BF_3-Induced Rearrangement of Aziridino Cyclopropanes Derived from 2-Phenylsulfonyl 1,3-Dienes. Application to the Total Synthesis of (±)-Ferruginine

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Total synthesis of the alkaloid (±)-ferruginine (**1**) has been developed via the 2-phenylsulfonyl 1,3-diene approach. BF_3-induced rearrangement of the *N*-protected cyclohexane aziridino cyclopropane **8**, derived from its corresponding epoxy cyclopropane, afforded the desired tropane alkaloid skeleton **9** in good yield. Michael addition of nitroethane (as an acyl anion equivalent) and transformation of the nitro group of the adduct **10** to a keto function gave **11**. Elimination of benzenesulfinic acid and subsequent replacement of the tosyl group by a methyl group afforded the title compound **1**.

Introduction

The organic chemistry of sulfones has undergone remarkable expansion over the last two decades, and a number of synthetic transformations involving the sulfone functional group have been developed.[1] A variety of versatile sulfone-containing synthons are known today, and among those, 2-arylsulfonyl 1,3-dienes have recently attracted attention.[1d,2−7] Such 2-sulfonyl 1,3-dienes are useful Diels−Alder dienes,[1d] and furthermore, they can be transformed into versatile synthetic intermediates via regioselective functionalization at either double bond by taking advantage of their different electron density.[1d,2b,f] In our group we have previously developed regioselective cyclopropanations[2f] and epoxidations.[2b,8] Recently, we reported on the Lewis acid catalyzed rearrangement of some 3,4-epoxy-1,2-methylene-2-(phenylsulfonyl)cycloalkanes[9] and their analogous 3,4-aziridines[10] to bicylic compounds. When the aziridine analogues are used, the rearrangement leads to a tropane alkaloid skeleton. In the present paper we have demonstrated the utility of the latter rearrangement and applied it to the total synthesis of the alkaloid (±)-ferruginine (Figure 1).

Ferruginine is a potent neurotoxin and has been isolated from the arboreal species *Darlingiana ferruginea*[11] and *D. darlingiana*.[12] Ferruginine (**1**) was found to be a good agonist for the nicotinic acetylcholine receptor (nAChR),[13] and its synthesis has attracted considerable attention.[14]

Our retrosynthetic analysis (Scheme 1) denotes the usefulness of **3** as starting material in the synthesis of ferruginine. Sequential cyclopropanation−epoxidation[9] would provide epoxy cyclopropane **6**. Compound **6** could subsequently be converted to the requisite *syn* aziridino cyclopropane, which on derivatization would give access to *N*-tosylamide **8**. Formation of the tropane alkaloid ring system (**9**) could be accomplished via a Lewis acid catalyzed rearrangement**,** which would serve as a key step in this synthesis. Michael addition of an acyl anion

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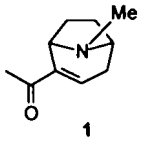

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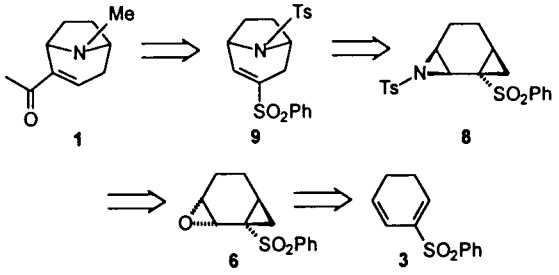
Figure 1. Ferruginine (**1**), isolated from *D. ferruginea* and *D. darlingiana*.

Scheme 1



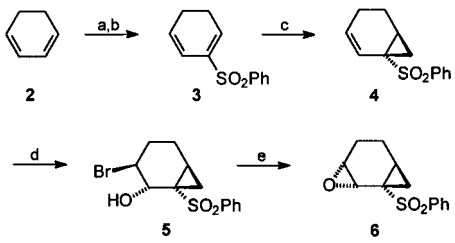
equivalent and transformation of the nitro group of the adduct to a keto function, followed by an elimination of benzenesulfinic acid, would lead to the *N*-derivatized intermediate. Subsequent *N*-deprotection of the nitrogen and reductive methylation would provide ferruginine **1**.

