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A STEREOCONTROLLED SYNTHESIS OF (±)-β-ISOSPARTEINE

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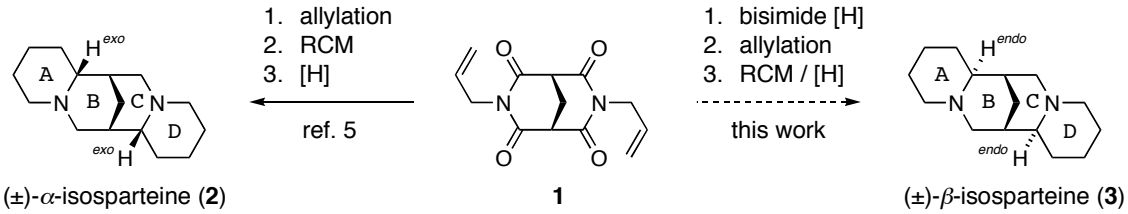
Abstract – A versatile tetraoxobispidine synthon, 3,7-diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (**1**), was converted to the title alkaloid via a synthetic sequence incorporating: imide reduction, Sakurai allylation, and ring-closing olefin metathesis reactions.

INTRODUCTION†

Widespread among common papilionaceous plant species, the sparteine family of quinolizidine alkaloids are constituted by all geometrically possible stereoisomeric variations of the 3,11-diazatetracyclo-[7.7.1.0^{3,8}.0^{11,16}]heptadecane nucleus.[1] Though of relatively minor biological importance,[2] sparteine alkaloids, and in particular, (–)-sparteine and (–)-α-isosparteine, have elicited intense interest because of their status as chiral diamine ligands *par excellence* for metal mediated enantioselective synthesis.[3,4] In an earlier report,[5] we identified that tetraoxobispidine derivatives may provide a versatile synthetic platform for the elaboration of all members of the sparteine alkaloid group.[6] In support of this modest hypothesis, we successfully demonstrated the conversion of *N,N´*-diallyltetraoxobispidine (**1**) to (±)-α-isosparteine (**2**). To ensure brevity of execution, our synthesis of **2** relied on two-directional advancement from **1** and proceeded *via* double nucleophilic allylation, followed by double ring-closing olefin metathesis (RCM) and thence exhaustive reduction to yield the target (Scheme 1).[5] In principle, a synthesis along similar lines in which the order of introduction of allyl and hydride nucleophiles onto **1** was strategically reversed, would result in endo configurated ring junction hydrogen-atoms and ultimately afford (±)-β-isosparteine (**3**).[7] This lesser known member of the sparteine subgroup of lupine alkaloids

† Dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.

