Enantiospecific Synthesis of Natural (−)-Cocaine and Unnatural (+)-Cocaine from D- and L-Glutamic Acid

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Natural (−)-cocaine and unnatural (+)-cocaine have been synthesized enantiospecifically from D- and L-glutamic acid, respectively. The axial−equatorial substitutents were introduced by a stereo- and regiospecific dipolar cycloaddition to the corresponding (1*R*,5*S*)- and (1*S*,5*R*)-*N*-BOC-nortropenes with (ethoxycarbonyl)formonitrile *N*-oxide. A sequence of subsequent stereochemically controlled transformations converted the fused isoxazoline to the requisite *β*-hydroxy ester. Synthesis of the key intermediate *N*-BOC-nortropenes involved construction of the 8-azabicyclo[3.2.1]octane framework by Dieckmann condensation of cis-5-substituted D- and L-proline esters. For comparison, (1*R*,5*S*)-*N*-BOC-nortropene also was derived by degradation from natural cocaine. The cis-5-substituted D- and L-proline esters were obtained by sulfide contraction and subsequent catalytic hydrogenation to induce stereospecifically the C-5 stereochemistry from D- and L-thiopyroglutamate, which in turn were prepared from D- and L-glutamic acids, respectively.

Introduction

(−)-Cocaine is the flagship compound of a family of tropane alkaloids isolated from the leaves of *Erythroxylon coca* that have been exhaustively reviewed.[1] The profound behavioral and neuronal reinforcing properties of cocaine are commonly believed to be associated with its inhibition of dopamine reuptake,[2] and its abuse is a major social and health problem. There is no effective medication for the treatment of cocaine addition. As a result, major efforts are being expended in the search for cocaine antagonists[3] and development of antibodies and vaccines.[4] For these purposes, a prodigious number of cocaine-related tropane analogues have been synthesized,[3,5] leading to high affinity and selective cocaine receptor ligands and providing information about the structure/activity relationship of cocaine-related tropane derivatives.

Cocaine contains an 8-azabicyclo[3.2.1]octane framework and is one of the eight possible stereoisomers of methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate.[2b] In addition to construction of this azabicyclo ring system, the major hurdle to its synthesis has been control of stereochemistry, both of enantiomeric integrity and of the thermodynamically unstable axial carboxylate function. Most of the nonracemic cocaine analogues were synthesized by the derivatization of natural cocaine,[3c,e,4d,5a−g,j,k] while others were obtained by resolution or separation of racemic or diastereomeric reaction mixtures.[5d,h,l,n,p,q] The original and classical Mannich-type construct for the tropane skeleton, developed over half a century ago by Willstätter, Robinson, and Schöpf[6] as the first biomimetic synthesis, is still employed, for example, in recent syntheses of 6- and 7-hydroxylated cocaine[7] and unnatural (+)-cocaine, which employed a chemical resolution.[8] Several methods em-

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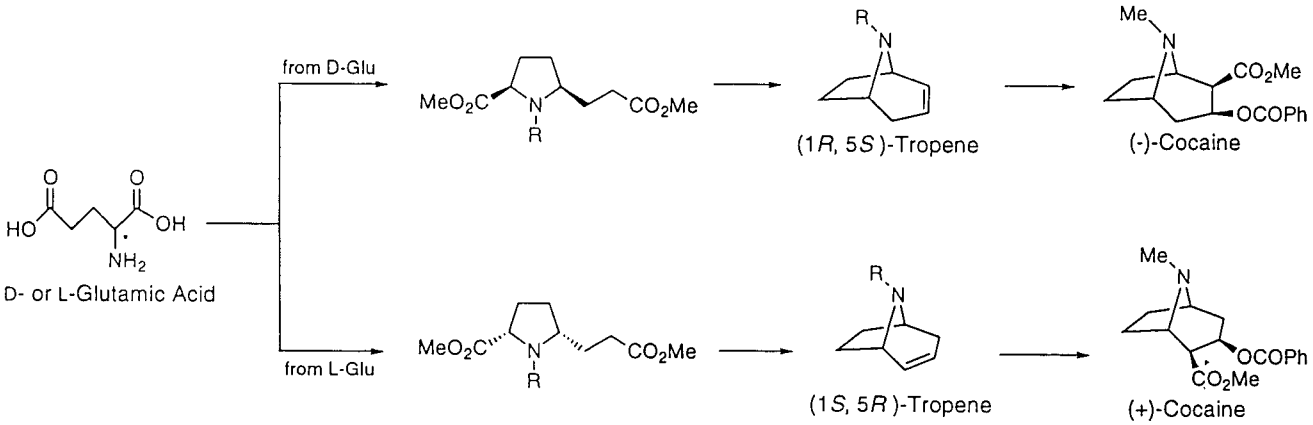

Figure 1. Proposed route to natural (−)-cocaine and unnatural (+)-cocaine from the corresponding glutamic acid.

ploy cycloaddition reactions, including the reaction of rhodium(II)-stabilized vinylcarbenoids with pyrroles,[9] [3 + 4] cycloaddition of iron oxyallyl cations to pyrrole,[10] nitrone cycloaddition,[11] nitroso cycloaddition,[12] and pyridinium betaine-based dipolar cycloaddition.[13] Asymmetric versions of cycloadditions for the stereospecific synthesis of cocaine-related tropane analogues are relatively few and still suffer from low yield and poor stereoselectivity. Thus, there are lacking satisfactory enantiospecific and generally applicable synthetic methods for the synthesis of cocaine and related tropane analogues.

Recently, we have developed a number of methods for the enantiospecific synthesis of aza apical azabicyclos[14] related to the tropane framework. We have sought to adapt and extend these routes to cocaine-related tropanes by methodology that might provide scope and accessibility. Herein we report an enantiospecific route for the synthesis of optically pure natural (−)-cocaine and unnatural (+)-cocaine from simple and readily available compounds.

Results and Discussion

Since cocaine is a cis-2,3-disubstituted tropane, the cis-disubstituents were to be introduced by regio- and stereospecific functionalization of the carbon−carbon double bond of chiral 2-tropenes. Design for synthesis of the 8-azabicyclo[3.2.1]octane skeleton of the tropane alkaloids, such as that of tropene, was related to our methods for the syntheses of ferruginine, anatoxin, and other bicyclos, which involved construction of the bicyclic framework by a transannular cyclization of appropriately cis-5-substituted D- or L-proline ester.[14] For the present case, Dieckmann condensation was proposed as the best route for construction of the functionalized 8-azabicyclo-[3.2.1]octane skeleton. The resulting β-keto ester product then would be converted to a tropene whose carbon−carbon double bond would be suitable for the cis-carboxyhydroxylation by dipolar cycloaddition procedures. As previously shown, the cis-5-substituted D- or L-proline ester would be obtained from thiopyroglutamate by sulfur contraction and subsequent catalytic hydrogenation to stereospecifically fix the geometry at C-5. This projection is shown in Figure 1.

Thiolactam, (*R*)-1-benzyl-5-thionoproline *tert*-butyl ester (**4**), was first prepared as reported[14e] from D-glutamic acid. As shown in Scheme 1, dibenzyl *dl*-malate (**2**) was easily obtained by esterification of *dl*-malic acid (**1**) in 95% yield. Triflate **3**, prepared in situ from the 2-hydroxy ester **2** by treatment with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine, reacted with the (*R*)-thiolactam **4**, followed by sulfide contraction (PPh_3/*N*-methylpiperidine), to give the vinylogous carbamate **5** as a 5.5/1 mixture of isomers in 69% yield. By changing the base to 2,6-lutidine, these procedures were significantly simplified, and the yield of **5** was increased to 76%.

Treatment of olefin **5** under catalytic hydrogenation conditions (H_2, 10% Pd/C) was expected to proceed by debenzylation, followed by decarboxylation, and then hydrogenation of the resultant pyrroline to give the cis-5-substituted D-proline esters **6**. But debenzylation was sluggish, and the major product resulted merely from olefin hydrogenation. Treatment of olefin **5** with ammonium formate in the presence of catalytic 10% Pd/C in MeOH at reflux, however, gave the debenzylated, decarboxylated, and hydrogenated product **6** in 87% yield. Esterification of the amino acid **6** with MeOH/HCl at room temperature afforded a mixture of the mixed methyl *tert*-butyl diester and methyl diester **7**; the same reaction at reflux gave the dimethyl ester **7** in 95% yield.

