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Asymmetric Synthesis of All the Known Phlegmarine Alkaloids

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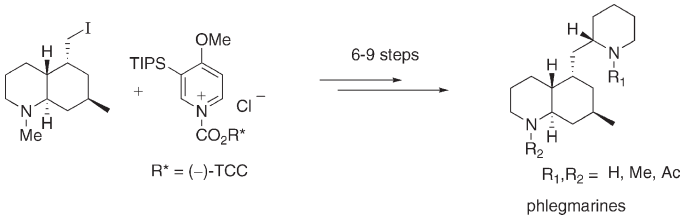
Received October 5, 2010



The asymmetric synthesis of all four of the known natural phlegmarines and one synthetic derivative has been accomplished in 19−22 steps from 4-methoxy-3-(triisopropylsilyl)pyridine. Chiral *N*-acylpyridinium salt chemistry was used twice to set the stereocenters at the C-9 and C-2′ positions of the phlegmarine skeleton. Key reactions include the use of a mixed Grignard reagent for the second *N*-acylpyridinium salt addition, zinc/acetic acid reduction of a complex dihydropyridone, and a von Braun cyanogen bromide *N*-demethylation of a late intermediate. These syntheses confirmed the absolute stereochemistry of all of the known phlegmarines.

Introduction

The lycopodiaceous plants have produced numerous and structurally interesting alkaloids that have proven to be challenging targets for total synthesis.[1] One of the *Lycopodium* alkaloids, huperzine A, is a potential therapeutic agent for treatment of Alzheimer's disease.[2] This medicinally important compound has spurred the isolation of several new *Lycopodium* alkaloids having various biological activities including cytotoxicity.[3] The discovery of significant biological activities among the *Lycopodium* alkaloids has prompted renewed interest in the development of new synthetic strategies for their preparation.[4] As part of our natural product synthesis program,[5,6] we have examined approaches to the phlegmarine alkaloids.

The phlegmarines are a $C_{16}N_2$ skeletal group of *Lycopodium* alkaloids discovered by Braekman and co-workers in 1978.[7a]

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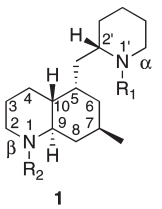
Published on Web 11/15/2010 DOI: 10.1021/jo1019688



1

1a, R_1=	H, R_2 = H	phlegmarine
b, R_1=	H, R_2 = Me	N_β-methylphlegmarine
c, R_1=	Me, R_2 = H	N_α-methylphlegmarine
d, R_1=	Ac, R_2 = Me	N_α-acetyl-N_β-methylphlegmarine
e, R_1=	Me, R_2 = Ac	N_α-methyl-N_β-acetylphlegmarine

FIGURE 1. Structures of the four known phlegmarine alkaloids and derivative **1e**.

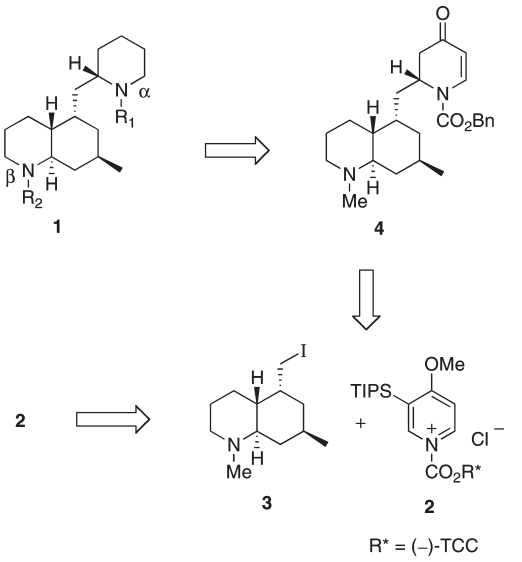
All four naturally occurring members of this group (**1a**−**d**) possess the same skeleton and differ only by their nitrogen atom substituents.[7b] Synthesis and spectroscopic structure studies carried out by Braekman's group[7a] determined the basic carbon skeleton, but it was not until the work of MacLean[8] and coworkers that the relative stereochemistry of all five stereogenic centers of the phlegmarines was defined. The absolute stereochemistry of these alkaloids was established in our laboratories through the asymmetric total synthesis of (−)-N_α-acetyl-N_β-methylphlegmarine (**1d**).[4c] We report herein the total synthesis of all the known phlegmarine alkaloids **1a**−**d**, and the N_β-acetyl derivative **1e** (Figure 1).

Results and Discussion

Our strategy for synthesizing the phlegmarines is depicted in Scheme 1. All of the alkaloid targets were to be prepared from the common dihydropyridone intermediate **4**, which would arise from the key fragment **3** and chiral 1-acylpyridinium salt **2**. Fragment **3** would also be prepared from the same antipode of **2** by a modification of our published procedure.[4c]

The Grignard of (*R*)-5-chloro-4-methylpentene[9] was added to chiral *N*-acylpyridinium salt **2**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[10] and the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC),[11] to give the crude *N*-acyldihydropyridone **5** in 90% yield and 88% de (Scheme 2). Purification by recrystallization from ethanol provided a 76% yield of the major diastereomer **5** as an isomerically pure white solid. A one-pot reaction of **5** with NaOMe/MeOH followed by aqueous 10% HCl furnished dihydropyridone **6** in 95% yield with 95% recovery of the chiral auxiliary, (−)-TCC. *N*-Acylation of **6** with *n*-BuLi and phenyl chloroformate gave a quantitative yield of enantiopure carbamate **7**. Conjugate reduction of **7** can be effected

SCHEME 1



with L-Selectride/$BF_3 \cdot OEt_2$[4c] (86% yield) or more conveniently with Zn/AcOH[12] to give **8** in 93% yield. Ozonolysis of the terminal alkene of **8** provided a high yield of aldehyde **9**, which on acid-mediated cyclization[13] was converted efficiently to bicyclic enone **10**.

