The Total Synthesis of the Crinine Alkaloid Hamayne via a Pd[0]-catalyzed Intramolecular Alder-ene Reaction

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Synthetic Studies

General Experimental Procedures

Proton (¹H) and carbon (¹³C) NMR spectra were recorded on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. Unless otherwise specified, spectra were acquired at 25 °C in deuterochloroform (CDCl₃) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (νmax) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on KBr plates. ESI mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low and high-resolution EI mass spectra were recorded on a VG Fisons AUTOSPEC three-sector double focussing instrument. Melting points were measured using a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip¹ followed by heating. Flash chromatographic separations were carried out following protocols defined by Still et al.² with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Solvents, drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, DMF, dichloromethane, benzene and toluene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.³ Methanol and ethanol were used as obtained from the above-mentioned suppliers. Where necessary, reactions were performed under a nitrogen atmosphere.
Specific Synthetic Procedures and Product Characterization

Compound 7

A magnetically stirred solution of cyclopentene\(^4\) (500 mg, 2.52 mmol) formed through ring-closing metathesis (RCM) of diene \(^4\) in benzene (2.5 mL) was treated with bromoform (3.18 g, 1.10 mL, 5.0 equiv.) and triethylbenzylammonium chloride (28 mg, 0.13 mmol, 5 mole %) then cooled to 0 °C (ice bath) and treated, dropwise over 0.166 h, with NaOH (4.0 mL of a 50% w/v aqueous solution). The ensuing mixture was allowed to slowly warm to 18 °C and stirred vigorously at this temperature for 16 h. Further portions of bromoform (3.18 g, 1.1 mL), triethylbenzylammonium chloride (28 mg, 0.13 mmol) and NaOH (2.0 mL of a 50% w/v aqueous solution) were added and the mixture so-formed was stirred vigorously at 18 °C for a further 24 h at which point \(^1\)H NMR analysis revealed that all of the starting cyclopentene had been consumed. Accordingly, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and water (20 mL). The separated aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 \(\times\) 20 mL) and the combined phases washed with brine (2 \(\times\) 30 mL), then dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give a dark-brown oil. This reaction was repeated twice more and the combined dark-brown oils thus obtained were subjected to flash chromatography (silica, hexane \(\rightarrow\) 99:1 v/v hexane ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (\(R_f = 0.25\) in 99:1 v/v hexane/ethyl acetate), dibromocyclopropane 7 (2.09 g from 3 runs, av 75%/run) as a clear, colorless oil and as a single diastereoisomer.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)\(_H\) 4.36 (m, 1H), 2.31 (m, 2H), 2.13 (dd, \(J = 14.8\) and 6.8 Hz, 2H), 1.97–1.91 (complex m, 2H), 0.86 (s, 9H), 0.02 (s, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)\(_C\) 76.1, 41.9, 40.1, 37.8, 25.8, 18.1, –4.9.

IR (KBr): \(\nu_{\text{max}}\) 2954, 2928, 2895, 2856, 1740, 1633, 1471, 1462, 1361, 1255, 1093 cm\(^{-1}\).

MS (El, 70 eV): \(m/z\) 372, 370 and 368 (M\(^+\), 51, 100 and 50%, respectively); 357, 355 and 353 (12, 20 and 10, respectively).

HRMS: M\(^+\), Calcd for C\(_{12}\)H\(_{22}\)\(^{79}\)Br\(^{81}\)BrOSi: 369.9786. Found: 369.9782.
Compound (±)-8

A magnetically stirred solution of gem-dibromocyclopropane 7 (1.20 g, 3.24 mmol) in dry chlorobenzene (32 mL) was heated at reflux for 3 h while being maintained under a nitrogen atmosphere. The cooled reaction mixture was concentrated under reduced pressure and the ensuing brown oil dissolved in DMF (20 mL). The resulting solution was treated with sodium azide (316 mg, 4.86 mmol, 1.5 equiv.) and this was then allowed to stir at 18 °C for 3 h before being diluted with ethyl acetate (50 mL) then washed with water (5 × 50 mL) and brine (1 × 50 mL). The organic phase was then dried (MgSO₄), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 95:5 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (Rᵋ = 0.4 in 95:5 v/v hexane/ethyl acetate) gave azide (±)-8 (990 mg, 92 %) as a clear, colorless oil and a ca. 15:1 mixture of diastereoisomers.

