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Formal Synthesis of (+)- and (–)-Ferruginine

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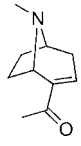
A formal synthesis of the naturally occurring (+)-ferrugine and of its enantiomer starting from the commercially available tropinone is reported. The desymmetrization of tropinone was achieved through formation of diastereomeric unsaturated sulfoxides using the Andersen procedure. Introduction of the acetyl C(2) side chain was achieved by conjugate addition of lithiated ethyl vinyl ether to an unsaturated sulfone. *N*-Boc-Norferruginine, an advanced intermediate for the synthesis of ferruginine, was prepared in six steps and 19 % overall yield.

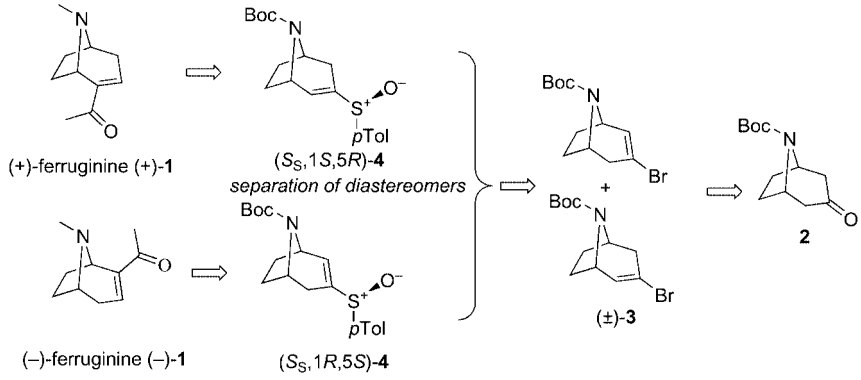
Introduction

The tropane alkaloid (+)-ferruginine [(+)-**1**] was isolated from the extracts of two arboreal species, *Darlingia Darlingiana* and *Darlingia Ferruginea*, in 1979.[1,2] It is a potent neurotoxin of potential interest for the treatment of neurodegenerative disorders such as Alzheimer's disease.[3,4] Its unnatural isomer (–)-**1** has shown interesting activities as a nicotine acetylcholine receptor (nAChR) agonist.[5]



(+)-ferruginine (+)-**1**

Due to their biological activity and their interesting structural features, 8-azabicyclo[3.2.1]octane derivatives (tropanes) are privileged target molecules for the development of new synthetic methods and strategies.[6] Ferruginine itself has been synthesized in racemic[7–9] and enantiomerically pure forms.[10–16] We present here a concise formal synthesis of both enantiomers of ferruginine using an easy resolution procedure based on the formation of diastereomeric alkenyl sulfoxides. The retrosynthetic analysis is depicted in Scheme 1. Late introduction of the acetyl side chain as in Bäckvall's synthesis[9] was planned in order to maximize the flexibility of our approach. The synthesis was to start with the commercially available *N*-Boc-nortropinone (**2**), and the vinyl bromide **3** was to be resolved by conversion into the two diastereomeric sulfoxides **4**. The acetyl C(2) side chain was to be introduced by conjugate addition close to the end of the synthesis.



Scheme 1. Retrosynthesis of (+)- and (–)-ferruginine.

Results and Discussion

The racemic vinyl bromide (±)-**3** was prepared from the commercially available *N*-Boc-nortropinone (**2**)[17] by the

