Photocyclization of Enamides. XXVIII.[1] A Formal Total Synthesis of (±)-Deserpidine[2]

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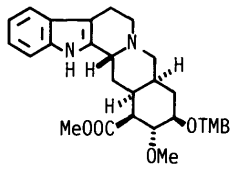
A formal total synthesis of (±)-deserpidine (1) was accomplished by preparing the known synthetic precursors, two hydroxyesters 19 and 20, *via* a route involving regioselective formation of the 18-methoxyenone 10a followed by regioselective C-acylation of the enone 10a.

Keywords deserpidine; total synthesis; yohimbine; reserpine; indole alkaloid; photocyclization; enamide; epoxyketone

In part XXVII,[1] we have reported the establishment of a practical synthetic route to the yohimbine group of alkaloids, and succeeded in total syntheses of five natural alkaloids. In the course of our studies on the total synthesis of biologically active benzindoloquinolizine alkaloids,[3] we now report the details of a new formal total synthesis of (±)-deserpidine (**1**) according to the same synthetic methodology, employing the *cis*-18-methoxyenone **10a** as a common synthetic key intermediate which was prepared by two independent methods. One is reductive photocyclization of the dimethoxyenamide **11** and the other is epoxidation of the known *cis*-enone **4**,[1] which had been employed as a key intermediate for the synthesis of yohimbine alkaloids,[1] followed by the rearrangement of the epoxyketone **6**.

Preparation of the *cis*-Methoxyenone 10a For the application of the synthetic route[1] employed in the total synthesis of yohimbine alkaloids to deserpidine, the *cis*-18-methoxyenone **10a** was regarded as an important common key intermediate and was prepared by the following two independent routes. Protection of the known amine **2a**[1] by the conventional acylation using methyl chloroformate–lithium diisopropylamide (LDA) gave the carbamate **2b** in 90% yield, and this was subjected to acid hydrolysis to afford the unconjugated enone **3** in a quantitative yield. The enone **3** exhibited infrared (IR) absorptions at 1740—1720 cm^{-1} due to carbamate and ketone carbonyl moieties and the proton nuclear magnetic resonance (^{1}H-NMR) signal of an olefinic proton at δ 5.53 (br s, 19-H). Treatment of the unconjugated enone **3** with silica gel resulted in stereoselective isomerization[1] of the double bond to give the conjugated enone **4** in 88% yield. The structure of the enone **4** was established from the following spectral data: IR absorption at 1675 cm^{-1} and ^{1}H-NMR signals of two olefinic protons at δ 6.88 (dt, J=10, 2 Hz, 19-H) and 5.97 (dd, J=10, 3 Hz, 18-H) suggested the presence of a D/E-*cis* conjugated enone system, which is in agreement with the result of chemical conversion to the known alloyohimbone **5b**[4] by catalytic hydrogenation on platinum dioxide followed by deprotection with base.



deserpidine(1)

TMB=3,4,5-trimethoxybenzoyl

Fig. 1

In order to introduce an oxygen function at the 18-position, we investigated epoxidation of the enone system in **4** and then regioselective ring-opening reaction of the resulting epoxyketone **6**. Treatment of the enone **4** with 30% hydrogen peroxide at 0 °C gave the α-epoxyketone **6** as a sole product in 84% yield. We encountered difficulty in the establishment of the stereochemistry of the epoxyketone **6** from the spectral data but the α-epoxy structure was unambiguously determined by X-ray analysis as shown in Fig. 2.[5] Thus, epoxidation of the enone **4** occurred from the convex α-face to give the α-epoxyketone **6**.

Next we investigated selective ring-opening of the epox-

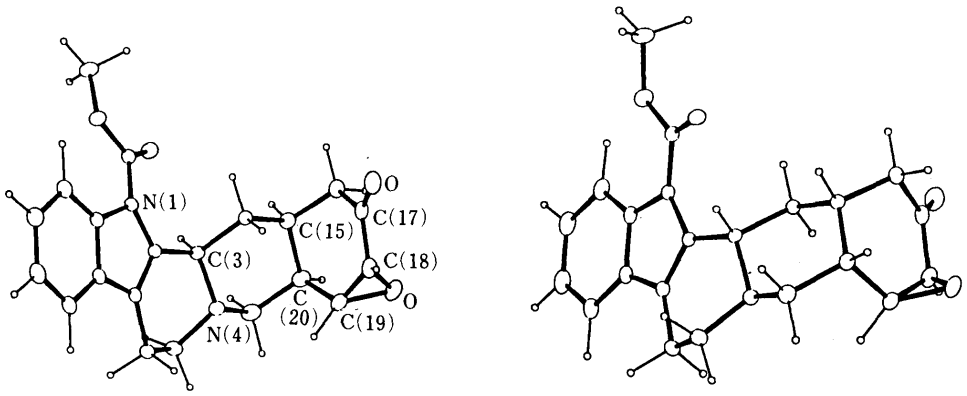


Fig. 2. X-Ray Crystal Structures of Compound **6**

yketone **6** under both acidic and basic conditions. Refluxing of the epoxyketone **6** in methanol in the presence of potassium hydroxide gave a mixture of several products, of which the D/E-*trans* ketone **7**, isolated by preparative thin-layer chromatography (p-TLC) in 15% yield, exhibited an IR absorption at 1700 cm^{-1} due to an α,β-unsaturated ketone and ^{1}H-NMR signals of an olefinic proton at δ 5.60 (d, J=2.5 Hz, 19-H) and an 18-methoxy group at δ 3.64 (s), suggesting the presence of an 18-methoxyenone group. The stereochemistry at the D/E-ring juncture of **7** was deduced by comparison of the spectral data with those of the corresponding *cis*-18-methoxyenone **10a** as described later.