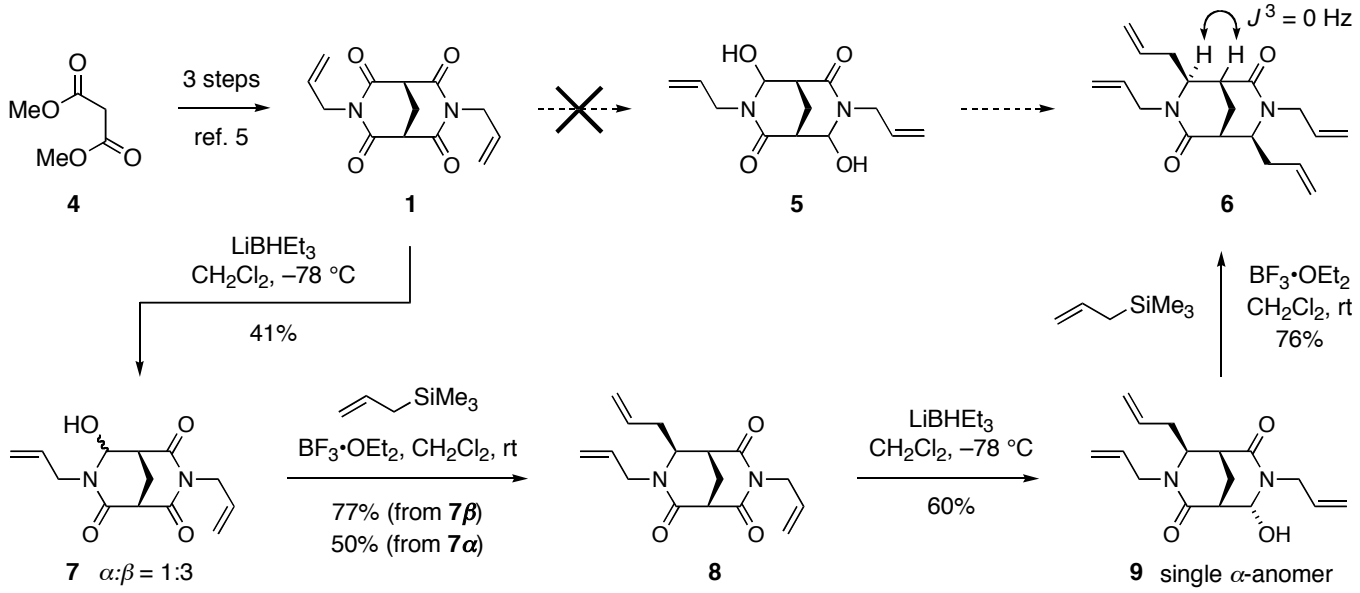
has received comparatively little attention and has never been the focus of a stereocontrolled target directed synthesis.[8] Herein, we advance such an undertaking and describe the successful elaboration of (±)-β-isosparteine (**3**) from readily available synthon (**1**).



Scheme 1. Overview of synthetic strategy for planned assault on (±)-β-isosparteine (**3**).

RESULTS AND DISCUSSION

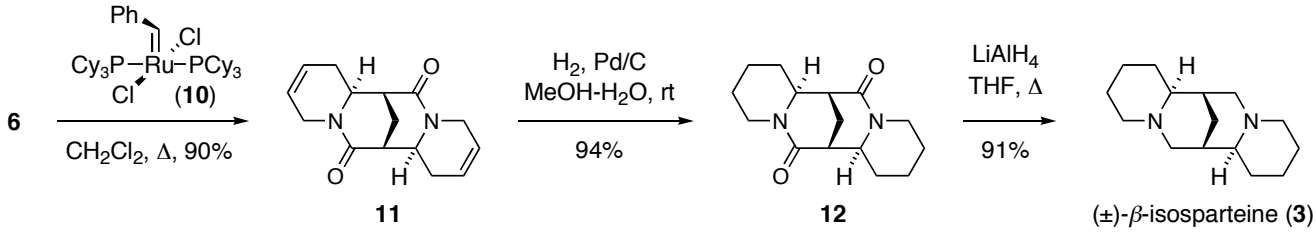
Synthesis of (±)-β-isosparteine commenced from tetraoxobispidine (**1**), itself prepared in short order from dimethyl malonate (**4**) as previously described (Scheme 2).[5] In keeping with the efficient two-directional approach of our earlier α-isosparteine synthesis, we planned to access β-isosparteine precursor (**6**) from bicycle (**1**) *via* a two step reductive allylation sequence comprising regioselective double hydride addition followed by double Sakurai-type allylation of the resulting bishemiaminal (**5**). In the event, and in spite of our best efforts, it proved impossible to prepare **5** from **1** in the desired manner. To obviate difficulties associated with the production and handling of a potentially sensitive bishemiaminal, a less direct route to **6** which avoided such an intermediate altogether was next investigated.



Scheme 2. Net double reductive regioselective *exo*-face allylation of tetraoxobispidine (**1**).

