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

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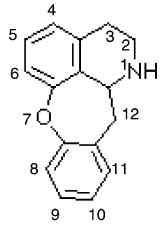
In preliminary communications, we reported the diastereoselective synthesis of cularine and sarcocapnine via the intramolecular ring closure of nitrenium and oxenium ions, a new highly diastereoselective reductive methylation with (+)-8-phenylmenthyl chloroacetate followed by reduction with sodium borohydride, 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* (Papaveracae).[3−6] These alkaloids have the same basic framework (**A**).



(A)

1',1,2,3-tetrahydro[1]benzoxepino[2,3,4-*ij*]isoquinoline

(+)-**1**	6,9,10-trimethoxy-N-methyl	CULARINE
(+)-**2**	6,9,10-trimethoxy	CULARIMINE
(+)-**3**	6-hydroxy-9,10-dimethoxy-N-methyl	CULARIDINE
(+)-**4**	6-hydroxy-9,10-methylenedioxy-N-methyl	CULARICINE
(+)-**5**	6,9-dihydroxy-10-methoxy-N-methyl	CLAVICULINE
(+)-**6a**	6,8,9-trimethoxy-N-methyl	SARCOCAPNINE
(+)-**6b**	8-hydroxy-6,9-dimethoxy-N-methyl	SARCOCAPNIDINE

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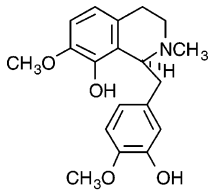
The biosynthesis of cularine alkaloids has been reported[7] and involves crassifoline (**7**) as the precursor. In



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preliminary communications, we reported a novel diastereoselective route to these alkaloids[8] 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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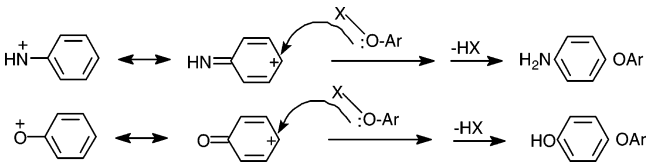
SCHEME 1



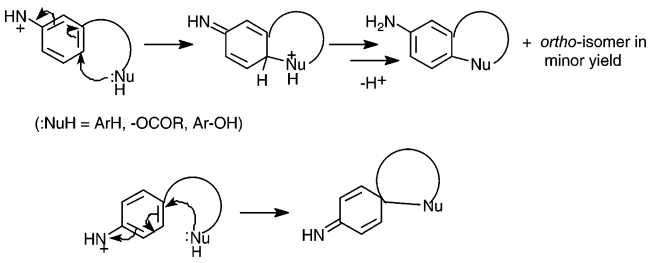
A number of syntheses of the cularines have been reported: (a) Formation of a diphenyl ether followed by building the tetrahydropyridine and seven-membered ring involves many steps and the yields are low.[11] (b) An Ullmann coupling reaction between an 8-hydroxy-1-(*o*-bromobenzyl)tetrahydroisoquinoline *or* 8-bromo-1-(*o*-hydroxybenzyl)tetrahydroisoquinoline gave better yields.[11] (c) Oxidative phenolic coupling using potassium ferricyanide (a free-radical process) gave mixtures of isomers in low yield.[10b,11−13] Oxidative phenolic coupling of crassifoline−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 derivative (65%).[14]

Results and Discussion

We conceived that the cularine-type alkaloids may be synthesized efficiently using a cationic process (Scheme 1), namely involving either arylnitrenium[15] or -oxenium[16,17] ions 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 2



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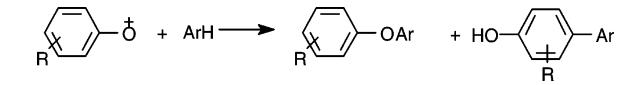
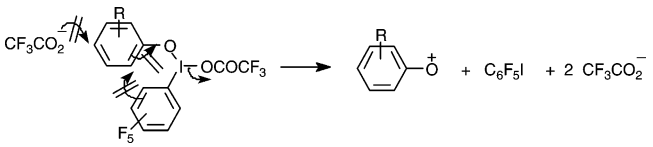


SCHEME 4



Aryloxenium ions have been generated from the thermolysis of *N*-aryloxypyridinium salts[16] and aryloxyamine 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 = $S(Pr^i)NR_2$, $S(Tol)NR_2$, SMe_2, NHOTs].[17−19]

Hypervalent 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-epipretazettine[21] and (+)-reticuline.[22] To generate a free aryloxenium ion from $ArOX^+$ 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 $C_6F_5I(OCOCF_3)_2$ (**8**) (Scheme 4):[23] not only is the $C_6F_5I^+(OCOCF_3)$ a good leaving group and $CF_3CO_2^-$ is a poor nucleophile, but also the electron-poor C_6F_5 is not likely to undergo intramolecular C−C bond formation.