¹H NMR (400 MHz, CDCl₃): 6.19 (m, 1H), 4.03–3.94 (complex m, 2H), 2.32–2.20 (complex m, 2H), 2.18–2.08 (complex m, 1H), 1.96–1.86 (complex m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δc 131.3, 120.6, 64.7, 61.6, 38.9, 36.8, 25.8, 18.2, −4.7, −4.9.

IR (KBr): νmax 2954, 2929, 2895, 2857, 2104, 1471, 1253, 1110 cm⁻¹.

MS (ESI, +ve): m/z 356 and 354 [(M+Na)⁺, 100 and 99%, respectively].

HRMS: (M + Na)⁺, Calcd for C₁₂H₂₂⁷⁹Br²³N₃OSi: 354.0613. Found: 354.0616.

Compound (±)-9

A magnetically stirred solution of azide (±)-8 (1.05 g, 3.16 mmol) in MeOH/H₂O (25mL of a 95:5 v/v mixture) was treated with triphenylphosphine (1.60 g, 6.32 mmol) and the ensuing mixture heated at reflux for 2 h then cooled to 18 °C and treated with anhydrous MgSO₄ (3.0 g). The mixture thus obtained was filtered and the solids so retained were washed the CH₂Cl₂ (25 mL). The
combined filtrates were concentrated under reduced pressure to yield a mixture of the anticipated amine and triphenylphosphine oxide as a white solid. This was dissolved in dry CH$_2$Cl$_2$ (20 mL) and the resulting solution cooled to 0 °C then treated with triethylamine (1.3 mL, 9.70 mmol) and nosyl chloride (851 mg, 3.84 mmol). The ensuing mixture was stirred at 0 °C for 2 h then diluted in CH$_2$Cl$_2$ (20 mL) and water (20 mL). The separated aqueous phase was extracted CH$_2$Cl$_2$ (2 × 20 mL) and the combined organic phases were washed with brine (1 × 50 mL) before being dried (MgSO$_4$), filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) gave, after concentration of the appropriate fractions ($R_f = 0.3$ in 4:1 v/v hexane/ethyl acetate), a ca. 10:1 mixture of compound (±)-9 and its diastereoisomer (1.29 g, 83 %) as a pale-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ$_H$ (major diastereoisomer) 8.18 (m, 1H), 7.86 (m, 1H), 7.72–7.65 (complex m, 2H), 6.31 (d, $J = 9.4$ Hz, 1H), 6.05 (tm, $J = 4.0$ Hz, 1H), 4.31 (m, 1H), 4.26 (m, 1H), 2.25 (m, 3H), 2.09 (ddd, $J = 14.0$, 5.8 and 2.0 Hz, 1H), 0.93 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ$_C$ (major diastereoisomer) 135.9, 133.6, 132.9, 132.4, 130.7, 129.6, 125.1, 121.1, 64.3, 54.8, 38.7, 36.2, 25.9, 18.3, −4.9, −5.0.

IR (KBr): $\nu_{\text{max}}$ 3351, 2929, 2857, 1541, 1471, 1410, 1362, 1258, 1166, 1103, 1060 cm$^{-1}$.

MS (ESI, +ve): m/z 515 and 513 [(M+Na)$^+$, 100 and 90%, respectively], 493 and 491 (80 and 72, respectively).

HRMS: (M + Na)$^+$, Caled for C$_{18}$H$_{27}$Br$_{23}$Na$_2$O$_5$: 513.0491. Found: 513.0491.

**Compound (±)-11**

A magnetically stirred solution of compound (±)-9 (1.28 g, 2.61 mmol, 1.0 equiv.), benzo[d][1,3]dioxol-5-yl-boronic acid (10) (867 mg, 5.22 mmol, 2.0 equiv.), PdCl$_2$dpff•CH$_2$Cl$_2$ (148 mg, 0.182 mmol, 0.07 equiv.) and triethylamine (2.6 mL) in THF/water (10 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h then heated at reflux for 2 h before being cooled, poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 50 mL) then dried (MgSO$_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 9:1
→ 7:3 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (Rf = 0.3 in 7:3 v/v hexane/ethyl acetate), a ca. 12:1 mixture of compound (±)-11 and its diastereoisomer (1.25 g, 90%) as a pale-yellow oil.