N-Benzyl diester **8a** was obtained by treatment of diester **7** with benzyl bromide in the presence of K_2CO_3 in 96% yield. Dieckmann condensation of this diester **8a** was readily accomplished in 90% yield by treatment with 200 mol % of KHMDS at −78 °C for 1 h. The cyclization product, β-keto ester **9a**, exists predominantly as its enol. Conceivably, Dieckmann condensation of diester **8a** could afford two β-keto esters. Exclusive formation of **9a**

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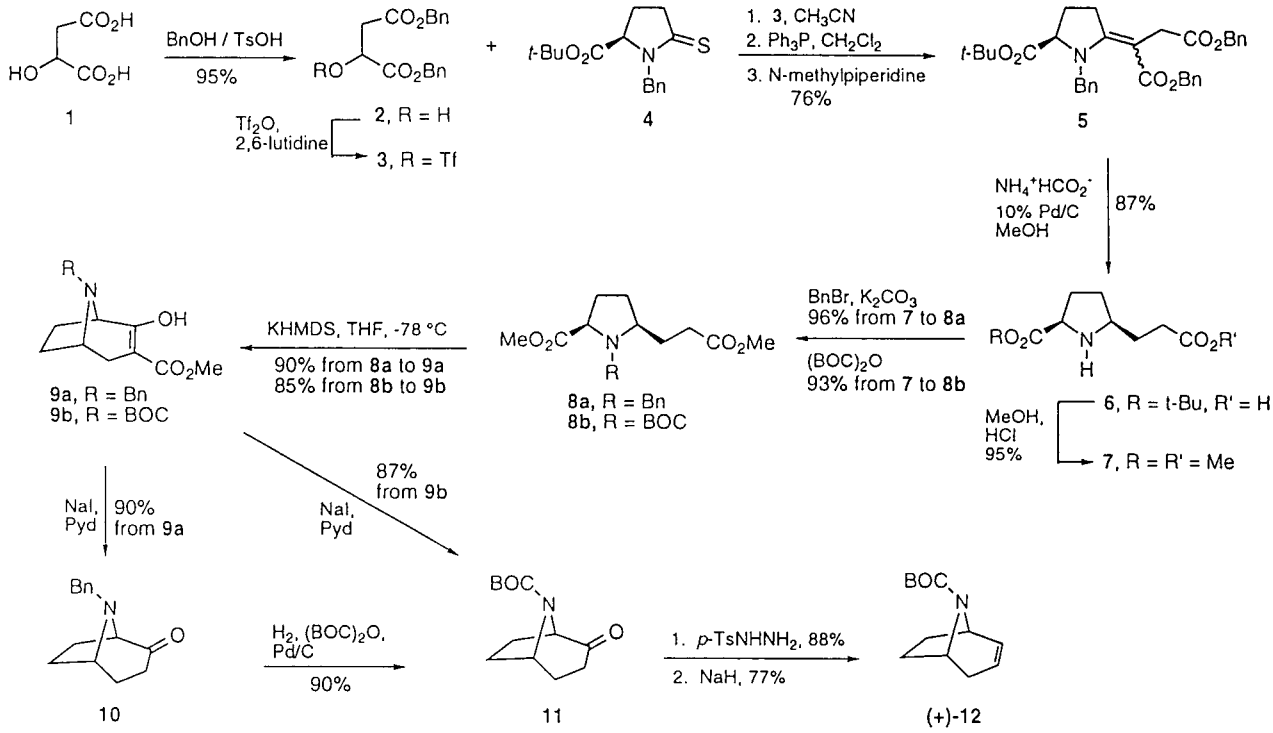
Scheme 1. Synthesis of (1*R*,5*S*)-*N*-BOC-nortropene



undoubtedly results from the use of excess base and the inability of the other isomer to form a stabilizing enolate at the bridgehead.

Many attempts to hydrolyze β-keto ester **9a** under conventional alkaline ($LiOH/THF/H_2O$, $LiOH/MeOH/H_2O$) or acidic ($HCl/MeOH/H_2O$) conditions were unsuccessful. Cleavage and simultaneous decarboxylation to ketone **10** by treatment of β-keto ester **9a** with TMSCl/NaI or n-BuSH/NaH also failed. Nucleophilic displacement of the methyl group and simultaneous decarboxylation to ketone **10** finally was achieved by treatment with NaI in pyridine at reflux in 90% yield.

Since it was clear that the olefin function in the projected tropene would best undergo dipolar cycloaddition with a nitrile oxide after the *tert*-amine had been converted to a nonnucleophilic carbamate (and as was confirmed by preliminary experiments, see the following text), ketone **10** was converted to *N*-BOC ketone **11** in 90% yield by catalytic hydrogenolytic debenzylation in the presence of $(BOC)_2O$.

The necessity of carbamate functionality led to consideration of introducing the BOC group initially and avoiding benzylation−debenzylation. Thus, secondary amine **7** was protected with a BOC group to give **8b** in 93% yield. Treatment of diester **8b** with 200 mol % of KHMDS at −78 °C for 6 h gave, in 85% yield, β-keto ester **9b**, also existing predominantly as its enol. As with the tertiary amine, nucleophilic cleavage and decarboxylation of β-keto ester **9b** with NaI in pyridine at reflux gave ketone **11** in 87% yield. Although these transformations with BOC protection eliminated two steps in the conversion of **7** to **11**, compared to the transformations with the *N*-benzyl group, the overall yield is slightly lower. *N*-BOC ketone **11** then was converted to its tosylhydrazone in 88% yield, from which olefin (1*R*,5*S*)-(+)-**12** was obtained by reaction with NaH in 70% yield.

For confirmation that we were on the correct path, we proceeded to obtain this key intermediate, *N*-BOC-nortropene ((+)-**12**), by degradation from natural cocaine. As shown in Scheme 2, ecgonidine hydrochloride (**13**) was first obtained by hydrolysis and dehydration of natural (−)-cocaine hydrochloride in concentrated HCl under reflux.[15] Catalytic hydrogenation of ecgonidine hydrochloride (**13**) afforded dihydroecgonidine hydrochloride (**14**), which was converted to phenyl selenides (**15**) by the photochemically induced radical decarboxylation protocol[16] in 72% combined yield. The phenyl selenide (**15**) was obtained as two separable diastereomers (3/1). Oxidation of the phenyl selenides (**15**) with $NaIO_4$ afforded corresponding mixtures of phenyl selenoxides in good yield. The phenyl selenoxides were found to undergo a slow elimination to (−)-tropene (**16**) at room temperature on the basis of ^1H NMR analysis. A similar oxidation and elimination of a pyridyl sulfide to give racemic tropene has been reported.[17] Pyrolysis and simultaneous Kugelrohr distillation of the phenyl selenoxides provided (−)-2-tropene (**16**) in 57% yield, in addition to recovered phenyl selenide (**15**) and diphenyl diselenide in 39% and 33% yield, respectively.

Cycloaddition of 2-tropene (**16**) with a nitrile *N*-oxide, (tetrahydro-2*H*-pyran-2-yloxy)acetonitrile oxide, which has been developed for the cis-carboxyhydroxylation of olefins,[18] was investigated. The nitrile *N*-oxide was prepared in situ in the presence of triethylamine,[18] but none of the cycloaddition product was observed under a large variety of conditions, and substantial quantities of 2-tropene (**16**) were recovered. Cycloaddition of 2-tropene with another nitrile *N*-oxide, (ethoxycarbonyl)formonitrile oxide, generated in situ and used for the cis-cyanohydroxylation of olefins,[18] also failed to afford any

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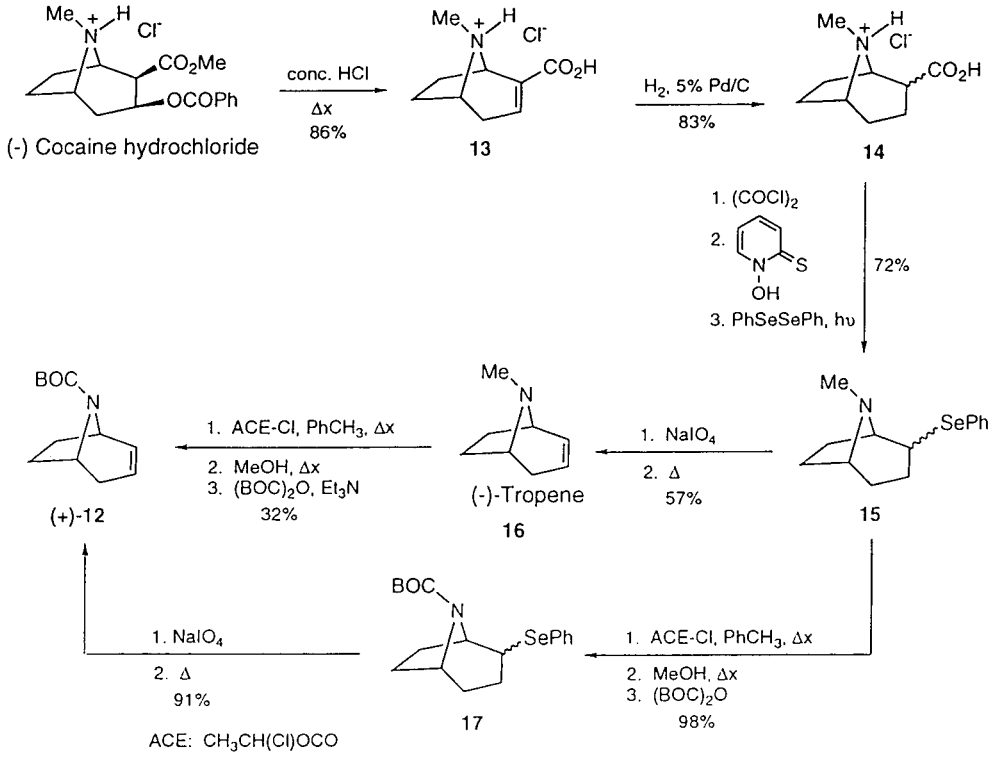
Scheme 2. Degradation of (−)-Cocaine to (1*R*,5*S*)-Tropenes



cycloadduct. The lack of cycloaddition to tropene with these two nitrile *N*-oxides was ascribed to a combination of factors: low reactivity of olefin and potential interaction of the nucleophilic electron lone pair on the nitrogen of tropene with the nitrile *N*-oxides or their precursors.

To convert (−)-tropene (**16**) to its BOC derivative, it was demethylated and carbamoylated in 45% yield by treatment with 1-chloroethyl chloroformate (ACE-Cl) in dry toluene at reflux. The resulting carbamate was methanolized by refluxing in MeOH and then converted to its BOC derivative. Although this approach provided access to compound (+)-**12**, the overall yield was low. Alternatively, the phenyl selenide **15** was demethylated and converted to a carbamate by treatment with ACE-Cl in refluxing toluene. Methanolysis and treatment with triethylamine and $(BOC)_2O$ gave compound **17** in 98% yield. Oxidation of the phenylselenide **17** with $NaIO_4$ in THF/H_2O and subsequent elimination of the resulting selenoxides in refluxing THF in the presence of triethylamine provided (1*R*,5*S*)-(+)-**12** in 91% yield.