With these concepts in hand, we turned to the synthesis of the alkaloid precursors, namely the 1-benzyldi- 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 intramolecular aza-Wittig reaction[25] and applied it successfully to the total synthesis of (+)-cularine-type

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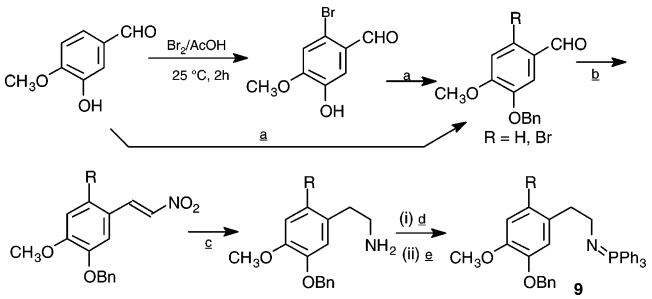
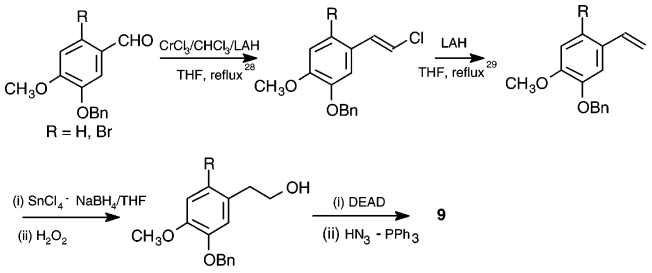
SCHEME 5 [a]



[a] Key: (a) $PhCH_2Cl/K_2CO_3$/EtOH; 75 °C, 2 h; (b) CH_3NO_2, $AcONH_4$, AcOH, 80 °C, 3 h; (c) LAH/THF, 70 °C, 8 h; (d) $Ph_3P/CCl_4/CH_2Cl_2$, 40 °C, 72 h; (e) $NaNH_2$, toluene, 100 °C, 1 h.

SCHEME 6



alkaloids. The required precursors were the iminophosphoranes (**9**) and the ketenes (**10**). We used two methods to prepare **9**: the Staudinger-type reaction[26] (Scheme 5) and the Mitsunobu reaction[27] (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/CH_3CO_2Na in a microwave oven,[30] followed by hydrolysis of the oxazolone with alkali and oxidation with hydrogen peroxide (Scheme 7). Dehydration of the homoveratric acid with dicyclohexylcarbodiimide and Et_3N in THF at 0 °C gave the desired ketenes in yields of around 80%.[31] The synthesis of the desired ketenes via a Wolff rearrangement of the diazaketone precursors gave much lower yields.

The electrocyclic aza-Wittig reaction between iminophosphoranes (**9**) and ketenes (**10**) gave the desired 3,4-dihydroisoquinolines (**12**) in 76−84% yield. When R_3 = N_3 in **10** the yield of **12** was only 30%, probably owing to a cycloaddition of the azide to the ketene. The bromine group in **9** was used to protect that position from cyclization at that position in the aza-Wittig reaction. When the bromine was replaced by hydrogen, a mixture of the two possible cyclization products **12d**,**e** was obtained. The bromine blocking group could be removed easily when $R_3 = OCH_3$, NO_2 and $R_1 = H$ with BuLi[32] at −10 °C, followed by the addition of H_2O or by reaction of **12a** with PPh_3.

TABLE 1. Yield of 16 as a Function of Temperature and Time

reaction	*T* (°C)	time (h)	yield (%)
1	5−10	2	30
2	0	2	54
3	−10 to −8	2	87
4	−10 to −8	4	87

The versatility of the aza-Wittig reaction for the preparation of isoquinolines was further demonstrated using 2-azido-1-(3,4-methylenedioxybenzene)propen-2-oate (**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).

With the desired 1-benzyl-3,4-dihydroisoquinolines in hand we turned to the synthesis of the target alkaloids. (±)-Didehydronorcularine (**16**) was synthesized from **13** ($R_3 = OCH_3$). *O*-Debenzylation with a catalytic amount of CF_3CO_2H/CCl_4 yielded phenol **18**. The corresponding aryloxenium (stepwise—in our opinion quite likely owing to the bulk of the leaving group) or oxeniumoid (concerted—shown in Scheme 4) was generated using a 1:1 ratio of the sodium salt of **18** and $C_6F_5I(OCOCF_3)_2$ (**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** (87%) 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,[33] 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** ($R_3 = NO_2$) 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

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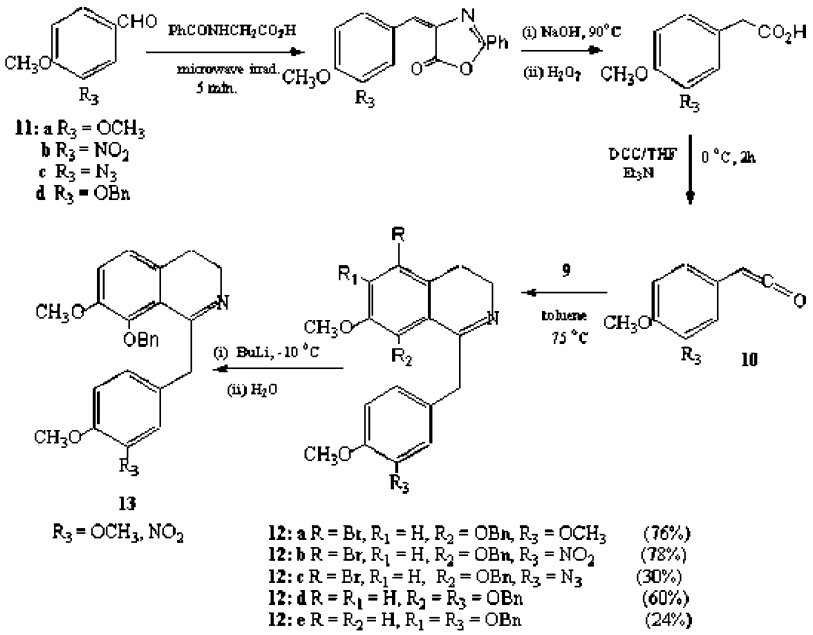
SCHEME 7



