Synthesis of (–)-Quinocarcin by Directed Condensation of α -Amino Aldehydes

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Supporting Information

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General Experimental Procedures. All reactions were performed in flame-dried, single-neck, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles ($\geq$ three iterations). Organic solutions were concentrated by rotary evaporation at 23–35 °C at 40 Torr (house vacuum). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in ethanolic phosphomolybdic acid (PMA), aqueous ceric ammonium molybdate solution (CAM), aqueous potassium permanganate solution (KMnO₄), acidic ethanolic *p*-anisaldehyde solution (anisaldehyde), or solutions of ninhydrin in *n*-butanol, followed by brief heating on a hot plate (~200 °C, 10–15 s). Flash-column chromatography was performed as described by Still et al.¹ employing silica gel (60-Å pore size, 230–400 mesh, Merck KGA; or 60-Å pore size, standard grade, Sorbent Technologies).

Materials. Commercial reagents and solvents were used as received unless otherwise indicated. Dichloromethane, ether, tetrahydrofuran, *N,N*-dimethylformamide and toluene were purified by the method of Pangborn et al.² Lithium chloride was pre-dried at 150 °C under vacuum (0.5 mm Hg) for 24 h, then was flame-dried under vacuum immediately prior to use. The molarity of solutions of *n*-butyllithium, phenyllithium and *t*-butyllithium was determined by titration using diphenylacetic acid as an indicator (average of four determinations).³

Instrumentation. Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded with Varian INOVA 600 (600 MHz), Varian INOVA 500 (500 MHz/125 MHz), or Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometers at 23 °C. Chemical shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, CHDCl₂: δ 5.29, C₆HD₅: δ 7.15, CD₂HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

² Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

³ Kofron, W. G.; Baclawski, L.M. *J. Org. Chem.* **1976**, *41*, 1879.

scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0, CH_2Cl_2 : δ 53.8, C_6D_6 : δ 128.0, CD_3OD : δ 49.2). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant in Hz, and assignment. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data is presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment. High resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facilities. Optical rotations were determined using JASCO DIP-370 digital polarimeter equipped with a sodium lamp source (589 nm). Reported readings are an average of six measurements for each sample. The X-ray crystal structure of intermediate **28** was obtained by Dr. Richard J. Staples at the Harvard University X-ray Crystallography Laboratory.

Determination of the Diastereomeric Excesses of Alkylation Products by Capillary GC Analysis.

The diastereomeric excess (de) of certain alkylation products (so indicated in the experimental procedures) was determined by acetylation followed by capillary GC analysis (Chirasil-Val column, 25 m $\times$ 0.25 mm, 235 $^\circ\text{C}$, injection port: 250 $^\circ\text{C}$, detector: 275 $^\circ\text{C}$). The procedure for acetylation is as follows. Acetic anhydride (1 mL) and 4-(dimethylamino)pyridine (ca. 2 mg) were added to a solution of the alkylation product (10–20 mg) in pyridine (1 mL). The resulting solution was stirred at 23 $^\circ\text{C}$ for 1 h and then was diluted with water (20 mL). The product was extracted with ethyl acetate (2 $\times$ 20 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL). The organic layer was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate (10 mL) and the resulting solution was analyzed by capillary GC analysis.

Determination of the Diastereomeric Excesses of Alkylation Products by HPLC Analysis. The diastereomeric excess (de) of certain alkylation products (so indicated in the experimental procedures) was determined by benzoylation followed by HPLC analysis. The procedure for benzoylation is as follows. Benzoyl chloride (5 equiv) was added to a cold (-78 $^\circ\text{C}$) solution of triethylamine (5 equiv) and an alkylation product (10–20 mg) in dichloromethane. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (8 mL) and ethyl acetate (10 mL). The organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate solution (8 mL), water (8 mL) and brine (8 mL). The washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate (10 mL) and the resulting solution was analyzed by HPLC.

Synthetic Procedures for the Synthesis of Quinocarcin. (*For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the Supporting Information beginning with 11.*)

Pseudoephedrine Amide **11**:

Lithium hexamethyldisilazide (1 M solution in THF, 21.9 mL, 21.9 mmol, 3.20 equiv) was added dropwise via syringe to an ice-cooled solution of (*R,R*)-(-)-pseudoephedrine glycine amide hydrate (1.64 g, 6.83 mmol, 1 equiv) and lithium chloride (1.16 g, 27.3 mmol, 4 equiv) in tetrahydrofuran (20

mL). After 20 min, (4-bromo-2-(*E*)-butenyl)trimethylsilane (1.49 g, 7.17 mmol, 1.05 equiv)⁴ was injected slowly into the orange enolate solution. After addition of the electrophile was complete, the reaction mixture was stirred at 0 °C for 3 h. Water (50 mL) was added and the biphasic mixture was extracted sequentially with ethyl acetate (1 × 70 mL) and dichloromethane (3 × 70 mL). The combined organics were dried over anhydrous potassium carbonate. The dried solution was filtered and the filtrate was concentrated. The de of the crude reaction product was determined to be 91% by capillary GC analysis of an acetylated sample (major t_R = 13.3 min, minor t_R = 12.2 min), as described in the general procedures. The residue was purified by flash-column chromatography (98:1:1 dichloromethane–methanol–ammonium hydroxide) to afford the pseudoephedrine amide **11** as a clear oil (2.03 g, 89% yield).

¹H NMR (500 MHz, CDCl₃, 2.9:1 mixture of rotamers, * denotes the minor rotamer), δ: 7.37–7.25 (m, 5H, ArH), 5.48 (dt, 1H, J = 14.7, 7.7 Hz, CHCH₂Si), 5.61–5.55 (m, 1H, CHCH₂Si*), 5.12 (dt, 1H, J = 15.0, 7.2 Hz, CHCH₂CHNH₂), 5.32–5.28 (m, 1H, CHCH₂CHNH₂*), 4.63–4.48 (m, 2H, CHOH and CH₃CH), 4.08 (br s, 1H, CHOH*), 3.66 (dd, 1H, J = 8.3, 3.3 Hz, NCOCH*), 3.60 (app t, 1H, J = 6.0 Hz, NCOCH), 2.94 (s, 3H, NCH₃*), 2.87 (s, 3H, NCH₃), 2.25–2.18 (m, 1H, COCHCH₂), 2.09–2.03 (m, 1H, COCHCH₂*), 1.49 (d, 2H, J = 8.0 Hz, CHCH₂Si*), 1.43 (d, 2H, J = 8.0 Hz, CHCH₂Si), 1.06 (d, 3H, J = 6.6 Hz, CH₃CHN), 0.97 (d, 3H, J = 6.7 Hz, CH₃CHN*), 0.02 (s, 9H, Si(CH₃)₃*), –0.01 (s, 9H, Si(CH₃)₂).

¹³C NMR (100 MHz, CDCl₃, * denotes the minor rotamer), δ: 176.7, 174.7*, 142.2, 141.6*, 130.7, 130.5*, 128.7*, 128.3, 127.6*, 126.9, 126.7*, 126.5, 124.0*, 123.2, 75.8, 75.2*, 58.3, 57.7*, 52.0, 39.1, 31.9, 29.6*, 27.0*, 22.9, 15.5*, 14.4, –1.8*, –2.0.

FTIR (thin film), cm^{–1}: 3355 (br m, NH₂), 2953 (m), 1633 (s, C=O), 1453 (m), 1411 (w), 1247 (s), 1119 (w), 1052 (w), 968 (w), 850 (s), 760 (w), 701 (s), 464 (m).

TLC (88:10:2 CH₂Cl₂–MeOH–NH₄OH), R_f : Pseudoephedrine Glycinamide Hydrate: 0.15 (ninhydrin)
Pseudoephedrine Amide **11**: 0.41 (ninhydrin).

HRMS (ES)⁺: Calcd for C₁₉H₃₂N₂O₂Si [M+H]⁺: 349.2311
Found: 349.2300.

Alcohol **12**:

n-Butyllithium (2.53 M solution in hexanes, 17.8 mL, 45.0 mmol, 4.8 equiv) was added dropwise to a cold (–78 °C) solution of diisopropylamine (6.84 mL, 48.8 mmol, 5.2 equiv) in tetrahydrofuran (27 mL; substrate concentration ~0.35 M). After 10 min, the cloudy solution was transferred to an ice bath, whereupon the solution was observed to clarify. Solid borane-ammonia

⁴ Mastalerz, H. *J. Org. Chem.* **1984**, 49, 4092–4094.

complex (90%, 1.61 g, 46.9 mmol, 5 equiv) was added to the solution after 10 min. The ice bath was removed 10 min later and, after 20 min, the warmed solution (23 °C) was cooled to –78 °C. After 10 min, a solution of the amide **11** (3.14 g, 9.38 mmol, 1 equiv) in tetrahydrofuran (20 mL, followed by 5-mL and 3-mL rinses) was transferred to the reaction mixture via cannula. The resulting solution was allowed to warm to 0 °C and the warmed solution was stirred for 3 h at 0 °C. Sodium bisulfate (2 M aqueous solution, 14 mL, 15 equiv) and ethyl acetate (20 mL) were then added sequentially to the reaction mixture. The resulting emulsion (pH 2) was stirred vigorously for 2 h at 0 °C. The biphasic solution was brought to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The organic layer was separated and extracted with dichloromethane (4 × 60 mL). The combined organic extracts were dried over anhydrous potassium carbonate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (96.5:2:1.5 dichloromethane–methanol–ammonium hydroxide) to furnish a 1:1 mixture of the amino alcohol and pseudoephedrine. The highly crystalline by-product pseudoephedrine was removed by crystallization from hot hexanes. The filtrate (now containing <10% of pseudoephedrine) was then purified by flash-column chromatography (97:2:1 dichloromethane–methanol–ammonium hydroxide) to afford the alcohol **12** (1.39 g, 79% yield) as a clear oil.

¹H NMR (400 MHz, CDCl₃), δ:

5.52–5.44 (m, 1H, SiCH₂CH), 5.23–5.16 (m, 1H, SiCH₂CH=CH), 3.58 (dd, 1H, *J* = 10.6, 4.0 Hz, HOCH₂), 3.29 (dd, 1H, *J* = 10.6, 7.7 Hz, HOCH₂), 2.87–2.81 (m, 1H, CHNH₂), 2.00–1.93 (m, 1H, NH₂CHCH₂), 1.83 (br s, 3 H, NH₂ & OH), 1.44 (d, 2H, *J* = 8.0 Hz, SiCH₂), –0.01 (s, 9H, Si(CH₃)₃).

¹³C NMR (100 MHz, CDCl₃), δ:

129.5, 124.3, 66.5, 52.6, 38.1, 22.9, –2.0.

FTIR (thin film), cm^{–1}:

3237 (w br, NH₂ & OH), 2952 (m), 1571 (w), 1248 (s), 1155 (w), 1058 (m), 966 (m), 850 (s), 693 (m).

HRMS (CI)⁺:

Calcd for C₉H₂₁NOSi [M+H]⁺: 188.1471

Found: 188.1473.

TLC (88:10:2 CH₂Cl₂–MeOH–NH₄OH), R_f:

Amide **11**: 0.38 (ninhydrin)

Alcohol **12**: 0.28 (ninhydrin).

Carbamate **13**:

Triethylamine (1.51 mL, 10.9 mmol, 1.2 equiv) and *N*-(9-fluorenylmethoxycarbonyloxy)-succinimide (3.21 g, 9.51 mmol, 1.05 equiv) were added sequentially to an ice-cooled solution of the amino alcohol **12** (1.39 g, 7.42 mmol, 1 equiv) in tetrahydrofuran (90.5 mmol; substrate concentration ~0.1 M). After 1 h at 0 °C, the reaction mixture was partitioned between saturated aqueous ammonium chloride solution (40 mL) and ethyl acetate (40 mL). The organic solution was separated and washed with saturated aqueous sodium bicarbonate solution (1 × 20 mL), then brine (1 × 20 mL). The washed organic layer was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (90:10 dichloromethane–ethyl acetate) to afford the carbamate **13** (3.04 g, 100% yield) as a pale yellow foam. The ee of the product was determined to be 92% by Mosher ester analysis (¹H NMR, CDCl₃).

^1H NMR (400 MHz, CDCl_3), δ : 7.77 (d, 2H, $J = 7.3$ Hz, FmocArH), 7.59 (d, 2H, $J = 7.8$ Hz, FmocArH), 7.40 (t, 2H, $J = 7.3$ Hz, FmocArH), 7.31 (t, 2H, $J = 7.6$ Hz, FmocArH), 5.55–5.49 (m, 1H, SiCH_2CH), 5.22–5.19 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.93 (br d, 1H, $J = 4.9$ Hz, FmocNH), 4.40 (d, 2H, $J = 6.3$ Hz, FmocCH₂), 4.21 (t, 1H, $J = 6.6$ Hz, FmocCH), 3.69 (d, 2H, $J = 8.8$ Hz, HOCH₂), 3.62 (br m, 1H, CHNH₂), 2.36 (br s, 1H, OH), 2.72–2.21 (m, 2H, NH₂CHCH₂), 1.45 (d, 2H, $J = 8.3$ Hz, SiCH₂), –0.01 (s, 9H, Si(CH₃)₃).

^{13}C NMR (100 MHz, CDCl_3), δ : 156.8, 143.9, 141.3, 130.8, 127.7, 127.0, 125.0, 123.2, 119.9, 66.7, 65.2, 53.1, 47.2, 34.8, 22.9, –2.0.

FTIR (thin film), cm^{-1} : 3409 (br w), 3328 (br w), 2952 (m), 2890 (w), 1702 (s, C=O), 1512 (m), 1450 (m), 1247 (s), 1054 (m), 862 (m), 850 (s), 758 (m), 739 (s).

HRMS (CI)⁺: Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_3\text{Si}$ [M+H]⁺: 410.2151
Found: 410.2144.

TLC (40:60 EtOAc–hexanes), R_f : Alcohol **12**: baseline (CAM)
Carbamate **13**: 0.43 (CAM).

TLC (30:70 MeOH–CH₂Cl₂), R_f : Alcohol **12**: 0.07 (CAM)
Carbamate **13**: 0.95 (CAM).

C-Protected α -Amino Aldehydes (*S,S*)-**2** and (*R,S*)-**2**:

Dess-Martin periodinane (106 mg, 0.273 mmol, 2 equiv) was added to an ice-cooled solution of the alcohol **13** (50.8 mg, 0.124 mmol, 1 equiv) in dichloromethane (0.9 mL; substrate concentration ~0.15 M). A cloudy suspension formed almost instantly. After 40 min at 0 °C, ether (3 mL), saturated aqueous sodium bicarbonate solution (3 mL), and solid sodium thiosulfate (738 mg, 2.97 mmol, 24 equiv) were added to the reaction mixture in sequence. After 10 min of vigorous stirring, the cloudy organic layer turned clear. The mixture was diluted with ether (20 mL) and the two layers of the biphasic mixture were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (7 mL), water (7 mL), and brine (7 mL). The washed organic layer was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude aldehyde **14** as a pale yellow oil.

Acetic acid (16 μL , 0.28 mmol, 2.25 equiv) was added to an ice-cooled suspension of potassium cyanide (17 mg, 0.26 mmol, 2.1 equiv) in methanol (0.3 mL; substrate concentration ~0.4 M). After 10

min, the solid potassium cyanide appeared to have dissolved and a clear, colorless solution was formed (Caution: HCN!). The clear solution was transferred via syringe to an ice-cooled solution of the aldehyde **14** (crude, prepared as described in the paragraph above) in dichloromethane (0.6 mL; substrate concentration ~0.2 M). After 4 h at 0 °C, the reaction mixture was partitioned between a 4:1 mixture of brine and saturated aqueous sodium bicarbonate solution (6 mL) and ethyl acetate (35 mL). The organic layer was separated and washed with a 4:1 mixture of brine and saturated aqueous sodium bicarbonate solution (2 × 6 mL). The washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a mixture of the diastereomeric cyanohydrins **15**.

Morpholine (54 µL, 0.620 mmol, 5 equiv) was added dropwise to a solution of the mixture of diastereomeric cyanohydrins **15** (prepared as described in the previous paragraph) in 2,2,2-trifluoroethanol (0.25 mL; substrate concentration ~0.5 M). The reaction mixture was allowed to stir for 14 h, after which time the solution was concentrated. The residue was dissolved in toluene (2 mL) and the resulting solution was concentrated, affording the diastereomeric morpholino nitriles **16** in crude form, as a pale yellow oil.

1,8-Diazabicyclo[5.4.0]undec-7-ene (26 µL, 0.174 mmol, 1.4 equiv) was added to an ice-cooled solution of the mixture of morpholino nitriles **16** (prepared as described in the previous paragraph) in dichloromethane (1.2 mL; substrate concentration ~0.1 M). The ice bath was removed after 10 min and the warmed solution was allowed to stir for 25 min at 23 °C. The reaction mixture was loaded directly on a column of silica gel and the column was eluted with 0.4% → 0.6% → 1% → 2% methanol–dichloromethane to afford separately the C-protected α-amino aldehyde (*S,S*)-**2** (17.2 mg, 49% yield) and the C-protected α-amino aldehyde (*R,S*)-**2** (15.5 mg, 44% yield) as clear oils. Both diastereomers were determined to be 92% ee by Mosher amide analysis (¹H NMR, CDCl₃).

C-Protected α-Amino Aldehyde (*S,S*)-**2**

¹ H NMR (400 MHz, CDCl ₃), δ:	5.55 (dt, 1H, <i>J</i> = 15.1, 8.0 Hz, CHCH ₂ Si), 5.19–5.12 (m, 1H, CHCHCH ₂ Si), 3.78–3.68 (m, 4H, CH ₂ OCH ₂), 3.19 (d, 1H, <i>J</i> = 8.6 Hz, N≡CCH), 3.05 (td, 1H, <i>J</i> = 8.0, 4.0 Hz, CHNH ₂), 2.69–2.64 (m, 2H, CH ₂ NCH ₂), 2.54–2.49 (m, 2H, CH ₂ NCH ₂), 2.45–2.39 (m, 1H, CH ₂ CHNH ₂), 2.11–2.04 (m, 1H, CH ₂ CHNH ₂), 1.46 (d, 2H, <i>J</i> = 8.0 Hz, CH ₂ Si), 1.38 (br s, 2H, NH ₂), –0.01 (s, 9H, Si(CH ₃) ₃).
¹³ C NMR (100 MHz, CDCl ₃), δ:	131.8, 122.5, 116.3, 66.6, 65.2, 50.8, 50.1, 37.1, 23.1, –1.9.
FTIR (thin film), cm ^{–1} :	3379 (br w, NH), 2955 (w), 2225 (w, C≡N), 1454 (w), 1118 (s).
TLC (40:60 EtOAc–hexanes), R _f :	Alcohol 13 : 0.22 (CAM) Aldehyde 14 : 0.53 (CAM) Morpholino Nitriles 16 : 0.37 (CAM).
TLC (3% MeOH–CH ₂ Cl ₂), R _f :	Morpholino Nitriles 16 : 0.60 (ninhydrin) C-Protected α-Amino Aldehyde (<i>S,S</i>)- 2 : 0.30 (ninhydrin) Dibenzofulvene: 0.85 (UV).
HRMS (ES) ⁺ :	Calcd for C ₁₄ H ₂₇ N ₃ OSi [M+H] ⁺ : 282.2002 Found: 282.2011.

