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Total Synthesis of (−)-Cocaine and (−)-Ferruginine

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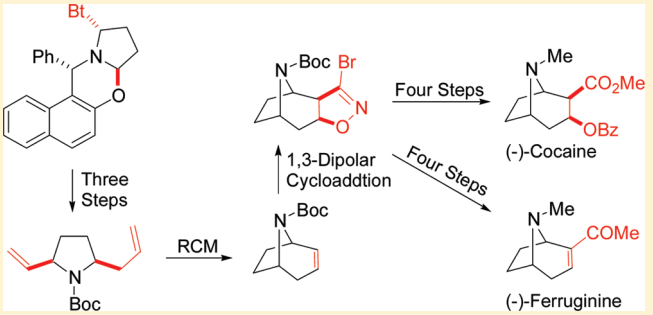
Supporting Information

ABSTRACT: Total synthesis of tropane alkaloids (−)-cocaine and (−)-ferruginine were accomplished in nine steps each and in 55% and 46% overall yields, respectively, starting from the known Betti base derivative (+)-(7a*R*,10*R*,12*S*)-10-(1*H*-benzotriazol-1-yl)-7a,8,9,10-tetrahydro-12-phenyl-12*H*-naphtho-[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine. In this novel route, RCM reaction and 1,3-dipolar cycloaddition were employed as key steps for the enantioselective construction of tropane skeleton and the regioselective introduction of 3-bromo-2-isoxazoline ring as masked *cis*-2,3-disubstituents. To obtain the desired precursor (2*S*,5*R*)-2-allyl-5-vinylpyrrolidine for RCM reaction, we developed a general and practical method for the preparation of enantiopure *cis*-2,5-disubstituted pyrrolidines bearing alkene- and/or alkyne-containing substituents. We also offered two highly efficient pathways for the conversion of the 3-bromo-2-isoxazoline ring into the desired *cis*-2,3-disubstituted groups in (−)-cocaine and (−)-ferruginine.



INTRODUCTION

Many tropane alkaloids exhibit biologically important properties and serve as lead compounds in drug discovery. As shown in Chart 1, the natural (−)-cocaine (**1**)[1] is a serotonin-norepinephrine-dopamine reuptake inhibitor, which mediates functionality of these neurotransmitters and leads to cocaine abuse. The unnatural (−)-ferruginine (**2**)[2] has proved to be a potent agonist for nicotinic acetylcholine receptor (nAchR), although its natural enantiomer has a negligible affinity for nAchR. For a long time, their typical structures and biologically important properties have made them highly attractive targets for total synthesis.[3]

Both alkaloids **1** and **2** have identical nonracemic tropane skeleton, but different substituents on C2 and C3. In fact, the first asymmetric synthesis[4] of **2** was started from **1** in 1977. In recent years, many asymmetric routes have been reported for total synthesis of **1**,[5] **2**,[6] and their enantiomers by using different strategies. On the basis of the published works, a highly efficient route may be expected to have three key points: (a) highly stereoselective construction of the tropane skeleton; (b) highly regioselective introduction of *cis*-2,3-disubstituents on the tropane ring; and (c) highly efficient functional group transformations. According to this opinion, two references attracted our attention as shown in Scheme 1. Aggarwal[6b] reported that the tropene derivative **4** could be stereoselectively constructed by RCM reaction of *cis*-2-allyl-5-vinylpyrrolidine derivative **3b**. Rapoport[5d] reported that 1,3-dipolar cycloaddition of **4** yielded the tricyclic **5a**, in which the *cis*-2,3-disubstituents on the tropane ring were regioselectively introduced as an 2-isoxazoline ring. However, these two excellent transformations have never been used together for total synthesis of **1** or **2**, most possibly because the preparation of **3b** is still a challenging project to date and the functional group transformations of **5a** are associated with tedious performances.

Herein, we would like to report a novel route for the total synthesis of **1** and **2**, in which RCM reaction and 1,3-dipolar cycloaddition mentioned in Scheme 1 were used together as key steps. Meanwhile, we also developed a practical method for the preparation of enantiopure **3b** and offered the 2-isoxazoline derivative **5b** as a versatile precursor, by which **1** and **2** were synthesized by controlling selectivity with highly efficient functional group transformations.

RESULTS AND DISCUSSION

Efficient Preparation of Enantiopure (2*S*,5*R*)-2-Allyl-5-vinyl-*N*-Boc-pyrrolidine (3b). In recent years, RCM reaction of *cis*-2,5-disubstituted pyrrolidines has emerged as an efficient method in the synthesis of azabicyclics.[6b,7,8] Depending on whether the substituent was alkene or alkyne, as well as the chain lengths, different sized and substituted azabicyclics were prepared. However, the method was rarely employed to construct the nonracemic azabicyclics because the preparation of the corresponding nonracemic *cis*-2,5-disubstituted pyrrolidines still remains a challenging task to date.[6b,8,9] In a few examples,[6b,8] the RCM reaction was so efficient that the method was indeed the preparation of the corresponding nonracemic *cis*-2,5-disubstituted pyrrolidines.

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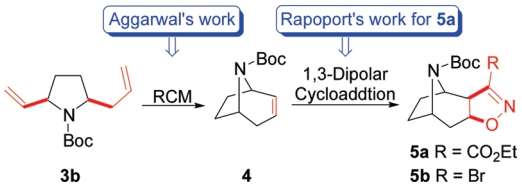
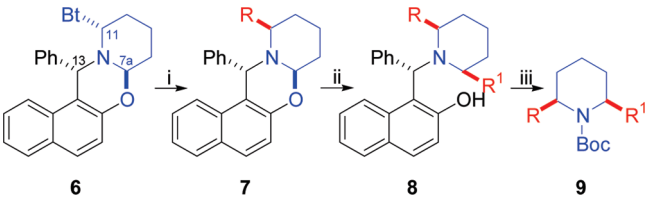
Chart 1

Scheme 1



Scheme 2[a]

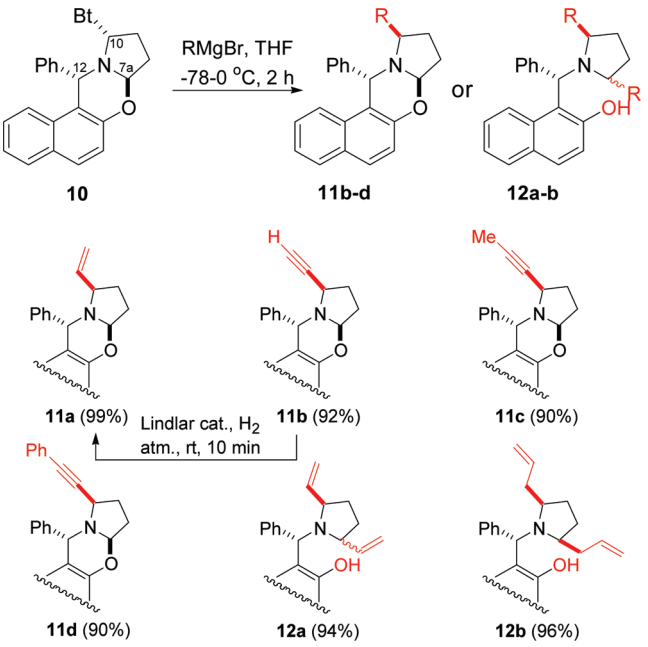


[a] Conditions: (i) RMgBr, THF, 0 °C; (ii) RMgBr, Et_2O, 0 °C; (iii) (a) aq NaOH, MeOH, THF, 60 °C, (b) Boc_2O, K_2CO_3, CH_2Cl_2, rt.

