

Enantioselective synthesis of strobamine and its analogues

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Dedicated to Professor James M. Cook, celebrating his 65th birthday

Abstract

(2*S*,5*S*,8*R*)-Strobamine (+)-**1a** was synthesized by adding cinnamoyl cyanide **6a** to tropinone **3** lithium enolate generated by treatment of (*S,S'*)- α,α -dimethyldibenzylamide with butyl lithium in the presence of lithium chloride to give (-)-chalcostrobamine (-)-**7a**, which yielded a one-to-one mixture of (+)-**1a** and its C-2 epimer (-)-**2a** on treatment with 2N sulfuric acid. Compounds (+)-**1a** and (-)-**2a** could be separated by column chromatography. (-)-Strobamine (-)-**1a** and (+)-**2a** were synthesized by a similar set of reactions using the tropinone **3** lithium enolate generated with butyl lithium in the presence of (*R,R'*)- α,α' -dimethyldibenzylamide and lithium chloride. (+)- and (-)-*p*-Methylstrobamine (+)- and (-)-**1b** and (+)- and (-)-*epi-p*-methylstrobamine (+)- and (-)-**2b** were synthesized by a similar procedure. The absolute configuration of (+)-*epi-p*-methylstrobamine (+)-**2b** was determined by X-ray analysis to have the (2*S*,5*R*,8*S*) configuration.

Keywords: Strobamine, *epi*-strobamine, heterocycles

Introduction

Strobamine (+)-**1a** was first isolated from the leaves of the endemic New Caledonian plant *Knightia strobilina* Labill in 1980.^{1,2} However, the synthesis of (+)-**1a** has not been reported, and its absolute stereochemistry is unknown. The synthesis of (\pm)-strobamine (\pm)-**1a** and (\pm)-*epi*-strobamine (\pm)-**2a** was reported by Lounasmaa et al. in 1983.³ In their preparation, tropinone was deprotonated with NaH, and the resulting enolate was treated with cinnamoyl cyanide to form chalcostrobamine (\pm)-**7a**. Subsequent cyclization under acidic conditions afforded (\pm)-**1a** and (\pm)-**2a**. To the best of our knowledge, no additional report has been published on the synthesis or the absolute configuration of strobamine. The observation that (\pm)-strobamine, prepared in our

