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Concise Catalytic Asymmetric Total Synthesis of Biologically Active Tropane Alkaloids

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Abstract: A general strategy for the total asymmetric synthesis of valuable tropane alkaloids by catalytic stereoselective transformations is disclosed. The power of this approach is exemplified by the concise catalytic enantioselective total syntheses of (+)-methylecgonine, (−)-cocaine and (+)-cocaine as well as the first catalytic asymmetric total syntheses of a cocaine C-1 derivative and (+)-ferruginine starting from 5-oxo-protected-α,β-unsaturated enals using only two and three column chromatographic purification steps, respectively.

Keywords: asymmetric catalysis; cocaine; cycloadditions; ferruginine; multi-component reactions; stereoselectivity; tandem reactions

Introduction

The tropane (8-azabicyclo[3.2.1]octane) ring-system is present in several valuable biologically active natural products and unnatural compounds (e.g., **1**–**4**, Figure 1).[1,2] Among them, (−)-cocaine **1** is a powerful analgesic and stimulant of the central nervous system,[3] (+)-ferruginine **2** has potential in the treatment of the neurodegenerative disorder Alzheimer's disease[4] and its unnatural enantiomer *ent*-**2** is an agonist for the nicotine acetylcholine receptor.[5] With respect to cocaine **1**, a challenge is the search for a therapeutically useful antagonist and partial agonist for the treatment of its abuse that is a major worldwide concern. Here the stereochemistry is of the utmost importance since of the eight possible stereoisomers of cocaine only the (*R*)-isomer (−)-**1** is addictive.[6] When cocaine **1** and alcohol have been ingested simultaneously the more potent cocaethylene (−)-**1a′** is formed.[7] In addition, cocaine can also be used as the starting material for the synthesis of valuable biologically active 2β-substituted-3β-aryltropanes **3**.[8] Thus, there is a need for the development of efficient and versatile methods for the total synthesis of natural tropane alkaloids and their derivative in a highly stereoselective fashion. In 1898, Willstätter starting from tropinone first accomplished the total synthesis of cocaine.[9]

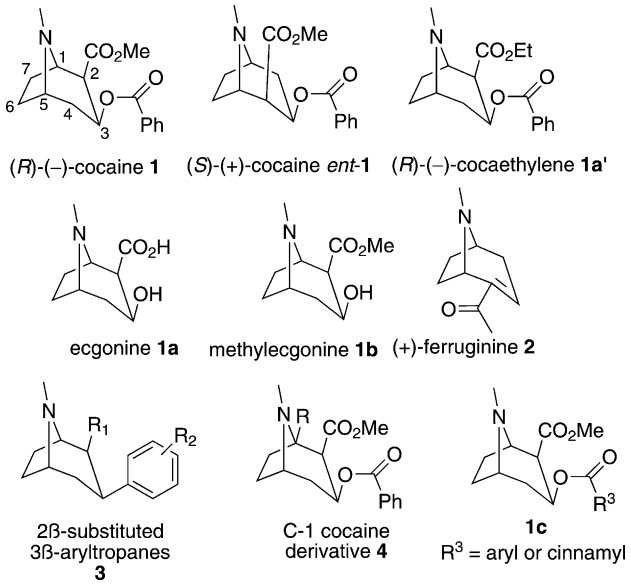
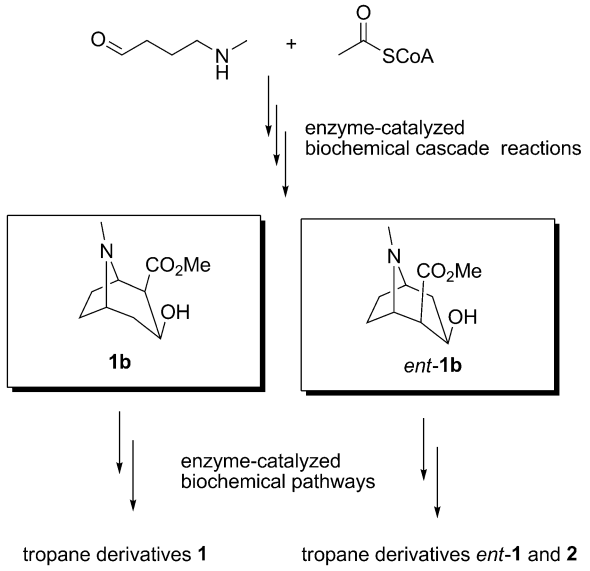


Figure 1. Examples of natural tropane alkaloids and their derivatives **1**–**4**.

Robinson's classical total synthesis of tropinone by means of a multicomponent cascade reaction stands also as an important bench mark in organic synthesis.[10] After these two pioneering works, several approaches to construct chiral tropane alkaloids have been developed.[2e,11] However, traditionally most of

these syntheses were accomplished on a case by case basis. In this context, there are only a few reports on the asymmetric synthesis of cocaine and only four total asymmetric syntheses that do not rely on resolution to produce enantiomerically pure materials.[12] In fact, to the best of our knowledge, there is only one elegant 14 linear step total synthesis of (+)-cocaine *ent*-**1** (6.5% overall yield, 1:1 *dr* and 84% *ee*) that involves a catalytic desymmetrization step.[13] Ferruginine **2** is also an attractive target for the synthetic community due to its biological activity.[12a,14] However, **2** has never been synthesized by means of asymmetric catalysis. This is also the case for the valuable C-1 cocaine derivatives **4**.[12c]

The tropane alkaloid biosynthesis is still not resolved. What is known is that it involves iminium formation and cascade reactions.[2] In the case of naturally occurring tropane alkaloids **1**, methylecoginine **1b** is the natural common biosynthetic intermediate prior to further enzymatic manipulations (Scheme 1).[2e]



Scheme 1. Biosynthesis and biomimetic synthetic strategy of tropane alkaloids.

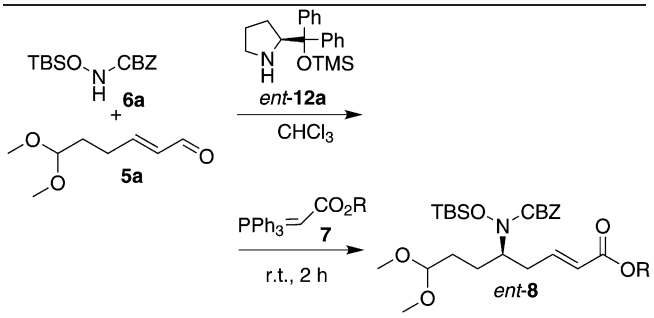
While for tropanes of type **2**, *ent*-**1b** is the common biosynthetic intermediate. Inspired by nature, we envisioned an expeditious route for the asymmetric synthesis of both enantiomers of a common advanced synthetic intermediate (e.g., **1b**) by means of one-pot catalytic multicomponent and stereoselective reaction sequences[15] (Scheme 2). This would include important "green chemistry" parameters (e.g., reduction of synthetic steps, waste and solvents).[16–18] The common synthetic intermediate could next be further manipulated to the desired enantiomer of different tropane alkaloids (e.g., **1**–**4**) by additional transformations.