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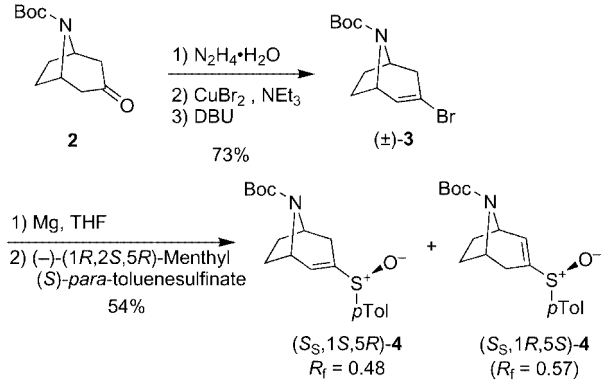
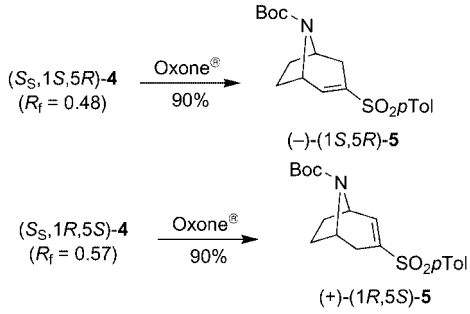
procedure of Marchand and Takeda,[18,19] and the hydrazone derived from **2** was treated with $CuBr_2$ and triethylamine in methanol. The reaction afforded a mixture of the expected *gem*-dibromide and bromoalkene **3**. This mixture of products was treated with 1,8-diazabicyclo[5.4.0]undecene (DBU) in benzene at reflux to give the desired racemic bromide (±)-**3** in 73% yield from **2** (Scheme 2). The racemic bromide (±)-**3** was converted into the corresponding organomagnesium derivative and allowed to react with (–)-(1*R*)-menthyl (*S*)-*para*-toluenesulfinate according to Andersen's procedure[20–22] to afford a 1:1 mixture of diastereomeric unsaturated sulfoxides (S_S,1*S*,5*R*)-**4** and (S_S,1*R*,5*S*)-**4**. Interestingly, the two diastereoisomers are very easily separated by flash chromatography [R_f(S_S,1*S*,5*R*)-**4** = 0.48; R_f(S_S,1*R*,5*S*)-**4** = 0.57 (hexane/EtOAc, 1:3)]. This difference in R_f values is remarkable and may be attributed to a shielding of the nitrogen atom by the *para*-tolyl group in the less polar (S_S,1*R*,5*S*)-**4**, indicating that this diastereomer exists preferentially in a conformation in which the C=C bond is coplanar with the S–O bond of the sulfoxide.[23] No crystal suitable for an X-ray analysis was obtained and it was therefore not possible to confirm this hypothesis experimentally. The relative configurations of both diastereomers of (S_S,1*S*,5*R*)-**4** and (S_S,1*R*,5*S*)-**4** were attributed by conversion into the known enantiomers of *N*-Boc-norferruginine (**8**; vide infra).



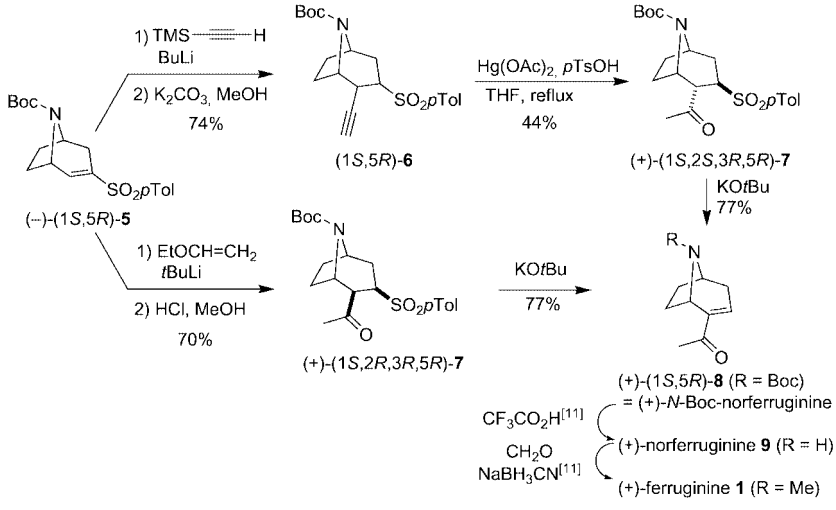
Scheme 2. Preparation of the diastereomeric unsaturated sulfoxides **4**.

All attempts to introduce the C(2) side chain by conjugate additions to the alkenyl sulfoxides **4** were unsatisfactory, so we decided to convert the sulfoxides into the sulfones, which are known to be more reactive. Both diastereomers of **4** were separately treated with Oxone® to afford the enantiomeric sulfones (–)-**5** and (+)-**5** in 90% yields (Scheme 3).



Scheme 3. Preparation of the unsaturated sulfones (–)-**5** and (+)-**5**.

In order to introduce the acetyl side chain, Bäckvall's approach using conjugated addition of nitroethane followed by a Nef reaction was attempted first.[9] However, the conjugate addition of nitroethane to **5** gave unsatisfactory results. A more satisfactory outcome was obtained through conjugate addition of lithium trimethylsilylacetylide to (–)-(1*R*,5*S*)-**5**, followed by desilylation with K_2CO_3 to afford the terminal alkyne (1*S*,5*R*)-**6** in 74% yield (Scheme 4). The mercury(II)-catalyzed hydrolysis of the terminal alkyne proceeded in moderate yield (44%) and delivered the sulfonylated ketone (+)-(1*S*,2*S*,3*R*,5*R*)-**7** as a single diastereomer. A third approach involving conjugate addition of lithiated ethyl vinyl ether to (–)-(1*R*,5*S*)-**5** afforded the methyl ketone (+)-(1*S*,2*R*,3*R*,5*R*)-**7** in 70% overall yield as a single diastereomer (after treatment of the intermediate enol ether with HCl/MeOH). Surprisingly, the two methyl



Scheme 4. Synthesis of (+)-*N*-Boc-norferruginine [(+)-**8**] from unsaturated sulfone (–)-**5**.

