Stereoselective Syntheses of α-Isosparteine

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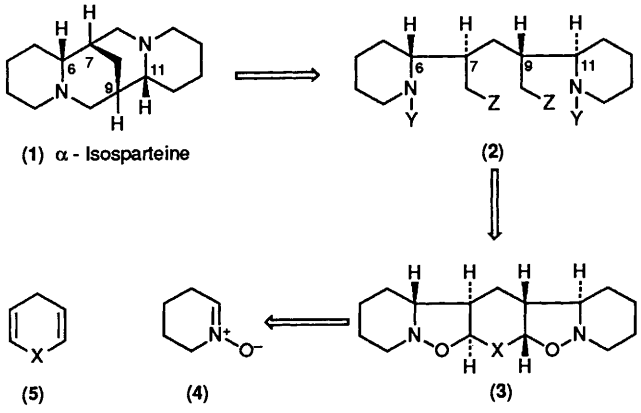
Stereoselective syntheses of α-isosparteine were accomplished by means of 1,3-dipolar cycloadditions. The cycloaddition of nitrone (**4**) to cyclopentadiene proceeded stereoselectively to afford 2:1-adduct (**7a**), which in turn led to the construction of the tetracyclic quinolizidine framework. The synthesis using 4*H*-pyran as a dipolarophile was more convenient, for the cycloaddition proceeded with high regio- and stereo-selectively to afford 2:1-adduct (**16a**), which was converted into α-isosparteine by catalytic hydrogenation in high yield.

Quinolizidine alkaloids are distributed in various plant families, mainly the Compositae and Leguminosae, and show a wide range of physiological activity.[1] Of these alkaloids, α-isosparteine (**1**) was found to be a basic component in members of the Leguminosae family[2] and was demonstrated to decrease the concentration of cholesterol in the blood.[3]

A notable structural feature of α-isosparteine is the presence of a symmetrical tetracyclic quinolizidine skeleton having four chiral carbon atoms, in which two hydrogen atoms at the bridgeheads are in an α configuration and the others are β as shown in Scheme 1.

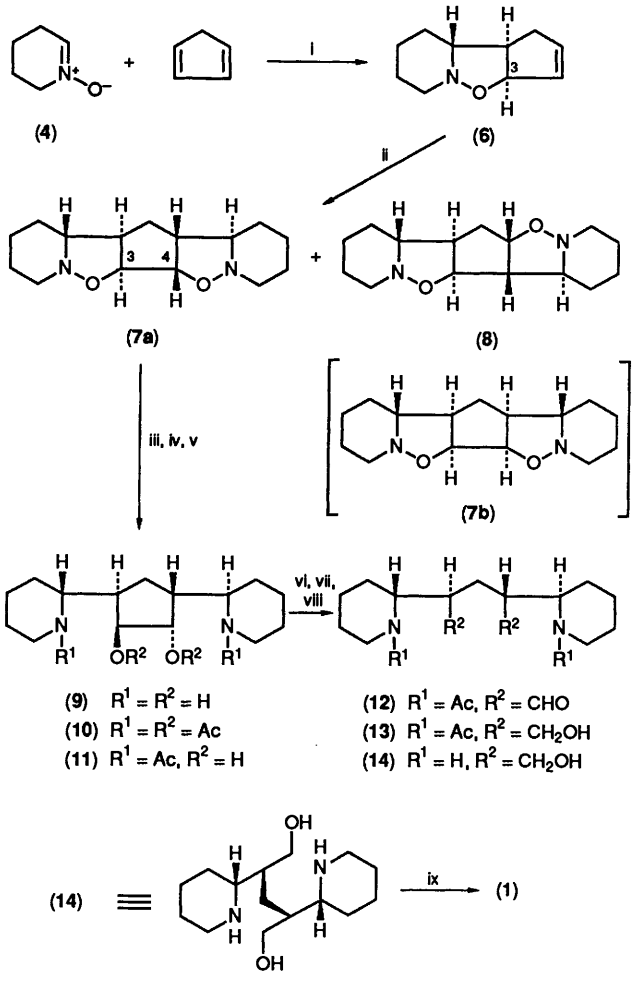


Scheme 1.