Herein we disclose the concise catalytic asymmetric total synthesis of valuable tropane alkaloids [e.g., (+)-methylecgonine, (−)-cocaine, (+)-cocaine, (−)-1-methylcocaine and (+)-ferruginine] by employment of this versatile synthetic strategy.

Results and Discussion

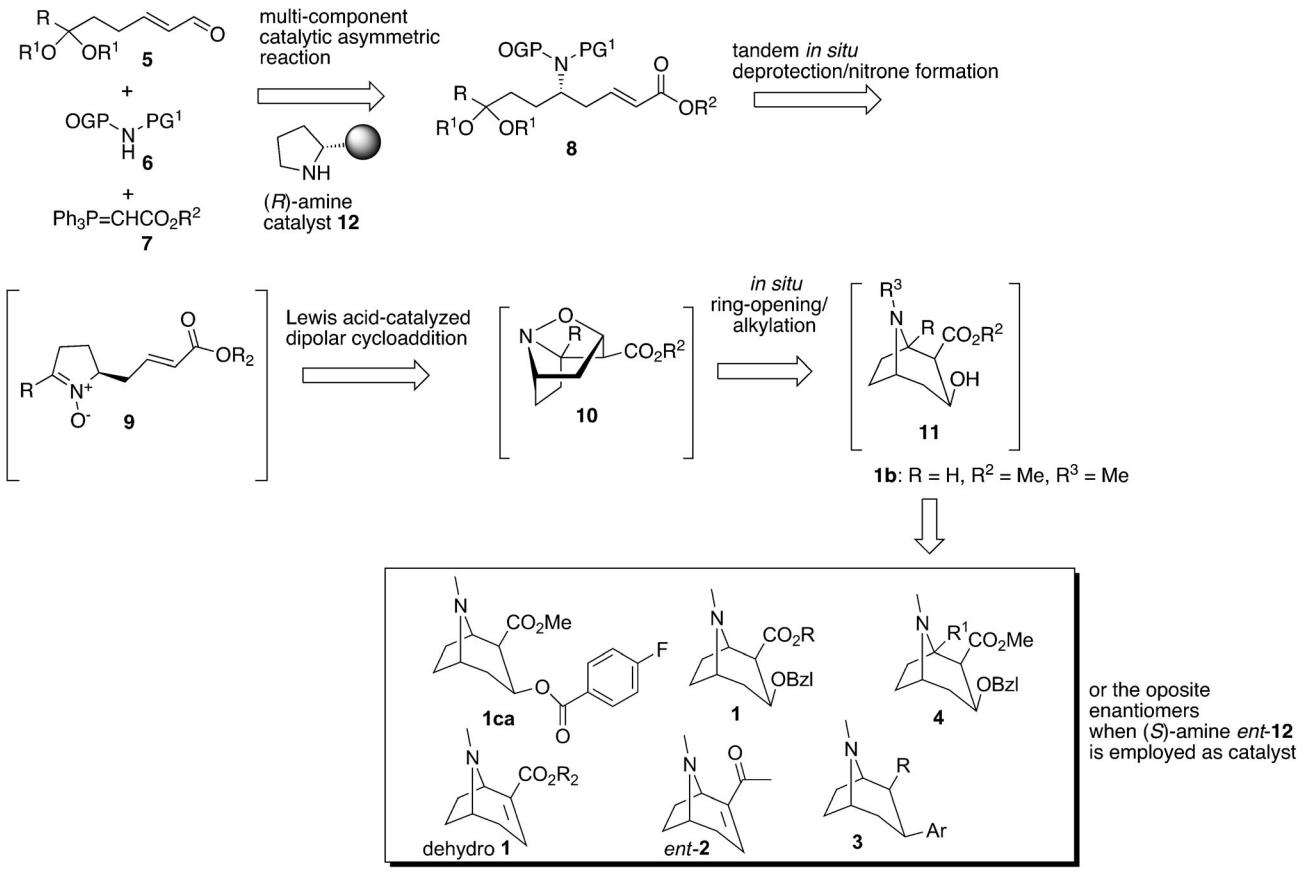
We began our synthesis with the investigation of the one-pot catalytic enantioselective three-component catalytic aza-Michael/Wittig tandem reaction between acetal-functionalized enals **5**, hydroxylamines **6** and alkyl 2-(triphenylphosphoranylidene)acetates **7** using chiral amine **12** or *ent*-**12** as the catalysts (Scheme 1, Table 1).[19,20] The acetal-functionalized enals **5** were readily synthesized in five steps from simple chemical such as propargyl alcohol and ethyl leuvinate, respectively (see the Supporting Information).[12c] Our hypothesis was that the corresponding α,β-unsaturated δ-amino acid derivatives **8** (or *ent*-**8**) with a protected

Table 1. Screening of conditions for the one-pot three-component reaction between amine **12a**, enal **13**, and **14**.[a]



Entry	Prod.	R	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1[d]	*ent*-**8a**	Me	r.t.	40	40	90
2	*ent*-**8a**	Me	r.t.	24	67	90
3	*ent*-**8a**	Me	4	40	68	92
4	*ent*-**8a**	Me	–20	135	48	96
5[e]	*ent*-**8a**	Me	4	96	41	92
6[f]	*ent*-**8a**	Me	4	40	69	92
7[f]	*ent*-**8a**	Me	4	17	68	96
8[g]	**8a**	Me	4	17	70	96
9[g]	**8a'**	Et	4	17	71	96

[a] Enal **5a** (0.25 mmol), amine **6a** (2 mmol), and catalyst *ent*-**12a** (20 mol%) were stirred in $CHCl_3$ (0.5 mL).
[b] Isolated yield of pure compound.
[c] Determined by chiral-phase HPLC analysis.
[d] 1 mL of $CHCl_3$ and 0.5 mmol **6a**.
[e] 10 mol% of *ent*-**12a**.
[f] 1 mmol of enal **5a**.
[g] 1 mmol of enal **5a** and catalyst **12a** (20 mol%).