Results and Discussion

The requisite 2-(phenylsulfonyl)-1,3-cyclohexadiene **3** is readily available from 1,3-cyclohexadiene **2** in 83% overall yield according to known procedures developed in our laboratory.[1d,2c−e] Vinylcyclopropane **4** was synthesized in 95% yield by performing a regioselective cyclopropanation of the electron-deficient double bond of **3** using a nucleophilic cyclopropanation reagent, according to an earlier published procedure.[2g,9] The remaining olefinic double bond in **4** was then subjected to epoxidation via the bromohydrin **5** to afford the *anti* epoxy cyclopropane **6** in 75% yield from **4** with complete stereoselectivity.[9] Apparently, the phenylsulfonyl group exerts a more powerful blocking effect toward the incoming electrophilic reagent (NBS) than the cyclopropane moiety. Direct epoxidation with *m*-CPBA gives exclusively the epoxide *syn* to the cyclopropane.[2f,9] The regioselectivity exhibited by these transformations appears to stem from the electron-withdrawing nature of the sulfonyl group, which is dictating the course of these reactions by forcing the cyclopropanation to occur at the electron deficient alkene of the diene system.

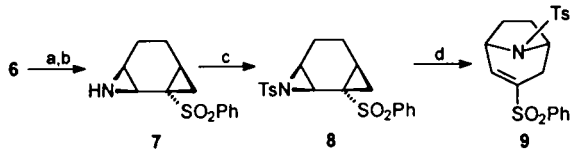
Anti epoxy cyclopropane **6** was converted to *syn* aziridino cyclopropane **7** via ring opening with sodium azide[15] and subsequent cyclization with triphenylphosphine.[15b] Aziridine **7** was then easily derivatized into tosylamide **8** (Scheme 3).[16] Compound **8** was isolated in 51% yield from **6**. The electron-deficient aziridine **8** was reacted with $BF_3 \cdot Et_2O$ in dichloromethane/nitroethane 9:1 for 40 h at −78 °C, which resulted in rearrangement to the tropane alkaloid skeleton **9**.[9,10] The long reaction time, the low temperature, and the polar solvent system strongly favored the formation of **9**, and to our delight we were able to isolate **9** in a yield of 76%. We have previously suggested that the rearrangement reaction

Scheme 2[a]



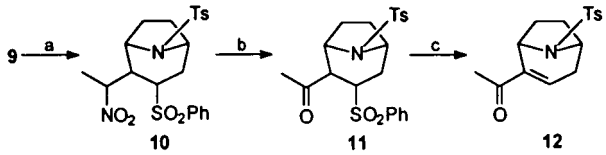
[a] Reagents: (a) $HgCl_2$, $NaSO_2Ph$, 97%; (b) Na_2CO_3, 2 M NaOH, 86%; (c) Me_3SOI, NaH, 95%; (d) NBS, H2O, 98% crude yield; (e) 2 M NaOH, 75% from **4**.

Scheme 3[a]



[a] Reagents: (a) NaN_3, NH_4Cl; (b) PPh_3; (c) TsCl, NEt_3, 51% from **6**; (d) BF_3, 76%.