C-Protected α-Amino Aldehyde (*R,S*)-**2**

¹ H NMR (400 MHz, CDCl ₃), δ:	5.61 (dt, 1H, <i>J</i> = 15.0, 8.1 Hz, CHCH ₂ Si), 5.23 (dt, 1H, <i>J</i> = 15.0, 7.2 Hz, CHCHCH ₂ Si), 3.80–3.71 (m, 4H, CH ₂ OCH ₂), 3.16 (d, 1H, <i>J</i> = 10.3 Hz, NCCH), 3.08 (ddd, 1H, <i>J</i> = 10.2, 7.5, 2.9 Hz, NCCH), 2.72–2.68 (m, 2H, CH ₂ NCH ₂), 2.53–2.49 (m,
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^3H , CH_2NCH_2 and CH_2CHNH_2), 2.12–2.06 (m, 1H, CH_2CHNH_2), 1.64 (br s, 2H, NH_2), 1.47 (d, 2H, $J = 8.1$ Hz, CH_2Si), 0.00 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz, CDCl_3), δ : 131.9, 122.0, 115.2, 66.6, 64.1, 50.3, 50.1, 36.9, 27.1, –1.9.

FTIR (thin film), cm^{-1} : 3382 (br w, NH), 2954 (s), 2225 (w, $\text{C}\equiv\text{N}$), 1454 (w), 1248 (s), 1118 (s).

TLC (3% MeOH in CH_2Cl_2), R_f : Amino Nitriles **16**: 0.60 (ninhydrin)
C-Protected α -Amino Aldehyde (*R,S*)-**2**: 0.16 (ninhydrin)
Dibenzofulvene: 0.85 (UV).

HRMS (ES) $^+$: Calcd for $\text{C}_{14}\text{H}_{27}\text{N}_3\text{OSi}$ $[\text{M}+\text{H}]^+$: 282.2002
Found: 282.2011.

Pseudoephedrine Amide **17**:

Lithium hexamethyldisilazide (1 M solution in THF, 5.25 mL, 5.25 mmol, 3.2 equiv) was added dropwise over 3 min to an ice-cooled solution of lithium chloride (278 mg, 6.57 mmol, 4 equiv) and (*R,R*)-(-)-pseudoephedrine glycinamide hydrate (395 mg, 1.64 mmol, 1 equiv) in tetrahydrofuran (2.5 mL). After 20 min, (4-bromo-2-butynyl)trimethylsilane (370.6 mg in 1.0 mL THF, 1.81 mmol, 1.1 equiv) was added dropwise via cannula over 15 min. Tetrahydrofuran (1 $\times$ 1.0 mL, then 1 $\times$ 0.5 mL) was used to quantitate the transfer. After 2.5 h at 0 °C, water (25 mL) was added and the mixture was extracted sequentially with ethyl acetate (1 $\times$ 25 mL) and dichloromethane (3 $\times$ 25 mL). The combined organic extracts were dried over anhydrous potassium carbonate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (98:1:1 dichloromethane–methanol–ammonium hydroxide) to afford the pseudoephedrine amide **17** (387 mg, 68% yield) as a yellow oil.

^1H NMR (400 MHz, CDCl_3 , 2.4:1 mixture of rotamers, * denotes the minor rotamer), δ : 7.40–7.27 (m, 10H, ArH & ArH*), 4.67 (d, 1H, $J = 8.1$ Hz, CH_3CH), 4.59 (d, 1H, $J = 9.1$ Hz, CH_3CH^*), 4.36 (br t, 1H, CHOH), 4.19 (br t, 1H, CHOH^*), 3.84 (dd, 1H, $J = 9.1, 3.7$ Hz, COCH), 3.72 (dd, 1H, $J = 7.3, 5.9$ Hz, COCH^*), 2.95 (s, 3H, NCH_3^*), 2.91 (s, 3H, NCH_3), 2.49–2.45 (m, 2H, $\text{NH}_2\text{CHCH}_2^*$), 2.33–2.30 (m, 2H, NH_2CHCH_2), 1.68 (br s, 6H, NH_2 & NH_2^* , OH & OH*), 1.48 (br s, 2H, SiCH_2^*), 1.43 (t, 2H, $J = 2.6$ Hz, SiCH_2), 1.13 (d, 3H, $J = 7.0$ Hz, NCHCH_3), 1.01 (d, 3H, $J = 6.6$ Hz, NCHCH_3^*), 0.12 (s, 9H, $\text{Si}(\text{CH}_3)_3^*$), 0.09 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

FTIR (thin film), cm^{-1} : 3354 (br w, OH), 2956 (w), 2892 (w), 2216 (w, $\text{C}\equiv\text{C}$), 1638 (s, $\text{C}=\text{O}$), 1491 (w), 1453 (m), 1408 (w), 1249 (m), 1050 (w), 846 (s), 760 (m), 701 (m).

HRMS (ES) $^+$: Calcd for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 347.2155
Found: 347.2150.

TLC (88:10:2 CH_2Cl_2 –MeOH– NH_4OH), R_f : XψGly·H₂O: 0.11 (ninhydrin)
Pseudoephedrine Amide **17**: 0.33 (ninhydrin).

Alcohol **18**:

n-Butyllithium (2.76 M solution in hexanes, 1.68 mL, 4.63 mmol, 4.8 equiv) was added dropwise to a cold ($-78\text{ }^{\circ}\text{C}$) solution of diisopropylamine (704 μL , 5.02 mmol, 5.2 equiv) in tetrahydrofuran (2.68 mL; substrate concentration $\sim 0.36\text{ M}$). After 10 min, the cloudy solution was transferred to an ice bath, whereupon the solution was observed to clarify. Solid borane-ammonia complex (90%, 166 mg, 4.83 mmol, 5 equiv) was added to the solution after 10 min. The ice bath was removed 10 min later and, after 10 min, the warmed solution ($23\text{ }^{\circ}\text{C}$) was cooled to $-78\text{ }^{\circ}\text{C}$. After 10 min, a solution of the amide **17** (335 g, 0.965 mmol, 1 equiv) in tetrahydrofuran (1.5 mL, followed by 0.8-mL and 0.4-mL rinses) was transferred to the reaction mixture via cannula. The resulting solution was allowed to warm to $0\text{ }^{\circ}\text{C}$ and the warmed solution was stirred for 4 h at $0\text{ }^{\circ}\text{C}$. Ether (10 mL) and sodium bisulfate (2 M aqueous solution, 8 mL, ca. 15 equiv) were then added to the reaction mixture in sequence. The resulting emulsion (pH 2) was stirred vigorously for 2 h at $0\text{ }^{\circ}\text{C}$. The biphasic mixture was adjusted to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The organic layer was separated and extracted sequentially with ethyl acetate ($1 \times 20\text{ mL}$) and dichloromethane ($3 \times 20\text{ mL}$). The combined organic extracts were dried over anhydrous potassium carbonate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (97:2:1 dichloromethane–methanol–ammonium hydroxide) to afford the alcohol **18** (128.5 mg, 72% yield) as a clear oil.

^1H NMR (400 MHz, CDCl_3), δ :

3.61 (dd, 1H, $J = 10.6, 4.4\text{ Hz}$, HOCH_2), 3.40 (dd, 1H, $J = 10.6, 7.3\text{ Hz}$, HOCH_2), 2.96 (app t, 1H, $J = 5.9\text{ Hz}$, HOCH_2CH), 2.32 (ddt, 1H, $J = 16.5, 5.5, 2.7\text{ Hz}$, $\text{CH}_2\text{C}\equiv\text{C}$), 2.24 (ddt, 1H, $J = 16.5, 6.6, 2.7\text{ Hz}$, $\text{CH}_2\text{C}\equiv\text{C}$), 1.77 (br s, 1H, OH), 1.44 (t, 2H, $J = 2.7\text{ Hz}$, SiCH_2), 0.09 (d, 9H, $J = 1.1\text{ Hz}$, $\text{Si}(\text{CH}_3)_3$).

FTIR (thin film), cm^{-1} :

3350 (br w, OH), 3282 (w), 2955 (m), 2902 (m), 2219 (w), 1578 (w), 1249 (s), 1170 (w), 1053 (m), 849 (s).

HRMS (ES) $^{+}$:

Calcd for $\text{C}_9\text{H}_{19}\text{NOSi}$ $[\text{M}+\text{H}]^{+}$: 186.1314

Found: 186.1312.

TLC (88:10:2 CH_2Cl_2 –MeOH– NH_4OH), R_f :

Amide **17**: 0.33 (ninhydrin)

Alcohol **18**: 0.24 (ninhydrin).

Carbamate **19**:

N-(9-Fluorenylmethoxycarbonyloxy)succinimide (241 mg, 0.716 mmol, 1.1 equiv) was added in one portion to a solution of the amino alcohol **18** (121 mg, 0.651 mmol, 1 equiv) and triethylamine (100 μL , 0.716 mmol, 1.10 equiv) in tetrahydrofuran (8.1 mL; substrate concentration $\sim 0.08\text{ M}$). After 1 h at $23\text{ }^{\circ}\text{C}$, the reaction mixture was partitioned between saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (50 mL). The organic layer was separated and washed with saturated aqueous

sodium bicarbonate solution (1 × 15 mL). The washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (30:70 ethyl acetate–hexanes) to provide the carbamate **19** (260 mg, 98% yield) as a clear oil.

^1H NMR (400 MHz, CDCl_3), δ : 7.77 (d, 2H, $J = 7.3$ Hz, FmocArH), 7.60 (d, 2H, $J = 7.8$ Hz, FmocArH), 7.41 (app t, 2H, $J = 7.3$ Hz, FmocArH), 7.31 (app t, 2H, $J = 7.3$ Hz, FmocArH), 5.21 (br d, 1H, $J = 5.9$ Hz, CO_2NH), 4.41 (d, 2H, $J = 6.8$ Hz, FmocCHCH₂), 4.22 (t, 1H, $J = 6.8$ Hz, FmocCH), 3.80 (d, 2H, $J = 8.3$ Hz, HOCH_2), 2.49 (br s, 2H, $\text{CH}_2\text{C}\equiv\text{C}$), 1.45 (br s, 2H, SiCH_2), 0.10 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz, CDCl_3), δ : 156.3, 143.8, 141.2, 127.6, 127.0, 125.0, 119.9, 80.9, 73.7, 66.8, 64.1, 51.5, 47.1, 21.6, 6.9, -2.1.

FTIR (thin film), cm^{-1} : 3418 (br m, OH), 3331 (w), 2954 (m), 2890 (w), 2221 (w), 1704 (s, C=O), 1514 (m), 1450 (m), 1336 (m), 1249 (s), 1057 (m), 850 (s), 759 (s), 739 (s).

HRMS (ES)⁺: Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 408.1995
Found: 405.1998.

TLC (40:60 EtOAc–hexanes), R_f : Amine **18**: baseline (PMA)
Carbamate **19**: 0.24 (PMA).

Alkene **20**:

A suspension of sodium borohydride (9.3 mg, 0.25 mmol, 1.5 equiv) in ethanol (500 μL) was added dropwise to a suspension of nickel acetate (53.1 mg, 0.21 mmol, 1.3 equiv) in ethanol (3.3 mL; substrate concentration ~ 0.05 M) under a blanket of hydrogen gas. The transfer of sodium borohydride was quantitated with ethanol (2 × 500 μL). Ethylene diamine (11 μL , 0.16 mmol, 1.0 equiv) was added. A solution of the alkyne **19** (66.9 mg, 0.16 mmol, 1 equiv) in ethanol (500 μL) was added dropwise to the black suspension (P-2 nickel) and the transfer was quantitated with ethanol (2 × 500 μL). After 3 h at 23 °C, the reaction mixture was concentrated. The residue was purified by flash-column chromatography (70:30 hexanes–ethyl acetate) to provide the alkene **20** (60.2 mg, 90% yield) as a clear oil.

^1H NMR (400 MHz, CDCl_3), δ : 7.76 (d, 2H, $J = 7.7$ Hz, FmocArH), 7.59 (d, 2H, $J = 7.7$ Hz, FmocArH), 7.40 (d, 2H, $J = 7.3$ Hz, FmocArH), 7.31 (d, 2H, $J = 7.5$ Hz, FmocArH), 5.62–5.55 (m, 1H, SiCH_2CH), 5.27–5.25 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.99 (d, 1H, $J = 6.9$ Hz, CO_2NH), 4.41 (d, 2H, $J = 2.9$ Hz, FmocCH₂), 4.22 (t, 1H, $J = 6.6$ Hz, FmocCH), 3.71–3.63 (m, 2H, HOCH_2), 3.62 (m, 1H, CHNH), 2.38 (br s, 1H, OH), 2.29–2.27 (m, 2H, NHCHCH_2), 1.50 (d, 2H, $J = 8.8$ Hz, SiCH_2), 0.02 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz, CDCl_3), δ : 156.7, 143.9, 141.3, 129.2, 127.6, 127.0, 125.0, 121.9, 119.9, 66.7, 65.0, 53.2, 47.2, 28.8, 18.7, -1.8.

FTIR (thin film), cm^{-1} : 3301 (w), 3344 (w), 2952 (m), 2895 (w), 1700 (s, C=O), 1528

(m), 1450 (m), 1334 (m), 1247 (s), 1055 (m), 854 (s), 758 (m), 739 (s).

HRMS (ES)⁺:

Calcd for C₂₄H₃₁NO₃Si [M+H]⁺: 410.2151

Found: 410.2138.

TLC (40:60 EtOAc–hexanes), R_f:

Alkene **19**: 0.29 (PMA)

Alkyne **20**: 0.29 (PMA).

C-Protected α -Amino Aldehydes (*S,S*)- and (*R,S*)-**21**:

Dess-Martin periodinane (124.3 mg, 0.293 mmol, 2 equiv) was added to an ice-cooled solution of the alcohol **20** (60.0 mg, 0.146 mmol, 1 equiv) in dichloromethane (2.9 mL; substrate concentration ~0.05 M). A cloudy suspension formed almost instantly. After 40 min, ethyl acetate (7 mL), saturated aqueous sodium bicarbonate solution (7 mL), and solid sodium thiosulfate (872 mg, 3.51 mmol, 24 equiv) were added sequentially to the vigorously stirring suspension. After 10 min, the cloudy organic layer turned clear. The resulting solution was diluted further with ethyl acetate (20 mL). The organic layer was separated and washed with water (20 mL) and brine (20 mL). The washed organic layer was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the crude aldehyde as a pale yellow oil.

Acetic acid (18.8 μ L, 0.330 mmol, 2.25 equiv) was added to an ice-cooled suspension of potassium cyanide (20.0 mg, 0.308 mmol, 2.1 equiv) in methanol (366 μ L). After 10 min, the solid potassium cyanide appeared to have dissolved and a clear, colorless solution was formed (Caution: HCN!). The clear solution was transferred via syringe to an ice-cooled solution of the crude aldehyde in dichloromethane (732 μ L; substrate concentration ~0.2 M). After 5 h at 0 °C, a 4:1 mixture of brine and saturated aqueous sodium bicarbonate solution (15 mL) was added and the biphasic solution was extracted with dichloromethane (3 $\times$ 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the crude mixture of diastereomeric cyanohydrins as a pale yellow oil.

Morpholine (63.9 μ L, 0.73 mmol, 5.0 equiv) was added dropwise to a mixture of the cyanohydrins in trifluoroethanol (293 μ L; substrate concentration ~0.5 M). The reaction mixture was allowed to stir for 14 h at 23 °C. The resulting solution was partitioned between dichloromethane (30 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was separated and extracted with dichloromethane (2 $\times$ 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude mixture of diastereomeric morpholino nitriles as a yellow oil.

1,8-Diazabicyclo[5.4.0]undec-7-ene (30.7 μ L, 0.205 mmol, 1.4 equiv) was added to an ice-cooled solution of the mixture of morpholino nitriles in dichloromethane (2.9 mL; substrate concentration ~0.05 M). The ice bath was removed after 10 min and the warmed solution was stirred for 50 min at 23 °C. The reaction mixture was loaded directly on a column of silica gel and the column was eluted with 0.5% $\rightarrow$ 1% $\rightarrow$ 2% $\rightarrow$ 3% methanol in dichloromethane to afford separately the C-protected α -amino aldehyde (*S,S*)-**21** (17.5 mg, 42% yield) and the C-protected α -amino aldehyde

(*R,S*)-**21** (16.1 mg, 39% yield) as clear oils. The ee of both diastereomers were each determined to be 92% by Mosher ester analysis (^1H NMR).

C-Protected α -Amino Aldehyde (*S,S*)-21****

^1H NMR (400 MHz, CDCl_3), δ : 5.68–5.61 (m, 1H, SiCH_2CH), 5.28–5.22 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 3.78–3.69 (m, 4H, CH_2OCH_2), 3.23 (d, 1H, $J = 8.8$ Hz, CHCN), 3.10 (td, 1H, $J = 8.0, 4.0$ Hz, NH_2CH), 2.70–2.65 (m, 2H, CH_2NCH_2), 2.56–2.51 (m, 2H, CH_2NCH_2), 2.42 (td, 1H, $J = 14.3, 5.0$ Hz, NH_2CHCH_2), 2.18–2.10 (m, 1H NH_2CHCH_2), 1.59 (dd, 1H, $J = 13.4, 9.3$ Hz, SiCH_2), 1.47 (dd, 1H, $J = 13.5, 8.4$ Hz, SiCH_2), 1.40 (br s, 2H, NH_2), 0.01 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz, CDCl_3), δ : 130.3, 121.2, 116.3, 66.6, 65.4, 50.8, 50.5, 31.1, 18.9, –1.8.

FTIR (thin film), cm^{-1} : 2955 (m), 2854 (s), 2824 (s), 2224 (w), 1454 (w), 1294 (w), 1247 (m), 1148 (w), 1118 (s), 1007 (w), 851 (s).

HRMS (CI^+): Calcd for $\text{C}_{14}\text{H}_{27}\text{N}_3\text{OSi}$ $[\text{M}+\text{H}]^+$: 282.2002
Found: 282.2004.