Recently, we reported a general three-step method[10] for the preparation of enantiopure *cis*-2,6-disubstituted piperidines bearing alkene- and/or alkyne-containing substituents from Betti base derivative **6**.[11] As shown in Scheme 2, when **6** underwent two solvent-controlled regioselective alkylations, the alkene- or alkyne-containing substituent was introduced to C11 (**7**) or C7a (**8**), respectively. Finally, the desired product **9** was obtained by a novel base-catalyzed *N*-debenzylation of **8**. Encouraged by this success, we tried to use the same strategy to prepare the required (2*S*,5*R*)-2-allyl-5-vinyl-*N*-Boc-pyrrolidine (**3b**).

Thus, Betti base derivative **10**, which contains a pyrrolidine ring, was prepared in 93% yield as a single diastereomer by the reported procedure.[11d] Unfortunately, no solvent-controlled regioselectivity was observed in the alkylation of **10** with vinyl or allyl Grignard reagent. As shown in Scheme 3, when **10** was treated with $H_2C{=}CHMgBr$ in THF below −40 °C, no reaction occurred at all. Instead of the expected **11a**, a mixture of *trans*- and *cis*-dialkylated product **12a** was obtained when the reaction proceeded above −40 °C. Although a single product was obtained in the alkylation of **10** with $H_2C{=}CHCH_2MgBr$ at −78 °C, it was assigned as dialkylated product **12b**. These results may be caused by the fact that the pyrrolidine ring in **10** has a planar configuration, which led to higher reactivity and less selectivity. Thus, several less active organometallic reagents were tested for the alkylation of **10**, such as $(H_2C{=}CH)_2CuLi$ (from $H_2C{=}CHLi$ and CuI in situ), $(H_2C{=}CH)_2Zn$ (from $H_2C{=}CHMgBr$ and $ZnBr_2$ in situ), and $H_2C{=}CHCH_2TMS/BF_3{\cdot}Et_2O$. However, the former one was inert at 0 °C or gave a complicated mixture along with unreacted

Scheme 3



10 at 25 °C. The later two could stop at the monoalkylation stage regioselectively at −40 °C, but the epimeric mixtures were obtained [3:1 ratio of **11a** and its epimer for $(H_2C{=}CH)_2Zn$; 3:2 ratio of (*R*)- and (*S*)-allyl substituted on C10 for $H_2C{=}CHCH_2TMS/BF_3{\cdot}Et_2O$]. On the basis of these results, we suggested that the alkylation may go through an iminium salt pathway that may be caused by the Lewis acid properties of the $ZnBr_2$ and $BF_3{\cdot}Et_2O$. Therefore, Nu^- could attack both sides of the iminium salt intermediate to give an epimeric mixture. Luckily, when **10** was treated with $HC{\equiv}CMgBr$ in THF at −40 °C, a highly regioselective and diastereoselective alkylation occurred on C10 to give **11b** in 92% yield as a single product. Similarly, **11c** and **11d** were obtained when $MeC{\equiv}CMgBr$ and $PhC{\equiv}CMgBr$ were used as alkylation reagents, respectively. These alkylations may go through the S_N2 mechanism because the Bt-group in **10** was replaced by an alkynyl group with complete inversion of configuration. Finally, the required intermediate **11a** was obtained in almost quantitative yield by hydrogenation of **11b** over Lindlar catalyst.

As shown in Scheme 4, when **11a**−**d** were treated with different allyl Grignard reagents in Et_2O, 2,5-disubstituted pyrrolidine intermediates **12c**−**g** were obtained smoothly. Since **12b**−**g** showed ambiguous NMR spectra caused by the unusual coalescence phenomenon,[11c] they were directly used in the next step without characterization. As was expected, their *N*-debenzylations proceeded much easier than that of the counterpart **8**. When the mixtures of **12b**−**g** in aq NaOH−MeOH−THF (1:2:2 by v/v)[10] were heated at 60 °C for 1 h, the *N*-debenzylations of **12b**−**g** were finished completely. The crude products were then captured by Boc_2O in situ to give 2,5-disubstituted *N*-Boc-pyrrolidines **3a**−**f** in high yields for two steps. Since the two chiral carbons were formed in separated steps, **3a**−**f** were easily confirmed to be enantiopure products by their ^1H and ^{13}C NMR spectra.

Efficient Preparation of the Tropene Derivative 4 by RCM and the Versatile Precursor 3-Bromo-2-isoxazoline Derivative 5b by 1,3-Dipolar Cycloaddition. In practice, the precursor

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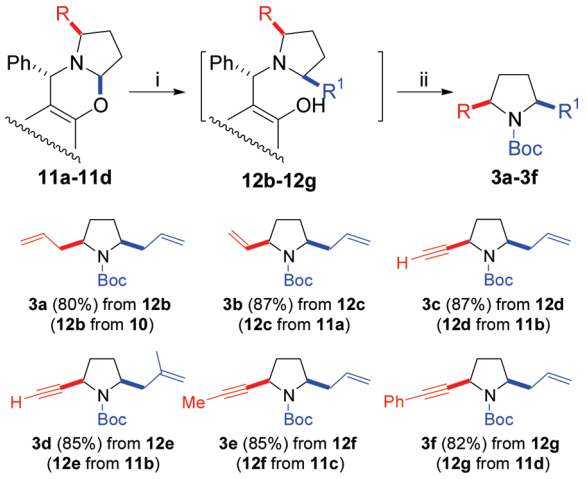
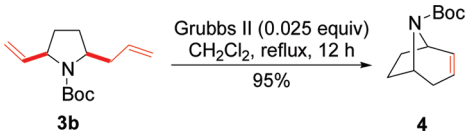
Scheme 4[a]



[a] Conditions: (i) $H_2C{=}CHCH_2MgBr$ or $H_2C{=}C(Me)CH_2MgBr$, Et_2O, −40 °C, 1 h; (ii) (a) 6 M aq NaOH, MeOH, THF, 60 °C, 1 h, (b) Boc_2O, K_2CO_3, CH_2Cl_2, rt, 30 min, 80−87% yields for two steps.