On the other hand, refluxing of the epoxyketone **6** in methanol in the presence of concentrated sulfuric acid for 8 h gave the D/E-*cis*-18-methoxyenone **9** in 55% yield; it exhibited the following spectral signals [IR: 1680 cm^{-1} (C=C–CO); ^{1}H-NMR δ: 5.70 (br s, 19-H), 3.64 (s, OMe)]. The stereochemistry of the D/E-*cis* ring juncture was deduced on the basis of the chemical conversion to the known synthetic key intermediates[3d] of the desired (±)-deserpidine as described later. Refluxing of the epoxyketone **6** for 1.5 h under the same conditions afforded the ketal **8** in a quantitative yield. Without purification, **8** was then converted into the identical D/E-*cis*-18-methoxyenone **9** by prolonged refluxing (8 h) under the same reaction conditions. Thus, the formation of the enone **9** from **6** is suggested to occur *via* the ketal **8**.

Finally, removal of the protective group on indole nitrogen by treatment with potassium carbonate afforded the desired D/E-*cis*-18-methoxyenone **10a** in 28% overall yield from harmalane.

An alternative route with fewer steps for the synthesis of the enone **10a** consists of the application of the reductive photocyclization of the dimethoxyenamide **11**, which was readily prepared by the conventional acylation of harmalane with 3,4-dimethoxybenzoyl chloride. Reductive photocyclization[6] of the enamide **11** in the presence of sodium borohydride in acetonitrile–methanol (10:1) proceeded smoothly to give a mixture of two hydrogenated lactams **12** and **13**, which were readily separated by medium-pressure column chromatography on silica gel in 23 and 35% isolated yields, respectively. The structures of these two lactams **12** and **13** were established from the following spectral data. Both lactams **12** and **13** showed an identical molecular ion peak at m/z 350 in their mass spectra (MS), two mass units larger than that of the parent enamide **11**. The lactam **12** exhibited an IR absorption at 1625 cm^{-1} due to a lactam carbonyl group and ^{1}H-NMR signals of two olefinic protons at δ 4.79 (d, J=7 Hz, 16-H) and 4.72 (br dd, J=2, 1 Hz, 19-H), of two methoxyl groups at δ 3.62 and 3.57 (each s), and of the angular proton at the 20-position at δ 3.65 (br dd, J=8, 2 Hz), suggesting the 17,18-dimethoxy-*cis*–*syn* structure, which is in agreement with the result of chemical conversion to the key in-

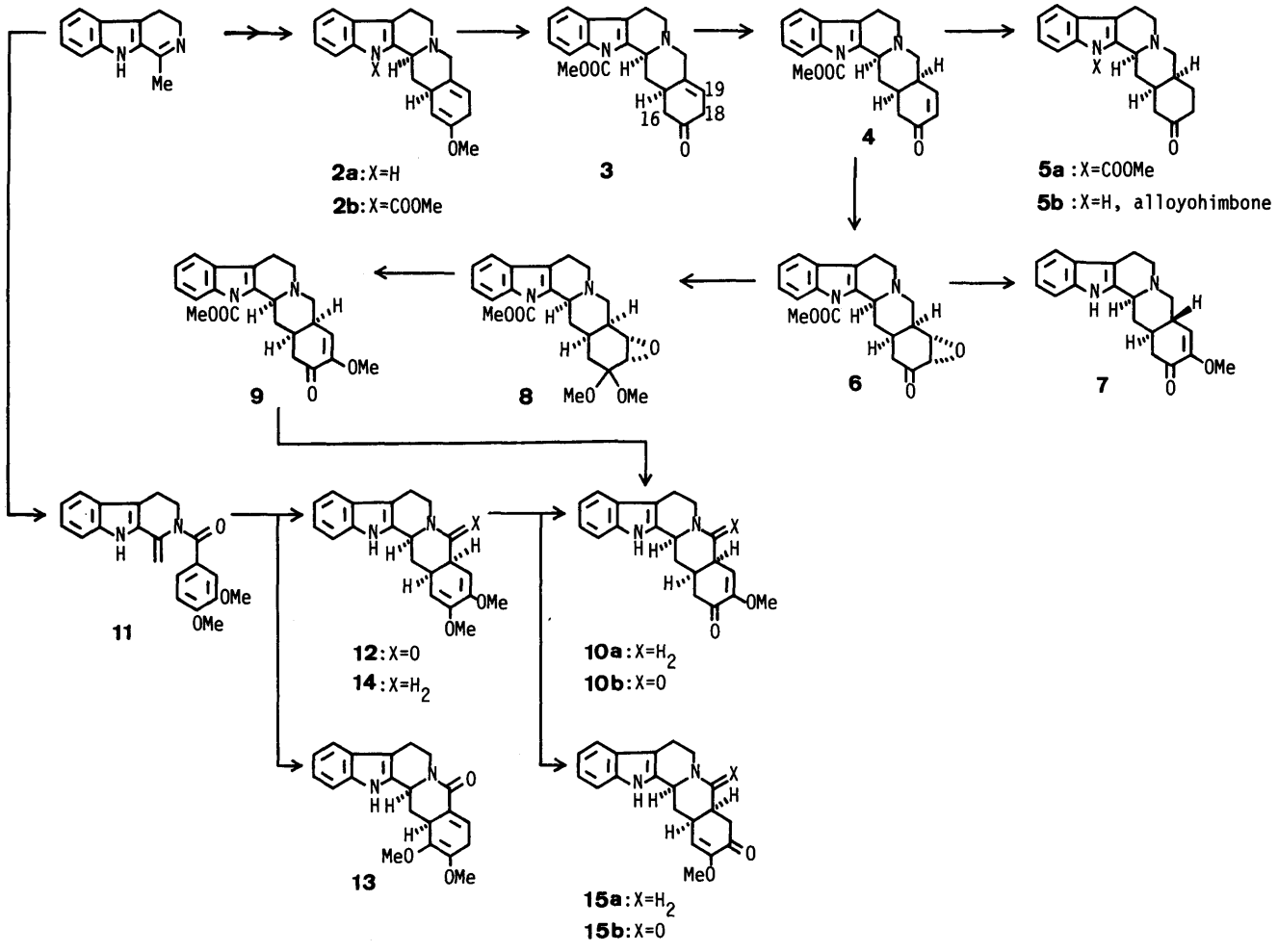


Chart 1

termediates **19** and **20** for the synthesis of deserpidine as described later.