After some experimentation, it was discovered that bisimide (**1**) could be successfully monoreduced, albeit in modest yield, by the action of lithium triethylborohydride.[9] Subjection of either anomer of the resulting hemiaminal (**7**)[10] to a Sakurai-type allylation reaction gave allyl addition product (**8**) as a single

isomer.[11,12] Repetition of the same two step reduction/allylation sequence from **8** proceeded in a remarkably regio- and stereoselective fashion to afford tetraene (**6**), an appropriate RCM precursor to the *β*-isosparteine ring system. The C_2-symmetric nature of **6** was clearly evident from its ^{1}H and ^{13}C NMR spectral signatures; furthermore, the absence of *J*-coupling between vicinal bridgehead and CHN methine protons within **6** indicated the expected *exo*-configurations for the newly introduced pair of allyl moieties.[13] Subsequent conversion of tetraene (**6**) to the target of ultimate interest was uneventful (Scheme 3). Thus, treatment of **6** with Grubbs' first generation metathesis catalyst (**10**),[14] gave the expected tetracyclic product (**11**) in 90% yield. Adjustment of the oxidation level of **11** *via* hydrogenation followed by reduction of the resulting (±)-10,17-dioxo-*β*-isosparteine (**12**)[15] with lithium aluminum hydride gave (±)-*β*-isosparteine (**3**) as a colorless oil. The synthetic sample of (±)-**3** so produced exhibited identical ^{1}H NMR and ^{13}C NMR spectral data to those previously reported for this alkaloid in the literature.[8b,16]



Scheme 3. Completion of synthesis of (±)-*β*-isosparteine (**3**).

In summary, (±)-*β*-isosparteine (**3**) was synthesized in seven steps from *N,N´*-diallyltetraoxobispidine (**1**) *via* strategic application of reduction, Sakurai, and RCM transformations. This work serves to further exemplify the inherent versatility of the tetraoxobispidine approach to the stereocontrolled synthesis of sparteine group alkaloids. Studies directed at the realization of enantioselective nucleophilic additions to tetraoxobispidine platforms are ongoing as are allied efforts to conclude a synthesis of the eponymous sparteine group alkaloid from **1**. This work will be reported in due course.

EXPERIMENTAL

General techniques: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of N_2. Prior to use, THF was freshly distilled from sodium benzophenone ketyl and CH_2Cl_2 was distilled from CaH_2. Preparative chromatographic separations were performed on silica gel 60 (35-75 *μ*m) and reactions followed by TLC analysis using silica gel 60 plates (2-25 *μ*m) with fluorescent indicator (254 nm) and visualized with UV or phosphomolybdic acid. All commercially available reagents were used as received unless otherwise noted. Melting points were determined from open capillary tubes on a melting point apparatus and are uncorrected. Infra-red spectra were recorded in Fourier transform mode from KBr disks for solids, and as a thin film supported between NaCl plates for

oils. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified and from the indicated deuterated solvents in standard 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: $CDCl_3$ δ_H ($CHCl_3$) = 7.26 ppm, δ_C = 77.2 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution (HRMS) mass spectra were obtained using electrospray (ES) ionization. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.