ketones obtained by conjugate addition either of lithiated TMS-acetylene or of lithiated ethyl vinyl ketones are epimeric at C(2). Their relative configurations have been attributed from coupling constants and NOE difference spectra (Figure 1). Treatment of either diastereomer of **7** with KO*t*Bu gave (+)-*N*-Boc-norferruginine [(+)-(1*S*,5*R*)-**8**] in 77% yield; physical and spectroscopic data are in agreement with literature data.[11] The conversion of (+)-Boc-norferruginine [(+)-**8**] into (+)-norferruginine [(+)-**9**] and (+)-ferruginine [(+)-**1**] by removal of the *N*-Boc group (CF_3CO_2H) and *N*-methylation (CH_2O, $NaBH_3CN$) has been reported by Davies with the racemic mixture[7] and by Rapoport with the optically pure material.[11] Therefore, our synthesis of norferruginine can also be considered a formal synthesis of ferruginine.

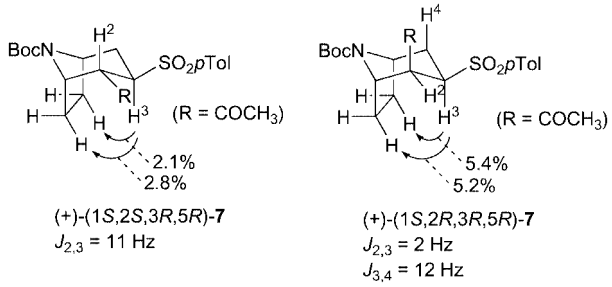


Figure 1. Relative configurations of diastereomers **7** from ^1H NMR coupling constants and NOE difference spectra.

Starting from the unsaturated sulfone (+)-(1*R*,5*S*)-**5**, (–)-Boc-norferruginine [(–)-**8**] was prepared by both routes presented for (+)-**8** in similar yields. Details for these transformations are given in the Experimental Section.

Conclusions

A short synthesis of both enantiomers of *N*-Boc-norferruginine (**8**) in six steps and 19% yield from *N*-Boc-tropinone (**2**) has been developed. The desymmetrization of tropinone has been achieved through the formation of diastereomeric unsaturated sulfoxides by Andersen's procedure. Introduction of the acetyl side chain is best achieved by conjugate addition of lithiated ethyl vinyl ether to an α,β-unsaturated sulfone. It is expected that this strategy will be efficient for the synthesis of a range of optically pure 2,3-disubstituted 8-azabicyclo[3.2.1]octane (tropane) alkaloids.

Experimental Section

General Techniques: C_6H_6, CH_2Cl_2, and THF were dried and purified by passing these solvents through activated alumina columns prior to use. MeOH was used without previous distillation; elimination of excess H_2O was performed by adding activated molecular sieves (4 Å). Other reagents were obtained from commercial sources and used as received. Filtration and flash column chromatography (FC): SdS silica gel (40–63 μm); EtOAc, hexane as eluents. Thin-layer chromatography (TLC): Macherey–Nagel SIL G-25 UV_{254}, or Merck silica gel 60 F_{254} precoated TLC plates; detection either with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (3 mL) in H_2O (300 mL) and subsequent heating. Melting points are not corrected. NMR spectroscopy: chemical shifts (δ) in ppm relative to $CHCl_3$ for ^1H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm) for room-temperature spectra, or relative to DMSO for ^1H (δ = 2.50 ppm) and $(CD_3)_2SO$ for ^{13}C (δ = 39.52 ppm) for high-temperature spectra.

