Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates: Asymmetric Synthesis of (−)-Septicine and (−)-Tylophorine

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Received June 24, 1997[⊗]

A concise asymmetric synthesis of (−)-septicine (**1**) and (−)-tylophorine (**2**) was accomplished with a high degree of stereocontrol in eight and nine steps, respectively. Addition of 4-(1-butenyl)magnesium bromide to 1-acylpyridinium salt **3**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol, gave a 91% yield of diastereomerically pure dihydropyridone **7**. Oxidative cleavage of **7** and subsequent reduction provided alcohol **6** in 81% yield. Conversion of **6** to the chloride followed by treatment with sodium methoxide gave indolizidinone **9** in high yield. Bromination and conjugate reduction of **9** with L-Selectride, and trapping the intermediate enolate with *N*-(5-chloro-2-pyridyl)triflimide, provided bromovinyl triflate **11**. Palladium-catalyzed cross-coupling of excess (3,4-dimethoxyphenyl)zinc bromide and **11** gave (−)-septicine (**1**). On the basis of this synthesis, (−)-**1** was assigned the *R* configuration. Reaction of **1** with vanadium(V) trifluoride oxide in TFA/CH_2Cl_2 effected oxidative coupling to give a 68% yield of (−)-tylophorine (**2**).

The indolizidine alkaloid septicine (**1**) was isolated by Russel[1] from *Ficus septica*, a plant belonging to the Moraceae family, and is considered to be a biogenetic precursor to the phenanthroizidine alkaloid, tylophorine (**2**). Tylophorine has also been found in various plants of the Asclepiadarceae family.[1] The configuration at C-13a in naturally occurring (−)-tylophorine (**2**) was originally assigned to be *S* on the basis of correlation to degradation products.[2] The stereochemistry at C-13a of **2** was latter revised to *R* since synthetic (*S*)-tylophorine had a positive rotation and CD.[3]

Septicine isolated from *F. septica* and from *Tylophora crebriflora* has been reported to have a negative rotation; however, (+)-septicine has been found in extracts of *T. asthmatica*.[4] The only enantioselective synthesis of septicine was reported in 1969 by Russel and Hunziker.[5] Their synthesis used L-prolinol as a building block and produced (−)-septicine ($[\alpha]^{22}_D$ −16.2), which apparently assigned the stereochemistry of (−)-**1** as *S*.

The phenanthoindolizidine alkaloids, i.e., **2**, exhibit a wide range of biological properties including antitumor activity.[1,6] A considerable amount of synthetic work has produced a variety of racemic syntheses of both septicine and tylophorine.[7,8] In contrast, only one preparation of (−)-septicine,[5] two syntheses of unnatural (+)-tylophorine,[3] and one asymmetric synthesis of (−)-tylophorine have been reported.[9] Our approach to alkaloid synthesis using *N*-acyldihydropyridones as building blocks allowed us to prepare racemic septicine and tylophorine in five and six steps, respectively.[7f] We now report a modification of our racemic synthesis which incorporates our recently developed enantioselective preparation of 2-alkyl-2,3-dihydro-4-pyridones.[10] This approach has allowed us to prepare (-)-septicine and (-)-tylophorine in a concise asymmetric fashion.

Our synthetic plan called for the preparation of enantiopure dihydropyridone **6**. Initially, we investigated the addition of Grignard reagent **4** to chiral 1-acylpyridinium salt **3**, which was prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[11] and the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC)[12] (Scheme 1). The crude dihydropyridone product **5** was reduced to give a