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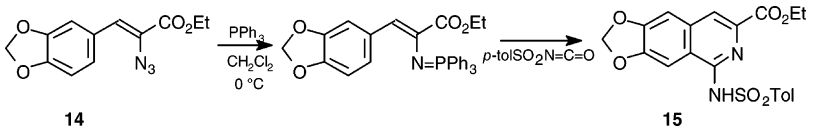
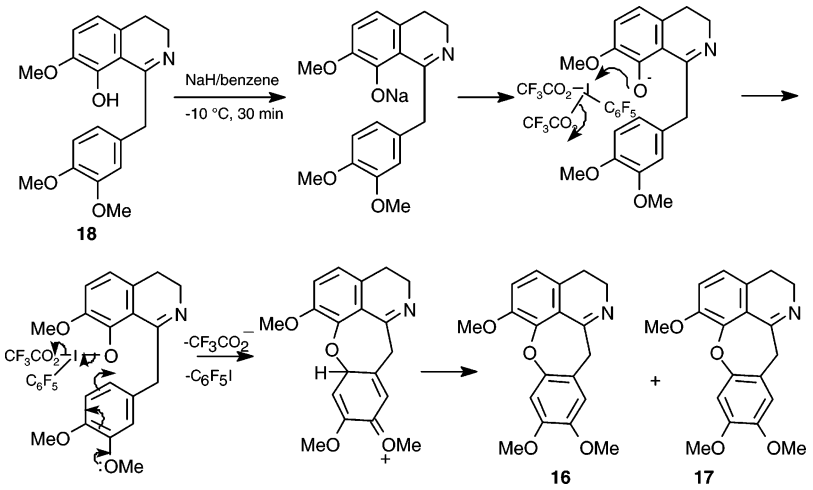


SCHEME 9



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).

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

reaction[a]	*T* (° C)	time (h)	yield (%)
1	25	10	28
2	0	10	51
3	−5	10	81
4	−5	15	81

[a] The ratio of TFMSA to TFA was the same in all cases.

The acid-catalyzed (TFMSA, TFA) decomposition of **20** as a function of time and temperature to give the

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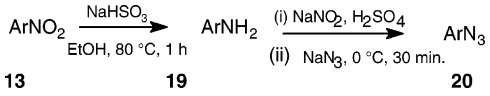
SCHEME 10



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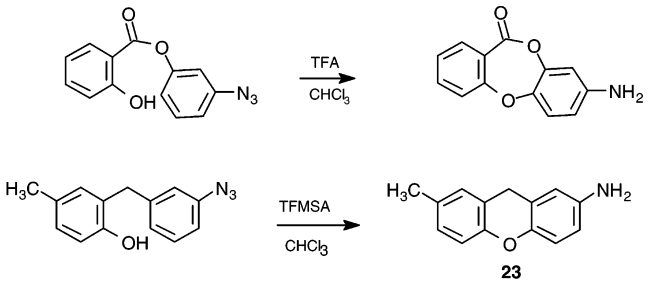
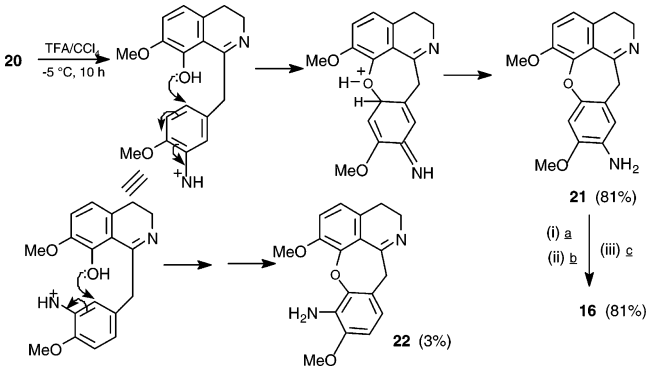


SCHEME 12 [a]



[a] Key: (a) $H_2SO_4/NaNO_2$/0 °C, 1 h; (b) H_2O, 60 °C, 2 h; (c) CH_2N_2.

intramolecular cyclization product **21** was monitored by TLC (Table 2).

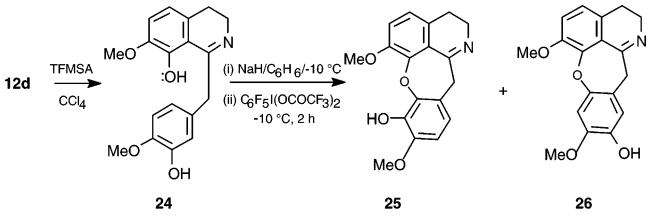
Tetracycle **16** was converted to (±)-cularine by *N*-methylation followed by reduction with sodium borohydride.[35]

The didebenzylation of **12d** was effected with TFMSA in CCl_4 to give the bis-phenol **24** in 89% yield. The latter was oxidized with $C_6F_5I(OCOCF_3)_2$, which resulted in the formation of 2,12-dihydro-6,9-dimethoxy-3*H*-[1]benzoxepino[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 C=N in the IR and exhibited ^{1}H 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 didehydronorcularine (**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).

(35) PC Model from Serena software and MMX force field derived from MM2 (QCPE−395, 1977) of N. L. Allinger, with π-VESCF routines from MMPI (QCPE−318), also of N. C. Allinger, as modified by J. McKelvery, J. J. Gajewski, and K. E. Gilbert.