The next step required a facial selective conjugate addition of a nucleophile containing the latent functionality of a hydroxymethyl group. Based on our earlier model studies,[14] (dimethylphenylsilyl)methylmagnesium chloride was chosen for use in a copper-mediated 1,4-addition to enone **10**. The resulting facial selectivity was anticipated to be high based on conformational and stereoelectronic arguments. Due to $A^{(1,3)}$ strain,[15] the reactive conformation is concave as shown in Figure 2. Stereoelectronically controlled axial attack of the nucleophile at C-5 would afford the desired stereochemical outcome. In the presence of copper iodide, addition of Grignard **11** to **10** and trapping of the resulting enolate with *N*-(5-(chloro-2-pyridyl)triflimide[16] provided a 96% yield of vinyl triflate **12**. Since protonation of the enolate leads to the cis-fused ring juncture,[14] in situ vinyl triflate formation was necessary to set up the eventual incorporation of the required stereochemistry at C-10. The vinyl triflate function would not survive the subsequent hydrolysis of the carbamate group, so **12** was cleanly reduced to the more stable alkene **13** using Cacchi's conditions.[17]

Carbamate hydrolysis using KOH/2-propanol at reflux gave a high yield of the secondary amine **14**. The use of 2-propanol was essential to obtaining a clean product, for the analogous reaction with KOH/ethanol gave a significant amount of the corresponding ethyl carbamate via carbamate

(7) (a) Nyembo, L.; Goffin, A.; Hootele, C.; Braekman, J.-C. *Can. J. Chem.* **1978**, *56*, 851. For the recent isolation and synthesis of related phlegmarine-type *Lycopodium* alkaloids, see: (b) Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, *74*, 8675 and references cited therein.

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(9) The chloride was prepared (NCS, Ph_3P, CH_2Cl_2) from the known enantiopure alcohol, see: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

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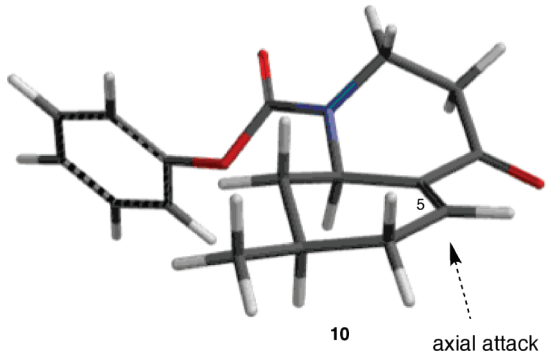
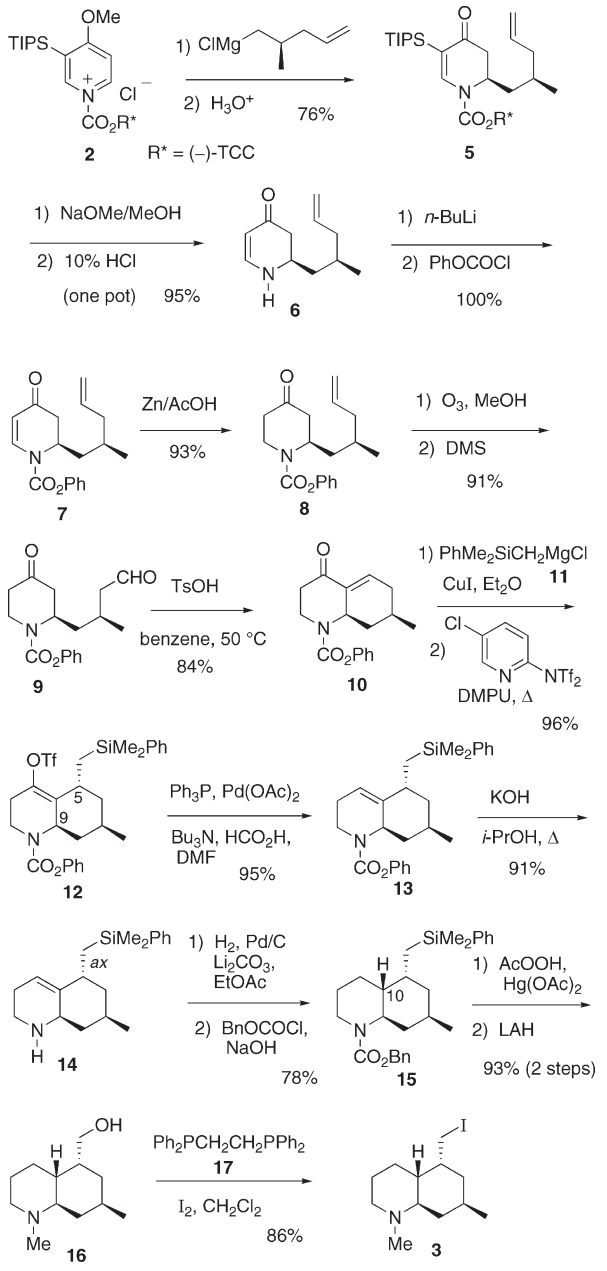


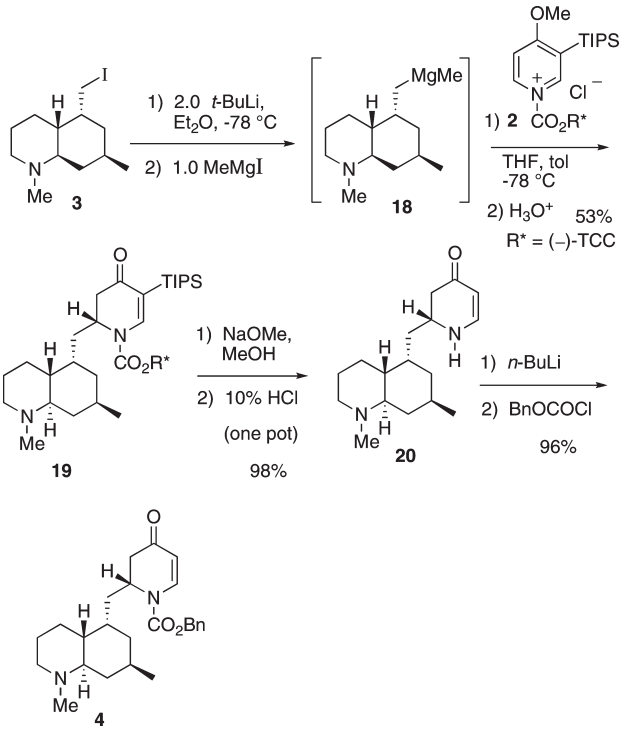
FIGURE 2. Calculated lowest energy conformation of **10** (MMFF).