The 2-tropene derivative ((1*R*,5*S*)-(+)-**12**) obtained by degradation of natural cocaine is identical to the totally synthetic product obtained from D-glutamic acid and *dl*-malic acid. Thus, the degradation product served to confirm the identity and stereochemistry of tropene analogues obtained from D-glutamic acid and also to establish the absolute configuration of the final products. Moreover, though 2-tropinone[19] as well as ecgonidine[15] have been reported as cocaine degradation products and, especially ecgonidine, have been widely used as chiral building blocks for the synthesis of cocaine-related tropane analogues, the enantiomeric pure 2-tropene (**16**) and its derivative (+)-**12** described here have not been reported previously. In particular, tropene **12**, readily prepared in 32% overall yield from *dl*-malic acid and either D- or L-glutamic acid, provides an attractive basis for the synthesis of numerous analogues derived from the reactions of the double bond.

The dipolar cycloaddition of (1*R*,5*S*)-*N*-BOC nortropene (**12**) was investigated with ethoxycarbonylformonitrile oxide. An addition product was isolated in good yield, to which structure **18** was assigned as shown in Scheme 3. The optimal procedure for the cycloaddition requires a slow addition of excess ethyl chlorooximidoacetate solution to a mixture of (+)-**12** and Na_2CO_3 in binary THF/H_2O solvents so as to minimize the dimerization of the nitrile *N*-oxide and to maintain a weakly alkaline medium, avoiding deprotection of the BOC group on (+)-**12**. The stereo- and regiochemistry of the adduct was predicated on projections that the exo-face was less sterically congested and qualitative calculations of the polarization of the double bond. Of course, definitive proof would await ultimate conversion of **18** to cocaine.

Treatment of **18** with NaOH in $EtOH/H_2O$ at reflux resulted in epimerization at C-2 while forming a β-hydroxy carboxylic acid, *N*-BOC-pseudonorecgonine, instead of the desired *N*-BOC-norecgonine. Presumably, *N*-BOC-pseudonorecgonine was formed via hydrolysis of the ethyl ester, decarboxylation, and fragmentation of the isoxazoline ring and hydrolysis of the resulting β-hydroxy nitrile, accompanied by epimerization of the C-2 axial substituent, either nitrile, amide, or carboxylate.[20] Mild hydrolysis, however, of ethyl ester **18** with NaOH in $EtOH/H_2O$, followed by careful acidification, gave the carboxylic acid **19** in 95% yield. Thermal decarboxylation and fragmentation of the isoxazoline ring of **19** was best achieved by heating at 105−110 °C to give β-hydroxy

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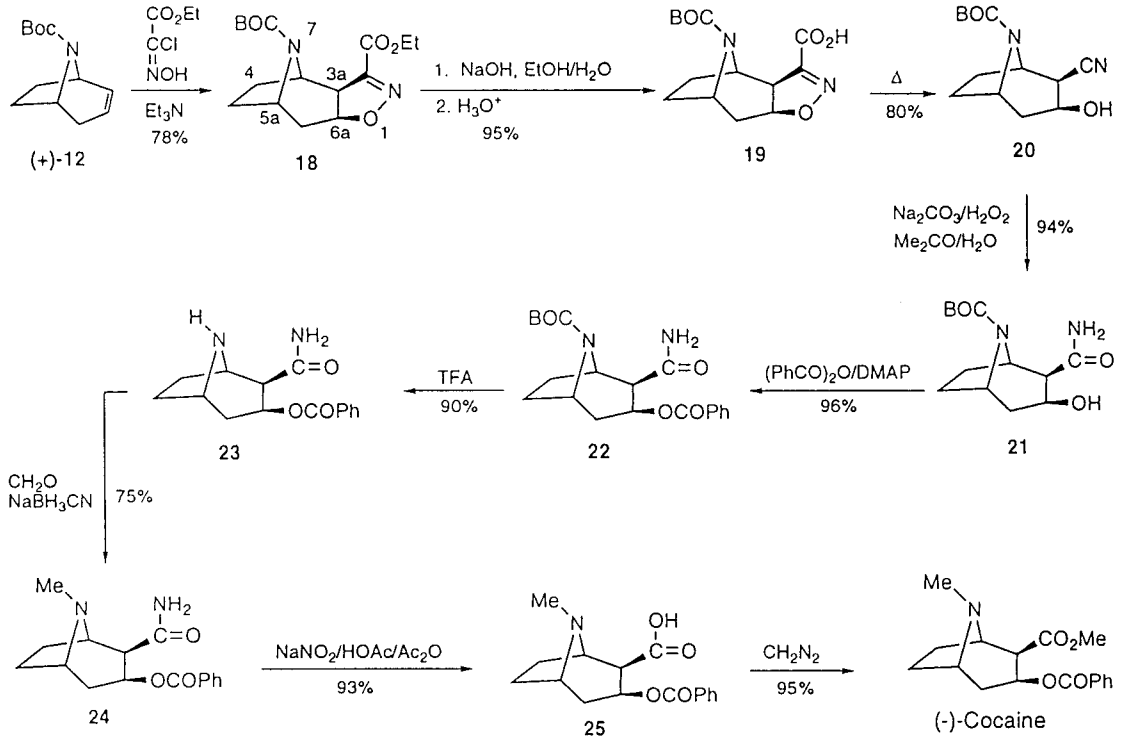
Scheme 3. Synthesis of (−)-Cocaine from (+)-*N*-BOC-nortropene, (+)-12



nitrile **20**. What remained was to convert the nitrile to acid without epimerization.

Hydrolysis of the β-hydroxy nitrile **20** under acidic conditions (HCl, H_2SO_4, BF_3/HOAc) to the β-hydroxy carboxylic acid was unsuccessful. Under these acidic conditions, the BOC group was readily cleaved, and the generated protonated nitrogen caused protonation of the nitrile to become more difficult; also, elimination of the β-hydroxy group became significant. A much milder and stepwise route was devised. The β-hydroxy nitrile was hydrolyzed in 94% yield to the corresponding β-hydroxy amide **21** without epimerization at C-2, by treatment of nitrile **20** with aqueous H_2O_2 in the presence of Na_2CO_3 in acetone/H_2O.

To decrease the hydrophilicity of hydroxy amide **21**, it first was converted to benzoate **22** (benzoic anhydride, DMAP) in 96% yield. Removal of the BOC group in 90% yield was followed by reductive methylation at the bridgehead nitrogen of **23** with aqueous formaldehyde and $NaBH_3CN$ to give tertiary amine **24** in 75% yield. Nitrosation of the primary amide proved to be an ideal way to generate carboxylic acid **25** with the stereochemistry at C-2 unaffected. This was accomplished by treatment of amide **24** with a $NaNO_2$, glacial HOAc/Ac_2O (1/2) solution in 93% yield. Methyl ester formation then furnished the target molecule, natural (−)-cocaine, in 95% yield.

Following the same protocols, unnatural (+)-cocaine was synthesized from (1*S*,5*R*)-*N*-BOC nortropene (−)-**12**, itself prepared from L-glutamic and *dl*-malic acid.

The enantiomeric integrity of synthesized natural and unnatural cocaine was determined by chiral HPLC analysis. Authentic natural (−)-cocaine was prepared from (−)-cocaine hydrochloride.[21] Thus, the enantiomeric purity of our synthetic (−)-cocaine prepared from D-glutamic acid was found to be 100%, while that of unnatural (+)-cocaine synthesized from L-glutamic acid had an er of 98/2, which could be improved to 100% by a single recrystalization.

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Conclusion

We have developed an enantiospecific synthetic route to enantiomerically pure natural and unnatural cocaines. The component compounds of this synthesis are D- or L-glutamic acid, *dl*-malic acid, and glycine. The key intermediate is the chiral tropene **12**, formed via Dieckmann condensation of cis-5-substituted D- or L-proline ester and the regio- and stereospecific functionalization of this tropene. The protocols and starting and intermediate compounds are quite versatile and should provide scope for further extension to chiral cocaine analogues.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. Column chromatography was performed using 230−400 mesh silica gel, and TLC analyses were performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates visualized with UV light (254 nm), followed by heating with ethanolic phosphomolybdic acid. Final organic solutions were dried over Na_2SO_4 before filtration and evaporation using a Berkeley Rotavap. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane (δ 0.0 for ^1H), and $CDCl_3$ (δ 77.0 for ^{13}C), $(CD_3)_2SO$ (δ 39.5 for ^{13}C), and CD_3OD (δ 49.0 for ^{13}C) as internal reference. ^1H coupling constants, *J*, are reported in Hz; DEPT experiments were carried out with ^{13}C NMR acquisition, and the carbon multiplicities are listed as (0) quaternary, (1) methine, (2) methylene, (3) methyl. All chemical shifts are reported in δ ppm. THF and Et_2O were dried by distillation from Na−benzophenone ketyl under nitrogen; pyridine, 2,6-lutidine, hexanes, C_6H_6, Et_3N, DMF, CH_3CN, CH_2Cl_2, $ClCH_2CH_2Cl$, and *N*-methylpiperidine were dried by distillation from CaH_2 under argon; anhydrous MeOH was

distilled from Mg; acetyl chloride, oxalyl chloride, benzaldehyde, and benzyl alcohol were distilled prior to use. Tf_2O was freshly distilled from P_2O_5 before use. Elemental microanalyses were determined by the Microanalytical Laboratory, University of California, Berkeley.