Scheme 5

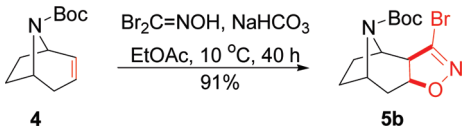


3b can be prepared in gram scale within a few hours from the intermediate **10**. As shown in Scheme 5, when **3b** was treated with Grubbs II catalyst in refluxed CH_2Cl_2 for 12 h, the desired tropene derivative **4** was obtained in 95% yield.

In 1998, Rapoport[5d] reported that 1,3-dipolar cycloaddition between **4** and $EtO_2C(Cl)C{=}NOH$ yielded 3-carboethoxy-2-isoxazoline derivative **5a**. Since the 2-isoxazoline ring can be opened easily, it in fact is a masked *cis*-2,3-disubstituent. However, **5a** seriously suffered from tedious functional group transformations to remove an extra carbon under very mild conditions, by which the epimerization of the 3-carbomethoxy group [which occupies the thermodyamically unfavorable axial position in (−)-cocaine (**1**)] could be avoided. Since this drawback comes from the structural nature of the reagent $EtO_2C(Cl)C{=}NOH$ rather than from the strategy, we believed that it may be overcome by using an alternative reagent.

In the further investigation, the one-carbon 1,3-dipolar precursor dibromoformaldoxime ($Br_2C{=}NOH$) attracted our attention, which can take place by 1,3-dipolar cycloaddition with alkenes to yield the corresponding 3-bromo-2-isoxazolines under base conditions.[12−14] The most important to us is that 3-bromo-2-isoxazoline can be converted into the β-hydroxy ester[13] or β-hydroxy nitrile[14] by different ring-opening methods. By a series of conditional experiments, we found that the regioselectivity of 1,3-dipolar cycloaddition between **4** and $Br_2C{=}NOH$ significantly benefited from the reaction temperature. When it proceeded at 10 °C, the desired precursor **5b** was prepared in 91% yield (Scheme 6). As shown in Figure 1, the structure and stereochemistry

Scheme 6



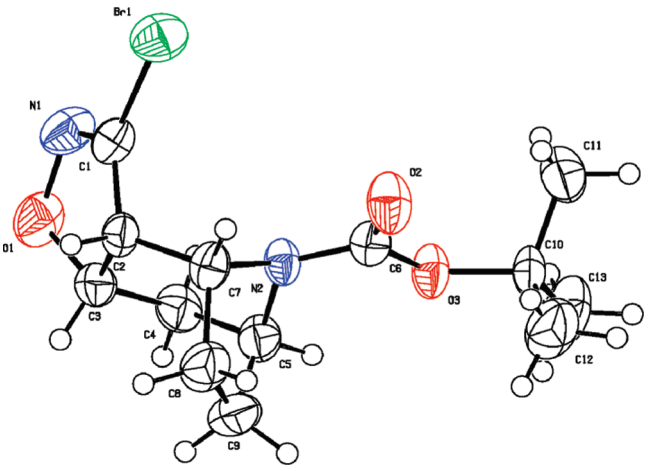


Figure 1. The structure and stereochemistry of **5b**.

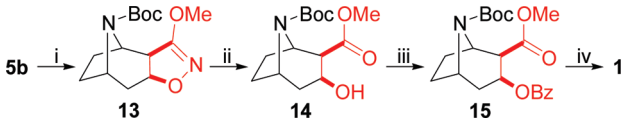
of **5b** was further confirmed by the single-crystal X-ray diffraction analysis.

Total Synthesis of (−)-Cocaine. It has been reported that 3-bromo-2-isoxazolines can be easily converted into 3-alkoxy-2-isoxazolines under base conditions.[12a,c,d,14c] As shown in Scheme 7, when the mixture of **5b** and NaOMe in MeOH was refluxed for 8 h, 3-methoxy-2-isoxazoline derivative **13** was obtained in 99% yield. In literature, the reductive cleavage of 3-methoxyisoxazoline into the corresponding β-hydroxy ester can be affected by several protocols.[13] We found that the Raney-Ni-catalyzed hydrogenation originally reported by Curran[13d,15] was the most practical one, by which the quantitative conversion of **13** into **14** was achieved in the presence of H_3BO_3. After **14** was esterified with BzCl, its product **15** was subjected to carry out a deprotection and a reductive amination in one-pot to give (−)-cocaine (**1**) in excellent yield. Thus, the total synthesis of (−)-cocaine (**1**) was accomplished in nine steps and in 55% overall yield (starting from **10**).

Total Synthesis of (−)-Ferruginine (2). To obtain the best result, three practical protocols for the conversion of 3-bromo-2-isoxazoline into β-hydroxyl nitrile were tested. When **5b** was treated with NaSEt[14d] or NaI-TMSCl,[14b] the former gave the desired product **16** in moderate yield (63%) and the latter led to a mixture because *N*-Boc was partially cleaved. However, when **5b** was hydrogenated in the presence of Raney-Ni and H_3BO_3,[14c,15] **16** was obtained in quantitative yield (Scheme 8).

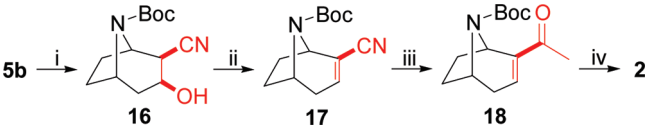
Although a reported conversion of β-hydroxyl nitrile into α,β-unsaturated nitrile with excess MeMgCl is very attractive,[16] it failed in our hands. Thus, **17** was prepared in 85% yield by treatment of **16** with MsCl in the presence of Et_3N. Under the mild conditions, α,β-unsaturated ketone **18** was obtained in 87% yield by reaction of **17** with an excess of MeLi followed by a PPTS-catalyzed hydrolysis. In the one-pot reaction, **18** was

Scheme 7[a]



[a] Conditions: (i) NaOMe, MeOH, reflux, 8 h, 99%; (ii) Raney-Ni, H_2 (balloon), H_3BO_3, aq MeOH, rt, 3 h, 100%; (iii) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h, 96%; (iv) (a) TFA, CH_2Cl_2, rt, 1 h, (b) 37% aq CH_2O, $NaBH_3CN$, rt, 1 h, 85%.

Scheme 8[a]



[a] Conditions: (i) Raney-Ni, H_2 (balloon), H_3BO_3, aq MeOH, rt, 3 h, 99%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, then rt, 12 h, 85%; (iii) (a) MeLi, Et_2O, 0−25 °C, 2 h, (b) aq PPTS, rt, 12 h, 87%; (iv) (a) TFA, CH_2Cl_2, rt, 1 h, (b) 37% aq CH_2O, $NaBH_3CN$, rt, 1 h, 91%.

subjected to carry out a deprotection and a reductive amination to give (−)-ferruginine (**2**) in excellent yield. Thus, the total synthesis of (−)-ferruginine (**2**) was accomplished in nine steps and in 46% overall yield (starting from **10**).

