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A new divergent synthesis of (+)- and (−)-ferruginine utilizing PLE-catalyzed asymmetric dealkoxycarbonylation

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Abstract—A new divergent synthesis of (+)- and (−)-ferruginine **4**, via the optically active 8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]octane-2-carboxylates **6** is described. The β-keto ester intermediates **6** were prepared by a novel PLE-catalyzed asymmetric dealkoxycarbonylation of the symmetric tropinone-type diesters **5**. The key problem in the synthesis is controlling the regioselectivity of the reaction at the 2- and 4-positions in the tropane framework of the β-keto ester **6** for introduction of the acetyl group.

1. Introduction

8-Azabicyclo[3.2.1]octane (tropane) skeletons are found in numerous naturally occurring alkaloids. Among the tropane-type compounds, the optically active 2β-substituted-3β-aryltropanes **1**, such as 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT)[1] and 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (β-CFT),[1] have attracted considerable attention as radiopharmaceuticals in the diagnosis of Parkinson's disease.[2] Traditionally these compounds have been synthesized from the important intermediate (−)-anhydroecgonine methyl ester **2**[3] derived[4] from (−)-cocaine, **3** (Fig. 1). However, since (−)-cocaine is difficult to obtain commercially, many groups have attempted to synthesize the intermediate using other more readily available starting materials. Recently, we published a new synthesis of (−)-**2** using a novel porcine liver esterase (PLE)-catalyzed asymmetric dealkoxycarbonylation[5,6] (asymmetric desymmetrization) which should be useful in the synthesis of optically active tropane alkaloids.

The tropane-type alkaloid (+)-ferruginine (+)-**4** was isolated from the arboreal species *Darlingia ferruginea*[7] and *D. darlingiana*.[8] Its unnatural enantiomer (−)-**4** prepared[7] from (−)-cocaine **3** was found to be an agonist for the nicotine acetylcholine receptor (nAchR).[9,10] Several asymmetric syntheses of ferruginine **4** have been reported as a result of its on its nicotinic agonist activity: These include the tandem rhodium(II)-catalyzed cyclopropanation/Cope rearrangement for the asymmetric synthesis of (−)-**4** by Davies et al.[11] and the enantiospecific synthesis of (+)- and (−)-**4** from L-glutamic acid, presented by Rapoport et al.[12] Aside from these asymmetric syntheses, the practical synthesis of (−)-**4** and its analogues for evaluation as nAChR ligands still depends on (−)-cocaine **3** as the optically active starting material.[10] For the asymmetric synthesis of natural (+)-**4**, the CN(*R*,*S*) method and a metal-promoted [6π+2π] cycloaddition were reported by Royer et al.,[13] and Rigby and Pigge,[14] respectively. We report herein a new divergent synthesis of (+)- and (−)-ferruginine **4** utilizing a novel PLE-catalyzed asymmetric dealkoxycarbonylation method.

2. Results and discussion

Our synthetic strategy towards (+)- and (−)-ferruginine **4** is outlined in Scheme 1. The tropinone-type diesters **5** prepared by Robinson's tropinone synthesis[15] from 1,3-acetonedicarboxylates, succindialdehyde and a primary amine in one step, could be converted to the monoesters **6** having excellent enantiomeric excesses by the use of our PLE-catalyzed asymmetric dealkoxycarbonylation. The optically active monoesters **6** are suitable divergent intermediates, which can lead to both (+)- and (−)-ferruginine **4** by the introduction of a

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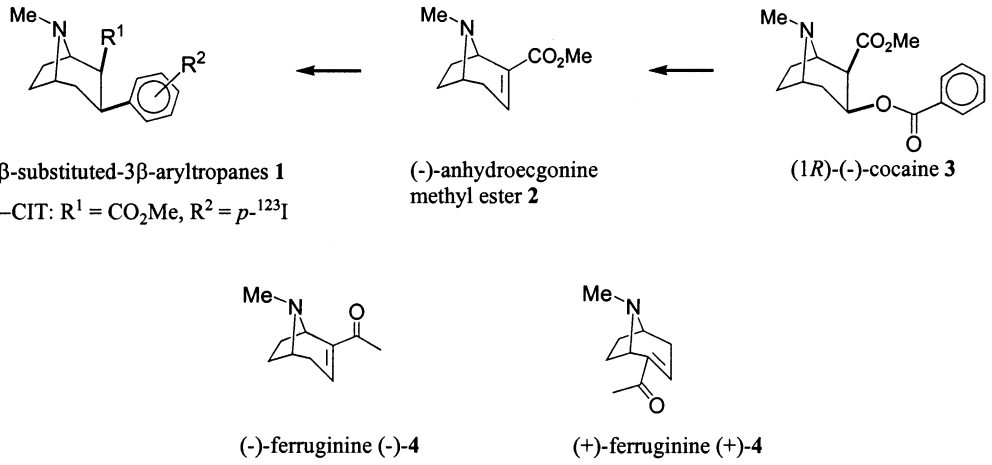
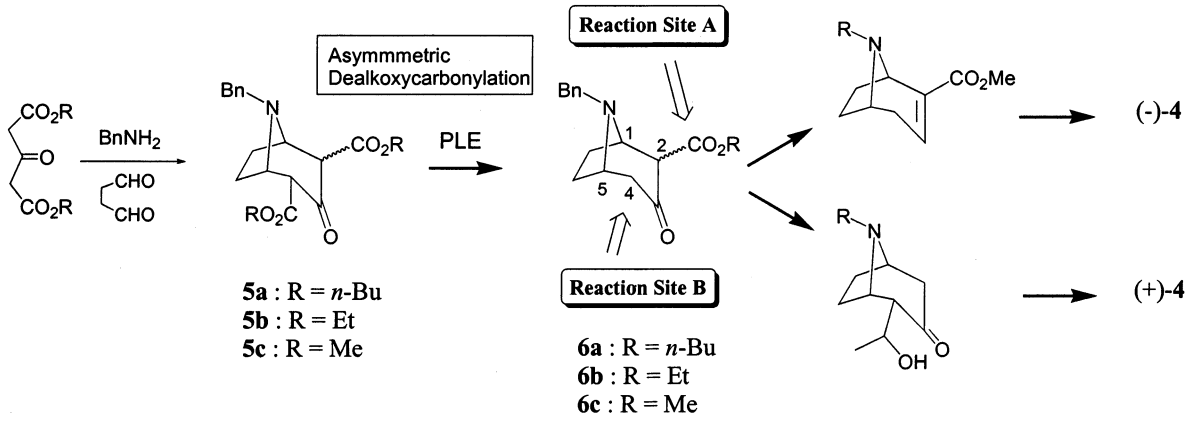