SCHEME 2



exchange. Catalytic hydrogenation of **14** provided an 89/11 mixture of crude amines that were converted to Cbz carbamate **15** (78%) and the corresponding cis C-10 epimer. The trans selectivity can be attributed to significant shielding of the bottom face of the alkene in **14** by the axial (phenyldimethylsilyl)methyl group. Oxidation using Fleming's conditions[18] and subsequent lithium aluminum hydride reduction gave amino alcohol **16** in high yield. Conversion to iodide **3** was effected using 1,2-*bis*-(triphenylphosphino)ethane (**17**) and I_2.[19] This method proved superior to the more common procedure using triphenylphosphine/I_2 due to ease of product purification.

SCHEME 3

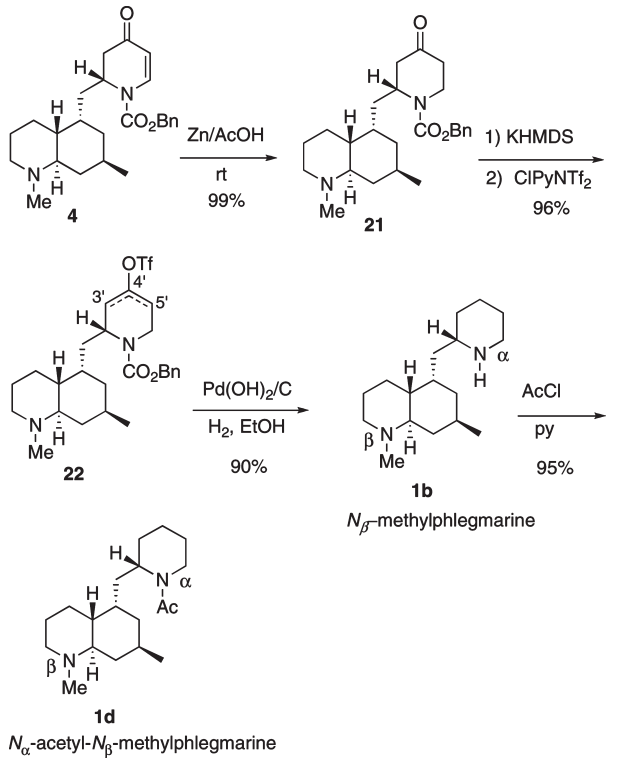


The key intermediate **4** was prepared as shown in Scheme 3. The mixed Grignard reagent **18** was prepared from iodide **3**, by lithium-halogen exchange and addition of methylmagnesium iodide, and treated with 2 equiv of *N*-acylpyridinium salt **2** to give dihydropyridone **19** in 53% yield. The five stereocenters were correctly installed as determined by single-crystal X-ray analysis.[4c] The TIPS group and TCC auxiliary were removed from **19** in one step using our standard procedure to afford **20**, which was converted to key intermediate **4** in high yield on lithiation and treatment with benzyl chloroformate. With the intermediate **4** in hand, the five target alkaloids were prepared as described below.

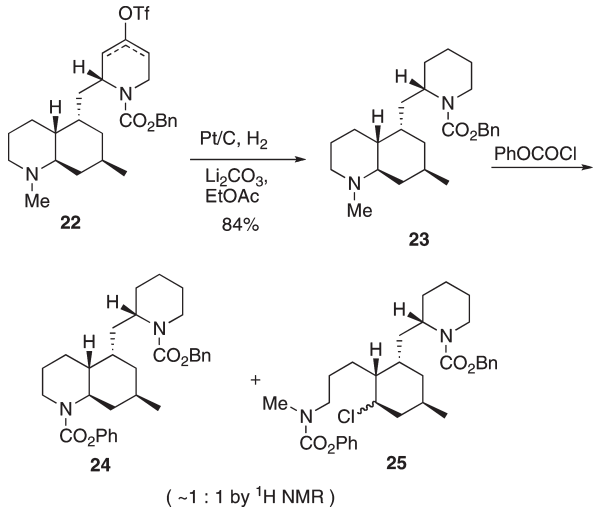
***N*$_\beta$-Methylphlegmarine (1b) and *N*$_\alpha$-Acetyl-*N*$_\beta$-methylphlegmarine (1d).** Conjugate reduction of **4** with zinc in acetic acid gave piperidone **21** in near quantitative yield (Scheme 4). Deprotonation with KHMDS and trapping with *N*-(5-chloro-2-pyridyl)triflimide provided the vinyl triflates **22** in a 3:1 ratio favoring olefin formation at the 4,′5′ position. Catalytic hydrogenation over Pearlman's catalyst afforded the natural product **1b**, which exhibited spectral data and optical rotation in agreement with its assigned structure.

(18) Fleming, I.; Sanderson, P. E. *Tetrahedron Lett.* **1987**, *28*, 4229.
(19) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *48*, 1313.

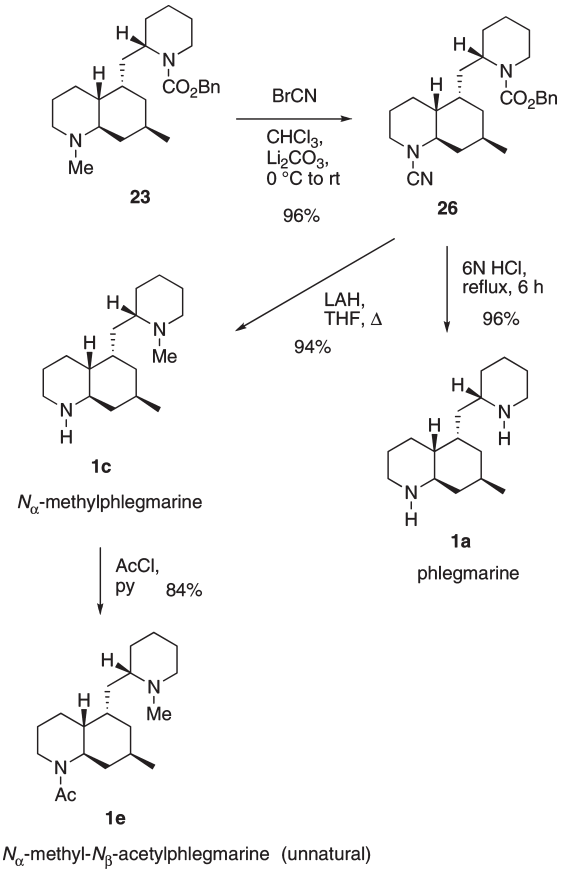
SCHEME 4



SCHEME 5



SCHEME 6



The alkaloid N_α-acetyl-N_β-methylphlegmarine (**1d**) was prepared in one step from **1b** by simple acetylation. Although the rotation of **1d** was higher than that previously reported for the natural product, all spectral data were in agreement with literature values.[7a]

