81. Total Synthesis of (−)-Crinine. Use of Tandem Cationic Aza-*Cope* Rearrangement/*Mannich* Cyclizations for the Synthesis of Enantiomerically Pure *Amaryllidaceae* Alkaloids[1])

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Dedicated to the memory of Professor *R. V. Stevens*

(17.I.85)

The total synthesis of enantiomerically pure (−)-crinine (**1**) in 10 steps and 6% overall yield from cyclopentene oxide is reported. The key step was the rearrangement of **7** upon reaction with $AgNO_3$ at 25°C to give *cis*-perhydroindolone **8** in 81% yield.

Although the total synthesis of *Amaryllidaceae* alkaloids has been the object of intense investigation[3])[4]), few methods have been developed for preparing these alkaloids in optically active form. To our knowledge, the pioneering synthesis of (+)-maritidine by the *Yamada* group [4] represents the only published enantioselective synthesis of a member of the widely occurring 5,10b-ethanophenanthridine class of *Amaryllidaceae* alkaloids[5]). In this paper, we report the first efficient method for preparing enantiomerically pure alkaloids of this type. Specifically, we detail the total synthesis of (−)-crinine (**1**)[6]) in 10 steps and 6% overall yield from cyclopentene oxide.

The starting point for the synthesis of **1** (see *Scheme*) was aminoalcohol **3**, which is available on a large scale from the reaction [7] of cyclopentene oxide with the aluminium amide **2** formed from (*R*)-α-methylbenzylamine and trimethylaluminium[7]).

Although this reaction gave **3** and its (1*S*, 2*S*)-diastereoisomer **4** in equal amounts, these aminoalcohols were easily separated by chromatography on silica gel to afford **3** (m.p. 74–75°C) in 45% yield. Reaction of the hydrochloride salt of **3** with paraformaldehyde and KCN [1] provided the oily aminoacetonitrile **5** in 92% yield. *Swern* oxidation [10] of **5** followed by recrystallization of the crude product from CH_2Cl_2/hexane afforded the oxo derivative **6** (m.p. 83–84°C) in 95% yield. Crystalline **6** could be stored at 0°C without epimerization, however attempted purification on silica gel yielded a 1:1

[1]) Part 14 in the series 'Synthesis Applications of Aza-*Cope* Rearrangements'; for Part 13, see [1].

[2]) On sabbatical leave from the Agricultural Chemicals Research Laboratories of the *Sankyo Company*, Tokyo, Japan.

[3]) For recent reviews, see [2].

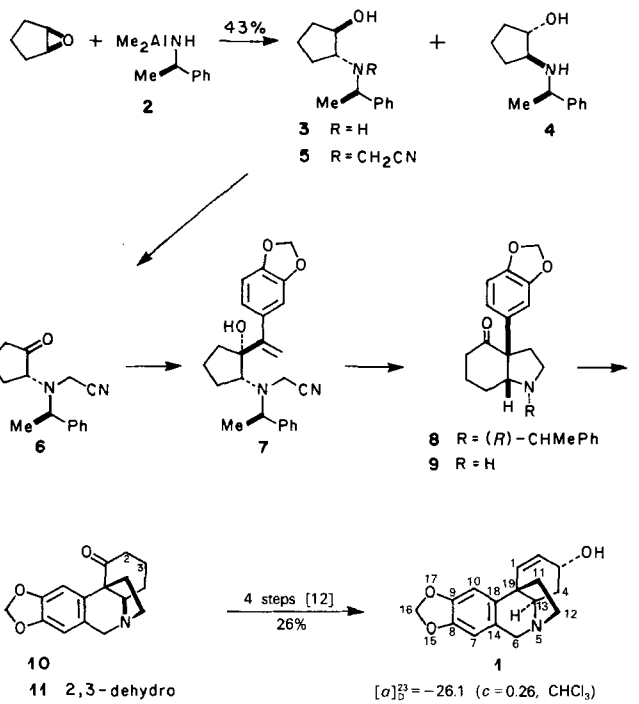
[4]) For new approaches for preparing these alkaloids in racemic form, see, *inter alia*, [3].

[5]) Several enantioselective syntheses of structurally related *Sceletium* alkaloids have been described, see [5].