Dibenzyl *dl*-Malate (2). To a solution of *dl*-malic acid (26.80 g, 200 mmol) and benzyl alcohol (41.3 mL, 43.2 g, 400 mmol) in dry C_6H_6 (400 mL) in a 1 L round-bottom flask was added *p*-toluenesulfonic acid monohydrate (3.8 g, 20 mmol). To the flask was attached a Dean−Stark water separator with a reflux condenser. The reaction mixture was heated at reflux for 4 h, cooled to room temperature, and then washed with H_2O (100 mL), 5% aqueous K_2CO_3 (100 mL), saturated $NaHCO_3$ (100 mL), and saturated NaCl (100 mL). The organic layer was dried, filtered, and evaporated. Chromatography of the residue on silica gel, eluting first with 2% MeOH/ CH_2Cl_2 and then with 5% MeOH/CH_2Cl_2, gave the product as a pale yellow oil (59.4 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.40−7.35 (m, 10H), 5.20 (s, 3H), 5.12 (s, 3H), 4.60 (m, 1H), 3.22 (d, 1H, J = 5.4, exchangeable with D_2O), 2.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.1 (0, 1C), 170.2 (0, 1C), 135.4 (0, 1C), 135.0 (0, 1C), 128.6, 128.5, 128.4, 128.3, and 128.2 (1, 6C), 67.6 (2, 1C), 67.3 (1, 1C), 66.7 (2, 1C). Anal. Calcd for $C_{34}H_{37}NO_6$: C, 68.8; H, 5.8. Found: C, 69.0; H, 5.8.

(2*R*)-(*E* and *Z*)-*N*-Benzyl-5-[1′,2′-bis(benzyloxycarbonyl)ethylidene]proline *tert*-Butyl Ester ((−)-5). To a solution of dibenzyl *dl*-malate (15.51 g, 49.4 mmol) and 2,6-lutidine (5.80 g, 6.27 mL, 54.1 mmol) in CH_2Cl_2 (150 mL) at −25 °C under N_2 was added dropwise Tf_2O (12.86 g, 7.67 mL, 45.5 mmol) over 15 min, and the reaction mixture was stirred for 2.75 h between −10 and −5 °C. To the resulting solution of crude triflate **3** at −10 °C was added D-thiolactam **4**[14e] (11.53 g, 39.5 mmol), and the solution was stirred for 24 h at room temperature. The reaction mixture was then cooled at 0 °C, PPh_3 (19.45 g, 74.1 mmol) was added, and the resulting solution was allowed to warm to room temperature over 1 h. After the solution was cooled to −12 °C, *N*-methylpiperidine (9.0 mL, 74.2 mmol) was added dropwise over 15 min, and the mixture was allowed to warm to −3 °C and stirred for 14 h. The reaction mixture was washed with 0.5 M KH_2PO_4 (2 × 400 mL) and saturated $NaHCO_3$ (400 mL), the aqueous washes were extracted separately with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The gummy residue was then triturated with 7/3 hexanes/EtOAc. The hexanes/EtOAc extracts were dried, filtered, and evaporated to a gummy solid, which was dissolved in CH_2Cl_2. Chromatography, eluting with 1/4 EtOAc/hexanes, gave the product (+)-**5** as a colorless thick oil (16.70 g, 76%): $[\alpha]^{21}_D$ −16.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.12 (m, 15H), 5.10 (d, J = 2.1, 2H), 5.00 (s, 2H), 4.82 (d, J = 16.3, 1H), 4.40 (d, J = 16.3, 1H), 3.88 (dd, J = 8.4, 4.9, 1H), 3.48 (m, 2H), 3.35−3.20 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.2 (0, 1C), 169.0 (0, 1C), 164.9, (0, 1C), 137.3 (0, 1C), 136.8 (0, 1C), 136.0 (0, 1C), 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.4, and 127.1 (each 1, each 1C), 88.8 (0, 1C), 81.8 (2, 1C), 66.1 (1, 1C), 65.2 (2, 1C), 53.1 (2, 1C), 34.0 (2, 1C), 34.0 (2, 1C), 33.9 (2, 1C), 27.8 (3, 1C), 26.3 (2, 1C). Anal. Calcd for $C_{34}H_{37}NO_6$: C, 73.5; H, 6.7; N, 2.5. Found: C, 73.1; H, 6.9; N, 2.2.

(2*S*)-(*E* and *Z*)-*N*-Benzyl-5-[1′,2′-bis(benzyloxycarbonyl)ethylidene]proline *tert*-Butyl Ester ((+)-5, Structure Not Shown). This enantiomer was prepared similarly from **2** and L-thiolactam **4**:[14e] $[\alpha]^{22}_D$ +17.4° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**5**.

(2*R*,5*S*)-5-[1′-(2′-Hydroxycarbonyl)ethyl]proline *tert*-Butyl Ester ((+)-6). To a degassed solution of the ethylidene compound (−)-**5** (20.84 g, 37.5 mmol) and ammonium formate (35.43 g, 563 mmol) in MeOH (250 mL) was added 10% Pd/C (12 g), and the resulting suspension was heated at reflux for 12 h; the white solid condensing on the wall of the condenser was removed repeatedly. The reaction mixture was then filtered, the filter was rinsed with MeOH, and the filtrate was evaporated to give an oil residue. ^{1}H NMR analysis showed that the residue was mainly the desired amino acid containing small amounts of ammonium formate and solvent. Chromatography on a short column (20% MeOH/CH_2Cl_2) gave (+)-**6** (7.93 g, 87%): $[\alpha]^{22}_D$ +1.5° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.12 (dd, 1H), 3.42 (m, 1H), 2.50−1.62 (m, 8H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.7, 170.3, 83.0, 60.5, 59.4, 34.0, 30.8, 29.7, 29.0, 27.9.

(2*S*,5*R*)-5-[1′-(2′-Hydroxycarbonyl)ethyl]proline *tert*-Butyl Ester ((−)-6, structure not shown): $[\alpha]^{22}_D$ −1.4° (*c* 1.4, MeOH); spectral and chromatographic properties identical with (+)-**6**.

(2*R*,5*S*)-5-[1′-(2′-Methoxycarbonyl)ethyl]proline Methyl Ester ((+)-7). Acetyl chloride (1 mL) was added dropwise to MeOH (5 mL) at 0 °C, the solution was stirred for 15 min, and then to this solution was added a MeOH solution (5 mL) of crude (+)-**6** (199 mg). The resulting mixture was heated at reflux for 14 h and then evaporated. The residue was dissolved in CH_2Cl_2 and washed with 10% Na_2CO_3; the organic layer was dried, filtered, and evaporated; and the residue was chromatographed, eluting with 10% MeOH/CH_2Cl_2 to give the diester (+)-**7** as a colorless oil (170 mg, 95%): $[\alpha]^{21}_D$ +20.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.75 (s, 3H), 3.15 (br, 1H), 2.80 (m, 1H), 2.60−1.85 (m, 8H), 1.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 175.2, 173.7, 59.7, 59.1, 52.0, 51.5, 31.7, 31.3, 30.7, 29.9. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.8; H, 8.1; N, 6.5. Found: C, 55.5; H, 8.1; N, 6.4.

(2*S*,5*R*)-5-[1′-(2′-Methoxycarbonyl)ethyl]proline Methyl Ester ((−)-7, structure not shown): $[\alpha]^{22}_D$ −19.4° (*c* 1.25, $CHCl_3$); spectral and chromatographic properties identical with (+)-**7**.

(2*R*,5*S*)-*N*-Benzyl-5-[1′-(2′-methoxycarbonyl)ethyl]proline Methyl Ester ((+)-8a). To an CH_3CN solution (14 mL) of (+)-**7** (2.33 g, 10.8 mmol) and benzyl bromide (1.97 g, 1.38 mL, 11.5 mmol) under magnetic stirring was added K_2CO_3 (4.93 g, 36.5 mmol). The resulting suspension was stirred at room temperature for 14 h and filtered, the solid was washed with CH_2Cl_2, and the filtrate was evaporated. Chromatography (1/4 EtOAc/hexanes) of the residue gave (+)-**8** as a colorless oil (3.16 g, 96%): $[\alpha]^{21}_D$ +2.8° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30−7.15 (m, 5H), 4.00 (d, J = 13.8, 1H), 3.66 (m, 4H), 3.46 (s, 3H), 3.30 (dd, 1H), 2.80 (m, 1H), 2.42 (m, 1H), 2.28 (m, 1H) 2.25−1.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.8, 174.0, 138.0, 129.3, 127.9, 126.9, 66.0, 63.2, 57.3, 51.3, 51.2, 30.1, 29.4, 29.0, 28.1. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.9; H, 7.6; N, 4.6. Found: C, 66.5; H, 7.8; N, 4.5.

(2*S*,5*R*)-*N*-Benzyl-5-[1′-(2′-methoxycarbonyl)ethyl]proline Methyl Ester ((−)-8a, structure not shown): $[\alpha]^{22}_D$ −1.9° (*c* 1.05, $CHCl_3$); spectral and chromatographic properties identical with (+)-**8a**.

