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A Practical Synthesis of (±)-α-Isosparteine from a Tetraoxobispidine Core

Paul R. Blakemore,*[†] Colin Kilner,[‡] Neil R. Norcross,[‡] and Peter C. Astles[§]

[†]Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003
[‡]School of Chemistry, University of Leeds, Leeds, West Yorkshire, LS2 9JT, U.K.
[§]Eli Lilly & Co. Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, U.K.

Supporting Information: Experimental Procedures

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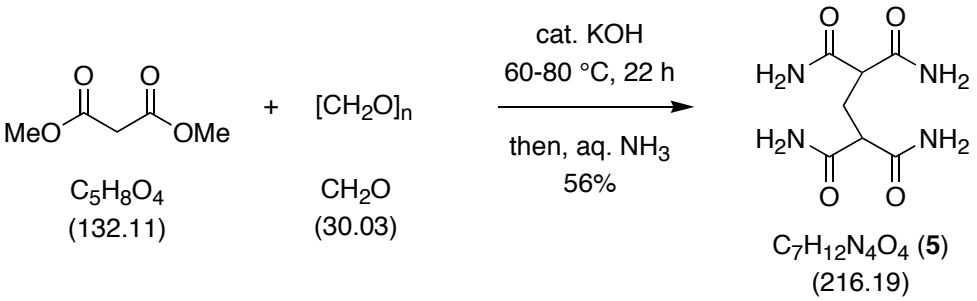
General techniques: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of N_2 or Ar. THF was freshly distilled from sodium benzophenone ketyl prior to use. Preparative chromatographic separations were performed on silica gel 60 (35-75 μm) and reactions followed by TLC analysis using silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV or phosphomolybdic acid. All commercially available reagents were used as received unless otherwise noted.

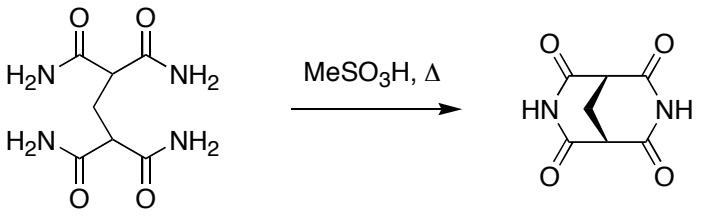
Melting points were recorded on an oil immersion well melting point apparatus and are uncorrected. Infra-red spectra were recorded in Fourier transform mode from KBr disks. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified and from the indicated deuterated 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; $(CD_3)_2SO$ δ_H (CD_3SOCHD_2) = 2.50 ppm, δ_C = 39.5 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 either electron impact (EI), chemical ionization (CI), or electrospray (ES) ionization techniques. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.



$C_5H_8O_4$ (132.11) + CH_2O (30.03) → $C_7H_{12}N_4O_4$ (**5**) (216.19)

1,1,3,3-Tetra(aminocarbonyl)propane (5): A stirred mixture of dimethyl malonate (500 mL, d = 1.15, 575 g, 4.36 mol) and paraformaldehyde (32.8 g, 1.09 mol) at 60 °C was treated with 10 wt.% KOH in MeOH (5 mL). The temperature of the reaction mixture was then increased to 80 °C and stirring continued for a further 22 h. After this time, the mixture was allowed to cool to rt and shaken with H_2O (100 mL). The lower organic phase layer was separated and excess dimethyl malonate removed by distillation at reduced pressure (H_2O aspirator). After cooling, the residue was treated with conc. aq. NH_3 (300 mL) and the resulting biphasic mixture stirred vigorously for 24 h. The resulting precipitated product was removed by filtration and washed successively with EtOAc-MeOH (4:1, 250 mL), acetone (100 mL), and then dried in an oven (120 °C, 15 h) to afford tetraamide **5** (131.4 g, 0.608 mol, 56%) as a cream colored powder of sufficient purity for immediate further elaboration: mp 265 °C dec. (MeOH-H_2O); IR