(±)-(1*R*/*S,5*S**,6*R**)-3,7-Diallyl-6-hydroxy-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane (7):** A stirred solution of bisimide (**1**, 3.50 g, 13.4 mmol) in anhydrous CH_2Cl_2 (45 mL) at –78 °C under N_2, was treated dropwise with lithium triethylborohydride (14.7 mL, 1.0 M in THF, 14.7 mmol) during 20 min. The resulting mixture was stirred for 1 h at –78 °C and then quenched with sat. aq. NH_4Cl (10 mL) and warmed to rt. Further H_2O (10 mL) and CH_2Cl_2 (20 mL) were added and the layers well shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (2x15 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 1% MeOH in CH_2Cl_2) to yield a mixture of hemiaminal anomers (**7**, 1.46 g, 5.53 mmol, 41%, α:β = 1:3) as a colorless oil. A sample of pure β-isomer (**7β**) was isolated as a colorless solid by careful chromatography. Data for **7β**: mp 94-98 °C (*t*-BuOMe); IR (KBr) 3380, 2978, 1736, 1669, 1455, 1272, 1206, 1059, 929, 760, 554 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (2H, ddt, *J* = 16.7, 10.3, 6.5 Hz), 5.22 (1H, bs), 5.21 (1H, dm, *J* = 10.2 Hz), 5.18 (1H, dm, *J* = 16.3 Hz), 5.14 (1H, dm, *J* = 10.1 Hz), 5.12 (1H, dm, *J* = 15.8 Hz), 4.39-4.28 (3H, m), 3.85 (1H, ddm, *J* = 14.8, 6.6 Hz), 3.75 (1H, q, *J* = 2.6 Hz), 3.35 (1H, d, *J* = 5.1 Hz), 3.26 (1H, dq, *J* = 4.4, 2.1 Hz), 2.77 (1H, ddd, *J* = 13.7, 3.4, 2.1 Hz), 2.29 (1H, dddd, *J* = 13.6, 3.7, 2.3, 1.1 Hz) ppm; ^{13}C NMR (75 MHz, CDCl3) δ 170.5 (0), 167.7 (0), 163.7 (0), 132.4 (1), 131.2 (1), 119.0 (2), 118.2 (2), 80.1 (1), 48.8 (1), 47.1 (2), 45.2 (1), 42.0 (2) 19.6 (2) ppm; MS (ES) *m/z* 265 $(M+H)^+$; HRMS (ES) *m/z* 287.1003 (calcd. for $C_{13}H_{16}N_2O_4Na$: 287.1008).

(±)-(1*R,5*S**,6*R**)-3,6,7-Triallyl-2,4,8-trioxo-3,7-diazabicyclo[3.3.1]nonane (8):** A stirred solution of isomerically pure hemiaminal (**7β**, 459 mg, 1.74 mmol) in anhydrous CH_2Cl_2 (6 mL) at rt under N_2, was treated sequentially in dropwise fashion with allyltrimethylsilane (2.75 mL, d = 0.72, 1.98 g, 17.3 mmol) followed by freshly distilled boron trifluoride diethyl etherate (1.07 mL, d = 1.13, 1.21 g, 8.52 mmol). The resulting yellow mixture was stirred at rt for 24 h. After this time, CH_2Cl_2 (20 mL) was added and the mixture washed with H_2O (2x5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 1% MeOH in CH_2Cl_2) to yield triallyl compound (**8**, 384 mg, 1.33 mmol, 77%) as a colorless oil. A comparable reaction from **7α** (127 mg, 0.48 mmol, α:β = 5:1) gave an identical product (**8**, 69 mg, 0.24 mmol, 50%). Data for **8**: IR (neat) 3453, 3082, 2950, 1737,

1684, 1651, 1454, 1417, 1356, 1330, 1275, 1228, 1191, 1122, 993, 925, 843, 731, 627, 553, 499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79-5.70 (2H, m). 5.64 (1H, dddd, *J* = 17.1, 10.2, 7.8, 4.9 Hz), 5.27-5.10 (6H, m), 4.55 (1H, ddt, *J* = 15.2, 5.0, 1.4 Hz), 4.37 (1H, ddt, *J* = 14.6, 5.8, 1.4 Hz), 4.32 (1H, ddt, *J* = 14.6, 5.8, 1.4 Hz), 3.73 (1H, dd, *J* = 9.6, 3.5 Hz), 3.70-3.68 (1H, m), 3.52 (1H, dd, *J* = 15.2, 7.4 Hz), 3.17-3.13 (1H, m), 2.73 (1H, dm, *J* = 7.1 Hz), 2.39 (1H, ddd, *J* = 12.6, 3.4, 2.1 Hz), 2.30-2.22 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (0), 168.1 (0), 162.9 (0), 132.8 (1), 132.0 (1), 131.4 (1), 120.0 (2), 119.0 (2), 118.2 (2), 58.6 (1), 48.2 (1), 47.8 (2), 42.0 (2), 39.8 (1), 36.7 (2), 19.7 (2) ppm; MS (ES) *m/z* 288 M^+; HRMS (ES) m/z 288.1471 (calcd. for $C_{16}H_{20}N_2O_3$: 288.1474).

