Diastereoselective Synthesis of Cularine Alkaloids via Enium Ions and an Easy Entry to Isoquinolines by Aza-Wittig Electrocyclic Ring Closure

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In preliminary communications, we reported the diastereoselective synthesis of cularine and sarcocapnine via the intramolecular ring closure of nitrenium and oxenium ions, a new highly diastereoselective reductive methylation with (+)-8-phenylmenthyl chloroacetate followed by reduction with sodium borohydride, and a facile entry to the isoquinoline precursors by aza-Wittig electrocyclic ring closure. We now report the full details of the syntheses of (+)-O-demethylcularine, (+)-cularine, (+)-sarcocapnidine, (+)-sarcocapnine, and (+)-crassifoline and describe different methods of synthesis of their precursors.

Introduction

The alkaloid (+)-cularine was isolated by Manske in 1938 from plants belonging to the genera Dicentra and Corydalis.1 Its structure (1) was determined in 1950.2 In addition, a number of related alkaloids have been isolated from some species of the genera Ceratocapnos, Corydalis, Dicentra, and Sarcocapnos (Papaveraceae).3-6 These alkaloids have the same basic framework (A). The biosynthesis of cularine alkaloids has been reported7 and involves crassifoline (7) as the precursor. In preliminary communications, we reported a novel diastereoselective route to these alkaloids8 and a new entry to the isoquinoline precursors.9 We now give the full details as well as additional ones on the possible mechanisms of the reactions. The cularines and isocrassifoline possess muscle relaxant activity by inhibiting calcium entry in uterine smooth muscle. Increases in the number of O-methyl groups enhances the relaxant activity, probably owing to a greater lipophilicity of the molecules.10

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A number of syntheses of the cularine have been reported: (a) Formation of a diphenyl ether followed by building the tetrahydropridine and seven-membered ring involves many steps and the yields are low.11 (b) An Ullmann coupling reaction between an 8-hydroxy-1-(o-bromobenzyl)tetrahydroisoquinoline or 8-bromo-1-(o-hydroxybenzyl)tetrahydroisoquinoline gave better yields.11 (c) Oxidative phenolic coupling using potassium ferrocyanide (a free-radical process) gave mixtures of isomers in low yield.10b,11 Oxidative phenolic coupling of cissifoline–borane complex using VOF$_3$ in trifluoroacetic acid led to 10-demethylcularine in 40% yield. (d) Intramolecular addition of a phenol to a benzyne gave the desired compound (20%) together with a tetracyclic indole (65%).

**Results and Discussion**

We conceived that the cularine-type alkaloids may be synthesized efficiently using a catonic process (Scheme 1), namely involving either arylnitrenium ions15 or -oxenium ions16,17 in which the positive charge is delocalized mainly to the para position, whence it can be trapped by a nucleophilic oxygen atom at C-8 of a 3,4-dihydroisoquinoline.

Intramolecular cyclizations involving arylnitrenium ions have been carried out successfully, resulting in the formation of C=C and C-O bonds (e.g., Scheme 2).15

**Scheme 1**

\[
\text{Scheme 1: Cularine Alkaloid Synthesis.}
\]

**Scheme 2**

\[
\text{Scheme 2: Arylnitrenium-Catalyzed Cyclization.}
\]

 Arylnitrenium ions have been generated from the thermalolysis of N-aryloxypyridinium salts16 and aryloxamine derivatives,17 and these have reacted with arenes to form biaryls and diaryl ethers (Scheme 3). Other starting materials for the generation of ArO$^+$ are ArOX: [X = (SPri)$NR_2$, STol$NR_2$, SMe$_2$, NHTos].17-19

Hyperivalent iodine compounds have been used extensively in the oxidative coupling of phenols and the synthesis of a number of natural products.20 Among the alkaloids synthesized in this way are (+)-codeine and 6a-epipretazettine21 and (+)-reticuline.22 To generate a free arylnitrenium ion from ArO$^+$ it is essential that X be a good leaving group. Also, any counterion present should be a very weak nucleophile if it is not to intercept the very reactive ArO$^+$. To that end, we chose to use C$_6$F$_5$I-(OCOCF$_3$)$_2$ (8) (Scheme 4); not only is the C$_6$F$_5$I$^+$-(OCOCF$_3$)$_2$ a good leaving group and CF$_3$CO$_2^-$ is a poor nucleophile, but also the electron-poor C$_6$F$_5$ is not likely to undergo intramolecular C=C bond formation.