Figure 1.

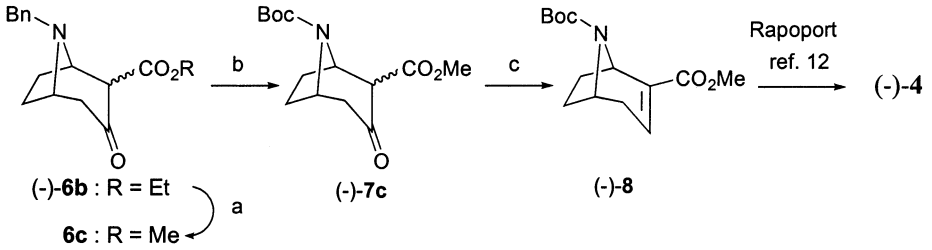


Scheme 1. A new divergent synthetic strategy for (+)- and (–)-ferruginine **4**.

C_2-unit at the 4-position (reaction site B) or by conversion of the ester moiety at the 2-position to an acetyl group (reaction site A), respectively.

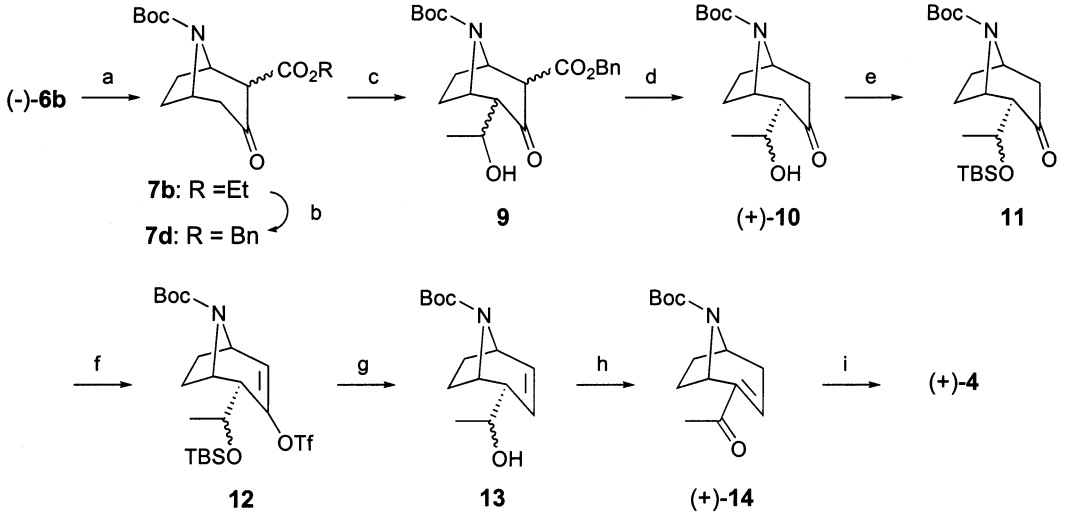
Although the *n*-butyl diester **5a** was the most effective compound for this enzymatic reaction, the preparation of **5a** required ester interchange with commercially available dimethyl or diethyl 1,3-acetonedicarboxylate before Robinson's tropinone synthesis. The ethyl diester **5b** is more stable to autohydrolysis with buffer and subsequent decarboxylation during the enzymatic reaction than the methyl diester **5c**.[5] Thus, we selected the ethyl diester **5b** as our starting material. We reoptimized the reaction conditions for the PLE-catalyzed asymmetric dealkoxycarbonylation of the readily accessible tropinone-type diethyl ester **5b**. Since the yield of the monoethyl ester product **6b**[16] was reduced on prolonged reaction time probably due to over dealkoxycarbonylation of the product **6b** to tropinone by PLE, we added dimethyl sulfoxide (DMSO) to the phosphate buffer to reduce the activity of PLE. As a result, (–)-**6b** was obtained in 38% yield with high enantiomeric excess (96% ee). The exact reaction conditions were as follows: PLE (5000 units) in 1.0 M phosphate buffer (pH 8.0)–DMSO (9:1) for 24 h at room temperature. Addition of DMSO greatly improved the reaction.