The other lactam **13** exhibited an IR absorption at 1620 cm^{-1} due to a lactam carbonyl group and ^{1}H-NMR signals of two methoxyl groups at δ 3.76 and 3.63 (each s) and of an olefinic proton at δ 6.84 (td, J=3.5, 2 Hz, 19-H), of which the 19-H signal appeared at low field due to the anisotropic effect of the lactam carbonyl group. For the deserpidine synthesis, the dimethoxylactam **12** was converted into the desired *cis*-18-methoxyenone **10a** by regioselective hydrolysis of an enolether group at the 16-position after investigation of several reaction conditions. Treatment of the lactam **12** with 10% hydrochloric acid gave a 1 : 1 mixture of two methoxyenones **10b** and **15b** in 95% combined yields; both showed an identical molecular ion peak at *m/z* 336 in their MS, and IR absorptions at 1695—1700 cm^{-1} due to an α,β-unsaturated enone. ^{1}H-NMR signals of **10b** [δ 5.80 (d, J=2.5 Hz, 19-H), 3.57 (s, 18-OMe), 3.80 (br dd, J=5, 2.5 Hz, 20-H)] and **15b** [δ 5.66 (d, J=6 Hz, 16-H), 3.46 (s, 17-OMe), 3.18 (dt, J=12, 5.5 Hz, 20-H)] suggested their structures; the former **10b** is 18-methoxyenone, and the latter **15b**, 17-methoxyenone.

On the other hand, treatment of the amine **14**, prepared by reduction of the lactam **12** with lithium aluminum hydride, with the same acid as above, gave the desired 18-methoxyenone **10a** as a major product (73%) in addition to a small amount of the 17-methoxyenone **15a** (10%). The 18-methoxyenone **10a**, thus obtained from the dimethoxylactam **12**, was identical with the enone **10a** which was prepared previously from the epoxyketone **6**. Another enone **15a** was characterized from the spectral data [IR: 1690 cm^{-1} (C=C–CO); ^{1}H-NMR δ: 5.82 (d, J=6 Hz, 16-H) and 3.57 (s, 17-OMe)]. Different behaviors under acid hydrolysis between the dimethoxylactam **12** and the dimethoxyamine **14** can be explained as follows. In acidic media, the amine **14** would form the salt A as shown in Chart 2 which would then undergo protonation at either the 19- or 16-position to give two types of oxonium salts B and C. Comparison of steric hindrance between 19-H and $\geqslant N^+$-H in these two intermediates B and C clearly showed that hydrolysis *via* the intermediate C was preferred to that *via* B. On the other hand, since the lactam **12** could not form a salt with acid even in hydrochloric acid, there would be virtually no difference in steric hindrance between the same two hydrogens in the two corresponding oxonium forms which would undergo hydrolysis at the same rate to afford equal amounts of the two methoxyenones **10b** and **15b**. Thus, we prepared the key intermediate, D/E-*cis*-18-methoxyenone **10a** in four steps from harmalane, in 11% overall yields.

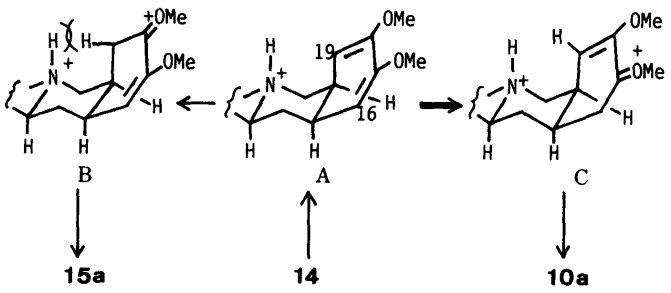
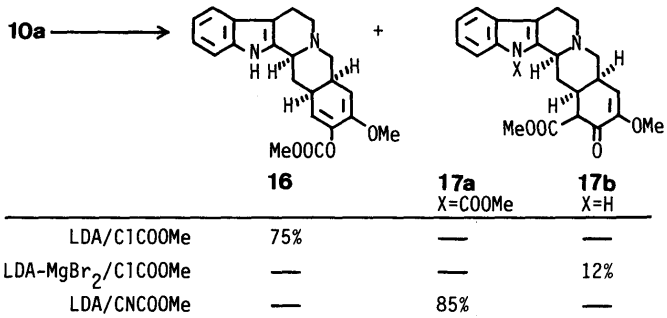


Chart 2

Conversion of the 18-Methoxyenone 10a into the Hydroxyesters 19 and 20 Based on the regioselective acylation at the 16-position in the total synthesis of yohimbine alkaloids,[1] we have finally accomplished the formal total synthesis of (±)-deserpidine by converting the 18-methoxyenone **10a** to the known 17-hydroxy-18-methoxyesters **19** and **20**. Acylation of the lithium enolate, prepared *in situ* from the 18-methoxyenone **10a** and LDA at −78 °C, with methyl chloroformate gave exclusively the O-acylated product **16** (75% yield), which exhibited an IR absorption at 1765 cm^{-1} (OCOOMe) and ^{1}H-NMR signals of two olefinic protons at δ 5.58 (d, J=6 Hz, 16-H) and 4.67 (br s, 19-H) and of the ester methyl group at δ 3.76 (s). Acylation of the corresponding magnesium enolate,[7] prepared *in situ* from the corresponding lithium enolate and anhydrous magnesium dibromide, with methyl chloroformate gave only a small amount of the desired 16-acylated product **17b** (12% yield) in addition to large amount of the starting enone **10a**. Use of a soft acylating agent, methyl cyanoformate, known as Mander's reagent,[8] accomplished regioselective acylation at the 16-position leading to the formation of the N,C-diacylated enone **17a** in 85% yield; this was found to exist as a 5 : 4 equilibrium mixture of the keto and enol forms from spectral data [IR: 1730, 1690, 1625, 1595 cm^{-1} (COCHCOOMe+C(OH)=CHCOOMe); ^{1}H-NMR δ: 12.06 (4/9H, br s, C=C–OH), 4.06 (5/3H, s),