**1H NMR** (400 MHz, CDCl3): δH (major diastereoisomer) 7.75 (dd, J = 7.7 and 1.6 Hz, 1H), 7.68 (dd, J = 7.7 and 1.6 Hz, 1H), 7.53–7.44 (complex m, 2H), 6.53 (dd, J = 8.0 and 1.7 Hz, 1H), 6.45 (d, J = 1.7 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.34 (d, J = 9.3 Hz, 1H), 5.83 (s, 2H), 5.67 (t, J = 3.7 Hz, 1H), 4.64 (m, 1H), 4.30 (m, 1H), 2.33–2.28 (complex m, 3H), 2.07 (m, 1H), 0.96 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H)

**13C NMR** (100 MHz, CDCl3): δc (major diastereoisomer) 146.9, 146.5, 137.4, 136.1, 134.8, 132.9, 132.3, 131.7, 130.1, 125.2, 124.9, 120.6, 107.8, 107.6, 100.8, 65.1, 50.4, 37.7, 34.4, 25.9, 18.4, –4.9 (two signals overlapping).

**IR** (KBr): vmax 3365, 2954, 2928, 2857, 1539, 1504, 1489, 1440, 1342, 1249, 1162, 1099, 1039 cm⁻¹.

**MS** (ESI, +ve): m/z 555 [(M+Na)⁺, 100%], 533 (60).


**Compound (±)-12**

A magnetically stirred solution of compound (±)-11 (1.10 g, 2.06 mmol, 1.0 equiv.) in DMF (10 mL) maintained under a nitrogen atmosphere at 0 °C was treated with sodium hydride (165 mg of a 60% suspension in oil, 4.12 mmol). After 0.33 h the reaction mixture was treated with 1-bromobuty-2-yne (900 µL, 10.32 mmol), allowed to warm to 18 °C, stirred at this temperature for 2 h then quenched with water (40 mL) before being diluted with ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers washed with water (5 × 20 mL) then brine (1 × 40 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 9:1 → 7:3 v/v hexane/ethyl acetate gradient elution) to afford, after
concentration of the appropriate fractions ($R_f = 0.3$ in 7:3 v/v hexane/ethyl acetate), *compound (±)-I2* (1.16 g, 96%) as a white crystalline solid, mp 170–172 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 8.11 (d, $J = 7.7$ Hz, 1H), 7.67 (dt, $J = 7.7$ and 1.1 Hz, 1H), 7.59 (dt, $J = 7.7$ and 1.1 Hz, 1H), 7.54 (dd, $J = 7.7$ and 1.1 Hz, 1H), 6.73–6.70 (complex m, 2H), 6.63 (d, $J = 7.9$ Hz, 1H), 5.88 (m, 3H), 5.21 (m, 1H), 4.00–3.94 (complex m, 2H), 3.56 (ddm, $J = 18.3$ and 2.3 Hz, 1H), 2.46–2.39 (complex m, 1H), 2.25–2.11 (complex m, 3H), 1.64 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_c$ 148.3, 147.2, 146.7, 137.5, 133.9, 133.3, 131.4, 130.7, 129.7, 123.4, 120.5, 110.0, 107.8, 107.6, 100.9, 81.3, 74.8, 66.8, 57.3, 37.9, 35.6, 34.2, 25.8, 18.1, 3.44, −4.6, −4.7.

IR (KBr): $\nu_{max}$ 3459, 2955, 2929, 2856, 1644, 1546, 1490, 1438, 1373, 1248, 1169, 1102, 1078, 1038 cm$^{-1}$.

MS (ESI, +ve): $m/z$ 607 [(M+Na)$^+$, 100%], 585 (18).

HRMS: (M + Na)$^+$, Calcd for C$_{29}$H$_{36}$NaN$_2$O$_7$Si: 607.1910. Found: 607.1908.