Since Davies et al.[11] and Rapoport et al.[12] reported asymmetric syntheses of (–)-ferruginine **4** via the α,β-unsaturated methyl ester (–)-**8**, we tried to convert (–)-**6b** into (–)-**8**. A formal asymmetric synthesis of (–)-ferruginine **4** is illustrated in Scheme 2. Ester exchange of the monoethyl ester (–)-**6b** (96% ee) with methoxide gave the methyl ester **6c** in high yield. Hydrogenolysis of the *N*-benzyl group of **6c** followed by *tert*-butoxycarbonylation afforded the β-keto ester (–)-**7c** in excellent yield (95%, two steps). Reduction of (–)-**7c** with tetrabutylammonium borohydride and subsequent β-elimination by trifluoroacetylation afforded (–)-**8** in 80% yield (two steps). The spectroscopic data and specific rotation of (–)-**8** were identical with those reported.[11,12]



Scheme 2. A formal asymmetric synthesis of (–)-ferruginine **4**. *Reagents and conditions*: (a) Na, MeOH, 95%; (b) (1) 10% Pd–C/H_2, (2) $(Boc)_2O$, Et_3N, 95% (two steps); (c) (1) Bu_4NBH_4, 85%, (2) $(CF_3CO)_2O$, Et_3N, DMAP, $CHCl_3$, 94%.

A new total asymmetric synthesis of natural (+)-ferruginine **4** was carried out, as shown in Scheme 3. The *N*-benzyl group of (–)-**6b** (96% ee) was exchanged for an *N*-Boc group in **7b** by hydrogenolysis/carbamoylation. In preliminary experiments, decarboxylation using alkaline hydrolysis of the β-keto ester after introduction of the 1-hydroxyethyl substituent at the 4-position was unsuccessful because of the steric bulkiness of the axial substituent at the 4-position.[16] In order to use hydrogenolysis to remove the ester moiety in the β-keto ester **7b**, the ester exchange of **7b** with benzyl alcohol and 4-dimethylaminopyridine (DMAP) gave the benzyl ester **7d** in excellent yield. At this stage, the 1-hydroxyethyl group was introduced at the 4-position of the tropane framework of the β-keto ester **7d** by reacting the dianion formed with sodium hydride and lithium diisopropylamide (LDA) with acetaldehyde to give the alcohol **9**. Before oxidation of the alcohol moiety, the β-keto ester **9** was subjected to hydrogenolysis in the presence of Pd/C and decarboxylation with the assistance of catalytic hydrochloric acid to give the β-hydroxy ketone (+)-**10** as a single diastereomer[17] in high yield, even in the presence of the *N*-Boc group. The keto alcohol (+)-**10** was protected by the TBS ether and the ketone moiety of **11** was transformed to the enol triflate **12** with *N*-phenyltrifluoromethanesulfonimide in the presence of potassium *tert*-butoxide. The palladium(0)-catalyzed reduction of the triflate **12** with formic acid[18] followed by deprotection of the OTBS group with tetrabutylammonium fluoride (TBAF) gave the homoallylic alcohol **13** in moderate yield. Oxidation of the alcohol **13** and subsequent isomerization of the olefin with DBU afforded the conjugated enone (+)-**14** in good yield. The specific rotation of (+)-**14** (96% ee) showed the same value {$[\alpha]_D^{25}=+123.3$ (0.81, $CHCl_3$)} as reported by Rapoport {$[\alpha]_D^{24}=+129.1$ (1.0, $CHCl_3$)}.[12] Conversion of the *N*-Boc group of (+)-**14** into the *N*-Me by the usual method[12] completed the asymmetric total synthesis of (+)-ferruginine **4**. Physical data of the synthesized (+)-**4** was identical with those reported for the natural (+)-ferruginine **4**, {the synthesized (+)-**4**: $[\alpha]_D^{25}=+41.3$ (0.21, $CHCl_3$)}; lit.[7]{$[\alpha]_D^{19}=+37$ ($CHCl_3$)}.



Scheme 3. Total asymmetric synthesis of (+)-ferruginine **4**. *Reagents and conditions*: (a) (1) Pd–C/H_2, (2) $(Boc)_2O$, 83% (two steps); (b) BnOH, DMAP, toluene/reflux, 98%; (c) NaH, LDA, CH_3CHO, THF, 56%; (d) (1) Pd–C/H_2, (2) HCl (cat.), Δ, 85% (two steps); (e) TBSCl, imidazole, DMF, 95%; (f) KO-*t*-Bu, $PhNTf_2$, THF, 73%; (g) (1) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, (2) TBAF, 66% (two steps); (h) (1) PCC, (2) DBU, 83% (two steps); (i) (1) TFA, (2) HCHO, $NaBH_3CN$, 94% (two steps).

3. Conclusion

In conclusion, we were able to develop divergent synthetic routes to (+)- and (−)-ferruginine **4** via the optically active ethyl 8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]-octane-2-carboxylate (−)-**6b** by controlling the regioselectivity of the reaction at the 2- and 4-positions of the tropane framework for introduction of the acetyl group.

4. Experimental

4.1. General

Melting points were taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded with a Shimadzu FT-IR 8300. ^{1}H NMR spectra were obtained with a JEOL JNM-AL 300, Varian XL 300 and Varian Unity INOVA 400 NMR spectrometer. Signals are given in ppm using tetramethylsilane as an internal standard. MS spectra were determined on a JEOL JMS SX-102A QQ and JEOL JMS-GCmate mass spectrometer. Combustion analyses were performed by a Yanaco CHN-corder MT-3. Silica Gel 60N (Kanto Chemical Co., Inc.) was used for flash column chromatography. Kieselgel 60 F_{254} plates (Merck) were used for thin-layer chromatography (TLC). If necessary, the compounds were purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd.) on GPC columns (JAIGEL 1H and 2H) after purification on silica gel.