With these concepts in hand, we turned to the synthesis of the alkyl precursors, namely the 1-benzylidene- and tetrahydroisoquinoline derivatives. Classically, dihydro- or tetrahydroquinolines are prepared by Bischler–Napieralsky, Pictet–Spengler, or Pomeranz–Fritsch reactions.24 We developed an efficient route to rutecarpine via an intramolecularaza-Wittig reaction25 and applied it successfully to the total synthesis of (+)-cularine-type
alkaloids. The required precursors were the iminophosphoranes (9) and the ketenes (10). We used two methods to prepare 9: the Staudinger-type reaction (Scheme 5) and the Mitsunobu reaction (Scheme 6). Isovanillin was obtained. The bromine blocking group could be removed easily when R3

\[ \text{halogen} \rightarrow \text{R} = \text{H}, \text{Br} \]

of the two possible cyclization products

\[ \text{cyclization at that position in the aza-Wittig reaction.} \]

When the bromine was replaced by hydrogen, a mixture of the 1-benzyl-3,4-dihydroisoquinolines in hand we turned to the synthesis of the target alkaloids. The required precursors were the iminophosphoranes (9) and the ketenes (10). We used two methods to prepare 9: the Staudinger-type reaction (Scheme 5) and the Mitsunobu reaction (Scheme 6). Isovanillin was the starting material in both cases.

Ketenes (10) were prepared by dehydration of the corresponding homoveratric acids (prepared in two steps: condensation in quantitative yield of the aromatic aldehyde 6 with hippuric acid/CH₃CO₂Na in a microwave oven, followed by hydrolysis of the oxazolone with alkali) and dehydration of the homoveratric acid with dicyclohexylcarbodiimide and Et₃N in THF at 0 °C, followed by dehydration of the oxazolone with alkali phosphoranes (Scheme 5) and the Mitsunobu reaction (Scheme 6). Isovamillin was the starting material in both cases.

The electrocyclic aza-Wittig reaction between iminophosphoranes (9) and ketenes (10) was used to protect that position from the reaction of arylnitrenium ions to form C₭ (stepwise—in our opinion quite likely owing to the bulk of the leaving group) or oxiennium (concerted—shown in Scheme 4) was generated using a 1:1 ratio of the sodium salt of 18 and C₆F₅I(OCOCF₃)₂ (8), and the yield of 16 was monitored by TLC as a function of reaction temperature and time (Table 1). Two cyclization products were formed: the desired 16 (67%) and the product of ortho attack 17 (~2%) (Scheme 9). The yield of intramolecular cyclization product is higher than those reported when other hypervalent iodo compounds are used.

The structures of 16 and 17 was established unambiguously: IR, NMR, mass spectroscopy, and microanalysis (see the Experimental Section).

The ortho/para ratio for the capture of the ArOH group of 18 presents no ambiguity. The intramolecular cyclizations of arylnitrenium ions to form C=C or C=O bonds take place mainly at the position para to the nitrenium cation. Similarly, the oxidative cyclization of 18 is also unambiguous since only the 8-hydroxy function can undergo oxidation by the iodonium salt—which leads to C=O bond formation mostly at the position para to the 3'-methoxy group of the 1-benzyl group yielding 16.

The synthesis of the corresponding (±)-10-amino-2,3-dihydro-6,9-dimethoxy[1]benzoexepino[2,3,4-ij]isoquinoline (19) was effected via the nitrenium ion produced by the acid-catalyzed decomposition of azide (20). The latter was obtained by the reduction of 13 (R₃ = NO₂) to the corresponding amine (19) and thence to the azide (20) (Scheme 10).

As was the case with the oxenium ion cyclizations, the arylnitrenium ion was attacked by the OBN (or OH) preferentially at the para position to give 21 (81%); attack at the position ortho to the nitrenium ion gave a very minor amount of product 22 (3%). Compound 21 had no

\[ \text{yield} = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100 \]

-10 °C, followed by the addition of H₂O or by reaction of 12a with PPh₃.

The versatility of the aza-Wittig reaction for the preparation of isoquinolines was further demonstrated using 2-azido-1-(3,4-methylenedioxybenzene)propen-2-ol (14) synthesized from piperonal and ethyl azidoacetate(NaOEt), followed by a Staudinger reaction to give the corresponding iminophosphorane. Reaction with p-toluenesulfonyl isocyanate gave isoquinoline (15) in 95% yield (three easy steps to give the 1-aminoisoquinoline derivative in 88% overall yield) (Scheme 8).
azide band in the infrared, but exhibited bands for a primary amine. No attack by triflate anion on the arylnitrenium ion ring was detected (cf. ref 34). Amine 21 was converted to the corresponding methoxy precursor (16) to cularine by standard methods (Scheme 12). This is the first example of the formation of an oxepine ring via an arylnitrenium ion. A seven-membered ring lactone has been synthesized (Scheme 11) from an arylnitrenium ion involving a 1,2-shift of an ipso-lactone.34b Also, the intramolecular trapping of a phenolic group by a nitrenium ion to form a six-membered ring (23) has been effected (see the Experimental Section).