**Compound (±)-13**

A solution of compound (±)-13 (323 mg, 0.55 mmol, 1.0 equiv.) in benzene (2.5 mL) containing Pd(OAc)$_2$ (25 mg, 0.11 mmol, 20 mole %) and BBEDA (27 mg, 0.11 mmol) was purged with nitrogen for 0.25 h then subjected to microwave irradiation (100W, 120 °C, 200 psi) for 4 h in a CEM Discover microwave reactor. The cooled reaction mixture was combined with those arising from repeating the same process twice and then treated with TLC-grade silica. The mixture thus obtained was concentrated under reduced pressure and the resulting free-flowing solid was subject to flash chromatography (silica, dry loading, 9:1 → 7:3 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions ($R_f = 0.3$ in 7:3 v/v hexane/ethyl acetate), *compound (±)-I3* (730 mg from three runs, av. 75%/run) as a white glass.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.52–7.47 (complex m, 2H), 7.38 (dd, $J = 7.9$ and 1.2 Hz, 1H), 7.30 (m, 1H), 6.53–6.48 (complex m, 2H), 6.41 (d, $J = 8.0$ Hz, 1H), 5.85 (dd, $J = 5.9$ and 1.3 Hz,
2H), 5.70 (dm, J = 10.1 Hz, 1H), 5.57 (dd, J = 10.1 and 2.0 Hz, 1H), 5.50–5.44 (complex m, 1H), 4.54 (m, 1H), 4.34 (m, 2H), 4.30 (dd, J = 12.7 and 4.2 Hz, 1H), 2.31 (m, 1H), 1.76 (d, J = 6.9 Hz, 3H), 1.70 (m, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).

^{13}C\text{ NMR} (100 MHz, CDCl}_3): \delta c 147.8, 147.3, 146.2, 139.2, 138.7, 132.5, 132.2, 131.6, 130.9, 129.7, 129.6, 123.3, 122.6, 120.4, 107.8, 107.7, 101.0, 67.3, 66.8, 55.0, 48.9, 38.2, 25.9, 18.2, 14.7, –4.5, –4.7.

IR (KBr): v_{max} 3401, 2929, 1637, 1544, 1484, 1359, 1248, 1166, 1084, 835, 756 cm^{-1}.

MS (ESI, +ve): m/\zeta 607 [(M+Na)^+, 38\%], 585 (14), 453 (100).

HRMS: (M + Na)^+, Calcd for C_{29}H_{36}^{23}\text{NaN}_2O_7SSi: 607.1910. Found: 607.1917.

**Compound (±)-14**

![Diagram of Compound (±)-14]

**(±)-14**

**Step i:** A magnetically stirred solution of compound (±)-13 (102 mg, 0.17 mmol) in acetonitrile/water (0.5 mL of a 4:1 v/v mixture) maintained at 18 °C was treated with citric acid (101 mg, 0.52 mmol), N-methylmorpholine N-oxide (60 mg, 0.35 mmol) and potassium osmate dihydrate (6.4 mg, 0.017 mmol). The ensuing mixture, which developed a green coloration within a few minutes, was stirred vigorously at 18 °C for 30 h then diluted with ethyl acetate (10 mL) and HCl (10 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were washed with brine (1 × 20 mL) then dried (MgSO_4), filtered and concentrated under reduced pressure. The resulting light-brown oil was dissolved in a minimum volume of CH_2Cl_2 and the resulting solution treated with TLC-grade silica gel (100 mg) before being concentrated under reduced pressure. The free-flowing solid thus obtained was loaded onto the top of a short plug of TLC-grade silica gel that was then rinsed with ethyl acetate/hexane (100 mL of a 1:1 v/v mixture). The filtrate was concentrated under reduced pressure and the crude diol (now free from osmium-containing impurities) was subjected to step ii of the reaction sequence as described immediately below.

**Step ii:** The crude diol obtained as described above was dissolved in CH_2Cl_2 (1.5 mL) and the solution thus obtained treated with iodobenzene diacetate (61 mg, 0.19 mmol). The ensuing mixture was vigorously stirred at 18 °C for 2 h then treated with TLC-grade silica (100 mg) and concentrated under reduced pressure. The resulting free-flowing solid was subject to flash
chromatography (silica, dry loading, 4:1 → 3:2 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 7:3 v/v hexane/ethyl acetate), compound (+)-14 (50 mg, 53%) as a white glass.