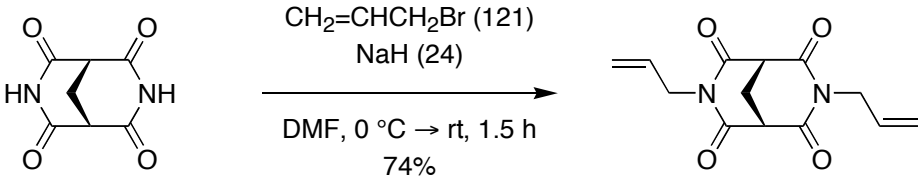
(KBr) 3385, 3188, 1656, 1419, 1383, 1346, 615 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 7.18 (4H, s), 7.05 (4H, s), 2.95 (2H, t, *J* = 7.5 Hz), 2.00 (2H, t, *J* = 7.4 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) d 170.7 (4C, 0), 50.3 (2C, 1), 28.3 (2) ppm; MS (ES) *m/z* 239 $(M+Na)^+$, 217 $(M+H)^+$; HRMS (ES) *m/z* 239.0755 (calcd. for C7H12N4O4Na: 239.0756).



$C_7H_{12}N_4O_4$ (**5**)
(216.19)

$C_7H_6N_2O_4$ (**6**)
(182.13)

2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonane (6): A mechanically stirred paste of finely powdered tetraamide **5** (64.8 g, 300 mmol) and methanesulfonic acid (60 mL) in a 1 L RB flask was carefully heated with a cool Bunsen burner flame for 10 min. During heating, an initial period of fairly intense effervescence was observed which subsided to leave a gently boiling homogenous yellow solution (int. temp. 150-160 °C). The mixture was allowed to cool to ca. 55 °C and then MeOH (120 mL) was added. The resulting thick precipitate was triturated thoroughly and removed by filtration. The filter-cake was then transferred to a 500 mL conical flask and H_2O (120 mL) added. Subsequent vigorous stirring (5 min) resulted in dissolution of the majority of ammonium methanesulfonate by-product and left a fine milky suspension of the desired bisimide. The fine solid matter was removed by filtration, washed with acetone (30 mL), and dried (70 °C, 6 h), to yield tetraoxobispidine **6** (12.9 g, 96 wt.%, 68.1 mmol, 23%) as a colorless powder. The material was contaminated by a small quantity of residual ammonium methanesulfonate (4 wt.% as adjudged by ^1H NMR analysis) but was otherwise of excellent purity and suitable for immediate further elaboration. Recrystallization from H_2O gave colorless needles of pure material: mp 295 °C dec. (H_2O); IR (KBr) 3257, 2838, 1740, 1714, 1339, 1274, 1201, 833, 800, 768 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 11.44 (2H, s), 3.64 (2H, t, *J* = 2.8 Hz), 2.59 (2H, t, *J* = 2.8 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 166.9 (4C, 0), 47.2 (2C, 1), 22.8 (2) ppm; MS (EI) m/z 182 $M^{+\bullet}$.

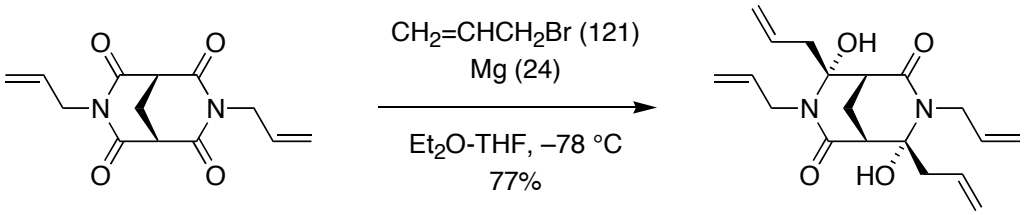


$C_7H_6N_2O_4$ (**6**)
(182.13)

$C_{13}H_{14}N_2O_4$ (**7**)
(262.26)

3,7-Diallyl-2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane (7): A vigorously stirred suspension of bisimide **6** (10.9 g, 96 wt.%, 57.6 mmol) in anhydrous DMF (50 mL) at 0 °C under Ar, was treated portionwise with sodium hydride (5.76 g, 60 wt.% disp. in oil, 144 mmol). The ensuing gas evolution ceased within 1 min. The resulting solution was stirred for 3 min and then treated dropwise with neat allyl bromide (12.2 mL, d = 1.43, 17.4 g, 144 mmol). The mixture was warmed to rt and stirred for an