[6]) For the determination of the absolute configuration of this alkaloid, see [6].

[7]) A wide variety of enantiomerically pure 2-aminoalcohols are easily prepared in this way [8]. The absolute configuration of **3** was established [8] by conversion to (−)-(1*R*, 2*R*)-2-aminocyclopentanol [9].

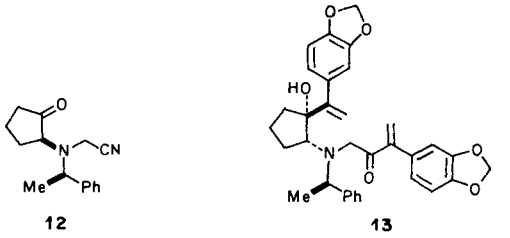
Scheme



mixture of **6** and epimer **12**. Exposure of **6** to 2.2 equiv. of [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium [1] at −72 to −75 °C in THF gave **7** as a colorless oil in 91% yield. The diastereoselectivity of this reaction was extremely high, since no trace of an isomer of **7** could be detected. However, temperature control was critical since competitive addition to the nitrile group to give **13** was observed when this reaction was conducted at −60 °C.

Exposure of **7** to 1.03 equiv. of $AgNO_3$ in EtOH (25 °C, 3 h) affected the desired rearrangement [3b] to perhydroindolone **8** (m.p. 105–106 °C), which was isolated in 80% yield after chromatography. Hydrogenolysis of **8** was best accomplished using a transfer-hydrogenation procedure [11] and provided **9** (m.p. 119–120 °C; $[\alpha]_D^{23} = +249°$ (c = 1.02, MeOH)) in 94% yield.

Conversion of perhydroindolone **9** to the pentacyclic ketone **10** was accomplished in 79% yield (91% based on consumed starting material) by *Pictet-Spengler* cyclization



[12]. The overall yield of enantiomerically pure 5,10b-ethanophenanthridinone **10** was 26% from cyclopentene oxide.

Following the procedure utilized by *Whitlock and Smith* [12] in their synthesis of racemic crinine, **10** was converted in 4 steps and 26% overall yield into (−)-crinine. Synthetic (−)-crinine (m.p. 207–209 °C; $[\alpha]_D^{23} = -26.1°$ ($c = 0.26$, $CHCl_3$)) was identical in all respects (mixed m.p., spectroscopic and chromatographic data) with a natural sample[8]) ($[\alpha]_D^{23} = -25.8°$ ($c = 0.24$, $CHCl_3$)) of this alkaloid.

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Experimental Part

General. (+)-(*R*)-α-Methylbenzylamine ($[\alpha]_D^{25} = +39.4°$, neat) was purchased from *Norse Laboratories*, Newbury Park, CA. Tetrahydrofuran (THF) and Et_2O were distilled from Na and benzophenone. Dimethylformamide (DMF) was distilled from CaH_2 at 20 Torr and CH_2Cl_2 from CaH_2 at atmospheric pressure. The molarities indicated for *sec*-butyllithium and *tert*-butyllithium were established by titration with 2,5-dimethoxybenzyl alcohol [13]. ^{1}H-NMR and ^{13}C-NMR spectra were determined at 250 MHz and 63 MHz, resp., with a *Bruker WM 250* spectrometer. ^{1}H-NMR and ^{13}C-NMR shifts are reported as δ values in ppm relative to internal tetramethylsilane. ^{1}H-NMR coupling constants (J) are reported in Hz and refer to apparent multiplicities and not true coupling constants. Optical rotations were measured with a *Perkin-Elmer-141* polarimeter and IR (cm^{-1}) spectra with a *Perkin-Elmer-283* spectrometer. Electron impact and high resolution MS were determined with a *Kratos-MS-50* spectrometer at the *Midwest Center for Mass Spectroscopy*, University of Nebraska. Chemical ionization mass spectra were determined on a *Finnigan 4000 GC/MS/DS*. Microanalyses were performed by *Atlantic Microlabs*, Atlanta, Georgia. For TLC and column chromatography *E. Merck* silica gel was used. Radial chromatography was done with *Harrison Research* Chromatotron. All reactions were run under N_2 or Ar and evaporations were performed under reduced pressure using a *Büchi* rotary evaporator.