4.2. Materials

THF and toluene were distilled from sodium benzophenone ketyl under a nitrogen atmosphere before use. *N*,*N*-Dimethylformamide, dichloromethane, diisopropylamine and triethylamine were distilled from calcium hydride under a nitrogen atmosphere before use. Chloroform was distilled from calcium chloride under a nitrogen atmosphere before use. Methanol was distilled from magnesium under a nitrogen atmosphere before use.

4.3. Diethyl 8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]octan-2,4-dicarboxylate, 5b

To an solution of 2,5-dimethoxyTHF (6.48 ml, 50.0 mmol) in water (30 ml) was added concd hydrochloric acid (4 ml). The reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was neutralized with potassium carbonate, then concentrated in vacuo. The residue was applied to an Extrelut® column (eluent: chloroform). The extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. A methanol (15 ml) solution of benzylamine (9.08 ml, 50 mmol) was added to a methanol (15 ml) solution of the residue, and the reaction mixture was stirred at 0°C for 2 h under a nitrogen atmosphere. A methanol (15 ml) solution of diethyl 1,3-acetonedicarboxylate (5.46 ml, 50 mmol) was added, and the resulting mixture was stirred at 0°C for 16 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:acetone = 5:1) to give **5b** (14.7 g, 82%). Compound **5b**: pale yellow oil (a mixture of keto–enol tautomers); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.0 (s, 0.25H), 11.9 (s, 0.25H), 7.36–7.24 (m, 5H), 4.32–3.57 (m, 8H), 3.36 (s, 0.33H), 3.31 (s, 0.33H), 3.16 (d, J = 2.5 Hz, 0.33H), 2.93 (d, J = 1.2 Hz, 0.5H), 2.25–1.77 (m, 4H), 1.34–1.03 (m, 6H); IR ($CHCl_3$): 1732, 1654, 1622, 1321, 1301, 1261, 1230, 1182, 1029 cm^{-1}; MS (FAB) m/z 360 (M^++H, 100); HRMS calcd for $C_{20}H_{26}NO_5$ (FAB): 360.1811 (M^++H), found: 360.1821.

4.4. Ethyl (1*R*,5*S*)-8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]-octan-2-carboxylate, (−)-6b

To a 0.1 M phosphate buffer (pH 8.0, 9 ml)–dimethyl sulfoxide (1 ml) solution of diethyl 8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]octan-2,4-dicarboxylate **5b** (276 mg, 0.77 mmol) was added PLE (202 mg, 5000 units/mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered with Hyflo Super-Cel® (eluent: chloroform), then the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 4:1) to give (−)-**6b** (83 mg, 38%). (−)-**6b**; pale yellow oil (mixture of keto–enol tautomers); $[\alpha]_D^{24}$ = −20.5 (c 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.9 (s, 0.3H), 7.44–7.22 (m, 5H), 4.29–3.97 (m, 2H), 3.88–3.43 (m, 4H), 3.39–3.36 (m, 0.4H), 3.11 (t, J = 2.0 Hz, 0.3H), 2.96–2.89 (m, 0.5H), 2.80–2.68 (m, 1H), 2.31–2.03 (m, 2.5H), 1.92–1.75 (m, 1H), 1.69–1.49 (m, 1H), 1.38–1.04 (m, 3H); IR ($CHCl_3$): 1732, 1714, 1647, 1604, 1301, 1236, 1224 cm^{-1}; MS (FAB) m/z 288 (M^++H, 100); HRMS (FAB) calcd for $C_{17}H_{22}NO_3$ (M^++H): 288.1599, found: 288.1590. The enantiomeric excess of (−)-**6b** was determined by chiral HPLC analysis after conversion into the enol triflate, according to the following procedure.

4.5. Ethyl (1*R*,5*S*)-3-trifluoromethanesulfonyloxy-8-azabicyclo[3.2.1]oct-2-en-2-carboxylate

To a suspension of sodium hydride (60% in mineral oil, 17 mg, 0.43 mmol) in THF (1 ml) was added a solution of (−)-**6b** (83 mg, 0.29 mmol) in THF (2 ml) at 0°C. The mixture was stirred at 0°C for 30 min under a nitrogen atmosphere. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (162 mg, 0.43 mmol) was added at 0°C, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into brine (20 ml), then extracted with chloroform (5×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform) to give ethyl (1*R*,5*S*)-3-trifluoromethanesulfonyloxy-8-azabicyclo[3.2.1]oct-2-en-2-carboxylate as a pale yellow oil (91 mg, 75%); $[\alpha]_D^{25}$ = +14.6 (c 0.742, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.26 (m, 5H), 4.28 (q, J = 7.5 Hz, 2H), 3.93 (d, J = 5.1 Hz, 1H), 3.68 (s, 2H), 3.46–3.44 (m, 1H), 2.84 (dd, J = 18.3 and 4.5 Hz, 1H),

2.17–1.94 (m, 4H), 1.61–1.56 (m, 1H), 1.32 (t, $J=7.5$ Hz, 3H); IR ($CHCl_3$): 3028, 1713, 1423, 1223, 1142 cm^{-1}; MS (FAB) m/z 420 (M^++H, 83); HRMS (FAB) calcd for $C_{18}H_{21}F_3NO_5S$ (M^++H): 420.1093, found: 420.1096; a HPLC analysis [DAICEL CHIRALCEL OD (25×0.46), eluent: hexane:2-propanol=99:1, flow rate: 0.2 ml/min, temp.: 23°C, detector: 254 nm, (−)-: 34.0 min, (+)-: 36.4 min], 96% ee.