CONCLUSION

A general and practical method for the preparation of enantiopure *cis*-2,5-disubstituted pyrrolidines bearing alkene- and/or alkyne-containing substituents (**3a**−**f**) was developed. The desired tropene derivative **4** was constructed in excellent yield by RCM reaction of (2*S*,5*R*)-2-allyl-5-vinylpyrrolidine (**3b**). When **4** reacted with dibromoformaldoxime, the 1,3-dipolar cycloadduct **5b** was obtained regioselectively. The 3-bromo-2-isoxazoline unit in **5b** has been proved to be an excellent masked *cis*-*β*-hydroxy ester or *cis*-*β*-hydroxyl nitrile. Finally, total synthesis of the tropane alkaloids (−)-cocaine (**1**) and (−)-ferruginine (**2**) was accomplished in nine steps each from **10**. The novel route was characterized to employ the RCM reaction and 1,3-dipolar cycloaddition together as key steps and had the highest overall yields.

EXPERIMENTAL SECTION

Preparation of (7a*R*,10*R*,12*S*)-7a,8,9,10-Tetrahydro-10-vinyl-12-phenyl-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (11a). A stirred mixture of **11b** (6.50 g, 20 mmol) and 5% Lindler catalyst (16.3 mg, 2.5 wt %) in THF (50 mL) was hydrogenated at room temperature and atmospheric pressure until the hydrogen-absorbing rate was suddenly reduced (ca. 10 min). After the catalyst was filtered out, the filtrate was evaporated to give product **11a** (6.48 g, 99%) as colorless crystals. Mp 103−105 °C (Et_2O); $[\alpha]^{25}_D$ +231.4 (*c* 0.2, $CHCl_3$); IR *ν* 3059, 2976, 1620, 1597 cm^{-1}; ^1H NMR *δ* 7.70−7.63 (m, 2H), 7.33−7.26 (m, 1H), 7.22−7.12 (m, 7H), 7.08 (d, *J* = 8.7 Hz, 1H), 5.66−5.55 (m, 1H), 5.42 (s, 1H), 5.19−5.07 (m, 2H), 4.88−4.83 (m, 1H), 3.86−3.79 (m, 1H), 2.14−1.92 (m, 3H), 1.90−1.78 (m, 1H); ^{13}C NMR *δ* 153.0, 142.6, 141.1, 131.5, 128.9 (2C), 128.8 (2C), 128.3, 128.2 (2C), 127.0, 126.2, 123.0, 122.9, 119.1, 116.9, 114.2, 85.6, 64.6, 54.8, 30.4, 28.7; MS *m*/*z* (%) 327 (M^+, 6.49), 231 (100). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.60; H, 6.39; N, 4.16.

Preparation of (7a*R*,10*R*,12*S*)-7a,8,9,10-Tetrahydro-10-ethynyl-12-phenyl-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]-oxazine (11b). To a solution of **10** (2.09 g, 5 mmol) in dry THF (50 mL) was added a solution of HC≡CMgCl in THF (1.0 M, 25 mmol) dropwise under nitrogen at −40 °C. After the reaction was stirred at 0 °C for 1 h (monitored by TLC), a saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction. The resulting mixture was then extracted with Et_2O (2 × 30 mL). Combined organic layers were washed with brine (2 × 30 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent, the residue was purified by recrystallization to give product **11b** (1.49 g, 92%) as colorless crystals. Mp 160−162 °C (Et_2O); $[\alpha]^{25}_D$ +294.5 (*c* 0.2, $CHCl_3$); IR *ν* 3205, 2935, 2104, 1622, 1599 cm^{-1}; ^1H NMR *δ* 7.71−7.66 (m, 2H), 7.40−7.32 (m, 1H), 7.26−7.16 (m, 7H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.65 (s, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 4.20−4.15 (m, 1H), 2.30−2.14 (m, 3H), 2.11−1.96 (m, 1H), 1.84 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR *δ* 152.9, 142.4, 131.7, 129.0, 128.9, 128.8, 128.7 (2C), 128.4 (2C), 127.2, 126.2, 123.1, 122.9, 118.8, 113.1, 84.9, 84.2, 71.6, 55.7, 51.1, 30.6, 29.4; MS *m*/*z* (%) 325 (M^+, 4.88), 231 (100). Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.62; H, 6.01; N, 4.42.

By a similar procedure as that used for **11b**, compounds **11c**,**d** were prepared.

Preparation of (7a*R*,10*R*,12*S*)-7a,8,9,10-Tetrahydro-10-(prop-1-ynyl)-12-phenyl-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*]-[1,3]oxazine (11c). By reaction of **10** with MeC≡CMgCl at −15 °C for 2 h, **11c** was obtained in 90% yield. Mp 144−146 °C (Et_2O); $[\alpha]^{25}_D$ +378.9 (*c* 0.2, $CHCl_3$); IR *ν* 2993, 2962, 2195, 1622, 1597 cm^{-1}; ^1H NMR *δ* 7.75−7.65 (m, 2H), 7.43−7.36 (m, 1H), 7.28−7.16 (m, 7H), 7.10 (d, *J* = 8.9 Hz, 1H), 5.67 (s, 1H), 5.04 (d, *J* = 4.1 Hz, 1H), 4.11−4.06 (m, 1H), 2.23−2.11 (m, 3H), 2.10−1.90 (m, 1H), 1.20 (d, *J* = 3.1 Hz, 3H); ^{13}C NMR *δ* 152.9, 142.2, 131.8, 128.9 (2C), 128.5, 128.3 (2C), 128.2 (2C), 127.2, 126.2, 123.0, 122.8, 118.9, 113.5, 85.1, 80.1, 79.5, 55.7, 51.5, 30.6, 29.4, 2.9; MS *m*/*z* (%) 339 (M^+, 10.8), 231 (100). Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.75; H, 6.40; N, 4.14.