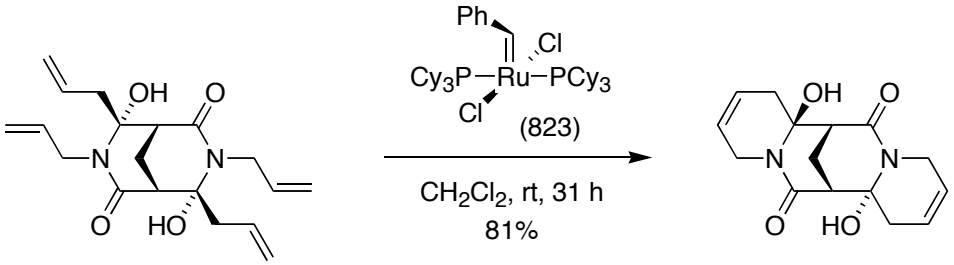
additional 1 h. After this time, sat. aq. NH_4Cl (30 mL) was added and the quenched reaction mixture partitioned between H_2O (100 mL) and EtOAc (150 mL). The layers were separated and the aqueous phase extracted with EtOAc (2x50 mL). The combined organic extracts were washed successively with H_2O (2x50 mL) and brine (20 mL), and then dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was triturated with hexanes (40 mL), filtered-off and sucked dry to afford the pure diallylated product **7** (11.0 g, 41.9 mmol, 73%) as a colorless crystalline solid: mp 130-132 °C (EtOAc); IR (KBr) 3006, 1699, 1361, 1328, 1190, 982, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (2H, ddt, J = 16.8, 10.5, 5.9 Hz), 5.14 (2H, dq, J = 10.5, 1.2 Hz), 5.13 (2H, dq, J = 16.6, 1.2 Hz), 4.36 (4H, dt, J = 5.9, 1.3 Hz), 4.07 (2H, t, J = 2.9 Hz), 2.57 (2H, t, J = 2.9 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (4C, 0), 130.7 (2C, 1), 119.0 (2C, 2), 48.5 (2C, 1), 42.5 (2C, 2), 22.6 (2) ppm; MS (ES) m/z 263 $(M+H)^+$; HRMS (ES) *m/z* 263.1027 (calcd. For $C_{13}H_{15}N_2O_4$: 263.1032).



$C_{13}H_{14}N_2O_4$ (**7**)
(262.26)

$C_{19}H_{26}N_2O_4$ (**8**)
(346.42)

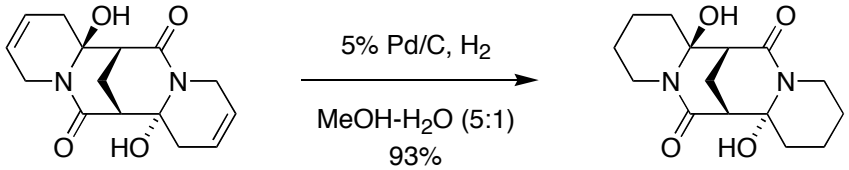
4,8-Dihydroxy-2,6-dioxo-3,4,7,8-tetraallyl-3,7-diazabicyclo[3.3.1]nonane (8): A stirred suspension of mechanically activated magnesium (5.76 g, 240 mmol) in anhydrous Et_2O (75 mL) at rt under Ar was treated dropwise with allyl bromide (6.77 mL, d = 1.43, 9.68 g, 80.0 mmol) in anhydrous Et_2O (75 mL) over 50 min. The rate of addition was carefully controlled such that the internal temperature of the reaction mixture did not rise above 28 °C (an ice-water cooling bath was employed periodically to tame any exotherm). After stirring for 2 h at rt, the resulting dark grey solution of allylmagnesium bromide was added rapidly (over 1 min) *via* canula to a cooled solution of bisimide **7** (5.24 g, 20.0 mmol) in anhydrous THF (150 mL) at –78 °C under Ar. A thick white precipitate formed instantaneously upon addition, and the resulting suspension was stirred vigorously for 10 min before being quenched with sat. aq. NH_4Cl (50 mL). The mixture was warmed to rt, partitioned between EtOAc (100 mL) and H_2O (100 mL), and the layers well shaken and separated. The aqueous phase was extracted (50 mL, EtOAc) and combined organic phases washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was triturated with refluxing hexanes (75 mL) and the supernatent liquor decanted away a small quantity of an insoluble yellow oil which was discarded. The hexanes triturate was slowly cooled to induce crystallization of the desired product **8** (5.36 g, 15.5 mmol, 77%) which was isolated as large colorless needles by filtration: mp 85-86 °C (hexanes); IR (KBr) 3334, 2988, 1612, 1430, 1073, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93-5.70 (4H, m), 5.62 (2H, s), 5.20-5.06 (8H, m), 4.16 (2H, ddt, J = 15.2, 6.3, 1.4 Hz), 3.98 (2H, ddt, J = 15.3, 5.2, 1.6 Hz), 2.87 (2H, t, J = 3.1 Hz), 2.86 (2H, ddt, J = 14.4, 4.6, 1.6 Hz), 2.37 (2H, dd, J = 14.4, 9.7 Hz), 2.16 (2H, t, J = 3.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (2C, 0), 134.1 (2C, 1), 132.5 (2C, 1), 119.5 (2C, 2), 117.1 (2C, 2), 87.3 (2C, 0), 43.4 (4C, 2), 42.9 (2C, 1), 18.1 (2) ppm; MS (ES) *m/z* 347 $(M+H)^+$; HRMS (ES) *m/z* 347.1970 (calcd. for $C_{19}H_{27}N_2O_4$: 347.1971).