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

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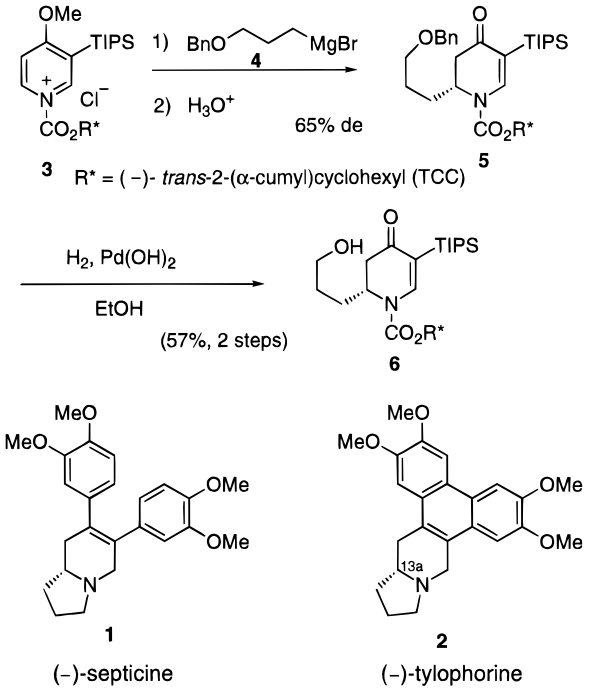
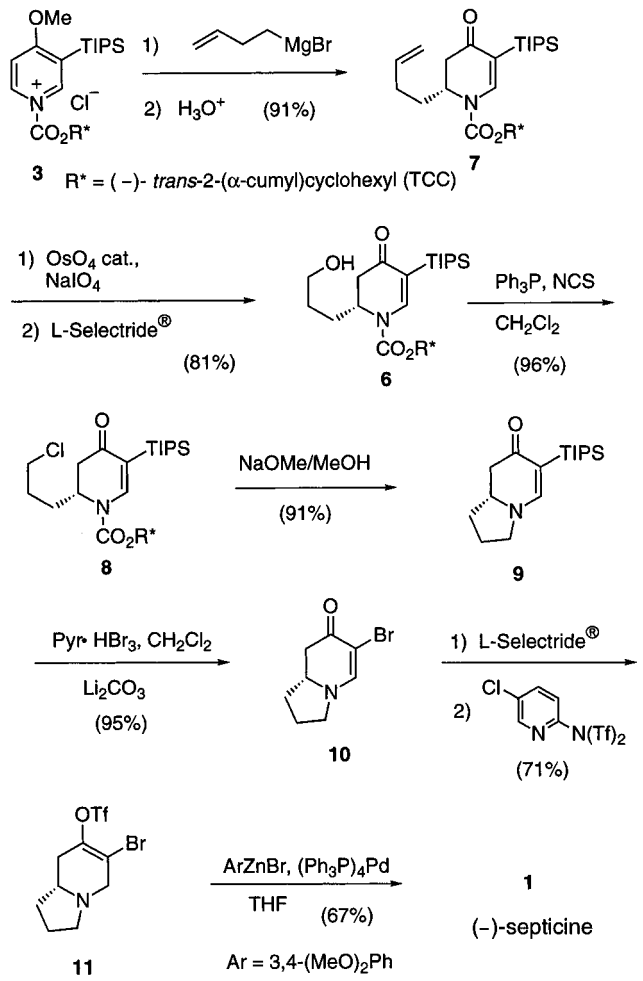
S0022-3263(97)01149-3 CCC: $14.00

Scheme 1

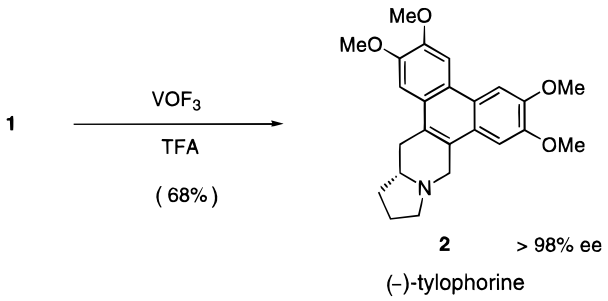


57% overall yield of **6**. Although this route was quite convenient, the diastereoselectivity was only 65%. This is low in contrast to similar reactions with most other primary Grignard reagents where the de is usually in the 90−95% range.[11] The decreased degree of asymmetric induction must be due to the presence of a coordinating oxygen atom in the Grignard reagent. Although we had previously been successful in using similar functionalized Grignards, a less practical chiral auxiliary was required in order to obtain a high de.[13] An alternative route to alcohol **6** was investigated as shown in Scheme 2. The Grignard reagent prepared from commercially available 4-bromo-1-butene was added to chiral 1-acylpyridinium salt **3** using our standard conditions.[11] This time the desired crude product **7** was obtained in 90% de. Recrystallization from methanol and chromatography of the mother liquor gave a 91% yield of diastereomerically pure **7**. Oxidative cleavage and subsequent reduction of the crude aldehyde with L-Selectride provided alcohol **6** in 81% yield. Conversion of **6** to chloride **8** was carried out in 96% yield using triphenylphosphine and *N*-chlorosuccinimide.[14] On treatment of **8** with sodium methoxide in methanol, the chiral auxiliary (TCC) was removed and concomitant cyclization occurred to give indolizidinone **9** in 91% yield. In addition, the chiral auxiliary, (−)-TCC, was recovered (92%) during the purification step. Bromodesilylation of **9** using pyridinium bromide perbromide efficiently provided bromide **10**. Conjugate reduction with L-Selectride followed by addition of *N*-(5-chloro-2-pyridyl)triflimide[15] gave a 71% yield of bromovinyl triflate **11**. Palladium-catalyzed cross-coupling of excess (3,4-dimethoxyphenyl)zinc bromide and **11** provided (−)-septicine (**1**). The specific rotation of our synthetic **1** was $[\alpha]^{28}_D$ −172, a