Preparation of (7a*R*,10*R*,12*S*)-7a,8,9,10-Tetrahydro-10-phenylethynyl-12-phenyl-12*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*]-[1,3]oxazine (11d). By reaction of **10** with PhC≡CMgCl at 0 °C for 1 h, **11d** was obtained in 90% yield. Mp 166−168 °C (Et_2O); $[\alpha]^{25}_D$ +488.1 (*c* 0.2, $CHCl_3$); IR *ν* 3467, 2948, 2208, 1623, 1597 cm^{-1}; ^1H NMR *δ* 7.80−7.59 (m, 2H), 7.43−7.34 (m, 1H), 7.33−7.15 (m, 7H), 7.13−7.05 (m, 1H), 7.04−6.96 (m, 1H), 6.95−6.84 (m, 2H), 6.46 (d, *J* = 7.2 Hz, 2H), 5.74 (s, 1H), 5.12 (d, *J* = 3.8 Hz, 1H), 4.57−4.53 (m, 1H), 2.40−2.18 (m, 3H), 2.16−2.01 (m, 1H); ^{13}C NMR *δ* 153.1, 143.1, 131.8, 131.0 (2C), 129.1, 128.7 (2C), 128.6, 128.4 (2C), 128.3, 127.6 (2C), 127.4, 127.2, 126.4, 123.1, 122.9, 122.6, 118.9, 113.2, 90.0, 85.3, 83.8, 55.5, 52.4, 31.1, 29.7; MS *m*/*z* (%) 401 (M^+, 11.7), 231 (100). Anal. Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49. Found: C, 86.49; H, 5.68; N, 3.54.

Preparation of (2*S*,5*R*)-2,5-Diallylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3a). To a stirred solution of $H_2C{=}CHCH_2$-MgBr made from Mg (1.20 g, 50 mmol) and $H_2C{=}CHCH_2Br$ (5.05 g, 50 mmol) in anhydrous Et_2O (30 mL) was added dropwise a solution of **10** (2.09 g, 5 mmol) in anhydrous toluene (50 mL) at −78 °C within 10 min. Then a saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction at 0 °C. The separated organic layer was

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washed with H_2O and brine, then dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product **12b** as a yellowish solid (1.84 g, 96%), which was used in the next step without characterization.

To an aqueous solution of NaOH (6.0 M, 1 mL), THF (2 mL), and MeOH (2 mL) was added the crude **12b** (384 mg, 1 mmol). The resulting mixture was heated at 60 °C for 1 h and then cooled to room temperature. $(Boc)_2O$ (655 mg, 3 mmol) was then added and the mixture was stirred for another 0.5 h. After the organic solvent was removed, the residue was diluted with Et_2O (20 mL) and H_2O (20 mL). The separated organic layer was washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc−PE) to give product **3a** (219 mg, 87%). IR ν 2975, 1693, 1390 cm^{-1}; ^1H NMR (50 °C) δ 5.80−5.71 (m, 2H), 5.07−5.02 (m, 4H), 3.82 (br, 2H), 2.54 (br, 2H), 2.16−2.10 (m, 2H), 1.89−1.83 (m, 2H), 1.70−1.65 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (50 °C) δ 154.7, 135.3 (2C), 116.6 (2C), 79.0, 58.2 (2C), 39.8 (2C), 28.5 (5C); MS m/z (%) 252 (M + 1, 2.18), 57 (100). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.49; H, 10.21; N, 5.50.

Preparation of (2*S*,5*R*)-2-Allyl-5-vinylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3b). To a stirred solution of **11a** (655 mg, 2.0 mmol) in anhydrous Et_2O (20 mL) was added dropwise a solution of $H_2C{=}CHCH_2MgBr$ made from Mg (0.24 g, 10 mmol) and $H_2C{=}CHCH_2Br$ (1.21 g, 10 mmol) in anhydrous Et_2O (15 mL) at −40 °C. After the reaction was stirred at −40 °C for 1.0 h (monitored by TLC), a saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction. The separated organic layer was washed with H_2O and brine, then dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product **12c** as a yellowish solid (709 mg, 96%), which was used in the next step without characterization.

To an aqueous solution of NaOH (6.0 M, 1 mL), THF (2 mL), and MeOH (2 mL) was added the crude **12c** (370 mg, 1.0 mmol). The resulting mixture was heated at 60 °C for 1 h, and then cooled to room temperature. $(Boc)_2O$ (655 mg, 3 mmol) was then added and the mixture was stirred for another 0.5 h. After the organic solvent was removed, the residue was diluted with Et_2O (20 mL) and H_2O (20 mL). The separated organic layer was washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc−PE) to give the desired product **3b** (209 mg, 88%) as a yellow oil; $[\alpha]^{25}_D$ −45.1 (*c* 0.2, $CHCl_3$) {lit.[6b] $[\alpha]^{20}_D$ +40.7 (*c* 0.2, $CHCl_3$) for the enantioisomer}; IR ν 3077, 2975, 1692, 1641, 1478 cm^{-1}; ^1H NMR (50 °C) δ 5.81−5.72 (m, 2H), 5.15−5.00 (m, 4H), 4.28 (br, 1H), 3.86 (br, 1H), 2.63 (br, 1H), 2.15−2.08 (m, 1H), 2.02−1.94 (m, 1H), 1.93−1.87 (m, 1H), 1.73−1.64 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (50 °C) δ 154.7, 140.1, 135.3, 116.6, 113.7, 77.2, 60.5, 58.2, 39.7, 30.4, 28.9, 28.4 (3C); MS m/z (%) 273 (M^+, 0.15), 96 (100). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.56; H, 9.73; N, 5.98.

By a similar procedure as that used for **3b**, compounds **3c**−**f** were prepared.

Preparation of (2*S*,5*R*)-2-Allyl-5-ethynylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3c). From **11b** and $H_2C{=}CHCH_2MgBr$, **3c** was obtained as a yellowish oil, $[\alpha]^{25}_D$ +32.6 (*c* 0.2, $CHCl_3$) {lit.[6b] $[\alpha]^{20}_D$ −30 (*c* 0.2, CH_3Cl_2) for the enantioisomer}; IR ν 3295, 2978, 2117, 1685, 1639 cm^{-1}; ^1H NMR δ 5.80−5.64 (m, 1H), 5.14−5.05 (m, 2H), 4.51 (br, 1H), 3.83 (br, 1H), 2.63 (br, 1H), 2.35−2.20 (m, 2H), 2.08−1.80 (m, 4H), 1.52 (s, 9H); ^{13}C NMR δ 153.7, 134.7, 116.9, 84.5, 79.6, 69.6, 57.5, 48.4, 39.5, 38.8, 31.6, 29.6, 28.8, 28.2 (3C); MS m/z (%) 194 (23.92), 57 (100). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.29; H, 9.13; N, 6.07.

Preparation of (2*S*,5*R*)-2-(2-Methyl-2-propenyl)-5-ethynylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3d). From **11b** and $H_2C{=}C(Me)CH_2MgBr$, **3d** was obtained as a yellowish oil. $[\alpha]^{25}_D$ +14.6 (*c* 0.2, $CHCl_3$); IR ν 3252, 2976, 2935, 2123, 1781, 1690 cm^{-1}; ^1H NMR δ 4.75 (d, *J* = 11.3 Hz, 2H), 4.49 (br, 1H), 3.96 (br, 1H), 2.68 (br, 1H), 2.26−2.27 (m, 1H), 1.80−2.18 (m, 5H), 1.76 (s, 3H), 1.48 (s, 9H); ^{13}C NMR δ 153.6, 142.7, 112.4, 84.6, 79.5, 69.5, 56.3, 48.1, 43.1, 31.6, 29.2, 28.2 (3C), 22.1; MS m/z (%) 249 (M^+, 0.02), 57 (100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.10; H, 9.35; N, 5.74.