Total syntheses of α-isosparteine (**1**) have been reported by several groups,[4] but all of these syntheses were non-stereoselective. In our synthetic studies on quinolizidine alkaloids,[5] we have succeeded in a stereoselective synthesis of α-isosparteine by using a 1,3-dipolar cycloaddition reaction as a key step.[6] Our initial strategy for the synthesis of compound (**1**) was based on the retrosynthetic analysis outlined in Scheme 1. We envisaged formation of compound (**1**) *via* stereospecific intramolecular cyclization of diamine (**2**). The four chiral centres at C-6, -7, -9, and -11 of compound (**2**) would be introduced by the regio- and stereo-selective cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide (**4**)[7] to an appropriate cyclic C_5 unit (**5**), and this would be followed by reductive cleavage of N–O bonds of the 2:1-adduct (**3**) thus formed.

Synthesis using Cyclopentadiene as a Dienophile—In our first synthetic approach, cyclopentadiene[8] was chosen as a dipolarophile for the 1,3-dipolar cycloaddition. The reaction of nitrone (**4**) with cyclopentadiene occurred in benzene solution at room temperature to afford a single 1:1-adduct (**6**) in 65% yield (Scheme 2). The ^{1}H NMR spectrum showed signals for the angular proton (3-H) of compound (**6**) at room temperature as two doublets at δ_H 4.82 and 5.21 which were both assignable to this proton. However, both peaks coalesced to one doublet at δ_H 5.14 (J 8.0 Hz) when the spectrum was taken at 100 °C. This change can be explained by a rate difference in the comformational isomerization of the adduct (**6**) based on pyramidal inversion at the nitrogen atom (Figure 1). The stereochemistry of compound (**6**) was inferred by considering the stability of the transition state; the *exo* transition state should be much more stabilized by the steric repulsion than is the *endo* one.

The second 1,3-dipolar reaction of the nitrone (**4**), with the adduct (**6**), was rather slow, but proceeded by refluxing toluene solution for 3 h to give a mixture of the desired adduct (**7a**) and its regioisomer (**8**) in 1:3 ratio. The structure of the major isomer (**8**) was unequivocally determined; the ^{1}H NMR spectrum of compound (**8**) showed proton signals of the H–C–O groups at different fields at δ_H 4.40 (d) and 4.77 (dt), indicating the non-symmetric structure of the adduct. In the ^{1}H NMR spectrum of compound (**7a**), the signals due to the protons 3-H and 4-H appear as a sharp doublet (δ_H 4.53), indicating that this molecule has a symmetric structure. The stereochemistry of the adduct (**7a**) was assumed to be *exo,trans,exo* (**7a**) rather than *exo,cis,exo* (**7b**) from the reaction mechanism because of a disfavoured steric interaction of the isoxazolidine ring in the transition state for the formation of the isomeric adduct (**7b**). The full stereochemical structure of compound (**7a**) was confirmed unambiguously by its conversion into α-isosparteine (**1**). The reductive cleavage of two N–O bonds of adduct (**7a**) was carried out with palladium(II) hydroxide under hydrogen to give diamino diol (**9**) quantitatively. Attempted glycol-bond scission of compound (**9**) by periodate oxidation was unsuccessful, indicating the *trans* diaxial orientation of the two hydroxy groups at C-3 and C-4.[9] Thus diamino diol (**9**) was converted into *N,N'*-diacetyl diol (**11**) by acetylation with acetic anhydride followed by hydrolysis with methanolic sodium hydroxide. The *trans* glycol bond of compound (**11**) was cleaved with lead tetra-acetate (LTA) to give *N*-acetyl dialdehyde (**12**). Dialdehyde (**12**) was further converted into diamino diol (**14**) in the following manner [37% from (**11**)]; the crude dialdehyde (**12**) was reduced with sodium borohydride and the resulting alcohol (**13**) was hydrolysed by methanolic sodium hydroxide to give compound (**14**). The cyclization reaction which finally led to α-isosparteine (**1**) was accomplished by treatment of diamino diol (**14**) with triphenylphosphine, carbon tetrachloride, and triethylamine in 37% isolated yield. The spectral data of this synthetic product completely coincided with those of an authentic sample.[10]



Scheme 2. *Reagents and conditions:* i, benzene, room temp., 15 h; ii, (**4**), toluene, 110 °C, 3 h; iii, H_2 (3 atm), $Pd(OH)_2$, room temp., 20 h; iv, Ac_2O–pyridine, room temp., 22 h; v, methanolic 1M-NaOH, room temp., 20 min; vi, $Pd(OAc)_4$, pyridine, room temp., 5 h; vii, $NaBH_4$, EtOH, room temp., 15 h; viii, methanolic 2M-NaOH, room temp., 30 h; ix, triphenylphosphine, CCl_4, Et_3N, MeCN, room temp., 15 h. Non-systematic numbering is shown.