Scheme 2



Scheme 3



value significantly higher than those reported for the natural material ($[\alpha]_D$ −16 to −42). In addition, our synthesis allows us to assign the absolute configuration of (−)-**1** as *R*, not *S* as is suggested by previous synthetic work.[5] The stereochemical assignment was further confirmed by conversion of (−)-**1** to (*R*)-(−)-tylophorine (**2**) as discussed below.

Reaction of our synthetic (−)-septicine with vanadium(V) trifluoride oxide in TFA/CH_2Cl_2 at room temperature effected oxidative coupling to provide a 68% yield of (−)-tylophorine (**2**) as a yellow solid (Scheme 3). The melting point, specific rotation ($[\alpha]^{30}_D$ −76), and NMR data were in agreement with literature values.

This synthetic work has again demonstrated the versatility of enantiopure 2,3-dihydro-4-pyridones as building blocks for the concise asymmetric synthesis of alkaloids. The synthetic route is highly stereoselective and efficient, allowing (−)-septicine and (−)-tylophorine

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to be prepared from readily available 4-methoxy-3-(triisopropylsilyl)pyridine in eight and nine steps, respectively. Our asymmetric synthesis of (−)-septicine has established the absolute stereochemistry of this alkaloid as *R*, and the specific rotation of the synthetic material indicates that the natural septicine is isolated or present in the plant in low enantiomeric purity.

Experimental Section

2(*R*)-(3′-(Benzyloxy)propyl)-1-[((((1*R*,2*S*)-2-(α-cumyl)cyclohexyl)oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (5). Magnesium turnings (340 mg, 14 mmol) were mechanically stirred at rt overnight under argon, and then 2 mL of anhydrous THF was added to the flask. Benzyl 3-bromopropyl ether (0.71 mL, 4 mmol) was added dropwise at 0 °C. The mixture was stirred 20 min at rt and then 4 h at 0 °C. In a separate flask, the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol (TCC) (589 mg, 2.1 mmol) in 6 mL of anhydrous toluene was added to a solution of 4-methoxy-3-(triisopropylsilyl)pyridine[11a] (531 mg, 2 mmol) in 10 mL of toluene at −42 °C. The reaction mixture was stirred at −42 °C for 1 h and then cooled to −78 °C. THF (4 mL) was added, and the mixture was stirred for 1 h at −78 °C. The previously prepared Grignard reagent was transferred dropwise *via* a double-tipped stainless steel needle to the flask containing the newly formed chiral *N*-acylpyridinium salt solution at −78 °C over a period of 1 h, and the resulting solution was stirred for 1.5 h at −78 °C. Saturated aqueous oxalic acid (10 mL) was added, the reaction mixture was warmed to room temperature, and the mixture was stirred 0.5 h. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration and concentration in vacuo gave 2.05 g of the crude product. (This crude material was used directly in the next step.) Purification by radial PLC (silica gel, 10% EtOAc/hexanes) gave **5** as white needles: mp 73.6−74.5 °C; $[\alpha]^{24}_D$ −48.1 (*c* 0.585, $CHCl_3$); IR (KBr) 2939, 2861, 1716, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (br s, 1 H), 7.38−7.24 (m, 10 H), 7.11 (t, 1 H, *J* = 6.8 Hz), 4.85 (br s, 1 H), 4.47 (s, 2 H), 3.34 (br s, 2 H), 2.71 (br s, 1 H), 2.45−2.33 (m, 1 H), 2.28−2.16 (m, 1 H), 2.05−1.90 (m, 3 H), 1.82−1.66 (m, 2 H), 1.36−1.17 (m, 16 H), 1.05 and 1.01 (dd due to rotamer, 18 H, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 196.8, 152.23, 152.18 (rotamer), 147.4, 147.3 (rotamer), 138.5, 128.3, 128.1, 127.7, 127.4, 125.1, 110.2, 78.1, 72.8, 69.7, 51.4, 51.0 (rotamer), 40.4, 39.4, 33.4, 30.9, 27.5, 26.8, 25.8, 24.6, 21.6, 18.9, 18.8, 11.1. Anal. Calcd for $C_{40}H_{59}NO_4Si$: C, 74.37; H, 9.21; N, 2.17. Found: C, 74.28; H, 9.26; N, 2.18.