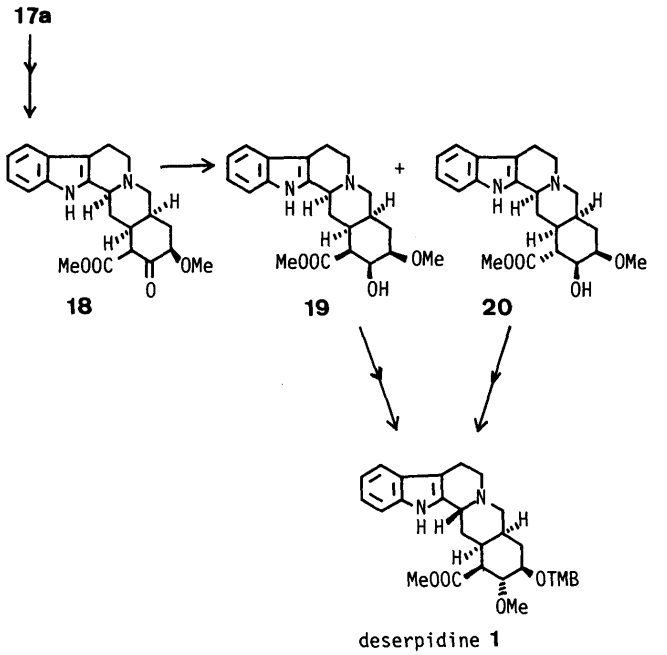


Chart 3

4.03 (4/3H, s), 3.88 (4/3H, s), 3.76 (5/3H, s), 3.70 (4/3H, s), 3.66 (5/3H, s) (OMe)]. N-Deacylation of the N,C-diacylated product **17a** by treatment with potassium carbonate in methanol gave the ketoester **17b** in quantitative yield. Thus, the fully functionalized pentacyclic compound **17b** was constructed and finally converted into the known hydroxyesters **19** and **20**. Catalytic hydrogenation of the ketoester **17b** over platinum dioxide in methanol at room temperature gave quantitatively the saturated ketone **18** while the same hydrogenation at 50 °C gave a mixture of two hydroxyesters **19** and **20**, which were isolated by p-TLC in 67 and 19% yields, respectively. The structures of the three products **18**, **19**, and **20** were deduced from their spectral data and established firmly by spectral comparisons with authentic samples which had been synthesized by Szantay's group.[3d]

Thus, we have succeeded in the formal total synthesis of (±)-deserpidine (**1**), since these two hydroxyesters **19** and **20** had already been converted into the alkaloid, deserpidine.[3d]

Experimental

The ^{1}H-NMR spectra were measured with JEOL PMX-60 (60 MHz), Varian NEVA NV-21 (90 MHz), and Varian XL-200 (200 MHz) instruments for solutions in deuteriochloroform unless otherwise stated (with tetramethylsilane as an internal reference), and the IR spectra were measured with a Hitachi 215 machine for solutions in chloroform. MS were taken with JEOL JMS-01SG and Hitachi M-80 spectrometers. All melting points were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixture were washed with water and dried over anhydrous sodium sulfate. Thin layer chromatography (TLC) was performed on pre-coated Silica gel 60F-254 (0.25 mm thick, Merck) and p-TLC on pre-coated Silica gel 60F-254 (0.5 mm thick, Merck), and spots were detected by ultraviolet (UV) irradiation of the plate at 254 and 300 nm. Medium-pressure column chromatography was undertaken on a 530-4-RI apparatus (Yamazen) using Lobar grösse B (310-25, Lichroprep Si60, Merck) as a column.

Methyl 16,17,19,20-Tetradehydro-17-methoxyyohimban-1-carboxylate (2b) A solution of the amine **2a**[1] (200 mg) in anhydrous tetrahydrofuran (THF) (20 ml) was added to an LDA solution, prepared from diisopropylamine (0.1 ml, 1.1 eq) and *n*-butyllithium (15% solution in *n*-hexane) (0.31 ml, 1.1 eq) at −78 °C with stirring at −78 °C under a nitrogen stream. This mixture was stirred at −78 °C for 1 h, methyl chloroformate (0.055 ml, 1.1 eq) was added at −78 °C, and the resulting solution was stirred at −78 °C for 1 h. After being quenched by the addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue, which was purified by p-TLC (AcOEt) to afford the carbamate **2b** (220 mg, 90%) as a yellow oil. IR: 1730 (COOMe), 1700 and 1660 (C=C) cm^{-1}. ^{1}H-NMR (90 MHz) δ: 8.04 (1H, m, 12-H), 5.51 (1H, br s, 19-H), 4.64 (1H, br d, J=12 Hz, 3-H), 4.51 (1H, br s, 16-H), 4.03 (3H, s, COOMe), 3.51 (3H, s, OMe), 2.28 (1H, br d, J=12 Hz, 14eq-H), 1.52 (1H, q, J=12 Hz, 14ax-H). High-resolution MS m/z: Calcd for $C_{22}H_{24}N_2O_4$ (M^+) 364.179. Found: 364.181.

Methyl 19,20-Didehydro-17-oxoyohimban-1-carboxylate (3) A solution of the enolether **2b** (200 mg) in THF (10 ml) containing 10% hydrochloric acid (4 ml) was stirred at room temperature for 30 min under a nitrogen stream. Water was added to the reaction mixture, which was then made alkaline by addition of sodium bicarbonate and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the unconjugated enone **3** (183 mg, 95%) as a yellow oil. IR: 1740—1720 (NCOOMe+C=O) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 7.97 (1H, m, 12-H), 5.53 (1H, br s, 19-H), 4.32 (1H, br d, J=10 Hz, 3-H), 4.00 (3H, s, COOMe). High-resolution MS m/z: Calcd for $C_{21}H_{22}N_2O_3$ (M^+) 350.163. Found: 350.163.