Part a. Synthesis of Optically Pure Sulfones (–)-5 and (+)-5

***tert*-Butyl (±)-3-Bromo-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate [(±)-3]:**[18,19] A solution of hydrazine monohydrate (46 mL, 946 mmol) in MeOH (125 mL) and powdered molecular sieves (4 Å) (25 g) was stirred for 30 min. Then, a solution of **2** (10.6 g, 47.0 mmol) in MeOH (63 mL) was added under N_2. The mixture was stirred at room temperature for 3 h and filtered through Celite, and the solvent was evaporated. Excess hydrazine was removed under high vacuum. The crude hydrazone (partially solid) was used without further purification for the preparation of the *gem*-dibromide. A suspension of $CuBr_2$ (63.1 g, 283 mmol) in MeOH (130 mL) and NEt_3 (19 mL, 136 mmol) was stirred for 15 min. Then, a solution of the crude hydrazone in MeOH (65 mL) was added dropwise at 0 °C. At the end of the addition, the ice bath was removed and the reaction mixture was stirred for 2 h. The mixture was then poured into CH_2Cl_2 and a solution of NH_4OH (3%) was added until dissolution of all the copper salts. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with NH_4OH (3% solution), H_2O, and brine. After drying with $MgSO_4$ and evaporation of the solvent, an orange oil was obtained. Filtration through silica gel (hexane/EtOAc, 9:1) gave a mixture of the *gem*-dibromide and the bromoalkene **3** (colorless oil). Benzene (110 mL) and DBU (11 mL, 73.6 mmol) were added and the solution was heated under reflux overnight. The mixture was cooled to room temperature and a saturated aqueous solution of NH_4Cl was added. The aqueous phase was extracted twice with Et_2O and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a yellowish oil that was purified by FC (hexane/EtOAc 9:1) to afford (±)-**3** (10.1 g, 74% from **2**). White solid. M.p. 53–55 °C. ^1H NMR (500 MHz, [D$_6$]DMSO, T = 338 K): δ = 6.42 (dt, J = 5.45, 1.49 Hz, 1 H), 4.27 (t, J = 5.7 Hz, 1 H), 4.22–4.18 (m, 1 H), 3.00–2.93 (m, 1 H), 2.26–2.20 (d, J = 17.3 Hz, 1 H), 2.13 (q, J = 10.6 Hz, 1 H), 1.93–1.80 (m, 2 H), 1.74–1.66 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, T = 338 K): δ = 152.7, 134.1, 119.1, 78.7, 54.3, 52.8, 43.1, 33.3, 28.7, 27.7 ppm. IR (KBr): $\tilde{\nu}$ = 2978, 2926, 2876, 2833, 1686, 1628, 1412, 1364, 1353, 1321, 1314, 1162, 1105, 1006, 972, 886, 751, 709 cm^{-1}. MS (EI): *m*/*z* (%) = 289 (1), 287 (1), 233 (25), 231 (25), 189 (5), 187 (5), 160 (11), 158 (11), 108 (38), 91 (10), 57 (100). HRMS: calcd. for $C_{12}H_{18}BrNO_2$ 287.0521; found 287.0521.

***tert*-Butyl (+)-(S_S,1*R*,5*S*)- and (–)-(S_S,1*S*,5*R*)-3-[(4-Methylphenyl)-sulfinyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate [(+)-(S_S,1*R*,5*S*)-4 and (–)-(S_S,1*S*,5*R*)-4]:** The organomagnesium reagent was prepared from a solution of (±)-**3** (7.6 g, 26.3 mmol) in THF (40 mL), Mg (960 mg, 39.5 mmol) and MeI (0.2 mL) to activate the Mg. On cooling to room temperature, a suspension was formed and then transferred by cannula at 0 °C to a solution of (–)-(1*R*,2*S*,5*R*)-menthyl (*S*)-*para*-toluenesulfinate (11.6 g, 39.4 mmol) in benzene (100 mL). The flask containing the organomagnesium reagent was rinsed with THF (2 × 10 mL) to transfer the remaining reagent. When the addition was finished, the ice bath was removed and the reaction mixture was stirred at room temperature for 20 h. Then Et_2O and a saturated solution of NH_4Cl were added to the reaction mixture. The H_2O phase was separated and extracted three times with Et_2O. The combined organic layers were washed with brine

and dried ($MgSO_4$). Evaporation of the solvent afforded a yellowish solid containing a 1:1 mixture of the two diastereoisomers, which was purified by FC (hexane/EtOAc, 1:2) to remove impurities. Further FC (hexane/EtOAc, 1:1.7) allowed the separation of the two diastereomeric sulfoxides (+)-(S_S,1*R*,5*S*)-**4** (R_f = 0.57; hexane/EtOAc, 1:3; 2.46 g, 27%) and (–)-(S_S,1*S*,5*R*)-**4** (R_f = 0.48; hexane/EtOAc, 1:3; 2.44 g, 27%).

Compound (+)-(S_S,1*R*,5*S*)-4: R_f = 0.57. White solid. M.p. 122–124 °C. $[\alpha]_D^{20}$ = +127.6 ($CHCl_3$, *c* = 1.1). ^{1}H NMR (400 MHz, [D_6]-DMSO, *T* = 333 K): δ = 7.45–7.43 (m, 2 H), 7.36–7.35 (m, 2 H), 6.89–6.86 (dm, *J* = 5.2 Hz, 1 H), 2.40–2.33 (m + s, 1 + 3 H), 2.10–2.00 (m, 1 H), 1.99–1.85 (m, 2 H), 1.63 (d, *J* = 17 Hz, 1 H), 1.41–1.29, (m, 1 H), 1.32 (s, 9 H) ppm. ^{13}C NMR (125 MHz, [D_6]-DMSO, *T* = 333 K): δ = 152.8, 141.1, 140.9, 139.4, 134.6, 129.5, 124.3, 78.7, 69.0, 53.2, 51.2, 33.2, 29.3, 29.2, 28.5, 27.6, 20.5 ppm. IR (KBr): ṽ = 3048, 2973, 2915, 2841, 1697, 1594, 1379, 1325, 1176, 1102, 1043, 1012, 807, 625, 527, 507, 436 cm^{-1}. MS (EI): *m*/*z* (%) = 347 (8), 291 (29), 274 (9), 246 (16), 230 (40), 208 (52), 202 (33), 152 (88), 140 (39), 124 (20), 123 (22), 108 (100), 106 (22), 92 (22), 91 (51), 81 (24), 79 (20), 57 (94), 41 (46). HRMS: calcd. for $C_{19}H_{25}NO_3S$ 347.1555; found 347.1554.

