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General Strategy for the Construction of Enantiopure Pyrrolidine-Based Alkaloids. Total Synthesis of (−)-Monomorine

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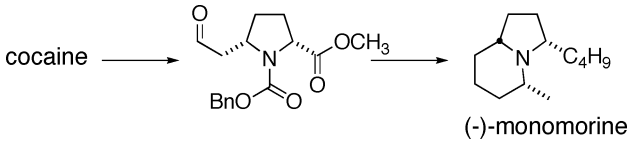
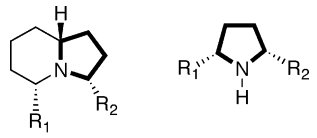


An enantiopure cis-2,5-disubstituted pyrrolidine building block was prepared from cocaine. The synthetic utility of this compound as a chiral building block was demonstrated by a short and efficient synthesis of the pyrrolidine-based alkaloid (−)-monomorine (six steps, 37% overall yield).

Alkaloids isolated from neotropical frogs have become important targets for synthesis due to their vast array of structural diversity and biological activity.[1] For many of the over 500 alkaloids that represent nearly 20 different structural classes, the stereochemical assignment and absolute configurations have yet to be unequivocally determined. The paucity of natural material has made total synthesis the only available avenue to obtain material for study of the structure and activity of these novel compounds. As part of an ongoing study in our laboratories, we have been very interested in the amphibian alkaloids that exhibit pharmacological activity mediated by nicotinic receptor ion channels.[2,3] Nicotinic receptor ligands have been identified as having potential therapeutic value for the treatment of Alzheimer's disease, Parkinson's disease, acute and chronic pain, as well as smoking cessation.[4,5] Several classes of the amphibian alkaloids have been reported to be noncompetitive blockers at nicotinic receptor ion channels.[1] Of these alkaloids, two classes share the common structural feature of a cis-2,5-disubstituted pyrrolidine ring system. This ring system can be found either incorporated in complex molecules such as the bicyclic 3,5-disubstituted indolizidines **1** or simply as the major structural element in the monocyclic 2,5-disubstituted pyrrolidine alkaloids **2**. In lieu of these structural similarities, it was of interest to develop a general and enantioselective synthetic method that would allow access to these as well as other novel classes of alkaloids.[6]



There are numerous reports describing the syntheses of the more common trans-2,5-disubstituted pyrrolidine moiety found in numerous pyrrolidine or indolizidine alkaloids.[7] However, there are only a few methods that have been reported that stereoselectively furnish cis-2,5-disubstituted pyrrolidine derivatives, and these methods are somewhat limited to fairly simple substitution patterns.[7i,8] Therefore, it was of interest not only to develop an enantioselective approach but also to develop a general strategy that would allow for the preparation of complex natural as well as nonnatural indolizidine and/or pyrrolidine alkaloids that could be used in future structure−activity studies.

The synthetic strategy for the preparation of an enantiopure cis-2,5-disubstituted pyrrolidine building block was envisaged to proceed from an intermediate derived from cocaine (**3**). The approach would exploit the inherent stereochemistry at C1 and C5 of cocaine, such that via a sequence of degradation reactions an unsymmetrical cis-2,5-disubstituted pyrrolidine **5** could be obtained (Scheme 1). Although not commercially available, confiscated grade cocaine can be obtained from the National Institute on Drug Abuse with appropriate DEA licensing in sufficient quantities to provide useful amounts of chiral building blocks. As described in some of our previous work, cocaine can be readily converted into (+)-2-tropinone (**4**).[9] It was

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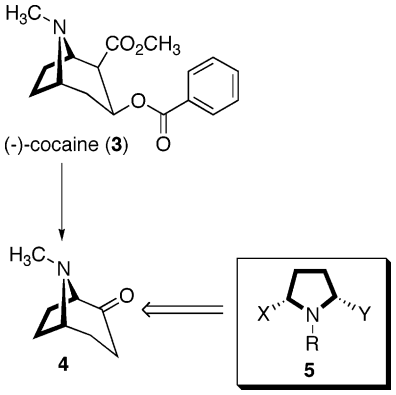
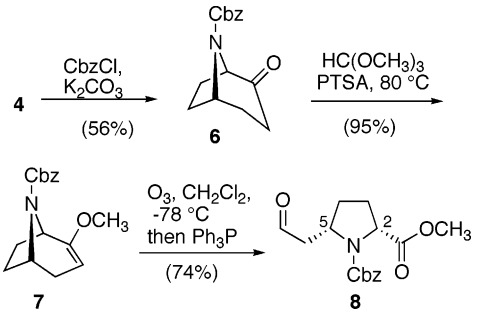
SCHEME 1