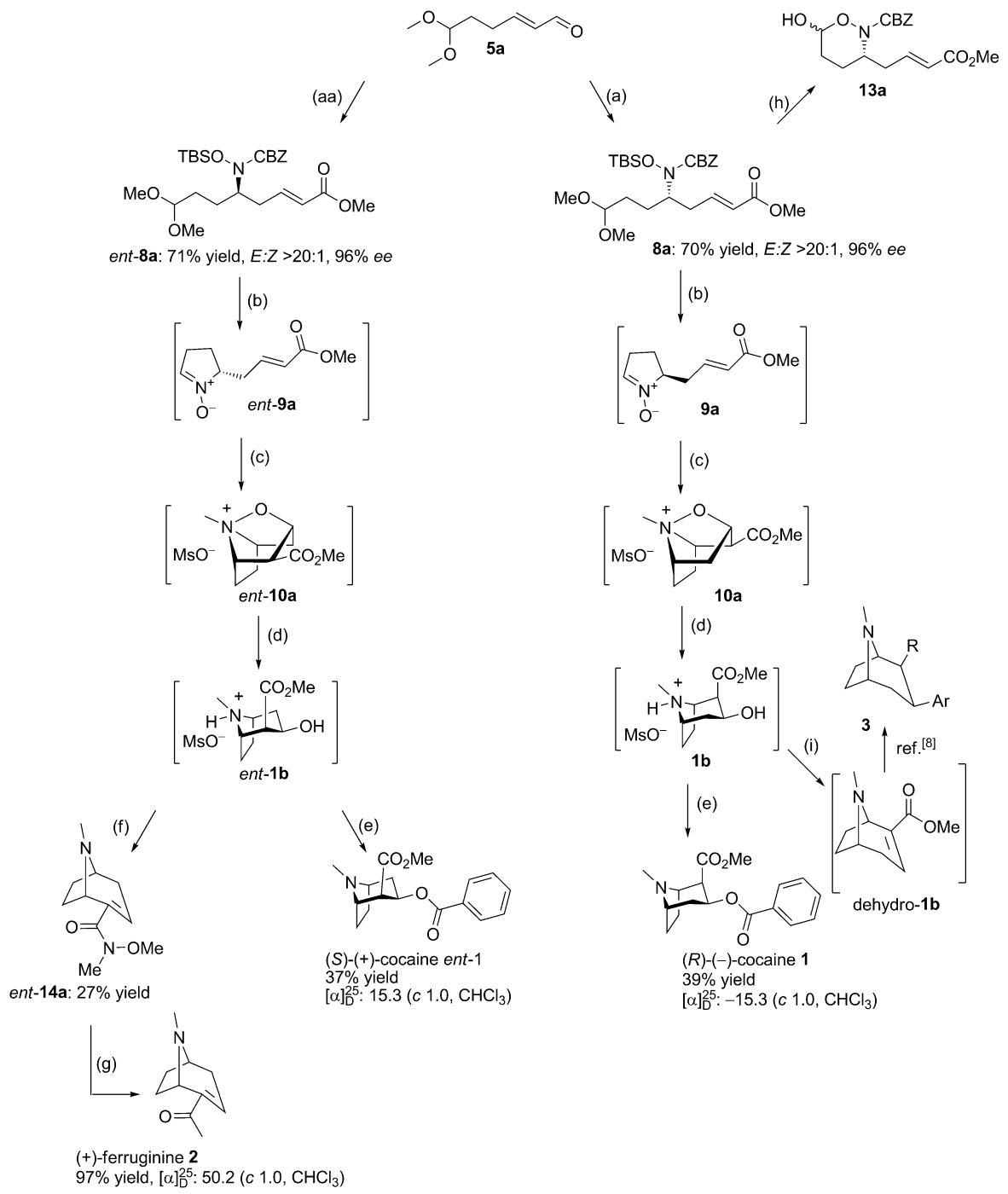
Scheme 2. A general strategy for the gathered total synthesis of tropane alkaloids.

acetal and hydroxylamine functionality could be triggered to undergo intermolecular nitrone formation by means of *in situ* deprotection to give nitrones **9** (or *ent*-**9**, Scheme 2). Next, a Lewis acid-catalyzed Tufariello–Davis intramolecular [1,3]-dipolar cycloaddition may set the stage for the assembly of tricyclic intermediates **10** (or *ent*-**10**)[12c,21] and a subsequent modified Davis alkylation/ring-opening N–O bond-cleavage[12c] sequence should give the advanced synthetic intermediates **11** (or *ent*-**11**). Thereafter both enantiomers of a broad range of different valuable tropane derivatives should be accessible by further manipulations (e.g., **1**–**4**, Scheme 2).

To our delight, the reaction between enal **5a**, amine **6a** and methyl 2-(triphenylphosphoranylidene)acetate **7a** in the presence of a catalytic amount of *ent*-**12a** gave the corresponding α,β-unsaturated δ-amino acid derivative *ent*-**8a** in high *ee*s. We found that the optimal conditions were to perform the reaction in $CHCl_3$ at 4 °C using 4 equivalents of amine **6a**, which was recycled. Changing the catalyst from (*S*)- to (*R*)-**12a** did not affect the enantioselectivity of the reaction (entries 7 and 8, Scheme 2). However, a prolonged reaction time slightly decreased the *ee* due to *retro*-Michael reactions (entries 6 and 7). The one-pot catalytic enantioselective tandem transformation with ethyl 2-(triphenylphosphoranylidene)acetate **7b** as a component afforded δ-amino acid derivative **8a′** in 71% yield with 96% *ee* (entry 9). In fact, this is the catalytic highly enantioselective entry to the total synthesis of (*R*)-cocaethylene **1a′** (Scheme 2),

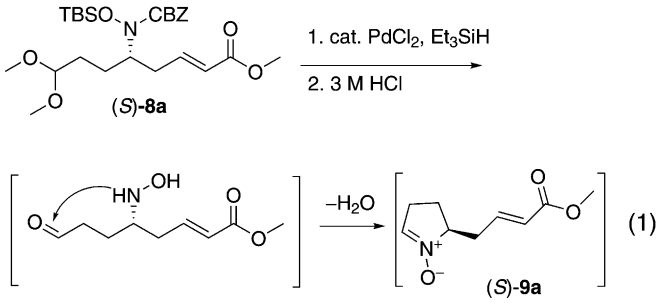
After successful development of the one-pot catalytic highly enantioselective three-component synthesis of **8a**, we embarked on the construction of (−)-cocaine **1** (Scheme 3). Thus, we initially attempted to form nitrone **9a** *via* an *in situ* deprotection/cyclization transformation. However, refluxing **8a** in an aqueous HCl solution led to complicated mixtures while performing this reaction by stirring at room temperature resulted in the formation of Cbz-protected hemiacetal **13a**. Instead we had to develop a Pd(II)-catalyzed triethylsilane[22] Cbz deprotection, acid-mediated acetal and silyl group deprotection and cyclization sequence for the successful formation of nitrone **9a** [Eq. (1)].

We next continued the synthesis by performing an $Al(O\text{-}t\text{-}Bu)_3$-catalyzed intramolecular [1,3]-dipolar cycloaddition and methylation sequence using MsOMe as the reagent. We were able to execute the sequence and compound **10a** was formed as a single diastereoisomer. Next, a Pd-catalyzed hydrogenation and benzoylation reaction sequence followed by final purifica-



