid ammonia (3 ml). Stirring was continued for 0.5 h, then the reaction mixture was treated with NH_4Cl and ammonia was evaporated off. The residue was diluted with water (5 ml) and extracted with CH_2Cl_2. The extract was washed with water, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give **4** (25 mg, 45.5%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). NMR ($CDCl_3$) δ: 3.67 (3H, s, $-OCH_3$). MS *m/e*: 272 (M^+). High resolution MS *m/e*: Calcd for $C_{18}H_{24}O_2$: 272.1836. Found: 272.1806.

Acetylation of 4———A mixture of **4** (20 mg), actic anhydride (0.25 ml) and pyridine was stirred under a stream of argon at room temperature for 13 h. After removal of the excess reagents, the residue was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give the acetate (**24**) (13 mg, 56.5%) as a colorless oil. NMR ($CDCl_3$) δ: 1.07 (3H, d, *J*=7 Hz, >CH-C<u>H</u>$_3$), 2.07 (3H, s, $-\underset{\underset{O}{\|}}{C}-CH_3$), 3.75 (3H, s, $-OCH_3$), 4.83 (1H, d, *J*=5 Hz, >C<u>H</u>-OAc). MS *m/e*: 314 (M^+). High resolution MS *m/e*: Calcd for $C_{20}H_{26}O_3$: 314.1866. Found: 314.1873.

Reduction of 20 giving 26———Diisobutylaluminium hydride (25% in hexane, 0.306 ml) was added dropwise to a stirred solution of **20** (80 mg) in dry toluene (1 ml) under a stream of argon at −78°C. After being stirred at −78°C for 0.5 h and at room temperature for 12 h, the mixture was treated with saturated aqueous NH_4Cl solution (0.3 ml) for 0.5 h and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and concentrated to give the crude aldehyde (**25**) (37 mg). A solution of the crude aldehyde (**25**) (37 mg) in MeOH (1 ml) was treated with $NaBH_3$ (7 mg) at 0°C. Stirring was continued at room temperature for 1 h, then the solvent was removed to give a colorless oil which was taken up with CH_2Cl_2, washed with water, dried over Na_2O_4, and concentrated to leave an oil. The oil was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give the diol (**26**) (25 mg, 30.7% from **20**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR ($CDCl_3$) δ: 1.05 (3H, d, *J*=7 Hz, >CH-C<u>H</u>$_3$), 3.78 (3H, s, $-OCH_3$). MS *m/e*: 302 (M^+). High resolution MS *m/e*: Calcd for $C_{19}H_{26}O_3$) δ: 302.1901. Found: 302.1891.

Wagner–Meerwein Rearrangement of 26———A solution of the alcohol (**26**) (20 mg) in pyridine (0.5 ml) was treated with *p*-toluenesulfonyl chloride (34 mg), and the mixture was stirred under a stream of argon at room temperature for 28 h. The reaction mixture was neutralized with 10% HCl and extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave an oil, which was chromatographed on silica gel using benzene–ethyl acetate (v/v 95:5) as an eluent to give **3** (10 mg,

53.2%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH). NMR ($CDCl_3$) δ: 0.99 (3H, d, J=7 Hz, CH-C<u>H</u>$_3$), 3.76 (3H, s, -OCH_3), 5.44 (1H, br, m, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 22.897, 30.294, 30.764, 34.169, 34.932, 42.154, 44.091, 48.083, 49.669, 55.070, 77.497, 111.198, 114.485, 120.413, 129.689, 132.624, 139.317, 140.844, 157.692. MS m/e: 284 (M^+). High resolution MS m/e: Calcd for $C_{19}H_{24}O_2$: 284.1705. Found: 284.1740.

References and Notes

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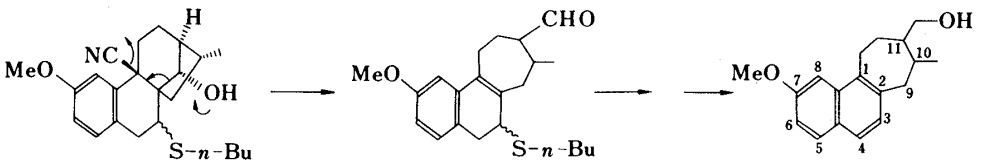
11) Although the cyclopentanone (**15**) showed a single spot on thin-layer chromatography (TLC) (Merck, Silica gel 60F-254; solvent, MeOH/$CHCl_3$=5/95), it is assumed to be a mixture of diastereomers at C-1. The conversion of **15** into **20** indicated that the stereostructure on the cyclopentanone ring of **15** was homogeneous.
12) One possible interpretation of the formation of **22** might be Raney nickel-induced retro Prins type reaction of **19** followed by reduction of the resulting aldehyde (**27**) and aromatization as shown below.



19 **27** **22**

The relative configuration of the C-10 methyl group and the C-11 hydroxymethyl group in **22** could not be determined since no useful characteristics appeared spectroscopically.

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