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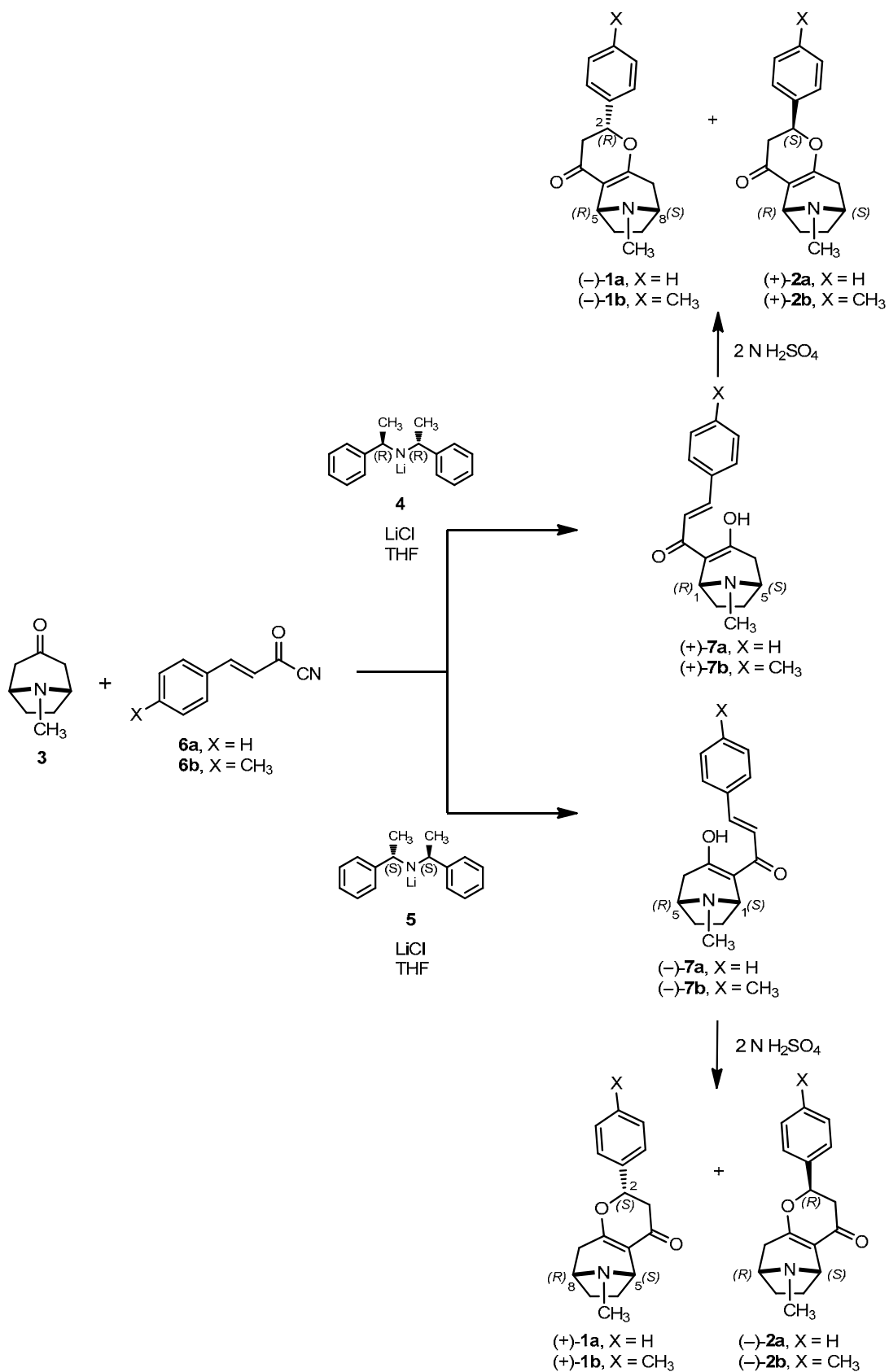
laboratory, showed an IC_{50} of 370 nM for inhibition of radioligand binding at the dopamine transporter, suggested that it would be interesting to evaluate the (+)- and (-)-isomers of strobamine (+)- and (-)-**1a** as well as its epimers (+)- and (-)-**2a**. In this communication, we report the enantioselective synthesis of (+)- and (-)-**1a** and their epimers (+)- and (-)-**2a**. In addition, we report the synthesis of (+)- and (-)-*p*-methylstrobamine (+)- and (-)-**1b**, (-)-*epi-p*-methylstrobamine (+)- and (-)-**2b**, and the X-ray structure of (+)-**2b**.

Results and Discussion

Since Majewski and Lazny⁴ reported that (-)-chalcostrobamine (-)-**7a** and (+)-ent-chalcostrobamine (+)-**7a** could be synthesized in >95% ee by enantioselective deprotonation of tropanone **3** using chiral lithium (*S,S'*)- α,α' -dimethylbenzylamide **4** and (*R,R'*)- α,α' -dimethyldibenzylamide **5**, we envisioned that (+)- and (-)-**1a**, (+)- and (-)-**2a** as well as (+)-**1b** and (-)-**1b** and (-)-**2b** and (+)-**2b** could be prepared by the route shown in Scheme 1. We first repeated the synthesis reported by Majewski and Lazny⁴ and, as expected, we found that the use of chiral amides **4** and **5** led to (-)-**7a** and (+)-**7a**, respectively.