Methyl (1*R*,5*S*)-8-Benzyl-8-azabicyclo[3.2.1]-2-octanone-3-carboxylate ((+)-9a). To a solution of diester (+)-**8a** (3.16 g, 10.34 mmol) in THF (100 mL) at −78 °C was added a 1 M KHMDS solution in THF (22.6 mL, 22.6 mmol). The reaction mixture was stirred at −78 °C for 1 h and then poured into an ice-cooled mixture of EtOAc (700 mL) and pH 7.0 phosphate buffer (700 mL). The resulting mixture was separated, the aqueous phase was further extracted with EtOAc (4 × 200 mL), and the combined organic phases were washed with saturated NaCl (200 mL), dried, filtered, and evaporated. Chromatography of the residue, using 1/4 EtOAc/hexanes as eluent, gave the bicyclic ketone (+)-**9a** (2.55 g, 90%). NMR analysis indicated this compound exists predominantly in the enol form: $[\alpha]^{20}_D$ +116° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.30 (br, 1H, exchangeable with D_2O), 7.40−7.12 (m, 5H), 3.80−3.60 (m, 5H), 3.40−3.30 (m, 2H), 2.62 (dd, 1H), 2.20−1.85 (m, 4H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.7, 172.7, 139.0, 128.7, 128.2, 126.9, 91.8, 59.9, 55.3, 52.7, 51.3, 32.8, 29.4, 27.4. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.3; H, 7.0; N, 5.1. Found: C, 70.0; H, 7.3; N, 5.0.

Methyl (1*S*,5*R*)-8-Benzyl-8-azabicyclo[3.2.1]-2-octanone-3-carboxylate ((−)-9a, structure not shown): $[\alpha]^{22}_D$ −108° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**9a**.

(1*R*,5*S*)-8-Benzyl-8-azabicyclo[3.2.1]-2-octanone ((−)-10). To a solution of (+)-**9a** (1.07 g, 3.91 mmol) in pyridine (35 mL) was added NaI (11.7 g, 78 mmol). The suspension was heated at reflux for 8 h and then evaporated, and the

residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with additional CH_2Cl_2 (3 × 50 mL), and the combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ (50 mL), dried, filtered, and evaporated. Chromatography of the residue, eluting with 1/2 EtOAc/hexanes, gave the ketone (−)-**10** as an oil (758 mg, 90%): $[\alpha]^{21}_D$ −9.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.10 (m, 5H), 3.68 (s, 2H), 3.38 (m, 2H), 2.42−2.15 (m, 4H), 1.82−1.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 210.0, 138.6, 128.5, 128.3, 127.1, 69.8, 56.9, 54.4, 33.0, 29.9, 26.8, 26.7.

(1*S*,5*R*)-8-Benzyl-8-azabicyclo[3.2.1]-2-octanone ((+)-10, structure not shown): $[\alpha]^{22}_D$ +9.6° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**10**.

(1*R*,5*S*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone ((−)-11). To a degassed solution of (−)-**10** (1.42 g, 6.70 mmol) in MeOH (60 mL) were added $(BOC)_2O$ (4.78 g, 21.9 mmol) and 10% Pd/C (321 mg). The resulting suspension was stirred under H_2 (balloon) for 5 h, filtered, and evaporated. The solid residue, dissolved in a small amount of CH_2Cl_2, was chromatographed, eluting with 1/2 EtOAc/hexanes, to give (−)-**11** as a white solid (1.43 g, 96%): mp 92−93 °C; $[\alpha]^{20}_D$ −21.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.42 (bs, 1H), 4.18 (bs, 1H), 2.50−2.15 (m, 4H), 1.90−1.70 (m, 4H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 205.9, 153.5, 80.2, 64.2, 52.5, 32.4, 30.4, 28.2, 27.6. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.0; H, 8.5; N, 6.2. Found: C, 64.2; H, 8.5; N, 5.9.

(1*S*,5*R*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone ((+)-11, structure not shown): $[\alpha]^{11}_D$ +21.6° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (−)-**11**.

(2*R*,5*S*)-*N*-(*tert*-Butyloxycarbonyl)-5-[1′-(2′-methoxycarbonyl)ethyl]proline Methyl Ester ((+)-8b). A solution of (+)-**7** (3.5 g, 16.26 mmol) in MeOH (100 mL), $(BOC)_2O$ (8.87 g, 40.65 mmol), and Et_3N (0.14 mL, 1 mmol) was stirred at room temperature for 14 h and then evaporated, giving an oily residue that was chromatographed, eluting with 1/2 EtOAc/hexanes, to give (+)-**8b** as a colorless oil (4.76 g, 93%): $[\alpha]^{20}_D$ +21° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 58 °C) δ 4.3 (bs, 1H), 3.9 (bs, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.45−1.50 (m, 8H), 1.43 (bs, 9H); ^{13}C NMR ($CDCl_3$, 58 °C) δ 173.5, 173.4, 79.9, 59.9, 57.7, 51.6, 51.1, 30.9, 29.7, 28.2, 27.3. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.4: H, 7.5; N, 4.9. Found: C, 59.8; H, 7.8; N, 4.9.

(2*S*,5*R*)-*N*-BOC-5-[1′-(2′-methoxycarbonyl)ethyl]proline Methyl Ester (−)-8b, structure not shown): $[\alpha]^{21}_D$ −19° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**8b**.

Methyl (1*R*,5*S*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone-3-carboxylate ((+)-9b). To a solution of diester (+)-**8b** (2.20 g, 7.0 mmol) in dry THF (70 mL) at −78 °C was added 1 M KHMDS solution in THF (15.3 mL, 15.3 mmol). The reaction mixture was stirred at −78 °C for 6 h and poured into an ice-cooled mixture of EtOAc (500 mL) and pH 7.0 phosphate buffer (500 mL), and the aqueous phase was further extracted with EtOAc (4 × 200 mL). The combined organic phase was washed with saturated NaCl (200 mL), dried, filtered, and evaporated. Chromatography of the residue using 1/2 EtOAc/hexanes as eluent gave the β-keto ester (1.69 g, 85%). NMR analysis indicated this compound exists predominantly in its enol form: $[\alpha]^{21}_D$ +60° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 58 °C) δ 8.18 (br, 1H), exchangeable with D_2O), 4.20 (bs, 2H), 3.75 (s, 1H), 2.80 (bs 1H), 2.20−1.58 (m, 5H), 1.45 (bs, 9H); ^{13}C NMR ($CHCl_3$, 58 °C) δ 174.4, 172.8, 153.9, 92.2, 80.0, 56.2, 52.6, 51.2, 33.2, 30.3, 29.3, 28.3. Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.1; H, 8.0; N, 4.4. Found: C, 57.4; H, 8.3; N, 4.6.

Methyl (1*S*,5*R*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone-3-carboxylate ((−)-9b, structure not shown): $[\alpha]^{22}_D$ −60° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**9b**.

(1*R*,5*S*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone ((−)-11). To a solution of (+)-**9b** (1.00 g, 3.53 mmol) in pyridine (35 mL) was added NaI (10.6 g, 70.6 mmol), and the suspension was heated at reflux for 7.5 h and then evaporated to dryness. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL), and the aqueous phase was extracted with additional CH_2Cl_2 (3 × 50 mL). The organic phases were combined and washed with saturated aqueous $Na_2S_2O_3$ solution (50 mL), dried, filtered, and evaporated to give an oily residue. Chromatography of this residue using 1/2 EtOAc/hexanes gave ketone (−)-**11** as a white solid (693 mg, 87%): mp 92−93 °C. Spectral and chromatographic properties were identical to those of (−)-**11** prepared from (−)-**10**.

(1*R*,5*S*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octene ((+)-12). To a solution of *p*-toluenesulfonhydrazide (1.42 g, 7.62 mmol) in MeOH (10 mL) was added ketone (−)-**11** (1.43 g, 6.35 mmol). The mixture was stirred at room temperature for 2 h, and the resulting white solid was recrystalized from CH_2Cl_2 to give **(1*R*,5*S*)-8-(*tert*-butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octanone *p*-tosylhydrazone** (2.2 g, 88%): mp 175−180 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.9 (s, 1H), 7.85 (m, 2H), 7.8−7.6 (m, 1H), 7.3−7.18 (m, 2H), 4.82 (d, 1H, major), 4.50 and 4.30 (each bs, each 1H, minor), 4.02 (bs, 1H, major), 2.22 and 2.20 (each s, each 3H), 2.30−1.40 (m, 8H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.7, 155.8, 143.9, 143.2, 135.5, 135.3, 129.5, 1229.2, 128.2, 128.1, 80.9, 79.7, 55.3, 51.4, 33.8, 29.2, 28.3, 28.2, 28.1, 27.0, 26.2, 21.5, 21.4, 18.8. Anal. Calcd for $C_{19}H_{27}N_3O_4S\cdot H_2O$: C, 55.5; H, 7.1; N, 10.2. Found: C, 55.8; H, 6.8; N, 10.3.

A suspension of the above hydrazone (100 mg, 0.254 mmol) and NaH (36.6 mg, 1.52 mmol) in toluene was stirred at room temperature for 30 min and then heated at reflux for 5 h. After being cooled to room temperature, the mixture was neutralized with saturated aqueous NH_4Cl solution, and the aqueous phase was further extracted with CH_2Cl_2. The combined organic phase was dried, filtered, and evaporated. Chromatography of the residue with 1/2 EtOAc/hexanes gave olefin (+)-**12** as an oil (37.0 mg, 70%): $[\alpha]^{22}_D$ +3.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.02 (bs, 1H), 5.55 (m, 1H), 4.35 (bs, 1H), 4.25 (bs, 1H), 2.68 (m, 1H), 2.18 (bs, 1H), 2.20−1.60 (m, 4H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.1, 133.1, 123.9, 79.1, 53.6, 35.0, 34.3, 30.2, 28.5, 28.4. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.2; N, 6.7. Found: C, 68.7; H, 9.3; N, 6.6.

(1*S*,5*R*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octene ((−)-12, structure not shown): $[\alpha]^{22}_D$ −3.0° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**12**.