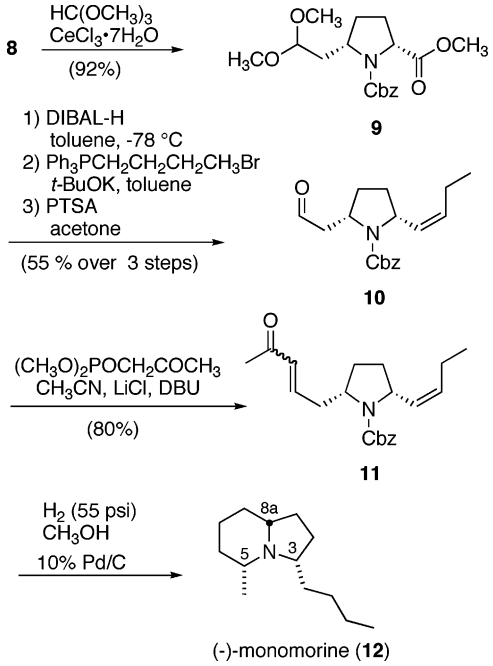
SCHEME 2



envisaged that further manipulation of this enantiopure tropane derivative could provide a useful intermediate for the total synthesis of 3,5-disubstituted indolizidine and/or cis-2,5-disubstituted pyrrolidine alkaloids.

Our initial task was to develop a synthetic sequence for the preparation of an enantiopure cis-2,5-disubstituted pyrrolidine building block from (+)-2-tropinone (**4**). The selection of (+)-2-tropinone (**4**) to be used as an early intermediate was based upon its availability and relative ease of preparation in our laboratory.[9] Confiscated grade (−)-cocaine was readily converted into (+)-2-tropinone (**4**) in 80% overall yield. This one-pot two-step procedure was typically performed on a 35 g scale and furnished 10 g quantities of optically pure **4**. As illustrated in Scheme 2, the 2-tropinone **4** was then N-demethylated and the nitrogen atom was simultaneously protected as the Cbz-carbamate **6** (56% yield) by heating **4** at reflux in a solution of Cbz−Cl and toluene. This step was necessary to reduce the nitrogen atom basicity and protect it from oxidation during ozonolysis in the succeeding step. The *N*-Cbz-2-tropanone **6** was then converted into the methyl enol ether **7** with trimethyl orthoformate catalyzed by PTSA. The intermediate enol ether **7** was obtained in 95% yield but was unstable to chromatography and thus required purification by vacuum bulb-to-bulb distillation. Because of its relative instability, the enol ether **7** was immediately subjected to ozonolysis conditions. The double bond of **7** was cleaved by ozone at −78 °C, and subsequent reductive workup with triphenylphosphine furnished the enantiopure cis-2,5-disubstituted pyrrolidine **8** in 74% yield. The pyrrolidine **8** existed as a mixture (3:1) of two conformers due to hindered rotation about the *N*−Cbz bond (rotomers). The formation of rotomers significantly complicated the NMR spectroscopy of later intermediates. As a result, it was difficult to spectroscopically characterize intermediate compounds. Therefore, it was often practical to advance intermediates to a point where the conformational isomers did not contribute to the complexity of the molecule and a meaningful structural characterization could be performed.

SCHEME 3



The orthogonal reactivity of the aldehyde, the ester, and the *N*-Cbz protecting group as well as the asymmetry of cis-2,5-appendages of pyrrolidine **8** offered the flexibility desired of a chiral building block for the syntheses of a variety of alkaloids. To demonstrate the synthetic utility of **8** as a building block for the construction of pyrrolidine-based alkaloids, (−)-monomorine (**12**) was selected as our initial target (Scheme 3). The natural alkaloid (+)-monomorine, isolated from ants (*Monomorium pharaonis*)[10] and more recently detected in amphibian skin extracts (*Melanophryniscus stelzneri*),[11] has been the target of a variety of synthetic efforts.[12] Both the natural isomer[13] and the unnatural antipode[14] have been enantioselectively synthesized and well characterized. Therefore, (−)-monomorine (**12**) was deemed an ideal target to evaluate the chemical and stereochemical efficiency of our approach.