(±)-(1*R,4*R**,5*R**,8*S**)-2,6-Dioxo-4-hydroxy-3,7,8-triallyl-3,7-diazabicyclo[3.3.1]nonane (9):** A stirred solution of imide (**8**, 69 mg, 0.240 mmol) in anhydrous CH_2Cl_2 (2 mL) at –78 °C under N_2, was treated dropwise with lithium triethylborohydride (0.29 mL, 1.0 M in THF, 0.29 mmol) during 2 min. The resulting mixture was stirred for 1 h at –78 °C and then quenched with sat. aq. potassium sodium tartrate (5 mL) and warmed to rt. H_2O (10 mL) and EtOAc (10 mL) were added and the layers well shaken and separated. The aqueous layer was extracted with EtOAc (2x5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 5% MeOH in CH_2Cl_2) to yield hemiaminal (**9**, 42 mg, 0.145 mmol, 60%, single α-anomer) as a colorless oil: IR (neat) 3389, 3080, 2926, 1622, 1452, 1356, 1280, 1179, 1072, 985, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84-5.58 (3H, m), 5.20-5.12 (5H, m), 5.09 (1H, dq, *J* = 11.7, 1.3 Hz), 5.01 (1H, dd, *J* = 10.0, 4.4 Hz), 4.84 (1H, d, *J* = 10.0 Hz), 4.40 (1H, ddt, *J* = 15.4, 4.8, 1.7 Hz), 4.22 (1H, ddt, *J* = 14.8, 5.0, 1.4 Hz), 4.01 (1H, ddm, *J* = 14.8, 7.1 Hz), 3.69-3.59 (2H, m), 2.99-2.93 (1H, m), 2.82 (1H, dq, *J* = 4.3, 2.1 Hz), 2.66 (1H, dddt, *J* = 14.6, 5.6, 4.1, 1.5 Hz), 2.32-2.19 (2H, m), 1.87 (1H, ddm, *J* = 13.8, 4.4 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (0), 168.7 (0) 133.2 (1), 133.1 (1), 131.7 (1), 119.4 (2), 118.3 (2), 117.7 (2), 81.1 (1), 58.6 (1), 48.0 (2), 43.8 (2), 41.4 (1), 39.7 (1), 36.5 (2), 19.0 (2) ppm; MS (ES) *m/z* 313 $(M+Na)^+$; HRMS (ES) *m/z* 313.1518 (calcd. for $C_{16}H_{22}N_2O_3Na$: 313.1523).

(±)-(1*R,4*S**,5*R**,8*S**)-2,6-Dioxo-3,4,7,8-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (6):** A stirred solution of hemiaminal (**9**, 68 mg, 0.234 mmol) in anhydrous CH_2Cl_2 (1 mL) at rt under N_2, was treated sequentially in dropwise fashion with allyltrimethylsilane (0.36 mL, d = 0.72, 259 mg, 2.27 mmol) followed by freshly distilled boron trifluoride diethyl etherate (0.15 mL, d = 1.13, 170 mg, 1.20 mmol). The resulting mixture was stirred at rt for 24 h. After this time, CH_2Cl_2 (20 mL) was added and the mixture washed with H_2O (2x5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 1% MeOH in CH_2Cl_2) to yield tetraene (**6**, 56 mg, 0.178 mmol, 76%) as a colorless solid: mp 97-99 °C (hexanes); IR (KBr) 2976, 1634, 1455, 1416, 1355, 1279, 1242, 1191, 1138, 1114, 1077, 1053, 998, 978, 956, 926, 842, 736, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80-5.64 (4H, m), 5.19-5.11 (8H, m), 4.43 (2H, dd, *J* = 15.2, 5.1 Hz), 3.67 (2H, dd, *J* = 10.4, 3.6 Hz),