Phlegmarine (1a), N_α-Methylphlegmarine (1c) and Unnatural N_α-Methyl-N_β-acetyl-phlegmarine (1e). To prepare the remaining two natural phlegmarines (**1a,c**) and the known synthetic derivative **1e** from intermediate **4**, a demethylation of the beta nitrogen would be required toward the end of the synthesis. The vinyl triflate mixture **22** was reduced selectively via hydrogenation over platinum on carbon to afford the benzyl carbamate **23** (Scheme 5). Initial attempts to *N*-demethylate **23** with phenyl chloroformate proved problematic giving an inseparable mixture of dicarbamate **24** and the ring-opened product **25** as determined by ^{1}H NMR and MS analysis. The use of other chloroformates[20] led to similar results with a poor ratio of products regardless of temperature, solvent, or the addition of additives (LiBr, LiCl). The von Braun demethylation reaction using cyanogen bromide[21] was examined next. To our delight, treatment of tertiary amine **23** with cyanogen bromide at rt gave a near quantitative conversion to cyanamide **26** (Scheme 6). When **26** was treated with dilute HCl at reflux, both the cyanamide and Cbz groups were hydrolyzed to the secondary amines providing natural phlegmarine (**1a**) in high yield. N_α-Methylphlegmarine (**1c**) was also prepared in excellent yield from **26** in one step by concomitant reduction of the cyanamide and carbamate groups with LAH. *N*-Acylation of **1c** afforded N_α-methyl-N_β-acetylphlegmarine (**1e**) in good yield. All three of our synthetic phlegmarines (**1a**,**c**,**e**) exhibited characterization data in agreement with literature values for the known compounds.

In summary, all four of the known phlegmarine alkaloids and one previously reported synthetic derivative have been synthesized enantiopure from key dihydropyridone intermediate

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(21) (a) von Braun, J. *Chem. Ber.* **1900**, *33*, 1438. Review: (b) Hageman, H. A. *Org. React.* **1953**, *7*, 198.

4. These syntheses have confirmed the absolute stereochemistry of the phlegmarines as 2′*S*, 5*S*, 7*R*, 9*R*, 10*R*. Our chiral *N*-acylpyridinium salt chemistry was used twice during the synthetic route to set the stereocenter at C-9 and the remote center at C-2′ of the phlegmarines. The syntheses ranged from 19 to 22 steps and were accomplished with excellent stereocontrol.

Experimental Section

The experimentals for compounds **5**−**10** and **12**−**17** have been previously published.[4c]

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1,7-dimethyl-5-ylmethyl)-1-[(benzyloxy)carbonyl]-2,3-dihydro-4-pyridone (4). To a cooled (−78 °C) solution of dihydropyridone **20** (58.2 mg, 211 μmol) in THF (5.0 mL) was added *n*-BuLi (84 μL, 230 μmol, 1.1 equiv) dropwise. The solution immediately turned bright yellow and became heterogeneous. After 10 min the anion was rapidly quenched with freshly distilled benzyl chloroformate (60 μL, 420 μmol, 2.0 equiv). The solution was allowed to stir for an additional 2.5 h and then a 50% saturated aqueous solution of $NaHCO_3$ (2.0 mL) was added. The aqueous phase was extracted with EtOAc (4 × 3.0 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered (Celite) and concentrated in vacuo. The crude oil was purified by radial PLC (silica gel, 75% EtOAc/hexanes, 2% TEA) to give **4** (82.7 mg, 96%) as a colorless oil. $[\alpha]_D^{24}$ + 6.0 (*c* 0.81, MeOH); IR (film, NaCl) 2922, 1725 (C═O), 1672 (O−C═O), 1603 (C═C), 1327, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6.3 Hz, 1H) 7.40−7.37 (m, 5H), 5.35−5.31 (m, 2H), 5.21 (d, *J* = 11.7 Hz, 1H), 4.55 (br s, 1H), 2.81−2.71 (m, 2H), 2.45 (d, *J* = 16.5 Hz, 1H), 2.21 (s, 3H), 1.98−1.89 (m, 2H), 1.79 (m, 1H), 1.63−1.28 (m, 9H), 1.13−0.66 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 152.5, 141.9, 135.0, 129.1, 129.0, 128.8, 107.2, 69.3, 62.7, 57.7, 52.2, 44.3, 43.0, 39.9, 38.3, 37.3, 34.5, 28.9, 26.6, 26.0, 25.6, 22.9; HRMS calcd for $C_{25}H_{34}N_2O_3$ $(M + H)^+$ 411.2648, found 411.2653.

2*R*-2-[(*R*)-2-Methyl-4-pentenyl]-1-(phenoxycarbonyl)-2,3,5,6-tetrahydro-4-pyridone (8).[4c] **Improved procedure.** To a rapidly stirred solution of dihydropyridone **7** (1.25 g, 4.18 mmol) in glacial acetic acid (38 mL) was added zinc powder (5.5 g, 84 mmol, 20 equiv) in small portions, to prevent the zinc from clumping. The mixture was allowed to stir for 17 h, filtered (Celite) and then concentrated in vacuo. The heterogeneous oil was purified by radial PLC (silica gel, 10−20% EtOAc/hexanes) to provide piperidone **8** (1.17 g, 93%) as a colorless oil. Spectral data is identical to that previously reported.