2(*R*)-(3′-Hydroxypropyl)-1-[((((1*R*,2*S*)-2-(α-cumyl)cyclohexyl)oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (6). A flask containing a solution of crude **5** (2.05 g) in 50 mL of absolute ethanol at rt was purged with argon. To this solution was added 0.81 g (40% by weight) of palladium hydroxide (Pearlman's catalyst, 20% on carbon/31% H_2O). The mixture was stirred for 14 h under hydrogen at balloon pressure. Filtration and concentration in vacuo gave the desired crude product (63.5% de). Purification by radical PLC (silica gel, 30−50% EtOAc/hexanes) yielded 633 mg (99.8% de) of desired **6** as a white solid: mp 122−3 °C; $[\alpha]^{27}_D$ −98.1 (*c* 0.995, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (s, 1 H), 7.34−7.14 (m, 5 H), 7.11 (t, 1 H, *J* = 6.7 Hz), 4.86 (m, 1 H), 3.49 (d, 3 H, *J* = 5.5 Hz), 2.65 (br s, 1 H), 2.40−1.63 (series of m, 7 H), 1.46−1.09 (m, 16 H), 1.04 and 1.01 (dd, 18 H, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 196.9, 152.7, 152.1 (due to rotamer), 147.4, 128.0, 125.1, 110.2, 78.2, 62.2, 51.2, 50.9, 40.3, 39.4, 33.4, 30.9, 28.5, 26.9, 25.8, 24.6, 21.4, 18.81, 18.74, 11.1. Anal. Calcd for $C_{33}H_{53}NO_4Si$: C, 71.30; H, 9.61; N, 2.52. Found: C, 71.36; H, 9.58; N, 2.48.

2(*R*)-(3′-Butenyl)-1-[((((1*R*,2*S*)-2-(α-cumyl)cyclohexyl)-oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (7). Magnesium turnings (1.60 g, 66 mmol) were mechanically stirred at room temperature overnight under argon, and then 16.5 mL of anhydrous THF was added to the flask. Neat 4-bromo-1-butene (2.26 mL, 22 mmol) was added dropwise at 0 °C. The mixture was stirred for 20 min at room temperature, 1 h at 0 °C, and 2 h at room temperature.

In a separate flask, to a solution of 4-methoxy-3-(triisopropylsilyl)pyridine[11a] (2.92 g, 11 mmol) in 20 mL of anhydrous toluene was added a solution of the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol (3.24 g, 11.55 mmol) in 20 mL of anhydrous toluene at −42 °C. The reaction mixture was stirred at −42 °C for 1.5 h and then cooled to −78 °C. The previously prepared Grignard reagent was transferred dropwise *via* a double-tipped stainless steel needle to the flask containing the newly formed chiral *N*-acylpyridinium salt solution, and stirring was continued at −78 °C for 4 h. Saturated aqueous oxalic acid (30 mL) was added. The reaction mixture was warmed to rt and stirred overnight. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration and concentration in vacuo gave 7.24 g (90% de) of the desired crude product. Crystallization from 5% H_2O/MeOH yielded 4.80 g (100% de) of desired (2*R*)-2,3-dihydro-4-pyridone **7**. The mother liquid was concentrated and purified by radical PLC (silica gel, 2−5% EtOAc/hexanes) to yield another 0.85 g (99.8% de) of **7**: mp 117−8 °C; $[\alpha]^{25}_D$ −62.3 (*c* 0.975, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (br s, 1 H), 7.23−7.38 (m, 5 H), 7.11 (t, 1 H, *J* = 6.6 Hz), 5.63 (m, 1 H), 5.05−4.80 (m, 3 H), 2.77 (br s, 1 H), 2.43−1.65 (series of m, 8 H), 1.40−1.17 (m, 15 H), 1.05 and 1.01 (dd, 18 H, *J* = 7.4 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 196.7, 152.5, 152.2 (due to rotamer), 147.4, 137.1, 128.1, 125.1, 115.2, 110.2, 78.1, 51.1, 40.1, 39.5, 33.5, 30.7, 30.0, 29.5, 26.8, 25.8, 24.6, 21.7, 18.84, 18.78, 11.1. Anal. Calcd for $C_{34}H_{53}NO_3Si$: C, 74.00; H, 9.68; N, 2.54. Found: C, 73.93; H, 9.68; N, 2.53.