Methyl (20α)-18,19-Didehydro-17-oxoyohimban-1-carboxylate (4) A solution of the unconjugated enone **3** (100 mg) in methylene dichloride (15 ml) in the presence of silica gel (150 mg) was stirred at room temperature overnight under a nitrogen stream. The solution was filtered and the resulting filtrate was concentrated to give a residue, which was purified by p-TLC (methylene dichloride : methanol=95 : 5) to afford the conjugated enone **4** (88 mg, 88%) as a yellow oil. IR: 1730 (COOMe), 1675 (C=C–CO), 1620 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.98 (1H, dd, J=8, 2 Hz, 12-H), 6.88 (1H, dt, J=10, 2 Hz, 19-H), 5.97 (1H, dd, J=10, 3 Hz, 18-H), 4.01 (3H, s, COOMe), 3.98 (1H, br d, J=13 Hz, 3-H), 3.22 (1H, dd, J=12, 2 Hz, 21eq-H), 3.12 (1H, dd, J=12, 4 Hz, 21ax-H), 2.00 (1H, dt, J=13, 2 Hz, 14eq-H), 1.62 (1H, q, J=13 Hz, 14ax-H). High-resolution MS m/z: Calcd for $C_{21}H_{22}N_2O_3$ (M^+) 350.163. Found: 350.164.

Conversion of the Conjugated Enone 4 into Alloyohimbone ((20α)-Yohimban-17-one, 5b) Catalytic hydrogenation of the conjugated enone **4** (30 mg) over platinum dioxide (10 mg) in methanol (10 ml) under a hydrogen atmosphere at room temperature for 1 h and purification of the crude product by p-TLC (benzene : methylene dichloride : methanol = 4 : 4 : 1) gave 1-methoxycarbonylalloyohimbone (methyl (20α)-17-oxoyohimban-1-carboxylate, **5a**) (29 mg, 96%). A mixture of the above carbamate (29 mg), potassium carbonate (60 mg), and methanol (20 ml) was stirred under a nitrogen stream at room temperature for 3 h. After being diluted with water, the reaction mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid, which was recrystallized from methanol–methylene dichloride to afford alloyohimbone (**5b**) (23.5 mg, 97%), mp 262—264 °C (dec.) as colorless crystals (lit.[4] 262—265 °C); this product was identical with authentic alloyohimbone[4] based on comparisons of their IR and ^{1}H-NMR spectra and *Rf* values.

Methyl (18α,19α,20α)-18,19-Epoxy-17-oxoyohimban-1-carboxylate (6) Hydrogen peroxide (30%, 0.62 ml) and 10% methanolic sodium hydroxide solution (0.42 ml) were successively added to a solution of the conjugated enone **4** (58 mg) in methanol (2.1 ml) with stirring under ice-cooling and a nitrogen stream. Stirring was continued at 0 °C for 45 min, and water was added to the reaction mixture, which was then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p-TLC (methylene dichloride : methanol=95 : 5) to afford a solid. Recrystallization from methanol gave the epoxyketone **6** (51 mg, 84%) as colorless crystals, mp 175—177 °C. IR: 1720 (COOMe+C=O) cm^{-1}. MS m/z: 366 (M^+). ^{1}H-NMR (200 MHz) δ: 7.98 (1H, dd, J=8, 2 Hz, 12-H), 4.03 (3H, s, COOMe), 3.81 (1H, br d, J=10.5 Hz, 3-H), 3.50 (1H, dd, J=4, 2 Hz, 19-H), 3.19 (1H, d, J=4 Hz, 18-H), 3.24 (1H, dd, J=12, 2 Hz, 21eq-H), 3.02 (1H, dd, J=12, 4.5 Hz, 21ax-H), 2.86 (1H, dd, J=14, 4 Hz, 16-H), 2.50 (1H, br s, 20-H), 2.35 (1H, dm, J=13 Hz, 15-H), 2.14 (1H, br d, J=13 Hz, 14eq-H), 2.06 (1H, dd, J=14, 4 Hz, 16-H), 1.17 (1H, td, J=13, 10.5 Hz, 14ax-H). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68,82; H, 5.99; N, 7.69.

18,19-Didehydro-18-methoxyyohimban-17-one (7) A solution of the epoxyketone **6** (47 mg) in 12% methanolic potassium hydroxide solution (1 ml) was refluxed for 2 h under a nitrogen stream. After being cooled, the reaction mixture was diluted with water and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue, which was purified by p-TLC (methylene dichloride : methanol = 98 : 2) to give the D/E-*trans* enone **7** (6.2 mg, 15%) as a yellow oil. IR: 3500 (NH), 1700 (C=C–CO), 1630 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.80 (1H, br s, NH), 5.60 (1H, d, J=2.5 Hz, 19-H), 3.64 (3H, s, OMe), 3.40 (1H, br d, J=12 Hz, 3-H), 2.12 (1H, dt, J=12, 3 Hz, 14eq-H), 1.60 (1H, q, J=12 Hz, 14ax-H). High-resolution MS m/z: Calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.168. Found: 322.169.

Methyl (20α)-18,19-Didehydro-18-methoxy-17-oxoyohimban-1-carboxylate (9) Concentrated sulfuric acid (0.011 ml) was added to a solution of the epoxyketone **6** (30 mg) in methanol (5 ml). The resulting solution was refluxed for 1.5 h under a nitrogen stream. After being made alkaline by addition of sodium bicarbonate, the reaction mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give methyl (18α,19α,20α)-18,19-epoxy-17,17-dimethoxyyohimban-1-carboxylate (**8**) as a yellow oil. IR: 1725 (COOMe) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.03 (1H, dd, J=8, 2 Hz, 12-H), 4.03 (3H, s, COOMe), 3.75 (1H, br d, J=9 Hz, 3-H), 3.34 and 3.18 (each 3H, s, OMe×2), 3.30 (1H, d, J=4 Hz, 18-H), 3.20 (1H, br d, J=4 Hz, 19-H). High-resolution MS m/z: Calcd for $C_{23}H_{28}N_2O_5$ (M^+) 412.200. Found: 412.200.