Scheme 4[a]



[a] Reagents: (a) $EtNO_2$, DBU, 91%; (b) H_2O_2, K_2CO_3, 98%; (c) *t*-BuOK, THF, 87%.

proceeds via a cyclopropyl carbinyl cation.[9,10] It was found that for the six-membered ring it is necessary to have a *syn* relationship between the cyclopropane and aziridine[10] (or epoxide[9]) functionalities. An *anti* relationship gave no bicyclic compound in the Lewis acid-induced reaction of the six-membered ring analogues.[9,10]

The transformation of a vinyl sulfone to an α,β-unsaturated ketone via addition of an acyl anion equivalent followed by elimination of phenylsulfinic acid has previously been demonstrated in our group.[17] A nitroalkane was employed as acyl anion equivalent in this transformation. This methodology was employed to introduce an acetyl group in the 2-position of **9**. Michael-type addition of nitroethane to the tropane alkaloid skeleton **9** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced the nitrosulfone **10** as a 2:1 diastereomeric mixture in 91% yield (Scheme 4). It was not possible to separate the isomers by column chromatography, but this is not a problem since the stereogenic centers causing the diastereomeric mixture are removed later in the synthesis (vide infra). Attempts to use a catalytic amount of DBU were unsuccessful. However, in the presence of an equimolar amount of DBU the reaction proceeded smoothly.

The Nef-type transformation of the nitrosulfone to the ketone **11** was accomplished by using 30% aqueous H_2O_2 and potassium carbonate in a methanol solution, which produced exclusively ketone **11** in 98% yield.[17,18] Subse-

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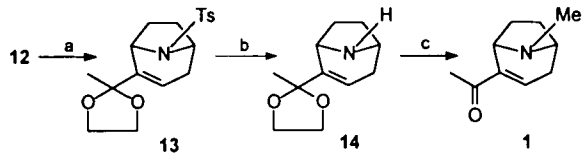
Scheme 5[a]



[a] Reagents: (a) Me_3SiOTf, BTSE, 63%; (b) Mg, MeOH, ultrasound; (c) CH_2O, $Na(CN)BH_3$, 75% from **13**.

quent elimination of benzenesulfinic acid by treatment of **11** with potassium *tert*-butoxide in tetrahydrofuran (THF) proceeded smoothly to give **12** as the only product in 87% yield.

Attempts to detosylate **12** using sodium naphthalenide[19] proved to be unsuccessful. A milder method using magnesium in dry methanol under ultrasonic conditions was therefore tried.[20] Using this cleaving agent, the *N*-sulfonyl group was removed, but unfortunately the presence of the enone function affected the selectivity and thereby precluded this method on **12**. We therefore decided to protect the keto group of **12** (63%) using 1,2-bis((trimethylsilyl)oxy)ethene (BTSE) in the presence of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) as catalyst−Noyori's reagent (Scheme 5).[21] This protocol made it possible to remove the tosyl group employing the magnesium-in-methanol method on **13** to afford the free amine **14** (NMR analysis), not isolated but immediately subjected to reductive methylation in the presence of aqueous formaldehyde and sodium cyanoborohydride ($Na(CN)BH_3$).[22] In the subsequent workup, including acid−base extraction, the protecting group on the ketone was cleaved off to give (±)-ferruginine **1** in good yield (75% from **13**). Spectral data were in accordance with those previously reported.[14c,e]

In conclusion, we have developed a new and efficient synthesis of (±)-ferruginine from 1,3-cyclohexadiene in 10% overall yield, via 2-(phenylsulfonyl)-1,3-cyclohexadiene **3** and involving a BF_3-induced rearrangement of a tosyl-protected aziridino cyclopropane. The rearrangement of the aziridine cyclopropane constitutes a novel route for constructing tropane alkaloids. This rearrangement should allow easy access to a range of analogues.