3.54 (2H, dd, *J* = 15.1, 7.1 Hz), 2.78 (2H, t, *J* = 3.0 Hz), 2.64 (2H, dddt, *J* = 14.5, 5.3, 3.9, 1.4 Hz), 2.22 (2H, dt, *J* = 14.4, 9.4 Hz) 2.08 (2H, t, *J* = 3.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (2C, 0), 133.6 (2C, 1), 132.6 (2C, 1), 119.0 (2C, 2), 118.2 (2C, 2), 59.8 (2C, 1), 47.7 (2C, 2), 39.3 (2C, 1), 36.4 (2C, 2), 16.4 (2) ppm; MS (ES) *m/z* 315 $(M+H)^+$; HRMS (ES) *m/z* 315.2061 (calcd. for $C_{19}H_{27}N_2O_2$: 315.2067).

(±)-Δ^{3,13}-Didehydro-10,17-dioxo-β-isosparteine (11): A stirred solution of tetraene (**6**, 41 mg, 0.131 mmol) in CH_2Cl_2 (1.5 mL) at rt under N_2, was treated with Grubbs' 1st generation catalyst (**10**, 11 mg, 0.013 mmol)[14] in one portion. The resulting mixture was heated to a gentle reflux for 16 h, cooled to rt, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 1% MeOH in CH_2Cl_2) to yield tetracycle (**11**, 30 mg, 0.12 mmol, 90%) as a colorless solid: mp 195-197 °C (hexanes-EtOAc); IR (KBr) 2915, 1636, 1455, 1356, 1250, 1147, 959, 674, 661 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84-5.78 (2H, m), 5.72-5.67 (2H, m), 4.82 (2H, bd, *J* = 18.4 Hz), 3.84 (2H, dd, *J* = 11.4, 3.6 Hz), 3.46 (2H, bd, *J* = 18.4 Hz), 2.70 (2H, t, *J* = 2.7 Hz), 2.40 (2H, bt, *J* = 14.4 Hz), 2.18 (2H, bd, *J* = 16.8 Hz), 2.13 (2H, t, *J* = 2.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (2C, 0), 124.6 (2C, 1), 124.3 (2C, 1), 56.2 (2C, 1), 42.8 (2C, 2), 41.5 (2C, 1), 31.6 (2C, 2), 17.4 (2) ppm; MS (ES) *m/z* 281 $(M+Na)^+$; HRMS (ES) *m/z* 281.1249 (calcd. for $C_{15}H_{18}N_2O_2Na$: 281.1260).

(±)-10,17-Dioxo-β-isosparteine (12): A suspension of diene (**11**, 20 mg, 0.078 mmol) and 10 wt.% Pd/C (2 mg) in MeOH-H_2O (2:1, 1.5 mL) was stirred vigorously under an atmosphere of H_2 gas for 7 h. After this time, the active gas was purged with inert gas (N_2) and the reaction mixture filtered through a celite pad. The pad was washed with CH_2Cl_2 (2x20 mL) and the filtrate and combined washings concentrated *in vacuo* to yield (±)-10,17-dioxo-*β*-isosparteine (**12**, 19 mg, 0.073 mmol, 94%) as a colorless solid: mp 172-174 °C (hexanes-Et_2O); IR (KBr) 2928, 2851, 1627, 1459, 1436, 1358, 1269, 1236, 1201, 1143, 1055, 1011, 898, 856, 755, 572, 562 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (2H, dm, *J* = 12.9 Hz), 3.52 (2H, dm, *J* = 11.3 Hz), 2.58 (2H, t, *J* = 2.9 Hz), 2.45 (2H, td, *J* = 12.8, 2.5 Hz), 2.10 (2H, t, *J* = 3.0 Hz), 1.97-1.92 (2H, m), 1.75-1.52 (8H, m), 1.48-1.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (2C, 0), 60.6 (2C, 1), 43.6 (2C, 2), 42.7 (2C, 1), 32.3 (2C, 2), 25.4 (2C, 2), 25.0 (2C, 2), 18.9 (2) ppm; MS (ES) *m/z* 263 $(M+H)^+$; HRMS (ES) *m/z* 263.1746 (calcd. for $C_{15}H_{23}N_2O_2$: 263.1754).