4.6. Methyl (1*R*,5*S*)-8-benzyl-3-*oxo*-8-azabicyclo[3.2.1]-octan-2-carboxylate, 6c

To a solution of (−)-**6b** (1.22 g, 4.26 mmol) in methanol (20 ml) was added sodium methoxide (28% in methanol, 4.8 ml, 85.2 mmol). The reaction mixture was heated under refluxed for 48 h under a nitrogen atmosphere. The reaction mixture was poured into a saturated ammonium chloride solution (20 ml), and concentrated in vacuo. The residue was extracted with chloroform (3×30 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform) to give **6c** as a pale yellow oil (1.10 g, 95%—mixture of keto–enol tautomers); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.8 (s, 0.4H), 7.42–7.23 (m, 5H), 3.85–3.76 (m, 1H), 3.74 (s, 2H), 3.72 (s, 1H), 3.64 (s, 1.33H), 3.62 (s, 0.67H), 3.61–3.47 (m, 1H), 3.37 (t, $J=5.7$ Hz, 1H), 3.12 (t, $J=2.0$ Hz, 0.3H), 2.97–2.90 (m, 0.3H), 2.80–2.69 (m, 1H), 2.32–2.03 (m, 2H), 1.92–1.49 (m, 2H); IR ($CHCl_3$): 1736, 1713, 1655, 1445, 1350, 1221, 1217 cm^{-1}; MS (FAB) m/z 274 (M^++H, 100); HRMS (FAB) calcd for $C_{16}H_{20}NO_3$: 274.1443 (M^++H), found: 274.1433.

4.7. Methyl (1*R*,5*S*)-8-*tert*-butoxycarbonyl-3-*oxo*-8-azabicyclo[3.2.1]octan-2-carboxylate, (−)-7c

To a solution of **6c** (424 mg, 1.55 mmol) in methanol (5 ml)–acetic acid (5 ml) was added a catalytic amount of 10% palladium on activated carbon, and the reaction mixture was stirred at room temperature for 16 h under a hydrogen atmosphere. The palladium on activated carbon was filtered off with Celite® (eluent: methanol), and the filtrate was concentrated in vacuo. A saturated sodium hydrogen carbonate solution (20 ml) was added to the residue, and the mixture was extracted with chloroform (3×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in a chloroform (20 ml), and di-*tert*-butyl dicarbonate (428 μl, 1.86 mmol) and triethylamine (260 μl, 1.86 mmol) were added, and finally the resulting mixture was stirred at room temperature for 4 h under a nitrogen atmosphere. The reaction mixture was poured into brine (10 ml), and extracted with chloroform (3×20 ml). The combined organic layer dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=5:1) to give (−)-**7c** as a pale yellow oil (416 mg, 95%—mixture of keto–enol tautomers); $[\alpha]_D^{27}=-30.9$ (c 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.8 (s, 0.33H), 4.85 (br s, 1H), 4.36 (br m, 1H), 3.78 (s, 1H), 3.77 (s, 1H), 3.71 (s, 1H), 3.26 (s, 0.33H), 3.09–3.01 (m, 0.67H), 2.42–1.81 (m, 3.67H), 1.70–1.56 (m, 2H), 1.51 (s, 2H), 1.47 (s, 3.5H), 1.45 (s, 3.5H); IR ($CHCl_3$): 1811, 1755, 1691, 1396, 1373, 1340, 1315, 1286, 1261, 1226, 1203, 1164, 1120, 1074 cm^{-1}; MS (FAB) m/z 283 (M^++H, 18); HRMS (FAB) calcd for $C_{14}H_{22}NO_5$ (M^++H): 284.1498, found: 284.1493.

4.8. Methyl (1*R*,5*S*)-8-*tert*-butoxycarbonyl-8-azabicyclo-[3.2.1]oct-2-en-2-carboxylate, (−)-8

To a solution of **7c** (126 mg, 0.44 mmol) in methanol (5 ml) was added tetrabutylammonium borohydride (230 mg, 0.89 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h. The reaction mixture was concentrated in vacuo. The residue was added a saturated ammonium chloride solution (20 ml), then extracted with chloroform (5×30 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=5:1) to give methyl (1*R*,5*S*)-3-hydroxy-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-2-carboxylate (107 mg, 85%).