Experimental Section

General Methods. ^1H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) spectra were recorded on a Varian Mercury spectrometer. Chemical shifts (δ) are reported in ppm, using residual solvent as internal standard, and coupling constants (J) are given in hertz. IR spectra were obtained using a Perkin-Elmer 1600 FT-IR instrument, and the samples were examined as $CDCl_3$ solutions on NaBr plates. Only the strongest/structurally most important peaks (cm^{-1}) are listed. Merck silica gel 60 (240−400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Melting points (mp) are uncorrected. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. Unless otherwise noted, all material was otained from commercial suppliers and used without further purification. All reactions were performed at room temperature unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. In the Mg-in-methanol reduction under ultrasonic conditions, magnesium powder (Aldrich, −50 mesh 99+%), anhydrous methanol (Aldrich, 99.8%), and a NEY 19*H* ULTRAsonic ultrasonic bath were used. The sulfonyl diene **3** was synthesized according to previously published procedures.[2a,c−e]

1,2-Methylene-2-(phenylsulfonyl)-3-cyclohexene (3) was prepared according to a previously reported procedure.[9]

***c*-3,4-Epoxy-*t*-1,2-methylene-*r*-2-(phenylsulfonyl)cyclohexane (6)**, was synthesized according to a previously published procedure.[9]

***t*-3,4-*N*H-Aziridino-*t*-1,2-methylene-*r*-2-(phenylsulfonyl)-cyclohexane (7).** Compound **6** (2.05 g, 10.0 mmol) was dissolved in 36 mL of 2-methoxyethanol and 4.5 mL of water. Sodium azide (2.11 g, 10.0 mmol), ammonium chloride (720 mg, 14.2 mmol) was added, and the reaction mixture was refluxed for 3 h. After cooling down the mixture, water (100 mL) was added, and the resulting mixture was extracted with ether (4 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL) and dried (Na_2SO_4). After evaporation of the solvent, 2.08 g of the crude azido alcohol remained. This material was without further purification dissolved in benzene (50 mL). Triphenylphosphine (2.28 g, 8.69 mmol) was added, and the resulting solution heated at reflux for 4 h. After the mixture had been cooled down the solvent was evaporated. The oily residue was subjected to flash chromatography (EtOAc). Removal of the solvent gave a residue of 2.85 g. However, this material still contained ∼35 mol % of triphenylphosphine oxide (determined by NMR). As a result, no thorough spectral characterization of **7** was made and the material was used without further purification for the next transformation. ^1H NMR (300 MHz, $CDCl_3$): δ 7.97−7.87 (m, 2H, ArH), 7.70−7.40 (m, containing PPh_3O and ArH signals), 2.63 (br d, J = 5.5 Hz, 1H), 2.13 (br d, J = 5.5 Hz, 1H), 1.88−1.56 (m, 5H), 1.52−1,37 (m, 1H), 1.11 (dd, J = 5.6 Hz, 1H, cyclopropyl).

***t*-3,4-*N*-Tosylaziridino-*t*-1,2-methylene-*r*-2-(phenylsulfonyl)cyclohexane (8).** Compound **7** containing ∼35 mol % triphenylphospine (1.38 g, ∼3.5 mmol) was dissolved in CH_2Cl_2 (25 mL). TsCl (1.53 g, 8.0 mmol) and Et_3N (1 mL, 7.2 mmol) were added, and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was washed with saturated $NaHCO_3$ (3 × 20 mL) and dried (Na_2SO_4). After evaporation of the solvent the oily residue (2.86 g) was purified by flash chromatography (gradient EtOAc/pentane 30:70 to 50:50) giving 1.29 g of pure **8** as white crystals. The yield was 51% in three steps from **6**. Mp: 171−172 °C (EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.78 (m, 4H, ArH), 7.65−7.60 (m, 1H, ArH), 7.56−7.49 (m, 2H, ArH), 7.31 (br d, J = 8 Hz, 2H, ArH), 3.32 (dd, J = 7.7, 1.4 Hz, 1H, H-3), 2.92 (br d, J = 7.4 Hz, 1H, H-4), 2.43 (s, 3H, MeAr), 2.05−2.00 (m, 1H), 1.94−1.80 (m, 2H), 1.76−1.61 (m, 2H), 1.55−1.43 (m, 1H), 1.10 (dd, J = 6.9, 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 138.2, 134.7, 133.4, 129.4, 129.0, 128.5, 128.0, 39.3, 38.9, 38.6, 21.7, 19.4, 17.7, 16.1, 15.3. IR ($CDCl_3$): 3426, 2943, 1654, 1597, 1447, 1306, 1184, 1156, 1091, 983 cm^{-1}. Anal. Calcd: C, 59.53; H, 5.25; N, 3.47; Found: C, 59.68; H, 5.35; N, 3.54.