Scheme 3. (a) i. **5a** (1 equiv.), (*R*)-**12a** (20 mol%), **6a** (4 equiv.), $CHCl_3$, 4 °C, 17 h; ii. **7a** (1 equiv.), room temperature, 2 h; (aa) same as (a) but (*S*)-*ent*-**12a** (20 mol%) was the catalyst; (b) i. cat. $PdCl_2$ (10 mol%), Et_3N (0.7 equiv.), Et_3SiH (4 equiv.), CH_2Cl_2, reflux, 6 h; ii. 3 M HCl:THF (3:1), room temperature, 2 h.;(c) i. $Al(O\text{-}t\text{-}Bu)_3$ (50 mol%), toluene, room temperature, 4 h next 150 °C, 64 h; ii. MsOMe (5 equiv.), CH_2Cl_2, reflux, 24 h; (d) cat. Pd/C, H_2 balloon, MeOH, room temperature, 48 h; (e) PhCOCl (2 equiv.), Et_3N (16 equiv.), cat. DMAP, CH_2Cl_2, room temperature, 17 h; (f) i. 6 M HCl, reflux, 6 h; ii. $POCl_3$, reflux, 4 h; iii. MeO(Me)NH·HCl (5 equiv.), Et_3N (10 equiv.), CH_2Cl_2, room temperature, 2 h; (g) MeLi (2 equiv.), THF, −78 °C, 30 min next 0 °C, 30 min; (h) 6 M HCl, room temperature, 17 h; (i) $POCl_3$, reflux, 2.5 h according to ref.[8f]

tion with silica gel column chromatography afforded (*R*)-(−)-cocaine **1** in 39% yield from **8a**. Thus, starting from enal **5a** we were able to execute the catalytic asymmetric total synthesis of **1** {$[\alpha]_D^{25}$: −15.3 (*c* 1.0, $CHCl_3$), lit. (*S*)-cocaine *ent*-**1**: $[\alpha]_D^{24}$: +15.5 (*c* 1.0, $CHCl_3$)[9b,11d]} in 27% overall yield with 96% *ee* using only two column chromatographic purification steps. The key steps were a catalytic enantioselective aza-

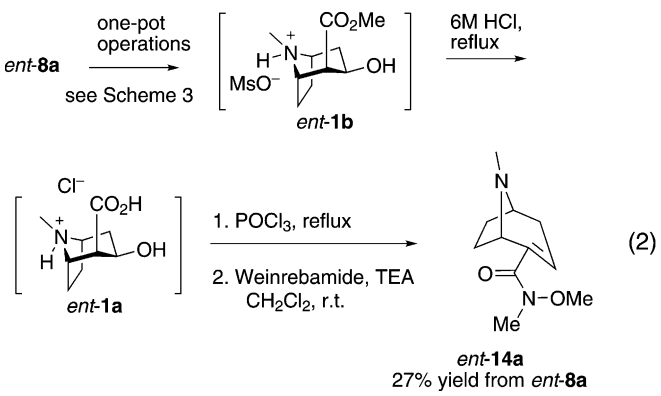


(1)

Michael/Wittig transformation, a catalytic nitrone-formation/methylation sequence, a catalytic stereoselective intramolecular dipolar cycloaddition and a catalytic hydrogenation/benzoylation sequence. Using this procedure we were also able to isolate methylecgonine **1b** in 39% yield starting from **8a**. Based on these results, we decided to investigate the yields of the *vide supra* described catalytic reaction sequences. Thus, it was possible to isolate **9a** in 89% yield starting from **8a**, **10a** in 44% yield from **9a**, methylecgonine **1b** in >99% yield from **10a** and cocaine **1** in >99% yield from **1b**. The investigation shows that it was the catalytic intramolecular [1,3]-dipolar cycloaddition/methylation sequence that gave the lowest yield. With the above results in hand, we continued the expeditious total syntheses of tropane alkaloids. Thus, we first synthesized *ent*-**8a** using *ent*-**12a** as the catalyst for the one-pot three-component catalytic enantioselective tandem reaction between **5a**, **6a** and **7a** (Scheme 3). Subsequent conversion of *ent*-**8a** according to the above described catalytic transformations gave (*S*)-(+)-cocaine *ent*-**1** in 37% yield {$[\alpha]_D^{24}$: +15.3 (*c* 1.0, $CHCl_3$), lit. (*S*)-cocaine *ent*-**1**: $[\alpha]_D^{25}$: +15.5 (*c* 1.0, $CHCl_3$)[9b,11d]}. In addition, hydrolysis of *ent*-**1b** gave (+)-ecgonine *ent*-**1a** and subsequent $POCl_3$-mediated[23] anhydroecgonine chloride formation and amidation gave Weinreib amide *ent*-**14a** in 27% yield from *ent*-**8a** (Scheme 3 and Eq. [2]).

Next, natural (+)-ferrunginine **2** {$[\alpha]_D^{25}$: +50.2 (*c* 1.0, $CHCl_3$), lit. (−)-ferrunginine *ent*-**2**: $[\alpha]_D^{25}$: −50.8 (*c* 0.94, $CHCl_3$)[14f]} was obtained in 97% yield using Weinreb's conditions. It is noteworthy that this is the first catalytic asymmetric total synthesis of **2** and based on only three column chromatographic steps. In addition, the disclosed synthetic strategy is also an entry to anhydroecgonine methyl ester (dehydro-**1b**) by simply extending the catalytic reaction sequence to **1b** with $POCl_3$-mediated dehydration. In fact, this is the starting point for the total synthesis of 2β-substituted-3β-aryltropanes **3**, which have attracted considerable attention as inhibitors of dopamine, norepinephrine and serotonin reuptake as well as inhibitors of the nicotinic acetylcholine receptor.[8] In addition, the total synthesis of biologically active cocaine derivatives such as **1c** can be readily accomplished by means of the disclosed strategy by just changing the acylation reagent for the final one-pot esterification of methylecgonine **1b**. The total synthesis of C-1 cocaine derivatives **4** with a quaternary stereocenter is very challenging and has only been performed using chiral auxiliaries.[12c] Thus, we wanted to explore our catalytic strategy for the preparation of these types of valuable cocaine analogues (Scheme 4).

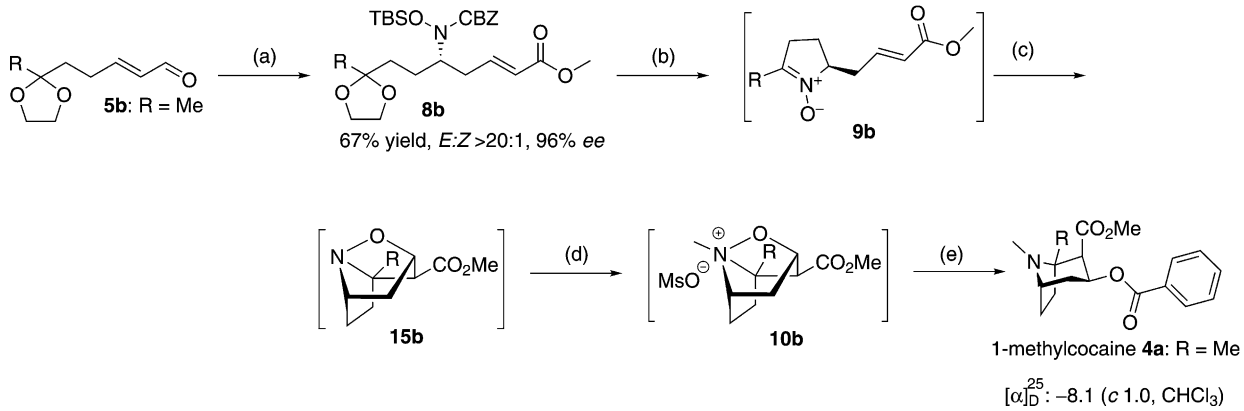
The one-pot catalytic enantioselective three-component aza-Michael/Wittig transformation using **12a** as the catalyst gave protected α,β-unsaturated δ-amino acid derivative **8b** in 67% yield with 96% *ee*. We next continued with the catalytic deprotection and cyclization recation sequence, which afforded nitrone **9b**. The subsequent Lewis acid-catalyzed stereoselective intramolecular [1,3]-dipolar cycloaddition was followed by methylation to deliver tricyclic isoxazoline **10b** *via* intermediate **15b** as a single diastereoisomer. The final catalytic ring-opening/acylation sequence furnished 1-methylcocaine **4a** {$[\alpha]_D^{25}$: −8.1 (*c* 1.0, $CHCl_3$), lit. **4a**: $[\alpha]_D^{20}$: −8.32 (*c* 1.25, $CHCl_3$)[12c]} in 51% yield with 96% *ee*. Thus, the first catalytic asymmetric synthesis of a C-1 cocaine derivative was accomplished in 34% overall yield employing only two column chromatographic purification steps. We next decided to investigate the catalytic stereoselective intramolecular [1,3]-dipolar cycloaddition and methylation reaction sequence to see if the conversion to product improved as compared to when **9a** was used as the starting material. Indeed, the tricyclic compound **15b** was isolated in 72% yield from **9b** and **10b** in 99% yield from **15b**, respectively. In this context, nitrone **9b** was isolated in 76% yield from **8b** by the catalytic tandem sequence at the catalytic deprotection and cyclization reaction sequence.