$C_{19}H_{26}N_2O_4$ (**8**)
(346.42)

$C_{15}H_{18}N_2O_4$ (**9**)
(290.31)

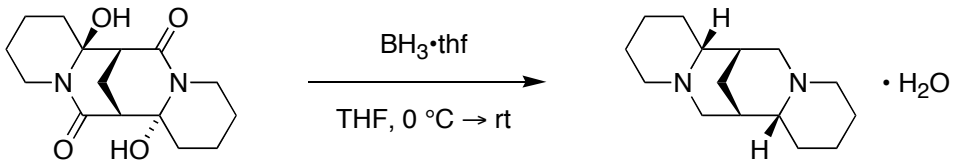
(±)-$\Delta^{3,13}$-Didehydro-6,11-dihydroxy-10,17-dioxosparteine (9): A solution of tetraene **8** (3.52 g, 10.2 mmol) in CH_2Cl_2 (100 mL) at rt under Ar was treated with Grubbs' 1st generation ruthenium alkylidene complex (170 mg, 0.21 mmol). The resulting mixture was stirred for 31 h and at regular intervals within this time frame, additional portions of Grubbs' catalyst were added (3x50 mg, 3x0.06 mmol: overall 320 mg, 0.39 mmol, 4 mol%). After this time, the by then heavy precipitate was removed by filtration and the solid washed with CH_2Cl_2 (5 mL) to afford sparteine derivative **9** (2.41 g, 8.30 mmol, 81%) as a colorless powder: mp 268 °C dec. (EtOH-H_2O); IR (KBr) 3165, 2951, 1616, 1437, 1303, 1234, 1199, 1125, 1019, 995, 897 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 5.70 (2H, dm, *J* = 10.2 Hz), 5.60 (2H, dm, *J* = 10.4 Hz), 5.50 (2H, s, OH), 4.69 (2H, dm, *J* = 17.0 Hz), 3.40 (2H, dm, *J* = 17.0 Hz), 2.68 (2H, t, *J* = 3.1 Hz), 2.59 (2H, dm, *J* = 17.0 Hz), 2.13 (2H, dm, *J* = 17.0 Hz), 2.08 (2H, t, *J* = 3.0 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 165.7 (2C, 0), 123.7 (2C, 1), 122.5 (2C, 1), 82.3 (2C, 0), 47.4 (2C, 1), 37.6 (2C, 2), 37.4 (2C, 2), 20.4 (2) ppm; MS (ES) *m/z* 273 $(M–OH)^+$; HRMS (ES) *m/z* 273.1237 (calcd. for $C_{15}H_{17}N_2O_3$: 273.1239).