3-(Phenylsulfonyl)-8-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]-2-octene (9). Compound **8** (1.0 g, 2.48 mmol) was dissolved in a mixture of 90% v/v CH_2Cl_2 and 10% v/v of $MeNO_2$ (44 mL). An argon atmosphere was established, and the solution was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (997 μL, 7.94 mmol) was introduced dropwise via a syringe. When the addition was complete, the stirring continued at −78 °C for 40 h, and then the reaction mixture was allowed to rise to room temperature over 5 h. Water (40 mL) was added, and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$). Evaporation followed by flash chromatography using pentane/Et_2O (gradient 80:20 to 50:50) as eluent afforded **9** (0.76 g, 76%) as white crystals. Mp: 128.5−129.5 °C (EtOAc/hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80−7.78 (m, 2H, ArH), 7.69−7.62 (m, 3H, ArH), 7.56−7.52 (m, 2H, ArH), 7.32−

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7.28 (m, 2H, ArH), 7.13 (d, J = 5.5 Hz, 1H, H-2), 4.57 (br t, J = 5.9 Hz, 1H, H-1), 4.41 (m, 1H, H-5), 2.59 (br d, J = 16.5 Hz, 1H, H-4), 2.42 (s, 3H, Me Ar), 2.18 (d, J = 17.2 Hz, 1H, H-4′), 1.95−1.87 (m, 2H), 1.75−1.71 (m, 1H), 1.53−1.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 139.3, 138.1, 137.8, 136.5, 133.6, 129.7, 129.2, 127.9, 127.2, 55.4, 54.6, 34.5, 33.8, 29.5, 21.7. IR ($CDCl_3$): 3172, 2978, 2955, 2919, 2872, 1596, 1449, 1343, 1314, 1308, 1161, 1091, 1149, 1020, 967, 949 cm^{-1}. Anal. Calcd: C, 59.53; H, 5.25; N, 3.47; Found: C, 59.51; H, 5.45; N, 3.38.

3-(Phenylsulfonyl)-8-[(4-methylphenyl)sulfonyl]-2-(1-nitroethyl)-8-azabiyclo[3.2.1]octane (10). To a solution of **9** (0.88 g, 2.18 mmol) in nitroethane (22 mL) was added DBU (326 μL, 2.18 mmol). The reaction mixture was stirred at room temperature for 3.5 h. Ether and water were added to the reaction mixture, and the layers were separated. The aqueous phase was extracted three times with ether, and the combined organic phases were washed with 2 M HCl, H_2O (twice), and brine. The resulting organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography using pentane/EtOAc (gradient 8:1 to 8:3) gave 0.95 g (91%) of **10** as white crystals in a 2:1 diastereomeric mixture. Mp: 172−174 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) for the combined diastereoisomers: δ 7.85−7.76 (m, 2H, ArH), 7.72−7.65 (m, 3H, ArH), 7.62−7.54 (m, 2H, ArH), 7.32−7.28 (m, 2H, ArH), 4.92−4.83 (m, 1/3H), 4.83−4.73 (m, 2/3H), 4,28−4.09 (m, 2H), 3.32 (dt, J = 9.9, 2.1 Hz, 1/3H), 3.18 (dt, J = 9.3, 2.7 Hz, 2/3H), 3.08 (dm, J = 6 Hz, 1/3H), 2.93 (dt, J = 8.7, 2.4, 2/3H), 2.44 (s, 3H), 2.33−1.91 (m, 4H), 1.76 (d, J = 6.6 Hz, 2H), 1.67−1.53 (m, 1H), 1.48 (d, J = 6.9 Hz, 1H), 1.41−1.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ **Diastereoisomer A** (major): 144.4, 138.2, 136.0, 134.2, 130.0, 129.5, 128.4, 127.4 (**A** + **B**), 86.0, 57.7, 55.7, 55.2, 45.1, 30.3, 28.4, 27.1, 21.6 (**A** + **B**), 16.6. **Diastereoisomer B** (minor): 144.3, 137.8, 136.1, 134.3, 129.9, 129.6, 128.8, 127.4 (**A** + **B**), 85.4, 57.6, 55.8, 55.1, 43.7, 30.7, 28.7, 27.5, 21.6 (**A** + **B**), 16.2. IR ($CDCl_3$): 3064, 2955, 1596, 1550, 1447, 1341, 1306, 1150, 1093, 1024, 948 cm^{-1}.