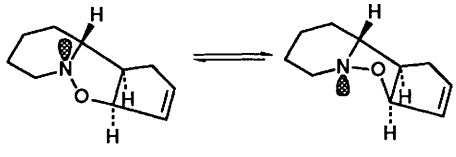
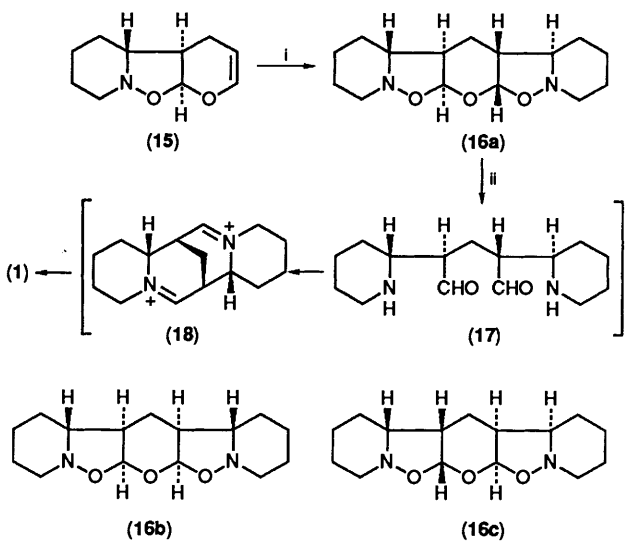


Figure 1. Conformational isomerization of adduct (**6**).

Synthesis using 4H-*Pyran as a Dienophile.*—In our first synthetic approach, the results of the second 1,3-dipolar cycloaddition for the preparation of 2:1-adduct (**7a**) were not satisfactory, because undesired regioisomer (**8**) was produced as a major product. This can be explained by an allylic effect caused by the oxygen atom adjacent to the C-3 carbon of intermediate (**6**).* To preclude this disadvantage, 4*H*-pyran[11] was used as a dipolarophile for synthesis of α-isosparteine (**1**).



Scheme 3. *Reagents and conditions:* i, (**4**), 190 °C, benzene, 10 h; ii, $Pd(OH)_2$, H_2 (3 atm), 15 h.

The 1,3-dipolar cycloaddition of the nitrone (**4**) to 4*H*-pyran at 140 °C gave a 1:1-adduct (**15**) with high regio- and stereoselectivity in 70% yield (Scheme 3).† Further reaction of the adduct (**15**) with nitrone (**4**) at 190 °C gave the desired 2:1-adduct (**16a**). The ^1H NMR spectrum of the 2:1-adduct (**16a**) showed only one doublet (for an acetal proton), at δ_H 5.50, which was sufficiently downfield to indicate that the oxygen atoms of two molecules of nitrone (**4**) were bound to the α- and α′-position of the 4*H*-pyran.

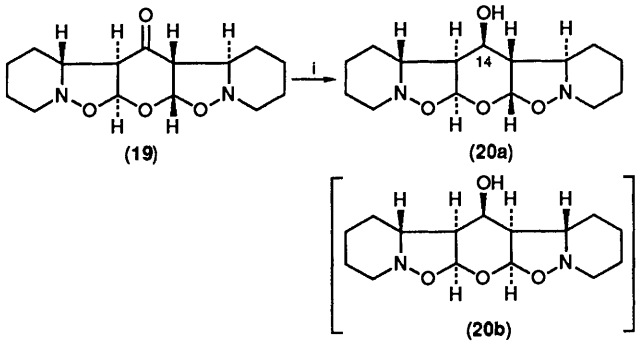
The stereochemistry of the 2:1-adduct was assumed to be *exo,trans,exo* [as in structure (**16a**)] or *exo,cis,exo* [as in structure (**16b**)] from reaction pathways. The 1,3-dipolar additions of unconjugated nitrones to enol ethers give exclusively the *exo* addition product [*i.e.*, (**16a**) or (**16b**)] rather than the *endo*-product [*i.e.*, (**16c**)] owing to steric hindrance in the transition state of the *endo* mode of addition.