2(*R*)-(3′-Hydroxypropyl)-1-[((((1*R*,2*S*)-2-(α-cumyl)cyclohexyl)oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (6) from 7. A stirred solution of **7** (1.04 g, 1.88 mmol) in 80 mL of H_2O/THF (1:1) was treated with $NaIO_4$ (3.66 g, 17.1 mmol) and OsO_4 (0.12 mL, 0.0196 mmol, 4 wt % in H_2O), and stirring was continued for 19 h at room temperature. The reaction mixture was filtered through Celite and extracted with methylene chloride. The organic extracts were dried over anhydrous K_2CO_3. Filtration and concentration in vacuo gave a clear oil that was treated with L-Selectride (2.1 mL, 2.1 mmol, 1.0 M solution in THF) in 80 mL of anhydrous THF at −78 °C. After 2 h of stirring, 5 mL of water and 1 g of sodium perborate tetrahydrate ($NaBO_3 \cdot 4H_2O$) were added and stirring was continued for 6 h as the reaction mixture warmed to room temperature. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration, concentration, and purification by radial PLC (silica gel, 30−50% EtOAc/hexane) yielded 851 mg (81%) of the desired dihydropyridone **6**.

2(*R*)-(3′-Chloropropyl)-1-[((((1*R*,2*S*)-2-(α-cumyl)cyclohexyl)oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (8). To a stirred solution of dihydropyridone **6** (0.97 g, 1.75 mmol) in 20 mL of anhydrous dichloromethane at −23 °C was added triphenylphosphine (0.92 g, 3.43 mmol). *N*-Chlorosuccinimide (0.47 g, 3.43 mmol) was added at −23 °C, and the mixture was stirred for 1 h. After being warmed to 25 °C, the reaction mixture was stirred for another 2 h and then quenched with methanol (0.2 mL). After removal of the solvent, the residue was dissolved in ethyl ether. Filtration, concentration, and purification by radial PLC (silica gel, 20% EtOAc/hexane) yielded 0.96 g (96%) of the desired chloroalkyldihydopyridone **5** as a white solid: mp 117−118 °C; $[\alpha]^{25}_D$ −61.3 (*c* 0.955, $CHCl_3$); IR (KBr) 2941, 2864, 1715, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (br s, 1 H), 7.36−7.26 (m, 5 H), 7.11 (t, 1 H, *J* = 6.6 Hz), 4.85 (br s, 1 H), 3.37 (br s, 2 H), 2.57 (br s, 1 H), 2.36−1.56 (series of m, 7 H), 1.36−1.24 (m, 16 H), 1.04 and 1.00 (dd due to rotamer, 18 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.6, 152.9, 152.1 (rotamer), 147.3, 128.1, 125.1, 124.9, 110.4, 78.4, 50.9, 50.7 (rotamer), 44.2, 40.4, 39.4, 33.4, 31.2, 28.5, 27.8, 26.8, 25.9, 24.7, 21.2, 18.9, 18.8, 11.1. Anal. Calcd for $C_{33}H_{52}NO_3SiCl$: C, 68.56; H, 9.16; N, 2.60. Found: C, 69.01; H, 9.13; N, 2.44.