2-Acetyl-8-[(4-methylphenyl)sulfonyl]-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane (11). To a stirred solution of **10** (0.1 g, 0.21 mmol) in methanol (7 mL), cooled to 0 °C was added 30% aqueous hydrogen peroxide (418 μL, 4.06 mmol), followed by a solution of potassium carbonate (0.17 g, 1.21 mmol) in water (0.5 mL). Stirring continued for 23 h at room temperature. The solution was then acidified with dilute hydrochloric acid (7 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give almost pure carbonyl compound **11**. The product was further subjected to flash chromatography using pentane/Et_2O (gradient 8:1 to 8:3) to provide ketone **11** in 98% yield (92.1 mg). Mp: 202−203 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85−7.81 (m, 2H), 7.70−7.62 (m, 3H), 7.58−7.52 (m, 2H), 7.30−7.27 (m, 2H), 4.72 (br d, 8.1 Hz, 1H), 4.21 (dt, J = 9.6, 2.7, 1H), 4.11 (br t, J = 6.2 Hz, 1H), 3.36 (t, J = 2.0 Hz, 1H), 2.42 (s, 3H), 2.30 (s, 3H), 2.24−1.87 (m, 5H), 1.68−1.58 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 144.1, 138.4, 136.2, 133.9, 129.8, 129.4, 128.4, 127.6, 55.8, 55.3, 54.5, 53.7, 29.6, 29.0, 28.3, 27.4, 21.6. IR ($CDCl_3$): 3427, 1642, 1447, 1340, 1304, 1169, 1148, 1093, 1034 cm^{-1}.

1-Acetyl-8-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]-oct-2-ene (12). Potassium *tert*-butoxide (42.4 mg, 0.38 mmol) was added to a stirred solution of **11 (**169 mg, 0.38 mmol) in THF (4.8 mL) at room temperature. A precipitate formed immediately, and stirring was continued for 55 min. Water (5 mL) was added, and the mixture was extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash chromatography using pentane/Et_2O (gradient 8:2 to 1:1) to give 100 mg (87%) of **12** as white crystals. Mp: 202−203 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74−7.72 (m, 2H), 7.27−7.25 (m, 2H), 6.52 (t, J = 3.3 Hz, 1H), 4.90 (d, J = 5.5 Hz, 1H), 4.42−4.40 (t, J = 5.1 Hz, 1H), 2.88 (dm, J = 19.4 Hz, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.10 (dd, J = 19.4, 4.4 Hz, 1H), 1.94−1.85 (m, 1H), 1.76−1.65 (m, 2H), 1.50−1.43 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 144.3, 143.3, 139.9, 139.3, 129.4, 127.3, 54.8, 54.0, 36.4, 35.4, 30.1, 24.9, 21.6. IR ($CDCl_3$): 2954, 2923, 1664, 1447, 1340, 1246, 1160, 1095, 1056 cm^{-1}. Anal. Calcd: C, 62.93; H, 6.27; N, 4.59; Found: C, 62.78; H, 6.39; N, 4.54.