With the structures of (+)- and (-)-**7a** verified, strobamine (+)-**1a** and its analogues were synthesized from tropinone **3** in a one-pot reaction. Lithium (*R,R'*)- α,α' -dimethyldibenzylamide **4** and lithium (*S,S'*)- α,α' -dimethyldibenzylamide **5** were generated in situ from the corresponding amine hydrochloride and 1.98 equivalents of *n*-BuLi. The required tropinone lithium enolates were then produced by adding the lithium amide base to a tetrahydrofuran solution of tropinone **3**. Treatment of the above enolates derived from **4** or **5** with aroyl cyanides⁵ **6a** or **6b** afforded (+)- or (-)-chalcostrobamines **7a** or **7b**, respectively (Scheme 1). (-)-Chalcostrobamines (-)-**7a** or (-)-**7b** were cyclized under acidic (H_2SO_4) conditions to give nearly equal quantities of (+)-**1a** or (+)-**1b** and their C-2 epimers (-)-**2a** or (-)-**2b**, which were separated by chromatography. Cyclization of (+)-**7a** or (+)-**7b** under the same conditions provided (-)-**1a** or (-)-**1b** and (+)-**2a** or (+)-**2b**. The absolute configuration of (2*S*,5*R*,8*S*)-(+)-*epi-p*-methylstrobamine (+)-**2b** was assigned on the basis of X-ray spectroscopic analysis (Figure 1). The NMR spectra and optical rotation of (+)-strobamine synthesized in this study were consistent with natural (\pm)-strobamine; see comparison of the ¹³C NMR data in Table 1; for additional details, see the Experimental Section. Major differences in the ¹³C NMR spectra are the lower field chemical shifts of C-2, C-3, and C-7 and higher field shifts for C-6 and C-9 for strobamine **1a** relative to *epi*-strobamine **2a** (Table 1). Because (+)-**2b** was shown by X-ray analysis to have the (2*S*,5*R*,8*S*) configuration, (-)-strobamine (-)-**1a**, which was generated in the same type of reaction, has the (2*R*,5*R*,8*S*)-configuration and its enantiomer, (+)-strobamine [(+)-**1a**], has the (2*S*,5*S*,8*R*) configuration.

The IC_{50} value of 265 nM for the inhibition of binding to the dopamine transporter for (+)-**1a** was not appreciably different from that of the racemate.



Scheme 1

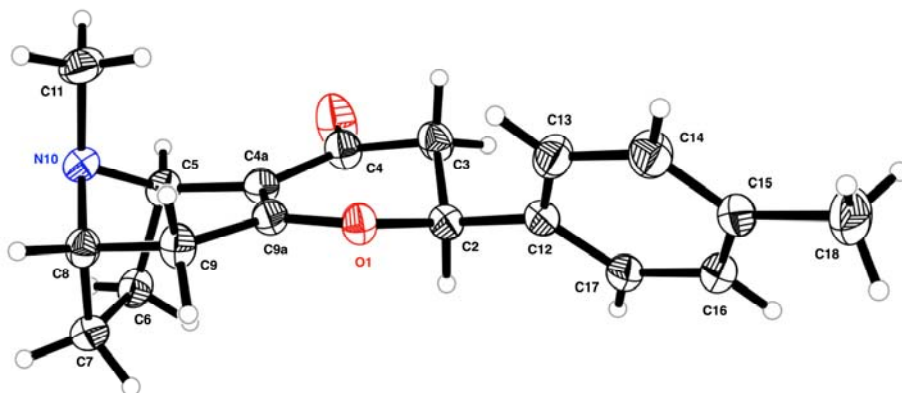


Figure 1. Structure of compound (+)-**2b** showing labeling of the non-hydrogen atoms.

Table 1. Comparison of ^{13}C NMR data for (+)-strobamine (+)-**1a** and (-)-*epi*-strobamine (-)-**2** to reported values for (\pm)-strobamine and (\pm)-*epi*-strobamine^a

C	(+)- 1a	(-)- 2a	(\pm)- 1a ^a	(\pm)- 2a ^a
	δ_c	δ_c	δ_c	δ_c
2	80.80	79.84	80.5	79.7
3	42.90	42.33	42.7	42.2
4	189.63	189.44	189.2	189.2
4a	117.19	116.73	116.8	116.4
5	58.25	58.22	58.0	58.0
7	35.65	34.74	35.4	34.6
6	32.70	33.46	32.6	33.3
8	55.93	55.18	55.7	55.0
9	28.45	29.16	28.3	29.0
9a	168.94	168.82	168.6	168.6
10	37.64	36.95	37.4	36.8

^aValues taken from ref 3.

Conclusions

The enantioselective synthesis of the natural product (+)-strobamine (+)-**1a** and its *p*-methyl analogue has been achieved. The absolute configuration of strobamine has also been determined for the first time by NMR and X-ray spectroscopic analysis of the (+)-*p*-methyl analogue (+)-**2b**.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 Spectrometer using TMS as an internal standard. Optical rotations were measured with an Autopol IV automatic polarimeter. HPLC analyses were carried out on a Dynamax HPLC system. The optical purity was determined by chiral HPLC [Sumichiral OA-4900 (4.6 mm \times 25 cm)]. Flash column chromatography was performed using EM Science silica gel 60 (particle size 40–63 μm). CMA80 is a mixture of 80% chloroform, 18% methanol, and 2% concentrated ammonium hydroxide. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