Compound (–)-(S_S,1*S*,5*R*)-4: R_f = 0.48. M.p. 114–115 °C. $[\alpha]_D^{20}$ = –65.5 ($CHCl_3$, *c* = 1.1). ^{1}H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.42–7.40 (m, 2 H), 7.35–7.30 (m, 2 H), 6.96 (dt, *J* = 5.1, 1.7 Hz, 1 H), 4.51–4.40 (m, 1 H), 4.25–4.19 (m, 1 H), 2.36 (s, 3 H), 2.23 (dm, *J* = 17 Hz, 1 H), 2.16–2.05 (m, 1 H), 1.99–1.85 (m, 3 H), 1.49–1.37 (m, 1 H), 1.28 (s, 9 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO, *T* = 343 K): δ = 152.6, 141.4, 140.4, 139.2, 136.8, 129.2, 123.8, 78.5, 52.8, 51.3, 32.9, 28.4, 27.4, 27.3, 20.2 ppm. IR (KBr): ṽ = 3047, 2971, 2927, 1686, 1591, 1415, 1365, 1326, 1172, 1113, 1081, 1047, 1008, 890, 813, 624, 511 cm^{-1}. MS (EI): *m*/*z* (%) = 347 (6), 291 (16), 274 (6), 246 (12), 230 (24), 208 (34), 202 (19), 152 (80), 140 (21), 124 (9), 123 (9), 109 (90), 91 (19), 80 (17), 57 (100), 41 (14). HRMS: calcd. for $C_{19}H_{25}NO_3S$ 347.1555; found 347.1554.

***tert*-Butyl (–)-(1*S*,5*R*)-3-[(4-Methylphenyl)sulfonyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate [(–)-(1*S*,5*R*)-5]:**[24] A buffered H_2O solution (20 mL, pH = 5) of Oxone® (1.98 g, 3.22 mmol) was added at 0 °C to a solution of (S_S,1*S*,5*R*)-**4** (1.12 g, 3.22 mmol) in MeOH (40 mL). The cooling bath was removed and the reaction mixture was stirred for 3 h. H_2O and CH_2Cl_2 were added to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried ($MgSO_4$). FC (hexane/AcOEt, 2:1) afforded (–)-(1*S*,5*R*)-**5** (1.09 g, 3.0 mmol, 93% yield). White solid. M.p. 113–114 °C. $[\alpha]_D^{20}$ = –51.9 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.69–7.63 (m, 2 H), 7.46–7.40 (m, 2 H), 7.20 (dt, *J* = 5.3, 1.7 Hz, 1 H), 4.49 (t, *J* = 5.2 Hz, 1 H), 4.25 (dd, *J* = 7.2, 4.9 Hz, 1 H), 2.57 (dm, *J* = 17.2 Hz, 1 H), 2.41 (s, 3 H), 2.16–2.04 (m, 1 H), 1.99 (d, *J* = 17.2 Hz, 1 H), 1.99–1.85 (m, 2 H), 1.48–1.38 (m, 1 H), 1.28 (s, 9 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO, *T* = 343 K): δ = 152.8, 143.8, 141.6, 137.2, 135.5, 129.4, 127.0, 78.8, 52.6, 51.0, 32.6, 31.0, 28.6, 27.4, 20.5 ppm. IR: ṽ = 3091, 3056, 3004, 2970, 2952, 2877, 1932, 1698, 1627, 1595, 1463, 1393, 1371, 1354, 1325, 1312, 1165, 1147, 1106, 1093, 1028, 946, 817, 665, 611 cm^{-1}. MS (EI): *m*/*z* (%) = 363 (3), 308 (12), 307 (50), 263 (36), 247 (14), 234 (12), 199 (13), 198 (13), 139 (24), 108 (100), 91 (50), 80 (25), 79 (50), 57 (95), 52 (12), 41 (43). HRMS: calcd. for $C_{19}H_{25}NO_4$ 363.1504; found 363.1507.

***tert*-Butyl (+)-(1*R*,5*S*)-3-[(4-Methylphenyl)sulfonyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate [(+)-(1*R*,5*S*)-5]:**[24] This compound was produced as described in the procedure for (–)-(1*S*,5*R*)-**5** starting from (S_S,1*R*,5*S*)-**4** (920 mg, 2.65 mmol). Compound (+)-(1*R*,5*S*)-**5** (870 mg, 90%) was obtained. White solid. M.p. 110–112 °C. $[\alpha]_D^{20}$ = +42.9 ($CHCl_3$, *c* = 1.0). HRMS: calcd. for $C_{19}H_{25}NO_4$ 363.1504; found 363.1509. Spectral data identical to those for (–)-(1*S*,5*R*)-**5**.