Ecgonidine ((1*R*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]-2-octene-2-carboxylic Acid) Hydrochloride (13). (−)-Cocaine hydrochloride (20.0 g, 58.86 mmol) was refluxed in concentrated HCl for 24 h.[15] The reaction mixture was cooled to room temperature, diluted with H_2O (150 mL), and extracted with Et_2O (4 × 150 mL). The aqueous solution was evaporated to give a white solid (14.27 g) that was recrystallized from EtOH/EtOAc (1/1) to give ecgonidine hydrochloride (**13**, 11.31 g, 86%): mp 240−242 °C dec (lit.[15] mp 253−258 °C); $[\alpha]^{22}_D$ −54° (*c* 0.93, MeOH). Anal. Calcd for $C_9H_{14}NO_2Cl$: C, 53.1; H, 6.9; N, 6.9. Found: C, 53.0; H, 6.9; N, 6.8.

Dihydroecgonidine Hydrochloride (14). To a degassed solution of ecgonidine hydrochloride (**13**, 6.20 g, 30.44 mmol) in MeOH was added 5% Pd/C (2.30 g), and the resultant suspension was hydrogenated (60 psi, rt) for 6.5 h. The reaction mixture was filtered, the filtrate was evaporated, and the solid residue was digested with MeOH. Evaporation of the methanol solution and recrystallization from 1/3 EtOH/EtOAc gave hydroecgonidine hydrochloride (**14**, 5.84 g, 93%): mp 260−262 °C dec (lit.[22] mp 263 °C); $[\alpha]^{22}_D$ −8.9° (*c* 1.10, MeOH); ^{1}H NMR analysis of **14** in CD_3OD revealed that this compound existed as a 5/1 diastereomeric mixture: for major diastereomer, ^{1}H NMR (CD_3OD) δ 4.13 (m, 1H), 3.89 (m, 1H), 3.03 (m, 1H), 2.81 (s, 3H), 2.31−2.29 (m, 2H), 2.05−1.96 (m, 4H), 1.86−1.82 (m, 2H); ^{13}C NMR (CD_3OD) δ 18.7 (2), 23.2 (2), 24.9 (2), 29.6 (3), 40.0 (3), 45.1 (1), 65.3 (1), 65.8 (1), 173.4

(22) Keimatsu, S.; Inoue, S. *J. Pharm. Soc. Jpn.* **1925**, *518*, 354; *Chem. Abstr.* **1925**, *19*, 2671.

(0); for minor diastereomer, ^{1}H NMR (CD_3OD) δ 4.10 (m, 1H), 3.82 (m, 1H). Anal. Calcd for $C_9H_{16}NO_2Cl$: C, 52.6; H, 7.8; N, 6.8. Found: C, 52.9; H, 8.1; N, 6.7.

(1*R*,5*S*)-8-Methyl-2-(phenylseleno)-8-azabicyclo[3.2.1]-octane (15). To a suspension of carboxylic acid **14** (11.95 g, 58.10 mmol) and oxalyl chloride (2.8 mL, 4.01 g, 31.60 mmol) in CH_2ClCH_2Cl (550 mL) in a 2 L round-bottom flask under N_2 was added DMF (1.72 mL) over 0.5 h. The mixture was stirred at room temperature for 12 h and then evaporated to dryness. Dry CH_2ClCH_2Cl (300 mL) was added to the solid residue and evaporated; this process was repeated. The resultant pale yellow solid was dissolved in 570 mL of CH_2ClCH_2Cl by gentle warming; the solution was cooled to 0 °C and then covered with aluminum foil, and in the dark, Et_3N (17.9 mL) was added, followed by dropwise addition over 50 min of *N*-hydroxy-2-thiopyridone (8.13 g)[23] in CH_2ClCH_2Cl (460 mL). The mixture was allowed to warm to room temperature, stirred for 1.5 h, then evaporated to dryness at room temperature. To the residue in the dark and under a N_2 atmosphere was added 1 L of CH_2Cl_2, cooled 0 °C, and then diphenyl diselenide (60.2 g)[24] was added. The solution was irradiated with two tungsten lamps at 0 °C for 2 h and then allowed to warm to room temperature over 30 min. The resulting mixture was concentrated to about 500 mL, and H_2O (200 mL) was added. After the aqueous phase was basified, with solid Na_2CO_3, it was extracted with CH_2Cl_2 (4 × 200 mL). The organic layers were combined and extracted with 10% tartaric acid (5 × 200 mL) and the tartaric acid extracts were basified with solid Na_2CO_3 and then extracted with CH_2Cl_2, which was dried and evaporated. The residue was chromatographed (15% MeOH/Et_2O) to give the product as two diastereomers in 72% total yield, composed of a major diastereomer as a pale yellow oil (8.84 g, 54%) and a minor diastereomer as a light brown crystalline solid (2.88 g, 18%): major diastereomer, $[\alpha]^{22}_D$ +84° (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.50−1.51 (m, 1H), 1.52−1.56 (m, 2H), 1.80−2.10 (m, 5H), 2.26 (s, 3H), 3.13 (m, 2H), 3.61 (ddd, J = 12.6, 4.8, 2.7, 1H), 7.18−7.26 (m, 3H), 7.45−7.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.9 (2), 24.2 (2), 25.8 (2), 32.2 (3), 40.5 (3), 45.7 (1), 60.6(1), 65.8 (1), 126.9 (1), 128.7 (1), 129.1 (0), 133.6 (1). Anal. Calcd for $C_{14}H_{19}NSe$: C, 59.8; H, 6.8; N, 5.0. Found: C, 59.8; H, 6.8; N, 5.2. For minor diastereomer: $[\alpha]^{22}_D$ +58° (*c* 1.15, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.35 (d, J = 12.8, 1H), 1.53 (q, J = 8.7, 1H), 1.71 (dd, J = 9.3, 5.2, 1H), 1.9−2.1 (m, 5H), 2.23 (s, 3H), 3.07 (m, 1H), 3.28 (m, 1H), 3.42 (m, 1H), 7.21−7.28 (m, 3H) 7.50−7.91 (m, 2H); ^{13}C NMR (CD_3OD) δ 23.2 (2), 24.6 (2), 26.7 (2), 29.6 (2), 42.3(3), 49.6 (1), 62.3 (1), 67.5 (1), 126.4 (1), 128.7 (1), 132.3 (0), 133.0 (1). Anal. Calcd for $C_{14}H_{19}NSe$: C, 59.8; H, 6.8; N, 5.0. Found: C, 59.5; H, 6.9; N, 4.9.

(−)-Tropene (16). To a solution of the phenyl selenide **15** (major diastereomer, 1.59 g, 5.67 mmol) in THF (20 mL) cooled to 0 °C was added dropwise a solution of $NaIO_4$ (3.61 g, 16.89 mmol) in H_2O (20 mL). The mixture was stirred at room temperature for 2 h, and the resulting precipitate was removed by filtration and washed with THF (50 mL) and CH_2Cl_2 (100 mL). The filtrate and washings were concentrated to about one-fifth volume, poured into saturated $NaHCO_3$ (150 mL), and then extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extract was dried, filtered, and evaporated to give the corresponding selenoxide as a 1/1 mixture of diastereomers by ^{1}H NMR analysis. The selenoxide (1.68 g, 5.67 mmol) was pyrolyzed and distilled from a Kugelrohr apparatus in a preheated oven at 75 °C/0.08−0.10 Torr. The product was condensed into a bulb, cooled with dry ice−acetone. When pyrolysis was completed (0.5 h) the system was swept with N_2; the distillate was tropene **16** (0.40 g, 57%). The pyrolysis residue was dissolved in a small amount of CH_2Cl_2 and chromatographed (10% MeOH/CH_2Cl_2) to give diphenyl diselenide (0.29 g, 33%) and recovered phenylselenide **15** (0.63 g, 39%). For tropene (−)-**16**: $[\alpha]^{21}_D$ −47° (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.54−1.75 (m, 2H), 1.81−1.87 (m, 1H), 1.97−2.20 (m, 2H), 2.37 (s, 3H), 2.50 (d, J = 19, 1H), 3.19 (m, 2H), 5.52−5.55 (m, 1H), 5.74−5.77 (m, 1H); ^{13}C NMR δ 29.7 (2), 31.8 (2), 33.8 (2), 36.5 (3), 57.7 (1), 58.9 (1), 122.9 (1), 130.7 (1).

Tropene hydrochloride was prepared by adding methanolic HCl to an ether solution of tropene (**16**): mp 258−260 °C dec. Anal. Calcd for $C_8H_{13}N\cdot HCl\cdot H_2O$: C, 54.1; H, 9.1; N, 7.9. Found: C, 54.2; H, 9.1; N, 7.9.

(1*R*,2*S*,5*S*)-8-(*tert*-Butyloxycarbonyl)-2-(phenylseleno)-8-azabicyclo[3.2.1]octane (17). To a solution of the phenylselenide **15** (major diastereomer, 1.36 g, 4.84 mmol) in toluene was added dropwise 1-chloroethyl chloroformate (ACE-Cl, 0.70 mL, 6.78 mmol). The resulting solution was refluxed for 24 h and then evaporated to give **(1*R*,2*S*,5*S*)-8-(1′-chloroethoxycarbonyl)-2-(phenylseleno)-8-azabicyclo[3.2.1]-octane:** ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 2H), 7.25 (m, 3H), 6.62 (m, major, 1H) and 6.55 (m, minor, 1H), 4.40−4.15 (m, 2H), 3.70−3.38 (m, 1H), 2.20−1.45 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 150.2, 150.0, 133.4, 133.0, 132.9, 129.1, 127.3, 127.2, 127.0, 82.9, 82.6, 57.8, 57.7, 53.7, 53.5, 45.0, 44.5, 31.6, 31.5, 27.4, 27.3, 25.4, 25.3, 24.7, 24.6, 24.2, 23.5.