Construction of the C3 side chain of (−)-monomorine prior to ring closure to form the indolizidine ring system was deemed preferable to the alternative sequence. This approach would avoid protection of reactive functionality during the late stages of the synthesis and has been successful in recent syntheses of

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(+)-monomorine and related indolizidine alkaloids.[15] This approach would then require the initial conversion of the C2 ester moiety of **8** into the butyl side chain at C3 of indolizidine **12**. Thus, the aldehyde moiety of **8** was protected as the acetal with trimethyl orthoformate catalyzed by cerric chloride to afford **9** in 92% yield. Reduction of the ester with DIBAL-H to the aldehyde followed by concomitant Wittig olefination afforded the four-carbon unit necessary for the indolizidine C3 side chain. Conversion of the butenyl group of **10** into the required butyl group was deemed unnecessary at this stage because this could ultimately be achieved during the deprotection/indolizidine ring-forming steps. Therefore, subsequent hydrolysis of the acetal moiety with PTSA·H_2O in acetone gave the *Z*-alkenal **10** in 55% overall yield.

The indolizidine ring system was constructed by exploiting a common synthetic strategy of side-chain elongation via olefination followed by a simultaneous hydrogenation/reductive amination sequence.[13a] As illustrated in Scheme 3, olefination of **10** with trimethylphosphonoacetate, lithium chloride, and DBU gave the enone **11** in 80% yield as a mixture of rotomers and isomers. Separation of the isomers was not pursued because the planned hydrogenation/ring-closing reaction sequence was envisaged to give a single product regardless of olefin geometry. The hydrogenation of the two olefin moieties, simultaneous deprotection of the pyrrolidine nitrogen atom, and concomitant reductive amination/ring closure was achieved smoothly by hydrogenation (55 psi) over 10% Pd−carbon. This one-pot transformation furnished (−)-monomorine (**12**) in 87% yield as a single enantiomer. It is noteworthy that only *R*-stereochemistry was obtained at C5 of the indolizidine system. This result was consistent with previous reports that describe the delivery of hydrogen to the intermediate imine double bond, syn to the C8a H-atom.[13a] The relative stereochemistry and absolute configuration of the (−)-monomorine was confirmed by comparison to the published ^{1}H NMR spectrum,^{13}C NMR spectrum, and the specific rotation, respectively, and all were in excellent agreement.[14]

In summary, we have developed a synthetic route that exploits the natural stereochemistry inherent to cocaine for the synthesis of an enantiopure *cis*-2,5-pyrrolidine building block (**8**). The enantiopure building block **8** was ideally suited for the construction of more complex pyrrolidine-based alkaloids due to the asymmetry of the appendages and the orthogonal reactivity of the functional/protecting groups. The utility of this compound as a chiral building block was demonstrated by the short and efficient synthesis of (−)-monomorine (**12**, six steps, 37% overall yield from **8**). This approach will undoubtedly be equally as effective for providing other natural and nonnatural derivatives for structure−activity studies and will be the subject of future investigations.

Experimental Section

(1*R*)-*N*-Benzyloxycarbonyl-2-oxo-8-azabicyclo[3.2.1]octane (6). Benzyl chloroformate (18 mL, 128 mmol) was added to a solution of **4** (3.6 g, 26 mmol) and potassium carbonate (180 mg, 1.3 mmol) in toluene (80 mL). The solution was heated to reflux for 48 h. The solvent was removed under reduced pressure, and the residue was dissolved in water (50 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1:1) to yield **6** as a colorless oil (3.42 g, 56%). $[\alpha]^{20}_D$ −5.7 (*c* 2.5, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.36−7.27 (m, 5H), 5.17−5.11 (m, 2H), 4.51−4.45 (m, 2H), 2.48−2.42 (m, 2H), 2.38−2.32 (m, 2H), 2.25−2.18 (m, 2H), 1.86−1.77 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 205.3, 153.8, 136.2, 128.4, 128.2, 128.0, 127.8, 67.0, 64.1, 52.8, 32.4, 30.4, 27.8. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.65; H, 6.74; N, 5.62.