Preparation of (2*S*,5*R*)-2-Allyl-5-(prop-1-ynyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3e). From **11c** and $H_2C{=}CHCH_2MgBr$, **3e** was obtained asa yellowish oil. $[\alpha]^{25}_D$ +28.9 (*c* 0.2, $CHCl_3$); IR ν 3292, 2978, 2237, 1783, 1713 cm^{-1}; ^1H NMR (50 °C) δ 5.86−5.72 (m, 1H), 5.11−5.01 (m, 2H), 4.48 (br, 1H), 3.84−3.75 (m, 1H), 2.66−2.60 (m, 1H), 2.31−2.20 (m, 1H), 2.02−1.83 (m, 4H), 1.80−1.79 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (50 °C) δ 154.0, 135.2, 116.6, 80.1, 79.4, 77.2, 57.6, 49.1, 39.4, 32.2, 29.4, 28.5 (3C), 3.4; MS m/z (%) 235 (M, 0.01), 84 (92.99), 57 (100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.04; H, 9.47; N, 5.48.

Preparation of (2*S*,5*R*)-2-Allyl-5-phenylethynylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3f). From **11d** and $H_2C{=}CHCH_2MgBr$, **3f** was obtained as a yellowish oil. $[\alpha]^{25}_D$ +37.7 (*c* 0.2, $CHCl_3$); IR ν 3075, 2976, 2214, 1783, 1720, 1695 cm^{-1}; ^1H NMR (50 °C) δ 7.32−7.30 (m, 2H), 7.19−7.17 (m, 3H), 5.80−5.71 (m, 1H), 5.04−4.93 (m, 2H), 4.66 (br, 1H), 3.81 (br, 1H), 2.61−2.54 (m, 1H), 2.32−2.27 (m, 1H), 2.06−1.96 (m, 2H), 1.95−1.83 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (50 °C) δ 154.0, 135.0, 131.5 (2C), 128.1 (2C), 127.9, 123.5, 116.9, 90.5, 81.9, 79.7, 57.7, 49.5, 39.2, 32.2, 29.5, 28.5 (3C); MS m/z (%) 311 (M^+, 1.08), 170 (100). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.87; H, 8.02; N, 4.68.

Preparation of (1*R*,5*S*)-8-Azabicyclo[3.2.1]-2-octene-8-carboxylic Acid *tert*-Butyl Ester (4). To a stirred solution of **3b** (2.37 g, 10 mmol) in CH_2Cl_2 (15 mL) was added Grubbs 2nd generation catalyst (212 mg, 0.25 mmol) in one portion at room temperature under N_2. After the resulting mixture was refluxed for 12 h, it was cooled to room temperature and the solvent was evaporated under vacuum. The residue was purified by chromatography (silica gel, 16% EtOAc in PE) to give the product **4** (1.98 g, 95%) as colorless crystals. Mp 35−36 °C (hexane−EtOAc), $[\alpha]^{25}_D$ +3.6 (*c* 0.2, $CHCl_3$) {lit.[5d] $[\alpha]^{20}_D$ +3.0 (*c* 1.0, $CHCl_3$)}; IR (KBr) ν 2977, 1697, 1391 cm^{-1}; ^1H NMR δ 5.98 (br, 1H), 5.50−5.53 (m, 1H), 4.32 (br, 1H), 4.25 (br, 1H), 2.65−2.85 (m, 1H), 2.15 (br, 1H), 1.60−2.05 (m, 4H), 1.45 (s, 9H); ^{13}C NMR δ 154.0, 133.0, 132.4, 123.9, 123.4, 79.0, 53.5, 52.7, 51.8, 34.9, 34.5, 34.2, 33.9, 30.2, 29.0, 28.3 (3C); MS m/z (%) 210 (M + 1, 1.03), 57 (100).

Preparation of (3a*S*,3b*R*,5a*S*,6a*S*)-3-Bromo-7-azabicyclo-[3.2.1]octane[2,3-*d*]isoxazole-7-carboxylic Acid *tert*-Butyl Ester (5b). The mixture of **4** (2.1 g, 10 mmol), $Br_2C{=}NOH$ (4.2 g, 20 mmol), and $NaHCO_3$ (8.4 g, 100 mmol) in EtOAc (30 mL) was stirred vigorously at 10 °C for 40 h. After the reaction was finished (monitored by TLC), H_2O (50 mL) was added. The organic layer was separated and dried over anhydrous Na_2SO_4. After the removal of the solvent, the residue was purified by chromatography (silica gel, 20% EtOAc in PE) to give **5b** (3.0 g, 81%) as colorless crystals. Mp 103−104 °C (hexane−EtOAc), $[\alpha]^{25}_D$ +3.7 (*c* 0.2, $CHCl_3$); IR ν 2973, 2930, 1697, 1378 cm^{-1}; ^1H NMR δ 4.93−5.01 (m, 1H), 4.69 (br, 1H), 4.38 (br, 1H), 3.35 (d, 1H, *J* = 8.94 Hz), 1.55−2.19 (m, 6H), 1.48 (s, 9H); ^{13}C NMR δ 152.7, 141.0, 80.1, 75.8, 58.0, 51.8, 50.3, 36.6, 29.8, 28.2 (3C), 27.2; MS m/z (%) 330 (M^+, 0.04), 57 (100). Anal. Calcd for $C_{13}H_{19}BrN_2O_3$: C, 47.14; H, 5.78; N, 8.46. Found: C, 47.31; H, 5.69; N, 8.52.

Preparation of (3a*S*,3b*R*,5a*S*,6a*S*)-3-Methoxyl-7-azabicyclo[3.2.1]octane[2,3-*d*]isoxazole-7-carboxylic Acid *tert*-Butyl Ester (13). To a solution of **5a** (1.0 g, 3 mmol) in dry MeOH (20 mL) was added NaOMe (810 mg, 15 mmol) at room temperature and the resulting mixture was refluxed for 8 h (monitored by TLC). After the reaction was cooled to 0 °C, H_2O (60 mL) was added. The aqueous mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent under vacuum, the product **13** (850 mg, 99%)

was obtained as a colorless oil, which was pure enough for most analytic purposes. The analytical sample was purified by chromatography (silica gel, 20% EtOAc in PE). $[\alpha]^{25}_D$ +36.3 (*c* 0.2, $CHCl_3$); IR ν 2975, 1695, 1618, 1415 cm^{-1}; ^1H NMR δ 4.88−4.97 (m, 1H), 4.60 (br, 1H), 4.23−4.39 (m, 1H), 3.87 (s, 3H), 3.31 (d, 1H, *J* = 8.94 Hz), 1.85−2.11 (m, 4H), 1.55−1.78 (m, 2H), 1.46 (s, 9H); ^{13}C NMR δ 167.0, 151.9, 78.8, 75.3, 56.6, 51.2, 50.7, 50.0, 36.1, 29.6, 27.7 (3C), 26.4; MS *m*/*z* (%) 282 (M^+, 3), 83 (100). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.44; H, 7.91; N, 9.83.