Without purification, the ketal **8**, obtained as above, was dissolved in methanol (5 ml) and then concentrated sulfuric acid (0.022 ml) was added. The solution was refluxed for 8 h under a nitrogen stream with monitoring by TLC. During the course of the reaction, concentrated sulfuric acid was added to the mixture. After being made alkaline by the addition of sodium bicarbonate, the reaction mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p-TLC (methylene dichloride : methanol=96 : 4) to afford a solid. Recrystallization from benzene–ether gave the 18-methoxyenone **9** (17 mg, 55%) as colorless crystals, mp 247—249 °C (dec.). IR: 1725

(COOMe), 1680 (C=C–CO), 1620 (C=C) cm^{-1}. MS *m/z*: 380 (M^+). ^{1}H-NMR (200 MHz) δ: 7.98 (1H, dd, *J*=8, 2 Hz, 12-H), 5.70 (1H, br s, 19-H), 4.04 (3H, s, COOMe), 4.02 (1H, dd, *J*=10.5, 2.5 Hz, 3-H), 3.64 (3H, s, OMe), 1.96 (1H, ddd, *J*=12, 4, 2.5 Hz, 14eq-H), 1.66 (1H, td, *J*=12, 10.5 Hz, 14ax-H). *Anal.* Calcd for $C_{22}H_{24}N_2O_4 \cdot 1/4H_2O$: C, 68.39; H, 6.37; N, 7.13. Found: C, 68.64; H, 6.42; N, 7.28.

(20α)-18,19-Didehydro-18-methoxyyohimban-17-one (10a) According to the deprotection procedure described for **5a**, deprotection of the carbamate **9** (17 mg) with potassium carbonate gave the enone **10a** (14 mg, 97%), mp 114—115 °C (from ether–benzene) as colorless crystals. IR: 3500 (NH), 1680 (C=C–CO), 1625 (C=C) cm^{-1}. MS *m/z*: 322 (M^+). ^{1}H-NMR (200 MHz) δ: 8.60 (1H, br s, NH), 5.75 (1H, br s, 19-H), 3.61 (3H, s, OMe), 3.30 (1H, br d, *J*=11 Hz, 3-H), 2.42 (1H, m, 15-H), 1.85 (1H, dt, *J*=11, 4 Hz, 14eq-H), 1.78 (1H, q, *J*=11 Hz, 14ax-H). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 6.91; N, 8.61.

Preparation of the Enamide 11 and Its Reductive Photocyclization Acylation of harmalane (1.10 g) with 3,4-dimethoxybenzoyl chloride, prepared from the corresponding acid (1.20 g), in the presence of triethylamine (2 ml) in benzene (100 ml) gave the unstable enamide **11** as a yellow glass, which was dissolved in acetonitrile (900 ml). Sodium borohydride (1.80 g) and methanol (90 ml) were successively added to the above solution at 5 °C. After the added hydride agent had dissolved, the resulting solution was irradiated with a high-pressure (300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-300) at 5 °C for 45 min. After evaporation of the solvent at room temperature, water was added and the resulting mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue, the methylene dichloride-soluble part of which was chromatographed on a medium-pressure column (ethyl acetate:*n*-hexane=15:2) to give (20α)-16,17,18,19-tetradehydro-17,18-dimethoxyyohimban-21-one (**12**, 490 mg, 23%) as a yellow oil and 16,17,19,20-tetradehydro-16,17-dimethoxyyohimban-21-one (**13**, 735 mg, 35%), mp 234—235 °C (dec.) (colorless crystals from methanol). The enamide **11**: ^{1}H-NMR (60 MHz) δ: 5.23 and 4.49 (each 1H, br s, C=CH_2), 3.83 and 3.77 (each 3H, s, OMe×2). The lactam **12**: IR: 3490 (NH), 1625 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.76 (1H, br s, NH), 5.18 (1H, d-like, *J*=8 Hz, 5eq-H), 4.79 (1H, d, *J*=7 Hz, 16-H), 4.72 (1H, br dd, *J*=2, 1 Hz, 19-H), 3.65 (1H, br dd, *J*=8, 2 Hz, 20-H), 3.62 and 3.57 (each 3H, s, OMe×2), 2.08 (2H, m, 14-H_2). High-resolution MS *m/z*: Calcd for $C_{21}H_{22}N_2O_3$ (M^+) 350.163. Found: 350.166. The lactam **13**: IR: 3490 (NH), 1670 (C=C), 1620 (NCO) cm^{-1}. MS *m/z*: 350 (M^+). ^{1}H-NMR (200 MHz) δ: 8.10 (1H, br s, NH), 6.84 (1H, td, *J*=3.5, 2 Hz, 19-H), 5.20 (1H, m, 5eq-H), 4.92 (1H, br dd, *J*=11, 4.5 Hz, 3-H), 3.76 and 3.63 (each 3H, s, OMe×2), 3.40 (1H, m, 15-H), 2.96 (1H, dt, *J*=11, 4.5 Hz, 14eq-H), 1.62 (1H, q, *J*=11 Hz, 14ax-H). *Anal.* Calcd for $C_{21}H_{22}N_2O_3 \cdot 1/4H_2O$: C, 71.06; H, 6.39; N, 7.89. Found: C, 71.15; H, 6.24; N, 7.82.