(±)-β-Isosparteine (3): Protocol taken from O'Brien's synthesis of (–)-sparteine.[4e] A stirred solution of bislactam (**12**, 21 mg, 0.080 mmol) in anhydrous THF (0.5 mL) at 0 °C under N_2, was treated with excess lithium aluminum hydride (37 mg, 0.97 mmol) and the resulting suspension heated at reflux for 13 h. The mixture was then cooled, diluted with Et_2O (5 mL), and quenched by the careful addition of hydrated Na_2SO_4 (100 mg). After vigorous stirring for 30 min, the mixture was filtered through a celite pad and the residue washed well with 10% MeOH in CH_2Cl_2 (20 mL). The filtrate and combined washings were dried (Na_2SO_4) and concentrated *in vacuo* to afford essentially pure (±)-*β*-isosparteine (**3**, 17 mg, 0.073, 91%) as a colorless oil: IR (neat) 3420 (H_2O), 2926, 1643, 1443, 1298, 1221, 1129 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.01 (2H, dd, *J* = 10.8, 6.6 Hz), 2.79 (2H, dm, *J* = 12.6 Hz), 2.44 (2H, td, *J* = 12.7, 2.8 Hz), 2.25 (2H, dm, *J* = 11.7 Hz), 2.16 (2H, dd, *J* = 10.8, 3.0 Hz), 1.81-1.72 (2H, m), 1.70-1.48 (8H, m), 1.45-1.20 (6H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0 (2C, 1), 55.3 (2C, 2), 55.1 (2C, 2), 34.6 (2C, 1), 28.8 (2C, 2), 25.6 (2C, 2), 22.8 (2C, 2), 20.0 (2) ppm; MS (ES) *m/z* 235 $(M+H)^+$, 159; HRMS (ES) *m/z* 235.2164 (calcd. for $C_{15}H_{27}N_2$: 235.2169). ^{1}H and ^{13}C NMR data are in agreement with those reported by Wanner and Koomen.[8b] ^{13}C NMR data are also in agreement with those reported by Galasso *et al*.[16]