SCHEME 13



We have carried out simple molecular modeling (MMX) calculations[36] 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-OH_2^+) **18**$^+$ 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-

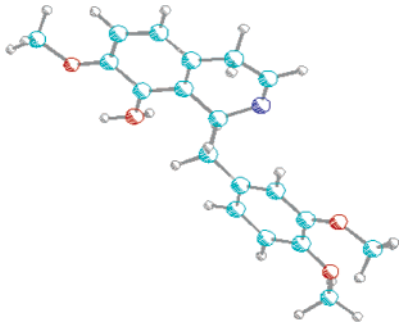


FIGURE 1. C8−OH protonated **18**. Distance from $C_8OH_2^+$ to position ortho to C3′-methoxy group: 5.913 Å. Distance from $C_8OH_2^+$ to position para to C3′-methoxy group: 4.594 Å.

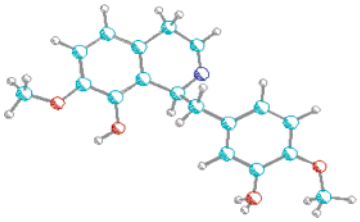


FIGURE 2. C3′-OH protonated **24**. Distance from position ortho to C3′-OH_2^+ to 8-OH group: 4.366 Å. Distance from position para to C3′-OH_2^+ to 8-OH group: 5.599 Å.

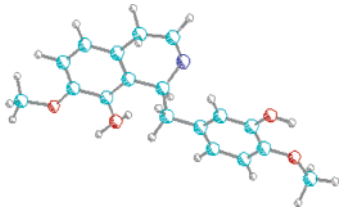


FIGURE 3. C8−OH protonated **24**. Distance between $C_8OH_2^+$ and position ortho to C3′-OH group: 5.768 Å. Distance between $C_8OH_2^+$ and position para to C3′-OH group: 4.597 Å.

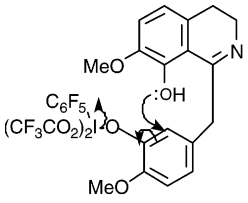
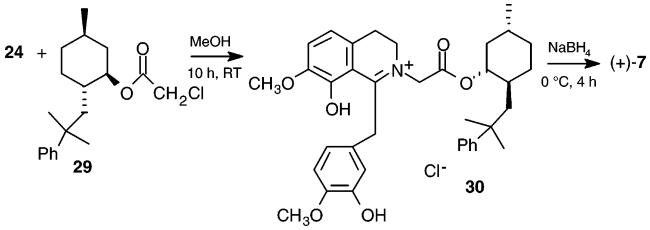


FIGURE 4. S_N2' mechanism.

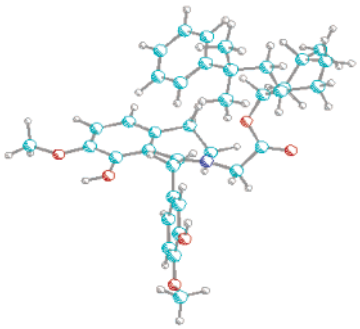
SCHEME 14



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 S_N2' 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.

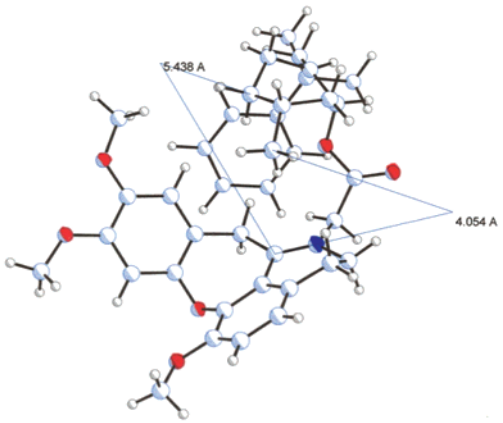
Bisphenol **24** was now *N*-alkylated with 2 equiv of the chiral auxiliary (+)-8-phenylmenthyl chloroacetate (**29**) in methanol at room temperature for 10 h, followed by reduction with sodium borohydride at 0 °C for 4 h, to yield (+)-crassifoline (**7**) in 91% yield (Scheme 14). The spectral properties were consistent with the structure of the molecule (see the Experimental Section). The optical rotation of (+)-**7** reported[6b] is $[\alpha]^{25}_D = +20.6$ (MeOH). The observed rotation for (+)-**7** was $[\alpha]^{25}_D = +18.2$ (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 decarboxylation. 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.

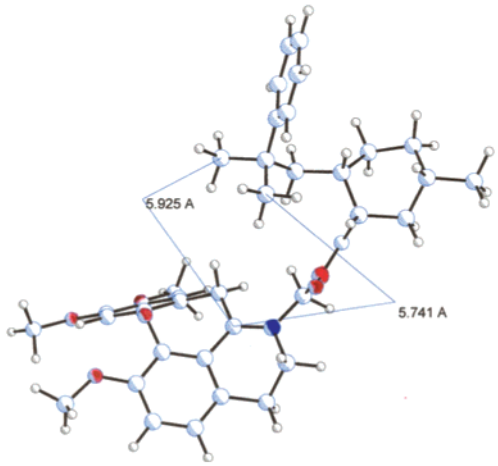


30a

(±)-Didehydronorcularine (**18**) was similarly reductively methylated using **29** to give (+)-cularine in 94% yield [mp 114−115 °C (lit.[37] mp 115 °C); $[\alpha]^{25}_D = +284.3$ (MeOH) (lit.[34] $[\alpha]^{25}_D = +285.0$, corresponding to an ee > 99%)]. 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.[36] mp 126−127 °C); $[\alpha]^{25}_D = +323.5$ (MeOH)].