The *exo,cis,exo*-structure (**16b**) was excluded by a control reaction (Scheme 4). Addition of the nitrone (**4**) to γ-pyrone proceeded regio- and stereo-selectively to give a 2:1-adduct (**19**) in 65% yield, and the stereochemistry of which was tentatively assigned as structure (**19**) arising from consecutive *exo* additions. Reduction of the carbonyl group of compound (**19**) with sodium borohydride proceeded stereospecifically to afford a single alcohol (**20a**) in quantitative yield. If the alcohol product had *exo,cis,exo*-stereochemistry as in structure (**20b**), the ^1H NMR signal of the proton at C-14 should appear as a triplet owing to coupling with the two equivalent angular protons. Instead of that, however, compound (**20a**) showed a double doublet (*J* 5.5 and 7.5 Hz) at δ_H 4.10. This indicated that the adduct from γ-pyrone has the *exo,trans,exo*-stereochemistry as in structure (**19**), and that hydride attack on the carbonyl group of compound (**19**) from either the α- or the β-side resulted in the formation of the alcohol (**20a**). These facts‡ strongly suggested that the adduct from 4*H*-pyran has *exo,trans,exo*-stereochemistry [*i.e.*, (**16a**)].

* In-house data. The regioselectivity in 1,3-dipolar cycloadditions of various nitrones was significantly affected by the presence of a heteroatom, such as oxygen and silicon, at the allylic position of the dipolarophile. Details of this study will be described in forthcoming publications.

† The yield was based on consumed 4*H*-pyran; a considerable amount (70%) of unchanged 4*H*-pyran was recovered. The nitrone (**4**) decomposed at the reaction temperature to give δ-valerolactam and a nitrone dimer. No other cycloaddition product of 4*H*-pyran with the nitrone (**4**) was detected in the reaction mixture.

‡ Attempts to convert compounds (**19**) and (**20a**) into the 4*H*-pyran adduct (**16a**) were unsuccessful.



Scheme 4. *Reagents and conditions:* i, NaBH4, MeOH, room temp., 2 h. Non-systematic numbering is shown.

Catalytic hydrogenation of a methanolic solution of the adduct (**16a**) in the presence of palladium(II) hydroxide directly gave a tetracyclic product (**1**),† the spectral properties (IR, mass, and ^{13}C NMR) of which agreed with those of authentic α-isosparteine[10] and the synthetic product previously obtained using cyclopentadiene. Hydrogenation was considered to proceed through consecutive steps; the reductive cleavage of N–O bonds of compound (**16a**) to give diamino dialdehyde (**17**), cyclization to an iminium salt (**18**), and hydrogenation of the iminium bonds as shown in Scheme 3.

Experimental

Analytical TLC was performed using E. Merck silica gel 60F-254 plates and aluminium oxide 60F-254 plates. Column chromatography was performed on Wakogel C-60 (70–230 mesh) and E. Merck aluminium oxide 90 (activity II–III). Flash chromatography was performed on Wakogel C-300 (silica gel). M.p.s were determined on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 215 grating spectrophotometer. ^1H NMR spectra were measured on the following spectrometers with tetramethylsilane as internal standard: JEOL-JNM-PMX60si (60 MHz), JEOL-JNM-FX90Q (90 MHz), and JEOL-MH-100 (100 MHz). ^{13}C NMR spectra were obtained on a JEOL-JXNM-FX90Q (22.5 MHz) spectrometer. Mass spectra were measured on a Hitachi-RMU-6M mass spectrometer. GLC data were obtained on a Hitachi 063 gas chromatograph. Elemental analyses were performed at the Chemical Analysis Center in the University of Tsukuba.

