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(11) The C-7 vinyl hydrogen has been reported to appear in the nmr spectrum of this isomer at δ 5.18 (see ref 1).
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A Total Synthesis of Cassamedine

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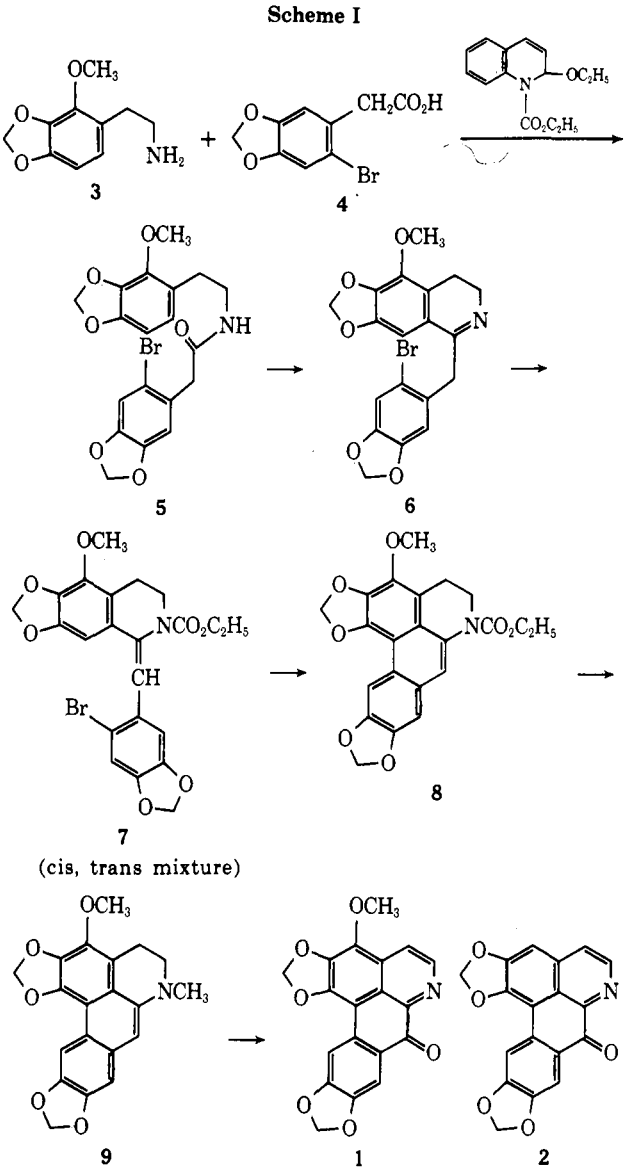
The orange alkaloid cassamedine, which was isolated from *Cassytha americana*, has been assigned structure **1**, solely on the basis of its spectral properties.[1] We now report a total synthesis of cassamedine which unambiguously confirms structure **1** for the alkaloid.

The synthetic methodology employed was generally similar to that used in our synthesis of the companion alkaloid cassameridine (**2**).[1,2] The reaction of β-(2-methoxy-3,4-methylenedioxyphenyl)ethylamine (**3**)[3] with 6-bromohomopiperonylic acid (**4**) in the presence of EEDQ (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline)[4] gave the amide **5**, which was converted smoothly by phosphorus oxychloride in acetonitrile into the dihydroisoquinoline **6**. Reaction of **6** with triethylamine and ethyl chloroformate gave the benzylidine urethane **7** as a mixture of cis and trans isomers. Direct irradiation of crude **7** in benzene–*tert*-butyl alcohol containing potassium *tert*-butoxide afforded *N*-carbethoxy-6a,7-dehydrocassythidine (**8**). Reduction of **8** by lithium aluminum hydride–aluminum chloride in ether gave *N*-methyl-6a,7-dehydrocassythidine (**9**). Peracetic acid oxidation of **9** afforded, in 28% yield, orange needles of **1**, identical in all respects with cassamedine from natural sources (Scheme I).

Scheme I



Experimental Section

Melting points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Ultraviolet spectra were determined in ethanol with a Perkin-Elmer Model 202 spectrophotometer. Nmr spectra were recorded with Varian A-60A and HA-100 instruments.

β-(2-Methoxy-3,4-methylenedioxyphenyl)ethylamine (3) was prepared according to Govindachari, *et al.*[3] The oily amine was characterized and stored in the form of its acid oxalate salt, mp 173–175°, prepared by addition of an equimolar quantity of ethanolic oxalic acid.

Anal. Calcd for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30; N, 4.91. Found: C, 50.31; H, 5.16; N, 5.00.

***N*-(2′-Methoxy-3′,4′-methylenedioxyphenylethyl)-2-bromo-4,5-methylenedioxyphenylacetamide (5).** Amine **3** was liberated from its acid oxalate (2.00 g, 7.0 mmol) by treatment with ammonium hydroxide and extraction with benzene. The dried benzene extract (70 ml) was added to 6-bromohomopiperonylic acid[5] (**4**, 1.81 g, 7.0 mmol) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (1.91 g, 7.7 mmol). The solution was stirred at room temperature for 2 hr, and the precipitated amide **5** (2.32 g, 76%) was removed by filtration. Recrystallization from CH_2Cl_2 gave microneedles, mp 185°.