31a



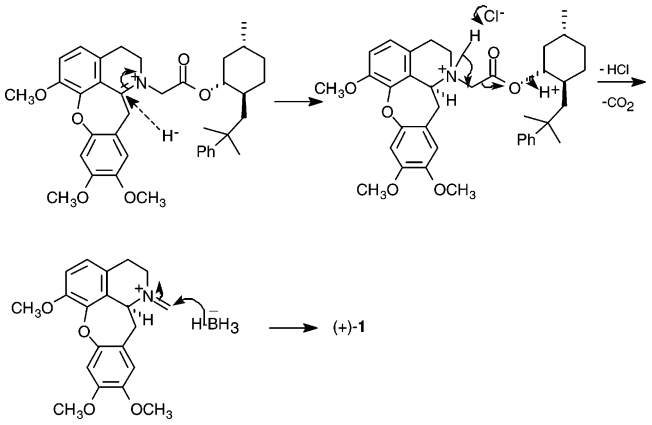
31b

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); $[\alpha]^{25}_D$ +384 (MeOH) (lit.[6b] $[\alpha]^{25}_D$

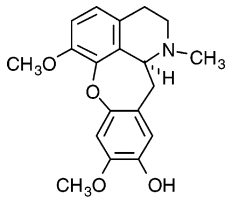
(36) Kametani, T.; Shibuya, S. *J. Chem. Soc.* **1965**, 5565.

(37) Jackson, A. A.; Stewart, G. W.; Charnod, G. A.; Martin, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1911.

SCHEME 15



+385.4 (MeOH)); ee > 99%]. The latter was *O*-methylated to give (+)-sarcocapnine (**6a**) in 97% yield, whose hydrochloride had mp 212−213 °C (lit.[6a] mp 213−215 °C); $[\alpha]^{25}_D$ = +217 (EtOH) (lit.[6a] $[\alpha]^{25}_D$ = +218) (ee > 99%).



32

Since HCl is liberated in the first step of the stereoselective reduction using **29**, protonation of the tetrahydroisoquinoline nitrogen may take place, facilitating decarboxylation. Carbon dioxide evolution was detected by its absorption with $Ba(OH)_2$ solution. Very small amounts of 8-phenylmenthane and 8-phenylmenthol were separated by TLC. No other products could be 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 (±)-didehydronorcularine, -sarcoconine, -norcularine, 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 diastereselective reductive *N*-methylation of these compounds, resulting in the synthesis of (+)-crassifoline (**7**), (+)-*O*-demethylcularine (**32**), (+)-cularine (**1**), (+)-sarcocapnine (**6a**), and (+)-sarcocapnidine (**6b**) in high yield and excellent enantiomeric excess.

Experimental Section

All solvents used were anhydrous.

3-Benzyloxy-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-4-methoxy-*β*-nitrostyrene[38] (500 mg, 1.37 mmol) in THF (15 mL) which was then boiled under reflux for 8 h. Addition of water followed by extraction with ether and drying the ether layer (K_2CO_3) gave the corresponding phenethylamine, which was purified by column chromatography on silica gel (hexane−CH_2Cl_2, 6:4 v/v): yellow oil (330 mg, 72%); IR (film) 3379 cm^{-1}; NMR (CCl_4) δ 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_2Cl_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*-triphenylphosphonium chloride (220 mg) as a yellow solid: mp 172−173 °C (79% yield); IR (KBr) 3600−3300 (NH), 1430 (CP), 1020 (NP); NMR ($CDCl_3$) δ 7.55 (m, 21H), 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 recystallization form acetone/chloroform (1:1 v/v) gave **9** (R = Br) (180 mg, 95%) as a yellow solid: mp 152−153 °C; NMR ($CDCl_3$) δ 7.56 (m, 21H), 6.80 (s, 1H), 5.15 (s, 2H), 3.78 (s, 3H), 3.10 (m, 4H). Anal. Calcd for $C_{34}H_{31}BrNO_2P$: C, 68.46; H, 5.24; N, 2.35. Found: C, 68.48; H, 5.25; N, 2.36.

Method B. Anhydrous $CrCl_3$[39] (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-4-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_2SO_4), filtration, and evaporation gave 3-benzyloxy-6-bromo-4-methoxy-(*E*)-*β*-chlorostyrene (1.96 g, 89%) as a yellow oil: IR (film) 3060−3020, 1670 cm^{-1} (RCH=CHCl); NMR (CCl_4) δ 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 LAH (710 mg, 18.7 mmmol) in THF at 0 °C. 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_2Cl_2. The extract was dried (Na_2SO_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) δ 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. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74. Found: 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.[40] 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_2Cl_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) δ 7.39 (s, 1H), 7.28 (m, 5H), 6.70 (s, 1H), 5.02 (s, 2H), 4.60 (s, 1H), 3.80 (s, 3H), 3.63 (t, 3H), 2.65 (t, 2H). Anal. Calcd for $C_{16}H_{17}BrO_3$: 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 HN_3 [prepared from NaN_3 (2.2 g) in benzene:[41] CAUTION!] 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

(38) Vinogradova, V. I.; Yunusov, M. S.; Kuchin, A. V.; Tolchikov, G. A.; Sagindytov, R. T.; Khalmuratov, Kh. A.; Alimov, A. *Khim. Prir. Soeden.* **1990**, 67; *Chem. Abstr.* **1990**, *113*, 11479.

(39) Moeler, T. *Inorg. Synth.* **1957**, *V*, 153.

(40) Kano, S.; Yuaso, Y.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1979**, 796.

(41) Wolff, H. In Organic Reactions; J. Wiley & Sons: New York, 1967; Vol. III, Chapter 8..

3-benzyloxy-4-methoxyphenethyltriphenylphosphorane (**9**, R = H) in 94% yield, mp 150−151 °C.