Preparation of (1*R*,2*R*,3*S*,5*S*)-3-Hydroxy-8-azabicyclo[3.2.1]-octane-2,8-dicarboxylic Acid 8-*tert*-Butyl Ester 2-Methyl Ester (14). To a solution of **13** (520 mg, 1.84 mmol) in H_2O−MeOH (1:5 by v/v, 12 mL) was added H_3BO_3 (250 mg, 4 mmol) and wet W-2 Raney nickel (50 mg). The resulting suspension was hydrogenated for 3 h under atmospheric pressure (balloon) and room temperature. After the catalyst was filtered off, the filtrate was diluted with H_2O (30 mL) and the aqueous mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum gave **14** (530 mg, 100%) as a colorless oil, which was pure enough for most analytic purpose. The analytical sample was purified by chromatography (silica gel, 20% EtOAc in PE). $[\alpha]^{25}_D$ −10.9 (*c* 0.2, $CHCl_3$); IR ν 2990, 1737, 1672, 1419 cm^{-1}; ^1H NMR δ 4.66 (br, 1H), 4.20−4.45 (m, 1H), 3.95−4.10 (m, 1H), 3.70 (s, 3H), 3.17 (d, 1H, *J* = 10.98 Hz), 2.85−2.91 (m, 1H), 1.80−2.18 (m, 4H), 1.52−1.70 (m, 2H), 1.43 (s, 4.5H), 1.41 (s, 4.5H); ^{13}C NMR δ 172.5, 152.3, 79.1, 63.6, 54.6, 52.8, 51.5, 50.9, 37.8, 28.0 (3C), 27.6, 27.3; MS *m*/*z* (%) 285 (M^+, 4), 83 (100). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.01; H, 8.00; N, 4.99.

Preparation of (1*R*,2*R*,3*S*,5*S*)-3-Benzoyloxy-8-aza-bicyclo-[3.2.1]octane-2,8-dicarboxylic Acid 8-*tert*-Butyl Ester 2-Methyl Ester (15). To a solution of **14** (390 mg, 1.4 mmol) in DCM (5 mL) was added PhCOCl (300 mg, 2.1 mmol), TEA (710 mg, 7.0 mmol), and 4-dimethylaminopyridine (30 mg, 0.25 mmol). After the mixture was stirred at room temperature for 12 h, it was diluted with DCM (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated to afford **15** (510 mg, 96%) as colorless crystals. Mp 128−129 °C (hexane−EtOAc); $[\alpha]^{25}_D$ −11.4 (*c* 0.2, $CHCl_3$) {lit.[5b] $[\alpha]^{23}_D$ +4.3 (no concentration and solvent were reported) for the enantioisomer}; IR ν 2977, 1744, 1719, 1680, 1410, 1275 cm^{-1}; ^1H NMR δ 7.96−7.98 (m, 2H), 7.53 (t, 1H, *J* = 7.23 Hz), 7.40 (t, 2H, *J* = 7.56 Hz), 5.48 (m, 1H), 4.68 (d, 0.5H, *J* = 5.16 Hz), 4.55 (s, 1H), 4.37 (s, 0.5H), 3.70 (s, 1.5H), 3.69 (s, 1.5H), 3.07 (d, 1H, *J* = 5.49 Hz), 2.57 (td, 1H, *J* = 12.0, 3.0 Hz), 1.77−2.14 (m, 5H), 1.47 (s, 4.5H), 1.45 (s, 4.5H); ^{13}C NMR δ 170.1, 170.0, 165.7, 152.4, 152.0, 133.0, 129.8, 129.5, 128.3, 79.5, 79.4, 66.6, 54.4, 52.6, 51.7, 51.5, 49.0, 48.8, 33.4, 33.3, 28.8, 28.3 (3C), 28.0, 27.8, 27.1; MS *m*/*z* (%) 389 (M^+, 2), 57 (100). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.63; H, 7.03; N, 3.81.

Preparation of (−)-Cocaine (1). To a solution of **15** (510 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise CF_3CO_2H (5.0 g, 43.9 mmol) and the resulting solution was stirred at room temperature for 1 h. After the reaction system was diluted by CH_2Cl_2 (15 mL), saturated aqueous $NaHCO_3$ was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude amine was obtained as a yellow oil.

To a solution of the crude amine and formaldehyde (37% aqueous solution, 0.6 mL, 8 mmol) in MeCN (20 mL) was added $NaBH_3CN$ (170 mg, 2.7 mmol). Then the resulting mixture was stirred for 1 h at room temperature and acidified to pH 6 with HOAc. After the mixture was stirred for an additional 0.5 h, it was neutralized to pH 9 with ammonia. The mixture was diluted by addition of CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified by chromatography (silica gel, Et_3N:MeOH:CH_2Cl_2 = 0.25:1:100) to give (−)-cocaine (**1**) (330 mg, 85%) as colorless crystals. Mp 97−98 °C (Et_2O) (lit.[5d] mp 93−94 °C); $[\alpha]^{25}_D$ −16.5 (*c* 0.2, $CHCl_3$) {lit.[5d] $[\alpha]^{25}_D$ −16.2 (*c* 1.2, $CHCl_3$)}; IR ν 2946, 1737, 1709 cm^{-1}; ^1H NMR δ 8.02 (dd, 2H, *J* = 8.22, 1.38 Hz), 7.53 (tt, 1H, *J* = 7.56, 1.51 Hz), 7.42 (t, 2H, *J* = 7.56 Hz), 5.25 (m, 1H), 3.71 (s, 3H), 3.56−3.57 (m, 1H), 3.30 (br, 1H), 3.00−3.03 (m, 1H), 2.43 (td, 1H, *J* = 10.35, 2.70 Hz), 2.23 (s, 3H), 2.08−2.21 (m, 2H), 1.85−1.90 (m, 1H), 1.70−1.73 (m, 2H); ^{13}C NMR δ 170.7, 166.1, 132.8, 130.2, 129.6, 128.2, 66.8, 64.8, 61.5, 51.3, 50.1, 41.1, 35.5, 25.4, 25.2; MS *m*/*z* (%) 303 (M^+, 4), 82 (100).