Anal. Calcd for $C_{19}H_{18}NO_6Br$: C, 52.31; H, 4.13; N, 3.21. Found: C, 52.22; H, 4.18; N, 3.18.

Hydrochloride of 1-(2′-Bromo-4′,5′-methylenedioxybenzyl)-3,4-dihydro-5-methoxy-6,7-methylenedioxyisoquinoline (6). A mixture of acetonitrile (60 ml), amide **5** (2.72 g, 6.2 mmol), and phosphorus oxychloride (4.9 ml, 53 mmol) was warmed on the steam bath until the amide dissolved. The solution was then stirred at room temperature for 20 hr. Absolute ethanol (5.5 ml) was then added dropwise. Addition of a large volume of ether gave the hydrochloride of **6** (2.62 g, 90%) as a yellow powder. Recrystallization from acetic acid–ether afforded the pure salt as yellow cubes, mp 243° dec.

Anal. Calcd for $C_{19}H_{17}NO_5BrCl$: C, 50.19; H, 3.77; N, 3.08. Found: C, 49.97; H, 3.82, N, 3.01.

1-(2′-Bromo-4′,5′-methylenedioxybenzylidine)-2-carbethoxy-1,2,3,4-tetrahydro-5-methoxy-6,7-methylenedioxyisoquinoline (7). A solution of ethyl chloroformate (0.72 ml, 7.5 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a mixture of the hydrochloride of **6** (1.374 g, 3.02 mmol), triethylamine (1.26 ml, 9.05 mmol), and CH_2Cl_2 (15 ml) with ice bath cooling. The mixture

was warmed to room temperature and allowed to stand for 3 hr, then placed directly on a silica column. Elution with CH_2Cl_2 and solvent evaporation afforded a pale yellow crystalline mass (1.33 g, 90%) of about equimolar amounts of the cis and trans isomers of **7**. The presence of the two isomers was evident from nmr analysis ($CDCl_3$), which showed two distinct ethyl triplets centered at *ca.* δ 0.92 and 1.35.[6] A small sample of trans isomer, mp 222–224°, was obtained as colorless crystals from $CHCl_3$–methanol, uv spectrum λ_{max} 329 nm (log ϵ 4.21).

Anal. Calcd for $C_{22}H_{20}NO_7Br$: C, 53.87; H, 4.11; N, 2.86. Found: C, 53.69; H, 4.24; N, 2.62.

***N*-Carbethoxy-6a,7-dehydrocassythidine (8).** A solution of crude **7** (cis-trans mixture, 1.298 g) in benzene (750 ml), *tert*-butyl alcohol (100 ml), and 15% potassium *tert*-butoxide in *tert*-butyl alcohol (9.5 ml) was irradiated (Hanovia 450-W lamp, Corex filter) for 7 hr under N_2; the photolysis was interrupted three times in order to clean the irradiation probe. Dilution with water and evaporation of the washed and dried benzene layer gave a residue which was dissolved in $CHCl_3$ and chromatographed on silica. Elution by $CHCl_3$, followed by crystallization from $CHCl_3$–methanol, gave colorless crystals of **8** (0.345 g, 32%): mp 260–261°; uv spectrum λ_{max} 261 nm (log ϵ 5.33), 301 (4.56), 336 (4.56), 378 (4.16); nmr ($CDCl_3$) δ 8.32 (s, 1 H), 7.33 (s, 1 H), 7.06 (s, 1 H), 6.14 (s, 2 H), 6.01 (s, 2 H), 4.26 (q, J = 8 Hz, 2 H), 4.03 (s, 3 H), 3.98 (t, J = 6 Hz, 2 H), 3.06 (t, J = 6 Hz, 2 H), 1.31 (t, J = 8 Hz, 3 H).

Anal. Calcd for $C_{22}H_{19}NO_7$: C, 64.55; H, 4.68; N, 3.42. Found: C, 64.21; H, 4.63; N, 3.16.

***N*-Methyl-6a,7-dehydrocassythidine (9).** Ester **8** (0.164 g, 0.040 mmol) was added to a slurry of lithium aluminum hydride (0.0456 g, 1.14 mmol) and $AlCl_3$ (0.080 g, 0.60 mmol) in dry ether (5 ml), and the mixture was refluxed with stirring for 90 min. Water was added slowly, followed by ammonium hydroxide, and the product was extracted into $CHCl_3$. Evaporation of the dried organic extract gave crystalline **9** (0.102 g, 87%). Recrystallization from $CHCl_3$–methanol gave pure **9**: mp 198–201°; uv spectrum λ_{max} 262 nm (log ϵ 4.71), 301 (4.33), 336 (4.32).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.13; H, 4.90; N, 4.07.