_1^1^H NMR (400 MHz, CDCl_3): δ_H 7.76 (dd, J = 7.9 and 1.3 Hz, 1H), 7.64–7.60 (complex m, 1H), 7.52–7.47 (complex m, 2H), 6.50–6.45 (complex m, 3H), 5.91–5.85 (complex m, 3H), 5.66 (dd, J = 10.1 and 2.1 Hz, 1H), 4.65 (dd, J = 12.9 and 4.7 Hz, 1H), 4.45 (m, 1H), 4.41 (d, J = 18.7 Hz, 1H), 4.02 (d, J = 18.7 Hz, 1H), 2.47–2.42 (complex m, 1H), 1.66 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

_1^3^C NMR (100 MHz, CDCl_3): δ_c 208.2, 148.0, 147.1, 134.8, 133.4, 133.0, 132.6, 131.5, 130.0, 126.1, 123.9, 119.7, 108.2, 106.9, 101.3, 65.9, 64.0, 59.4, 52.1, 37.8, 25.7, 18.1, –4.6, –4.7 (one signal obscured or overlapping)

IR (KBr): ν_max 2956, 1761, 1648, 1545, 1506, 1486, 1372, 1250, 1164, 1086 cm⁻¹.

HRMS: (M + K)^+ Calcd for C_{27}H_{32}^{39}KN_O_Si: 611.1286. Found: 611.1285.

**Compound (+)-15**

A magnetically stirred solution of ketone (+)-14 (38 mg, 0.066 mmol) in THF/methanol (1.2 mL of a 1:1 v/v mixture) maintained at 0 °C was treated with anhydrous potassium carbonate (18 mg, 0.132 mmol,) and the ensuing mixture stirred at this temperature for 0.5 h then treated with TLC-grade silica gel (100 mg) and concentrated under reduced pressure. The resulting free-flowing solid was IMMEDIATELY subjected to rapid flash chromatography (silica, dry loading, 4:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 9:1 v/v hexane/ethyl acetate), compound (+)-15 (22 mg, 88%) as a rather unstable white glass.

_1^1^H NMR (400 MHz, CDCl_3): δ_H 7.84 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.55–6.52 (complex m, 2H), 6.09 (dd, J = 9.9 and 4.1 Hz, 1H), 5.93 (s, 2H), 5.74 (dm, J = 9.9 Hz, 1H), 4.68 (m, 1H), 4.35 (m, 1H), 2.32 (dd, J = 13.8, 6.0 and 4.2 Hz, 1H), 2.04 (td, J = 13.8 and 5.7 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 203.0, 163.1, 160.4, 148.2, 146.8, 134.6, 134.5, 126.5, 120.0, 108.5, 107.3, 101.2, 63.9, 54.8, 35.7, 25.5, 18.0, –4.6, –4.7.

IR (KBr): $\nu_{\text{max}}$ 2953, 2928, 2855, 1736, 1636, 1504, 1489, 1246, 1072, 1040 cm$^{-1}$.

MS (ESI, +ve): $m/z$ 424 [(M+K)$^+$, 100%], 408 [(M+Na)$^+$, 75], 386 [(M+H)$^+$, 60].

HRMS: M$^+$, Calcd for C$_{21}$H$_{27}$NO$_4$Si: 385.1709. Found: 385.1720.

**Compound (±)-1 [(±)-Hamayne]**

![Chemical Structure](image)

(±)-1

**Step i:** Sodium borohydride (16 mg, 0.42 mmol, 7.0 equiv.) maintained at 20 °C (water bath) was treated, dropwise, with glacial acetic acid (0.6 mL). The resulting solution was stirred at this temperature for 0.33 h then added, dropwise, to a magnetically stirred solution of compound (±)-15 (23 mg, 0.056 mmol) in ethyl acetate (0.6 mL) maintained at 0 °C (ice bath). Stirring was continued at 0 °C for 1 h and then the ice bath was allowed to melt over a further 1 h and the mixture stirred at 18 °C for an additional 22 h. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between CH$_2$Cl$_2$ (5 mL) and NaHCO$_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 5 mL) and the combined organic layers were then washed brine (1 × 10 mL) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to give the crude amino-alcohol (±)-16 as a light-yellow oil. This material was used without purification in the next step of the reaction sequence.