Syntheses of Ketenes 10 (R_3 = OCH_3). Method A. 4-(3,4-Dimethoxyphenylmethylidene)-2-phenyl-5(4)-oxazolone was synthesized in 76% yield and 2.5 h reaction time by the procedure of Buck and Ide[42] using conventional heating.

Method B. Solvent-Free Conditons. 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 Erlenmeyer flask and triturated to produce a semi-homogeneous mixture. The flask was plugged 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.

Homoveratric acid was synthesized from the azalactone using a literature method[43] to give the acid in 83% yield: mp 97−98 °C.

3,4-Dimethoxyphenylketene (**10**) was prepared using the method of Olah et al.[32] (who used it to prepare alkylketenes from alkylacetic acids), using DCC and catalytic amounts of Et_3N. **10** was obtained in 78% yield: mp 81−82 °C; IR (KBr) 2118 cm^{-1} (−C═C═O); NMR ($CDCl_3$) δ 8.10 (d, 1H, J = 1.18Hz), 7.95 (dd, 1H, J = 8.4 and 1.8 Hz), 7.10 (s, 1H), 6.80 (dd, 1H, J = 8.4 Hz), 3.88 (s, 3H), 3.87 (s, 1H).

Synthesis of 5-Bromo-8-benzyloxy-1-(3,4-dimethoxybenzyl)-7-methoxy-3,4-dihydroisoquinoline (12a) Using an Aza-Wittig Reaction. To a solution of iminophosphorane **9** (R = Br) (1.0 g, 1.68 mmol) in toluene at 0 °C under dry N_2 was added a solution of ketene **10** (R_3 = 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═N); ^{1}H NMR ($CHCl_3$) δ 7.50, (m, 5H), 7.35 (s, 1H), 7.10 (d, 1H, J = 2.3 Hz), 7.04 (d, 1H, J = 8.3 Hz), 6.92 (dd, 1H, J = 8.3, 2.3 Hz), 5.02 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 3.10 (s, 2H), 2.55 (t, 2H), 2.25 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 37.3, 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, 151.3,159.2. Anal. Calcd for $C_{26}H_{26}BrNO_4$: C, 62.91; H, 5.28; N, 2.82. Found: C, 62.91; H, 5.26; N, 2.82.

Synthesis of 13 (R = CH_3O). Using Triphenylphosphine:[44] A solution of **12a** (R = Br) (300 mg, 0.60 mmol) and Ph_3P (160 mg, 0.60 mmol) was stirred and boiled under reflux for 10 h. The cooled solution was stirred with cold water (30 mL) for 1 h and extracted with benzene. The extract was dried (K_2CO_3) and evaporated to give **13** (R = MeO) (160 mg, 65%): mp 142−143 °C (petroleum ether); IR (KBr) 1627 (C═N), 1183 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.45 (m, 5H), 7.18 (d, 1H, J = 8.3 Hz), 7.08 (d, 1H, J = 2.3 Hz), 7.05 (d, 1H, J = 8.3 Hz), 6.99 (d, 1H, J = 8.3 Hz), 6.95 (dd, 1H, J = 8.3, 2.3 Hz), 5.01 (s, 2H), 3.84, (s, 3H), 3.81, (s, 3H), 3.77 (s, 3H), 3.10 (s, 2H), 2.53 (t, 2H), 2.24 (t, 2H). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80, H, 6.52; N, 3.35. Found: C, 74.81; H, 6.51; N, 3.35.

Using BuLi. To a solution of **12a** (R = Br) (250 mg, 0.50 mmol) in THF (15 mL) at −10 °C was added with stirring *n*-BuLi (2.0 mL, 2.4 M in hexane). After 1 h, the temperature was raised to 5 °C and kept there for 2 h. Standard workup gave pure **13** (R = MeO) (92% yield).

Synthesis of 18. A solution of **13** (R_3 = MeO) (100 mg, 0.31 mmol) and TFMSA (40 mg, 0.27 mmol) was stirred at 60 °C for 3 h. The solution was extracted with water repeatedly, dried (K_2CO_3), and evaporated to give **18** (65 mg, 83%): mp 137−138 °C (petroleum ether); IR (KBr) 3437 (OH), 1626 cm^{-1} (C═N); NMR ($CDCl_3$) δ 7.16 (d, 1H, J = 8.3 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.02 (d, 1H, J = 8.3 Hz), 6.98 (d, 1H, J = 8.3 Hz), 6.93 (dd, 1H, J = 8.3, 2.3 Hz), 4.85 (s, 1H) (OH), 3.88 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.15 (s, 2H), 2.55 (t, 2H), 2.27 (t, 2H).

Oxidation of 18. To **18** (60 mg, 0.18 mmol) in toluene (15 mL) at −10 °C was added NaH (4.50 mg, 0.19 mmol), and the mixture stirred at that temperature for 30 min, at which point $C_6F_5I(OCOCF_3)_2$ (**8**)[23] (104 mg, 0.20 mmol) was added and stirring at −10 °C was continued for 2 h. The solution was dried (K_2CO_3) and evaporated to give a mixture of **16** and **17** (53.04 mg, 89% yield), which was separated by preparative layer chromatography (SiO_2 gel, $CHCl_3$/MeOH 99:1 v/v).