Part b. Synthesis of (+)-*N*-Boc-Norferruginine [(+)-8]

***tert*-Butyl (1*S*,5*R*)-2-Ethynyl-3-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]octane-8-carboxylate [(1*S*,5*R*)-6]:** *n*BuLi (4.6 mL, 6.4 mmol) was added at 0 °C to a solution of ethynyltrimethylsilane (930 μL, 6.7 mmol) in THF (19 mL). The reaction mixture was stirred for 30 min and was then added by cannula at 0 °C to a solution of (–)-(1*S*,5*R*)-**5** (780 mg, 2.14 mmol) in toluene (45 mL). When the addition was finished, the bath was removed and the reaction was allowed to proceed for 5 h at room temperature. A saturated solution of NH_4Cl and Et_2O were added. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine and dried ($MgSO_4$). After the evaporation of the solvent, the residue was dissolved in MeOH (11 mL), and K_2CO_3 (300 mg, 2.17 mmol) was added. The reaction mixture was stirred for 16 h, and H_2O and Et_2O were added. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by FC (cyclohexane/EtOAc, 2:1) afforded (1*S*,5*R*)-**6** (600 mg, 1.55 mmol, 73% yield). White solid. M.p. 148–150 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.83–7.79 (m, 2 H), 7.46–7.41 (m, 2 H), 4.40–4.35 (m, 1 H), 4.35–4.30 (m, 1 H), 3.58 (dt, *J* = 12.7, 4.8 Hz, 1 H), 2.84–2.80 (m, 1 H), 2.77–2.73 (m, 1 H), 2.43 (s, 3 H), 1.98 (td, *J* = 12.7, 2.8 Hz, 1 H), 1.86–1.65 (m, 3 H), 1.51–1.40 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, *T* = 343 K): δ = 151.6, 143.9, 134.9, 129.0, 128.4, 79.5, 78.1, 74.9, 57.1, 56.9, 51.2, 32.5, 27.8, 27.6, 26.7, 26.5, 20.5 ppm. IR (KBr): ṽ = 3272, 2985, 2932, 2874, 1684, 1421, 1318, 1288, 1147, 1110, 1086, 875, 817, 679 cm^{-1}. MS (EI): *m*/*z* (%) = 316 (40), 235 (7), 234 (40), 179 (20), 178 (72), 135 (27), 134 (84), 132 (19), 117 (15), 106 (17), 91 (50), 68 (23), 65 (12), 57 (100). $C_{21}H_{27}NO_4S$ (389.17): calcd. C 64.75, H 6.99, N 3.60; found C 64.75, H 6.98, N 3.68.

***tert*-Butyl 2-Acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate [(+)-(1*S*,2*S*,3*R*,5*R*)-7]:**[25] A solution of (1*S*,5*R*)-**6** (890 mg, 2.28 mmol), $Hg(OAc)_2$ (220 mg, 0.68 mmol), and *para*-toluenesulfonic acid (440 mg, 2.3 mmol) in THF (70 mL) was heated under reflux for 1.5 h. After cooling to room temperature, the solution was concentrated to 10 mL and filtered through a short pad of silica gel (Et_2O). After evaporation, the yellow residue was dissolved in Et_2O (5 mL) and (+)-(1*S*,2*S*,3*R*,5*R*)-**7** (418 mg, 45%) was obtained by two successive crystallizations at 4 °C. White solid. M.p. 142–143 °C. $[\alpha]_D^{20}$ = +78.0 ($CHCl_3$, *c* = 1.00). ^{1}H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.69–7.64 (m, 2 H), 7.48–7.43 (m, 2 H), 4.23 (dd, *J* = 6.8, 3.3 Hz, 1 H), 4.15–4.09 (m, 1 H), 4.03 (td, *J* = 11.6, 6.44Hz, 1 H), 3.25 (dd, *J* = 11.3, 3.24 Hz, 1 H), 2.42 (s, 3 H), 2.22 (s, 3 H), 1.92–1.54 (m, 6 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, *T* = 343 K): δ = 203.9, 151.8, 144.3, 133.9, 129.4, 128.1, 79.1, 55.9, 53.3, 52.1, 48.9, 29.2, 28.5, 27.6, 26.3, 22.4, 20.5 ppm. NOE difference spectra (400 MHz, *T* = 343 K): δ = 3.29–3.22 (C*H*COCH$_3$) → 7.69–7.64 (3.41%), 4.26–4.21 (8.93%), 4.08–3.99 (1.72%), 2.24–2.19 (6.19%), 1.90–1.79 (1.23%); 4.09–3.99 (C*H*SO$_2$Ar) → 7.69–7.64 (3.78%), 3.31–3.23 (1.77%), 1.91–1.80 (0.57%), 1.80–1.71 (2.80%), 1.71–1.63 (3.13%), 1.63–1.54 (2.10%). IR (KBr): ṽ = 2966, 2932, 2890, 1711, 1688, 1595, 1457, 1388, 1368, 1331, 1314, 1302, 1172, 1130, 1106, 1083, 827, 820, 770, 743, 647 cm^{-1}. MS (EI): *m*/*z* (%) = 407 (0.2), 389 (0.3), 253 (20), 252 (56), 195 (51), 180 (17), 153 (64), 152 (100), 139 (55), 136 (36), 135 (32), 122 (28), 108 (46), 91 (35), 68 (81), 57 (89).