(2)

Conclusions

In summary, we have disclosed a general strategy for the total synthesis of tropane alkaloids in combination with catalytic enantioselective and stereoselective reaction sequences. As in nature it is based on the asymmetric assembly of an advanced common syn-



Scheme 4. (a) 1. **5b** (1 equiv.), (*R*)-**12a** (20 mol%), **6a** (4 mmol), $CHCl_3$, 4 °C, 41 h; ii. **7a** (1 equiv.), r.t., 2 h; (b) i) cat. $PdCl_2$ (10 mol%), Et_3N (0.7 equiv.), Et_3SiH (4 equiv.), CH_2Cl_2, reflux, 8 h; ii) 3 M HCl:THF (3:1), room temperature, 2 h; c) i. $Al(O\text{-}t\text{-}Bu)_3$ (50 mol%), toluene, room temperature, 4 h; ii. 150 °C, 64 h; d) MsOMe (3 equiv.), benzene, 85 °C, 24 h; e) i. cat. Pd/C, H_2 (50–70 psi), MeOH, room temperature, 24 h; ii) PhCOCl (2 equiv.), Et_3N (7 equiv.), cat. DMAP, CH_2Cl_2, room temperature, 17 h.

thetic intermediate prior to the final synthesis of the specific natural product. The versatility of this approach was demonstrated by the expeditious catalytic asymmetric total synthesis of methylecgonine, (*R*)-(−)-cocaine and (*S*)-(+)-cocaine starting from 5-oxo-protected-α,β-unsaturated enals using only two column chromatographic separation steps, respectively. In addition, the first catalytic enantioselective total synthesis of (+)-ferruginine and a cocaine C-1 derivative starting from 5-oxo-protected-α,β-unsaturated enals was completed with two and three column chromatographic purification steps, respectively. The presented strategy was also applied in the formal catalytic asymmetric total synthesis of valuable unnatural 3β-aryltropanes **3** and substituted cocaine derivatives **1c**. Thus, the versatility of the disclosed total synthesis approach makes it amenable for combinatorial synthesis as well as the total synthesis of a plethora of cocaine derivatives. It should also be applicable for the concise synthesis of the novel haptens that are necessary for the generation of *anti*-cocaine antibodies.[24] Further applications of the disclosed synthetic design approach in catalytic asymmetric total synthesis of other natural product and medicinal agent classes are ongoing and will be communicated in due course.

Experimental Section

General Remarks

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standards techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of ammoniummolybdate (100 g), $Ce(SO_4)_2$ (2 g) and 10% H_2SO_4 (1 L) followed by heating or by treatment with a solution of potassium permanganate (3 g), K_2CO_3 (20 g), 5% aqueous NaOH (5 mL) and water (300 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, $CDCl_3$ served as internal standard ($\delta = 7.26$ ppm for ^1H NMR and $\delta = 77.16$ ppm for ^{13}C NMR). Peaks are labelled as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). HPLC was carried out using a Waters 2690 Millenium with photodiode array detector. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter ($d = 589$ nm, 1 dm cell). High-resolution mass (ESI) spectra were obtained with a Bruker MicroTOF spectrometer. The acetal-functionalized enals **5** were made according to literature procedures.[12c]

Typical Experimental Procedure for the One-Pot Three-Component Synthesis of α,β-Unsaturated δ-Amino Acid Derivatives

(*E*)-6,6-Dimethoxyhex-2-enal (**5a**) (158 mg, 1 mmol), benzyl (*tert*-butyldimethylsilyl)oxycarbamate (1126 mg, 4 mmol), and (*R*)-catalyst **12a** (65 mg, 0.2 mmol) were vigorously stirred in $CHCl_3$ for 17 h at 4 °C (>95% conversion as monitored by ^1H NMR analysis). Next, methyl 2-(triphenylphosphoranylidene)acetate (334 mg, 1 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. Next, the reaction mixture was concentrated under reduced pressure and loaded up on a silica-gel column and immediate flash chromatography (pentane:EtOAc mixtures, 10:1 to 5:1) gave the excess benzyl (*tert*-butyldimethylsilyl)oxycarbamate (870 mg) and the amino acid product: (*S*,*E*)-methyl 5-{[(benzyloxy)carbonyl][(*tert*-butyldimethylsilyl)oxy]amino}-8,8-dimethoxyoct-2-enoate (**8a**); yield: 348 mg (70%, *E*:*Z* > 20:1); $R_f = 0.48$ (pentane:EtOAc = 4:1); ^1H NMR: $\delta = 7.35$–7.29 (m, 5H), 6.95–6.88 (m, 1H), 5.88

(dt, $J=15.6$, 1.2 Hz, 1H), 5.11 (t, $J=12.3$ Hz, 2H), 4.31 (t, $J=11.1$ Hz, 1H), 4.06–3.99 (m, 1H), 3.71 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.68–2.60 (m, 1H), 2.36–2.29 (m, 1H), 1.83–1.74 (m, 1H), 1.72–1.64 (m, 1H), 1.61–1.55 (m, 1H), 1.54–1.45 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR: $\delta=166.8$, 159.2, 145.6, 135.8, 128.7, 128.6, 128.5, 123.4, 104.3, 68.1, 61.7, 53.3, 52.7, 51.6, 35.4, 29.5, 27.3, 26.1, 18.5, −4.2, −4.3; HR-MS (ESI): $m/z=518.2550$, calcd. for $[M+Na]^+$ ($C_{25}H_{41}NO_7SiNa$): 518.2545. $[\alpha]_D^{25}$: 7.1 ($c=1.0$, $CHCl_3$) for an enantiomerically enriched sample of 96% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, 99.5/0.5 *i*-hexane/*i*-PrOH, 0.5 mL min^{-1}, 210.5 nm): t_r (major enantiomer) = 105.4 min, t_r (minor enantiomer) = 123.9 min.