Preparation of (1*R*,2*R*,3*S*,5*S*)-2-Cyano-3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic Acid *tert*-Butyl Ester (16). To a solution of **5b** (330 mg, 1.0 mmol) in H_2O−MeOH (1:5 by v/v, 10 mL) was added H_3BO_3 (190 mg, 3 mmol) and wet W-2 Raney nickel (40 mg). The resulting suspension was hydrogenated for 3 h under atmospheric pressure (balloon) and room temperature. After the catalyst was filtered off, the filtrate was diluted with H_2O (30 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum gave **16** (250 mg, 99%) as colorless crystals. Mp 140−141 °C (hexane−EtOAc) (lit.[5d] mp 139−140 °C); $[\alpha]^{25}_D$ −10.2 (*c* 0.2, $CHCl_3$) {lit.[5d] $[\alpha]^{25}_D$ −9.0 (*c* 1.0, $CHCl_3$)}; IR ν 2977, 2240, 1685 cm^{-1}; ^1H NMR δ 4.53−4.61 (m, 1H), 4.32−4.45 (m, 1H), 4.15−4.26 (m, 1H), 3.71 (d, 1H, *J* = 5.16 Hz), 3.12 (br, 1H), 1.75−2.05 (m, 4H), 1.58−1.65 (d, 2H, *J* = 7.56 Hz), 1.49 (s, 9H); ^{13}C NMR δ 152.2, 117.8, 80.4, 62.6, 53.7, 51.5 41.5, 37.6, 28.1 (3C), 27.5 (2C); MS *m*/*z* (%) 252 (M^+, 0.65), 57 (100).

Preparation of (1*R*,5*S*)-2-Cyano-8-azabicyclo[3.2.1]-2-oc-tene-8-carboxylic Acid *tert*-Butyl Ester (17). To a solution of **16** (1.30 g, 5.20 mmol) in CH_2Cl_2 (40 mL) was successively added Et_3N (1.04 g, 10.4 mmol) and $MeSO_2Cl$ (1.2 g, 1.04 mmol) at 0 °C. After the resulting mixture was stirred at 0 °C for 1 h, it was allowed to stir at room temperature for another 12 h. Then it was quenched with ice−water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, 16% EtOAc) to give pure **17** (1.04 g, 85%) as colorless crystals. Mp 96−97 °C (hexane−EtOAc); $[\alpha]^{25}_D$ −94.4 (*c* 0.2, $CHCl_3$); IR ν 2971, 2209, 1693 cm^{-1}; ^1H NMR δ 6.50 (br, 1H), 4.45 (br, 1H), 4.34 (br, 1H), 2.87 (br, 1H), 1.97−2.35 (m, 4H), 1.62−1.75 (m, 1H), 1.46 (s, 9H); ^{13}C NMR δ 153.2, 141.9, 118.8, 116.8, 80.0, 54.8, 50.9, 34.4, 33.6, 29.1, 27.9 (3C); MS *m*/*z* (%) 234 (M^+, 0.10), 57 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.77; H, 7.80; N, 12.10.

Preparation of (1*R*,5*S*)-2-Acetyl-8-azabicyclo[3.2.1]-2-oc-tene-8-carboxylic Acid *tert*-Butyl Ester (18). To a stirred solution of **17** (230 mg, 1.0 mmol) in Et_2O (10 mL) was added a solution of MeLi in Et_2O (1.6 M, 3.0 mL, 4.80 mmol) dropwise at 0 °C under N_2. After the resulting mixture was warmed to room temperature and stirred for 2 h, it was quenched with H_2O (3 mL) at 0 °C. PPTS (10 mg, 0.04 mmol) was then added and the new mixture was stirred for another 12 h at room temperature. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, 16% EtOAc) to give pure **18** (220 mg, 87%) as colorless crystals. Mp 62−63 °C (hexane−EtOAc) (lit.[6f] mp 64−65 °C); $[\alpha]^{25}_D$ −114.5 (*c* 0.2, $CHCl_3$) {lit.[6f] $[\alpha]^{25}_D$ −126.8 (*c* 1.0, $CHCl_3$)}; IR ν 2977, 1699, 1660 cm^{-1}; ^1H NMR δ (as rotamers) 6.67 (s, 1H), 4.91 (d, 1H, *J* = 5.83 Hz), 4.35 (s, 1H), 2.93 (m, 1H), 2.27 (s, 3H), 2.10−2.20 (m, 3H), 1.80 (dt, 1H, *J* = 2.4, 10.98

Hz), 1.50−1.61 (m, 1H), 1.43 (s, 9H); ^{13}C NMR δ (as rotamers) 196.2, 153.6 (0), 145.3, 137.2, 79.4, 51.9, 51.1, 34.7, 34.5, 29.5, 28.2 (3C), 24.7; MS m/z (%) 251 (M^+, 0.50), 57 (100).

Preparation of (−)-Ferruginine (2). To a solution of **18** (330 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise CF_3CO_2H (5.0 g, 43.86 mmol) and the resulting mixture was stirred for 1 h at room temperature. After the reaction was diluted by CH_2Cl_2 (15 mL), saturated aqueous $NaHCO_3$ was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude amine product was obtained as a yellow oil.

To a solution of the crude amine product and formaldehyde (37% aqueous solution, 0.6 mL, 8 mmol) in MeCN (20 mL) was added $NaBH_3CN$ (170 mg, 2.7 mmol). Then the resulting mixture was stirred for 1 h at room temperature and acidified to pH 6 with HOAc. After the mixture was stirred for an additional 0.5 h, it was neutralized to pH 9 with ammonia. The mixture was diluted by addition of CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified by chromatography (silica gel, Et_3N:MeOH:CH_2Cl_2 = 0.5:10:100) to give (−)-ferruginine (**2**) (200 mg, 91%) as a yellow oil. $[\alpha]^{25}_D$ −52.5 (*c* 0.2, $CHCl_3$) {lit.[6e] $[\alpha]^{25}_D$ −50.8 (*c* 0.94, $CHCl_3$)}; IR ν 2942, 1662 cm^{-1}; ^{1}H NMR δ 6.73 (br, 1H), 3.90 (d, 1H, J = 4.47), 3.23 (br, 1H), 2.72 (d, 1H, J = 20.79 Hz), 2.32 (s, 3H), 2.26 (s, 3H), 2.05−2.20 (m, 2H), 1.93 (dd, 1H, J = 19.59, 3.78 Hz), 1.70 (t, 1H, J = 9.63 Hz), 1.48 (t, 1H, J = 8.91 Hz); ^{13}C NMR δ (as rotamers) 196.9, 143.1, 136.3, 57.0, 56.9, 36.7, 33.2, 32.4, 29.1, 24.4; MS m/z (%) 165 (M^+, 22), 57 (100).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for **11a**−**d**, **3a**−**f**, **4**, **5b**, **13**−**18**, **1**, and **2**, as well as the crystallographic data of compound **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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