(1R*,2R*,6R*)-7-*oxa*-8-*azatricyclo*[6.4.0.0^{2,6}]*undec*-4-*ene* (**6**).—2,3,4,5-Tetrahydropyridine 1-oxide (**4**)[7] prepared from 1-hydroxypiperidine was used immediately without further purification. Cyclopentadiene[8] was prepared by pyrolysis of dicyclopentadiene and was purified before use. A solution of crude nitrone (**4**) (11.45 g, 116 mmol) and cyclopentadiene (7.65 g, 116 mmol) in dry benzene (30 ml) was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure to give an oil (17.65 g), which was purified by flash chromatography (eluted with ethyl acetate–hexane, 1:1) to afford *adduct* (**6**) (10.02 g, 65%) as an oil; b.p. 70–75 °C at 3 mmHg (Kugelrohr); $\nu_{max}(CHCl_3)$ 2 940, 2 855, 1 615, 1 440, 1 360, and 985 cm^{-1}; δ_H[100 MHz; $(CD_3)_2SO$; room temperature] 1.0–2.1 (6 H, m), 2.1–3.4 (6 H, m), 4.82 and 5.21 (total 1 H, each d, *J* 8.0 Hz), and 5.72 (2 H, m); δ_H [100 MHz; $(CD_3)_2SO$; 100 °C] 1.0–2.1 (6 H, m), 2.0–3.3 (6 H, m), 5.12 (1 H, d, *J* 8.0 Hz), and 5.86 (2 H, m); *m/z* 165 (M^+), 148, 100 (base), 99, 69, 66, and 65 (Found: C, 72.35; H, 9.2; N, 8.5. $C_{10}H_{15}NO$ requires C, 72.68; H, 9.15; N, 8.47%).

(1S*,2S*,9R*,10R*,12R*,13R*)-3,19-*Dioxa*-4,18-*diaza-pentacyclo*[10.7.0.0^{2,10}.0^{4,9}.0^{13,18}]*nonadecane* (**7a**) *and* (1S*,2S*,3R*,10S*,12R*,13R*)-9,19-*Dioxo*-8,18-*diazapenta-cyclo*[10.7.0.0^{2,10}.0^{3,18}.0^{13,18}]*nonadecane* (**8**).—A solution of nitrone (**4**) (11.23 g, 113 mmol) and adduct (**6**) (10.89 g, 66 mmol) in dry toluene (80 ml) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residual oil was purified by flash chromatography (eluted with $CHCl_3$–MeOH, 97:3) to give a mixture (10.66 g, 61%) of 2:1-adducts (**7a**) and (**8**) (1:3 ratio, respectively; determined by GLC). A portion of this mixture (2.24 g) was separated on a Lober prepacked column (Kieselgel 60; eluted with $CHCl_3$–MeOH, 97:3) to give *compound* (**8**) (1.16 g) as a pale yellow oil; b.p. 145 °C at 3 mmHg (Kugelrohr); $\nu_{max}(CHCl_3)$ 2 940, 2 850, 1 440, 1 010, 985, and 905 cm^{-1}; δ_H[100 MHz; $(CD_3)_2SO$; 50 °C] 1.0–2.1 (14 H, m), 2.1–3.4 (8 H, m), 4.40 (1 H, d, *J* 8.0 Hz), and 4.77 (1 H, br); δ_H[100 MHz; $(CD_3)_2SO$; 90 °C] 1.0–2.1 (14 H, m), 2.1–3.4 (8 H, m), 4.40 (1 H, d, *J* 8.0 Hz), and 4.77 (1 H, td, *J* 8.0 and 4.5 Hz) (Found: C, 67.7; H, 9.25; N, 10.6. $C_{15}H_{24}N_2O_2$ requires C, 68.14; H, 9.15; N, 10.59%).

Further elution gave the isomer (**7a**) (0.96 g) as white crystals; m.p. 119–120 °C (from hexane); $\nu_{max}(CHCl_3)$ 2 940, 2 850, 1 440, and 990 cm^{-1}; δ_H(100 MHz; $CDCl_3$) 1.1–2.1 (12 H, m), 1.85 (2 H, t, *J* 7.0 Hz), 2.1–3.4 (8 H, m), and 4.49 (2 H, d, *J* 7.0 Hz); *m/z* 264 (M^+), 165, 100 (base), and 83 (Found: C, 68.0; H, 9.2; N, 10.5%).