To a solution of methyl (1*R*,5*S*)-3-hydroxy-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-2-carboxylate (288 mg, 1.01 mmol) in chloroform (10 ml) was added trifluoroacetic anhydride (430 μl, 3.03 mmol), triethylamine (1.2 ml, 6.06 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was refluxed for 22.5 h under a nitrogen atmosphere. The reaction mixture was poured into brine (30 ml), then neutralized with a saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with chloroform (5×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate=5:1) to give (−)-**8** as a colorless oil; (254 mg, 94%); $[\alpha]_D^{25}=-70.6$ (c 1.55, $CHCl_3$), {lit.[11] $[\alpha]_D^{25}=-47.2$ (c 2.45, $CHCl_3$) (66% ee), lit.[12] $[\alpha]_D^{21}=-52.4$ (c 1.00, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.78–6.75 (m, 1H), 4.85–4.78 (m, 1H), 4.37–4.28 (m, 1H), 3.78 (s, 3H), 2.89–2.81 (m, 1H), 2.20–1.87 (m, 4H), 1.65–1.53 (m, 1H), 1.44 (s, 9H); IR (KBr): 1716, 1701, 1641, 1442, 1419, 1380, 1369, 1340, 1323, 1259, 1224, 1164, 1105, 1089 cm^{-1}; MS (FAB) m/z 268 (M^++H, 19); HRMS (FAB) calcd for $C_{14}H_{22}NO_4$: 268.1548 (M^++H), found: 268.1552. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.69; H, 7.90; N, 5.53; a HPLC analysis [DAICEL CHIRALCEL OD (25×0.46); eluent: hexane:2-propanol=100:1; flow rate: 0.5 ml/min; temperature: 25°C; detector: 254 nm; (−)-**8**; 20.5 min, (+)-**8**; 24.9 min], 96% ee.

4.9. Ethyl (1*R*,5*S*)-8-*tert*-butoxycarbonyl-3-*oxo*-8-azabicyclo[3.2.1]octan-2-carboxylate, 7b

To a solution of (−)-**6b** (253 mg, 0.88 mmol) in methanol (5 ml)–acetic acid (5 ml) was added a catalytic amount of 10% palladium on activated carbon, and the reaction mixture was stirred at room tempera-

ture for 20 h under a hydrogen atmosphere. The palladium on activated carbon was filtered off with Celite® (eluent: methanol), and the filtrate was concentrated in vacuo. A saturated sodium hydrogen carbonate solution (20 ml) was added to the residue, and the mixture was extracted with chloroform (3×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in chloroform (15 ml), and di-*tert*-butyl dicarbonate (240 μl, 1.05 mmol) and triethylamine (140 μl, 1.05 mmol) were added, and finally the resulting mixture was stirred at room temperature for 30 min under a nitrogen atmosphere. The reaction mixture was poured into brine (10 ml), and extracted with chloroform (3×20 ml). The combined organic layer dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 5:1) to give **7b** as a colorless oil (218 mg, 83%—mixture of keto–enol tautomers); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.9 (s, 0.25H), 4.68–4.10 (m, 4H), 3.10–2.80 (m, 0.75H), 2.41–1.53 (m, 6H), 1.47 (s, 2.25H), 1.45 (s, 6.75H), 1.32 (t, J = 7.2 Hz, 2.25H), 1.28 (t, J = 6.9 Hz, 0.75H); IR ($CHCl_3$): 2982, 1736, 1690, 1612, 1408, 1169, 1111 cm^{-1}; MS (FAB) m/z 298 (M^++H, 21); HRMS (FAB) calcd for $C_{15}H_{24}NO_5$ (M^++H): 298.1654, found: 298.1647.

4.10. Benzyl (1*R*,5*S*)-8-*tert*-butoxycarbonyl-3-*oxo*-8-azabicyclo[3.2.1]octan-2-carboxylate, 7d

To a solution of **7b** (326 mg, 1.10 mmol) in toluene (50 ml) was added benzyl alcohol (2.84 ml, 2.74 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was heated under reflux with a Dean–Stark trap for 16 h under a nitrogen atmosphere. The reaction mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 10:1) to give **7d** as a colorless oil (385 mg, 98%—mixture of keto–enol tautomers); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.8 (s, 0.25H), 7.40–7.29 (m, 5H), 5.22–5.06 (m, 2H), 4.89 (s, 1H), 4.37 (s, 1H), 3.03 (s, 0.75H), 2.41–1.82 (m, 5H), 1.70–1.60 (m, 1H), 1.57 (s, 2.25H), 1.49 (s, 6.75H); IR ($CHCl_3$): 2982, 1736, 1690, 1655, 1394, 1285, 1229, 1167 cm^{-1}; MS (FAB) m/z 360 (M^++H, 8); HRMS (FAB) calcd for $C_{20}H_{26}NO_5$ (M^++H): 360.1811, found: 360.1807.

4.11. Benzyl(1*R*,5*S*)-8-*tert*-butoxycarbonyl-4-(1′-hydroxyethyl)-3-*oxo*-8-azabicyclo[3.2.1]octan-2-carboxylate, 9

To a suspension of sodium hydride (60% in mineral oil, 91 mg, 2.26 mmol) in THF (5 ml) was added a THF (7 ml) solution of **7d** (387 mg, 1.08 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1.5 h under a nitrogen atmosphere. A THF (5 ml) solution of lithium diisopropylamide, which was prepared from *n*-butyl lithium (2.6 M in hexane, 870 μl, 2.26 mmol) and diisopropylamine (317 μl, 2.26 mmol), was added at −78°C. The reaction mixture was stirred for 6 h. Acetaldehyde (301 μl, 5.39 mmol) was added at −78°C, and the reaction mixture was stirred for 20 min. The reaction mixture was poured into 2N hydrochloric acid (20 ml), and neutralized with a saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with chloroform (5×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 5:1) to give **9** as a pale yellow oil (244 mg, 56%, mixture of keto–enol tautomers); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.2 (s, 0.4H), 7.36–7.33 (m, 5H), 5.25–5.00 (m, 2.6H), 4.69 (m, 0.4H), 4.49 (m, 1H), 4.09 (m, 1H), 3.82 (m, 0.3H), 3.08 (m, 0.3H), 2.31–2.05 (m, 4H), 1.89–1.81 (m, 1H), 1.69–1.50 (m, 1H), 1.49 (s, 2.25H), 1.46 (d, J = 6.6 Hz, 1.5H), 1.45 (s, 6.75H), 1.39 (d, J = 6.3 Hz, 1.5H); IR ($CHCl_3$): 3020, 2982, 1690, 1612, 1416, 1269, 1204, 1165 cm^{-1}; MS (FAB) m/z 404 (M^++H, 19); HRMS (FAB) calcd for $C_{22}H_{30}NO_6$ (M^++H): 404.2073, found: 404.2079.