Diastereoselective Synthesis of Cularine Alkaloids

**TABLE 2. Yield of 21 as a Function of Time and Temperature**

<table>
<thead>
<tr>
<th>reaction</th>
<th>T (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>10</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>-5</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>-5</td>
<td>15</td>
<td>81</td>
</tr>
</tbody>
</table>

*The ratio of TFMSA to TFA was the same in all cases.*
intramolecular cyclization product 21 was monitored by TLC (Table 2).

Tetracycle 16 was converted to (+)-cularine by N-methylation followed by reduction with sodium borohydride.35

The didebenzylolation of 12d was effected with TFMSA in CCl4 to give the bis-phenol 24 in 89% yield. The latter was oxidized with C6F5I(OCOCF3)2, which resulted in the formation of 2,12-dihydro-6,9-dimethoxy-3H-[1]benzoxepin[2,3,4-ij]isoquinolin-10-ol (26) (36%) and (+)-didehydronorsarcocapnidine (25) (58%) (which are axially chiral) (Scheme 12). They were separated by preparative TLC. Both 25 and 26 showed bands for OH and C3-N in the IR and exhibited 1H NMR peaks consistent with the assigned structures.

Oxidation of bis-phenol 24 (Scheme 13) could take place at either of the phenolic groups (or possibly partially at both). Contrary to the preferred selectivity observed with the nitrenium ion and the oxidation of 18, the main product was that of attack at the 2′-C-atom ortho to the 3′-OH group to give 25 (58%) with the yield of didehydroncularine (26) being 36%. This would suggest that oxidation is taking place mainly (if not exclusively) at the C3′-OH and not at the C8′-OH (cf. Scheme 4).

SCHEME 10

SCHEME 11

SCHEME 12

SCHEME 13

We have carried out simple molecular modeling (MMX) calculations36 to determine the possible conformations of C8-OH protonated 18, C8-OH protonated 12d, and C3′-OH protonated 12d. Since there are no parameters in MMX for the oxenium and nitrenium ions, we hoped that the protonated hydroxyl group might be a very rough model for the positively charged oxenium cation. The resulting global energy minimum conformation of the C8-OH protonated (i.e., C-OH2+′) is shown in Figure 1, together with the distances between the -O+- and the positions ortho and para to the C3′-OH group.

The corresponding minimum energy conformation of C3′-OH protonated 24 is shown in Figure 2, and that of C8′-OH protonated 24 is shown in Figure 3. If these distances mean anything, they would suggest that oxida-

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FIGURE 1. C8′-OH protonated 18. Distance from CgOH2+′ to position ortho to C3′-methoxy group: 5.913 Å. Distance from CgOH2+′ to position para to C3′-methoxy group: 4.594 Å.

FIGURE 2. C3′-OH protonated 24. Distance from position ortho to C3′-OH2+′ to 8-OH group: 4.366 Å. Distance from position para to C3′-OH2+′ to 8-OH group: 5.599 Å.

FIGURE 3. C8′-OH protonated 24. Distance between CgOH2+′ and position ortho to C3′-OH group: 5.766 Å. Distance between CgOH2+′ and position para to C3′-OH group: 4.597 Å.
tion of 24 would take place preferentially at C3'-OH (ortho attack greater than para attack), as observed. An alternate possibility that the oxidative cyclizations proceeded by an SN2' mechanism (Figure 4) instead of an oxenium ion one is highly unlikely since nucleophilic attack would have to occur at a carbon atom flanked by two groups, one of which is quite large, as pointed out above.

Bisphenol 24 was now N-alkylated with 2 equiv of the chiral auxiliary (+)-8-phenylmenthyl chloroacetate (29) in methanol at room temperature for 10 h, followed by reduction with sodium borohydride at 0 °C for 4 h, to yield (+)-crassifoline (7) in 91% yield (Scheme 14). The spectral properties were consistent with the structure of the molecule (see the Experimental Section). The optical rotation of (+)-7 reported is [α]25D = +20.6 (MeOH). The observed rotation for (+)-7 was [α]25D = +18.2 (MeOH), corresponding to an ee > 88%.