(1S*,2S*,3R*,5R*)-3,5-*Bis*[(R*)-2-*piperidyl*]*cyclopentane*-1,2-*diol* (**9**).—A vigorously stirred solution of 2:1-adduct (**7a**) (503 mg, 1.88 mmol) in methanol (30 ml) was hydrogenated under H_2 (3 atm) at room temperature for 20 h in the presence of palladium(II) hydroxide (470 mg). The catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford diamino diol (**9**) (505 mg, 100%) as white crystals; m.p. 172–176 °C (from EtOH); $\nu_{max}(CHCl_3)$ 3 630, 3 600–3 000, 2 940, 2 860, 1 580, 1 420, and 1 010 cm^{-1}; δ_H(60 MHz; CD_3OD) 1.2–2.4 (16 H, m), 2.3–3.2 (6 H, m), 3.97 (2 H, dd, *J* 8.0 and 4.5 Hz), and 4.69 (4 H, s, D_2O exchange); *m/z* 268 (M^+), 185, 166, and 84 (base).

(1S*,2S*,3R*,5R*)-3,5-*Bis*[(R*)-1-*acetyl*-2-*piperidyl*]*cyclo-pentane*-1,2-*acyl Diacetate* (**10**).—A solution of diamino diol (**9**) (497 mg, 1.85 mmol) and acetic anhydride (4 ml) in pyridine (4 ml) was stirred at 50 °C for 7 h. The reaction mixture was concentrated under reduced pressure and the residual oil was purified by flash chromatography (eluted with CH_2Cl_2–MeOH, 96:4) to afford the *tetra-acetate* (**10**) (769 mg, 95%) as white crystals; m.p. 113–115 °C (from EtOH); $\nu_{max}(CHCl_3)$ 2 920, 1 725, 1 610, 1 420, 1 350, and 970 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.2–1.9 (12 H, m), 1.97 (6 H, s), 2.06 (6 H, s), 2.4–3.8 (8 H, m), 4.6–4.9 (2 H, m), and 4.92 (2 H, d, *J* 4.0 Hz); *m/z* 436 (M^+), 393, 317, 273, 206, 192, 191, 116 (base), and 84 (Found: C, 62.85; H, 8.4; N, 6.3. $C_{23}H_{36}N_2O_6$ requires C, 63.28; H, 8.31; N, 6.41%).

(1S*,2S*,3R*,5R*)-3,5-*Bis*[(R*)1-*acetyl*-2-*piperidyl*]*cyclo-pentane*-1,2-*diol* (**11**).—A solution of tetra-acetate (**10**) (696 mg, 1.60 mmol) in 1M-methanolic sodium hydroxide (12 ml) was stirred at room temperature for 20 min. The mixture was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to afford the N-*acetyl diol* (**11**) (490 mg, 87%) as white crystals; m.p. 169–170 °C (from Et_2O); $\nu_{max}(CHCl_3)$ 3 650, 3 500–3 100, 2 940, 1 600, 1 440, 1 350, 1 080, 1 030, and 990 cm^{-1}; δ_H(60 MHz; $CDCl_3$)

† The same reaction of the adduct (**16a**) in acidic solution afforded a mixture of α-isosparteine (**1**) and sparteine.

1.2–1.9 (12 H, m), 2.10 (6 H, s), 2.5–3.8 (8 H, m), 3.67 (2 H, d, *J* 4.0 Hz), and 4.5 (2 H, m) (Found: C, 64.65; H, 9.2; N, 7.85. $C_{19}H_{32}N_2O_4$ requires C, 64.74; H, 9.15; N, 7.94%).

(2R*,4R*)-2,4-*Bis*[(R*)-1-*acetyl*-2-*piperidyl*]*pentane*-1,5-*dial* (**12**).—To a solution of *N*-acetyl diol (**11**) in pyridine (5 ml) was added LTA (3.1 g, 7.0 mmol). The mixture was stirred at room temperature for 5 h and then treated with a few drops of water. The precipitate was filtered off, and the filtrate was diluted with ethyl acetate. The solution was washed successively with water and brine, and the organic layer was dried ($MgSO_4$). The solution was concentrated under reduced pressure to afford crude dialdehyde (**12**) (706 mg), which was used for the next reaction without further purification; δ_H(60 MHz; $CDCl_3$) 1.2–2.3 (12 H, m), 2.05 (6 H, s), 2.3–3.9 (8 H, m), 4.85 (2 H, m), and 9.33 (2 H, d, *J* 4.0 Hz).