(*S*,*E*)-Ethyl 5-{[(benzyloxy)carbonyl][(*tert*-butyldimethylsilyl)oxy]amino}-8,8-dimethoxyoct-2-enoate (8a′): $R_f=0.20$ (pentane:EtOAc = 10:1); ^{1}H NMR: $\delta=7.35$–7.29 (m, 5H), 6.94–6.88 (m, 1H), 5.86 (dt, $J=12.5$, 1.0 Hz, 1H), 5.11 (dd, $J=10.7$, 9.6 Hz, 2H), 4.31 (t, $J=4.4$ Hz, 1H), 4.17 (q, $J=5.7$ Hz, 2H), 4.04–3.98 (m, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 2.67–2.61 (m, 1H), 2.35–2.30 (m, 1H), 1.83–1.75 (m, 1H), 1.71–1.64 (m, 1H), 1.60–1.46 (m, 2H), 1.27 (t, $J=5.7$ Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR: δ 166.4, 159.2, 145.2, 135.9, 128.7, 128.6, 128.4, 123.8, 104.3, 68.1, 61.8, 60.3, 53.3, 52.7, 35.4, 29.5, 27.2, 26.1, 18.5, 14.4, −4.25, −4.30; HR-MS (ESI): $m/z=532.2708$, calcd. for $[M+Na]^+$ ($C_{26}H_{43}NO_7SiNa$): 532.2701. $[\alpha]_D^{25}$: 6.9 ($c=1.0$, $CHCl_3$) for an enantiomerically enriched sample of 96% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AD column, 98/2 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}, 210.5 nm): t_r (major enantiomer) = 10.5 min, t_r (minor enantiomer) = 12.9 min.

Catalytic Nitrone Synthesis

Under an N_2 atmosphere, (*S*,*E*)-methyl 5-{[(benzyloxy)carbonyl][(*tert*-butyldimethylsilyl)oxy]amino}-8,8-dimethoxyoct-2-enoate **8a** (348 mg, 0.70 mmol), Et_3N (68 μL, 0.49 mmol) and Et_3SiH (0.45 mL, 2.8 mmol) were stirred in dry CH_2Cl_2 (7 mL). To this solution, $PdCl_2$ (12 mg, 0.07 mmol) was added. Next, the reaction mixture was refluxed for 6 h. After cooling the reaction mixture to room temperature, the solution was washed with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The organic phases were combined, and concentrated to give an oily residue, which was then used in the next step without purification.

This oill residue was stirred in aqueous HCl (3 M, 3 mL) and THF (1 mL) for 2 h at room temperature. The solution was then washed with Et_2O (5 mL × 2) to remove Et_3SiH. The aqueous layer was neutralized with excess solid Na_2CO_3 and then extracted with CH_2Cl_2 (6 mL × 3). The organic phases were combined, dried with Na_2SO_4, filtered, and concentrated to give the nitrone product (*S*,*E*)-2-(4-methoxy-4-oxobut-2-en-1-yl)-3,4-dihydro-2*H*-pyrrole 1-oxide (**9a**) which was then used in the next step without purification; yield: 114 mg (89%); $R_f=0.54$ (MeOH:$NH_3\cdot H_2O$ = 50:1); ^{1}H NMR: $\delta=6.89$–6.82 (m, 2H), 5.95 (d, $J=16.0$ Hz, 1H), 4.10 (br, 1H), 3.71 (s, 3H), 2.98–2.93 (m, 1H), 2.67–2.60 (m, 3H), 2.42–2.33 (m, 1H), 1.97–1.88 (m, 1H); ^{13}C NMR: $\delta=$ 166.4, 142.6, 134.2, 124.8, 70.9, 51.7, 34.7, 26.5, 24.3; HR-MS (ESI): $m/z=206.0781$, calcd. for $[M+Na]^+$ ($C_9H_{13}NO_3Na$): 206.0788; $[\alpha]_D^{25}$: −5.5 (*c* 1.0, CH_2Cl_2).

Representative Procedure for the Catalytic Dipolar/Methylation Reaction

The crude nitrone **9a** (114 mg, 0.62 mmol) was dissolved in anhydrous toluene (31 mL) and transferred to a pressure tube. Al(O-*t*-Bu)$_3$ (76 mg, 0.31 mmol) was added and the tube was sealed. The reaction mixture was stirred at room temperature for 4 h and then heated at 150 °C for 64 h. After cooling to room temperature, the mixture was extracted with aqueous 1 M HCl (10 mL × 3). The aqueous layers were neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (15 mL × 3). The CH_2Cl_2 extracts were combined, dried with Na_2SO_4, filtered, and refluxed with MsOMe (0.26 mL, 3.1 mmol) under an N_2 atmosphere for 24 h. The solution was cooled to room temperature and extracted with water (50 mL). The aqueous phase was concentrated under reduced pressure to give the methylated product **10a**; yield: 80 mg (44%). ^{1}H NMR: $\delta=5.57$ (d, $J=5.2$ Hz, 1H), 4.74–4.72 (m, 1H), 4.43–4.38 (m, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.50 (d, $J=3.2$ Hz, 1H), 2.93–2.86 (m, 1H), 2.70 (s, 3H), 2.66–2.36 (m, 4H), 2.21 (dd, $J=12.8$, 2.8 Hz, 1H); ^{13}C NMR: $\delta=170.7$, 84.6, 79.4, 76.8, 58.7, 53.6, 44.6, 40.5, 39.5, 26.1, 25.4; HR-MS (ESI): $m/z=198.1127$, calcd. for $[M]^+$ ($C_{10}H_{16}NO_3$): 198.1125; $[\alpha]_D^{25}$: 25.4 (*c* 1.0, MeOH). The opposite enantiomer was obtained using the same procedures; yield: 45% yield; $[\alpha]_D^{25}$: −25.0 (*c* 1.0, MeOH).

Representative Procedures for the Catalytic Hydrogenation/Benzoylation Sequence

24 mg of the above product were dissolved in MeOH (5 mL). Pd/C (10%, 5 mg) was added. The hydrogenation was conducted under an H_2 atmosphere (balloon) for 48 h. Upon completion, the solution was filtered through celite, and concentrated to give methylecgonine **1b**; yield: 25 mg (>99%). ^{1}H NMR: $\delta=4.33$–4.27 (m, 1H), 4.05 (brd, $J=7.2$ Hz, 1H), 3.88–3.86 (m, 1H), 3.75 (s, 3H), 3.27 (br, 1H), 3.17–3.15 (m, 1H), 2.78 (s, 3H), 2.66 (s, 4H), 2.40–2.23 (m, 2H), 2.19–1.98 (m, 4H); ^{13}C NMR: $\delta=175.4$, 65.5, 64.8, 61.6, 53.1, 50.6, 39.4, 36.8, 29.9, 25.0, 24.0; HR-MS (ESI): $m/z=200.1284$, calcd. for $[M]^+$ ($C_{10}H_{18}NO_3$): 200.1281; $[\alpha]_D^{25}$: 5.7 (*c* 1.0, MeOH).