The chloroethoxy intermediate was dissolved in MeOH (40 mL) and refluxed for 2 h, and then the solution was evaporated to a white foam that was redissolved in MeOH (45 mL). To this solution was added Et_3N (0.94 mL, 7.74 mmol) dropwise over 10 min; $(BOC)_2O$ (1.69 g, 14.49 mmol) was then added, and stirring was continued at room temperature for 15 h. Evaporation left a residue that was dissolved in a small amount of 10% CH_3OH/CH_2Cl_2 and chromatographed, eluting with CH_2Cl_2 and then 2% CH_3OH/CH_2Cl_2, to give **17**, major diastereomer, as a colorless oil (1.73 g, 98%): $[\alpha]^{22}_D$ −52° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.52 (bs, 2H), 7.25 (bs, 3H), 4.30−4.10 (m, 2H), 3.65−3.48 (bs, 1H), 2.20−1.15 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 153.0, 146.7, 133.4, 129.1, 127.1, 79.3, 57.7, 52.7, 45.0, 31.4, 27.5, 27.4, 24.9, 24.1. Anal. Calcd for $C_{18}H_{25}NO_2Se$: C, 59.0; H, 6.9; N, 3.9. Found: C, 58.9; H, 6.9; N, 4.5.

The minor diastereomer of **17** was obtained as a white solid similarly from the minor diastereomer of phenylselenide **15**: mp 104−105 °C; $[\alpha]^{22}_D$ +71° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.65 (bs, 2H), 7.22 (bs, 3H), 4.70−4.20 (m, 2H), 3.40 (bs, 1H), 2.20−1.30 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 152.7, 133.5, 130.3, 128.6, 126.9, 79.1, 57.2, 52.4, 47.0, 29.7, 28.2, 27.4, 26.6, 22.9. Anal. Calcd for $C_{18}H_{25}NO_2Se$: C, 59.0; H, 6.9; N, 3.9. Found: C, 58.9; H, 7.2; N, 3.8.

(1*R*,5*S*)-8-(*tert*-Butyloxycarbonyl)-8-azabicyclo[3.2.1]-2-octene ((+)-12). From 17: To a solution of **17** (1.00 g, 2.73 mmol) in THF (35 mL) at 0 °C was added dropwise a solution of $NaIO_4$ in water (35 mL). The reaction mixture was stirred at room temperature for 1 h. The THF was evaporated under reduced pressure at room temperature, and the remainder was partitioned between water and CH_2Cl_2 (50 mL). The aqueous phase was further extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phase was dried, filtered, and evaporated. Chromatography of the residue, eluting with CH_2Cl_2, gave (+)-**12** as a colorless oil (520 mg, 91%); spectral and chromatographic data were identical to those reported above.

From (−)16. To a solution of (−)-**16** (50 mg, 0.41 mmol) in dry toluene (2.0 mL) was added dropwise 1-chloroethyl chloroformate (0.70 mL, 6.78 mmol). The resulting solution was refluxed for 16 h and then evaporated. The residue was chromatographed (10% MeOH/CH_2Cl_2) to give an oil that was dissolved in MeOH (2.0 mL) and refluxed for 16 h. Evaporation left a white foam, which was redissolved in MeOH (2.0 mL); Et_3N (44 μL, 0.365 mmol) was added dropwise, followed by stirring for 10 min; and then $(BOC)_2O$ (159 mg, 0.73 mmol) was added. The reaction mixture was stirred at room temperature for 14 h and then evaporated. Chromatography of the resulting residue (1/2 EtOAc/hexanes) gave (+)-**12** as a colorless oil (26 mg, 32% from **16**), which was identical to the compound obtained from **17** above.

Ethyl (3a*S*,3b*R*,5a*S*,6a*S*)-7-(*tert*-Butyloxycarbonyl)-7-azabicyclo[3.2.1]octano[2,3-*d*]isooxazole-3-carboxylate ((−)-18). To a solution of (+)-**12** (1.00 g, 4.78 mmol) in THF (20 mL) was added a solution of $Na_2CO_3\cdot H_2O$ (12.32 g, 99.4

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mmol) in H_2O (40 mL). To this stirred mixture was added ethyl chlorooximidoacetate (14.49 g, 95.56 mmol)[18] in THF (40 mL) at 0.39 mL/h with a syringe pump, and stirring was continued at room temperature for 16 h. The aqueous layer was extracted with Et_2O (5 × 60 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was chromatographed, eluting with 1/2 EtOAc/hexanes, to give (−)-**18** as a colorless oil (1.22 g, 78%): $[\alpha]^{22}_D$ −20° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1740, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, J = 7.2, 3H), 1.42 (s, 9H), 1.55−1.90 (m, 2H), 1.9−2.2 (bs, 4H), 3.4−3.6(m, 1H), 4.0−4.6 (m, 3H), 4.92 (bs, 1H), 5.24 (dd, J = 8.0, 18.2, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8 (3), 27.3 (2), 28.0 (3), 29.1 (2), 30.3 (22), 36.0 (2), 49.6 (1), 50.5 (1), 51.2 (1), 53.3 (1), 62.3 (2), 76.7 (1), 77.7 (1), 79.7 (0), 151.6 (0), 152.4 (0), 153.0 (0), 160.3 (0). Anal. Calcd for $C_{16}H_{24}NO_{25}$: C, 59.2; H, 7.4; N, 8.6. Found: C, 59.3; H, 7.3; N, 8.9.

Enantiomer (+)-18 (structure not shown): $[\alpha]^{25}_D$ +12° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (−)-**18**.

(3a*S*,3b*R*,5a*S*,6a*S*)-7-(*tert*-Butyloxycarbonyl)-7-azabicyclo[3.2.1]octano[2,3-*d*]isooxazole-3-carboxylic Acid ((−)-19). To a solution of (−)-**18** (795 mg, 2.45 mmol) in EtOH at 0 °C was added 10% aqueous NaOH (35 mL) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1.5 h. The resulting clear solution was cooled to 0 °C, diluted with H_2O (45 mL), and acidified to pH 5.0 by dropwise addition of cold 10% HCl and then it was extracted with 1/3 *i*-PrOH/$CHCl_3$ (7 × 45 mL). The combined organic phase was dried, filtered, and evaporated to give a hygroscopic white foam ((−)-**19**, 700 mg, 96%): $[\alpha]^{22}_D$ −17.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (t, J = 7.2, 3H), 1.50−2.10 (m, 6H), 3.40−3.60 (m, 1H), 4.14 and 4.35 (bs, 1H), 4.92 and 5.05 (bs, 1H), (5.16 (q, J = 8.5, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7 (3), 27.4 and 28.5 (2), 49.8 (1), 51.3 and 52.9 (1), 77.2 and 78.0 (1), 80.7 (0), 152.0 (0), 152.7 and 153.2 (0), 161.8 (0). Anal. Calcd for $C_{14}H_{20}N_2O_5 \cdot H_2O$: C, 53.5; H, 7.0; N, 8.9. Found: C, 53.7; H, 7.0; N, 8.7.

Enantiomer (+)-19 (structure not shown): $[\alpha]^{22}_D$ +17.2° (*c* 1.0, MeOH); spectral and chromatographic properties identical with (+)-**19**.

(1*R*,2*R*,3*S*,5*S*)-8-(*tert*-Butyloxycarbonyl)-2-cyano-3-hydroxy-8-azabicyclo[3.2.1]octane ((−)-20). Acid (−)-**19** (5.96 g, 20.11 mmol) under N_2 was heated in an oil bath at 105−110 °C for 40 min. After being cooled to room temperature, the solid residue was chromatographed (10% MeOH/CH_2Cl_2) to give (−)-**20** as a white solid (4.06 g, 80%): mp 139−140 °C; $[\alpha]^{23}_D$ −9.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 58 °C) δ 1.50 (s, 3H), 1.58−1.65 (dd, 2H), 1.79−2.05 (m, 4H), 2.42 (bs, 1H), 3.07 (dd, 1H), 4.15 (m, 1H), 4.42 (m, 1H), 4.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.3, 38.2, 41.9, 52.1, 54.0, 63.1, 80.5, 117.4, 152.5. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.9; H, 8.0; N, 11.1. Found: C, 61.6; H, 8.2; N, 11.2.

Enantiomer (+)-20 (structure not shown): $[\alpha]^{24}_D$ +7.2° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**19**.

(1*R*,2*R*,3*S*,5*S*)-8-(*tert*-Butyloxycarbonyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-2-carboxamide ((+)-21). To a solution of (−)-**20** (3.18 g, 12.60 mmol) in acetone (60 mL) were added H_2O (30 mL) and 10% Na_2CO_3 (60 mL). To the resulting solution at 0 °C was added 30% aqueous H_2O_2 dropwise (30 mL), and the reaction mixture was stirred at room temperature for 24 h and then concentrated to about 100 mL. The remaining aqueous phase was extracted with 1/3 *i*-PrOH/$CHCl_3$ (6 × 300 mL), and the combined organic phase was dried, filtered, and evaporated. Recrystallization from THF/hexanes gave (+)-**21** (3.20 g, 94%): mp 153−154 °C; $[\alpha]^{22}_D$ +18.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.64−2.02 (m, 6H), 2.79 (dd, 1H), 4.15 (bs, 1H), 4.38 (bs, 1H), 4.65 (bs, 1H), 5.63 (bs, 2H), 7.28 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.2, 39.0, 49.5, 52.8, 54.1, 64.4, 80.1, 153.4, 175.7. Anal. Calcd for $C_{13}H_{20}N_3O_3$: C, 57.8; H, 8.3; N, 10.4. Found: C, 58.0; H, 8.3; N, 10.6.