TLC (40:60 EtOAc–hexanes), R_f : Alcohol **20**: 0.27 (CAM)
Aldehyde: 0.47 (CAM)
Cyanohydrins: 0.62 (CAM)

TLC (4% MeOH– CH_2Cl_2), R_f : Morpholino Nitriles: 0.44 (CAM).
C-Protected α -Amino Aldehyde (*S,S*)-**21**: 0.26 (ninhydrin)
Dibenzofulvene: 0.81 (UV).

C-Protected α -Amino Aldehyde (*R,S*)-21****

^1H NMR (400 MHz, CDCl_3), δ : 5.69–5.62 (m, 1H, SiCH_2CH), 5.34–5.27 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 3.80–3.70 (m, 4H, CH_2OCH_2), 3.21 (d, 1H, $J = 10.2$ Hz, CHCN), 3.12 (td, 1H, $J = 9.0, 2.9$ Hz, NH_2CH), 2.73–2.68 (m, 2H, CH_2NCH_2), 2.55–2.50 (m, 2H, CH_2NCH_2), 2.47 (m, 1H, NH_2CHCH_2), 2.16 (td, 1H, $J = 14.6, 6.8$ Hz, NH_2CHCH_2), 1.67 (br s, 2H, NH_2), 1.60 (dd, 1H, $J = 13.4, 9.3$ Hz, SiCH_2), 1.50 (dd, 1H, $J = 13.4, 8.4$ Hz, SiCH_2), 0.01 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (100 MHz, CDCl_3), δ : 130.4, 121.0, 115.4, 66.6, 64.1, 50.2, 49.6, 31.1, 18.9, –1.8.

FTIR (thin film), cm^{-1} : 2954 (m), 2856 (m), 2221 (w), 1454 (w), 1294 (w), 1248 (m), 1143 (m), 1118 (s), 1006 (w), 858 (s).

HRMS (CI^+): Calcd for $\text{C}_{14}\text{H}_{27}\text{N}_3\text{OSi}$ $[\text{M}+\text{H}]^+$: 282.2002
Found: 282.2010.

TLC (4% MeOH– CH_2Cl_2), R_f : Morpholino Nitriles: 0.44 (ninhydrin)
C-Protected α -Amino Aldehyde (*R,S*)-**21**: 0.16 (ninhydrin)
Dibenzofulvene: 0.81 (UV).

Methyl-3-(*tert*-Butyldimethylsilyloxy)Benzoate:

Imidazole (10.8 g, 158.9 mmol, 1.6 equiv) and *tert*-butyldimethylsilyl chloride (21.0 g, 139.0 mmol, 1.4 equiv) were added sequentially to an ice-cooled solution of methyl 3-hydroxybenzoate (15.1 g, 99.3 mmol, 1 equiv) in dimethylformamide (66.2 mL; substrate concentration ~1.5 M). After 10 min,

the reaction mixture was removed from the ice bath and the warmed solution was allowed to stir for 6 h at 23 °C. A 2:1 mixture of ethyl acetate–hexanes (125 mL) was added and the diluted solution was cooled to 0 °C. Water (50 mL) was added at this point and the resulting aqueous layer was separated and extracted with a 1:1 mixture of ethyl acetate–hexanes (2 × 100 mL). The combined organic layers were washed with water (2 × 75 mL) and brine (1 × 75 mL). The washed organic layer was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography (gradient elution 100% hexanes → 1% ethyl acetate–hexanes) to afford methyl-3-(*tert*-butyldimethylsilyloxy)benzoate (26.18 g, 99% yield) as a clear oil.

^1H NMR (400 MHz, CDCl_3), δ :	7.63 (dt, 1H, $J = 7.7, 1.3$ Hz, ArH), 7.49 (app t, 1H, $J = 2.0$ Hz, ArH), 7.29 (app t, 1H, $J = 7.9$ Hz, ArH), 7.03 (ddd, 1H, $J = 8.1, 2.6, 1.1$ Hz, ArH), 3.90 (s, 3H, CO_2OCH_3), 0.99 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.21 (s, 6 H, $\text{Si}(\text{CH}_3)_2$).
^{13}C NMR (125 MHz, CDCl_3), δ :	166.9, 155.7, 131.5, 129.3, 124.8, 122.5, 121.0, 52.1, 25.6, 18.2, –4.5.
FTIR (thin film), cm^{-1} :	2955 (m), 2931 (m), 2859 (s), 1728 (s, C=O), 1585 (m), 1487 (m), 1444 (m), 1291 (s), 1227 (m), 1100 (m), 1005 (m), 930 (m), 839 (s), 782 (m), 759 (m), 685 (w).
HRMS (CI) $^+$:	Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{Si}$ [$\text{M}+\text{NH}_4$] $^+$: 284.1682 Found: 284.1678.
TLC (20:80 EtOAc–hexanes), R_f :	Methyl 3-Hydroxybenzoate: 0.21 (PMA) Methyl-3-(<i>tert</i> -Butyldimethylsilyloxy)-Benzoate: 0.62 (PMA).

3-(*tert*-Butyldimethylsilyloxy)Benzyl Bromide:

Solid lithium aluminum hydride (7.18 g, 179.7 mmol, 2 equiv) was added slowly to an ice-cooled solution of methyl-3-(*tert*-butyldimethylsilyloxy)benzoate (23.94 g, 89.9 mmol, 1 equiv) in tetrahydrofuran (180 mL; substrate concentration ~0.5 M). After 10 min, the ice bath was removed and the resulting suspension was allowed to warm to 23 °C. The reaction solution was stirred at 23 °C for 1 h, then was cooled to 0 °C. Water (15 mL) and saturated aqueous ammonium chloride solution (100 mL) were cautiously added in sequence and the resulting biphasic mixture was extracted with a 1:1 mixture of ethyl acetate–hexanes (1 × 100 mL), then ethyl acetate (4 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide 3-(*tert*-butyldimethylsilyloxy)benzyl alcohol as a clear oil.

Bromine (6.02 mL, 116.8 mmol, 1.3 equiv) was added to an ice-cooled solution of triphenylphosphine (31.82 g, 121.3 mmol, 1.35 equiv) and imidazole (9.18 g, 134.8 mmol, 1.5 equiv) in dichloromethane (359 mL; substrate concentration ~0.25 M). After 15 min at 0 °C, a solution of the crude alcohol (prepared as described in the preceding paragraph) in dichloromethane (60 mL) was added dropwise via cannula over 30 min. The transfer was quantitated with dichloromethane (2 × 30 mL). After 1 h at 0 °C, water (150 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane. (3 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The

residue was purified by column chromatography (gradient elution hexanes → 1% ether–hexanes) to afford 3-(*tert*-butyldimethylsilyloxy)benzyl bromide (21.83 g, 81% yield over 2 steps) as a clear oil.

^1H NMR (400 MHz, CDCl_3), δ :	7.19 (t, 1H, $J = 7.9$ Hz, ArH), 6.97 (d, 1H, $J = 7.7$ Hz, ArH), 6.87 (t, 1H, $J = 2.0$ Hz, ArH), 6.77 (ddd, 1H, $J = 8.0, 2.4, 0.7$ Hz, ArH), 4.43 (s, 2H, CH_2Br), 0.99 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.20 (s, 6H, $\text{Si}(\text{CH}_3)_2$).
^{13}C NMR (125 MHz, CDCl_3), δ :	139.3, 129.9, 122.1, 121.0, 120.4, 45.4, 33.6, 25.9, 18.4, -4.2 .
FTIR (thin film), cm^{-1} :	2954 (w), 2930 (w), 2856 (w), 1600 (w), 1587 (w), 1486 (m), 1443 (w), 1284 (s), 1251 (m), 1159 (w), 1003 (w), 980 (m), 840 (s), 782 (m), 694 (w).
HRMS (EI) $^+$:	Calcd for $\text{C}_{13}\text{H}_{21}\text{BrOSi}$ $[\text{M}]^+$: 300.0545 Found: 300.0539.
TLC (80:20 hexanes–EtOAc), R_f :	Methyl-3-(<i>tert</i> -Butyldimethylsilyloxy)-Benzoate: 0.55 (PMA) 3-(<i>tert</i> -Butyldimethylsilyloxy)Benzyl Alcohol: 0.25 (PMA) 3-(<i>tert</i> -Butyldimethylsilyloxy)Benzyl Bromide: 0.64 (PMA).

Pseudoephedrine Amide **22**:

Tetrahydrofuran (100 mL) was added to a vigorously stirred mixture of flame-dried lithium chloride (7.50 g, 177.0 mmol, 4 equiv) and solid (*R,R*)-(–)- pseudoephedrine glycineamide hydrate (10.6 g, 44.2 mmol, 1 equiv). The resulting solution was cooled to 0 °C and the cooled reaction flask was equipped with a pressure-equalizing addition funnel. The addition funnel was charged with lithium hexamethyldisilazide (1 M solution in THF, 141.6 mL, 141.6 mmol, 3.2 equiv). The first 66-mL portion of base (66.4 mL, 1.5 equiv) was added dropwise over 20 min. After 5 min, the stopcock of the addition funnel was opened fully to allow for rapid addition of the second portion of base (75.2 mL, 1.7 equiv). After 25 min, 3-(*tert*-butyldimethylsilyloxy)benzyl bromide (14.0 g, 46.5 mmol, 1.05 equiv) was added dropwise via cannula over a period of 20 min. The flask was rinsed with tetrahydrofuran (2 × 5 mL) to quantitate the transfer. After 2 h at 0 °C, the reaction mixture was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate–hexanes (150 mL). The organic layer was separated and dried over anhydrous potassium carbonate. The dried solution was filtered and the filtrate was concentrated. The de of the crude reaction product was determined to be 91% by HPLC analysis of a benzoylated sample (Chiracel-OD, 5% methanol–hexanes, 0.5 mL/min, major $t_R = 34.1$ min, minor $t_R = 39.0$ min), as described in the general procedures. The residue was purified by flash-column chromatography (gradient elution 98:1:1 → 97:2:1 dichloromethane–methanol–ammonium hydroxide) to provide the pseudoephedrine amide **22** (14.1 g, 72% yield) as a pale yellow foam.

^1H NMR (400 MHz, CDCl_3 , 4.1:1 mixture of rotamers, * denotes the minor rotamer), δ :	7.38–7.31 (m, 5H, X_ψArH), 7.28–7.25 (m, 5H, $\text{X}_\psi\text{ArH}^*$), 7.19 (t, 1H, $J = 7.8$ Hz, ArH*), 7.11 (t, 1H, $J = 7.8$ Hz, ArH), 6.85 (d, 1H, $J = 7.3$ Hz, ArH*), 6.75 (d, 1H, $J = 7.8$ Hz, ArH), 6.69 (dd, 1H, $J = 7.8, 2.4$ Hz, ArH), 6.65 (s, 1H, ArH), 4.63 (br s, 1H, CHOH), 4.56 (d, 1H, $J = 8.8$ Hz, CH_3CH^*), 4.50 (d, 1H, $J = 8.8$ Hz, CH_3CH), 4.16 (t, 1H, $J = 6.3$ Hz,
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¹³ C NMR (125 MHz, CDCl ₃ , * denotes the minor rotamer), δ:	179.3*, 176.4, 164.9, 155.7, 141.9, 139.1, 129.4, 128.7*, 128.4, 127.8*, 126.9*, 126.7, 122.2*, 121.1, 118.3, 90.6, 75.9, 53.4, 42.5, 42.1*, 25.7*, 25.6, 18.1*, 14.3, -4.4.
FTIR (thin film), cm ⁻¹ :	3350 (br w, OH), 2948 (m), 2930 (m), 2858 (m), 1628 (s), 1603 (s), 1584 (s), 1485 (s), 1274 (s), 1160 (m), 1004 (m), 981 (m), 840 (s), 782 (s), 700 (s).
HRMS (ES) ⁺ :	Calcd for C ₂₅ H ₃₈ N ₂ O ₃ Si [M+H] ⁺ : 443.2730 Found: 443.2725.
TLC (85:10:5 CH ₂ Cl ₂ -MeOH-NH ₄ OH), R _f :	X _ψ Gly•H ₂ O: 0.23 (ninhydrin) Pseudoephedrine Amide 22 : 0.44 (ninhydrin).

Amino Ester **23**:

Sodium hydroxide (1 M aqueous solution, 17 mL, 3.1 equiv) and water (25 mL) were added sequentially to a solution of the amide **22** (2.46 g, 5.56 mmol, 1 equiv) in dioxane (25 mL). The resulting suspension was heated to reflux, which caused the reaction mixture to clarify. After 5 h at reflux, the reaction mixture was allowed to cool to 23 °C and water (15 mL) was added. The product solution was washed with dichloromethane (4 × 75 mL) and the washed aqueous solution of the crude amino acid was cooled to 0 °C.

Dioxane (200 mL), sodium bicarbonate (1.4 g, 16.7 mmol, 3 equiv) and 9-fluorenylmethyl chloroformate (1.87 g, 7.22 mmol, 1.3 equiv) were added sequentially to the ice-cooled aqueous solution of the crude amino acid. After 21 h at 0 °C, the resulting suspension was washed with hexanes (2 × 100 mL). The aqueous layer was cooled to 0 °C and the cooled solution was acidified to pH 1 by the addition of aqueous hydrochloric acid solution (12 M, ~15 mL). The resulting aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the crude *N*-Fmoc carbamate.

Diazomethane (~0.26 M in ether) was added dropwise to a solution of the crude *N*-Fmoc carbamate in dichloromethane (150 mL) until the solution turned yellow. After 5 min, the resulting solution was concentrated to provide the crude methyl ester.

1,8-Diazabicyclo[5.4.1]undec-7-ene (831 μL, 5.56 mmol, 1.0 equiv) was added to an ice-cooled solution of the crude methyl ester in dichloromethane (30 mL). After 1.5 h at 0 °C the reaction mixture was concentrated. The residue was purified by flash-column chromatography (gradient elution 2% → 6% methanol in dichloromethane) to afford the amine **23** (978 mg, 90% yield over 4 steps) as a white solid.

^1H NMR (400 MHz, 10% CD_3OD in CDCl_3), δ : 7.12 (t, 1H, $J = 8.0$ Hz, ArH), 6.70 (dt, 1H, $J = 8.2$, 1.6 Hz, ArH), 6.63 (s, 1H, ArH), 6.61 (d, 1H, $J = 1.8$ Hz, ArH), 3.72 (s, 3H, CO_2CH_3), 3.70 (dd, 1H, $J = 7.7$, 4.8 Hz, NH_2CH), 3.01 (dd, 1H, $J = 13.5$, 5.1 Hz, ArCH_2), 2.80 (dd, 1H, $J = 13.5$, 7.7 Hz, ArCH_2), 2.14 (br s, 2H, NH_2).

^{13}C NMR (125 MHz, 10% CD_3OD in CDCl_3), δ : 174.9, 156.9, 137.8, 129.8, 120.3, 116.1, 114.1, 54.9, 52.0, 40.2.

FTIR (thin film), cm^{-1} : 2951 (br w, NH_2 , OH), 1732 (s, C=O), 1587 (s), 1482 (m), 1456 (m), 1275 (m), 1202 (m), 1155 (m), 1026 (m), 780 (m), 700 (w).

HRMS (ES) $^+$: Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 196.0973
Found: 196.0973.

TLC (88:10:2 CH_2Cl_2 –MeOH– NH_4OH), R_f : Amide **22**: 0.44 (ninhydrin)
Amino acid: baseline (ninhydrin).

TLC (80:20 CH_2Cl_2 –MeOH), R_f : Amino acid: baseline (ninhydrin)
N-Fmoc Carbamate: 0.23 (ninhydrin).

TLC (95:5 CH_2Cl_2 –MeOH), R_f : *N*-Fmoc Carbamate: baseline (PMA)
Methyl Ester: 0.43 (PMA)
Amine **23**: 0.13 (PMA).

Tetrahydroisoquinoline **24**:

Acetic acid (126 μL , 2.21 mmol, 1.1 equiv) and 4 Å molecular sieves were added sequentially to a solution of the amine **23** (393 mg, 2.01 mmol, 1 equiv) in dichloromethane (20.1 mL; substrate concentration ~ 0.1 M). The resulting solution was degassed by four freeze-pump-thaw cycles. A solution of benzyloxyacetaldehyde (332.4 mg, 2.21 mmol, 1.1 equiv) in dichloromethane (11 mL) was added slowly via syringe to the degassed solution over 500 min (8.3 h). After 23 h at 23 $^\circ\text{C}$ (including the addition period), the reaction suspension was filtered through Whatman No. 5 filter paper to remove the crushed molecular sieves. Saturated aqueous sodium bicarbonate solution (20 mL) was added to the filtrate and the resulting biphasic solution was extracted with dichloromethane (4 $\times$ 40 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (gradient elution 0.5% $\rightarrow$ 1% $\rightarrow$ 1.5% $\rightarrow$ 2% methanol–dichloromethane) to furnish separately the tetrahydroisoquinoline **24** (211.2 mg, 32% yield) and the tetrahydroisoquinoline **25** (343.6 mg, 52% yield) as pale yellow foams.

Tetrahydroisoquinoline **24**

^1H NMR (500 MHz, CDCl_3), δ : 7.35–7.28 (m, 5H, BnH), 7.06 (t, 1H, $J = 7.8$ Hz, ArH), 6.75 (d, 1H, $J = 7.8$ Hz, ArH), 6.69 (d, 1H, $J = 7.3$ Hz, ArH), 4.59 (d, 1H, $J = 11.7$ Hz, BnCH_2), 4.58 (br t, 1H, $J = 5.1$ Hz, ArCH), 4.52 (d, 1H, $J = 11.7$ Hz, BnCH_2), 3.83 (dd, 1H, $J = 8.8$, 6.8 Hz, BnOCH_2), 3.78–3.77 (m, 1H, BnOCH_2), 3.77 (s,

^{13}C NMR (100 MHz, CDCl_3), δ :

FTIR (thin film), cm^{-1} :

HRMS (ES) $^{+}$:

TLC (95:5 CH_2Cl_2 –MeOH), R_f :

3H, CO_2CH_3), 3.61 (dd, $J = 11.2, 2.9$ Hz, CO_2CH), 3.02 (dd, $J = 15.1, 2.9$ Hz, ArCH_2), 2.88 (dd, $J = 15.0, 11.2$ Hz, ArCH_2).
173.1, 154.4, 136.6, 136.0, 128.4, 127.9, 127.8, 127.6, 122.7, 120.7, 115.1, 75.3, 73.4, 54.4, 52.8, 52.2, 33.7.

3031 (w), 2951 (m), 2858 (m), 1739 (s, C=O), 1588 (m), 1467 (s), 1339 (m), 1278 (s), 1217 (m), 1096 (m), 1074 (m).

Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^{+}$: 328.1545

Found: 328.1560.

Amine **23**: 0.15 (PMA)

Tetrahydroisoquinoline **24**: 0.40 (PMA)

Tetrahydroisoquinoline **25**: 0.36 (PMA).