HRMS (ESI-POS, [M + Na^+], sample dissolved in MeOH/H_2O/Hfo, 74:25:1): calcd. for $C_{21}H_{29}NNaO_5S$ 430.1664; found 430.1669.

***tert*-Butyl (+)-(1*S*,2*R*,3*R*,5*R*)-2-Acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate [(+)-(1*S*,2*R*,3*R*,5*R*)-7]:**[26–28] *t*BuLi (1.1 mL, 1.5 M in hexane) was added dropwise at –78 °C to a solution of ethyl vinyl ether (425 μL, 4.42 mmol) in THF (1.5 mL). The reaction mixture turned yellow and it decolored at 0 °C. A solution of (–)-(1*S*,5*R*)-**5** (300 mg, 0.83 mmol) in THF (1.3 mL) was added at –20 °C. After 4 h, a solution of NH_4Cl was added and the mixture was allowed to warm to room temperature. H_2O and Et_2O were added, and the aqueous phase was separated and extracted with Et_2O. The combined organic layers were washed with brine and dried (Mg_2SO_4). Evaporation of the solvent and FC (cyclohexane/EtOAc, 7:3) afforded a colorless oil, which was dissolved in MeOH (3.6 mL) and treated with HCl (0.5 M). After 10 min, a white precipitate had formed and the reaction mixture was stirred for an additional 20 min. H_2O and EtOAc were added and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded (1*S*,2*R*,3*R*,5*R*)-**7** (236 mg, 70% yield). White solid. M.p. 187–188 °C. $[\alpha]_D^{20}$ = +47.3 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.71–7.65 (m, 2 H), 7.46–7.39 (m, 2 H), 4.51 (d, *J* = 6.72 Hz, 1 H), 4.31–4.25 (m, 1 H), 3.59 (dt, *J* = 12.6, 5.26 Hz, 1 H), 3.23 (dd, *J* = 4.82, 1.77 Hz, 1 H), 2.43 (s, 3 H), 2.36 (td, *J* = 12.5, 2.57 Hz), 2.18 (s, 3 H), 2.05–1.89 (m, 1 H), 1.87–1.72 (m, 2 H), 1.66–1.58 (m, 1 H), 1.51–1.39 (m, 1 H), 1.34 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, *T* = 343 K): δ = 203.5, 150.8, 143.6, 136.6, 129.1, 127.8, 78.3, 59.4, 53.5, 51.3, 29.2, 27.6, 27.4, 26.5, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 2975, 2928, 2984, 1709, 1685, 1410, 1174, 1105, 677 cm^{-1}. MS (EI): *m*/*z* (%) = 334 (9), 252 (10), 195 (18), 152 (100), 139 (29), 108 (63), 91 (61), 68 (48), 57 (94), 43 (19), 41 (55). HRMS (ESI-POS, [M + Na]$^+$, sample dissolved in H_2O/CH_3CN, 1:1): calcd. for $C_{21}H_{29}NNaO_5S$ 430.1664; found: 430.1651.

(+)-(1*S*,5*R*)-*N*-Boc-Norferruginine [(+)-(1*S*,5*R*)-8]:[9] A mixture of (+)-(1*S*,2*R*,3*R*,5*R*)-**7** (205 mg, 0.50 mmol) and *t*BuOK (57 mg, 0.50 mmol) in THF (7 mL) was stirred under N_2 for 1 h. The solution became yellow and a white salt precipitated. H_2O and Et_2O were added, and the two phases were separated. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil that was purified by FC (cyclohexane/EtOAc, 7:3) to afford (+)-(1*S*,5*R*)-**8** (100 mg, 80% yield). White solid. M.p. 65–66 °C (ref.[11] m.p. 64–65 °C). $[\alpha]_D^{20}$ = +113.7 ($CHCl_3$, *c* = 1.0) {ref.[11] $[\alpha]_D^{24}$ = +129.1 ($CHCl_3$, *c* = 1.0)}. Spectral data were in agreement with literature data.[11]