(1R,2R)-2-[(R)-α-(Methylbenzyl)amino]cyclopentanol (**3**) *and (1S,2S)-2-[(R)-α-(Methylbenzyl)amino]-cyclopentanol* (**4**). A soln. of Me_3Al (77 ml of a 2.0M soln. in toluene; 0.154 mol) was added dropwise at 0° to a rapidly stirred soln. of (+)-(*R*)-α-methylbenzylamine (18.6 g, 0.153 mol) in CH_2Cl_2 (400 ml). The resulting soln. was maintained for 1.5 h at 0°, and then a soln. of cyclopentene oxide (14.2 g, 0.169 mol) and CH_2Cl_2 (100 ml) was added dropwise. The soln. was maintained for 1 h additional at 0° and then left overnight at r.t. The aluminate salt was decomposed [14] by adding 26 g (0.62 mol) of NaF followed by 16.6 ml (0.92 mol) of H_2O. The resulting suspension was rapidly stirred for 1 h at r.t., filtered through a short column of *Celite*, and the column subsequently washed with 100 ml of CH_2Cl_2. The combined filtrates were dried (K_2CO_3), concentrated, and separated by column chromatography (hexane/AcOEt/Et_3N 3:1:0.2) to give, in the first fractions, 14 g (45%) of crystalline **3**, m.p. 74–75°, and, in later fractions, 13 g (41%) of **4** as a pale yellow oil. **3**: R_f 0.33 (hexane/AcOEt/Et_3N 1:1:0.1). M.p. (**3**·HCl) 244–247°. $[\alpha]_D^{23} = +22.1°$, $[\alpha]_{578}^{23} = +23.0°$, $[\alpha]_{546}^{23} = +26.5°$ ($c = 1.19$, MeOH). IR (film): 3373, 2966, 2880, 1607, 1452, 1090. ^{1}H-NMR ($CDCl_3$): 1.05–2.05 (*m*, 3 CH_2, OH, NH); 1.35 (*d*, $J = 6.6$, CH_3); 2.79 (apparent *q*, $J = 7$, NCH); 3.85–3.95 (*m*, OCH, NC*H*CH_3); 7.15–7.5 (*m*, C_6H_5). CI-MS (isobutane): 206, 190, 188, 147, 102, 91. **3**·HCl: Anal. calc. for $C_{13}H_{20}ClNO$ (241.75): C 64.58, H 8.34, Cl 14.67, N 5.79; found: C 64.71, H 8.37, Cl 14.64, N 5.79.

4: m.p. (**4**·HCl) 239–240°. $[\alpha]_D^{24} = +76.8°$, $[\alpha]_{578}^{24} = +79.8°$, $[\alpha]_{546}^{24} = +91.0°$, $[\alpha]_{435}^{24} = +156°$ ($c = 0.96$, MeOH). IR (film): 3373, 2966, 2880, 1607, 1452, 1100. ^{1}H-NMR ($CDCl_3$): 1.2–2.1 (*m*, 3 CH_2); 1.36 (*d*, $J = 6.6$, CH_3); 1.8 (br. *s*, OH, NH); 2.61 (apparent *q*, $J = 7$, NCH); 3.76 (apparent *q*, $J = 7$, OCH); 3.84 (*q*, $J = 6.6$, NC*H*CH_3); 7.2–7.4 (*m*, C_6H_5). CI-MS (isobutane): 206, 190, 188, 147, 102, 91. **4**·HCl: Anal. calc. for $C_{13}H_{20}ClNO$ (241.75): C 64.58, H 8.34, Cl 14.67, N 5.79; found: C 64.59, H 8.35, Cl 14.72, N 5.77.

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[8]) Kindly provided by Dr. *H. M. Fales*.