$C_{15}H_{18}N_2O_4$ (**9**)
(290.31)

$C_{15}H_{22}N_2O_4$ (**10**)
(294.35)

(±)-6,11-Dihydroxy-10,17-dioxosparteine (10): A suspension of diene **9** (1.98 g, 6.82 mmol) and 5 wt.% palladium on carbon (200 mg) in MeOH-H_2O (5:1, 240 mL) was vigorously stirred under an atmosphere of hydrogen gas for 22 h. After this time, the active gas was flushed away with Ar, and the reaction mixture filtered through a celite pad. The pad was washed well with MeOH (200 mL) and filtrate and combined washings concentrated *in vacuo*. The resulting residue was triturated with hexanes (50 mL) to afford the desired product **10** (1.87 g, 6.35 mmol, 93%) as a colorless powder: mp 230 °C dec. (EtOAc-MeOH); IR (KBr) 3258, 2955, 1614, 1444, 1287, 1138, 982 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 5.59 (1H, s, OH), 5.41 (1H, s, OH), 4.24 (1H, dm, *J* = 12.6 Hz), 4.13 (1H, dm, *J* = 12.9 Hz), 2.88 (1H, td, *J* = 12.9, 2.7 Hz), 2.75 (1H, td, *J* = 13.2, 3.2 Hz), 2.58-2.53 (2H, m), 2.41 (1H, ddd, *J* = 13.5, 3.7, 2.5 Hz), 1.99 (1H, ddd, *J* = 13.5, 3.5, 2.7 Hz), 1.92-1.70 (3H, m), 1.63-1.35 (7H, m), 1.30-1.13 (2H, m) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 167.5 (0), 166.3 (0), 83.9 (0), 82.6 (0), 49.5 (1), 49.1 (1), 37.2 (2), 36.3 (2), 36.2 (2), 35.5 (2), 24.4 (2C, 2), 20.0 (2), 18.9 (2C, 2) ppm; MS (ES) *m/z* 295 $(M+H)^+$; HRMS (ES) *m/z* 295.1643 (calcd. for $C_{15}H_{23}N_2O_4$: 295.1658).



$C_{15}H_{22}N_2O_4$ (**10**)
(294.35)

$C_{15}H_{26}N_2 \cdot H_2O$ (*dl*-**1**)
(252.40)

(±)-α-Isosparteine (*dl*-1): A stirred suspension of dihydroxybislactam **10** (1.47 g, 5.00 mmol) in anhydrous THF (20 mL) at 0 °C under Ar, was treated dropwise with borane tetrahydrofuran complex (20.0 mL, 1.0 M in THF, 20.0 mmol). Gas evolution was observed and upon its cessation an homogenous solution had formed. The reaction mixture was allowed to warm slowly to rt and stirred for 20 h. After this time, MeOH (10 mL) was cautiously added and the mixture concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL) and again concentrated *in vacuo*. Concentrated NH_3 / MeOH (20 mL) was added to the resulting residue and the mixture stirred for 2 h before being concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and extracted with 4 M aq. HCl (2x15 mL). The combined acidic extracts were basified to pH 14 by the addition of 15 wt%. aq. NaOH (*ca* 50 mL) and the resulting turbid solution cooled in an ice bath for 30 min. The solid which crystallized from the mixture was removed by filtration, briefly sucked-dry in air, then further dried under a stream of Ar, to afford (±)-α-isosparteine hydrate (592 mg, 2.35 mmol, 47%) as fine colorless needles: mp 75-76 °C (H_2O) [lit. [1] 78-80 °C (subl.); lit.[2] 76-79 °C]; IR (KBr) 2931, 2854, 2735, 1642, 1444, 1351, 1291, 1270, 1104, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (1H, s, H_2O of hydration, ½ eq), 2.93 (2H, br d, *J* = 11.5 Hz), 2.73 (2H, dm, *J* = 8.5 Hz), 2.04 (2H, dd, *J* = 11.5, 3.0 Hz), 1.91 (2H, dm, *J* = 10.9 Hz), 1.80-1.56 (10H, m), 1.55-1.43 (4H, m), 1.35-1.20 (4H, m) ppm; ^{13}C (75 MHz, $CDCl_3$) δ 66.5 (2C, 1), 57.5 (2C, 2), 56.4 (2C, 2), 36.7 (2), 35.9 (2C, 1), 30.5 (2C, 2), 25.8 (2C, 2), 25.3 (2C, 2) ppm; MS (CI, CH_4) *m/z* 234 (100) $M^{+\bullet}$, 193 (17), 137 (39), 98 (40); HRMS (CI, CH_4) *m/z* 234.2087 (calcd. for $C_{15}H_{26}N_2$: 234.2096).