Carbamate **26**:

N,N-Diisopropylethylamine (69.0 μL , 0.396 mmol, 1.3 equiv) and 9-fluorenylmethyl chloroformate (82.7 mg, 0.320 mmol, 1.05 equiv) were added sequentially to an ice-cooled solution of the amine **24** (99.7 mg, 0.304 mmol, 1 equiv) in tetrahydrofuran (30 mL; substrate concentration ~ 0.01 M). After 45 min at 0 $^{\circ}\text{C}$, saturated aqueous ammonium chloride solution (50 mL) was added and the resulting biphasic solution was extracted sequentially with ethyl acetate (50 mL) and dichloromethane (50 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:80 ethyl acetate–hexanes) to afford the carbamate **26** (167.0 mg, 100% yield) as a white foam.

^1H NMR (400 MHz, CDCl_3 , 1.6:1 mixture of rotamers, * denotes the minor rotamer), δ :

7.79–7.75 (m, 4H, FmocArH & FmocArH*), 7.69 (d, 2H, $J = 7.3$ Hz, FmocArH*), 7.62 (t, 2H, $J = 6.2$ Hz, FmocArH), 7.55 (d, 2H, $J = 7.7$ Hz, FmocArH*), 7.40 (app q, 4H, $J = 6.7$ Hz, FmocArH & FmocArH*), 7.34–7.21 (m, 5H, BnArH & BnArH*), 7.18 (t, 2H, $J = 7.9$ Hz, ArH & ArH*), 7.02 (br s, 2H, ArOH & ArOH*), 6.92 (t, 2H, $J = 8.2$ Hz, ArH & ArH*), 6.80 (d, 2H, $J = 7.3$ Hz, ArH & ArH*), 5.77 (dd, 1H, $J = 10.1, 3.8$ Hz, ArCH*), 5.49 (dd, 1H, $J = 10.1, 3.8$ Hz, ArCH), 4.65 (d, 1H, $J = 11.7$ Hz, BnCH $_2$ *), 4.56–4.50 (m, 6H, BnCH $_2$, FmocCH $_2$ & FmocCH $_2$ *), 4.49–4.46 (m, 1H, CO_2CH^*), 4.45–4.42 (m, 1H, CO_2CH), 4.26 (t, 2H, $J = 6.4$ Hz, FmocCH & BnOCH $_2$ *), 4.18–4.12 (m, 2H, FmocCH* & BnOCH $_2$), 3.94 (dd, 1H, $J = 8.1, 4.0$ Hz, BnOCH $_2$), 3.79 (s, 3H, CO_2CH_3), 3.70 (dd, 1H, $J = 9.6, 8.7$ Hz, BnOCH $_2$ *), 3.65 (s, 3H, CO_2CH_3^*), 3.63 (dd, 1H, $J = 10.6, 8.1$ Hz, BnOCH $_2$).

^{13}C NMR (100 MHz, CDCl_3 , * denotes the minor rotamer), δ :

173.1, 173.0*, 155.6, 155.4*, 153.5, 153.3*, 143.9, 143.7*, 143.5, 143.2*, 141.3, 141.2*, 141.2, 141.1*, 136.9, 136.7*, 132.6, 132.4*, 128.8, 128.6*, 128.4,

FTIR (thin film), cm^{-1} :

HRMS (ES)⁺:

TLC (50:50 EtOAc–hexanes), R_f :

127.9*, 127.8, 127.7*, 127.6, 127.4*, 127.1, 127.0*, 124.9, 124.9*, 124.8, 124.7*, 123.5, 123.1*, 119.9, 119.9*, 116.9, 116.1*, 73.6, 73.6*, 68.1, 67.9*, 55.5, 54.8*, 52.4, 52.3*, 50.0, 49.8*, 47.1, 47.0*, 30.5, 30.2*.

3350 (br w, OH), 3033 (w), 2949 (w), 1749 (s, C=O), 1698 (s), 1666 (s), 1598 (m), 1472 (s), 1451 (s), 1416 (s), 1322 (s), 1285 (s), 1200 (m), 1177 (m), 1131 (m), 1033 (m), 758 (m), 739 (s).

Calcd for $\text{C}_{34}\text{H}_{31}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 550.2229

Found: 550.2214.

Amine **24**: 0.17 (PMA)

Carbamate **26**: 0.46 (PMA).

N-Protected α -Amino Aldehyde **1**:

Diisobutylaluminum hydride (1 M solution in toluene, 4.35 mL, 4.35 mmol, 5 equiv) was added to a cooled ($-78\text{ }^{\circ}\text{C}$) solution of the ester **26** (478.6 mg, 0.871 mmol, 1 equiv) in toluene (87 mL; substrate concentration $\sim 0.01\text{ M}$). After 1.5 h at $-78\text{ }^{\circ}\text{C}$, methanol (1 mL) and aqueous hydrochloric acid solution (1 M, 30 mL) were added sequentially and the resulting emulsion was allowed to warm to $23\text{ }^{\circ}\text{C}$. After 10 min, the biphasic solution was extracted sequentially with ethyl acetate ($1 \times 50\text{ mL}$) and dichloromethane ($1 \times 100\text{ mL}$). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25:75 ethyl acetate–hexanes) to afford the N-protected α -amino aldehyde **1** (411.0 mg, 91% yield) as a white foam.

^1H NMR (400 MHz, CDCl_3 , 1.7:1 mixture of rotamers, * denotes the minor rotamer), δ :

9.43 (d, 1H, $J = 2.6\text{ Hz}$, CHO), 9.13 (d, 1H, $J = 1.8\text{ Hz}$, CHO^*), 7.79–7.75 (m, 4H, FmocArH & FmocArH^*), 7.67 (d, 1H, $J = 7.3\text{ Hz}$, FmocArH), 7.61 (d, 1H, $J = 7.3\text{ Hz}$, FmocArH), 7.55 (d, 1H, $J = 7.3\text{ Hz}$, FmocArH^*), 7.50 (d, 1H, $J = 7.3\text{ Hz}$, FmocArH^*), 7.38–7.43 (m, 4H, FmocArH & FmocArH^*), 7.25–7.35 (m, 10H, FmocArH & FmocArH^* , BnArH & BnArH^*), 7.11–7.20 (m, 6H, BnArH & BnArH^* , ArH & ArH^*), 6.90 (s, 1H, ArOH^*), 6.84 (d, 1H, $J = 8.0\text{ Hz}$, ArH), 6.83 (d, 1H, $J = 7.7\text{ Hz}$, ArH^*), 6.78 (d, 1H, $J = 7.7\text{ Hz}$, ArH), 6.75 (d, 1H, $J = 7.7\text{ Hz}$, ArH^*), 6.69 (s, 1H, ArOH), 5.70 (dd, 1H, $J = 8.4$ & 4.0 Hz , ArCH^*), 5.37 (dd, 1H, $J = 9.1$, 4.0 Hz , ArCH), 4.67 (d, 1H, $J = 5.8\text{ Hz}$, FmocCH_2^*), 4.64 (d, 1H, $J = 5.8\text{ Hz}$, FmocCH_2), 4.54–4.58 (m, 2H, FmocCH_2 & FmocCH_2^*), 4.45 (d, 2H, $J = 12.1\text{ Hz}$, BnCH_2), 4.40 (d, 2H, $J = 11.7\text{ Hz}$, BnCH_2), 4.24–4.29 (m, 1H, FmocCH & CHCHO),

^{13}C NMR (100 MHz, CDCl_3 , * denotes the minor rotamer), δ :

FTIR (thin film), cm^{-1} :

HRMS (ES) $^+$:

TLC (50:50 EtOAc–hexanes), R_f :

4.18 (t, 1H, $J = 5.5$ Hz, FmocCH*), 4.08 (td, 1H, $J = 8.8, 1.8$ Hz, CHCHO*), 3.86 (dd, 1H, $J = 8.6, 6.4$ Hz, BnOCH_2), 3.64 (dd, 1H, $J = 8.2, 4.2$ Hz, BnOCH_2), 3.58 (t, 1H, $J = 8.4$ Hz, BnOCH_2^*), 3.44 (t, 1H, $J = 8.6$ Hz, BnOCH_2), 2.81–2.94 (m, 4H, ArCH_2 & ArCH_2^*).

199.1, 156.3, 155.6*, 153.1, 153.0, 143.5, 143.5*, 143.3, 141.4, 141.3*, 136.9, 136.7*, 132.7, 132.5*, 128.8, 128.7*, 128.5, 128.0, 127.9*, 127.8, 127.6, 127.5*, 127.2, 127.1*, 125.0, 124.8*, 124.5, 122.6, 122.4*, 120.4, 120.0, 120.0*, 115.8, 115.6*, 73.6, 73.5*, 73.2, 67.8, 60.5, 60.0*, 50.1, 49.9*, 47.2, 47.1*, 27.7, 27.6*.

3360 (br w, OH), 3064 (w), 2863 (w), 1733 (m, C=O), 1682 (s), 1597 (m), 1471 (s), 1451 (s), 1416 (s), 1332 (s), 1285 (s), 1104 (m), 1074 (m), 1030 (m), 756 (m), 739 (s), 698 (m).

Calcd for $\text{C}_{33}\text{H}_{29}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 520.2124

Found: 520.2120.

Ester **26**: 0.46 (PMA)

N-Protected α -Amino Aldehyde **1**: 0.27 (PMA).

Bis-Amino Nitriles 3:

A solution of the C-protected α -amino aldehyde derivative **2** (129 mg, 0.457 mmol, 1.05 equiv) in benzene (1.25 mL) was added to a solution of the N-protected α -amino aldehyde derivative **1** (226.1 mg, 0.435 mmol, 1 equiv) in dichloromethane (4 mL) and the resulting solution was concentrated. Dichloromethane (4.3 mL; substrate concentration ~ 0.1 M) and solid sodium sulfate (1.85 g, 13.05 mmol, 30 equiv) were added to the residue. After stirring for 2 h at 23 $^{\circ}\text{C}$, the suspension was filtered through a pipette plugged with cotton wool and the filtrate was concentrated. Dichloromethane (8.7 mL; substrate concentration ~ 0.05 M) was added to the residue, the resulting solution was cooled in an ice bath, and 1,8-diazabicyclo[5.4.0]undec-7-ene (71.6 μL , 0.479 mmol, 1.1 equiv) was added to the cooled solution. The ice bath was removed after 10 min. In another round-bottom flask, acetic acid (129 μL , 2.26 mmol, 5.2 equiv) was added to an ice-cooled suspension of potassium cyanide (141.7 mg, 2.17 mmol, 5 equiv) in methanol (2.2 mL). After 10 min, the solids appeared to have completely dissolved, forming a clear solution (Caution: HCN!). The original reaction flask, containing the substrate, was cooled in an ice bath approximately 85 min from the point of addition of DBU, and after 5 min, the solution of methanolic hydrogen cyanide was added by cannula transfer. The resulting solution was allowed to stir for 1.5 h at 0 $^{\circ}\text{C}$. Saturated aqueous sodium bicarbonate solution (20 mL) was added and the biphasic mixture was extracted with dichloromethane (3×30 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (93:7 $\rightarrow$ 70:30 $\rightarrow$ 50:50

dichloromethane–ethyl acetate), providing a diastereomeric mixture of the bis-amino nitriles **3** (231.7 mg, 91% yield) as a pale yellow foam.

^1H NMR (500 MHz, CDCl_3), δ : 8.31 (br s, 1H, ArOH), 7.37–7.27 (m, 5H, BnArH), 7.10 (t, 1H, $J = 7.6$ Hz, ArH), 6.80 (d, 1H, $J = 7.8$ Hz, ArH), 6.70 (d, 1H, $J = 7.3$ Hz, ArH), 5.68–5.62 (m, 1H, SiCH_2CH), 5.14–5.08 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.64–4.57 (m, 3H, BnCH₂ & ArCH), 3.76–3.70 (m, 5H, CH₂OCH₂ & ArCHCH₂), 3.61 (dd, 1H, $J = 18.1, 8.8$ Hz, ArCHCH₂), 3.60 (d, 1H, $J = 7.3$ Hz, CNCH), 3.18–3.13 (m, 2H, CNCHCH & CNCHCH), 2.85 (d, 1H, $J = 14.2$ Hz, ArCH₂CHCH), 2.72–2.65 (m, 3H, ArCH₂ & CH₂NCH₂), 2.59–2.55 (m, 2H, CH₂NCH₂), 2.54–2.50 (m, 3H, ArCH₂), 2.41 (dd, 1H, $J = 14.2, 7.3$ Hz, NHCHCH₂), 2.22 (dd, 1H, $J = 9.3, 4.4$ Hz, NHCHCH₂), 1.49 (d, 2H, $J = 8.3$ Hz, SiCH₂), 0.02 (s, 9H, SiCH₃).

^{13}C NMR (125 MHz, CDCl_3), δ : 133.4, 128.6, 128.2, 128.0, 120.9, 120.3, 116.1, 76.7, 73.8, 66.5, 61.9, 53.5, 52.9, 52.0, 51.1, 33.8, 32.9, 23.4, –1.8.

FTIR (thin film), cm^{-1} : 3316 (br w), 2955 (m), 2854 (m), 2233 (w, CN), 1584 (m), 1467 (s), 1454 (m), 1275 (m), 1247 (s), 1148 (m), 1117 (s), 1071 (m), 1009 (w), 975 (w), 852 (s), 781 (w), 738 (m), 698 (m).

HRMS (ES)⁺: Calcd for C₃₃H₄₅N₅O₃Si [M+H]⁺: 588.3370
Found: 588.3384.

TLC (50:50 EtOAc–hexanes), R_f: Aldehyde **1**: 0.27 (PMA)
Bis-Amino Nitriles **3**: 0.47 & 0.25(PMA).

Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (189 μL , 1.42 mmol, 3.6 equiv) and a solution of zinc chloride in THF (0.5 M, 2.6 mL, 1.3 mmol, 3.3 equiv) were added sequentially to a solution of the bis-amino nitriles **3** (231.7 mg, 0.394 mmol, 1 equiv) in trifluoroethanol (19.7 mL; substrate concentration ~ 0.02 M). The resulting solution was degassed by four freeze-pump-thaw cycles. After 30 min, the degassed solution was heated for 15 h at 60 °C, then was allowed to cool to 23 °C. The cooled solution was immersed in an ice bath. Diethylene triamine (639 μL , 5.91 mmol, 15 equiv) was added, and the resulting dark red solution was then treated with an aqueous solution of tetrasodium EDTA (0.2 M, pH 11, 15 mL). The biphasic mixture was extracted with dichloromethane (3 $\times$ 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (73.5 mg, 46% yield) as a pale yellow solid.

^1H NMR (500 MHz, CDCl_3), δ : 7.37–7.28 (m, 5H, BnArH), 7.09 (t, 1H, $J = 7.8$ Hz, ArH), 6.78 (d,

^1H , $J = 7.8$ Hz, ArH), 6.67 (d, 1H, $J = 7.3$ Hz, ArH), 5.90–5.83 (m, 1H, $\text{CH}_2=\text{CH}$), 5.02 (d, 1H, $J = 17.1$ Hz, $\text{CH}_2=\text{CH}$), 4.97 (d, 1H, $J = 10.2$ Hz, $\text{CH}_2=\text{CH}$), 4.59 (d, 1H, $J = 11.7$ Hz, BnAr CH_2), 4.52 (d, 1H, $J = 12.2$ Hz, BnAr CH_2), 4.22 (dd, 1H, $J = 8.3$, 4.9 Hz, ArCH CH_2), 3.87 (d, 1H, $J = 2.4$ Hz, NCHCN), 3.71 (br dd, 1H, $J = 6.6$, 2.0 Hz, NHCHCHCN), 3.60 (dd, 1H, $J = 8.8$, 4.9 Hz, BnOCH $_2$), 3.54 (app t, 1H, $J = 8.3$ Hz, BnOCH $_2$), 3.06 (s, 1H, NHCHCH), 2.87–2.84 (m, 2H, ArCH $_2$ CH & $\text{CH}_2=\text{CHCH}$), 2.61 (t, 1H, $J = 12.9$ Hz, ArCH $_2$), 2.52 (dd, 1H, $J = 14.4$, 2.2 Hz, ArCH $_2$), 2.01–1.97 (m, 1H, NHCHCH $_2$), 1.73–1.68 (m, 1H, NHCHCH $_2$).

^{13}C NMR (100 MHz, CDCl_3), δ : 153.7, 142.7, 136.7, 135.7, 128.8, 128.6, 128.1, 127.8, 122.1, 120.4, 117.7, 115.8, 113.2, 76.4, 73.7, 64.7, 58.4, 57.9, 57.7, 56.4, 41.2, 35.8, 32.9.

FTIR (thin film), cm^{-1} : 2955 (s), 2966 (s), 2853 (m), 1726 (m), 1592 (m), 1469 (s), 1451 (m), 1382 (m), 1361 (m), 1284 (s), 1100 (m), 1069 (s), 1000 (m), 910 (m), 738 (m), 692 (m).

HRMS (ES) $^+$: Calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 402.2181
Found: 402.2178.

TLC (50:50 EtOAc–hexanes), R_f : Bis-Amino Nitriles **3**: 0.42 & 0.21 (ninhydrin)
Tetracyclic Cyanopiperazine **4**: 0.16 (ninhydrin).

O,N-Bismethylation Product **27**:

Dimethylsulfate (100.0 μL , 1.06 mmol, 6 equiv) and cesium carbonate (229.5 mg, 0.704 mmol, 4 equiv) were added sequentially to a solution of the phenol **4** (70.7 mg, 0.176 mmol, 1 equiv) in acetone (17.6 mL; substrate concentration $\sim 0.01\text{M}$) at 23 $^\circ\text{C}$. After 11.5 h at 23 $^\circ\text{C}$, saturated aqueous sodium bicarbonate solution (15 mL) was added and the resulting solution was extracted with dichloromethane (1 $\times$ 50 mL, then 2 $\times$ 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 hexanes–ethyl acetate) to afford the O,N-bismethylation product **27** (60.9 mg, 80% yield) as a pale yellow foam.