General procedure for the synthesis of chalcostrobamine (7a) and (7b)

Using a procedure similar to that reported by Majewski and Lazny,⁴ a solution of *n*-BuLi (0.95 mL, 2.5 M, 2.4 mmol) in hexane was added dropwise to a solution of bis[(*R,R*)- or (*S,S*)-phenylethylamine]-HCl (0.30 g, 1.2 mmol) in dry THF (28 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, then cooled to –78 °C. A solution of tropanone **3** (0.14 g, 1.0 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 3 h, and cinnamoyl cyanide (0.20 g, 1.3 mmol) in THF (4.0 mL) was added. The reaction mixture was stirred at –78 °C for another 1 h and treated with a solution of silver nitrate (0.17 g, 1.0 mmol) in THF (0.5 mL), water (0.25 mL), and acetic acid (0.25 mL). After warming to room temperature, the reaction mixture was treated with ammonium hydroxide solution (20%), water, and extracted with chloroform. The extracts were dried (MgSO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, CMA80/ CH_2Cl_2 1:3) to afford **7a,b** as yellow oil liquids.

(+)-Chalcostrobamine [(+)-7a]. $[\alpha]_{\text{D}}^{20} +166$ (c 1.75, CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 1.66 (m, 1H), 1.84 (m, 1H), 2.18 (m, 2H), 2.30 (m, 2H), 2.42 (s, 3H), 2.85 (m, 1H), 3.42 (m, 1H), 4.4 (d, $J = 5.4$ Hz, 1H), 6.84 (d, $J = 15.6$ Hz, 1H), 7.40 (m, 3H), 7.54 (m, 2H), 7.69 (d, $J = 15.6$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 29.11, 33.38, 37.11, 40.82, 57.66, 58.84, 113.06, 117.74, 127.97, 128.84, 129.91, 135.28, 140.82, 172.43, 197.60.

(–)-Chalcostrobamine [(–)-7a]. The ^1H and ^{13}C NMR spectra were identical to those of (+)-**7a**. $[\alpha]_{\text{D}}^{20} -167^\circ$ (c 1.7, CHCl_3).

General procedure for the synthesis of strobamine and analogs

A solution of *n*-BuLi (0.95 mL, 2.5 M, 23.7 mmol) in hexane was added dropwise to a solution of (*R,R*)- or (*S,S'*)- α,α' -dimethyldibenzylamine-HCl (0.30 g, 1.2 mmol) in anhydrous THF (28 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and cooled to –78 °C. A solution of tropanone **3** (0.14 g, 1.0 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 3 h, then the corresponding cinnamoyl cyanide (1.3 mmol) in THF (4.0 mL) was added. The mixture was stirred at –78 °C for another 1 h, treated with a solution of silver nitrate (0.17 g, 1.0 mmol) in THF (0.5 mL), water (0.25 mL), and acetic acid (0.25 mL). After warming to room temperature, the solution was extracted with chloroform. Chloroform was

removed under vacuum, and the residue was dissolved in aqueous 2N H₂SO₄ and heated at 50 °C for 24 h. After the solution cooled, it was adjusted to pH 11 with conc. ammonium hydroxide and extracted with ether. The organic layers were combined, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc/Et₃N 9:1) to afford (-)-**1a-c** and (+)-**2a,b** when (*R,R*)-**5** was used, and (+)-**1a,b** and (-)-**2a,b** when (*S,S*)-**4** was used as liquids.

(+)-*epi*-Strobamine [(+)-2a]. 100% ee by HPLC. $[\alpha]_{\text{D}}^{20} +91^{\circ}$ (*c* 0.61, CHCl₃). IR (neat): ν 1608, 1659 cm⁻¹. UV (MeOH): λ_{max} 274 nm. ¹H NMR (300 MHz, CDCl₃): δ 1.53 (m, 1H), 1.80 (m, 1H), 1.90 (d, *J* = 18.4 Hz, 1H), 2.16 (m, 2H), 2.29 (s, 3H), 2.62 (dd, *J* = 3.6, 16.7 Hz, 1H), 2.82 (dd, *J* = 5.0, 18.5 Hz, 1H), 2.84 (dd, *J* = 14.0, 17.0 Hz, 1H), 3.36 (m, 1H), 3.99 (d, *J* = 5.2 Hz, 1H), 5.34 (dd, *J* = 3.4, 13.8 Hz, 1H), 7.36 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 29.16, 33.46, 34.74, 36.95, 42.33, 55.18, 58.22, 79.84, 116.73, 126.00, 128.58, 128.63, 138.29, 168.82, 189.44. Fumarate salt: mp 131–132 °C. $[\alpha]_{\text{D}}^{20} +77^{\circ}$ (*c* 1.0, CH₃OH). Anal. calcd. for C₂₁H₂₃NO₆·0.5H₂O: C, 63.95; H, 6.13; N, 3.55. Found: C, 63.92; H, 6.18; N, 3.51.