Enantiomer (−)-21 (structure not shown): $[\alpha]^{22}_D$ −18.0° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**21**.

(1*R*,2*R*,3*S*,5*S*)-8-(*tert*-Butyloxycarbonyl)-3-(benzoyloxy)-8-azabicyclo[3.2.1]octane-2-carboxamide ((−)-22). A solution of (+)-**21** (1.85 g, 6.83 mmol), benzoic anhydride (3.09 g, 13.66 mmol) and DMAP (1.83 g, 15.03 mmol) in CH_2Cl_2 (16 mL) was stirred at room temperature for 12 h. The reaction mixture was diluted with Et_2O (300 mL), and the organic layer was washed with H_2O (2 × 230 mL), 10% aqueous $NaHCO_3$ (80 mL), and then H_2O (230 mL), dried, filtered, and evaporated. Chromatography of the crude solid with 5% MeOH/CH_2Cl_2 gave (−)-**22** (2.58 g, 96%): mp 207−208 °C; $[\alpha]^{22}_D$ −29.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 58 °C) δ 1.43 (s, 3H), 1.73 (dd, 2H), 1.89−2.01 (m, 4H), 2.53 (ddd, 1H), 2.98 (dd, 1H), 4.45 (bs, 1H), 5.43 (m, 1H), 5.91 (bs, 1H), 6.40 (bs, 1H), 7.36 (t, 2H), 7.51 (t, 1H), 7.97 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 27.3, 28.1, 28.2, 33.6, 49.0, 52.1, 54.8, 67.1, 79.6, 128.2, 129.5, 1290.7, 132.9, 152.9, 165.8, 171.6. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.2; H, 7.0; N, 7.5. Found: C, 64.1; H, 7.0; N, 7.3.

Enantiomer (+)-22 (structure not shown): $[\alpha]^{22}_D$ +28.1° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**21**.

(1*R*,2*R*,3*S*,5*S*)-3-(Benzoyloxy)-8-azabicyclo[3.2.1]octane-2-carboxamide ((−)-23). To a solution of (−)-**22** (374 mg, 1.0 mmol) in CH_2Cl_2 was added TFA (2.7 mL) dropwise, the solution was stirred at room temperature for 1 h, and the reaction mixture was evaporated to give a residue that was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was further extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phase was dried, filtered, and evaporated. Chromatography of the residue with 10% MeOH/CH_2Cl_2 gave (−)-**23** (247 mg, 90%): mp 163−164 °C; $[\alpha]^{22}_D$ −43.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.74−2.12 (m, 6H), 2.88 (d, J = 7.1, 1H), 3.09 (bs, 1H), 3.68 (d, J = 2.5, 1H), 3.74 (d, J = 5.0, 1H), 5.36 (m, 1H), 6.01 (bs, 1H), 7.38 (t, 2H), 7.52 (t, 1H), 7.97 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2, 29.2, 34.8, 49.2, 53.3, 56.3, 66.7, 128.2, 129.5, 129.9, 132.9, 165.8, 174.0. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.7; H, 6.6; N, 10.2. Found: C, 65.5; H, 6.8; N, 10.1.

Enantiomer (+)-23 (structure not shown): $[\alpha]^{22}_D$ +36.0° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**21**.

(1*R*,2*R*,3*S*,5*S*)-3-(Benzoyloxy)-8-methyl-8-azabicyclo-[3.2.1]octane-2-carboxamide ((−)-24). To a solution of (−)-**23** (325 mg, 1.19 mmol) in CH_3CN (25 mL) were added 37% aqueous formaldehyde solution (0.49 mL, 6.13 mmol) and $NaBH_3CN$ (0.123 g, 2.04 mmol), and the suspension was stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 6 with glacial HOAc, stirred for 0.5 h, basidifed to pH 8−9 with aqueous NH_4OH, and partitioned between CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was further extracted with CH_2Cl_2 (4 × 50 mL), and the organic layers were combined, dried, filtered, and evaporated to give a yellowish oil. Chromatography (gradient from 10%−20% MeOH/CH_2Cl_2 with 0.5% Et_3N) gave (−)-**24** as a hygroscopic foam (257 mg, 75%): $[\alpha]^{24}_D$ −19.5° (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.66−1.77 (m, 2H), 2.04−2.19 (m, 4H), 2.24 (s, 3H), 2.88 (d, J = 7.4, 1H), 3.27 (bs, 1H), 3.36 (d, J = 5.9, 1H), 5.32 (m, 1H), 6.44 (bs, 1H), 7.38 (t, 2H), 7.50 (t, 1H), 8.00 (d, 1H), 9.29 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.5, 35.4, 40.1, 51.0, 60.1, 62.8, 65.5, 127.9, 128.0, 129.4, 130.0, 132.6, 165.6, 173.6. Anal. Calcd for $C_{16}H_{22}N_2O_4 \cdot H_2O$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.47; H, 6.98; N, 9.48.

Enantiomer (+)-24 (structure not shown): $[\alpha]^{22}_D$ +19.0° (*c* 1.0, $CHCl_3$); spectral and chromatographic properties identical with (+)-**24**.

(1*R*,2*R*,3*S*,5*S*)-3-(Benzoyloxy)-8-methyl-8-azabicyclo-[3.2.1]octane-2-carboxylic Acid ((−)-25). To a solution of (−)-**24** (96 mg, 0.33 mmol) in a mixture of glacial HOAc and Ac_2O (1/2, 3.75 mL) at 0 °C was added $NaNO_2$ (230 mg, 3.33 mmol). The suspension was stirred at 0 °C for 16 h and room temperature for 8 h and then evaporated to dryness and triturated with 20% MeOH/CH_2Cl_2. The resulting solution was then concentrated, and the residue was chromatographed with 20% MeOH/CH_2Cl_2 to give (−)-**25** (89 mg, 93%): mp 191−192 °C (lit.[21] mp 196−197 °C, lit.[25] mp 194−195 °C); $[\alpha]^{22}_D$

−48.3° (*c* 1.6, H_2O) [lit.[25] −45.39° (50% aq EtOH)]; ^{1}H NMR ($CDCl_3$) δ 1.88−2.01 (m, 2H), 2.15−2.32 (m, 4H), 2.50 (s, 3H), 3.05 (dd, J = 4.6, 6.6, 1H), 3.49 (bs, 1H), 3.61 (bs, 1H), 5.38 (m, 1H), 7.40 (t, 2H), 7.53 (t, 1H), 8.02 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.4, 34.5, 38.6, 48.7, 60.6, 63.7, 64.4, 128.3, 129.5, 129.8, 133.1, 165.7, 172.3.

Enantiomer (+)-25) (structure not shown): $[\alpha]^{22}_D$ +47° (*c* 1.0, H_2O); spectral and chromatographic properties identical with (+)-**24**.

Methyl (1*R*,2*R*,3*S*,5*S*)-3-(Benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate ((−)-Cocaine). Into a solution of (−)-**25** (80 mg, 0.28 mmol) in CH_2Cl_2 (6 mL) was passed CH_2N_2 [generated by dropwise addition of 4 N NaOH solution (10 mL) to a solution of Diazald (920 mg, 4.34 mmol) in EtOH (10 mL)] via a N_2 stream. When the reaction was complete (persistent yellow color), the mixture was evaporated. Chromatography of the residue with 5% MeOH/CH_2Cl_2 gave (−)-cocaine (80 mg, 95%): mp 93−94 °C (lit.[21] mp 98 °C); $[\alpha]^{23}_D$ −16.2° (*c* 1.2, $CHCl_3$); er 100% (chiral HPLC, Chiralpak OD column, 10% *i*-PrOH/hexanes, 1 mL/min at 274 nm, t_R 5.02 min); ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 2H), 1.88 (m, 1H), 2.10−2.19 (m, 2H), 2.24 (s, 3H), 2.44 (m, J = 2.6, 11.8, 1H), 3.03 (t, 3H), 3.30 (bs, 1H), 3.57 (d, 1H), 3.72 (s, 3H), 5.25 (m, 1H), 7.42 (t, J = 7.5, 2H), 7.54 (t, J = 7.6, 1H), 8.02 (dd, J = 1.3, 7.5,1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.4, 35.5, 41.1, 50.2, 51.4, 61.6, 64.8, 66.9, 128.3, 129.7, 130.3, 132.9, 166.2, 170.7. Authentic natural (−)-cocaine was prepared from a solution of (−)-cocaine hydrochloride (280 mg) in H_2O (2.0 mL) at 0 °C, which was basified to pH 8−9 by dropwise addition of concentrated aqueous NH_4OH, extraction with Et_2O (5 × 20 mL), drying, filtering, and evaporating to give a white solid (237 mg, 95%): mp 93−94 °C (lit.[21] mp 98 °C); $[\alpha]^{23}_D$ −17.2° (*c* 1.0, $CHCl_3$), −28.4° (*c* 1.0, EtOH); er 100%.

(+)-Cocaine: mp 93−94 °C (lit.[8] mp 98 °C); $[\alpha]^{24}_D$ +16.5° (*c* 1.0, $CHCl_3$) (lit.[8] +15.5°); er 98/2 (chiral HPLC, Chiralpak OD column, 10% *i*-PrOH/hexanes, 1 mL/min at 274 nm, t_R 7.92 min); spectral and chromatographic properties identical with (−)-cocaine.

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