^1H NMR (500 MHz, CDCl_3), δ : 7.36–7.26 (m, 5H, BnArH), 7.13 (t, 1H, $J = 7.8$ Hz, ArH), 6.69 (d, 2H, $J = 8.5$ Hz, ArH), 6.03–5.96 (m, 1H, $\text{CH}_2=\text{CH}$), 5.02 (dt, 1H, $J = 17.1$, 1.5 Hz, $\text{CH}_2=\text{CH}$), 4.95 (dt, 1H, $J = 10.2$, 1.5 Hz, $\text{CH}_2=\text{CH}$), 4.55 (d, 1H, $J = 12.2$ Hz, BnAr CH_2), 4.50 (d, 1H, $J = 12.2$ Hz, BnAr CH_2), 4.42 (dd, 1H, $J = 8.5$, 1.7 Hz, ArCH CH_2), 4.29 (d, 1H, $J = 2.4$ Hz, NCHCN), 3.78 (s, 3H, ArOCH $_3$), 3.70 (dd, 1H, $J = 9.0$, 2.2 Hz, ArCHCH $_2$), 3.36–3.50 (m, 1H, NCHCHCN), 3.32 (t, 1H, $J = 8.8$ Hz, ArCHCH $_2$), 3.06–3.03 (m, 1H, CH=CH $_2$ CH), 3.01 (t, 1H, $J = 11.7$ Hz, ArCH $_2$ CH), 2.90 (s, 3H, NCH), 2.67 (t, 1H, $J = 13.2$ Hz, ArCH $_2$), 2.49 (dd, 1H, $J =$

¹³C NMR (100 MHz, CDCl₃), δ: 14.9, 2.2 Hz, ArCH₂), 2.45 (s, 3H, NCH₃), 2.12–2.08 (m, 1H, NCHCH₂), 1.99–1.94 (m, 1H, NCHCH₂).
 155.8, 144.8, 138.5, 136.8, 132.1, 128.3, 127.6, 127.5, 125.5, 122.0, 120.1, 119.0, 113.1, 108.3, 78.3, 73.0, 72.9, 64.9, 59.3, 58.7, 58.1, 55.6, 55.2, 42.6, 42.3, 33.0.
 FTIR (thin film), cm⁻¹: 2934 (m), 2855 (m), 2223 (w, CN), 1650 (w), 1591 (m), 1474 (s), 1454 (m), 1353 (w), 1264 (s), 1096 (s), 1072 (s), 911 (m), 783 (m), 737 (m), 698 (m).
 HRMS (ES)⁺: Calcd for C₂₇H₃₁N₃O₂ [M+H]⁺: 430.2494
 Found: 430.2498.
 TLC (50:50 EtOAc–hexanes), R_f: Phenol **4**: 0.30 (PMA)
 Bismethylation Product **27**: 0.49 (PMA).

Aldehyde **28**:

Osmium tetroxide (2.5 wt% in *t*-BuOH, 60.9 μL, 7.09 μmol, 0.05 equiv) and sodium periodate (91.0 mg, 0.425 mmol, 3.0 equiv) were added sequentially to a vigorously stirring solution of the alkene **27** (60.9 mg, 0.142 mmol, 1 equiv) in tetrahydrofuran (7.1 mL) and water (3.5 mL). The resulting biphasic mixture was allowed to stir for 1 h at 23 °C. Saturated aqueous sodium thiosulfate solution (15 mL) was added and the mixture was extracted with dichloromethane (3 × 40 mL). The organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (30:70 ethyl acetate–hexanes) to furnish the aldehyde **28** (53.7 mg, 88% yield) as a white solid.

¹H NMR (500 MHz, CDCl₃), δ: 9.80 (s, 1H, CHO), 7.36–7.28 (m, 5H, BnArH), 7.15 (t, 1H, *J* = 7.8 Hz, ArH), 6.72 (t, 2H, *J* = 7.6 Hz, ArH), 4.53 (d, 1H, *J* = 11.7 Hz, BnCH₂), 4.47 (dd, 1H, *J* = 12.2 Hz, BnCH₂), 4.43 (dd, 1H, *J* = 8.5, 2.2 Hz, ArCH), 4.32 (d, 1H, *J* = 2.9 Hz, NCHCN), 3.78 (s, 3H, ArOCH₃), 3.70 (dd, 1H, *J* = 9.0, 2.2 Hz, ArCHCH₂), 3.39–3.37 (m, 2H, NCH & NCH), 3.28 (t, 1H, *J* = 8.8 Hz, ArCHCH₂), 3.10 (dd, 1H, *J* = 10.2, 3.9 Hz, ArCH₂CH), 3.08 (dd, 1H, *J* = 10.2, 5.4 Hz, CHOCH), 2.63–2.56 (m, 2H, ArCH₂), 2.40–2.35 (m, 1H, NCHCH₂), 2.15 (s, 3H, NCH₃), 2.00 (m, 1H, NCHCH₂).
¹³C NMR (100 MHz, CDCl₃), δ: 203.4, 155.8, 138.3, 136.1, 128.4, 128.3, 127.8, 127.6, 127.6, 121.7, 120.2, 118.4, 108.5, 73.1, 69.4, 64.4, 59.2, 57.6, 55.5, 55.2, 51.5, 42.2, 33.0, 26.0.
 FTIR (thin film), cm⁻¹: 2925 (m), 2847 (m), 2221 (w, CN), 1716 (s), 1591 (m), 1474 (s), 1456 (m), 1355 (w), 1263 (s), 1136 (m), 1100 (s), 1074 (s), 910 (w), 783 (w), 735 (m), 699 (m).
 HRMS (ES)⁺: Calcd for C₂₆H₂₉N₃O₃ [M+H]⁺: 432.2287
 Found: 432.2279.

TLC (50:50 EtOAc–hexanes), R_f : Alkene **27**: 0.52 (PMA)
 Aldehyde **28**: 0.34 (PMA).

Carboxylic Acid **5**:

A solution of the Jones reagent (2.68 M in 8.2 N aqueous sulfuric acid solution, 43 μ L, 0.115 mmol, 1.2 equiv) in acetone (250 μ L) was added to an ice-cooled solution of the aldehyde **28** (41.5 mg, 0.096 mmol, 1 equiv) in acetone (4.8 mL; substrate concentration $\sim$ 0.02 M). After 10 min at 0 $^{\circ}$ C, isopropanol (500 μ L) was added. The resulting green suspension was concentrated. The residue was purified by flash-column chromatography (elution gradient 3% $\rightarrow$ 5% $\rightarrow$ 6% methanol–dichloromethane) to provide the carboxylic acid **5** (39.0 mg, 91% yield) as an oil.

^1H NMR (400 MHz, CDCl_3), δ : 7.29–7.36 (m, 5H, BnArH), 7.14 (t, 1H, $J = 7.8$ Hz, ArH), 6.71 (d, 1H, $J = 7.8$ Hz, ArH), 6.70 (d, 1H, $J = 7.7$ Hz, ArH), 4.52 (d, 1H, $J = 12.1$ Hz, BnCH₂), 4.47 (d, 1H, $J = 12.1$ Hz, BnCH₂), 4.32 (dd, 1H, $J = 8.4, 1.8$ Hz, ArCH), 4.29 (d, 1H, $J = 2.9$ Hz, NCHCN), 3.78 (s, 3H, ArOCH₃), 3.70 (dd, 1H, $J = 8.8, 2.2$ Hz, BnOCH₂), 3.46 (br s, 1H, CHCHCOOH), 3.42 (d, 1H, $J = 6.2$ Hz, CH₃NCH), 3.28 (t, 1H, $J = 8.8$ Hz, BnOCH₂), 3.21 (dd, 1H, $J = 9.7, 5.7$ Hz, CHCOOH), 3.07 (d, 1H, $J = 8.8$ Hz, ArCH₂CH), 2.56–2.67 (m, 2H, ArCH₂), 2.38 (dd, 1H, CH₃NCHCH₂), 2.38 (s, 3H, NCH₃), 2.04 (dd, 1H, CH₃NCHCH₂).

^{13}C NMR (100 MHz, CDCl_3), δ : 181.1, 155.8, 138.2, 136.2, 128.4, 127.8, 127.6, 127.6, 121.6, 120.2, 118.4, 108.4, 77.1, 73.1, 70.5, 64.5, 58.9, 57.5, 55.5, 55.2, 42.8, 41.6, 32.8, 28.5.

FTIR (thin film), cm^{-1} : 2926 (m), 2850 (m), 2227 (w, CN), 1713 (m), 1591 (m), 1469 (s), 1387 (m), 1269 (s), 1264 (s), 1209 (m), 1098 (s), 1074 (s), 787 (w), 740 (m), 699 (w).

HRMS (ES)⁺: Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 448.2236
 Found: 448.2234.

TLC (95:5 CH_2Cl_2 –MeOH), R_f : Aldehyde **28**: 0.62 (PMA)
 Acid **5**: 0.22 (PMA).

Quinocarcin:

A solution of boron trichloride in dichloromethane (1 M, 436 μ L, 0.436 mmol, 5 equiv) was added to an ice-cooled solution of the carboxylic acid **5** (39.0 mg, 0.087 mmol, 1 equiv) in dichloromethane (8.7 mL; substrate concentration $\sim$ 0.01 M). After 15 min at 0 $^{\circ}$ C, methanol (500 μ L) was added and the resulting solution was concentrated to afford a mixture of DX-52-1 (**6**, minor) and quinocarcin (major). Methanol (2.2 mL) and water (0.54 mL) were added, and to the resulting solution was added solid silver nitrate (74 mg, 0.436 mmol, 5 equiv) in one portion. After 1 h at 23 $^{\circ}$ C, Amberlite IRA-400 ($\sim$ 200 mg) was added. After 10 min, the suspension was filtered through a plug of Celite, eluting with methanol. The eluent was concentrated and the residue purified by semi-preparative rp-HPLC using a C-18 column (Ultrasphere ODS, 20% methanol–water, 3 mL/min, t_R = 10.8 min), affording pure quinocarcin (20.2 mg, 70% yield) as a white solid.

^1H NMR (500 MHz, CD_3OD), δ :	7.16 (t, 1H, J = 7.8 Hz, ArH), 6.84 (d, 1H, J = 8.3 Hz, ArH), 6.76 (d, 1H, J = 7.3 Hz, ArH), 4.57 (d, 1H, J = 2.9 Hz, NCHO), 4.54 (dd, 1H, J = 7.3, 2.9 Hz, ArCH), 4.08 (br s, 2H, CH_3NCH), 3.12 (s, 3H, ArOCH_3), 3.67 (dd, 1H, J = 10.5, 2.7 Hz, ArCHCH_2), 3.41–3.35 (m, 3H, ArCHCH_2 , ArCH_2CH & CHCO_2H), 2.79–2.74 (m, 1H, ArCH_2), 2.77 (s, 3H, NCH_3), 2.64 (dd, 1H, J = 14.4, 2.2 Hz, $\text{HO}_2\text{CCHCH}_2$), 2.63–2.59 (m, 1H, ArCH_2), 2.47 (dd, 1H, J = 13.7, 10.7 Hz, $\text{HO}_2\text{CCHCH}_2$).
^{13}C NMR (100 MHz, CD_3OD), δ :	174.9, 157.2, 137.0, 129.1, 123.8, 121.3, 110.0, 92.1, 72.3, 67.9, 66.8, 56.3, 55.9, 53.4, 40.6, 40.3, 32.5, 27.3.
HRMS (ES) $^{+}$:	Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^{+}$: 331.1658 Found: 331.1660
$[\alpha]_D$:	Literature ⁵ : -32° (c 0.5, H_2O) Found: -33° (c 0.1, H_2O).
TLC (90:10 CH_2Cl_2 –MeOH), R_f :	Benzyl Ether 5 : 0.43 (PMA) DX-52-1 (6): baseline (PMA) Quinocarcin: baseline (PMA).
HPLC (Ultrasphere ODS, 20% MeOH– H_2O , 3 mL/min), t_R	Synthetic Quinocarcin: 10.8 min Natural Quinocarcin: 10.8 min (coincident upon coinjection).

Synthetic Procedures for the Cyclization Reactions of Schemes 2–4.

Tricyclic Bis-Amino Nitrile Diastereomers **7a**, **7b**, **7c** and Tetracyclic Cyanopiperazine **4**:

⁵ Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468–470.

Trimethylsilyl cyanide (86 μ L, 0.644 mmol, 3.5 equiv) and a solution of zinc chloride in THF (0.5 M, 920 μ L, 0.46 mmol, 2.5 equiv) were added sequentially to a solution of the bis-amino nitriles **3** (108.2 mg, 0.184 mmol, 1 equiv) in trifluoroethanol (9.2 mL; substrate concentration $\sim$ 0.02 M). The resulting solution was stirred for 1 h at 23 $^{\circ}$ C. Saturated aqueous sodium bicarbonate solution (25 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3 $\times$ 40 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (gradient elution 1% $\rightarrow$ 2% $\rightarrow$ 5% $\rightarrow$ 15% ethyl acetate–dichloromethane) to afford separately the tricyclic bis-amino nitrile **7a** (40.8 mg, 44% yield), the tricyclic bis-amino nitrile **7b** (14.3 mg, 15% yield) and the tricyclic bis-amino nitrile **7c** (10.9 mg, 12%) as clear oils, and the tetracyclic cyanopiperazine **4** (13.0 mg, 18% yield) as a pale yellow solid.

Tricyclic Bis-Amino Nitrile **7a**

^1H NMR (500 MHz, CDCl_3), δ :	7.36–7.29 (m, 5H, BnArH), 7.25 (s, 1H, ArOH), 7.14 (t, 1H, J = 7.8 Hz, ArH), 6.80 (d, 1H, J = 8.3 Hz, ArH), 6.76 (d, 1H, J = 6.8 Hz, ArH), 5.55–5.48 (m, 1H, SiCH_2CH), 5.15–5.10 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.56 (d, 1H, J = 11.7 Hz, BnArCH ₂), 4.49 (d, 1H, J = 11.7 Hz, BnArCH ₂), 4.22 (t, 1H, J = 6.3 Hz, ArCH), 3.98 (s, 1H, NCHCN), 3.67 (d, 1H, J = 9.8 Hz, NHCHCN), 3.56–3.51 (m, 2H, BnOCH ₂), 3.16 (t, 1H, J = 7.3 Hz, NHCHCH ₂), 3.03–2.95 (m, 2H, ArCH ₂ CH), 2.59 (dd, 1H, J = 13.7, 11.2 Hz, ArCH ₂), 2.50–2.44 (m, 1H, NHCHCH ₂), 2.35–2.29 (m, 1H, NHCHCH ₂), 2.20 (br s, 1H, NH), 1.57–1.40 (m, 2H, SiCH ₂), 0.02 (s, 9H, Si(CH ₃) ₃).
^1H NMR (400 MHz, C_6D_6), δ :	7.13–7.04 (m, 5H, BnArH), 6.85 (t, 1H, J = 7.8 Hz, ArH), 6.46 (d, 1H, J = 8.3 Hz, ArH), 6.39 (d, 1H, J = 8.3 Hz, ArH), 5.84 (s, 1H, ArOH), 5.37–5.30 (m, 1H, SiCH_2CH), 4.89–4.83 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.26 (t, 1H, J = 6.1 Hz, ArCH), 4.18 (d, 1H, J = 11.7 Hz, BnArCH ₂), 4.12 (d, 1H, J = 11.7 Hz, BnArCH ₂), 3.65 (s, 1H, NCHCN), 3.27 (d, 1H, J = 9.8 Hz, NHCHCN), 3.39 (dd, 1H, J = 8.8, 5.9 Hz, BnOCH ₂), 3.18 (dd, 1H, J = 8.8, 6.3 Hz, BnOCH ₂), 2.93 (td, 1H, J = 10.2, 2.2 Hz, ArCH ₂ CH), 2.81 (dd, 1H, J = 14.4, 2.2 Hz, ArCH ₂), 2.50 (t, 1H, J = 7.3 Hz, NHCHCH ₂), 2.19 (dd, 1H, J = 14.4, 11.2 Hz, ArCH ₂), 2.13–2.08 (m, 1H, NHCHCH ₂), 1.86–1.80 (m, 1H, NHCHCH ₂), 1.64 (br s, 1H, NH), 1.33 (d, 1H, J = 4.4 Hz, SiCH ₂), 1.32 (d, 1H, J = 2.4 Hz, SiCH ₂), 0.02 (s, 9H, Si(CH ₃) ₃).
^{13}C NMR (100 MHz, CDCl_3), δ :	153.4, 136.5, 133.9, 131.8, 128.6, 128.2, 127.8, 122.8, 121.5, 120.5, 117.5, 117.3, 116.1, 76.2, 73.8, 57.9, 55.8, 55.2, 55.0, 47.6, 32.9, 32.8, 23.1, –1.9.
FTIR (thin film), cm^{-1} :	3370 (m), 2951 (m), 2903 (w), 2251 (w, CN), 2227 (w, CN), 1595 (m), 1471 (s), 1281 (m), 1247 (s), 1153 (m), 1101 (m), 1070 (m), 865 (s), 852 (s), 792 (m), 733 (m), 698 (m).
HRMS (ES) ⁺ :	Calcd for $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 501.2686 Found: 501.2674.
TLC (95:5 CH_2Cl_2 –EtOAc), R_f :	Bis-Amino Nitrile 3 : 0.04 (PMA) Tricyclic Bis-Amino Nitrile 7a : 0.18 (PMA).