The high yields of (+)-products (S-configuration) from axially chiral racemic imines requires a highly diastereoselective reduction and prior or subsequent kinetic resolution, followed by a facile hydrolysis and deacetylation. The minimum global energy conformation of 30 (MMX, 1000 iterations) is shown in 30a, and it is clear that the concave side is shielded, forcing the hydride ion to approach from the convex side to give the desired S-configuration.

Treatment of 32 with diazomethane gave (+)-cularine in 98% yield. Stereospecific reductive methylation of 25 gave (+)-sarcocapnidine (6b) in 93% yield [mp 125–126 °C (lit.6b mp 126–127 °C); [α]25D = +384 (MeOH) (lit.6b [α]25D = +384.3 (MeOH))]. We have carried out a similar MMX global minimization of each of the diastereomers of 31. These are shown in 31a, b. 31a has a lower global energy minimum than does 31b. In both, however, the 8-phenylmenthyl group is above the plane of the –C=N–: in 31a one of the isopropyl methyl groups is above the –C=N– carbon at a distance of 4.054 Å, the other methyl is at a distance of 5.438 Å indicating that the hydride ion must approach from below. In 31b, the distances are 5.741 and 5.925 Å, so that once again the hydride ion has to approach from below, which accounts for the high diastereoselectivity observed. (+)-O-Demethylcularine (32) was synthesized in the same way from (+)-26 in 95% yield [mp 127–128 °C (lit.37 mp 115 °C); [α]25D = +323.5 (MeOH)].

of water followed by extraction with ether and drying the ether layer (K$_2$CO$_3$) gave the corresponding phenethylamine, which was purified by column chromatography on silica gel (hexane–CH$_2$Cl$_2$, 6:4 v/v): yellow oil (330 mg, 72%); IR (film) 3379 cm$^{-1}$; NMR (CCl$_4$) $\delta$ 7.33 (m, 6H), 6.77 (s, 1H), 5.05 (s, 2H), 4.62 (s, 2H), 3.82 (s, 3H), 2.94 (m, 4H). The amine (160 mg, 0.48 mmol) and triphenylphosphine (130 mg, 0.48 mmol) in CCl$_4$ (100 mg) and CH$_2$Cl$_2$ (7 mL) were stirred at 40 °C for 72 h under dry N$_2$. Evaporation of the solvent and recrystallization from acetone–chloroform (1:1 v/v) gave the N-triphenylphosphorono chloride (220 mg) as a yellow solid: mp 172–173 °C (79% yield); IR (KBr) 3600–3300 (NH), 1430 (CP), 1020 (NP); NMR (CDCl$_3$) $\delta$ 7.55 (m, 2H), 6.80 (s, 1H), 5.20 (s, 2H), 3.87 (s, 3H), 3.0 (m, 5H). This (200 mg) was dissolved in toluene, sodamide (14 mg) was added, and the mixture was stirred at 100 °C under nitrogen for 1 h. Evaporation followed by recrystallization form acetone/chloroform (1:1 v/v) gave 9 (R = Br) (180 mg, 95%) as a yellow solid: mp 152–153 °C; NMR (CDCl$_3$) $\delta$ 7.56 (m, 2H), 6.80 (s, 1H), 5.15 (s, 2H), 3.78 (s, 3H), 3.10 (m, 4H). Anal. Calc. for C$_{19}$H$_{14}$BrNO: C, 68.48; H, 5.24; N, 2.35. Found: C, 68.48; H, 5.25; N, 2.36.