Hydrolysis of the Lactam 12 According to the hydrolysis procedure described for **3**, acid hydrolysis of **12** (100 mg) followed by purification by p-TLC (ethyl acetate:methanol=97:3) gave (20α)-18,19-didehydro-18-methoxyyohimban-17,21-dione (**10b**, 47 mg, 49%) as a yellow oil and (20α)-16,17-didehydro-17-methoxyyohimban-18,21-dione (**15b**, 44 mg, 46%), mp 264—266 °C (dec.) (colorless crystals from methanol). The 18-methoxyenone **10b**: IR: 3490 (NH), 1695 (C=C–CO), 1635 (NCO), 1605 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.12 (1H, br s, NH), 5.80 (1H, d, *J*=2.5 Hz, 19-H), 5.16 (1H, m, 5eq-H), 4.90 (1H, br dd, *J*=11.5, 5 Hz, 3-H), 3.80 (1H, br dd, *J*=5, 2.5 Hz, 20-H), 3.57 (3H, s, OMe), 2.58 (1H, d-like, *J*=14 Hz, 16-H), 2.24 (1H, br d, *J*=11.5 Hz, 14eq-H), 2.00 (1H, q, *J*=11.5 Hz, 14ax-H). High-resolution MS *m/z*: Calcd for $C_{20}H_{20}N_2O_3$ (M^+) 336.147. Found: 336.148. The 17-methoxyenone **15b**: IR: 3490 (NH), 1700 (C=C–CO), 1635 (NCO), 1605 (C=C) cm^{-1}. MS *m/z*: 336 (M^+). ^{1}H-NMR ($CDCl_3$+CD_3OD, 200 MHz) δ: 8.40 (1/3H, br s, NH), 5.66 (1H, d, *J*=6 Hz, 16-H), 5.12 (1H, m, 5eq-H), 4.94 (1H, br dd, *J*=11, 5 Hz, 3-H), 3.46 (3H, s, OMe), 3.18 (1H, dt, *J*=12, 5.5 Hz, 20-H), 3.08 (1H, m, 15-H), 2.90 (1H, dd, *J*=17, 5.5 Hz, 19eq-H), 2.71 (1H, dd, *J*=17, 12 Hz, 19ax-H), 2.54 (1H, dt, *J*=13, 5 Hz, 14eq-H), 2.04 (1H, dt, *J*=13, 11 Hz, 14ax-H). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.60; H, 5.95; N, 8.22.

(20α)-16,17,18,19-Tetradehydro-17,18-dimethoxyyohimban (14) A solution of the lactam **12** (500 mg) in anhydrous THF (50 ml) was added to a suspension of lithium aluminum hydride (600 mg) in anhydrous ether (50 ml) with stirring under ice-cooling in a nitrogen stream. The mixture was refluxed for 2 h and then additional lithium aluminum hydride (600 mg) was added to the mixture in several portions. After usual work-up, recrystallization of the crude solid from methanol gave the amine **14** (250 mg, 65%), mp 245—247 °C (dec.). IR: 3480 (NH), 1650 and 1610 (C=C) cm^{-1}. MS *m/z*: 336 (M^+). ^{1}H-NMR (60 MHz) δ: 7.68 (1H, br s, NH), 4.83 (1H, d, *J*=6 Hz, 16-H), 4.67 (1H, br s, 19-H), 3.55 (6H, s, OMe×2). *Anal.* Calcd for $C_{21}H_{24}N_2O_2 \cdot MeOH$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.97; H, 7.63; N, 7.71.

Hydrolysis of the Amine 14 According to the hydrolysis procedure described for **3**, acid hydrolysis of the amine **14** (250 mg) followed by purification on p-TLC (ether:methanol=95:5) gave the 18-methoxyenone **10a** (177 mg, 73%), mp 114—115 °C (colorless crystals from methanol) and (20α)-16,17-didehydro-17-methoxyyohimban-18-one (**15a**, 24 mg, 10%) as a yellow oil. The former **10a** was identical with the sample prepared from **9** based on a comparison of their *Rf* values and IR and ^{1}H-NMR spectra. The amine **15a**: IR: 3500 (NH), 1690 (C=C–CO), 1630 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.96 (1H, s, NH), 5.82 (1H, d, *J*=6 Hz, 16-H), 3.57 (3H, s, OMe), 3.20 (1H, br d, *J*=11.5 Hz, 3-H), 3.13 (1H, dd, *J*=18, 15 Hz, 19ax-H), 2.14 (1H, dt, *J*=11.5, 3 Hz, 14eq-H), 1.58 (1H, q, *J*=11.5 Hz, 14ax-H). High-resolution MS *m/z*: Calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.168. Found: 322.168.

Acylation of the 18-Methoxyenone 10a (a) By LDA-Methyl Chloroformate: According to the acylation procedure described for **2a**, treatment of the enone **10a** (20 mg) with diisopropylamine (0.019 ml), *n*-butyllithium (15% solution in *n*-hexane) (0.058 ml), and methyl chloroformate (0.01 ml) and purification of the crude product by p-TLC (methylene dichloride:methanol=95:5) gave (20α)-16,17,18,19-tetradehydro-18-methoxy-17-methoxycarbonyloxyyohimban (**16**, 17.5 mg, 75%) as a yellow oil. IR: 3490 (NH), 1765 (OCOOMe), 1690 and 1620 (C=C) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 7.73 (1H, br s, NH), 5.58 (1H, d, *J*=6 Hz, 16-H), 4.67 (1H, br s, 19-H), 3.76 (3H, s, COOMe), 3.50 (3H, s, OMe). High-resolution MS *m/z*: Calcd for $C_{22}H_{24}N_2O_4$ (M^+) 380.174. Found: 380.175.

(b) By LDA-Magnesium Dibromide–Methyl Chloroformate: A solution of freshly prepared anhydrous magnesium dibromide (35 mg) was added to a solution of the lithium enolate, prepared from the enone **10a** (50 mg), diisopropylamine (0.05 ml) and *n*-butyllithium (15% solution in *n*-hexane, 0.16 ml) according to the procedure described above, with stirring under a nitrogen stream at −78 °C. The mixture was stirred at −78 °C for 40 min, then methyl chloroformate (0.029 ml) was added and stirring was continued under a nitrogen stream at −78 °C for 1 h. Water was then added and the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue, which was purified by p-TLC (methylene dichloride:methanol=95:5) to afford the starting material **10a** (23 mg) and methyl (20α)-18,19-didehydro-18-methoxy-17-oxoyohimban-16-carboxylate (**17b**, 7 mg, 12%) as a yellow oil. IR: 3500 (NH), 1740, 1695, 1650, 1630, and 1600 (C=C–CO–CH–COOMe) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 12.35 (1/3H, s, enolic OH), 7.80 (2/3H, br s, NH of keto form), 7.74 (1/3H, br s, NH of enol form), 5.73 (2/3H, br s, 19-H of keto form), 5.17 (1/3H, br s, 19-H of enol form), 3.90 and 3.68 (each 1H, s, COOMe+OMe of enol form), 3.77 and 3.65 (each 2H, s, COOMe+OMe of keto form). High-resolution MS *m/z*: Calcd for $C_{22}H_{24}N_2O_4$ (M^+) 380.174. Found: 380.174.