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6. By tetraoxobispidines, we refer to 2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonanes, a class of bicyclic compounds also commonly known as Guareschi imides. These bisimides embed the central sparteine BC-ring domain in a form amenable for the regio- and stereocontrolled annulation of rings A and D. For seminal studies relating to the synthesis of Guareschi imides, see: (a) J. Guthzeit, *J. prakt. Chem.*, 1902, **2**, 11. (b) I. Guareschi, *Gazz. Chim. Ital.*, 1919, **49**, 126. (c) G. A. R. Kon and J. F. Thorpe, *J. Chem. Soc.*, 1919, 686. (d) A. I. Vogel, *J. Chem. Soc.*, 1934, 1758.
7. (–)-*β*-Isosparteine, also known as *l*-spartalupine and pusilline, belongs to the same enantiomorphic series as (+)-sparteine. Pusilline was first isolated from *Lupinus pusillus* Pursh (a source of (+)-sparteine) by Marion and Fenton and its structure initially misassigned as a dihydrosparteine: (a) L. Marion and S. W. Fenton, *J. Org. Chem.*, 1948, **13**, 780. Carmack and co-workers subsequently isolated *l*-spartalupine from *Lupinus sericeus* Pursh and correctly assigned its structure: (b) M. Carmack, B. Douglas, E. W. Martin, and H. Suss, *J. Am. Chem. Soc.*, 1955, **77**, 4435. (c) M. Carmack, S. I. Goldberg, and E. W. Martin, *J. Org. Chem.*, 1967, **32**, 3045. The identity of pusilline and *l*-spartalupine was established by Greenhalgh and Marion: (d) R. Greenhalgh and L. Marion, *Can. J. Chem.*, 1956, **34**, 456. (+)-*β*-Isosparteine also occurs in a variety of *Lupinus* species, for example, see: (e) A. El-Shazly, A.-M. M. Ateya, and M. Wink, *J. Biosciences*, 2001, **56**, 21.
8. Carmack and co-workers were the first to report a nonstereoselective synthesis of (±)-*β*-isosparteine (ref. 7b). Winterfeld obtained a mixture of (+)-*β*-isosparteine and (–)-*α*-isosparteine by isomerization of (–)-sparteine with $AlCl_3$ under forcing conditions: (a) E. Winterfeld, H. Bange, and K. S. Lalvani, *Liebigs Ann. Chem.*, 1966, **698**, 230. Koomen and Wanner obtained a 1:1 mixture of (±)-sparteine and (±)-*β*-isosparteine from a nonstereoselective bioinspired route to the eponymous sparteine group alkaloid: (b) M. J. Wanner and G.-J. Koomen, *J. Org. Chem.*, 1996, **61**, 5581.
9. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, 1973, **95**, 1669.
10. Hemiaminal (**7**) was obtained in variable *α:β* anomeric ratios (from 5:1 ≤ *α:β* ≤ 1:3), with the *β*-anomer (*exo* hydroxyl group) usually predominating. The isomers could be separated by careful column chromatography and were identified by ^{1}H NMR analysis of the anomeric proton signal, as follows: **7*α*** δ_H (anomeric) = 5.24 (1H, d, *J* = 5.7 Hz) ppm; **7*β*** δ_H (anomeric) = 5.22 (1H, bs) ppm.
11. For Sakurai-type allylation of acyl iminium ions, see: (a) P.-Q. Huang, B.-G. Wei, and Y.-P. Ruan, *Synlett*, 2003, 1663. (b) D. J. Adams, A. J. Blake, P. A. Cooke, C. D. Gill, and N. S. Simpkins, *Tetrahedron*, 2002, **58**, 4603. (c) H. Suzuki, S. Aoyagi, and C. Kibayashi, *J. Org. Chem.*, 1995, **60**, 6114. (d) R. P. Polniaszek, S. E. Belmont, and R. Alvarez, *J. Org. Chem.*, 1990, **55**, 215.
12. Harrison and O'Brien have observed that related bispidine derived acyl iminium ions experience nucleophilic attack exclusively from their open *exo* faces, see: J. R. Harrison and P. O'Brien,

Tetrahedron Lett., 2000, **41**, 6167.

13. Inspection of molecular models reveals that the dihedral angle between vicinal bridgehead and CHN methine protons within the conformationally rigid core of **6** is almost exactly 90°; *J*-coupling between these protons would therefore be expected to be of low magnitude (or absent altogether) in accordance with the Karplus relation.
14. R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413.
15. Interestingly, 10,17-dioxo-β-isosparteine is itself a naturally occurring member of the sparteine family and was first isolated from *Lupinus sericeus* Pursh, see: (a) I.-C. Kim, M. F. Balandrin, and A. D. Kinghorn, *J. Agric. Food. Chem.*, 1982, **30**, 796. (b) M. Wink, C. Meissner, and L. Witte, *Phytochem.*, 1995, **38**, 139.
16. For precise ^{13}C NMR data for (–)-**3** and a detailed analysis of its interesting conformational mobility, see: V. Galasso, F. Asaro, F. Berti, B. Kovac, I. Habus, and A. Sacchetti, *Chem. Phys.*, 2003, **294**, 155.