**Method B.** Anhydrous CrC$_2$O$_5$ (5.0 g, 31.6 mmol) suspended in THF (50 mL) was treated with LAH (0.60 g, 15.8 mmol) under nitrogen at 0 °C. A solution of 3-benzyloxy-6-bromo-methoxybenzaldehyde (2 g, 6.20 mmol) and chloroform (1.48 g) and THF (30 mL) was added to the suspension, which was then stirred for 6 h at 65 °C. Addition of water followed by extraction with CHCl$_3$, drying the extract (Na$_2$SO$_4$), filtration, and evaporation gave 3-benzyloxy-6-bromo-methoxy-(E)-stilbene (1.96 g, 89%) as a yellow oil: IR (film) 3061–3202, 1670 cm$^{-1}$; adducts with benzil (R = C(C$\equiv$C)) yielded: NMR (CCl$_4$) $\delta$ 7.54 (s, 1H), 7.25 (m, 5H), 7.04 (d, 1H, $J$ = 13.5 Hz), 6.94 (s, 1H), 6.35 (d, 1H, $J$ = 13.5 Hz), 4.93 (s, 2H), 3.77 (s, 3H). To the chlorostyrene (1.6 g, 4.53 mmol) in THF was added a suspension of H$_2$SO$_4$ (72%, 0.03 mL) under dry N$_2$. The mixture was boiled under reflux for 8 h, excess LAH was destroyed with water after cooling, and the mixture was filtered and then extracted with CH$_2$Cl$_2$. The extract was dried (Na$_2$SO$_4$) and evaporated, and the residual oil was purified by column chromatography (SiO$_2$, CHCl$_3$) to give the styrene (1.30 g, 90%) as a yellow solid: mp 40–41 °C; NMR (CCl$_4$) $\delta$ 7.25 (s, 1H), 7.17 (m, 5H), 6.97 (d of d, 1H, $J$ = 18 Hz, 8.2 Hz), 6.85 (s, 1H), 6.73 (dd, 1H, $J$ = 18 Hz, 2.7 Hz), 6.57 (dd, 1H, $J$ = 8.2 Hz, 2.7 Hz), 5.08 (s, 2H), 3.88 (s, 3H). Anal. Calc. for C$_{16}$H$_{15}$BrO: C, 60.21; H, 4.75. SnCl$_4$–NaBH$_4$ was prepared by mixing SnCl$_4$ (520 mg, 2.0 mmol) with NaBH$_4$ (300 mg, 8.0 mmol) in THF at room temperature for 3 h. A solution of the styrene (640 mg, 2.0 mmol) in THF was then added. After 7 h, 15% hydrogen peroxide (1 mL) was added, and the solution was left standing overnight. It was then made just acidic by the addition of 10% HCl. Extraction with CH$_2$Cl$_2$, drying, and purification by column chromatography (SiO$_2$, CHCl$_3$) gave the phenethyl alcohol (630 mg, 92%) as a yellow solid: mp 55–56 °C; IR (KBr) 3600–3200 (OH), 1410 (COH), 1130 cm$^{-1}$ (CO); NMR (CCl$_4$) $\delta$ 7.39 (s, 1H), 7.28 (m, 5H), 6.70 (s, 1H), 5.02 (s, 2H), 4.90 (s, 1H), 3.80 (s, 3H), 3.63 (t, 3H), 2.65 (t, 2H). Anal. Calc. for C$_{16}$H$_{15}$BrO: C, 56.99; H, 5.08. Found: C, 56.99; H, 5.09. To a solution of the alcohol (600 mg) in THF (5 mL) was added a solution of Na$_2$O$_2$ (prepared from Na$_2$O (2.2 g) in benzene$^{41}$) followed by a solution of DEAD (400 mg) in THF (5 mL). To that solution was added a solution of triphenylphosphine (1.03 g) in THF (8 mL) under dry N$_2$. After the solution was allowed to stand for 1 h, it was heated for 7 h at 65 °C. The solvent was then evaporated and the product was recrystallized from acetone–chloroform (1:1 v/v) to give 9 (1.04 g, 98%), identical to that obtained above.

The same procedure (method A) was used to synthesize 8- and 15-amino-derivatives, using oxenium and nitrenium ions. 15. Isolated. A possible reaction pathway is shown in Scheme 15.

In conclusion, we have described novel routes to 1-benzyl-3,4-dihydro- and -tetrahydroisoquinoline via the aza-Wittig reaction. This route is applicable to the synthesis of 1-aminoisoquinoline derivatives. We have also described synthetic routes to (±)-dihydrooxonicine, -sarcopine, -norcaroline, as well as the 8- and 10-amino-derivatives, using oxenium and nitrenium ions to form the oxepine ring. Finally, we have developed a novel highly diastereoselective reductive N-methylation of these compounds, resulting in the synthesis of (±)-crassifoline (7), (±)-O-demethylcaroline (32), (±)-caroline (1), (±)-sarcopine (6a), and (±)-sarcopinidine (6b) in high yield and excellent enantiomeric excess.

**Experimental Section**

All solvents were used anhydrous.

**3-Benzoxyl-6-bromo-4-methoxyphenethyliminophosphorane (9, R = Br).** Method A. To a solution of LAH (250 mg) in THF (15 mL) was added a solution of 3-benzyloxy-6-bromo-methoxy-N-nitrostyrene$^{39}$ (500 mg, 1.37 mmol) in THF (15 mL) which was then boiled under reflux for 8 h. Addition

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3-benzyloxy-4-methoxyphenylmethylyphosphorane (9, R = Me) in 94% yield, mp 150–151 °C.