The unnatural (−)-methylecgonine (*ent*-**1b**) was obtained using the same procedures; yield: quantitative yield; $[\alpha]_D^{25}$: −6.0 (*c* 1.0, MeOH).

Next, the methylecgonine (0.085 mmol) was stirred with Et_3N (0.2 mL, 1.4 mmol) and DMAP (2 mg, 0.017 mmol) in CH_2Cl_2 (1 mL) at 0 °C. Benzoyl chloride (20 μL, 0.17 mmol) was added dropwise. The mixture was stirred at room temperature for 17 h, and then purified with flash chromatography on silica gel (CH_2Cl_2:MeOH mixtures, 10:1 to 5:1) to furnish (*R*)-(−)-cocaine as a white solid; yield: 25 mg (> 99%); mp 97–98 °C; $R_f=0.48$ (CH_2Cl_2:MeOH = 5:1). ^{1}H NMR: $\delta=8.03$–8.01 (m, 2H), 7.56–7.51 (m, 1H), 7.41 (t, $J=7.8$ Hz, 2H), 5.27–5.21 (m, 1H), 3.71 (s, 3H), 3.57–3.55 (m, 1H), 3.29 (br, 1H), 3.02 (dd, $J=5.2$, 3.6 Hz, 1H), 2.43 (td, $J=11.8$, 2.8 Hz, 1H), 2.23 (s, 3H), 2.20–2.06 (m, 2H), 1.89–1.84 (m, 1H), 1.76–1.67 (m, 2H); ^{13}C NMR: $\delta=170.9$, 166.4, 133.1, 130.5, 129.9, 128.5, 67.1, 65.0, 61.7, 51.6, 50.4,

41.3, 35.7, 25.6, 25.4; HR-MS (ESI): $m/z = 304.1545$, calcd. for $[M+H]^+$ ($C_{17}H_{22}NO_4$): 304.1543; $[\alpha]_D^{25}$: −15.3 (*c* 1.0, $CHCl_3$).

(*S*)-(+)-Cocaine was obtained using the same procedures; yield: 98%; $[\alpha]_D^{25}$: +15.3 (*c* 1.0, $CHCl_3$) {lit. (*S*)-cocaine: $[\alpha]_D^{25}$: +15.5 (*c* 1.0, $CHCl_3$)[9b,11d]}.

(*S*,*E*)-Methyl 5-{[(benzyloxy)carbonyl][(*tert*-butyldimethylsilyl)oxy]amino}-7-(2-methyl-1,3-dioxolan-2-yl)hept-2-enoate (8b): Prepared using the representative catalytic asymmetric tandem aza-Michael/Wittig reaction; yield: 67%; *E*:*Z* >20:1; $R_f = 0.19$ (pentane:EtOAc = 10:1). ^{1}H NMR: $\delta = 7.35$–7.29 (m, 5H), 6.95–6.88 (m, 1H), 5.87 (d, $J = 15.6$ Hz, 1H), 5.10 (s, 2H), 4.09–4.02 (m, 1H), 3.93–3.82 (m, 4H), 3.70 (s, 3H), 2.67–2.59 (m, 1H), 2.35–2.28 (m, 1H), 1.87–1.78 (m, 1H), 1.76–1.68 (m, 1H), 1.62–1.48 (m, 2H), 1.27 (s, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR: $\delta = 166.8$, 159.2, 145.7, 135.9, 128.64, 128.59, 128.4, 123.3, 109.8, 68.1, 64.7, 61.9, 51.5, 36.0, 35.4, 27.0, 26.1, 24.0, 18.5, −4.26, −4.28; HR-MS (ESI): $m/z = 530.2534$, calcd. for $[M+Na]^+$ ($C_{26}H_{41}NO_7SiNa$): 530.2545; $[\alpha]_D^{25}$: 4.5 (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 96% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (AD column, 98/2 hexane/*i*PrOH, 1.0 mL min^{-1}, 210.5 nm): t_r (major enantiomer) = 12.5 min, t_r (minor enantiomer) = 14.1 min.

(*S*,*E*)-2-(4-Methoxy-4-oxobut-2-en-1-yl)-5-methyl-3,4-dihydro-2*H*-pyrrole 1-oxide (9b): Prepared using the representative catalytic nitrone tandem synthesis procedures; yield: 76%; $R_f = 0.23$ (EtOAc:MeOH = 3:1). ^{1}H NMR: $\delta = 6.86$ (dt, $J = 15.6$, 7.4 Hz, 1H), 5.95 (dt, $J = 15.6$, 1.5 Hz, 1H), 4.17–4.08 (m, 1H), 3.72 (s, 3H), 3.06–2.99 (m, 1H), 2.66–2.56 (m, 3H), 2.30–2.21 (m, 1H), 2.04 (s, 3H), 1.84–1.75 (m, 1H); ^{13}C NMR: $\delta = 166.1$, 144.0, 142.9, 124.2, 70.5, 51.3, 34.8, 30.9, 22.0, 12.6; HR-MS (ESI): $m/z = 220.0947$, calcd. for $[M+H]^+$ ($C_{10}H_{15}NO_3Na$): 220.0944 found; $[\alpha]_D^{25}$: −19.5 (*c* 1.0, $CHCl_3$).

The above crude nitrone **9b** (89 mg, 0.46 mmol) was dissolved in anhydrous toluene (23 mL) and transferred to a pressure tube. Al(O-*t*-Bu)$_3$ (56 mg, 0.23 mmol) was added and the tube was sealed. The reaction mixture was stirred at room temperature for 4 h and then heated at 150 °C for 64 h. After cooling to room temperature, the mixture was extracted with aqueous 1 M HCl (10 mL × 3). The aqueous layers were neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (15 mL × 3). The CH_2Cl_2 extracts were combined, dried with Na_2SO_4, filtered, and concentrated to give the isoxazoline product **15b** which can be used in the next step without purification; yield: 64 mg (72%. An analytical sample of **15b** could be obtained with flash chromatography on silica gel (EtOAc); $R_f = 0.47$ (EtOAc). ^{1}H NMR: $\delta = 4.92$ (d, $J = 3.6$ Hz, 1H), 3.67 (s, 3H), 3.61–3.57 (m, 1H), 2.43 (s, 1H), 2.21–2.12 (m, 3H), 1.83–1.74 (m, 2H), 1.25–1.22 (m, 4H); ^{13}C NMR: $\delta = 171.8$, 81.7, 75.8, 62.8, 61.3, 51.7, 42.1, 33.9, 26.2, 22.1; HR-MS (ESI): $m/z = 198.1129$, calcd. for $[M+H]^+$ ($C_{10}H_{16}NO_3$): 198.1125 found; $[\alpha]_D^{25}$: −52.7 (*c* 1.0, $CHCl_3$).