4.12. (1*R*,4*S*,5*S*)-8-*tert*-Butoxycarbonyl-4-(1′-hydroxyethyl)-8-azabicyclo[3.2.1]octan-3-one, (+)-10

To a solution of **9** (224 mg, 0.56 mmol) in methanol (7 ml) was added a catalytic amount of 10% palladium on activated carbon, and the reaction mixture was stirred at room temperature for 24 h under a hydrogen atmosphere. The palladium/carbon was removed by filtration through Celite® (eluent: methanol), and the filtrate was concentrated in vacuo. The residue was dissolved in methanol (7 ml), and was added one drop of 1% hydrochloric acid. The reaction mixture was refluxed for 2 h. The reaction mixture was poured into a saturated sodium hydrogen carbonate solution (10 ml), and the mixture was concentrated in vacuo. The residue was extracted with chloroform (3×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform) to give (+)-**10** (131 mg, 88%) as a single isomer; colorless powder; mp 104–105°C (hexane:ethyl acetate = 10:1); $[\alpha]_D^{26}$ = +81.1 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (s, 1H), 4.50 (d, J = 6.9 Hz, 1H), 4.05 (m, 1H), 2.74 (d, J = 12.9 Hz, 1H), 2.39–2.02 (m, 4H), 1.64 (d, J = 7.8 Hz, 2H), 1.51 (s, 9H), 1.36 (d, J = 3.0 Hz, 3H); IR ($CHCl_3$): 3009, 2978, 1686, 1420, 1369, 1346, 1161, 1111 cm^{-1}; MS (FAB) m/z 270 (M^++H, 34); HRMS (FAB) calcd for $C_{14}H_{24}NO_4$ (M^++H): 270.1705, found: 270.1711. Anal. calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.54; H, 8.82; N, 4.97%.

4.13. (1*R*,4*S*,5*S*)-8-*tert*-Butoxycarbonyl-4-{1′-(*tert*-butyldimethylsilyloxy)ethyl}-8-azabicyclo[3.2.1]octan-3-one, 11

To a *N*,*N*-dimethylformamide (5 ml) solution of (+)-**10** (132 mg, 0.49 mmol) was added *tert*-butyldimethylsilyl chloride (148 mg, 0.98 mmol) and imidazole (134 mg, 1.96 mmol). The reaction mixture was stirred at room temperature for 24 h under a

nitrogen atmosphere. The reaction mixture was poured into brine (20 ml), and extracted with chloroform (3×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 15:1) to give **11** (179 mg, 95%) as a single isomer; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.64 (br s, 1H), 4.44 (br s, 1H), 4.08–4.03 (m, 1H), 2.65 (br s, 1H), 2.29–2.25 (m, 2H), 2.08–1.96 (m, 2H), 1.62 (d, J = 8.4 Hz, 2H), 1.51 (s, 9H), 1.33 (d, J = 5.4 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); IR ($CHCl_3$): 3026, 3013, 2959, 2930, 1786, 1417, 1367, 1344, 1161, 1109 cm^{-1}; MS (FAB) m/z 384 (M^++H, 20); HRMS (FAB) calcd for $C_{20}H_{38}NO_4Si$ (M^++H): 384.2570, found: 384.2566.

4.14. (1*R*,4*S*,5*S*)-8-*tert*-Butoxycarbonyl-4-{1′-(*tert*-butyldimethylsilyloxy)ethyl}-8-azabicyclo[3.2.1]oct-2-enyl 3-trifluoromethanesulfonate, 12

To a solution of **11** (79 mg, 0.21 mmol) in THF (5 ml) was added potassium *tert*-butoxide (35 mg, 0.31 mmol) at 0°C. The reaction mixture was stirred at 0°C for 15 min under a nitrogen atmosphere. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (116 mg, 0.31 mmol) was added at 0°C, and the reaction mixture was stirred at 0°C for additional 5 h. The reaction mixture was poured into a solution of brine (20 ml) and saturated ammonium chloride (10 ml), and extracted with chloroform (3×20 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 50:1) to give **12** (78 mg, 73%) as a single isomer; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.06 (m, 1H), 4.73 (d, J = 7.8 Hz, 2H), 4.09–4.05 (m, 1H), 2.34 (d, J = 6.0 Hz, 1H), 2.17–2.09 (m, 1H), 2.02–1.95 (m, 1H), 1.86 (m, 1H), 1.67–1.60 (m, 1H), 1.46 (s, 9H), 1.22 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); IR ($CHCl_3$): 2955, 2932, 1690, 1420, 1231, 1207, 1142, 1099 cm^{-1}; MS (FAB) m/z 516 (M^++H, 7); HRMS (FAB) calcd for $C_{21}H_{37}F_3NO_6SSi$ (M^++H): 516.2063, found: 516.2055.