Syntheses of Ketones 10 (R3 = OCH3). Method A. 4-(3,4-Dimethoxyphenyl)methylene-2-phenyl-5-(4-oxazolone) was synthesized in 76% yield and 2.5 h reaction time by the procedure of Buck and Ide42 using conventional heating.

**Method B. Solvent-Free Conditions.** Veratraldehyde (10.67 g, 60.0 mmol), hippuric acid (12.8 g, 72.0 mmol), and sodium acetate (5.34 g, 70.0 mmol) (same ratio as used in method A, but in the absence of acetic anhydride) were placed in an Erlemeyer flask and triturated to produce a semi-homogeneous mixture. The plug was washed loosely with glass wool. Irradiation in a domestic microwave oven for 5 min, followed by washing with warm water, gave the azalactone in quantitative yield: mp 151–152 °C.

Homoveratic acid was synthesized from the azalactone using a literature method43 to give the acid in 83% yield: mp 97–98 °C.

3,4-Dimethoxyphenylketene (10) was prepared using the method of Olah et al.44 (who used to prepare alkylketenes from alkylacetic acids), using DCC and catalytic amounts of Et3N. from alkylacetic acids), using DCC and catalytic amounts of Et3N.

**Synthesis of 5-Bromo-8-benzylidene (1,3,4-dimethoxybenzyl)-7-methoxy-3,4-dihydrosoxazoline (12a) Using an Aza Wittig Reaction.** To a solution of iminophenazophine (9a) (1.0 g, 1.68 mmol) in toluene at 0 °C under dry N2, was added a solution of 10 (R3 = OMe) (430 mg, 2.43 mmol) in toluene. After 2 h, the temperature was slowly raised to 75 °C and maintained at that temperature for 14 h. The solvent was then evaporated, and the solid residue was recrystallized from petroleum ether to give 12a as a white solid: mp 158–159 °C (76%); IR (KBr) 1627 cm−1 (C=O); 1H NMR (CHCl3) δ 7.05 (d, 1H, J = 8.3 Hz), 7.02 (d, 1H, J = 8.3 Hz), 7.01 (d, 1H, J = 10.6 Hz), 6.86 (s, 1H, J = 8.1 Hz), 6.78 (d, 1H, J = 8.5 Hz), 6.52 (s, 1H), 4.78 (s, 2H) (NH 2), 3.83 (s, 3H), 3.76 (s, 3H), 3.14 (s, 2H), 2.57 (t, 2H), 2.25 (t, 2H), 2.37 (t, 2H); 13C NMR (CDCl3) δ 121.2, 37.2, 44.8, 56.6, 56.8, 57.8, 58.7, 112.2, 115.6, 117.1, 118.4, 119.2, 119.5, 120.2, 124.3, 125.4, 129.1, 133.4, 133.7, 148.9, 149.9, 150.2, 151.3, 152.8. Anal. Calcd for C26H26BrNO4: C, 62.91; H, 5.28; N, 2.82. Found: C, 62.91; H, 5.26; N, 2.82.

**Synthesis of 13 (R = CH3O). Using Triphenylphosphine.** A solution of 12a (R = Br) (300 mg, 0.60 mmol) and Ph3P (160 mg, 0.60 mmol) was stirred and boiled under reflux for 4 h. The solvent was then evaporated, and the residue was treated with diazomethane in ether to give 13 (R = OMe) (82%) and 165 °C); IR (KBr) 1627 cm−1 (C=O); 1H NMR (CDCl3) δ 7.05 (d, 1H, J = 8.3 Hz), 6.87 (d, 1H, J = 8.7 Hz), 6.73 (d, 1H, J = 8.7 Hz), 6.75 (dd, 1H, J = 8.7, 2.0 Hz), 6.62 (dd, 1H, J = 8.7, 2.0 Hz). 6.69 (d, 1H, J = 8.7 Hz), 5.03 (s, 2H), 4.80 (s, 2H) (NH2), 3.83 (s, 3H), 3.80 (s, 3H), 3.14 (s, 2H), 2.57 (t, 2H), 2.27 (t, 2H). Anal. Calcd for C25H22NO2: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.62; H, 6.52; N, 6.98.