Tricyclic Bis-Amino Nitrile **7b**

^1H NMR (600 MHz, CDCl_3), δ :	7.74 (s, 1H, ArOH), 7.35–7.31 (m, 5H, BnArH), 7.15 (t, 1H, J = 7.8 Hz, ArH), 6.87 (d, 1H, J = 8.3 Hz, ArH), 6.77 (d, 1H, J = 7.3 Hz, ArH), 5.76–5.70 (m, 1H, SiCH_2CH), 5.34–5.29 (m, 1H, NHCHCH_2CH), 4.56 (d, 1H, J = 11.7 Hz, BnCH_2), 4.53 (d, 1H, J = 11.7 Hz, BnCH_2), 3.98 (dd, 1H, J = 10.0, 3.2 Hz, ArCH), 3.84 (dd, 1H, J = 8.8, 3.4 Hz, ArCH CH_2), 3.77 (dd, 1H, J = 8.5, 1.7 Hz, NHCHCN), 3.52 (t, 1H, J = 9.3 Hz, ArCH CH_2), 3.10 (dd, 1H, J = 11.7, 1.9 Hz, NHCHCH), 2.99 (d, 1H, J = 6.1 Hz, ArCH CH_2), 2.67–2.64 (m, 2H, ArCH CH_2 & NCHCN), 2.61 (d, 1H, J = 11.7 Hz, ArCH CH_2), 2.46 (dd, 1H, J = 13.7, 6.3 Hz, NHCHCH_2), 2.42 (s, 1H, NH), 2.30 (dd, 1H, J = 13.4, 8.5 Hz, NHCHCH_2), 1.56 (d, 2H, J = 8.3 Hz, SiCH_2), 0.04 (s, 9H, $\text{Si}(\text{CH}_3)_3$).
^1H NMR (400 MHz, C_6D_6), δ :	7.72 (s, 1H, ArOH), 7.10–7.08 (m, 5H, BnArH), 6.98–6.92 (m, 2H, ArH), 6.45 (d, 1H, J = 7.3 Hz, ArH), 5.52–5.44 (m, 1H, SiCH_2CH), 5.21–5.14 (m, 1H, NHCHCH_2CH), 4.05 (d, 1H, J = 11.7 Hz, BnCH_2), 4.02 (d, 1H, J = 11.7 Hz, BnCH_2), 3.76 (dd, 1H, J = 9.5, 3.3 Hz, ArCH), 3.67 (dd, 1H, J = 8.8, 3.4 Hz, ArCH CH_2), 3.42 (dd, 1H, J = 8.8, 2.2 Hz, NHCHCN), 3.31 (dd, 1H, J = 9.5, 8.8 Hz, ArCH CH_2), 2.79 (d, 1H, J = 12.1 Hz, NHCHCH), 2.59 (dd, 1H, J = 11.9, 1.6 Hz, ArCH CH_2), 2.25–2.15 (m, 2H, ArCH CH_2 & ArCH CH_2), 1.88 (dd, 1H, J = 13.4, 7.0 Hz, NHCHCH_2), 1.82–1.76 (m, 1H, NHCHCH_2), 1.78 (d, 1H, J = 11.7 Hz, NCHCN), 1.68 (s, 1H, NH), 1.35 (d, 2H, J = 8.1 Hz, SiCH_2), 0.09 (s, 9H, $\text{Si}(\text{CH}_3)_3$).
^{13}C NMR (100 MHz, CDCl_3), δ :	154.0, 136.2, 135.9, 133.7, 128.6, 128.5, 128.3, 127.9, 123.2, 120.6, 119.7, 117.9, 117.1, 116.9, 76.5, 74.0, 60.4, 58.4, 58.1, 56.5, 50.8, 40.4, 32.7, 23.5, –1.9.
FTIR (thin film), cm^{-1} :	3297 (m), 2952 (w), 2895 (w), 2247 (w, CN), 2224 (w, CN), 1593 (w), 1469 (m), 1281 (m), 1248 (s), 1151 (w), 1097 (m), 1071 (m), 971 (m), 850 (s), 784 (m), 736 (m), 698 (m).
HRMS (ES) $^+$:	Calcd for $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 501.2686 Found: 501.2691.
TLC (95:5 CH_2Cl_2 –EtOAc), R_f :	Bis-Amino Nitrile 3 : 0.04 (PMA) Tricyclic Cyanopiperazine 7b : 0.57 (PMA).

Tricyclic Bis-Amino Nitrile **7c**

^1H NMR (600 MHz, CDCl_3), δ :	7.78 (s, 1H, ArOH), 7.36–7.30 (m, 5H, BnArH), 7.14 (t, 1H, J = 7.8 Hz, ArH), 6.87 (d, 1H, J = 8.3 Hz, ArH), 6.73 (d, 1H, J = 7.8 Hz, ArH), 5.72–5.65 (m, 1H, SiCH_2CH), 5.39–5.33 (m, 1H, NHCHCH_2CH), 4.59 (d, 1H, J = 11.2 Hz, BnCH_2), 4.55 (d, 1H, J = 11.2 Hz, BnCH_2), 4.09 (d, 1H, J = 2.4 Hz, NHCHCN), 4.03–3.97 (m, 2H, ArCH & ArCH CH_2), 3.63 (t, 1H, J = 9.0 Hz, ArCH CH_2), 3.20 (d, 1H, J = 11.7 Hz, NHCHCH_2), 2.98 (t, 1H, J = 12.9 Hz, ArCH CH_2), 2.73 (dt, 1H, J = 12.2, 2.4 Hz, ArCH CH_2), 2.65 (dd, 1H, J = 14.2, 2.4 Hz, ArCH CH_2), 2.61 (d, 1H, J = 11.7 Hz, NCHCN), 2.45 (dd, 1H, J = 13.2, 6.3 Hz, NHCHCH_2), 2.36 (s, 1H, NH), 2.24 (dd, 1H, J = 13.4, 8.5 Hz, NHCHCH_2), 1.56 (br s, 2H, SiCH_2), 0.01 (s, 9H, $\text{Si}(\text{CH}_3)_3$).
^1H NMR (400 MHz, C_6D_6), δ :	7.89 (s, 1H, ArOH), 7.09–6.99 (m, 7H, BnArH & ArH), 6.54 (d, 1H, J = 6.8 Hz, ArH), 5.55–5.49 (m, 1H, SiCH_2CH), 5.32–5.26 (m,

	1H, NHCHCH ₂ CH), 3.96 (d, 1H, <i>J</i> = 11.2 Hz, BnCH ₂), 3.92 (d, 1H, <i>J</i> = 11.2 Hz, BnCH ₂), 3.85 (dd, 1H, <i>J</i> = 8.8, 3.9 Hz, ArCHCH ₂), 3.80 (dd, 1H, <i>J</i> = 10.0, 3.9 Hz, ArCHCH ₂), 3.39 (t, 1H, <i>J</i> = 9.3 Hz, ArCH), 3.12 (s, 1H, NHCHCN), 2.92 (t, 1H, <i>J</i> = 13.2 Hz, ArCH ₂), 2.70 (d, 1H, <i>J</i> = 11.7 Hz, NHCHCH ₂), 2.09–2.04 (m, 2H, ArCH ₂ & ArCH ₂ CH), 1.93 (dd, 1H, <i>J</i> = 13.4, 7.1 Hz, NHCHCH ₂), 1.86 (dd, 1H, <i>J</i> = 13.4, 8.1 Hz, NHCHCH ₂), 1.82 (d, 1H, <i>J</i> = 11.7 Hz, NCHCN), 1.58 (s, 1H, NH), 1.39 (d, 2H, <i>J</i> = 8.3 Hz, SiCH ₂), 0.01 (s, 9H, Si(CH ₃) ₃).
¹³ C NMR (100 MHz, CDCl ₃), δ:	154.2, 136.3, 135.5, 134.1, 128.6, 128.5, 128.2, 127.9, 123.3, 120.2, 119.9, 118.3, 116.9, 116.5, 74.0, 61.9, 58.5, 56.4, 53.9, 49.6, 42.0, 32.9, 29.7, 23.4, –1.9.
FTIR (thin film), cm ^{–1} :	3323 (m), 2950 (m), 2923 (s), 2853 (m), 2230 (w, CN), 2193 (w, CN), 1595 (m), 1470 (s), 1453 (m), 1285 (m), 1248 (s), 1157 (m), 1105 (m), 1075 (m), 973 (m), 852 (s), 741 (s), 699 (m).
HRMS (ES) ⁺ :	Calcd for C ₂₉ H ₃₆ N ₄ O ₂ Si [M+H] ⁺ : 501.2686 Found: 501.2691.
TLC (95:5 CH ₂ Cl ₂ –EtOAc), R _f :	Bis-Amino Nitrile 3 : 0.04 (PMA) Tricyclic Bis-Amino Nitrile 7c : 0.57 (PMA).

Tricyclic Bis-Amino Nitrile Diastereomers **7b**, **7d**, and Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (10 μL, 0.076 mmol, 2 equiv) and a solution of ZnCl₂ in THF (0.5 M, 114 μL, 0.057 mmol, 1.5 equiv) were added sequentially to a solution of the bis-amino nitriles **3** (22.4 mg, 0.038 mmol, 1 equiv) in trifluoroethanol (1.9 mL; substrate concentration ~0.02 M). The resulting solution was stirred for 12 h at 23 °C. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (gradient elution 1% → 2% → 3% → 15% ethyl acetate–dichloromethane) to afford separately the tricyclic bis-amino nitrile diastereomer **7b** (3.7 mg, 19% yield) and the tricyclic bis-amino nitrile **7d** (3.7 mg, 19% yield) as white foams and the tetracyclic cyanopiperazine **4** (2.8 mg, 18% yield) as a pale yellow solid.

Tricyclic Bis-Amino Nitrile **7d**

¹H NMR (600 MHz, CDCl₃), δ: 7.37–7.25 (m, 5H, BnArH), 7.25 (s, 1H, ArOH), 7.12 (t, 1H, *J* = 7.8 Hz, ArH), 6.78 (d, 1H, *J* = 8.0 Hz, ArH), 6.75 (d, 1H, *J* = 7.8 Hz, ArH), 5.67–5.61 (m, 1H, SiCH₂CH), 5.11–5.05 (m, 1H, SiCH₂CH=CH), 4.56 (d, 1H, *J* = 11.8 Hz, BnArCH₂), 4.49 (d, 1H,

	$J = 11.8$ Hz, BnArCH ₂), 4.29 (t, 1H, $J = 6.3$ Hz, ArCH), 4.03 (d, 1H, $J = 2.9$ Hz, NCHCN), 3.57–3.49 (m, 3H, NHCHCN & BnOCH ₂), 3.02 (dd, 1H, $J = 14.5, 2.1$ Hz, ArCH ₂), 2.92–2.88 (m, 2H, ArCH ₂ CH & NHCHCH ₂), 2.55 (dd, 1H, $J = 14.1, 11.7$ Hz, ArCH ₂), 2.32–2.27 (m, 1H, CHCH ₂ CH=CH), 2.25–2.08 (m, 1H, CHCH ₂ CH=CH), 1.94 (br s, 1H, NH), 1.45 (d, 2H, $J = 8.3$ Hz, SiCH ₂), 0.01 (s, 9H, Si(CH ₃) ₃).
¹ H NMR (600 MHz, C ₆ D ₆), δ:	7.19–7.08 (m, 5H, BnArH), 6.84 (t, 1H, $J = 7.7$ Hz, ArH), 6.40–6.38 (m, 2H, ArH), 5.66 (s, 1H, ArOH), 5.54–5.46 (m, 1H, SiCH ₂ CH), 4.95–4.87 (m, 1H, SiCH ₂ CH=CH), 4.22 (d, 1H, $J = 12.1$ Hz, BnArCH ₂), 4.13 (d, 1H, $J = 11.7$ Hz, BnArCH ₂), 4.50 (t, 1H, $J = 6.2$ Hz, ArCH), 3.99 (d, 1H, $J = 2.9$ Hz, NCHCN), 3.45 (dd, 1H, $J = 8.8, 5.5$ Hz, BnOCH ₂), 3.19 (dd, 1H, $J = 8.8, 6.6$ Hz, BnOCH ₂), 2.88–2.84 (m, 3H, NHCHCH ₂ , ArCH ₂ CH & ArCH ₂ CH), 2.45 (td, 1H, $J = 7.3, 2.9$ Hz, NHCH), 2.43–2.18 (m, 1H, ArCH ₂), 1.99 (t, 2H, $J = 7.1$ Hz, NHCHCH ₂), 1.30 (d, 2H, $J = 8.1$ Hz, SiCH ₂), 0.01 (s, 9H, Si(CH ₃) ₃).
¹³ C NMR (100 MHz, CDCl ₃), δ:	153.2, 136.8, 134.2, 132.7, 128.6, 128.5, 128.1, 127.7, 121.3, 121.1, 120.4, 117.2, 115.9, 115.6, 76.2, 73.7, 58.4, 58.0, 56.3, 55.0, 52.8, 36.0, 32.7, 23.1, –1.9.
FTIR (thin film), cm ^{–1} :	2951 (w), 2246 (w, CN), 1595 (m), 1471 (s), 1313 (m), 1280 (m), 1247 (s), 1153 (w), 1105 (m), 1070 (m), 972 (m), 856 (s), 783 (m), 733 (m), 697 (m).
HRMS (ES) ⁺ :	Calcd for C ₂₉ H ₃₆ N ₄ O ₂ Si [M+H] ⁺ : 501.2686 Found: 501.2691.
TLC (95:5 CH ₂ Cl ₂ –EtOAc), R _f :	Bis-Amino Nitrile 3 : 0.04 (PMA) Tricyclic Bis-Amino Nitrile 7d : 0.44 (PMA).

Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (5.2 μ L, 0.039 mmol, 4 equiv) and a solution of zinc chloride in THF (0.5 M, 59 μ L, 0.029 mmol, 3 equiv) were added sequentially to a solution of the tricyclic bis-amino nitrile **7a** (4.9 mg, 9.8×10^{-3} mmol, 1 equiv) in trifluoroethanol (489 μ L; substrate concentration ~ 0.02 M). After 2 h at 23 °C, the solution was heated for 19 h at 61 °C, then was allowed to cool to 23 °C. Saturated sodium bicarbonate solution (10 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3×7 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (2.4 mg, 61% yield) as a pale yellow solid.

TLC (50:50 EtOAc–hexanes), R _f :	Tricyclic Bis-Amino Nitrile 7a : 0.61 (ninhydrin) Tetracyclic Cyanopiperazine 4 : 0.17 (ninhydrin).
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Tetracyclic Cyanopiperazine 4:

Trimethylsilyl cyanide (7.9 μL , 0.059 mmol, 4 equiv) and a solution of zinc chloride in THF (0.5 M, 89 μL , 0.044 mmol, 3 equiv) were added sequentially to a solution of the tricyclic bis-amino nitrile **7b** (7.4 mg, 0.015 mmol, 1 equiv) in trifluoroethanol (739 μL ; substrate concentration ~ 0.02 M). After 1.5 h at 23 $^\circ\text{C}$, the solution was heated for 19 h at 61 $^\circ\text{C}$, then was allowed to cool to 23 $^\circ\text{C}$. Saturated sodium bicarbonate solution (10 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3×7 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (1.8 mg, 30% yield) as a pale yellow solid.

TLC (50:50 EtOAc–hexanes), R_f : Tricyclic Bis-Amino Nitrile **7b**: 0.66 (ninhydrin)
 Tetracyclic Cyanopiperazine **4**: 0.17 (ninhydrin).

Tetracyclic Cyanopiperazine 4:

Trimethylsilyl cyanide (1.7 μL , 0.013 mmol, 4 equiv) and a solution of zinc chloride in THF (0.5 M, 19 μL , 9.6×10^{-3} mmol, 3 equiv) were added sequentially to a solution of the tricyclic bis-amino nitrile **7c** (1.6 mg, 3.2×10^{-3} mmol, 1 equiv) in trifluoroethanol (160 μL ; substrate concentration ~ 0.02 M). After 2 h at 23 $^\circ\text{C}$, the solution was heated for 4 h at 55 $^\circ\text{C}$, then was allowed to cool to 23 $^\circ\text{C}$. Saturated sodium bicarbonate solution (10 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3×7 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (0.7 mg, 54% yield) as a pale yellow solid.

TLC (50:50 EtOAc–hexanes), R_f : Tricyclic Bis-Amino Nitrile **7c**: 0.57 (ninhydrin)
 Tetracyclic Cyanopiperazine **4**: 0.17 (ninhydrin).

Tetracyclic Cyanopiperazine 4:

Trimethylsilyl cyanide (6.3 μ L, 0.047 mmol, 4 equiv) and a solution of zinc chloride in THF (0.5 M, 71 μ L, 0.035 mmol, 3 equiv) were added sequentially to a solution of the tricyclic bis-amino nitrile **7d** (5.9 mg, 0.012 mmol, 1 equiv) in trifluoroethanol (589 μ L; substrate concentration $\sim$ 0.02 M). After 2 h at 23 $^{\circ}$ C, the solution was heated for 19 h at 61 $^{\circ}$ C, then was allowed to cool to 23 $^{\circ}$ C. Saturated sodium bicarbonate solution (10 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3×7 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (1.6 mg, 41% yield) as a pale yellow solid.

TLC (50:50 EtOAc–hexanes), R_f : Tricyclic Bis-Amino Nitrile **7d**: 0.62 (ninhydrin)
Tetracyclic Cyanopiperazine **4**: 0.17 (ninhydrin).

Bis-Amino Nitriles **8**:

A solution of the C-protected α -amino aldehyde derivative (*R,S*)-**2** (28.9 mg, 0.103 mmol, 1.05 equiv) in benzene (289 μ L) was added to a solution of the N-protected α -amino aldehyde derivative **1** (50.8 mg, 0.098 mmol, 1 equiv) in dichloromethane (5 mL) and the resulting solution was concentrated. Dichloromethane (1 mL; substrate concentration $\sim$ 0.1 M) and solid sodium sulfate (417 mg, 2.93 mmol, 30 equiv) were added to the residue. After stirring for 2 h at 23 $^{\circ}$ C, the suspension was filtered through a pipette plugged with cotton wool and the filtrate was concentrated. Dichloromethane (1.9 mL; substrate concentration $\sim$ 0.05 M) was added to the residue, the resulting solution was cooled in an ice bath, and 1,8-diazabicyclo[5.4.0]undec-7-ene (16 μ L, 0.11 mmol, 1.1 equiv) was added to the cooled solution. The ice bath was removed after 10 min. In another round-bottom flask, acetic acid (29 μ L, 0.51 mmol, 5.2 equiv) was added to an ice-cooled suspension of potassium cyanide (32 mg, 0.49 mmol, 5 equiv) in methanol (0.49 mL). After 10 min, the solids appeared to have completely dissolved, forming a clear solution (Caution: HCN!). The original reaction flask, containing the substrate, was cooled in an ice bath approximately 1.5 h from the point of addition of DBU, and after 10 min, the solution of methanolic hydrogen cyanide was added by cannula transfer. The resulting solution was allowed to stir for 1.5 h at 0 $^{\circ}$ C. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the biphasic mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (92:8 dichloromethane–ethyl acetate), providing a diastereomeric mixture of the bis-amino nitriles **8** (49.5 mg, 86% yield) as a pale yellow foam.

^1H NMR (500 MHz, CDCl_3), δ : 8.05 (br s, 1H, ArOH), 7.37–7.29 (m, 5H, BnArH), 7.11 (t, 1H, $J = 7.8$ Hz, ArH), 6.81 (d, 1H, $J = 7.8$ Hz, ArH), 6.71 (d, 1H, $J = 7.3$ Hz, ArH), 5.68–5.62 (m, 1H, SiCH_2CH), 5.29–5.18 (m, 1H, $\text{SiCH}_2\text{CH}=\text{CH}$), 4.64 (d, 1H, $J = 12.2$ Hz, BNCH_2), 4.62–4.60 (m, 1H, ArCH), 4.53 (d, 1H, BnCH_2), 3.81–3.71 (m, 5H, CH_2OCH_2 & ArCH_2CHCH), 3.68 (dd, 1H, $J = 8.8, 3.9$ Hz,

^{13}C NMR (100 MHz, CDCl_3), δ :	ArCHCH ₂ , 3.63 (t, 1H, J = 8.8 Hz, ArCHCH ₂), 3.36 (d, 1H, J = 11.2 Hz, CNCH), 3.21–3.14 (m, 2H, CNCHCH & CNCHCH), 2.80–2.74 (m, 3H, ArCH ₂ & CH ₂ NCH ₂), 2.59–2.49 (m, 3H, CH ₂ NCH ₂ & NHCHCH ₂), 2.30–2.24 (m, 1H, NHCHCH ₂), 1.46 (d, 2H, J = 7.8 Hz, SiCH ₂), 0.02 (s, 9H, SiCH ₃).
FTIR (thin film), cm^{-1} :	3302 (br w), 2952 (m), 2851 (m), 2223 (w, CN), 1588 (w), 1467 (m), 1454 (m), 1279 (m), 1247 (m), 1116 (s), 1071 (m), 860 (s), 850 (s), 736 (m), 698 (m).
HRMS (ES) ⁺ :	Calcd for C ₃₃ H ₄₅ N ₅ O ₃ Si [M+H] ⁺ : 588.3370 Found: 588.3363.
TLC (50–50 EtOAc–hexanes), R _f :	Aldehyde 1 : 0.27 (PMA) Bis-Amino Nitriles 8 : 0.43 & 0.22 (PMA).