16 (51.85 mg, 87%): mp 128−129 °C (petroleum ether); IR (KBr) 1624 (C═N), 1260 cm^{-1} (ArOAr); NMR ($CDCl_3$) δ 6.87 (d, 1H, J = 8.5 Hz), 6.86 (s, 1H), 6.78 (d, 1H, J = 8.5 Hz), 6.52 (1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.10 (s, 2H), 2.55 (t, 2H), 2.40 (t, 2H); ^{13}C NMR δ 20.8, 35.8, 43.5, 58.2, 58.6, 60.6, 113.4, 116.3, 117.2, 118.3, 128.7, 129.4, 129.9, 149.3, 149.7, 149.9, 150.8, 151.1, 158.7; MS m/z 325 ($M^{\bullet+}$, 35.9, 310 (100), 294 (69.7) 224 (5.8), 190 (5.4),159 (12.2). Anal. Calcd for $C_{19}H_{18}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.16; H, 5.85; N, 4.32.

17 (1.10 mg, 2%): mp 131−132 °C. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.16; H, 5.86; N 4.31.

Synthesis of 16 via a Nitrenium Ion. Compound **12b** (see the Supporting Information) was debrominated using Ph_3P or BuLi as described for **12a** (Supporting Information) to give **13** (R_3 = NO_2). The latter (100 mg, 0.20 mmol) was dissolved in EtOH (2.5 mL) to which was then added sodium thiosulfate (350 mg, 2.20 mmol) in water (2.5 mL), and the solution was boiled under reflux for 1 h. On cooling the solution, a precipitate formed and was recrystallized with 40% aq pyridine to give **13** (R_3 = NH_2) (82 mg, 88%): mp 164−165 °C; IR (KBr) 3509 d (NH_2), 1624 cm^{-1} (C═N); NMR ($CDCl_3$) δ 7.32 (m, 5H), 6.85 (d, 1H, J = 8.7 Hz), 6.79 (d, 1H, J = 8.7 Hz), 6.75, (dd, 1H, J = 8.7, 2.0 Hz), 6.71 (d, 1H, J = 2.0 Hz), 6.69 (d, 1H, J = 8.7 Hz), 5.03 (s, 2H), 4.80 (s, 2H) (NH_2), 3.83 (s, 3H), 3.80 (s, 3H), 3.14 (s, 2H), 2.57 (t, 2H) 2.27 (t, 2H). Anal. Calcd for $C_{25}H_{26}N_2O_3$: 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_3) (72 mg, 83%) as a yellow solid: mp 149−150 °C; IR (KBr) 2138 (N_3), 1627 cm^{-1} (C═N); NMR ($CDCl_3$) δ 7.30 (m, 5H), 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 $C_{25}H_{24}N_4O_3$: 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_3) (70 mg, 0.16 mmol) in CCl_4 (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 extracted with water, and the organic layer was dried (K_2CO_3) and evaporated to give a mixture of **22** (81%) and **23** (∼3%). The mixture was resolved using TLC ($CHCl_3$/MeOH 99:1 v/v). **22** (41.31 mg): mp 135−136 °C (petroleum ether); IR (KBr) 3450−3555 d (NH_2), 1625 cm^{-1} (C═N); ^{1}H NMR ($CDCl_3$) 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) (NH_2), 3.83 (s, 3H), 3.76 (s, 3H), 3.05 (s, 2H), 2.54 (t, 2H) 2.37 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 22.8, 40.2, 45.7, 58.1, 60.1, 118.1, 118.9, 119.5, 123.1, 129.8, 132.1, 132.4, 148.1, 140.8, 150.1, 151.8, 152.3, 160.3. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.86; N, 9.03. Found: C, 69.69; H, 5.81; N, 9.04. **23** (1.44 mg): mp 138−139 °C. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.69; H, 5.88; N, 9.05. **22**: mp 138−139 °C. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.86; N, 9.03. Found: C, 69.66; H, 5.85; N, 9.03.

22 (30 mg, 0.10, 0.10 mmmol) was diazotized with aq 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 extracted with ether, the solvent was evaporated, and the residue was treated with diazomethane in ether to

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give pure **16** (25.47 mg, 81%), whose physical properties were identical to those described above.

Synthesis of (±)-Cularine (±-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, 4.9 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 (K_2CO_3), and evaporation of the filtered solvent and recrystallizing the residue (petroleum ether) gave (±)-cularine (23.14 mg, 89%): mp 113−114 °C (lit.[33] mp 113−114 °C).

Synthesis of (+)-Cularine. (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, 4.9 mmol) was added with stirring. The mixture was then stirred for 4 h at rt. Workup as above and separation of the resulting mixture by TLC ($CHCl_3$−hexane−MeOH 75:24:1 v/v) gave (+)-cularine (**1**) (34.52 mg, 94%): mp 114−115 °C (petroleum ether) (lit.[36] mp 115 °C); $[\alpha]^{25}_D = +284.3$ (MeOH) (lit.[37] $[\alpha]^{25}_D = +285$); IR (KBr) 2385 cm^{-1} (NCH_3); NMR ($CDCl_3$) δ 6.87 (d, 1H, J = 8.5 Hz) 6.85, s, 1H), 6.77 (d, 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. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.36; H, 6.80; N, 4.11. Also isolated were **29** (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 TFMSA (81 mg, 0.54 mmol) were heated for 8 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═N); ^{1}H NMR δ 6.85 (d, 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); ^{13}C 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. Calcd for $C_{18}H_{19}NO_4$: 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 (SiO_2, $CHCl_3$−hexane−MeOH 75:24:1 v/v).