The amine (82 mg, 0.20 mmol) was diazotized to give 13 (R = N) (72 mg, 63% as a yellow solid: mp 149–150 °C; IR (KBr) 1627 cm−1 (C=O); 1H NMR (CDCl3) δ 6.89 (d, 1H, J = 8.7 Hz), 6.84 (d, 1H, J = 8.7 Hz), 6.77 (dd, 1H, J = 8.7, 2.0 Hz), 6.73 (d, 1H, J = 2.0 Hz), 6.69 (d, 1H, J = 8.7 Hz), 5.02 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.12 (s, 2H), 2.56 (t, 2H), 2.26 (t, 2H). Anal. Calcd for C25H22N2O: C, 70.08; H, 5.65; N, 13.08. Found: C, 70.09; H, 5.66; N, 13.10.

A solution of azide 13 (R = N) (70 mg, 0.16 mmol) in CCl4 (10 mL) at −5 °C was treated with TFMSA (200 mg, 1.34 mmol) and stirred for 10 h at that temperature. The solution was then evaporated with the organic layer was (128 (81%) and 23 (−3%)). The mixture was resolved using TLC (CHCl3/MeOH 99:1 v/v). 22 (41.31 mg): mp 135–136 °C (petroleum ether); IR (KBr) 3450–3555 d (NH2), 1625 cm−1 (C=O); 1H NMR (CDCl3) δ 6.84 (d, 1H, J = 8.6 Hz), 6.82 (s, 1H), 6.76 (d, 1H, J = 8.6 Hz), 6.50 (s, 1H), 4.78 (s, 2H) (NH2), 3.83 (s, 3H), 3.76 (s, 3H), 3.05 (s, 2H), 2.54 (t, 2H), 2.37 (t, 2H); 13C NMR (CDCl3) δ 22.8, 40.2, 45.7, 58.1, 60.1, 118.1, 118.9, 119.5, 121.3, 129.8, 141.8, 140.8, 150.1, 151.8, 152.3, 160.3. Anal. Calcd for C19H19N3O: C, 69.69; H, 5.88; N, 9.03. Found: C, 69.69; H, 5.88; N, 9.04. 23 (1.44 mg): mp 138–139 °C. Anal. Calcd for C19H17N3O: C, 69.66; H, 5.86; N, 9.03. 22 (30 mg, 0.10, 0.10 mmol) was diazotized with acid sodium nitrite and 30% sulfuric acid at 0 °C with stirring for 1 h. Distilled water (10 mL) was added, and the solution was then heated to 60 °C and kept at that temperature for 2 h. After cooling it was evaporated with ether, the solvent was evaporated, and the residue was treated with diazomethane in ether to...
give pure 16 (25.47 mg, 81%), whose physical properties were identical to those described above.

**Synthesis of (+)-Cumarilane (−1).** (A) To a solution of 16 (25 mg, 0.08 mmol) in anhydrous methanol was added an excess of methyl iodide (78.07 mg, 0.55 mmol). The solution was allowed to stand for 10 h. It was then cooled to 0 °C, sodium borohydride (13.62 mg, 0.49 mmol) was added portionwise, and the mixture was stirred for 5 h at room temperature. Evaporation of the solvent, addition of water, extraction with chloroform, drying the solution (K₂CO₃), and evaporation of the filtered solvent and recrystallizing the residue (petroleum ether) gave (+)-cumarilane (23.14 mg, 89%); mp 113–114 °C (lit.³³ mp 113–114 °C).

**Synthesis of (+)-Cumarilane.** (B) To a solution of 16 (35 mg, 0.11 mmol) in methanol was added an excess of (+)-8-phenylmenthyl chloroacetate (29) (71.40 mg, 0.23 mmol), and the mixture was stirred for 10 h. The solution was cooled to 0 °C, and sodium borohydride (18.49 mg, 0.49 mmol) was added with stirring. The mixture was then stirred for 4 h at 0 °C. Workup as above and separation of the resulting mixture by TLC (CHCl₃–hexane–MeOH 75:24:1 v/v) gave (+)-cumarilane (1) (34.52 mg, 94%); mp 114–115 °C (petroleum ether) (lit.³⁶ mp 115 °C); [α]D²⁰ = +284.3 (MeOH) (lit.³⁶ [α]D²⁰ = +285); IR (KBr) 2385 cm⁻¹ (NCH₂); NMR (CDCl₃) δ 6.87 (1H, J = 8.5 Hz), 6.85, s (1H), 6.77 (1H, J = 8.5 Hz), 6.51 (s, 1H), 4.45 (dd, 1H, J = 16, 12 Hz), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.3 (dd, 1H, J = 16, 12 Hz), 3.10 (m, 2H), 2.60 (s, 3H), 2.50 (t, 2H), 2.35 (t, 2H). Anal. Calcld for C₁₈H₁₇NO₄: C, 70.36; H, 6.79; N, 0.10. Found: C, 70.36; H, 6.80; N, 0.41. Also we isolated were 20 (0.17 mg, −0.24%), 8-phenylmenthane (0.99 mg, −2%), and 8-phenylmenthol (0.27 mg), whose IR spectra were in agreement with those in the literature.⁴⁵