Bis-Amino Nitriles **9**:

A solution of the N-protected α -amino aldehyde derivative **1** (23.8 mg, 0.046 mmol, 1 equiv) in dichloromethane (2 mL) was added to a solution of the C-protected α -amino aldehyde derivative (*S,S*)-**21** (14.2 mg, 0.05 mmol, 1.1 equiv) in dichloromethane (5 mL) and the resulting solution was concentrated. Dichloromethane (0.46 mL; substrate concentration ~ 0.1 M) and solid sodium sulfate (195 mg, 1.38 mmol, 30 equiv) were added to the residue. After stirring for 2 h at 23 °C, the suspension was filtered through a pipette plugged with cotton wool and the filtrate was concentrated. Dichloromethane (0.92 mL; substrate concentration ~ 0.05 M) was added to the residue, the resulting solution was cooled in an ice bath, and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.5 μL , 0.05 mmol, 1.1 equiv) was added to the cooled solution. The ice bath was removed after 10 min. In another round-bottom flask, acetic acid (13.6 μL , 0.24 mmol, 5.2 equiv) was added to an ice-cooled suspension of potassium cyanide (14.9 mg, 0.23 mmol, 5 equiv) in methanol (0.23 mL). After 10 min, the solids appeared to have completely dissolved, forming a clear solution (Caution: HCN!). The original reaction flask, containing the substrate, was cooled in an ice bath approximately 1 h from the point of addition of DBU, and after 5 min, the solution of methanolic hydrogen cyanide was added by cannula transfer. The resulting solution was allowed to stir for 2 h at 0 °C. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the biphasic mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (gradient elution 93:7 $\rightarrow$ 80:20 $\rightarrow$ 50:50 dichloromethane–ethyl acetate), providing a diastereomeric mixture of the bis-amino nitriles **9** (23.6 mg, 88% yield) as a pale yellow foam.

^1H NMR (500 MHz, CDCl_3), δ :	8.24 (br s, 1H, ArOH), 7.84 (br s, 1H, ArOH), 7.37–7.28 (m, 5H, BnArH), 7.10 (t, 1H, J = 7.7 Hz, ArH), 7.09 (t, 1H, J = 7.7 Hz, ArH), 6.80 (d, 1H, J = 8.8 Hz, ArH), 6.69 (d, 1H, J = 6.2
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	Hz, ArH), 5.77–5.66 (m, 1H, SiCH ₂ CH), 5.30–5.16 (m, 1H, SiCH ₂ CH=CH), 4.64–4.51 (m, 3H, BnCH ₂ & ArCH), 3.92–3.90 (m, 1H, ArCHCH ₂), 3.86 (dd, 1H, <i>J</i> = 8.6, 3.1 Hz, ArCHCH ₂), 3.80–3.70 (m, 4H, CH ₂ OCH ₂), 3.65–3.59 (m, 1H, ArCHCH ₂), 3.40 (d, 1H, <i>J</i> = 8.0 Hz, CNCH), 3.29 (d, 1H, <i>J</i> = 9.5 Hz, CNCH), 3.25–3.23 (m, 1H, CNCHCH), 3.19–3.14 (m, 1H, CNCHCH), 3.13–3.09 (m, 1H, CNCHCH), 2.84 (d, 1H, <i>J</i> = 12.4 Hz, ArCH ₂ CHCH), 2.79–2.67 (m, 3H, ArCH ₂ & CH ₂ NCH ₂), 2.62–2.51 (m, 2H, CH ₂ NCH ₂), 2.47 (t, 1H, <i>J</i> = 5.8 Hz, ArCH ₂), 2.30 (dd, 1H, <i>J</i> = 15.0, 7.3 Hz, NHCHCH ₂), 2.19 (dd, 1H, <i>J</i> = 10.2, 4.8 Hz, ArCH ₂), 1.99 (dd, 1H, <i>J</i> = 11.0, 4.8 Hz, NHCHCH ₂), 1.61–1.53 (m, 2H, SiCH ₂), 0.04 (s, 9H, SiCH ₃), 0.03 (s, 9H, SiCH ₃).
¹³ C NMR (125 MHz, CDCl ₃), δ:	154.7, 154.3, 136.5, 136.4, 135.2, 131.9, 131.7, 128.6, 128.2, 128.0, 127.9, 124.0, 121.0, 120.9, 119.3, 119.1, 119.0, 118.3, 116.7, 116.2, 116.1, 115.9, 77.7, 73.7, 66.5, 63.8, 61.9, 60.4, 56.2, 55.5, 54.4, 53.6, 53.2, 52.5, 51.9, 51.0, 50.4, 33.7, 33.3, 28.6, 27.0, 19.2, 19.1, –1.7, –1.8.
FTIR (thin film), cm ^{–1} :	3316 (br w), 2952 (m), 2226 (w, CN), 1587 (m), 1467 (s), 1454 (s), 1248 (s), 1147 (m), 1118 (s), 1070 (m), 1008 (m), 856 (s), 782 (m), 736 (s), 699 (m).
HRMS (ES) ⁺ :	Calcd for C ₃₃ H ₄₅ N ₅ O ₃ Si [M+H] ⁺ : 588.3370 Found: 588.3365.
TLC (50:50 EtOAc–hexanes), R _f :	Aldehyde 1 : 0.27 (PMA) Bis-Amino Nitriles 9 : 0.43 & 0.25 (PMA).

Bis-Amino Nitriles **10**:

A solution of the N-protected α -amino aldehyde derivative **1** (20.8 mg, 0.040 mmol, 1 equiv) in dichloromethane (2 mL) was added to a solution of the C-protected α -amino aldehyde derivative (*R,S*)-**21** (12.4 mg, 0.044 mmol, 1.1 equiv) in dichloromethane (5 mL) and the resulting solution was concentrated. Dichloromethane (0.40 mL; substrate concentration ~0.1 M) and solid sodium sulfate (171 mg, 1.20 mmol, 30 equiv) were added to the residue. After stirring for 2 h at 23 °C, the suspension was filtered through a pipette plugged with cotton wool and the filtrate was concentrated. Dichloromethane (0.80 mL; substrate concentration ~0.05 M) was added to the residue, the resulting solution was cooled in an ice bath, and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.6 μ L, 0.044 mmol, 1.1 equiv) was added to the cooled solution. The ice bath was removed after 10 min. In another round-bottom flask, acetic acid (12 μ L, 0.21 mmol, 5.2 equiv) was added to an ice-cooled suspension of potassium cyanide (13 mg, 0.21 mmol, 5 equiv) in methanol (0.20 mL). After 10 min, the solids appeared to have completely dissolved, forming a clear solution (Caution: HCN!). The original reaction flask, containing the substrate, was cooled in an ice bath approximately 1 h from the point of addition of DBU, and after 5 min, the solution of methanolic hydrogen cyanide was added by cannula transfer. The

resulting solution was allowed to stir for 2 h at 0 °C. Saturated aqueous sodium bicarbonate solution (10 mL) was added and the biphasic mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (gradient elution 93:7 → 80:20 → 50:50 dichloromethane–ethyl acetate), providing a diastereomeric mixture of the bis-amino nitriles **10** (22.8 mg, 97% yield) as a pale yellow foam.

¹H NMR (500 MHz, CDCl₃), δ: 8.16 (br s, 1H, ArOH), 7.53–7.41 (m, 5H, BnArH), 7.26 (t, 1H, *J* = 7.7 Hz, ArH), 6.96 (d, 1H, *J* = 8.0 Hz, ArH), 6.86 (d, 1H, *J* = 7.7 Hz, ArH), 5.86–5.75 (m, 1H, SiCH₂CH), 5.49–5.43 (m, 1H, SiCH₂CH=CH), 4.79 (d, 1H, *J* = 11.7 Hz, BNCH₂), 4.75 (t, 1H, *J* = 4.2 Hz, ArCH), 4.68 (d, *J* = 11.7 Hz, 1H, BnCH₂), 3.87 (m, 4H, CH₂OCH₂), 3.82 (1H, *J* = 8.6 Hz, ArCH₂CHCH), 3.77 (t, 1H, *J* = 8.8, 3.9 Hz, ArCHCH₂), 3.55 (d, 1H, *J* = 11.0 Hz, CNCH), 3.41 (dt, 1H, *J* = 11.0, 3.7 Hz, CNCHCH), 3.33–3.28 (m, 1H, CNCHCH), 2.96–2.81 (m, 3H, ArCH₂ & CH₂NCH₂), 2.77–2.63 (m, 2H, CH₂NCH₂), 2.58 (dd, 1H, *J* = 9.3, 3.1 Hz, ArCH₂), 2.51 (d, 1H, *J* = 15.7 Hz, ArCH₂), 1.82 (dd, 1H, *J* = 13.5, 9.9 Hz, NHCHCH₂), 1.63 (dd, 1H, *J* = 13.2, 8.0 Hz, NHCHCH₂), 1.43–1.39 (m, 2H, SiCH₂), 0.18 (s, 9H, SiCH₃).

¹³C NMR (100 MHz, CDCl₃), δ: 154.5, 136.3, 135.3, 130.7, 128.6, 128.3, 128.1, 127.9, 123.6, 121.0, 119.3, 118.7, 116.0, 114.7, 73.8, 66.5, 60.7, 54.3, 53.1, 52.6, 52.0, 33.5, 27.3, 19.2, 14.2, –1.7.

FTIR (thin film), cm^{–1}: 3295 (br w), 2952 (m), 2858 (m), 2252 (w, CN), 2228 (w, CN), 1587 (m), 1467 (s), 1248 (s), 1117 (s), 1072 (m), 856 (s), 781 (m), 735 (s), 698 (m).

HRMS (ES)⁺: Calcd for C₃₃H₄₅N₅O₃Si [M+Na]⁺: 610.3184
Found: 610.3174.

TLC (50:50 EtOAc–hexanes), R_f: Aldehyde **1**: 0.27 (PMA)
Bis-Amino Nitriles **10**: 0.43 & 0.22 (PMA).

Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (68 μL, 0.51 mmol, 3.5 equiv) and a solution of zinc chloride in THF (0.5 M, 729 μL, 0.36 mmol, 2.5 equiv) were added sequentially to a solution of the bis-amino nitriles **8** (85.7 mg, 0.15 mmol, 1 equiv) in trifluoroethanol (7.3 mL; substrate concentration ~0.02 M). The resulting solution was degassed by four freeze-pump-thaw cycles. After 1 h, the degassed solution was heated for 15 h at 42 °C, then was allowed to cool to 23 °C. Saturated aqueous sodium bicarbonate solution (30 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography

(85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (23.2 mg, 40% yield) as a white solid.

TLC (50:50 EtOAc–hexanes), R_f : Bis-Amino Nitriles **8**: 0.46 & 0.25 (ninhydrin)
Tetracyclic Cyanopiperazine **4**: 0.19 (ninhydrin).

Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (19.5 μL , 0.15 mmol, 3.7 equiv) and a solution of zinc chloride in THF (0.5 M, 250 μL , 0.12 mmol, 3.1 equiv) were added sequentially to a solution of the bis-amino nitriles **9** (23 mg, 0.040 mmol, 1 equiv) in trifluoroethanol (2.1 mL; substrate concentration ~ 0.02 M). The resulting solution was degassed by four freeze-pump-thaw cycles. After 1 h, the degassed solution was heated for 17 h at 56°C , then was allowed to cool to 23°C . Diethylene triamine (80 μL) was added and the resulting dark red solution was treated with an aqueous solution of tetrasodium EDTA (0.2 M, pH 11, 6 mL). The resulting biphasic mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15 dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (8.4 mg, 53% yield) as a white solid.

TLC (50:50 EtOAc–hexanes), R_f : Bis-Amino Nitriles **9**: 0.43 & 0.25 (PMA)
Tetracyclic Cyanopiperazine **4**: 0.14 (ninhydrin).

Tetracyclic Cyanopiperazine **4**:

Trimethylsilyl cyanide (18.9 μL , 0.14 mmol, 3.7 equiv) and a solution of zinc chloride in THF (0.5 M, 243 μL , 0.12 mmol, 3.1 equiv) were added sequentially to a solution of the bis-amino nitriles **10** (22.6 mg, 0.038 mmol, 1 equiv) in trifluoroethanol (2.0 mL; substrate concentration ~ 0.02 M). The resulting solution was degassed by four freeze-pump-thaw cycles. After 1 h, the degassed solution was heated for 18 h at 61°C , then was allowed to cool to 23°C . Diethylene triamine (80 μL) was added and the resulting dark red solution was treated with an aqueous solution of tetrasodium EDTA (0.2 M, pH 11, 6 mL). The resulting biphasic mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (85:15

dichloromethane–ethyl acetate) to provide the tetracyclic cyanopiperazine **4** (6.9 mg, 45% yield) as a white solid.

TLC (50:50 EtOAc–hexanes), R_f : Bis-Amino Nitriles **10**: 0.41 & 0.21 (PMA)
Tetracyclic Cyanopiperazine **4**: 0.14 (ninhydrin).

Spectroscopic Data for Schemes 1–4.

1

7b (in CDCl_3)

7b (in C_6D_6)

10

X-Ray Crystal Structure Data for the Aldehyde Precursor to Carboxylic Acid 5. Data were collected using a Bruker SMART CCD (charge coupled device) diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 193 K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3 ° per frame for 45 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a maximum resolution of 0.76 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART¹ software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software², which corrects for Lp and decay. The structures were solved by the direct method using the SHELXS-97³ program and refined by least squares method on F², SHELXL-97⁴, incorporated in SHELXTL-PC V 6.10.⁵

The structure was solved in the space group P2₁2₁2₁ (# 19) by analysis of systematic absences. All non-hydrogen atoms were refined anisotropically. Hydrogens were found by difference Fourier methods and refined isotropically. The crystal used for the diffraction study showed no decomposition during data collection. All drawings depict 50% ellipsoids.

Acknowledgement. The CCD based x-ray diffractometer at Harvard University was purchased through NIH grant (1S10RR11937-01).

References

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^a Obtained with graphite monochromated Mo K α (λ = 0.71073 Å) radiation. ^b $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$. ^c $wR_2 = \{\sum [w(F_o^2 - F_c^2)^2] / \{\sum [w(F_o^2)^2]\}^{1/2}$.

Table 1. Crystal data and structure refinement for agm29t.

Identification code	agm29t	
Empirical formula	C ₂₆ H ₂₉ N ₃ O ₃	
Formula weight	431.52	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.3895(9) Å	a = 90°.
	b = 16.890(2) Å	b = 90°.
	c = 18.027(2) Å	g = 90°.
Volume	2250.0(5) Å ³	
Z	4	
Density (calculated)	1.274 Mg/m ³	
Absorption coefficient	0.084 mm ⁻¹	
F(000)	920	
Crystal size	0.12 x 0.06 x 0.06 mm ³	
Theta range for data collection	1.65 to 27.87°.	
Index ranges	-9 ≤ h ≤ 9, -9 ≤ k ≤ 22, -22 ≤ l ≤ 23	
Reflections collected	16105	
Independent reflections	5371 [R(int) = 0.0665]	
Completeness to theta = 27.87°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	5371 / 0 / 405	
Goodness-of-fit on F ²	0.726	
Final R indices [I > 2σ(I)]	R1 = 0.0408, wR2 = 0.0390	
R indices (all data)	R1 = 0.1028, wR2 = 0.0471	
Absolute structure parameter	-1.1(9)	
Largest diff. peak and hole	0.153 and -0.153 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for agm29t. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	10152(2)	8089(1)	7016(1)	40(1)
O(2)	9376(2)	8536(1)	9133(1)	41(1)
O(3)	2606(2)	5658(1)	6181(1)	80(1)
N(1)	7745(2)	6846(1)	7581(1)	29(1)
N(2)	7223(2)	5205(1)	7273(1)	33(1)
N(3)	10838(2)	5695(1)	8534(1)	51(1)
C(1)	8321(3)	7558(1)	7999(1)	31(1)
C(2)	7006(3)	7808(1)	8604(1)	29(1)
C(3)	7588(3)	8312(1)	9164(1)	34(1)
C(4)	6429(3)	8546(1)	9729(1)	39(1)
C(5)	4666(3)	8273(1)	9720(1)	43(1)
C(6)	4041(3)	7788(1)	9163(1)	38(1)
C(7)	5215(3)	7557(1)	8601(1)	31(1)
C(8)	4646(3)	6990(1)	8004(1)	37(1)
C(9)	6168(3)	6407(1)	7860(1)	30(1)
C(10)	5694(3)	5766(1)	7288(1)	34(1)
C(11)	5572(3)	6108(1)	6495(1)	39(1)
C(12)	7507(3)	6039(2)	6199(1)	41(1)
C(13)	8563(3)	5671(1)	6852(1)	33(1)
C(14)	9239(3)	6324(1)	7373(1)	33(1)
C(15)	8592(3)	8243(1)	7463(1)	35(1)
C(16)	10482(3)	8717(2)	6514(1)	45(1)
C(17)	12307(3)	8610(1)	6154(1)	35(1)
C(18)	13509(3)	9236(2)	6132(1)	47(1)
C(19)	15194(3)	9155(2)	5808(1)	49(1)
C(20)	15657(3)	8455(2)	5486(1)	47(1)
C(21)	14467(3)	7826(2)	5497(1)	45(1)
C(22)	12800(3)	7903(2)	5841(1)	41(1)
C(23)	10003(4)	9079(2)	9682(1)	45(1)
C(24)	10138(3)	5955(1)	8027(1)	35(1)
C(25)	6752(3)	4455(1)	6911(2)	41(1)
C(26)	4162(4)	5702(2)	6029(1)	53(1)

Table 3. Bond lengths [Å] and angles [°] for agm29t.