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1,7-dimethyl-5-ylmethyl)-1-[(1*R*,2*S*)-2-((1-methyl-1-phenyl)ethyl)-cyclohexyloxyl-oxycarbonyl]-5-(triisopropylsilanyl)-2,3-dihydro-4-pyridone (19).[4c] **Improved procedure.** The chiral *N*-acylpyridinium salt was prepared *in situ* by adding (−)-TCC chloroformate (253 mg, 901 μmol, 2.1 equiv) to a cooled (− 45 °C) solution of 3-(triisopropylsilyl)-4-methoxypyridine (241 mg, 901 μmol, 2.1 equiv) in toluene (27 mL). The solution was allowed to stir at −45 °C for 45 min followed by cooling to −78 °C before addition of the organometallic. The organometallic was prepared by dropwise addition of *t*-BuLi (559 μL, 944 μmol, 1.7 M in pentane, 2.2 equiv) to a cooled (−78 °C) solution of (4a*R*,5*S*,7*R*,8a*R*)-5-iodomethyl-1,7-dimethyl-1,2,3,4a,5,6,7,8,8a- decahydroquinoline[4c] (**17**) (132 mg, 429 μmol) in ether (9.0 mL). The solution was stirred for 45 min at −78 °C and then warmed to −42 °C (dry ice/acetonitrile) for 45 min. To the solution was added methylmagnesium iodide (154 μL, 429 μmol, 2.85 M in ether, 1.0 equiv), and the solution was allowed to stir for an additional 10 min. This solution was added dropwise via cannula over 3 min to the cooled (−78 °C) *N*-acylpyridinium salt solution. This mixture was allowed to stir for 5 h at −78 °C followed by addition of 10% $HCl_{(aq)}$ (4 mL). The mixture was allowed to warm to rt and stirred for an additional 30 min. The aqueous phase was made basic with solid K_2CO_3 and then extracted with EtOAc (5 × 3 mL). The combined organic phases were washed with brine (5 mL), dried (K_2CO_3), filtered (Celite), and concentrated in vacuo. The crude oil was purified by radial PLC (SiO_2, 50% EtOAc/hexanes, 1% TEA) providing **19** (198 mg, 69%) as a mixture of isomers at the newly generated stereocenter; diasteriomeric excess was found to be 84% by HPLC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.32−7.28 (m, 4H), 7.12 (t, *J* = 6.8 Hz, 1H), 4.89 (dt, *J* = 10.8, 4.4 Hz, 1H), 2.76 (d, *J* = 11.6 Hz, 1H), 2.64 (m,1H), 2.31 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.19 (s, 3H), 2.05−1.99 (m, 4H), 1.88−1.74 (m, 3H), 1.61−1.19 (m, 23H), 1.06−1.01 (m, 24H), 0.71 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 152.8, 152.2, 147.6, 128.3, 125.2, 125.1, 110.5, 77.8, 62.8, 57.7, 51.4, 50.7, 44.1, 43.0, 39.8, 39.5, 39.1, 37.5, 34.3, 33.8, 31.0, 28.9, 26.9, 26.8, 26.2, 26.0, 24.8, 23.0, 21.6, 19.0, 18.9, 11.3.

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1,7-dimethyl-5-ylmethyl)-2,3-dihydro-4-pyridone (20).[4c] **Improved Procedure.** Sodium methoxide (734 μL, 3.2 mmol, 4.36 M in MeOH, 10 equiv) was added to a suspension of **19** (217 mg, 320 μmol) in methanol (20 mL). The mixture was brought to reflux affording a homogeneous solution. The solution was refluxed for 17 h, allowed to cool to rt, and concentrated in vacuo. The residual oil was taken up in THF (20 mL) and then 10% $HCl_{(aq)}$ (2.0 mL), was added. The mixture was allowed to stir for 3 h. The acidic mixture was carefully quenched with $K_2CO_{3(s)}$ (∼500 mg). Anhydrous $K_2CO_{3(s)}$ (∼5−7 g) was then added until the solution appeared to be dry. The clumps of K_2CO_3 were broken up with a glass rod, and the mixture was filtered through Celite. The filter pad was washed with hot EtOAc (5 × 20 mL), and the filtrate was concentrated in vacuo. The crude oil was purified by radial PLC (silica gel, 50−100% EtOAc/hexanes, 1% TEA) to give the dihydropyridone **20** (86.9 mg, 98%) as an oil that solidified upon standing, mp 141−142 °C (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 7.6 Hz, 1H), 4.72 (br s, 1H), 3.65 (m, 1H), 2.83 (br d, *J* = 11.2 Hz, 1H), 2.49 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.54 (d, *J* = 16 Hz, 1H), 2.25 (s, 3H), 2.06 (m, 1H), 1.99 (m, 1H), 1.74−1.46 (m, 9H), 1.38 (m, 1H), 1.23 (m, 1H), 1.12 (dt, *J* = 13.0, 4.0 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.76 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 151.6, 98.7, 62.8, 57.6, 52.4, 44.2, 42.9, 41.5, 39.8, 38.5, 35.0, 32.1, 29.1, 26.0, 25.9, 22.9.

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1,7-dimethyl-5-ylmethyl)-1-[(benzyloxy)carbonyl]-4-piperidone (21). Zinc powder was added slowly to a rapidly stirred solution of **4** (24.6 mg, 60 μmol) in glacial acetic acid (1.0 mL). The reaction mixture was allowed to stir for 11 h, and then filtered through Celite, and the filter pad was washed with methanol (5 mL). The filtrate was concentrated in vacuo. The resulting amorphous solid was suspended in dichloromethane (5 mL) and passed through a plug of basic alumina (activity 2). The plug was washed with a 10% solution of methanol in dichloromethane (5 × 5 mL). The solution was concentrated in vacuo to provide a colorless oil. The crude material was purified by flash chromatography on silica gel (50% EtOAc/hexanes, 1% TEA) to provide **21** (24.6 mg, 99%) as a colorless oil. $[\alpha]_D^{23}$ −49 (*c* 0.69, $CHCl_3$); IR (film, NaCl) 2925, 2775 (N-Me), 1721 (C═O), 1698 (O−C(═O)N), 1422, 1233, 1104, 1005 cm^{-1}; ^1H NMR at 50 °C (300 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 5.24 (d, *J* = 9.0 Hz, 1H), 5.13 (d, *J* = 9.0 Hz, 1H), 4.59 (br s, 1H), 4.38 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.33 (ddd *J* = 11.2, 8.5, 2.9 Hz, 1H), 2.81 (br d, *J* = 8.4 Hz, 1H), 2.60 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.50 (ddd, *J* = 11.5, 8.5, 5.2 Hz, 1H), 2.34 (br d, *J* = 10.8 Hz, 1H), 2.22 (s, 3H), 2.04−1.94 (m, 2H), 1.64−1.42 (m, 9H), 1.30 (m, 1H), 1.20−1.12 (m, 1H), 1.03 (m, 1H), 0.83 (d, *J* = 4.2 Hz, 3H), 0.70 (q, *J* = 9.0 Hz, 1H); ^{13}C NMR at 50 °C (100 MHz, $CDCl_3$) δ 207.5, 155.5, 136.7, 128.8, 128.5, 128.4, 68.0, 63.1, 57.9, 52.3, 44.6 (2C,

determined by ^{13}C NMR at 70 °C in benzene-d_6 δ 45.5, 44.3), 43.0, 40.8, 40.1, 39.4, 39.1, 35.7, 31.2, 29.3, 26.2 (2C, determined by ^{13}C NMR at 70 °C in benzene-d_6 δ 26.9, 26.4), 22.9; HRMS calcd for $C_{25}H_{36}N_2O_3$ $(M + H)^+$ 413.2804, found 413.2797.