(2R*,4R*)-2,4-*Bis*[(R*)-1-*acetyl*-2-*piperidyl*]*pentane*-1,5-*diol* (**13**).—A solution of crude dialdehyde (**12**) (700 mg) in ethanol (10 ml) was added slowly to a solution of sodium borohydride (3.0 g, 79 mmol) in ethanol (70 ml). After 15 h at room temperature, the mixture was diluted with ethyl acetate, and washed successively with water and brine. The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to afford crude *N*-acetyl diol (**13**) as an oil (389 mg); ν_{max}($CHCl_3$) 3 600–3 100, 2 945, 1 605, 1 440, and 995 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.2–2.3 (12 H, m), 2.10 (6 H, s), 2.5–3.8 (8 H, m), 3.33 (4 H, br s), and 4.40 (2 H, m).

(2R*,4R*)-2,4-*Bis*[(R*)-2-*piperidyl*]*pentane*-1,5-*diol* (**14**).—A solution of *N*-acetyl diol (**13**) (388 mg) in 2M-methanolic sodium hydroxide (10 ml) was stirred at room temperature for 30 h. The mixture was diluted with dichloromethane and washed successively with water and brine. The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil, which was purified by chromatography (aluminium oxide; eluted with CH_2Cl_2–MeOH–NH_4OH, 90:9:1) to give *diamino diol* (**14**) [129 mg, 37% from (**11**)] as white crystals; m.p. 102–104 °C (from Et_2O–CCl_4); ν_{max}($CHCl_3$) 3 650, 3 500–2 800, 2 930, 1 620, 1 440, 1 325, 1 265, 1 140, 1 090, 1 050, 970, 945, and 855 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 0.9–2.2 (16 H, m), 2.2–3.2 (6 H, m), 3.65 (4 H, m), and 3.50 (4 H, br s, D_2O exchange); *m*/*z* 270 (M^+), 186 and 84 (base) (Found: C, 66.15; H, 11.0; N, 10.1. $C_{15}H_{30}N_2O_2$ requires C, 66.62; H, 11.18; N, 10.35%).

(±)-α-*Isosparteine* (**1**).—To a solution of triphenylphosphine (76 mg, 0.29 mmol), carbon tetrachloride (45 mg, 0.20 mmol), and triethylamine (29 mg, 0.29 mmol) in acetonitrile (1 ml) was added the diamino diol (**14**) (20 mg, 0.07 mmol). The mixture was stirred at room temperature for 15 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure to afford an oil, which was purified by preparative TLC (PLC) (aluminium oxide; developed with CH_2Cl_2–MeOH–NH_4OH, 95:5:0.5) to give α-isosparteine (**1**) as white crystals; m.p. 76–79 °C (lit.,[10] 78–80 °C); ν_{max}($CHCl_3$) 2 935, 2 860, 2 810, 2 765, 2 675, 2 590, 1 630, 1 465, 1 440, 1 380, 1 290, 1 270, 1 180, 1 160, 1 130, 1 100, 1 070, 1 050, 960, and 890 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.1–2.2 (16 H, m), 2.2–2.6 (2 H, m), 2.6–3.2 (4 H, m), and 3.2–3.65 (4 H, m); δ_C($CDCl_3$) 23.2 (2 × CH_2), 24.5 (2 × CH_2), 29.0 (2 × CH_2), 33.1 (2 × CH), 33.5 (2 × CH_2), 56.5 (2 × CH_2), 56.6 (2 × CH_2), and 66.5 (2 × CH); *m*/*z* 234 (M^+), 194, 157, 137, 136, 111, 97 (base), and 84.