(9*R*)-6-(Triisopropylsilyl)-5,6-didehydro-7-indolizidinone (9). To a mixture of dihydropyridone **8** (0.94 g, 1.64 mmol) in 80 mL of anhydrous methanol was added sodium

methoxide (2.39 mL, 10.45 mmol, 4.37 M in MeOH). After 6 h of reflux, the reaction mixture was cooled to rt and stirred for 14 h. Acetic acid (0.60 mL, 10.45 mmol) was added, and the mixture was stirred for 10 min. After removal of the solvent, the residue was dissolved in dichloromethane and dried over K_2CO_3. Filtration through Celite, concentration, and purification by radial PLC (silica gel, 20% EtOAc/hexanes) yielded 437 mg (91%) of the desired indolizidinone **9** as a white solid: $[\alpha]^{26}_D$ +501 (*c* 0.895, $CHCl_3$).[13]

(9*R*)-6-Bromo-5,6-didehydro-7-indolizidinone (10). To a mixture of indolizidinone **9** (67 mg, 0.228 mmol) in 3 mL of anhydrous dichloromethane at −23 °C was added pyridinium bromide perbromide (109 mg, 0.342 mmol). After 4.5 h of stirring at -23 °C, the resulting yellow slurry was quenched with 0.3 mL of saturated aqueous $Na_2S_2O_3$, and the mixture was warmed to rt. Dichloromethane (8 mL) and anhydrous K_2CO_3 (0.5 g) were added. Filtration, concentration, and purification by radial PLC (silica gel, 20−50% EtOAc/hexanes/1% TEA) yielded 47 mg (95%) of the desired indolizidinone **10** as a white solid: mp 96−97 °C; $[\alpha]^{25}_D$ +793 (*c* 1.53, $CHCl_3$); IR (KBr) 3033, 2977, 1632 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.58 (s, 1 H), 3.90−3.81 (m, 1 H), 3.66−3.51 (m, 2 H), 2.74−2.66 (m, 1 H), 2.45 (t, 1 H, *J* = 16.3 Hz), 2.39−2.27 (m, 1 H), 2.20−2.11 (m , 1 H), 2.03−1.92 (m, 1 H), 1.81−1.69 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 183.7, 150.4, 88.3, 58.1, 49.8, 41.0, 32.3, 24.5; MS (EI, *m*/*z*) 217 (M + 2, 98), 216 (M + 1, 24), 214 (M^+, 100), 136 (21), 108 (36); HRMS exact mass calcd for $C_8H_{10}NOBr$ 214.9946, found 214.9953.

(9*R*)-6-Bromo-7-[((trifluromethyl)sulfonyl)oxy]-5,6-didehydroindolizidine (11). To a solution of **10** (80 mg, 0.37 mmol) in 3.5 mL of anhydrous THF was added L-Selectride (0.41 mL, 0.41 mmol, 1 M in THF) dropwise. After the reaction was stirred at −23 °C for 3 h, 5-chloro-2-[*N*,*N*-bis((trifluromethyl)sulfonyl)amino]pyridine (174 mg, 0.44 mmol) was added, and the mixture was stirred for 14 h at −23 °C. The reaction was quenched with aqueous saturated $NaHCO_3$ (0.5 mL) and CH_2Cl_2 (10 mL). Drying over anhydrous K_2CO_3, filtration through Celite, concentration, and purification by column chromatography (neutral alumina, 0−10% EtOAc/hexanes) gave 92 mg (71%) of **11** as a colorless oil: $[\alpha]^{23}_D$ −62.3 (*c* 0.35, $CHCl_3$); IR (neat) 2969, 2800, 1676 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 3.78 (d, 1 H, *J* = 16.1Hz), 3.23−3.15 (m, 2 H), 2.60−2.41 (m, 3 H), 2.28 (dd, 1 H, *J* = 8.9, 17.5 Hz), 2.10−1.82 (m, 3H), 1.65−1.50 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 144.2, (124.7, 120.5, 116.2, 112.0) (Tf), 112.5, 60.0, 57.6, 52.9, 35.6, 30.2, 22.3; MS (EI, *m*/*z*) 351 (M + 2, 26), 350 (M + 1, 7), 349 (M^+, 124), 218 (16), 216 (17), 69 (100); HRMS exact mass calcd for $C_9H_{11}NSO_3F_3Br$ 348.9595, found 348.9586.

(−)-Septicine (1). A dry 10-mL round-bottomed flask containing anhydrous $ZnBr_2$ (0.401 g, 1.782 mmol) was heated to 160 °C under vacuum for 14 h. While the flask was still hot argon gas was introduced. The flask was then cooled to 25 °C, and anhydrous THF (4 mL) was added.