Part c. Synthesis of (–)-*N*-Boc-Norferruginine [(–)-8]

***tert*-Butyl (1*R*,5*S*)-2-Ethynyl-3-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]octane-8-carboxylate [(1*R*,5*S*)-6]:** This compound was produced by the procedure for the synthesis of (1*S*,5*R*)-**6**, starting from (+)-(1*R*,5*S*)-**5** (840 mg, 2.3 mmol); (1*R*,5*S*)-**6** (650 mg, 7%) was obtained. White solid. M.p. 148–149 °C. Spectral data are identical to those for (1*S*,5*R*)-**6**. ^1H NMR (400 MHz, [D_6]DMSO, *T* = 343 K): δ = 7.83–7.79 (m, 2 H), 7.46–7.41 (m, 2 H), 4.40–4.35 (m, 1 H), 4.35–4.30 (m, 1 H), 3.58 (dt, *J* = 12.7, 4.8 Hz, 1 H), 2.84–2.80 (m, 1 H), 2.77–2.73 (m, 1 H), 2.43 (s, 3 H), 1.98 (td, *J* = 12.7, 2.8 Hz, 1 H), 1.86–1.65 (m, 3 H), 1.51–1.40 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, *T* = 343 K): δ = 151.6, 143.9, 134.9, 129.0, 128.4, 79.5, 78.1, 74.9, 57.1, 56.9, 51.2, 32.5, 27.8, 27.6, 26.7, 26.5, 20.5 ppm. IR (KBr): $\tilde{\nu}$ = 3271, 2985, 2932, 2874, 1681, 1419, 1317, 1288, 1146, 1109, 1086, 875, 817, 678 cm^{-1}. MS (EI): *m*/*z* (%) = 389 (2), 316 (10), 235 (20), 234 (75), 179 (43), 178 (92), 135 (59), 134 (100), 132 (51), 117 (51), 106 (46), 91 (90), 67 (54), 65 (54), 57 (90). $C_{21}H_{27}NO_4S$ (389.17): calcd. C 64.75, H 6.99, N 3.60; found: C 64.72, H 6.94, N 3.61.

***tert*-Butyl (–)-(1*R*,2*R*,3*S*,5*S*)-2-Acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate [(–)-(1*R*,2*R*,3*S*,5*S*)-7]:**[25] This compound was produced according to the procedure for the synthesis of (+)-(1*S*,2*S*,3*R*,5*R*)-**7** starting from (1*R*,5*S*)-**6** (530 mg, 1.36 mmol); (–)-(1*R*,2*R*,3*S*,5*S*)-**7** (244 mg, 44% yield) was obtained. White solid. M.p. 141–142 °C. $[\alpha]_D^{20}$ = –74.2 ($CHCl_3$, *c* = 1.01). Spectral data are identical to those for (+)-(1*S*,2*S*,3*R*,5*R*)-**7**. HRMS (ESI-POS, [M + Na]$^+$, sample dissolved in MeOH/H_2O/Hfo, 74:25:1): calcd. for $C_{21}H_{29}NNaO_5S$ 430.1664; found 430.1646.

***tert*-Butyl (–)-(1*R*,2*S*,3*S*,5*S*)-2-Acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate [(–)-(1*R*,2*S*,3*S*,5*S*)-7]:**[26–28] This compound was produced according to the procedure for the synthesis of (+)-(1*S*,2*R*,3*R*,5*R*)-**7** starting from (+)-(1*R*,5*S*)-**5** (325 mg, 0.89 mmol); (–)-(1*R*,2*S*,3*S*,5*S*)-**7** (253 mg, 70% yield) was obtained. White solid. M.p. 184–185 °C. $[\alpha]_D^{20}$ = –40.0 (*c* = 1.0, $CHCl_3$). Spectral data are identical to those for (+)-(1*S*,2*R*,3*R*,5*R*)-**7**. HRMS (ESI-POS, [M + Na]$^+$, sample dissolved in H_2O/CH_3CN, 1:1): calcd. for $C_{21}H_{29}NNaO_5S$ 430.1664; found 430.1669.

(–)-(1*R*,5*S*)-*N*-Boc-Norferruginine [(–)-(1*R*,5*S*)-8]:[9] This compound was produced according to the procedure for the synthesis of (+)-(1*S*,5*R*)-**8**. Starting from (1*R*,2*S*,3*S*,5*S*)-**7** (194 mg, 0.48 mmol) afforded (–)-(1*R*,5*S*)-**8** (92 mg, 77% yield). White solid. M.p. 63–64 °C (ref.[11] m.p. 63–64 °C). $[\alpha]_D^{20}$ = –125.2 ($CHCl_3$, *c* = 1.0) {ref.[11] $[\alpha]_D^{24}$ = –126.8 ($CHCl_3$, *c* = 1.0)}. Spectral data are in agreement with literature data.[11]

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