O(1)-C(16)	1.417(3)
O(1)-C(15)	1.430(2)
O(2)-C(3)	1.375(2)
O(2)-C(23)	1.426(3)
O(3)-C(26)	1.185(3)
N(1)-C(14)	1.460(2)
N(1)-C(9)	1.470(2)
N(1)-C(1)	1.482(2)
N(2)-C(25)	1.468(3)
N(2)-C(10)	1.475(2)
N(2)-C(13)	1.475(2)
N(3)-C(24)	1.138(2)
C(1)-C(15)	1.520(3)
C(1)-C(2)	1.520(3)
C(1)-H(1)	1.067(16)
C(2)-C(3)	1.389(3)
C(2)-C(7)	1.390(3)
C(3)-C(4)	1.388(3)
C(4)-C(5)	1.382(3)
C(4)-H(2)	0.985(17)
C(5)-C(6)	1.377(3)
C(5)-H(3)	0.852(16)
C(6)-C(7)	1.390(3)
C(6)-H(4)	0.988(16)
C(7)-C(8)	1.499(3)
C(8)-C(9)	1.518(3)
C(8)-H(5)	0.999(17)
C(8)-H(6)	0.961(16)
C(9)-C(10)	1.535(3)
C(9)-H(7)	1.074(15)
C(10)-C(11)	1.544(3)
C(10)-H(8)	1.040(14)
C(11)-C(26)	1.504(3)
C(11)-C(12)	1.531(3)
C(11)-H(9)	0.968(17)
C(12)-C(13)	1.543(3)
C(12)-H(10)	0.922(19)
C(12)-H(11)	0.976(17)
C(13)-C(14)	1.533(3)
C(13)-H(12)	1.031(15)
C(14)-C(24)	1.491(3)
C(14)-H(13)	1.007(16)
C(15)-H(14)	1.000(16)
C(15)-H(15)	1.017(17)
C(16)-C(17)	1.508(3)
C(16)-H(16)	1.002(17)
C(16)-H(17)	1.00(2)
C(17)-C(22)	1.369(3)
C(17)-C(18)	1.382(3)
C(18)-C(19)	1.382(3)
C(18)-H(18)	0.977(19)
C(19)-C(20)	1.361(3)
C(19)-H(19)	1.00(2)
C(20)-C(21)	1.379(3)
C(20)-H(20)	1.003(17)

C(21)-C(22)	1.385(3)
C(21)-H(21)	0.985(19)
C(22)-H(22)	0.961(18)
C(23)-H(25)	1.016(19)
C(23)-H(23)	1.031(18)
C(23)-H(24)	1.04(2)
C(25)-H(27)	1.02(2)
C(25)-H(26)	0.983(17)
C(25)-H(28)	1.072(17)
C(26)-H(29)	1.018(18)

C(16)-O(1)-C(15)	111.23(17)
C(3)-O(2)-C(23)	117.48(18)
C(14)-N(1)-C(9)	112.55(15)
C(14)-N(1)-C(1)	113.76(15)
C(9)-N(1)-C(1)	117.52(15)
C(25)-N(2)-C(10)	112.41(17)
C(25)-N(2)-C(13)	113.03(17)
C(10)-N(2)-C(13)	100.44(15)
N(1)-C(1)-C(15)	109.39(17)
N(1)-C(1)-C(2)	114.01(16)
C(15)-C(1)-C(2)	109.23(18)
N(1)-C(1)-H(1)	111.3(9)
C(15)-C(1)-H(1)	107.1(9)
C(2)-C(1)-H(1)	105.6(8)
C(3)-C(2)-C(7)	118.99(19)
C(3)-C(2)-C(1)	119.59(18)
C(7)-C(2)-C(1)	121.40(18)
O(2)-C(3)-C(4)	122.9(2)
O(2)-C(3)-C(2)	115.91(19)
C(4)-C(3)-C(2)	121.1(2)
C(5)-C(4)-C(3)	118.6(2)
C(5)-C(4)-H(2)	119.0(11)
C(3)-C(4)-H(2)	122.4(11)
C(6)-C(5)-C(4)	121.5(2)
C(6)-C(5)-H(3)	121.4(13)
C(4)-C(5)-H(3)	117.0(13)
C(5)-C(6)-C(7)	119.4(2)
C(5)-C(6)-H(4)	122.0(10)
C(7)-C(6)-H(4)	118.6(10)
C(6)-C(7)-C(2)	120.4(2)
C(6)-C(7)-C(8)	121.79(19)
C(2)-C(7)-C(8)	117.68(19)
C(7)-C(8)-C(9)	109.21(18)
C(7)-C(8)-H(5)	111.4(10)
C(9)-C(8)-H(5)	108.3(10)
C(7)-C(8)-H(6)	110.2(10)
C(9)-C(8)-H(6)	111.7(10)
H(5)-C(8)-H(6)	106.0(14)
N(1)-C(9)-C(8)	108.67(17)
N(1)-C(9)-C(10)	107.85(16)
C(8)-C(9)-C(10)	113.80(17)
N(1)-C(9)-H(7)	110.1(8)
C(8)-C(9)-H(7)	109.9(8)
C(10)-C(9)-H(7)	106.5(9)
N(2)-C(10)-C(9)	106.91(16)
N(2)-C(10)-C(11)	105.49(17)

C(9)-C(10)-C(11)	111.76(18)
N(2)-C(10)-H(8)	108.7(8)
C(9)-C(10)-H(8)	111.7(8)
C(11)-C(10)-H(8)	112.0(8)
C(26)-C(11)-C(12)	114.6(2)
C(26)-C(11)-C(10)	112.8(2)
C(12)-C(11)-C(10)	103.95(19)
C(26)-C(11)-H(9)	105.0(10)
C(12)-C(11)-H(9)	108.7(11)
C(10)-C(11)-H(9)	111.9(10)
C(11)-C(12)-C(13)	103.62(19)
C(11)-C(12)-H(10)	113.8(12)
C(13)-C(12)-H(10)	109.7(13)
C(11)-C(12)-H(11)	112.0(11)
C(13)-C(12)-H(11)	110.3(11)
H(10)-C(12)-H(11)	107.4(16)
N(2)-C(13)-C(14)	106.70(16)
N(2)-C(13)-C(12)	105.58(17)
C(14)-C(13)-C(12)	110.05(19)
N(2)-C(13)-H(12)	111.1(8)
C(14)-C(13)-H(12)	109.1(8)
C(12)-C(13)-H(12)	114.0(8)
N(1)-C(14)-C(24)	112.76(17)
N(1)-C(14)-C(13)	110.14(17)
C(24)-C(14)-C(13)	109.21(17)
N(1)-C(14)-H(13)	106.7(9)
C(24)-C(14)-H(13)	108.3(9)
C(13)-C(14)-H(13)	109.7(9)
O(1)-C(15)-C(1)	109.01(17)
O(1)-C(15)-H(14)	111.5(9)
C(1)-C(15)-H(14)	108.9(10)
O(1)-C(15)-H(15)	111.2(10)
C(1)-C(15)-H(15)	109.7(9)
H(14)-C(15)-H(15)	106.5(14)
O(1)-C(16)-C(17)	109.8(2)
O(1)-C(16)-H(16)	112.2(11)
C(17)-C(16)-H(16)	110.6(11)
O(1)-C(16)-H(17)	109.8(12)
C(17)-C(16)-H(17)	107.2(12)
H(16)-C(16)-H(17)	107.0(16)
C(22)-C(17)-C(18)	118.9(2)
C(22)-C(17)-C(16)	121.4(2)
C(18)-C(17)-C(16)	119.7(2)
C(19)-C(18)-C(17)	121.1(2)
C(19)-C(18)-H(18)	122.2(12)
C(17)-C(18)-H(18)	116.7(12)
C(20)-C(19)-C(18)	119.5(3)
C(20)-C(19)-H(19)	117.9(12)
C(18)-C(19)-H(19)	122.5(12)
C(19)-C(20)-C(21)	120.2(2)
C(19)-C(20)-H(20)	119.6(12)
C(21)-C(20)-H(20)	120.2(12)
C(20)-C(21)-C(22)	120.1(3)
C(20)-C(21)-H(21)	118.4(12)
C(22)-C(21)-H(21)	121.6(12)
C(17)-C(22)-C(21)	120.2(2)
C(17)-C(22)-H(22)	119.2(11)

C(21)-C(22)-H(22)	120.5(11)
O(2)-C(23)-H(25)	111.9(11)
O(2)-C(23)-H(23)	105.9(12)
H(25)-C(23)-H(23)	110.3(17)
O(2)-C(23)-H(24)	110.7(11)
H(25)-C(23)-H(24)	103.7(15)
H(23)-C(23)-H(24)	114.4(17)
N(3)-C(24)-C(14)	177.9(2)
N(2)-C(25)-H(27)	109.0(12)
N(2)-C(25)-H(26)	110.3(11)
H(27)-C(25)-H(26)	106.6(14)
N(2)-C(25)-H(28)	113.4(10)
H(27)-C(25)-H(28)	110.9(15)
H(26)-C(25)-H(28)	106.4(15)
O(3)-C(26)-C(11)	124.8(2)
O(3)-C(26)-H(29)	120.3(11)
C(11)-C(26)-H(29)	114.7(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for agm29t. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	45(1)	31(1)	45(1)	5(1)	16(1)	1(1)
O(2)	39(1)	42(1)	42(1)	-12(1)	-1(1)	-3(1)
O(3)	44(1)	109(2)	86(2)	-19(1)	-11(1)	-9(1)
N(1)	26(1)	25(1)	35(1)	-2(1)	4(1)	-3(1)
N(2)	35(1)	28(1)	36(1)	-4(1)	-1(1)	-1(1)
N(3)	55(1)	40(1)	59(1)	-2(1)	-19(1)	-2(1)
C(1)	27(1)	32(1)	32(1)	-2(1)	0(1)	-1(1)
C(2)	30(1)	26(1)	31(1)	4(1)	2(1)	2(1)
C(3)	34(1)	32(1)	36(1)	3(1)	-2(1)	4(1)
C(4)	49(2)	34(1)	34(1)	0(1)	0(1)	9(1)
C(5)	52(2)	41(2)	35(2)	8(1)	15(1)	16(1)
C(6)	34(1)	34(1)	46(2)	9(1)	8(1)	5(1)
C(7)	34(1)	25(1)	34(1)	7(1)	6(1)	4(1)
C(8)	26(1)	38(2)	46(2)	3(1)	4(1)	-3(1)
C(9)	29(1)	28(1)	34(1)	1(1)	-1(1)	-1(1)
C(10)	28(1)	32(1)	43(1)	0(1)	2(1)	-5(1)
C(11)	38(1)	38(2)	40(1)	1(1)	-6(1)	3(1)
C(12)	48(2)	43(2)	33(2)	1(1)	1(1)	-3(2)
C(13)	32(1)	30(1)	36(1)	-3(1)	4(1)	4(1)
C(14)	29(1)	31(1)	38(1)	1(1)	4(1)	-2(1)
C(15)	34(1)	31(1)	42(2)	-4(1)	5(1)	-1(1)
C(16)	48(2)	41(2)	46(2)	9(2)	9(1)	-1(2)
C(17)	42(1)	36(1)	27(1)	6(1)	2(1)	2(1)
C(18)	62(2)	37(2)	42(2)	-3(1)	13(1)	-5(2)
C(19)	49(2)	54(2)	45(2)	3(1)	7(1)	-19(2)
C(20)	38(1)	62(2)	40(2)	7(1)	7(1)	0(2)
C(21)	51(2)	42(2)	41(2)	3(1)	9(1)	5(2)
C(22)	40(1)	40(2)	43(1)	6(1)	5(1)	-8(1)
C(23)	50(2)	43(2)	43(2)	-6(1)	-4(1)	-2(2)
C(24)	32(1)	27(1)	47(2)	-9(1)	-2(1)	-3(1)
C(25)	44(2)	30(2)	50(2)	-10(1)	-3(1)	-1(1)
C(26)	53(2)	55(2)	51(2)	-2(2)	-11(2)	7(2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for agm29t.

	x	y	z	U(eq)
H(1)	9580(20)	7462(10)	8272(8)	27(5)
H(2)	6820(20)	8892(10)	10138(10)	33(6)
H(3)	3990(20)	8411(11)	10080(9)	33(6)
H(4)	2770(20)	7613(10)	9138(9)	33(6)
H(5)	3550(20)	6685(10)	8153(9)	35(6)
H(6)	4320(20)	7275(9)	7562(9)	27(6)
H(7)	6510(20)	6103(9)	8364(9)	22(5)
H(8)	4528(19)	5460(9)	7436(8)	11(4)
H(9)	5230(20)	6660(10)	6497(9)	25(6)
H(10)	8020(20)	6518(11)	6071(10)	44(7)
H(11)	7580(20)	5696(11)	5764(9)	33(6)
H(12)	9640(20)	5325(9)	6692(8)	18(5)
H(13)	10160(20)	6663(9)	7108(9)	26(5)
H(14)	7480(20)	8302(10)	7152(9)	28(5)
H(15)	8730(20)	8756(10)	7751(9)	31(6)
H(16)	9510(20)	8763(11)	6128(10)	51(7)
H(17)	10510(30)	9232(13)	6788(10)	65(8)
H(18)	13110(30)	9730(12)	6362(10)	50(7)
H(19)	16130(30)	9583(13)	5826(12)	73(8)
H(20)	16880(20)	8394(11)	5254(10)	45(6)
H(21)	14840(30)	7325(11)	5263(10)	54(7)
H(22)	11950(20)	7472(11)	5838(10)	43(7)
H(25)	9820(30)	8868(11)	10204(11)	55(7)
H(23)	11360(20)	9161(13)	9576(11)	63(7)
H(24)	9240(30)	9597(13)	9673(10)	56(7)
H(27)	5850(30)	4155(13)	7236(11)	67(8)
H(26)	7830(20)	4115(11)	6868(10)	34(6)
H(28)	6240(20)	4528(11)	6359(10)	45(6)
H(29)	4620(20)	5487(12)	5536(10)	54(7)

Table 6. Torsion angles [$^\circ$] for agm29t.

C(14)-N(1)-C(1)-C(15)	94.1(2)
C(9)-N(1)-C(1)-C(15)	-131.29(18)
C(14)-N(1)-C(1)-C(2)	-143.25(17)
C(9)-N(1)-C(1)-C(2)	-8.7(2)
N(1)-C(1)-C(2)-C(3)	161.91(17)
C(15)-C(1)-C(2)-C(3)	-75.4(2)
N(1)-C(1)-C(2)-C(7)	-19.5(3)
C(15)-C(1)-C(2)-C(7)	103.2(2)
C(23)-O(2)-C(3)-C(4)	-4.7(3)
C(23)-O(2)-C(3)-C(2)	177.47(19)
C(7)-C(2)-C(3)-O(2)	179.92(18)
C(1)-C(2)-C(3)-O(2)	-1.5(3)
C(7)-C(2)-C(3)-C(4)	2.0(3)
C(1)-C(2)-C(3)-C(4)	-179.4(2)
O(2)-C(3)-C(4)-C(5)	-178.4(2)
C(2)-C(3)-C(4)-C(5)	-0.7(3)
C(3)-C(4)-C(5)-C(6)	-0.8(3)
C(4)-C(5)-C(6)-C(7)	0.9(3)

C(5)-C(6)-C(7)-C(2)	0.5(3)
C(5)-C(6)-C(7)-C(8)	176.3(2)
C(3)-C(2)-C(7)-C(6)	-2.0(3)
C(1)-C(2)-C(7)-C(6)	179.5(2)
C(3)-C(2)-C(7)-C(8)	-177.86(18)
C(1)-C(2)-C(7)-C(8)	3.6(3)
C(6)-C(7)-C(8)-C(9)	-138.0(2)
C(2)-C(7)-C(8)-C(9)	37.8(3)
C(14)-N(1)-C(9)-C(8)	-175.74(17)
C(1)-N(1)-C(9)-C(8)	49.2(2)
C(14)-N(1)-C(9)-C(10)	-51.9(2)
C(1)-N(1)-C(9)-C(10)	172.97(16)
C(7)-C(8)-C(9)-N(1)	-63.2(2)
C(7)-C(8)-C(9)-C(10)	176.64(18)
C(25)-N(2)-C(10)-C(9)	164.19(18)
C(13)-N(2)-C(10)-C(9)	-75.40(19)
C(25)-N(2)-C(10)-C(11)	-76.7(2)
C(13)-N(2)-C(10)-C(11)	43.70(19)
N(1)-C(9)-C(10)-N(2)	65.3(2)
C(8)-C(9)-C(10)-N(2)	-174.02(17)
N(1)-C(9)-C(10)-C(11)	-49.6(2)
C(8)-C(9)-C(10)-C(11)	71.0(2)
N(2)-C(10)-C(11)-C(26)	98.0(2)
C(9)-C(10)-C(11)-C(26)	-146.2(2)
N(2)-C(10)-C(11)-C(12)	-26.8(2)
C(9)-C(10)-C(11)-C(12)	89.1(2)
C(26)-C(11)-C(12)-C(13)	-124.1(2)
C(10)-C(11)-C(12)-C(13)	-0.5(2)
C(25)-N(2)-C(13)-C(14)	-167.07(18)
C(10)-N(2)-C(13)-C(14)	72.96(18)
C(25)-N(2)-C(13)-C(12)	75.8(2)
C(10)-N(2)-C(13)-C(12)	-44.1(2)
C(11)-C(12)-C(13)-N(2)	27.6(2)
C(11)-C(12)-C(13)-C(14)	-87.2(2)
C(9)-N(1)-C(14)-C(24)	-71.0(2)
C(1)-N(1)-C(14)-C(24)	65.8(2)
C(9)-N(1)-C(14)-C(13)	51.2(2)
C(1)-N(1)-C(14)-C(13)	-171.93(16)
N(2)-C(13)-C(14)-N(1)	-62.4(2)
C(12)-C(13)-C(14)-N(1)	51.6(2)
N(2)-C(13)-C(14)-C(24)	61.9(2)
C(12)-C(13)-C(14)-C(24)	175.98(18)
C(16)-O(1)-C(15)-C(1)	-179.07(19)
N(1)-C(1)-C(15)-O(1)	-69.6(2)
C(2)-C(1)-C(15)-O(1)	164.96(15)
C(15)-O(1)-C(16)-C(17)	169.68(19)
O(1)-C(16)-C(17)-C(22)	49.7(3)
O(1)-C(16)-C(17)-C(18)	-130.9(2)
C(22)-C(17)-C(18)-C(19)	-0.7(3)
C(16)-C(17)-C(18)-C(19)	179.8(2)
C(17)-C(18)-C(19)-C(20)	2.0(4)
C(18)-C(19)-C(20)-C(21)	-1.4(4)
C(19)-C(20)-C(21)-C(22)	-0.4(4)
C(18)-C(17)-C(22)-C(21)	-1.1(3)
C(16)-C(17)-C(22)-C(21)	178.4(2)
C(20)-C(21)-C(22)-C(17)	1.7(4)
N(1)-C(14)-C(24)-N(3)	-62(7)

C(13)-C(14)-C(24)-N(3)	175(100)
C(12)-C(11)-C(26)-O(3)	176.6(3)
C(10)-C(11)-C(26)-O(3)	57.9(4)

Symmetry transformations used to generate equivalent atoms.