(-)-*epi*-Strobamine [(-)-2a]. 100% ee by HPLC. $[\alpha]_{\text{D}}^{20} -90^{\circ}$ (CHCl₃). IR (neat): ν 1608, 1659 cm⁻¹. UV (MeOH): λ_{max} 274 nm. ¹H NMR and ¹³C NMR: same as (+)-*epi*-strobamine (+)-**2a**. The fumarate salt: mp 75–82 °C (dec). $[\alpha]_{\text{D}}^{20} +75^{\circ}$ (*c* 1.2, CH₃OH). Anal. calcd. for C₂₁H₂₃NO₆·0.5H₂O: C, 63.95; H, 6.13; N, 3.55. Found: C, 63.92; H, 6.18; N, 3.51.

(-)-Strobamine [(-)-1a]. 100% ee by HPLC. $[\alpha]_{\text{D}}^{20} -47^{\circ}$ (*c* 1.86, CHCl₃) IR (neat): ν 1666 cm⁻¹. UV (MeOH): λ_{max} 274 nm. ¹H NMR (300 MHz, CDCl₃): δ 1.53 (m, 1H), 1.74 (m, 1H), 2.03 (d, *J* = 18.6 Hz, 1H), 2.18 (m, 2H), 2.37 (s, 3H), 2.61 (dd, *J* = 3.4, 17.0 Hz, 1H), 2.81 (dd, *J* = 5.1, 18.9 Hz, 1H), 2.85 (dd, *J* = 14.6, 17.0 Hz, 1H), 3.38 (m, 1H), 4.04 (d, *J* = 4.8 Hz, 1H), 5.36 (dd, *J* = 3.4, 14.5 Hz, 1H), 7.40 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃): δ 28.45, 32.70, 35.65, 37.64, 42.90, 55.93, 58.25, 80.80, 117.19, 126.10, 128.71, 138.22, 168.94, 189.63. Fumarate salt: mp 161–162 °C. $[\alpha]_{\text{D}}^{20} -60^{\circ}$ (*c* 1.0, CH₃OH). Anal. calcd. for C₁₇H₂₀ClNO₂·1.5H₂O: C, 61.35; H, 6.97; N, 4.21. Found: C, 61.51; H, 6.90; N, 4.06.

(+)-Strobamine [(+)-1a]. 100% ee by HPLC. $[\alpha]_{\text{D}}^{20} +48^{\circ}$ (*c* 0.65, CHCl₃). IR (neat): ν 1613, 1666 cm⁻¹. UV (MeOH): λ_{max} 274 nm. ¹H NMR and ¹³C NMR are the same as (-)-strobamine. Fumarate salt: mp 162–163 °C. $[\alpha]_{\text{D}}^{20} +55^{\circ}$ (*c* 1.1, CH₃OH). Anal. calcd. for C₂₁H₂₃NO₆·0.5H₂O: C, 63.95; H, 6.13; N, 3.55. Found: C, 63.92; H, 6.18; N, 3.51.

(+)-*epi-p*-Methylstrobamine [(+)-*epi*-2b]. This compound was obtained as a solid. Recrystallization from a methanol and ether mixture gave crystals for the X-ray analysis; 100% ee by HPLC; mp 117–118 °C. $[\alpha]_{\text{D}}^{20} +106^{\circ}$ (*c* 1.4, CHCl₃). IR (neat): ν 1606, 1658 cm⁻¹. UV (MeOH): λ_{max} 272 nm. ¹H NMR (300 MHz, CDCl₃): δ 1.56 (m, 1H), 1.82 (m, 1H), 1.92 (d, *J* = 18.3 Hz, 1H), 2.19 (m, 2H), 2.29 (s, 3H), 2.37 (s, 3H), 2.62 (dd, *J* = 3.6, 16.8 Hz, 1H), 2.84 (dd, *J* = 4.8, 18.6 Hz, 1H), 2.89 (dd, *J* = 13.8, 16.8 Hz, 1H), 3.40 (m, 1H), 4.02 (d, *J* = 4.8 Hz, 1H), 5.34 (dd, *J* = 3.4, 13.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 21.10, 29.17, 33.50, 34.87, 37.10, 42.30, 55.22, 58.27, 79.90, 116.64, 126.15, 129.36, 135.27, 138.64, 169.09, 189.82. Fumarate salt: mp 120–122 °C; $[\alpha]_{\text{D}}^{20} +82^{\circ}$ (*c* 1.2,