Dissolution of 0.1 mmol each of **1** and picric acid in CH_2Cl_2 (5 mL), followed by concentration and recrystallization of the resulting yellow solid from EtOH, gave (±)-α-isosparteine monopicrate (*dl*-**1**•$C_6H_3N_3O_7$) as a microcrystalline material: mp 124-125 °C (EtOH) [lit.[1] 132.5-133.5 °C (EtOH)]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (2H, s), 7.60-7.25 (1H, br s), 3.54 (2H, br d, *J* = 12.5 Hz), 3.31 (2H, dm, *J* = 11.7 Hz), 2.73 (4H, br d, *J* = 12.1 Hz), 2.29 (2H, td, *J* = 11.4, 5.3 Hz), 2.00-1.75 (8H, m), 1.70-1.53 (6H, m), 1.49-1.30 (2H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (0), 142.0 (2C, 0), 127.1 (2C, 1), 126.2 (0), 67.1 (2C, 1), 56.9 (2C, 2), 56.7 (2C, 2), 34.2 (2), 33.5 (2C, 1), 28.9 (2C, 2), 24.1 (2C, 2), 23.5 (2C, 2) ppm.

As reported by Leonard and Beyler,[1] we observed *dl*-**1** to turn a pinky brown color upon gentle warming in air, or on standing in solution. The free-base was best stored in the solid state under Ar. Our material was obtained as a partial hydrate and its melting point, known to vary with the degree of hydration and rate of sample heating,[1] was in good agreement with figures reported previously (see above).[1,2]

^{13}C NMR data for *dl*-**1** free-base collected in $CDCl_3$ (*ca* 0.2 M) at 75 MHz were in excellent agreement with those recently reported by Galasso and co-workers for *l*-**1**[3] (Table 1). Although not stated as such, NMR data reported by Kakisawa and co-workers for *dl*-**1** obtained during the course of their total

[1] Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316.
[2] Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2593.

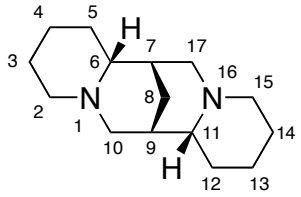
synthesis, likely pertain to a monoprotonated form of this strongly basic diamine.[2] Those Authors obtained their sample by preparative TLC; in our hands, chromatographic purification of *dl*-**1** on SiO_2 (eluting with NH_3/MeOH) proffered material suspected to be protonated which gave an identical NMR signature (^{1}H NMR and ^{13}C NMR) to that described by Kakisawa.[2] As expected based on this hypothesis, (±)-α-isosparteine monopicrate (*dl*-**1**•$C_6H_3N_3O_7$), prepared from our authenticated *dl*-**1** free-base (see above), exhibited very similar NMR spectral data to those reported by Kakisawa (excepting signals attributable to 2,4,6-trinitrophenoxide).

Table 1. *Comparison of ^{13}C NMR data for **1***

atom	*dl*-**1** δ_c ppm*	*l*-**1** lit.[3] δ_c ppm†	$\lvert\Delta\delta\rvert$ ppm
C6/11	66.5	66.4	0.1
C2/15	57.5	57.4	0.1
C10/17	56.4	56.1	0.3
C8	36.7	36.4	0.3
C7/9	35.9	35.6	0.3
C5/12	30.5	30.2	0.3
C3/14	25.8	25.4	0.4
C4/13	25.3	25.0	0.3

* Recorded at 75 MHz from $CDCl_3$ (see Figure 4)

† Recorded at 150 MHz from $CDCl_3$



α-isosparteine (**1**)