The above crude isoxazoline (40 mg, 0.20 mmol) was heated with MsOMe (52 μL, 0.61 mmol) in anhydrous benzene (10 mL) in a sealed pressure tube at 85 °C for 24 h. The solution was cooled to room temperature and extracted with water (25 mL × 2). The aqueous phase was concentrated under reduce pressure to give the product **10b**; yield: 66 mg (99%). ^{1}H NMR: $\delta = 5.44$ (d, $J = 4.0$ Hz, 1H), 4.51–4.47 (m, 1H), 3.78 (s, 3H), 3.56 (s, 1H), 3.48 (s, 3H), 2.87–2.80 (m, 1H), 2.72–2.66 (m, 4H), 2.62–2.54 (m, 1H), 2.38–2.28 (m, 2H), 2.18 (dd, $J = 10.0$, 1.6 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR: $\delta = 170.2$, 87.8, 83.8, 78.0, 60.6, 53.1, 41.6, 41.3, 39.6, 33.9, 25.4, 18.2; HR-MS (ESI): $m/z = 212.1276$, calcd. for $[M]^+$ ($C_{11}H_{18}NO_3$): 212.1281; $[\alpha]_D^{25}$: −2.6 (*c* 2.0, MeOH).

The above compound (66 mg, 0.20 mmol) was dissolved in MeOH (10 mL). Pd/C (10%, 10 mg) was added. The hydrogenation was conducted under H_2 atmosphere (50–70 psi) for 24 h. Upon completion, the solution was filtered through celite, and concentrated to give the hydrogenation product (yield: 66 mg), which was then dispersed in anhydrous CH_2Cl_2 (2 mL). With stirring, Et_3N (0.2 mL, 1.4 mmol) and DMAP (5 mg, 0.04 mmol) were added, followed by dropwise addtion of benzoyl chloride (47 μL, 0.41 mmol) at 0 °C. The mixture was stirred at room temperature for 17 h, then concentrated and purified with flash chromatography on silica gel (CH_2Cl_2:MeOH mixtures, 10:1 to 5:1) to furnish the desired 1-methylcocaine {(1*R*,2*R*,3*S*,5*S*)-methyl 3-(benzoyloxy)-1,8-dimethyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**4a**)}; yield: 60 mg (94%); $R_f = 0.33$ (CH_2Cl_2:MeOH = 10:1). ^{1}H NMR: $\delta = 7.97$–7.94 (m, 2H), 7.57–7.51 (m, 1H), 7.43–7.39 (m, 2H), 5.39–5.33 (m, 1H), 3.64 (s, 3H), 3.39–3.36 (m, 1H), 2.95 (d, $J = 6.8$ Hz, 1H), 2.49 (td, $J = 11.7$, 2.5 Hz, 1H), 2.26 (s, 3H), 2.21–2.10 (m, 1H), 1.92–1.87 (m, 1H), 1.86–1.77 (m, 2H), 1.75–1.67 (m, 1H), 1.28 (s, 3H); ^{13}C NMR: $\delta = 170.6$, 166.1, 133.1, 130.3, 129.7, 128.5, 68.7, 65.1, 63.0, 55.7, 51.3, 37.0, 34.7, 34.4, 26.9, 22.9; HR-MS (ESI): $m/z = 318.1711$, calcd. for $[M+H]^+$ ($C_{18}H_{24}NO_4$): 318.1700; $[\alpha]_D^{25}$: −8.1 (*c* 1.0, $CHCl_3$) {lit. **4a**: $[\alpha]_D^{20}$: −8.32 (*c* 1.25, $CHCl_3$)[12c]}.

Experimental Procedures for the Tandem Synthesis of Ferruginine from Methylecgonine

Ecgonine methyl ester *ent*-**1b** (50 mg, 0.17 mmol), which had been prepared as described above, was heated to reflux in 2 mL of 6 M HCl for 6 h. After cooling to room temperature, the solution was washed with Et_2O (2 mL), and then concentrated under reduced pressure to give the natural product (+)-ecgonine (*ent*-**1a**).

The crude acid product was then refluxed with 2 mL of $POCl_3$ for 4 h. The excess $POCl_3$ was then removed under reduced pressure. The residue was stirred with MeO(Me)NH·HCl (83 mg, 0.85 mmol) and Et_3N (0.24 mL, 1.7 mmol) in anhydrous CH_2Cl_2 (2 mL) for 2 h. The solution was washed with $NH_3 \cdot H_2O$ (1 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography on silica gel ($NH_3 \cdot H_2O$:MeOH mixtures, 20:1) to furnish the amide product (1*S*,5*R*)-*N*-methoxy-N,8-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxamide (*ent*-**14a**): yield: 25 mg (70%); $R_f = 0.30$ (CH_2Cl_2:MeOH = 5:1). ^{1}H NMR: $\delta = 6.21$ (t, $J = 3.0$ Hz, 1H), 3.65 (s, 3H), 3.62 (d, $J = 5.2$ Hz, 1H), 3.27 (t, $J = 5.6$ Hz, 1H), 3.23 (s, 3H), 2.60 (brd, $J = 18.8$ Hz, 1H), 2.43 (s, 3H), 2.23–2.11 (m, 2H), 2.09–2.01 (m, 1H), 1.78 (dd, $J = 19.0$, 4.2 Hz, 1H), 1.62–1.54 (m, 1H); ^{13}C NMR: $\delta = 169.7$, 136.6, 128.0, 61.3, 60.6, 57.0, 35.6, 35.0, 33.6, 30.5, 30.4; HR-

MS (ESI): $m/z = 211.1443$, calcd. for $[M+H]^+$ ($C_{11}H_{19}N_2O_2$): 211.1441; $[\alpha]_D^{25}$: 0.4 (*c* 1.0, $CHCl_3$).

Under an N_2 atmosphere, the above amide (25 mg, 0.12 mmol) was dissolved in anhydrous THF (2 mL) at −78 °C. To this solution, MeLi (1.6 M in Et_2O, 0.15 mL, 0.24 mmol) was added dropwise over 5 min. The reaction mixture was stirred at this temperature for 30 min and then at 0 °C for 30 min. After quenching with saturated aqueous NH_4Cl (2 mL), the solution was extracted with CH_2Cl_2 (5 mL × 3). The organic phases were combined, dried with anhydrous Na_2SO_4, filtered, concentrated, and purified flash chromatography on silica gel ($NH_3{\cdot}H_2O$:MeOH mixtures, 20:1) to furnish (+)-ferruginine; yield: 19 mg (97%); R_f = 0.27 (CH_2Cl_2:MeOH = 5:1). ^{1}H NMR: δ = 6.70 (t, J = 3.2 Hz, 1H), 3.91 (d, J = 5.2 hz, 1H), 3.25 (t, J = 5.2 Hz, 1H), 2.72 (brd, J = 19.2 Hz, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 2.19–2.09 (m, 2H), 1.92 (dd, J = 19.8, 4.2 Hz, 1H), 1.71 (t, J = 9.4 Hz, 1H), 1.52–1.42 (m, 1H); ^{13}C NMR: δ = 197.7, 143.9, 136.8, 57.7, 57.6, 37.4, 33.8, 33.2, 29.7, 25.0; HR-MS (ESI): m/z = 166.1229, calcd. for $[M+H]^+$ ($C_{10}H_{16}NO$): 166.1226; $[\alpha]_D^{25}$: 50.2 (*c* 1.0, $CHCl_3$) {lit. (−)-Ferruginine *ent*-**2**: $[\alpha]_D^{25}$: −50.8 (*c* 0.94, $CHCl_3$)[14f]}.

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