(c) By LDA–Methyl Cyanoformate: Acylation of the lithium enolate, prepared from the enone **10a** (100 mg) and LDA as described in (a), with methyl cyanoformate (58 mg) and purification of the crude product by p-TLC (ethyl acetate) gave dimethyl (20α)-18,19-didehydro-18-methoxy-17-oxoyohimban-1,16-dicarboxylate (**17a**, 116 mg, 85%) as a yellow oil. IR: 1730, 1690, 1625, and 1595 (NCOOMe+C=C–CO–CH–COOMe) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 12.06 (4/9H, br s, enolic OH), 5.70 (5/9H, br s, 19-H of keto form), 5.13 (4/9H, br s, 19-H of enol form), 4.06 (5/3H, s, NCOOMe of keto form), 4.03 (4/3H, s, NCOOMe of enol form), 3.88 and 3.70 (each 4/3H, s, CCOOMe+OMe of enol form), 3.76 and 3.66 (each 5/3H, s, CCOOMe+OMe of keto form). High-resolution MS *m/z*: Calcd for $C_{22}H_{26}N_2O_6$ (M^+) 438.179. Found: 438.174.

N-Deacylation of the N,C-Diacylated Compound 17a According to the hydrolysis procedure described for **5a**, basic hydrolysis of **17a** with potassium carbonate in methanol followed by purification of the crude product by p-TLC (ethyl acetate) gave the C-acylated product **17b** (42 mg, 97%) as a yellow oil, which was identical with the sample prepared from **10a** upon comparison of their *Rf* values and IR and ^{1}H-NMR spectra.

Methyl (18β,20α)-18-Methoxy-17-oxoyohimban-16-carboxylate (18) According to the catalytic hydrogenation procedure given for **4**, reduction of the ketoester **17b** (50 mg) followed by purification of the crude product by p-TLC (methylene dichloride:methanol=96:4) gave the saturated ester **18** (49 mg, 97%), mp 185—187 °C (dec.) (colorless crystals from ether–methanol) (lit.[3d] 183—185 °C), which was identical with an authentic sample provided by Professor Szántay, upon comparison of their *Rf* values and IR spectra. IR: 3490 (NH), 1740, 1725, 1655, and 1610 (CO–CH–COOMe) cm^{-1}. MS *m/z*: 382 (M^+). ^{1}H-NMR (200 MHz) δ:

12.45 (1/2H, s, enolic OH), 7.76 and 7.71 (each 1/2H, br s, NH), 4.19 (1/2H, dd, J=12.5, 6 Hz, 18-H), 4.14 (1/2H, dd, J=10, 7 Hz, 18-H), 3.90 and 3.80 (each 3/2H, s, COOMe), 3.46 and 3.40 (each 3/2H, s, OMe). *Anal.* Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.23; H, 6.85; N, 7.34.

Catalytic Hydrogenation of the Ketone 18 Catalytic hydrogenation of the ketone **18** (50 mg) in the presence of platinum dioxide (20 mg) in anhydrous methanol (10 ml) under a hydrogen stream at 50 °C for 20 h and the purification of the crude product by p-TLC (methylene dichloride: methanol=94:6) gave the β-ester **19** (34 mg, 67%), mp 244—247 °C (colorless crystals from methanol) (lit.[3d] 243—245 °C) and the α-ester **20** (9.5 mg, 19%), mp 164—167 °C (colorless crystals from methanol) (lit.[3d] 166—168 °C). IR and ^{1}H-NMR data for both hydroxyesters **19** and **20** were identical with those reported by Szántay's group. The β-ester **19**: IR: 3550 (OH), 3490 (NH), 1730 (COOMe) cm^{-1}. MS m/z: 384 (M^+). ^{1}H-NMR (200 MHz) δ: 7.82 (1H, br s, NH), 4.55 (1H, t, J=2.5 Hz, 17-H), 3.85 (3H, s, COOMe), 3.41 (3H, s, OMe), 3.24 (1H, ddd, J=12, 4.5, 2.5 Hz, 18-H). *Anal.* Calcd for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.77; H, 7.64; N, 7.29. The α-ester **20**: IR: 3550 (OH), 3490 (NH), 1730 (COOMe) cm^{-1}. MS m/z: 384 (M^+). ^{1}H-NMR (200 MHz) δ: 4.30 (1H, br s, 17-H), 3.76 (3H, s, COOMe), 3.56 (1H, dt, J=11, 3.5 Hz, 18-H), 3.38 (3H, s, OMe), 2.19 (1H, q, J=11 Hz, 19ax-H), 1.64 (1H, br d, J=11 Hz, 19eq-H). *Anal.* Calcd for $C_{22}H_{28}N_2O_4 \cdot 1/4H_2O$: C, 67.93; H, 7.38; N, 7.20. Found: C, 68.02; H, 7.27; N, 7.21.

X-Ray Analysis of the Epoxyketone 6 Crystals of **6** were grown in methanol: colorless needles, mp 175—177 °C.

Crystal Data: $C_{21}H_{22}N_2O_4$; M_r=366.42; monoclinic; $P2_1/c$; a=17.652(13); b=11.358(3); c=21.632(15) Å; β=121.27(6)°; V=3707(14) Å^{-3}; Z=8; D_c=1.314 g·cm^{-3}.

The diffraction intensities were collected from a crystal of the epoxyketone **6** with dimensions of 0.8×0.3×0.2 mm on a four-circle diffractometer (Rigaku AFC-5) using Cu K_α radiation monochromated by means of a graphite plate. A total of 5835 reflections were measured within a 2θ range of 130°. These were used in the solution and refinement of the structure.

Determination of the Structure: The structure was solved by the direct method using MULTAN 84 and refined by the blockdiagonal least-squares method. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. The final R factor was 0.069.

Other data are available from one of the authors (M.D.) upon request.

References and Notes

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