Mixture of Enol Triflate Isomers (22). To a cooled (−78 °C) solution of piperidone **21** (10.8 mg, 26.3 μmol) and 2-(5-chloropyridyl)triflimide (33 mg, 84 μmol, 3.2 equiv) in THF (2.0 mL) was added potassium bis(trimethylsilyl)amide (3 × 56 μL, 84 μmol, 0.5 M in toluene, 3 equiv) dropwise in three portions. The reaction mixture was allowed to stir at −78 °C for 30 min, saturated aqueous $NaHCO_3$ (1 mL) was rapidly added, and the mixture was allowed to warm to rt. The aqueous phase was diluted with water until it became homogeneous (1 mL). The aqueous phase was extracted with EtOAc (5 × 1 mL). The combined organic phases were washed with brine (1 mL), dried (Na_2SO_4), filtered (Celite), and concentrated in vacuo. The crude oil was purified by flash column chromatography with basic alumina (activity 2, elution with 5% MeOH/CH_2Cl_2), and then a second column with silica gel (elution with 50% EtOAc/hexanes) to afford the product (13.8 mg, 96%) as an inseparable mixture of enol triflate isomers **22** (ratio of 3,4- to 4,5-enol triflate found to be 1.0 to 3.1 by ^1H NMR). ^1H NMR at 50 °C (400 MHz, $CDCl_3$) δ 7.33 (br s, 5H, mixture of isomers), 5.81 (s, 1H, minor isomer), 5.75 (s, 1H, major isomer), 5.25−5.07 (m, 2H, mixture of isomers), 4.57−4.38 (m, 2H, mixture of isomers), 3.08 (m, 1H, minor isomer), 2.80 (d, J = 10 Hz, major isomer), 2.74−2.61 (m, 1H, mixture of isomers), 2.22−2.02 (m, 7H, mixture of isomers), 2.01−1.94 (m, 4H, mixture of isomers), 1.65−1.02 (m, 22H, mixture of isomers), 0.88−0.67 (m, 7H, mixture of isomers); HRMS calcd for $C_{26}H_{35}F_3N_2O_5S$ $(M + H)^+$ 545.2297, found 545.2310.

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1,7-dimethyl-5-ylmethyl)-1-[(benzyloxy)carbonyl]piperidine (23). A solution of the mixed triflates **22** (13.8 mg, 25 μmol), 5% platinum on carbon (14 mg) and lithium carbonate (18 mg, 240 μmol) in EtOAc was stirred under an atmosphere of hydrogen gas for 5.75 h. The solution was filtered through a plug of Celite and then concentrated in vacuo. The crude oil was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes, 1% TEA) providing piperidine **23** (8.3 mg, 84%) as a colorless oil. $[\alpha]_D^{24}$ −20.6 (*c* 0.65, MeOH); IR (film, NaCl) 2930, 1694 (C=O), 1422, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 5.18 (d, J = 12.3 Hz, 1H), 5.07 (d, J = 12.3 Hz, 1H), 4.23 (br s, 1H), 4.06 (br d, J = 13.2 Hz, 1H), 2.23−2.80 (m, 2H), 2.23 (s, 3H), 2.03−1.95 (m, 2H), 1.75−1.22 (m, 17H), 0.97 (dt, J = 13.4, 3.9 Hz, 1H), 0.82 (d, J = 6.0 Hz, 3H), 2.75 (q, J = 11.9 Hz, 1H); ^{13}C NMR at 50 °C (75 MHz, $CDCl_3$) δ 155.7, 137.2, 128.7, 128.2, 128.1, 67.2, 63.0, 57.8, 49.9, 44.7, 43.1, 40.1, 39.6, 38.5, 35.6, 29.2, 27.2, 27.0, 26.3, 26.0, 25.7, 23.1, 18.8; TLC R_f = 0.26 (30% EtOAc/hexanes, basic alumina); HRMS calcd for $C_{25}H_{38}N_2O_2$ $(M + H)^+$ 399.3012, found 399.3010.

2*S*-2-[(4a*R*,5*S*,7*R*,8a*R*)-1,2,3,4a,5,6,7,8,8a-Decahydroquinolin-1-cyano-7-methyl-5-ylmethyl)-1-[(benzyloxy)carbonyl]piperidine (26). To a cooled (0 °C) solution of **23** (8.3 mg, 21 μmol) and lithium carbonate (2.1 mg, 21 μmol, 1 equiv) in chloroform (1.0 mL) was added cyanogen bromide (10 μL, 31 μmol, 3 M solution in CH_2Cl_2, 1.5 equiv). The solution was allowed to stir at 0 °C for 30 min, warmed to rt, and concentrated in vacuo. The crude oil was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) to give **26** (8.2 mg, 96%) as a colorless oil. $[\alpha]_D^{23}$ −30 (*c* 0.79, $CHCl_3$); IR (film, NaCl) 2929, 2205 (C≡N), 1693 (CO), 1454, 1422, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 5.19 (d, J = 12.0 Hz, 1H), 3.05 (d, J = 12.0 Hz, 1H), 4.22 (br s, 1H), 4.07 (br d, J = 13.2 Hz, 1H), 3.41 (br d, J = 12.8 Hz, 1H), 2.95 (td, J = 11.4, 3.6 Hz, 1H), 2.85 (t, J = 12.8 Hz, 1H), 2.69 (br s, 1H), 2.01 (br d, J = 9.2 Hz, 1H), 1.67−1.25 (m, 16H), 1.07−0.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 137.0, 128.7, 128.3 (br s, 2C), 117.1, 67.3, 57.1, 51.3, 49.7, 43.9, 39.6, 39.2, 38.4, 35.2, 27.9, 26.9, 26.6, 26.0, 25.6, 25.2, 22.5, 18.8; TLC R_f = 0.21 (30% EtOAc/hexane); HRMS calcd for $C_{25}H_{35}N_3O_2$ $(M + H)^+$ 410.2808, found 410.2814.