CH₃OH). Anal. calcd. for C₂₂H₂₅NO₆·0.75H₂O: C, 63.99; H, 6.47; N, 3.39. Found: C, 64.02; H, 6.49; N, 3.44.

(-)-*epi-p*-Methylstrobamine [(-)-*epi-2b*]. 100% ee by HPLC. $[\alpha]_D^{20}$ -98° (*c* 0.59, CHCl₃). IR (neat): ν 1606, 1658 cm⁻¹. UV (MeOH): λ_{\max} 272 nm. ¹H and ¹³C NMR: same as (+)-*epi-1b*.

(-)-*p*-Methylstrobamine [(-)-*1b*]. 100% ee by HPLC. $[\alpha]_D^{20}$ -47° (0.275, CHCl₃). IR (neat): ν 1606, 1658 cm⁻¹; UV (MeOH): λ_{\max} 272 nm. ¹H NMR (300 MHz, CDCl₃): δ 1.52 (m, 1H), 1.74 (m, 1H), 2.00 (d, *J* = 18.3 Hz, 1H), 2.16 (m, 2H), 2.37 (s, 6H), 2.58 (dd, *J* = 3.3, 17.1 Hz, 1H), 2.80 (dd, *J* = 4.8, 18.6 Hz, 1H), 2.86 (dd, *J* = 14.7, 17.1 Hz, 1H), 3.68 (m, 1H), 4.04 (d, *J* = 4.5 Hz, 1H), 5.32 (dd, *J* = 3.3, 14.7 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 21.11, 28.42, 32.68, 35.67, 37.67, 42.78, 55.91, 58.21, 80.75, 117.08, 126.16, 129.35, 135.18, 138.67, 169.04, 189.85. The fumarate salt had mp 77–85 °C (dec); $[\alpha]_D^{20}$ -52° (*c* 1.4, CH₃OH). Anal. calcd. for C₂₂H₂₅NO₆·0.5H₂O: C, 64.69; H, 6.42; N, 3.43. Found: C, 64.70; H, 5.56; N, 3.48.

(+)-*p*-Methylstrobamine [(+)-*1b*]. 100% ee by HPLC. $[\alpha]_D^{20}$ +49° (0.275, CHCl₃). IR (neat): $\tilde{\nu}$ 1606, 1658 cm⁻¹. UV (MeOH): λ_{\max} 272 nm. ¹H and ¹³C NMR: same as (-)-*1b*.

X-Ray crystal structure determination of [(+)-*epi-2b*]

Single-crystal X-ray diffraction data on (+)-*epi*-methylstrobamine (+)-*epi-2b* was collected at 293 °K using CuK α radiation produced by a Bruker Micro-STAR rotating anode equipped with Helios optics and a Bruker Platinum-135 CCD area detector. Crystals were prepared for data by mounting on the end of a thin glass rod using an acrylic adhesive. Corrections were applied for Lorentz, polarization, and absorption effects. The crystal was orthorhombic in space group P21212 with unit cell dimensions *a* = 11.2517(6) Å, *b* = 21.5455(12) Å, *c* = 6.5032(4) Å. Data were 97.2% complete to 68.12° 2θ (approximately 0.83 Å), with an average redundancy of 4.92. The structure was solved by direct methods and refined by full-matrix least squares on F² values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model (coordinate shifts of C applied to H atoms) with C-H distance set at 0.96 Å. The absolute configuration was evaluated using likelihood methods in PLATON.^{6,7} Based on the analysis of 1077 Bijvoet pairs (90% coverage), this analysis indicated that the absolute structure had been correctly assigned. The method calculated that the probability that the structure is inverted is smaller than 1×10^{-34} . Atomic coordinates for compound (+)-*epi-2b* have been deposited with the Cambridge Crystallographic Data Centre (deposition number 776942). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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