To a separate flask containing 5 mL of THF at −78 °C was added *tert*-butyllithium (2.9 mL, 3.59 mmol, 1.23 M in THF), and then the 4-bromovertrole (0.25 mL, 1.713 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h, and the solution of $ZnBr_2$ in THF was transferred *via* a cannula. The resulting zinc reagent was stirred at −78 °C for 10 min, warmed to 25 °C, and cannulated to a stirred mixture of vinyl triflate **11** (120 mg, 0.343 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol). The resulting yellow mixture was stirred at 25 °C for 2 h and then refluxed for 2 d. The reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (20 mL). After drying with anhydrous K_2CO_3, the solvent was evaporated, and purification of the residue by radial PLC (silica gel, 10% EtOAc/hexanes/1% TEA) gave 91 mg of **1** as a white solid: mp 137−8 °C; $[\alpha]^{28}_D$ −172 (*c* 0.755, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66 (t, 4 H, *J* = 8.8 Hz), 6.52 (d, 2 H, *J* = 4.7 Hz), 3.88 (d, 1 H, *J* = 16.0 Hz), 3.81 (s, 6 H), 3.60 (s, 3 H), 3.58 (s, 3 H), 3.31 (t, 1 H, *J* = 7.7 Hz), 3.10 (d, 1 H, *J* = 15.8 Hz), 2.73 (dd, 1 H, *J* = 20.3, 9.0 Hz), 2.45−2.35 (m, 2 H), 2.26 (dd, 1 H, *J* = 17.9, 8.9 Hz), 2.30−2.04 (m, 1 H), 2.04−1.80 (m, 2 H), 1.62−1.52 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 148.2, 148.1, 147.5, 147.3, 135.2, 133.7, 132.8, 132.7, 121.0, 120.7, 113.1, 112.9, 110.7, 60.4, 57.6, 55.7, 55.6, 54.2, 38.5, 30.8, 21.5; IR (KBr) 1600, 1581, 1509, 1461, 1243, 1026 cm^{-1}. These data are in agreement with those reported.[4,5,7]

(−)-Tylophorine (2). To a mixture of (−)-septicine (50 mg, 0.1264 mmol) in 1 mL of anhydrous dichloromethane at 0 °C were added vanadium(V) oxytrifluoride (39 mg, 0.316 mmol) and TFA (1 mL). After the red solution was stirred at 0 °C for 1 h, it was warmed to room temperature and stirring was continued for 1 h. Another portion of vanadium(V) oxytrifluoride (16 mg, 0.126 mmol) was added, and the reaction was continued at 25 °C for 1 h. The reaction was quenched with 1 mL of saturated aqueous $Na_2S_2O_3$, diluted with 10 mL of dichloromethane, and neutralized with 10% NaOH. The mixture was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration, concentration, and purification by radial PLC (silica gel, 50% EtOAc/hexanes−10% EtOH/EtOAc/1% TEA) yielded 34 mg (68%) of the desired (−)-tylophorine (**2**) as a yellow solid: mp 273−275 °C; $[\alpha]^{30}_D$ −76.0 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 2 H), 7.34 (s, 1 H), 7.19 (s, 1 H), 4.65 (d, 1 H, *J* = 14.7 Hz), 4.13 (s, 6 H), 4.07 (s, 6 H), 3.70 (d, 1 H, *J* = 14.5 Hz), 3.50 (t, 1 H, *J* = 8.2 Hz), 3.40 (dd, 1 H, *J* = 2.3, 16.0 Hz), 2.95 (t, 1 H, *J* = 14.9 Hz), 2.59−2.42 (m, 2 H), 2.34−2.20 (m, 1 H), 1.90−2.14 (m, 2 H), 1.72−1.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.8, 148.6, 148.5, 126.3, 125.9, 124.4, 123.7, 123.5, 104.1, 103.6, 103.5, 103.3, 60.2, 56.1, 55.9, 55.1, 53.9, 33.7, 31.3, 21.6. These data were in agreement with those reported.[3b,9] The ee was determined to be >98% by chiral column HPLC analysis (Chiracel-OD, J. T. Baker, 10% 2-propanol/hexanes, 0.4 mL/min).

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. The 300-MHz NMR spectra 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 (CHE-9121380).

Supporting Information Available: Comparison tables of spectroscopic data for synthetic **1** and **2** and ^1H and ^{13}C NMR spectra of **1**, **2**, **10**, and **11** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9711495