2-(2-Methyl-1,3-dioxolan-2-yl)-8-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]oct-2-ene (13). Me_3SiOTf (5.0 μL, 0.03 mmol) was added into a reaction flask containing dry dichloromethane (0.5 mL) under argon. The mixture was cooled to −78 °C. 1,2-Bis((trimethylsilyl)oxy)ethane (115 μL, 0.56 mmol) was then added into the reaction flask, followed by injection of **12** (85 mg, 0.28 mmol) in CH_2Cl_2 (1 mL). Stirring continued at −78 °C for 5 h, then at room temperature for 14 h. The reaction was quenched by adding dry pyridine (6.0 μL, 0.07 mmol). The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution and extracted several times with CH_2Cl_2. The combined organic layers were washed with saturated NaCl aqueous solution and dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4. After the solution was concentrated, the residue was purified by flash chromatography to give 61.7 mg (63%) of **13** as white crystals. Mp: 121−122 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77−7.46 (2H, ArH), 7.26−7.24 (2H, ArH), 5.56 (t, J = 2.9 Hz, 1H), 4.36 (d, J = 5.5 Hz, 1H), 4.32 (t, J = 7.7 Hz, 1H), 3.97−3.91 (m, 2H), 3.85−3.79 (m, 2H), 2.63 (dt, J = 15.4, 2.2, 1H), 2.41 (s, 3H), 1.95−1.74 (m, 4H) 1.56−1.48 (m, 1H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 143.1, 137.6, 129.4, 127.4, 118.7, 107.8, 64.7, 64.5, 55.4, 54.9, 35.8, 35.2, 30.3, 24.3, 21.5. IR ($CDCl_3$): 2983, 2954, 2919, 1597, 1339, 1160, 1094, 1039 cm^{-1}.

2-(2-Methyl-1,3-dioxolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene (14). To a suspension of Mg (23 mg, 0.94 mmol) in anhydrous methanol (2 mL) was added a solution of **13** (62 mg, 0.18 mmol) in anhydrous methanol (2 mL). The resulting suspension was sonicated for 40 min. The reaction was then diluted with brine (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo (83%). No thorough spectral characterization of the free amine **14** was made, and the material was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): 5.59 (t, J = 2.7 Hz, 1H), 3.99−3.89 (m, 2H), 3.88−3.79 (m, 2H), 3.70 (t, J = 3.3 Hz, 1H), 3.65 (br t, J = 5.2 Hz, 1H), 2.48 (dm, 1H), 2.05−1.89 (m, 4H), 1.86 (dd, J = 17.9, 3.8 Hz, 1H), 1.60−1.44 (m, 1H), 1.47 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 129.3, 127.4, 117.8, 108.4, 64.8, 64.5, 52.6, 36.2, 35.4, 30.6, 24.4.

8-Methyl-2-(methylcarbonyl)-8-azabicyclo[3.2.1]oct-2-ene (1). To a stirred solution of **14** (42 mg, 0.22 mmol) and 87 μL (1.17 mmol) of 37% aqueous formaldehyde in 700 μL acetonitrile was added sodium cyanoborohydride (23.4 mg, 0.37 mmol). The reaction mixture was stirred for 15 min, and then glacial acetic acid was added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 min, glacial acetic acid being added occasionally to maintain the pH near neutrality. The solvent was evaporated at reduced pressure, and 1 mL of 2 N KOH was added to the residue. The resulting mixture was extracted with ether (3 × 5 mL). The combined ether extracts were washed with 5 mL of 0.5 N KOH and then extracted with three 5 mL portions of 1 N HCl. The acid extracts were combined and neutralized with solid KOH and then extracted with three 10 mL portions of ether. The combined ether extracts were dried (K_2CO_3) and evaporated in vacuo to afford 32 mg (90%) of (±)-ferruginine **1**. Spectral data were in accordance with those previously reported.[14c,e]

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **7**, **10**−**11**, **13**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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