(1*R*)-*N*-Benzyloxycarbonyl-2-methoxy-8-azabicyclo[3.2.1]oct-2-ene (7). A solution of trimethyl orthoformate (3.4 g, 32 mmol), **6** (5.5 g, 21 mmol), and PTSA·H_2O (400 mg, 2 mmol) was stirred vigorously at 80 °C under nitrogen for 5 h. The mixture was cooled to rt, and the solvent was evaporated to dryness under reduced pressure. The residue was purified via bulb-to-bulb distillation under a vacuum (1 mmHg) to afford **7** as a colorless oil (5.5 g, 95%). ^{1}H NMR ($CDCl_3$) 7.33 (brs, 5H), 5.13 (q_{AB}, J_{AB} = 12 Hz, $\Delta\nu$ = 2 Hz, 2H), 4.39 (m, 1H), 4.25 (m, 2H), 3.54 (s, 3H), 2.68 (m, 1H), 2.13−1.98 (m, 3H), 1.80 (dd, *J* = 15.2, 4.4 Hz, 1H), 1.64 (m, 1H). ^{13}C NMR ($CDCl_3$) δ161.0, 155.3, 136.6, 128.4, 128.0, 127.3, 92.8, 67.0, 54.5, 54.4, 52.2, 28.8, 28.0, 25.3. HRMS(EI) calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1358.

(2*R*,5*S*)-*N*-Benzyloxycarbonyl-2-methoxylcarbonyl-5-(2-oxoethyl)-pyrrolidine (8). Ozone was bubbled through a solution of **7** (5.3 g, 19 mmol) in CH_2Cl_2 (40 mL) at −78 °C until a slight blue color persisted. The mixture was then flushed with nitrogen for 10 min. Triphenylphosphine (10 g, 39 mmol) was then added to the solution, and the mixture was stirred overnight. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to yield **8** as a colorless oil (4.4 g, 74%). $[\alpha]^{20}_D$ +18.5 (*c* 2.5, MeOH). Major conformer: ^{1}H NMR ($CDCl_3$) 9.83 (s, 1H), 7.34−7.30 (m, 5H), 5.20−5.04 (m, 2H), 4.58−4.38 (m, 1H), 3.62 (s, 3H), 3.33 (m, 1H), 2.73−2.62 (m, 2H), 2.23−2.19 (m, 2H), 2.03−1.99 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 200.7, 173.1, 153.8, 136.2, 128.2, 127.9, 127.5, 66.9, 59.8, 59.4, 53.9, 48.1, 30.1, 28.0. Minor conformer: ^{1}H NMR ($CDCl_3$) 9.73 (s, 1H), 7.34−7.30 (m, 5H), 5.20−5.04 (m, 2H), 4.58−4.38 (m, 1H), 3.76 (s, 3H), 3.15 (m, 1H), 2.73−2.62 (m, 2H), 2.23−2.19 (m, 2H), 2.03−1.99 (m, 2H). Anal. Calcd for $C_{16}H_{19}NO_5$·1/2H_2O: C, 61.13; H, 6.41; N, 4.46. Found: C, 61.35; H, 6.32; N, 4.45.

(2*R*,5*S*)-*N*-Benzyloxycarbonyl-2-methoxycarbonyl-5-(2,2-dimethoxyethyl)-pyrrolidine (9). Trimethylorthoformate (2.5 g, 24 mmol) was added to a solution of aldehyde **8** (0.8 g, 2.6 mmol) and $CeCl_3$·7H_2O (1.0 g, 2.7 mmol) in methanol (10 mL) for 30 min. The reaction was quenched with saturated $NaHCO_3$ (5 mL), and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine solution, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. This afforded the acetal **9** (0.90 g, 92%) in sufficient purity for use in the next step. ^{1}H NMR ($CDCl_3$) δ 7.34−7.30 (m, 5H), 5.24−5.10 (m, 2H), 4.58−4.38 (m, 1H), 4.19 (m, 1H), 3.67 (s, 3H), 3.33−2.73 (m, 7H), 2.73−2.62 (m, 2H), 2.23−2.19 (m, 2H), 2.03−1.99 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 173.1, 153.8, 136.2, 128.2, 127.9, 127.5, 101.2, 66.9, 59.8, 59.4, 48.1, 42.1, 39.0, 26.6, 22.5. HRMS(EI) calcd for $C_{18}H_{25}NO_6$ 351.1682, found 351.1658.