{N-[(1R,2R)-2-Hydroxycyclopentyl]-N-[(R)-α-Methylbenzyl]amino}acetonitrile (**5**). Conc. HCl (6.1 ml, 73 mmol) was added at 0° to a soln. of **3** (14.3 g, 69.8 mmol) and acetone. Evaporation *in vacuo* gave 16.8 g of the crystalline **3**·HCl. This material was dissolved in cold H_2O (120 ml), KCN (5.4 g, 83 mmol) was added portionwise, and the resulting soln. was stirred at 5° for 1 h. Paraformaldehyde (2.5 g, 84 mmol) was then added [15], and the resulting suspension was stirred for 10 h at r.t. The mixture was saturated with K_2CO_3, extracted with Et_2O (4 × 150 ml), and the combined extracts were washed with H_2O (2 × 50 ml) and dried (Na_2SO_4). Concentration, followed by purification of the residue by column chromatography (hexane/AcOEt/Et_3N 8:1:0.45) gave 15.6 g (92%) of **5** as a chromatographically homogeneous colorless oil. $[\alpha]_D^{23} = -23.9°$ (*c* = 1.03, CH_3OH). IR ($CHCl_3$): 3350–3650, 2985, 2880, 2242, 1451. ^{1}H-NMR ($CDCl_3$): 1.35–2.2 (*m*, 3 CH_2); 1.47 (*d*, *J* = 6.8, CH_3); 2.13 (*s*, OH); 3.1–3.25 (*m*, NCH); 3.48 (*AB* '*q*', *J* = 17.7, *Δν* = 23, CH_2CN); 4.07 (apparent *q*, *J* = 7, OCH); 4.18 (*q*, *J* = 6.8, NC*H*CH_3); 7.2–7.5 (*m*, C_6H_5). CI-MS (isobutane): 245, 218, 114, 105. High-resolution MS (75 eV): 244.1583 ($C_{15}H_{20}N_2O$, calc. 244.1576).

{N-[(R)-α-Methylbenzyl]-N-[(1R)-2-oxocyclopentyl]amino}acetonitrile (**6**). Compound **5** (3.00 g, 12.3 mmol) was oxidized in CH_2Cl_2 (15 ml) at −50 to −60° with oxalyl chloride (1.16 ml, 13.3 mmol) and DMSO (1.03 ml, 14.5 mmol) following the procedure described in [10]. The mixture was allowed to warm to r.t., and after 10 h it was washed with H_2O (20 ml) and concentrated. The residue was dissolved in hexane/AcOEt 4:1 (100 ml), washed again with H_2O (4 × 20 ml), and dried (Na_2SO_4). Concentration followed by recrystallization of the residue from CH_2Cl_2/hexane gave 2.82 g (95%) of **6** as a crystalline solid: m.p. 83–84°. $[\alpha]_D^{23} = -98.2°$ (*c* = 1.0, CH_3OH). IR ($CHCl_3$): 2985, 2880, 2232 (weak), 1745, 1130. ^{1}H-NMR ($CDCl_3$): 1.48 (*d*, *J* = 6.7, CH_3); 1.65–2.5 (*m*, 3 CH_2); 3.41 ('*d*', part of *AB*, *J* = 18.1, 1H, CH_2CN); 3.55 ('*d*', part of *AB*, *J* = 18.1, 1H, CH_2CN); 3.5–3.7 (*m*, NCH); 4.17 (*q*, *J* = 6.7, NC*H*CH_3); 7.25–7.45 (*m*, C_6H_5). CI-MS (isobutane): 243, 216, 139, 105.

Ketone **6** was not stable for extended periods at r.t., but could be stored for a few days at 0°. Column chromatography of **6** on silica gel (hexane/AcOEt/Et_3N 5:1.0:0.3) gave a 1:1 mixture of **6** and **12**. Epimer **12**: ^{1}H-NMR ($CDCl_3$): 1.44 (*d*, *J* = 6.6, CH_3); 3.47 ('*d*', part of *AB*, *J* = 18.2, 1H, CH_2CN); 3.83 ('*d*', part of *AB*, *J* = 18.2, 1H, CH_2CN).