**Synthesis of 24.** 12d (320 mg, 0.65 mmol) and TFMFA (81 mg, 0.54 mmol) were heated for 80 h at 50 °C. After recrystallization from petroleum ether, 23 (180 mg, 89%) was isolated as a white solid: mp 127–128 °C; IR (KBr) 3470 (O–H), 1624 cm⁻¹ (C=O); NMR (CDCl₃) δ 6.89 (1H, J = 8.3 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.76 (dd, 1H, J = 8.3, 1.8 Hz), 6.71 (d, 1H, J = 1.8 Hz), 6.60 (d, 1H, J = 8.3 Hz), 4.85 (s, 2H (OH)), 3.80 (s, 3H), 3.74 (s, 3H), 3.50 (s, 2H), 2.80 (t, 2H). 2.52 (t, 2H); ¹³C NMR δ 20.9, 37.1, 44.9, 55.7, 56.8, 112.3, 113.4, 116.6, 118.4, 119.2, 120.1, 125.3, 128.3, 142.9, 145.9, 146.7, 146.8, 159.5. Anal. Calcld for C₁₈H₁₇NO₄: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.90; H, 6.11; N, 4.47.

**Oxidation of 24.** As was described for the oxidation of 18, a solution of 8 (296 mg, 0.56 mmol) was added to 24 (170 mg, 0.54 mmol) to give a mixture of 24 and 25 which was resolved by preparative TLC (SiO₂, CHCl₃–hexane–MeOH 75:24:1 v/v).

**Synthesis of (+)-Cumarilane.** (35 mg, 0.24 mmol) was converted into (+)-cumarilane (32) (75.05 mg, 95%) using 29 followed by NaBH₄ and purification by column chromatography on silica gel (CHCl₃–MeOH, 99:1 v/v): mp 127–128 °C (lit.³⁸ mp 126–127 °C); [α]D²⁰ = +323.5 (MeOH); IR (KBr) 3555 (OH), 2380 cm⁻¹ (NMe); ¹¹H NMR (CDCl₃) δ 6.88 (d, 1H, J = 8.5 Hz), 6.81 (s, 1H), 6.75 (d, 1H, J = 8.5 Hz), 6.58 (s, 1H), 4.90 (s, 1H, (OH)), 4.45 (dd, 1H, J = 12, 4.5 Hz), 4.86 (s, 1H), 3.85 (s, 3H), 3.25 (d of dd, 1H, J = 15.8, 4.5 Hz), 3.07 (dd, 1H, J = 15.8, 12.0 Hz), 2.58 (s, 3H), 2.54 (t, 2H), 2.42, t (2H).

**Synthesis of (-)-Sarcopinidine (6b).** Starting from 25 (55 mg, 0.17 mmol), 6b (54 mg, 93%) was synthesized in the same way as 7: mp 125–126 °C (lit.⁶⁶ mp 126–127 °C); [α]D²⁰ = +338.0 (MeOH); IR (lit.⁶⁶ [α]D²⁰ = +385.4 (MeOH); IR (KBr) 3486 (O–H), 2378 cm⁻¹ (NMe); ¹¹H NMR (CDCl₃) 7.15 (s, 1H), 6.93 (d, 1H, J = 8.5 Hz), 6.75 (d, 1H, J = 8.5 Hz), 6.63 (d, 1H, J = 8.5 Hz), 6.52 (d, 1H, J = 8.5 Hz), 4.51 (dd, 1H, J = 11.9, 4.6 Hz), 3.87 (s, 3H), 3.85 (s, 3H), 3.27 (dd, 1H, J = 15.9, 4.6 Hz), 3.09 (dd, 1H, J = 15.9, 11.9 Hz), 2.59 (s, 3H), 2.53 (t, 2H), 2.42 (t, 2H).

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Note Added after ASAP Posting. Structure 29 in Scheme 14 and the last structure in the TOC graphic contained errors in the version posted ASAP April 7, 2004; the corrected version posted April 9, 2004.

Supporting Information Available. Experimental details and characterization of 9 (R = H), ketenes 10 (R = NO₂, N(OCH₃)), and compounds 12b – e. This material is available free of charge via the Internet at http://pubs.acs.org.

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