Phlegmarine (1a). A mixture **26** and 6 M $HCl_{(aq)}$ (1.0 mL) was heated at reflux for 3 h. The solution was cooled to rt and then extracted with ether (3 × 0.5 mL). The organic phase was discarded and the aqueous phase was made basic by careful addition of solid K_2CO_3. More potassium carbonate was added until the solution became saturated. The aqueous phase was then extracted with EtOAc (14 × 1.0 mL) until the extracts no longer contained product by TLC. The crude solid was purified by flash chromatography (basic alumina (activity 2), MeOH) providing **1a** as a solid. The solid was then taken up in hexanes (1.0 mL) and passed through a plug of cotton providing phlegmarine (**1a**) (4.8 mg, 96%) as a solid. $[\alpha]_D^{24}$ −29 (*c* 0.39, $CHCl_3$); IR (film, NaCl) 3230 (N−H), 2923, 2852, 1120, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08−2.99 (m, 2H), 2.63 (dt, J = 11.8, 2.7 Hz, 1H), 2.56 (dt, J = 11.9, 2.5 Hz, 1H), 2.45−2.35 (m, 2H), 1.86−1.46 (m, 11H), 1.45−1.23 (m, 5H), 1.07 (tt, J = 11.2, 3.8 Hz, 1H), 1.05 (dt, J = 12.4, 4.0 Hz, 1H), 0.99−0.90 (m, 2H), 0.88 (d, J = 6.0 Hz, 3H), 0.80 (q, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 55.5, 47.5, 47.0, 46.1, 43.2, 39.7, 35.5, 35.2, 32.5, 28.9, 27.6, 27.0, 26.1, 25.0, 22.8; LRMS: 250 (M^+, 7), 235 (5) 167 (12), 150 (14), 124 (6), 110 (9), 97 (24), 84 (100), 70 (90) 56 (10), 44 (80) m/z; HRMS calcd for $C_{16}H_{30}N_2$ $(M + H)^+$ 251.2487, found 251.2485.

***N*$_\beta$-Methylphlegmarine (1b).** A solution of the mixed enol triflates **22** (17.7 mg, 32.5 μmol) and 20% palladium hydroxide on carbon (17.7 mg) in ethanol (1.0 mL) was stirred under an atmosphere of hydrogen gas for 6 h. The solution was filtered (Celite) and solid K_2CO_3 (100 mg) was added to the filtrate. The suspension was allowed to stir for 1 h, again filtered (Celite), and concentrated in vacuo. The residual oil was purified by flash chromatography (basic alumina (activity 2), 2% MeOH/CH_2Cl_2) to provide N_β-methylphlegmarine (**1b**) (7.7 mg, 90%) as a colorless oil. $[\alpha]_D^{22}$ −65 (*c* 0.39, $CHCl_3$); IR (film, NaCl) 3276 (N−H), 2925, 2774 (N-Me), 1455, 1331, 1118, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.06 (br d, J = 11.6 Hz, 1H) 2.82 (br d, J = 11.2 Hz, 1H), 2.63 (dt, J = 11.6, 2.8 Hz, 1H), 2.41 (m, 1H), 2.24 (s, 3H), 2.06−2.00 (m, 2H), 1.80−1.58 (m, 9H), 1.45 (m, 8H), 1.04 (dt, J = 12.7, 4.6 Hz, 1H), 0.96 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.72 (q, J = 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.0, 57.7, 56.1, 47.4, 44.6, 42.9, 39.9, 39.2, 35.5, 35.4, 32.3, 29.1, 26.8 (two carbons), 26.1, 24.9, 23.4; TLC R_f = 0.13 (5% MeOH/CH_2Cl_2, basic alumina); LRMS: 264 (M^+, 20), 249 (22), 207 (16), 180 (12), 166 (55), 164 (44), 150 (10), 124 (40), 111 (38), 97 (28), 84 (100), 44 (68) m/z; HRMS calcd for $C_{17}H_{32}N_2$ $(M + H)^+$ 265.2644, found 265.2654.

***N*$_\alpha$-Methylphlegmarine (1c).** Lithium aluminum hydride (400 μL, 400 μmol, 1.0 M in THF, 12 equiv) was added dropwise slowly into a solution of **26** (13.7 mg, 33.5 μmol) in THF (6.0 mL). The solution was then heated at reflux for 3 h, cooled to 0 °C, and water (10 μL) was added carefully followed by a 25% solution of NaOH (20 μL). The solution was warmed to rt and Celite (0.5 g) was added. After stirring for 1.5 h, the mixture was filtered through Celite, and the filter cake was washed with hot EtOAc (3 × 10 mL). Concentration of the filtrate gave a crude heterogeneous oil which was purified by flash column chromatography (basic alumina (activity 2), stepwise gradient from 75 to 100% EtOAc/hexanes then 5% MeOH/CH_2Cl_2) to afford N_α-methylphlegmarine (**1c**) (8.4 mg, 94%) as an oil. $[\alpha]_D^{22}$ −77 (*c* 0.42, $CHCl_3$); IR (film, NaCl) 3364 (N−H), 2926, 2777 (N-Me), 2852, 1455, 1371, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (br d, J = 12.2 Hz, 1H), 2.83 (br d, J = 11.4 Hz, 1H), 2.57 (dt, J = 12.2, 2.5 Hz, 1H), 2.42 (dt, J = 10.6, 3.6 Hz, 1H), 2.27 (s, 3H), 2.11 (dt, J = 11.4, 5.2 Hz, 1H), 1.84−1.4 (m, 15H), 1.39−1.05 (m, 4H), 1.00 (br t, J = 10 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.81 (q, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 57.3, 55.5, 47.1, 46.4, 43.4, 43.3, 38.4, 35.2, 30.7, 29.3, 28.9, 27.8,

26.2, 25.9, 24.3, 23.0; TLC R_f = 0.18 (5% MeOH/CH_2Cl_2, basic alumina); LRMS: 264 (M^+, 0.07), 249 (0.5), 150 (5), 134 (1), 122(1), 110 (3), 98 (100), 82 (2), 70 (4), 54 (2), 44 (23) *m*/*z*; HRMS calcd for $C_{17}H_{32}N_2$ $(M + H)^+$ 265.2644, found 265.2643.