{N-[(1R,2R)-2-Hydroxy-2-(1-(3,4-(methylenedioxy)phenyl)ethenyl)cyclopentyl]-N-[(R)-α-methylbenzyl]amino}acetonitrile (**7**). A soln. of **6** (152 mg, 0.628 mmol) in THF (5 ml) was added dropwise at −70 to −75° (internal temp.) to a stirred soln. of [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium (1.4 mmol; 0.12M in THF/pentane 10:1, prepared as described in [3b]). After 1.5 h at this temp., the light-orange solution was quenched by adding wet THF. The mixture was then allowed to warm to r.t., H_2O (5 ml) was added, and the mixture was extracted with AcOEt/hexane 1:4 (4 × 15 ml). The combined org. layers were washed with H_2O (4 × 15 ml), dried (Na_2SO_4), and concentrated to give an oil. Purification by column chromatography (hexane/AcOEt/Et_3N 20:1:0.05) gave 223 mg (91%) of pure **7**. $[\alpha]_D^{23} = -19.9°$, $[\alpha]_{578}^{23} = -21.2°$, $[\alpha]_{546}^{23} = -24.5°$ $[\alpha]_{435}^{23} = -41.1°$ (*c* = 1.57, CH_3OH). IR (film): 3300–3600, 2990, 2880, 1490, 1234, 1040. ^{1}H-NMR ($CDCl_3$): 1.51 (*d*, *J* = 6.9, CH_3); 1.35–2.3 (*m*, 3 CH_2); 3.30 ('*d*', part of *AB*, *J* = 17.8, 1H, CH_2CN); 3.43 ('*d*', part of *AB*, *J* = 17.8, 1H, CH_2CN); 3.4 (*s*, OH); 3.6–3.8 (*m*, NCH); 4.25 (*q*, *J* = 6.9, NC*H*CH_3); 5.15 (*d*, *J* = 1.0, =HC*H*); 5.50 (*d*, *J* = 1.0, =*H*CH); 5.94 (apparent *s*, OCH_2O); 6.7–6.9 (*m*, 3 arom. H); 7.3–7.5 (*m*, C_6H_5). CI-MS (isobutane): 391, 364, 285, 215, 105. Anal. calc. for $C_{24}H_{26}N_2O_3$ (390.47): C 73.82, H 6.71, N 7.18; found: C 73.48, H 6.62, N 7.31.

(3aS,7aR)-1-[(R)-α-Methylbenzyl]-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydro-4(1H)-indolone (**8**). A soln. of **7** (2.18 g, 5.58 mmol) and EtOH (40 ml) was deoxygenated at r.t. by evacuating the reaction flask and refilling it with Ar (5×). Solid $AgNO_3$ (950 mg, 5.59 mmol) was added and the resulting mixture stirred for 3 h at r.t., and then filtered through *Celite*. The residue was washed with EtOH (10 ml), the combined filtrates were concentrated, 1M NaOH (20 ml) was added, and the resulting mixture was extracted with hexane/AcOEt (4:1; 3 × 20 ml). After drying (Na_2SO_4), the org. extracts were concentrated and the residue purified by column chromatography (hexane/AcOEt/Et_3N 30:1:0.1) to give 1.63 g (80%) of pure **8** as a colorless crystalline solid: m.p. 105–106°, m.p. (**8**·HCl) 255–258°. $[\alpha]_D^{23} = +129°$, $[\alpha]_{578}^{23} = +136°$, $[\alpha]_{546}^{23} = +163°$, $[\alpha]_{435}^{23} = +360°$ (*c* = 1.02, CH_3OH). IR ($CHCl_3$): 2948, 2878, 1711, 1489, 1240, 1037, 933. ^{1}H-NMR ($CDCl_3$): 1.34 (*d*, *J* = 6.7, CH_3); 1.2–2.55 (*m*, 4 CH_2, H_β–C(2)); 3.83 (*ddd*, *J* = 4.6, 7.9, 12.0, H_α–C(2)); 3.70 (br. *s*, $w_{1/2}$ = 4.3, H–C(7a)); 4.14 (*q*, *J* = 6.7, NC*H*CH_3); 5.94 (apparent *s*, OCH_2O); 6.65–6.8 (*m*, 3 arom. H); 7.2–7.4 (*m*, C_6H_5). CI-MS (isobutane): 364, 260, 105. **8**·HCl: Anal. calc. for $C_{23}H_{26}ClNO_3$ (399.90): C 69.07, H 6.55, Cl 8.89, N 3.50; found: C 68.85, H 6.58, Cl 8.95, N 3.46.