(1R*,2R*,7S*)-6,8-*Dioxa*-9-*azatricyclo*[7.4.0.0^{2,7}]*tridec*-4-*ene* (**15**).—A solution of nitrone (**4**) (9.90 g, 100 mmol) and 4*H*-pyran[11] (4.10 g, 50.0 mmol) in dry benzene (10 ml) was put into a glass tube under argon, and the tube was sealed and heated at 140 °C for 10 h. The reaction mixture was concentrated under reduced pressure to afford an oil. An excess 4*H*-pyran (2.87 g, 70%) was recovered from the distilled solvent. The oil was purified by flash chromatography to give adduct (**15**) (1.71 g, 70% yield based on consumed 4*H*-pyran); δ_H(60 MHz; $CDCl_3$) 1.0–3.8 (9 H, m), 4.8 (3 H, m), 5.40 (2 H, s), and 6.15 (1 H, d, *J* 6.0 Hz).

(1R*,3R*,4R*,11S*,13S*,20R*)-10,12,14-*Trioxa*-9,15-*diaza*-*pentacyclo*[11.7.0.0^{3,11}.0^{4,9}.0^{15,20}]*eicosane* (**16a**).—A solution of adduct (**15**) (100 mg, 0.52 mmol) and nitrone (**4**) (109 mg, 1.10 mmol) in dry benzene (2 ml) was put into a glass tube under argon, and the tube was sealed and heated at 190 °C for 10 h. The reaction mixture was concentrated under reduced pressure to afford an oil, which was purified by flash chromatography to give 2:1-adduct (**16a**) (32 mg, 22%); *m*/*z* 280 (M^+); δ_H(60 MHz; $CDCl_3$; room temperature) 0.7–2.7 (16 H, m), 2.8–3.5 (6 H, m), and 5.50 (2 H, m); δ_H(60 MHz; $CDCl_3$; 60 °C) 0.7–2.7 (16 H, m), 2.8–3.5 (6 H, m), and 5.50 (2 H, d, *J* 6.0 Hz).

Preparation of (±)-α-*Isosparteine* (**1**) *by Hydrogenolysis of Adduct* (**16a**).—A vigorously stirred solution of adduct (**16a**) (7.0 mg, 0.025 mmol) in methanol (10 ml) was hydrogenated under H_2 (3 atm) at room temperature for 15 h in the presence of palladium(II) hydroxide (11 mg). The catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford an oil, which was purified by PLC chromatography (aluminium oxide; developed with CH_2Cl_2–MeOH–NH_4OH, 95:5:0.5) to give α-isosparteine (**1**) as white crystals. The spectral data of the synthetic compound were identical with those from an authentic sample.[10]

(1R*,3R*,4R*,11S*,13S*,20R*)-10,12,14-*Trioxa*-9,15-*diaza*-*pentacyclo*[11.7.0.0^{3,11}.0^{4,9}.0^{15,20}]*eicosan*-2-*one* (**19**).—A solution of nitrone (**4**) (3.50 g, 35.4 mmol) and γ-pyrone (1.70 g, 17.7 mmol) in dry benzene (30 ml) was refluxed for 12 h. The mixture was concentrated and the residual oil was purified by flash chromatography to afford adduct (**19**) (2.1 g, 40%); δ_H(60 MHz; $CDCl_3$) 1.0–2.3 (12 H, m), 2.7–3.9 (8 H, m), and 5.95 (2 H, d, *J* 6.8 Hz).

(1S*,3S*,4R*,11S*,13S*,20R*)-10,12,14-*Trioxa*-9,15-*diaza*-*pentacyclo*[11.7.0.0^{3,11}.0^{4,9}.0^{15,20}]*eicosan*-2-*ol* (**20a**).—To a solution of adduct (**19**) (294 mg, 1.0 mmol) in methanol (10 ml) was added a solution of sodium borohydride (200 mg) in water (1 ml). The mixture was stirred at room temperature for 2 h and extracted with diethyl ether. The extract was washed successively with water and brine. After being dried ($MgSO_4$), the solution was concentrated under reduced pressure to afford an oil, which was purified by flash chromatography to give the alcohol (**20a**) (258 mg, 87%); δ_H(60 MHz; $CDCl_3$) 1.0–3.8 (21 H, m), 4.10 (1 H, dd, *J* 7.5 and 5.5 Hz), and 5.68 (2 H, d, *J* 6.8 Hz).

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