4.15. (1*R*,4*S*,5*S*)-8-*tert*-Butoxycarbonyl-4-(1′-hydroxyethyl)-8-azabicyclo[3.2.1]oct-2-ene, 13

To a solution of **12** (348 mg, 0.67 mmol) in *N*,*N*-dimethylformamide (12 mL) was added palladium(II) acetate (3 mg, 0.013 mmol), triphenylphosphine (7 mg, 0.026 mmol), triethylamine (280 μl, 2.01 mmol) and formic acid (51 μl, 1.34 mmol). The resulting mixture was stirred at 60°C for 7 h. The reaction mixture was poured into brine (10 ml), and extracted with chloroform (3×30 ml). The combined organic layer was washed with brine (10 ml), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in THF (7 ml). Tetrabutylammonium fluoride (1.0 M in THF, 1.35 ml, 1.35 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h under a nitrogen atmosphere. The reaction mixture was poured into brine (10 ml), and neutralized with a saturated sodium carbonate solution. The aqueous layer was extracted with chloroform (3×30 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 5:1) to give **13** colorless oil (111 mg, 65%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.13 (ddd, J = 9.6, 5.4 and 2.1 Hz, 1H), 5.67 (ddd, J = 9.6, 3.9 and 1.5 Hz, 1H), 4.44 (s, 1H), 4.33 (d, J = 7.8 Hz, 1H), 3.96 (m, 1H), 2.34–2.12 (m, 1H), 1.89–1.83 (m, 3H), 1.66–1.54 (m, 2H), 1.45 (s, 9H), 1.27 (d, J = 6.3 Hz, 3H); IR ($CHCl_3$): 3429, 3028, 3008, 2978, 2936, 1678, 1651, 1477, 1443, 1230, 1165 cm^{-1}; MS (FAB) m/z 254 (M^++H, 45); HRMS (FAB) calcd for $C_{14}H_{24}NO_3$ (M^++H): 254.1756, found: 254.1761.

4.16. (1*R*,5*S*)-4-Acetyl-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]oct-3-ene, (+)-14

To a solution of **13** (205 mg, 0.81 mmol) in dichloromethane (15 ml) was added pyridinium chlorochromate (PCC) (1.01 g, 4.03 mmol). The reaction mixture was stirred at room temperature for 4.5 h under a nitrogen atmosphere. PCC was removed by filtration through silica gel (eluent: chloroform). The residue was dissolved with a dichloromethane (8 ml), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (603 μl, 4.03 mmol) was added. The resulting mixture was stirred at room temperature for 3 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 2:1) to give (+)-**14** as colorless needles (168 mg, 83%); mp 67–68°C (hexane:ethyl acetate = 5:1); $[\alpha]_D^{25}$ = +123.3 (c 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.65 (s, 1H), 4.92 (d, J = 5.4 Hz, 1H), 4.36 (brs, 1H), 2.91 (m, 1H), 2.27 (s, 3H), 2.18–2.00 (m, 3H), 1.83–1.76 (m, 1H), 1.60–1.51 (m, 1H), 1.43 (s, 9H); IR ($CHCl_3$): 3028, 3009, 2978, 2932, 1628, 1393, 1342, 1327, 1169, 1107 cm^{-1}; MS (FAB) m/z 252 (M^++H, 20); HRMS (FAB) calcd for $C_{14}H_{22}NO_3$ (M^++H): 252.1600, found: 252.1603. Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.99; H, 8.62; N, 5.60%.

4.17. (+)-Ferruginine, (+)-4

To a solution of (+)-**14** (39 mg, 0.15 mmol) in dichloromethane (3 ml) was added trifluoroacetic acid (118 μl, 1.53 mmol). The reaction mixture was stirred at room temperature for 4 h under a nitrogen atmosphere, then poured into saturated aqueous sodium hydrogen carbonate solution (5 ml), and extracted with chloroform (3×10 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Formaldehyde (37% in water, 57 μl, 0.77 mmol) and sodium cyanoborohydride (20 mg, 0.31 mmol) were added to an acetonitrile (3 ml) solution of the residue. The resulting mixture was stirred at room temperature for 40 min under a nitrogen atmosphere. 1N Hydrochloric acid (3 ml) was added, and reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was neutralized with a saturated

sodium hydrogen carbonate solution, and extracted with chloroform (3×15 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by aluminum oxide column chromatography (eluent: chloroform) to give (+)-**4** as a pale yellow oil (24 mg, 94%); $[\alpha]_D^{25}=+41.3$ (c 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.70 (br t, 1H), 3.91 (d, $J=5.1$ Hz, 1H), 3.25 (br t, 1H), 2.72 (br d, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 2.18–2.12 (m, 2H), 1.92 (dd, $J=19.8$ and 4.5 Hz, 1H), 1.71 (t, $J=9.3$ Hz, 1H), 1.54–1.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.5, 143.6, 136.7, 57.6, 57.4, 37.2, 33.6, 33.1, 29.5, 24.9; IR ($CHCl_3$): 2928, 2855, 1663, 1632, 1447, 1377, 1261 cm^{-1}; MS (70 eV) m/z 165 (M^+, 50), 150 (24), 136 (100), 122 (49); HRMS (70 eV) calcd for $C_{10}H_{15}NO$ (M^+): 165.1154, found: 165.1150.

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