(2*R*,5*S*)-*N*-Benzyloxycarbonyl-2-(1-butenyl)-5-(3-oxoethyl)-pyrrolidine (10). A solution of DIBAL-H (1.0 M in toluene, 1.1 mL, 1.1 mmol) was added dropwise over 30 min to a solution of **9** (0.20 g, 0.60 mmol) in toluene (3 mL) at −78 °C. After 10 min, Et_2O (5 mL), H_2O (2 mL), and 15% NaOH (3 mL) were added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with Et_2O (2 × 10 mL), washed with brine solution, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was dissolved in toluene (3 mL) and added to a previously prepared solution of $CH_3CH_2CH_2PPh_3Br$ (0.44 g, 1.1 mmol) and *t*-BuOK (0.12 g, 1.1 mmol) in toluene (5 mL) that had been stirred at rt for 1.5 h. The mixture was stirred at rt for 8

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h, then EtOAc (20 mL) and saturated $Na_2S_2O_3$ solution (10 mL) were added to the reaction mixture. The reaction mixture was extracted with EtOAc (2 × 10 mL), washed with brine, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue (0.11 g) was dissolved in acetone (10 mL). PTSA·H_2O (0.012 g, 0.06 mmol) was added, and the mixture was stirred for 30 min. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL). The organic solution was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield **10** as a colorless oil (0.086 g, 55% overall). ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 5.42 (brs, 1H), 5.29−5.24 (m, 1H), 4.61 (brs, 1H), 4.37−4.31 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.94 (brs, 1H), 2.56−2.49 (m, 1H), 2.18−1.99 (m, 2H), 1.73−1.64 (m, 4H), 1.51−1.33 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}CNMR ($CDCl_3$) δ 200.6, 153.8, 136.2, 132.4, 128.4, 128.2, 127.9, 127.5, 66.9, 55.2, 53.9, 48.1, 30.1, 28.0, 26.7, 15.1. HRMS(EI) calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1685.

(2*R*,5*S*)-*N*-Benzyloxycarbonyl-2-(1-butenyl)-5-(4-oxopent-2-enyl)-pyrrolidine (11). To a stirred solution of lithium chloride (15 mg, 0.4 mmol) in CH_3CN (10 mL) was added dimethyl (2-oxopropyl)phosphonate (125 mg, 0.8 mmol), DBU (0.4 mL, 0.3 mmol), and **10** (105 mg, 0.3 mmol). The mixture was stirred under nitrogen for 24 h. The solvent was evaporated to dryness under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to yield **11** as a colorless oil (83 mg, 80%). ^{1}H NMR ($CDCl_3$) δ 7.38−7.30 (m, 5H), 6.80−6.72 (m, 1H), 6.11−6.04 (m, 1H), 5.31−5.19 (m, 1H), 5.15−5.08 (m, 1H), 4.62 (brs, 1H), 4.08 (brs, 1H), 2.70 (brs, 1H), 2.40 (brs, 1H), 2.20 (s, 3H), 2.09−2.05 (m, 2H), 2.00−1.92 (m, 2H), 1.71−1.61 (m, 4H), 1.11−0.84 (m, 3H). HRMS(EI) calcd for $C_{21}H_{27}NO_3$ 341.1991, found 341.1983.

(−)-Monomorine (12). A solution of **11** (70 mg, 0.2 mmol) and 10% Pd/C (14 mg) in CH_3OH (10 mL) was hydrogenated at 55 psi for 24 h on a Parr hydrogenation apparatus. The solids were removed by filtration through a pad of celite, and the solvent was removed under reduced pressure. The residue was purified by chromatography using a short column of silica gel ($CH_3OH/CHCl_3$), and a light yellow oil was obtained. The oil was dissolved in CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide **12** (35 mg, 87%) as a light yellow oil. $[\alpha]^{20}_D$ −35.6 (*c* 0.5, *n*-hexane), lit. $[\alpha]^{20}_D$ −35.8 (*c* 1.35, *n*-hexane).[14c] ^{1}H NMR δ ($CDCl_3$) 2.54−2.44 (m, 1H), 2.25−2.20 (m, 1H), 2.08−2.01 (m, 1H), 1.86−1.42 (m, 8H), 1.40−1.26 (m, 8H), 1.13 (d, J = 6.4 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 67.1, 62.8, 60.2, 39.7, 35.8, 30.8, 30.3, 29.7, 29.4, 24.8, 22.8, 22.6, 14.4.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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