(3aS,7aR)-3a-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydro-4(1H)-indolone (**9**). Following the general procedure [11], a mixture of **8** (270 mg, 0.743 mmol), ammonium formate (473 mg, 7.50 mmol), 10% Pd/C (0.26 g), and DMF was heated for 0.5 h at 100°. After cooling to r.t., the mixture was filtered, and the insoluble residue was washed with a soln. of CH_3OH (200 ml) and conc. HCl (0.6 ml). The combined filtrates were concentrated, diluted with H_2O (100 ml), washed with Et_2O (2 × 20 ml), basified with excess solid KOH, and

extracted with Et_2O (3 × 15 ml). After drying (Na_2SO_4), the org. extracts were concentrated to give 181 mg (94%) of **9** as a crystalline solid whose purity was sufficient for the next step. Recrystallization from hexane gave a pure sample of **9**: m.p. 119–120°. $[\alpha]_D^{22} = +249°$, $[\alpha]_{578}^{22} = +265°$, $[\alpha]_{546}^{22} = +310°$, $[\alpha]_{435}^{22} = +866°$, $[\alpha]_{365}^{22} = 1720°$ ($c = 1.02$, CH_3OH). Other spectral and analytical properties were identical with those of the known [3b] [12] racemic material.

(−)-Crinan-1-one (= (4aR,5β,11bR)-5,11b-Ethano-3,4,4a,5,6,11b-hexahydro-2H-[1,3]dioxolo[4,5-j]phenanthridin-1(1H)-one; **10***).* A 398 mg (1.53 mmol) sample of crude **9** was cyclized according to [12] to give, after purification by column chromatography ($CHCl_3/CH_3OH$ 50:1), 328 mg (79%) of pure crystalline **10**: m.p. 178–180°. $[\alpha]_D^{23} = -115°$, $[\alpha]_{578}^{23} = -120°$, $[\alpha]_{546}^{23} = -139°$, $[\alpha]_{435}^{23} = -249°$, $[\alpha]_{365}^{23} = -552°$ ($c = 1.54$, CH_3OH). ^{1}H-NMR ($CDCl_3$): 1.5–3.0 (*m*, 4 CH_2); 3.4–3.6 (*m*, 2H–C(12)); 3.67 (*'d'*, part of *AB*, $J = 16.8$, H–C(6)); 4.36 (*'d'*, part of *AB*, $J = 16.8$, H–C(6)); 5.89 (*AB 'q'*, $J = 1.3$, $\Delta\nu = 3.7$, OCH_2O); 6.43 (*s*, H–C(7)); 7.71 (*s*, H–C(10)). Other spectral properties were identical to those described [12] for a racemic sample.

(−)-2,3-Didehydrocrinan-1-one (**11**). Following exactly the procedures described in [12] (racemic series), a 374 mg (1.38 mmol) sample of **10** was brominated and dehydrobrominated to give 257 mg (69%) of pure **11**: m.p. 154–155°. $[\alpha]_D^{23} = -65.6°$, $[\alpha]_{578}^{23} = -68.0°$, $[\alpha]_{546}^{23} = -85.0°$, $[\alpha]_{435}^{23} = -231°$ ($c = 0.84$, CH_3OH). Other spectral properties were identical to those reported [12] for a racemic sample.

(−)-Crinine (= 1,2-Didehydrocrinan-3α-ol; **1***).* Following exactly the procedures described in [12] (racemic series), a 257 mg (0.954 mmol) sample of **11** was reduced with $LiAlH_4$ and the resulting crude allylic alcohol hydrolyzed in 10% HCl to give 250 mg of a crude oil. Purification by radial chromatography (silica gel, CH_2Cl_2/CH_3OH/58% NH_4OH (15:1.0:0.1) gave, after recrystallization from acetone, 84 mg (39%) of pure **1**: m.p. 207–209°, mixed m.p. 207–208°. $[\alpha]_D^{23} = -26.1°$, $[\alpha]_{578}^{23} = -29.2°$, $[\alpha]_{546}^{23} = -36.2°$, $[\alpha]_{435}^{23} = -101°$, $[\alpha]_{365}^{23} = -304°$ ($c = 0.26$, $CHCl_3$). The corresponding $[\alpha]$'s for a recrystallized (acetone) sample of natural (−)-crinine[8]) were: −25.8, −27.0, −33.2, −90.1, and −265° ($c = 0.24$, $CHCl_3$). Other spectra and chromatographic properties of synthetic **1** were identical with those of natural (−)-crinine [6] [12].

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