N_α-Acetyl-N_β-methylphlegmarine (1d). To a cooled solution (0 °C) of N_β-methylphlegmarine (**1b**) (6.9 mg, 26 μmol) and pyridine (6.3 μL, 78 μmol) in dichloromethane (1.0 mL) was added acetyl chloride (5.6 μL, 78 μmol) dropwise. The solution was stirred at 0 °C for 30 min, warmed to rt for an additional 30 min, and then saturated $NaHCO_3$ (0.5 mL) was added. The aqueous phase was extracted with EtOAc (5 × 0.5 mL), and then the combined organic phases were concentrated in vacuo to give a colorless oil. The crude material was purified by flash chromatography over basic alumina (activity 2, 2% MeOH/CH_2Cl_2) providing N_α-acetyl-N_β-methylphlegmarine (**1d**) (7.6 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ −75 (*c* 0.37, $CHCl_3$); lit.[7] $[\alpha]_D$ −11 (*c* 0.7, $CHCl_3$) ; IR (film, NaCl) 2929, 2776 (NCH_3), 1643 (C═O), 1424, 1263, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 and 3.80 (2 br s due to rotamers, total 1H), 4.54 and 3.59 (2 br d due to rotamers, *J* = 13.0 Hz, total 1H), 3.15 and 2.63 (2 tt due to rotamers, *J* = 3.2, 13.2 Hz, total 1H) 2.83 (br d, *J* = 8.4 Hz, 1H), 2.25 and 2.23 (2 s due to rotamers, total 3H), 2.08 and 2.07 (2 s due to rotamers, total 3H), 2.02−1.90 (m, 3H), 1.68−1.24 (m, 18H), 1.09 and 1.02 (2 dt due to rotamers, *J* = 13.0, 3.8 Hz, total 1H), 0.92 (apparent t due to rotamers, *J* = 5.8 Hz, 3H), 0.75 and 0.71 (2 q due to rotamers, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 63.1, and 63.0 (doubled due to rotamers), 57.9 and 57.7 (doubled due to rotamers), 52.8 and 47.1 (doubled due to rotamers), 44.7 and 44.6 (doubled due to rotamers), 43.1, 42.3, 40.1, and 38.9 (doubled due to rotamers), 38.4 and 36.9 (doubled due to rotamers), 36.0 and 35.8 (doubled due to rotamers), 29.2, 27.3, and 27.2 (doubled due to rotamers), 26.8, 26.4, and 26.3 (doubled due to rotamers), 26.3 and 26.0 (doubled due to rotamers), 26.2 and 25.5 (doubled due to rotamers), 23.2 and 23.0 (doubled due to rotamers), 22.4 and 21.8 (doubled due to rotamers), 19.0 and 18.9 (doubled due to rotamers); TLC R_f = 0.23 (2.5% MeOH/CH_2Cl_2, basic alumina); LRMS: 306 (M^+, 10), 291(7), 264 (1), 263 (4), 250 (2), 249 (11), 206 (3), 181 (1), 180 (6), 167 (13), 166 (100), 164 (7), 127 (3), 126 (32), 124 (5), 123 (4), 98 (2), 97 (10), 96 (8); HRMS calcd for $C_{19}H_{34}N_2O$ $(M + H)^+$ 307.2749, found 307.2750.

N_α-Methyl-N_β-acetylphlegmarine (1e). To a cooled (0 °C) solution N_α-methylphlegmarine (**1c**) (8.4 mg, 32 μmol) and pyridine (8.6 μL, 110 μmol, 3.5 equiv) in dichloromethane (1.0 mL) was added acetyl chloride (7.5 μL, 110 μmol) dropwise. The solution was allowed to stir for 30 min at 0 °C and then warmed to rt for an additional 30 min. Saturated $NaHCO_3$ (1.0 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (5 × 1 mL), and the combined organic phases were washed with brine (1.0 mL), dried (Na_2SO_4), filtered (Celite) and concentrated in vacuo. The crude oil was purified by flash column chromatography (basic alumina (activity 2), stepwise elution with 50−100% EtOAc/hexanes then 10% MeOH/CH_2Cl_2) providing N_α-methyl-N_β-acetylphlegmarine (**1e**) (8.2 mg, 84%) as a colorless oil. $[\alpha]_D^{23}$ −192 (*c* 0.40, $CHCl_3$); IR (film, NaCl) 2928, 2777 (N-Me), 1640 (C═O), 1439, 1247, 1027 cm^{-1}; ^1H NMR at 50 °C (400 MHz, $CDCl_3$) δ 3.71 (br m, 2H), 3.11 (br m, 1H), 2.82 (dt, *J* = 11.6, 3.4 Hz, 1H), 2.27 (s, 3H), 2.13 (dt, *J* = 11.6, 6.8 Hz, 1H), 2.05 (s, 3H), 2.03 (m, 1H), 1.92−1.55 (m, 13H), 1.42 (m, 1H), 1.35−1.02 (m, 6H), 0.94−0.85 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR at 50 °C (100 MHz, $CDCl_3$) δ 169.9, 62.2, 56.8, 54.8, 43.2, 41.5, 39.6, 38.6, 37.9, 35.4, 30.7, 28.5, 26.8, 25.9, 24.1, 23.1, 23.0, 22.5, 22.1; TLC R_f = 0.29 (2.5% MeOH/CH_2Cl_2, basic alumina); LRMS: 306 (M^+, 0.96), 291 (0.41), 263 (1.6), 207 (1.9), 192 (1.3), 150 (5.2), 110 (2.8), 98 (100), 70 (5.1), 55 (3.0), 44 (49) *m*/*z*; HRMS calcd for $C_{19}H_{34}N_2O$ $(M + H)^+$ 307.2749, found 307.2747.

Acknowledgment. This work was supported in part by the National Institutes of Health (Grant No. GM 34442). NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grant No. CHE-0078253).

Supporting Information Available: Characterization data sheets for **1a**,**b** and comparison data tables for **1c**−**e**. NMR spectra for **1**, **8**, **19**−**23**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.