**Step ii:** A magnetically stirred solution of the above-mentioned amino-alcohol in formic acid (2.0 mL) maintained at 18 °C under a nitrogen atmosphere was treated with paraformaldehyde (30 mg) then heated at reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure to give di-formate (±)-17 as a light-yellow oil. This material was used without purification in the next step of the reaction sequence.

**Step iii:** The above-mentioned di-formate was treated with ammonia-saturated methanol (3.0 mL) at 0 °C and the resulting mixture stirred at this temperature for 1 h then at 18 °C for a further 1 h before being concentrated under reduced pressure to give a brown oil. Evaporation of the solvents gave a brown oil. Subjection of this material to flash chromatography (silica, CH$_2$Cl$_2$ → 4:1 v/v
CH$_2$Cl$_2$/methanol gradient elution) to afford, after concentration of the appropriate fractions ($R_f = 0.2$ in 4:1 v/v CH$_2$Cl$_2$/methanol), compound (±)-1 (11 mg, 65%) as a white, crystalline solid, mp >230 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ See Table 1 of paper

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_c$ See Table 1 of paper

IR (KBr): $\nu_{\text{max}}$ 3332, 2917, 2849, 1476, 1383, 1236, 1061, 1038, 929 cm$^{-1}$.

MS (EI, 70 eV): $m/z$ 287 (M$^+$, 4%), 286 (5), 269 (100), 268 (28), 240 (31), 181 (45).

HRMS: (M $+$ H)$^+$, Calcd for C$_{16}$H$_{17}$NO$_4$: 288.1236. Found: 288.1236.
X-ray Crystallographic Studies

X-ray Crystallographic Data

**Compound** (±)-12: C_{29}H_{36}N_{2}O_{7}Si, \( M = 584.77 \), \( T = 200 \) K, monoclinic, space group \( C2/c \), \( Z = 16 \), \( a = 25.6392(3) \), \( b = 14.1998(2) \), \( c = 34.5075(5) \) Å, \( \beta = 98.0857(7) \)°, \( V = 12438.3(3) \) Å\(^3\), \( D_x = 1.249 \) g cm\(^{-3}\), 10996 unique data (\( 2\theta_{\text{max}} = 50^\circ \)), \( R = 0.059 \) [for 7271 with \( I > 2.0\sigma(I) \)]; \( R_w = 0.164 \) (all data), \( S = 0.97 \).

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoK\(\alpha \), graphite monochromator, \( \lambda = 0.71073 \) Å) and data extracted using the DENZO package.\(^5\) Structure solution was by direct methods (SIR92).\(^6\) The structures of the above-mentioned compound was refined using the CRYSTALS program package.\(^7\) There is some disorder in the packing of the –SiMe\(_2\)Bu groups. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 840331). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
Anisotropic Displacement Ellipsoid Plots

**Figure S1.** Structure of molecule one of C_{29}H_{36}N_{2}O_{7}SSi (compound (±)-12, CCDC 840331) with labelling of non-hydrogen atoms. The minor alternative site for the Si atom is not shown. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

**Figure S2.** Structure of molecule two of C_{29}H_{36}N_{2}O_{7}SSi (compound (±)-12, CCDC 840331) with labelling of non-hydrogen atoms, showing the major (a) and minor (b) sites for atoms of the disordered –SiMe₂Bu group. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
400 MHz $^1$H NMR Spectrum of Compound 7 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 7 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-8 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-8 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-9 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-9 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (α)-11 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-11 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-12 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (e)-12 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-13 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-13 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-14 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-14 Recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound (a)-15 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (±)-15 Recorded in CDCl₃

* = impurity
400 MHz $^1$H NMR Spectrum of Compound (a)-1 Recorded in CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound (a)-1 Recorded in CDCl$_3$
References