25 (98.6 mg, 58%): mp 143−144 °C; IR (KBr) 3483 (OH), 1626 cm^{-1} (C═N); ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 1H), 6.95 (d, 1H, J = 8.5 Hz), 6.76 (d, 1H, J = 8.5 Hz), 6.68 (d, 1H, J = 8.5 Hz), 6.55 (d, 1H, J = 8.5 Hz), 3.88 (a, 3H), 3.86 (s, 3H), 3.33 (s, 2H), 2.57 (t, 2H), 2.45 (t, 2H). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.44; H, 5.49; N, 4.50.

26 (61.2 mg, 36%): mp 135−136 °C; IR (KBr) 3561 (OH), 1624 cm^{-1} (C═N); ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 1H, J = 8.5 Hz), 6.83 (s, 1H), 6.78 (d, 1H, J = 8.5 Hz), 6.59 (s, 1H), 4.90 (s, 1H (OH)), 3,87 (s, 3H) 3.84 (s, 3H), 3.30 (s, 2H), 2.56 (t, 2H), 2.43 (t, 2H). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.46; H, 5.51; N, 4.51.

Synthesis of (+)-Demethylcularine (32). As was described for the asymmetric synthesis of (+)-cularine, **26** (75 mg, 0.24 mmol) was converted into (**32**) (75.05 mg, 95%) using **29** followed by $NaBH_4$ and purification by column chromatography on silica gel ($CHCl_3$/MeOH, 99:1 v/v): mp 127−128 °C (lit.[38] mp 126−127 °C); $[\alpha]^{25}_D = +323.5$ (MeOH)); IR (KBr) 3555 (OH), 2380 cm^{-1} (NMe); ^{1}H NMR ($CDCl_3$) 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 = 12.0, 4.5 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.25 (dd, 1H, J = 15.8,d 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). **32** (55 mg) was converted to **(+)-cularine** (56 mg, 98%) (identical with that synthesized above) using an ethereal solution of diazomethane.

Synthesis of (+)- Sarcocapnidine (6b). Starting from **25** (55 mg, 0.17 mmmol), **6b** (54 mg, 93%) was synthesized in the same way as **7**: mp 125−126 °C (lit.[6b] mp 126−127 °C); $[\alpha]^{25}_D = +384$ (MeOH) (lit.[6b] $[\alpha]^{25}_D = +385.4$, MeOH); IR (KBr) 3486 (OH), 2378 cm^{-1} (NMe); ^{1}H NMR ($CDCl_3$) δ 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).

Synthesis of (+)-Sarcocapnine (6a). An ethereal solution of diazomethane was added to a solution of **6b** (36 mg. 0.11 mmol) to give **6a** (37 mg, 97%) as a viscous yellow oil, which was crystallized as the hydrochloride (MeOH/HCl): mp 212−213 °C (lit.[6a] mp 213−215 °C); $[\alpha]^{25}_D = +217$ (EtOH) (lit.[6a] $[\alpha]^{25}_D = +218$); IR of the oil (film) 2379 cm^{-1} (NMe); ^{1}H NMR (of the oil) ($CDCl_3$) δ 6.85 (d, 1H, J = 8.6 Hz), 6.78 (d, 1H, J = 8.5 Hz), 6.75 (d, 1H, J = 8.6 Hz), 6.56 (d, 1H, J = 8.5 Hz), 4.30 (dd, 1H, J = 10.7, 3.7 Hz), 3.91 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 3.36 (d of d, 1H, J = 15.8, 3.7 Hz), 3.17 (d of d, 1H, J = 15.8, 10.7 Hz), 2.73 (t, 2H), 2.54 (s, 3H) 2.50 (t, 2H).

Synthesis of (+)-Crassifoline (7). In the same way as **1** was synthesized using **29** and $NaBH_4$, so was **24** (30 m, 0.096 mmol) converted to (+)-crassifoline (28.69%, 91%): mp 62−63 °C (petroleum ether) (lit.[37] mp 61−63 °C); $[\alpha]^{25}_D = +18.2$ (MeOH) (lit.[6b] $[\alpha]^{25}_D = +20.6$). IR (KBr) 3554 (OH), 2375 cm^{-1} (NMe); ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, J = 9 Hz), 6.84 (d, 1H, J = 2.3 Hz), 6.79 (dd, 1H, J = 9, 2.3 Hz), 6.73 (d, 1H, J = 9 Hz), 6.58 (d, 1H, J = 9 Hz), 4.88 (s, 2H), 4.12 (dd, 1H, 8.7, 3.9 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.22 (dd, 1H, J = 14, 3.9 Hz), 3.05 (dd, 1H, J = 14, 8.7 Hz), 2.52 (t, 2H, 2.40 (t,2H), 2.37 (s, 3H).

Synthesis of 2-Amino-7-methylxanthene (21). 3-Azido-2′-hydroxy-5′-methyldiphenylmethane (0.478 g, 2.0 mmol) in $CHCl_3$ (30 mL) was cooled to −20 °C and then treated with TFMSA (0.330 g, 2.2 mmol). It was stirred at that temperature for 6 h and then kept at room temperature overnight. After addition of water, the organic layer was dried (K_2CO_3) and the product was isolated by column chromatography (SiO_2, CH_2Cl_2/EtOAc 3:1 v/v) and recrystallized from hexane to give **21** (0.171 g, 36%) as a yellow solid: mp 147−148 °C; IR (KBr) 3460, 3400, 3370, 3320, 1640, 1612, 1500, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.40−6.96 (m, 6H), 3.38 (s, 2H), 3.35 (br, 2H), 2.22 (s, 3H);. MS m/z 211 (100, $M^{\bullet+}$), 210 (95). Anal. Calcd for $C_{14}H_{15}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.55; H, 6.18; N, 6.59.

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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_3 = NO_2, N_3, OCH_2Ph), and compounds **12b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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