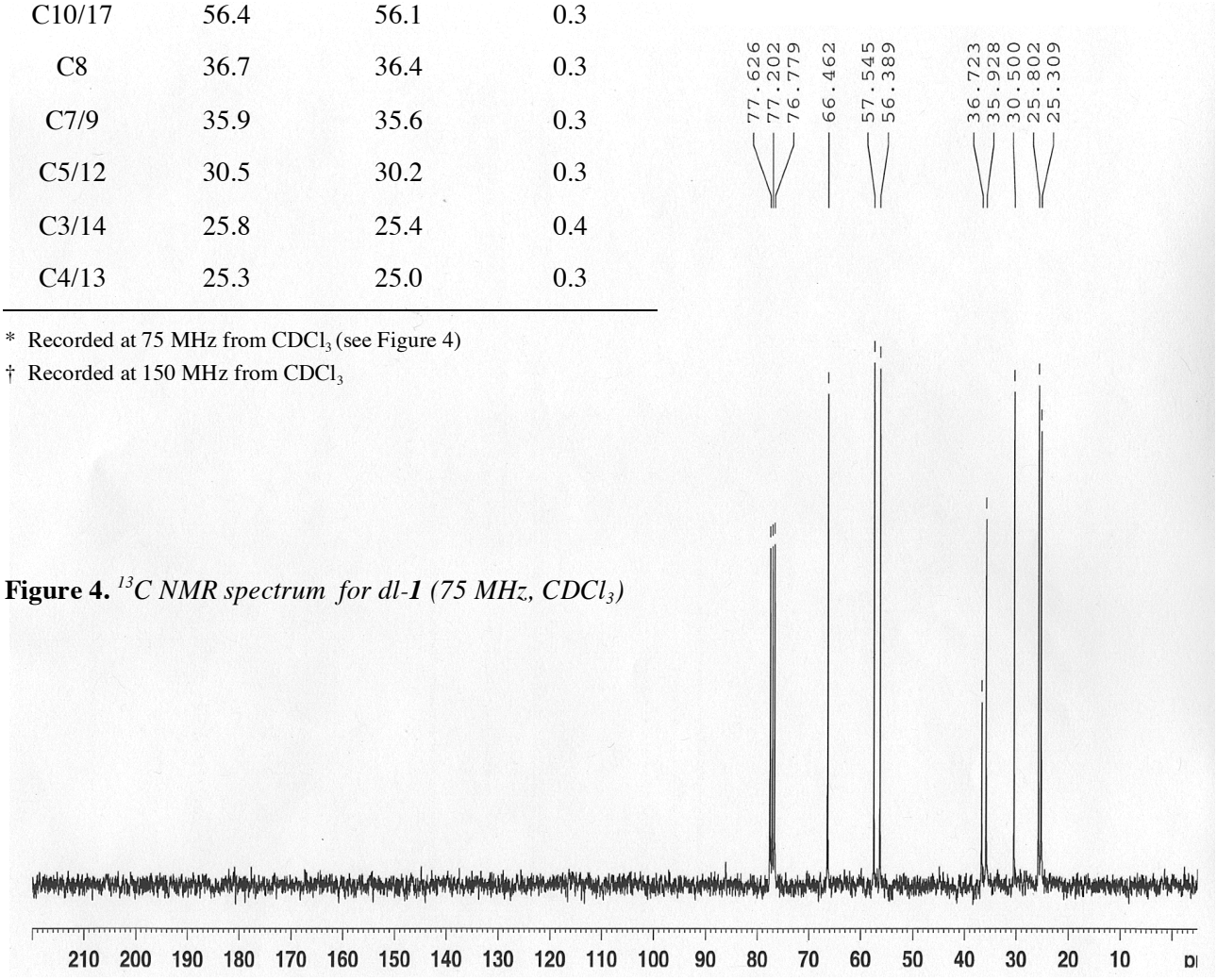


Figure 4. *^{13}C NMR spectrum for dl-**1** (75 MHz, $CDCl_3$)*

[3] Galasso, V.; Asaro, F.; Berti, F.; Kovac, B.; Habus, I.; Sacchetti *Chem. Phys*. **2003**, *294*, 155.