Cassamedine (1). A solution of peracetic acid (0.254 ml of a 40% acetic acid solution) in acetic acid (20 ml) was added dropwise to a cooled solution of **9** (0.186 g, 0.53 mmol) in acetic acid (40 ml). After warming to room temperature, the solution was allowed to stand for 1 hr, then basified with aqueous ammonia and extracted with $CHCl_3$. Evaporation of the dried extract gave a residue which was chromatographed ($CHCl_3$) on grade II neutral alumina. The desired orange band was eluted by 2% methanol in CH_2Cl_2. The chromatographic purification was repeated in exactly the same way using a second alumina column. Crystallization from $CHCl_3$–benzene gave bright orange needles (0.060 g, 28%) of cassamedine: mp 278° (lit.[1] 278°); uv spectrum 251 nm (log ϵ 4.32), 281 (4.43), 323 (3.77), 361 (3.58), 460 (3.28); nmr (CF_3CO_2D) δ 8.83 (m, 2 H), 8.18 (s, 1 H), 7.83 (s, 1 H), 6.61 (s, 2 H), 6.21 (s, 2 H), 4.48 (s, 3 H); *m/e* (M^+ 349); reported uv spectrum[1] 252 nm (log ϵ 4.47), 281 (4.53), 324 (4.12), 364 (3.97), 460 (3.76); reported nmr[1] (CF_3CO_2H) δ 8.85 (2 H), 8.19, 7.83, 6.62 (2 H), 6.23 (2 H), 4.48 (3 H). The infrared spectrum (KBr) of synthetic cassamedine was superimposable upon that of the natural alkaloid.

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Registry No.—**1**, 16408-75-6; **3** oxalate salt, 49689-85-2; **4**, 5470-14-4; **5**, 49689-87-4; **6** HCl, 49844-61-3; *cis*-**7**, 49689-88-5; *trans*-**7**, 49689-89-6; **8**, 49689-90-9; **9**, 49689-91-0.

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Reactions of Organometallic Reagents with Unsaturated Epoxides. II.[1a,b] Control of Product Ratios

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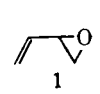
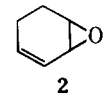
The addition of Grignard reagents to α,β-unsaturated ketones has been commonly recognized as a versatile synthetic tool since an option of two distinct pathways is available: 1,2 addition is generally obtained in the absence of cuprous catalysts, whereas 1,4 addition results in the presence of cuprous catalysts.[2,3] Recently, the analogous regioselectivity was reported for 3,4-epoxy-1-butene[4,5] (**1**) and a cyclic conjugated epoxide, 3,4-epoxycyclohexene[6,7] (**2**).



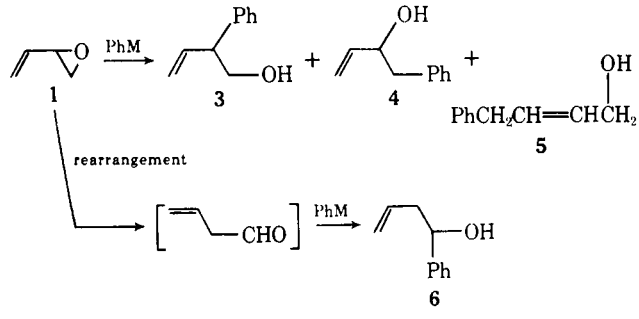
1



2

Scheme I illustrates the possible products resulting from the reaction of **1** with metallophenyl reagents.

Scheme I



1 **3** **4** **5** **6**

Although pathways to products **3** and **5** had been regioselectively demonstrated,[1,4-8] pathways to products **4** and **6** had not. Prior related work with amines and methoxides,[8d,e,9] organolithium compounds,[5,10] and bulky Grignard reagents[11] suggested that product **4** could be made to predominate, and Kharasch's studies[12] with styrene oxide seemed to indicate that **5** could be obtained by using appropriate inverse addition conditions. Thus, any one of the four specific sites of alkylation could be chosen by modifying the reagent and/or reaction parameters. To do this would disclose the full but implicit synthetic potential of **1**, a model for the general conjugated epoxide structural unit.

Furthermore, it appeared highly desirable to explore the effect of solvent upon the course of this reaction. Tetrahydrofuran appeared to be an ideal solvent to use inasmuch as current reports suggested that tetrahydrofuran, relative to ether, shifted the Schlenk equilibrium to the right.[13] Since rearrangement products in Grignard reactions with epoxides are known to result from magnesium halide induced rearrangement,[8,14] a shift in the Schlenk equilibrium (and hence the amount of MgX_2) should be reflected in the amount of rearrangement product. A demonstration of this phenomenon corroborating the Schlenk equilibrium studies, product control factors, and metal ion influence is herein described.

$$2RMgX \rightleftharpoons R_2M + MgX_2$$

Results and Discussion

The products formed from the reactions of **1** with metallophenyl reagents are summarized in Table I. Several