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Application of the β-Azidonation Reaction to the Enantioselective Synthesis of the Lycorane Amaryllidaceae Alkaloids

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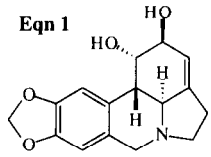
Abstract: The prochiral ketone **5** was treated with the lithium salt of (+)-bis(α-methylbenzyl)amine, followed by triisopropylsilyl trifluoromethanesulfonate to give **10** (96%). β-Azidonation of **10** with $(PhIO)_n/TMSN_3$ rapidly produced **11** (95%) as a mixture of *trans*- and *cis*- diastereomers in a 3.5:1 ratio. Reduction of **11** with $LiAlH_4$ followed by TsCl/NaH gave **13**. *N*-Alkylation of **13** with 1,2-dibromoethane followed by radical cyclization led to **15**, which was converted into the lycorane derivative **22**. The absolute configuration of **22** was determined by the x-ray crystal structure of the *p*-bromobenzoate **24**

Keywords: alkaloid, β-azidonation, triisopropylsilyl (TIPS) enol ethers, prochiral, desymmetrization, radical cyclization.

Introduction

Eqn 1

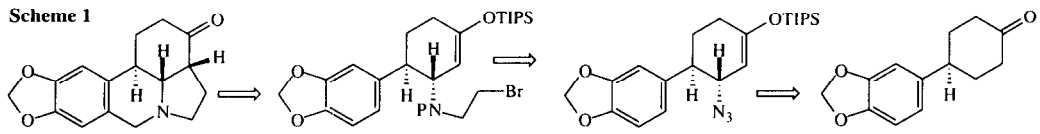


1, Lycorine

The Amaryllidaceae alkaloids have played a central role in the development of alkaloid chemistry. The elucidation of their structures, and the strategies and methodology developed for their synthesis have been motivated by their diverse and important pharmacological properties.[1] Lycorine **1** (Eqn 1) is one of the most abundant alkaloids from this family, and several syntheses of the racemate have been reported.[2] More recently, Schultz reported the first synthesis of (+)-**1** using the asymmetric adaptation of the Birch reduction.[3,4]

As part of our efforts to illustrate the use of the β-azidonation reaction[5] we have recently reported the synthesis of (+)-pancratistatin,[6] and in this paper is described the synthesis of the lycorane core structure in an enantiomerically enriched form.

Scheme 1



2 **3** **4** **5**, prochiral ketone

We envisioned that a functionalized lycorane core structure such as **2**, Scheme 1, could be assembled from **3** *via* a cobalt mediated radical addition-dehydrogenation process.[7] The precursor to **3** is **4**, which can be made from **5** in an enantiomerically enriched form through the desymmetrization of the prochiral ketone **5**.[8]

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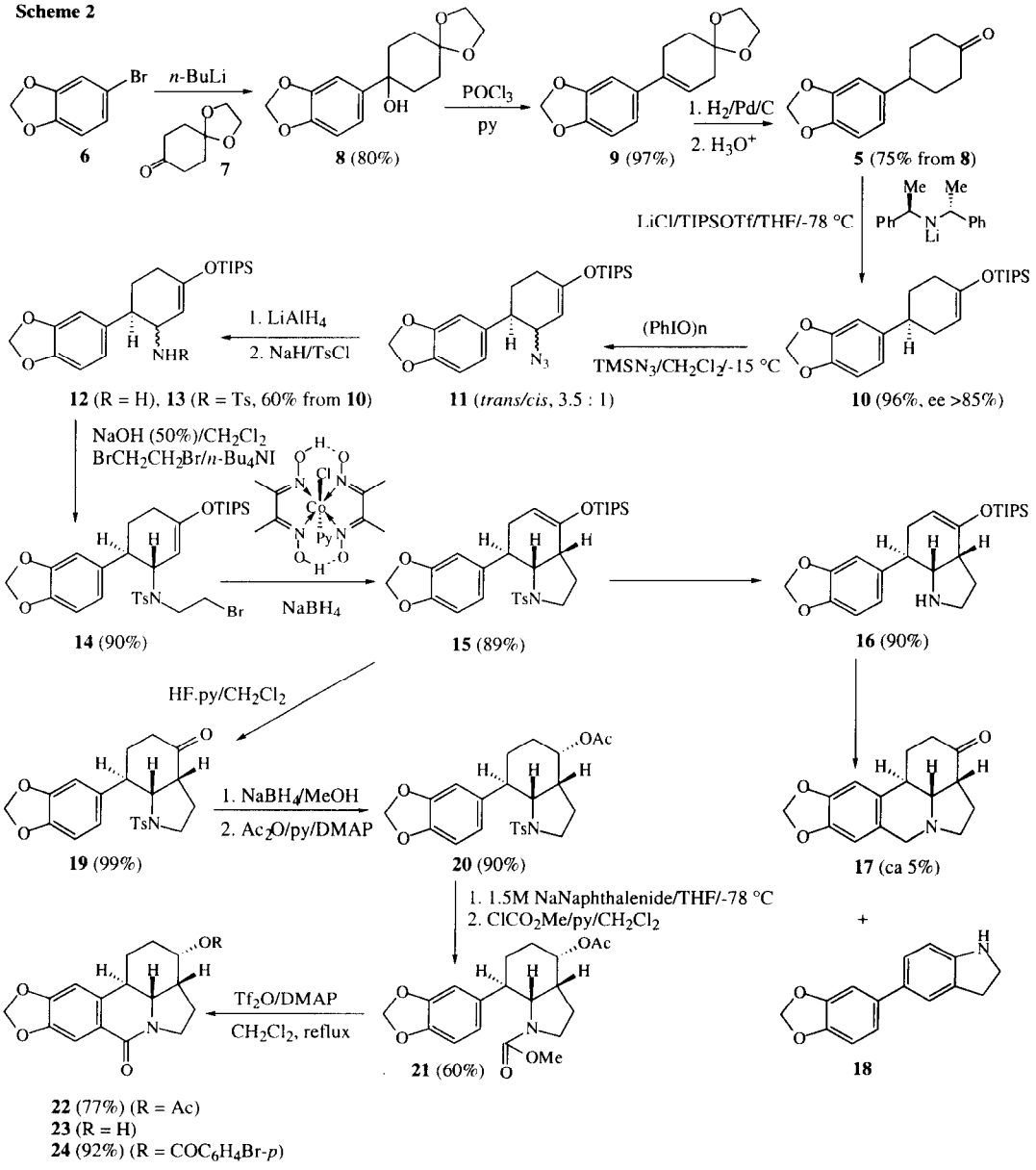
Scheme 2



Treatment of **6** with *n*-BuLi in tetrahydrofuran at -30 °C, followed by addition of **7** gave **8**. The tertiary alcohol **8** was dehydrated ($POCl_3$/pyridine/DBU) to give **9** (97%). Hydrogenation of **9** over 10% Pd/C followed by acidic hydrolysis gave **5**. Deprotonation of **5** with the lithium salt of (+)-bis(α-methylbenzyl)amine[9] in the presence of lithium chloride at -78 °C followed by triisopropylsilyl trifluoromethanesulfonate gave **10** (96%), Scheme 2. The absolute stereochemistry shown for **10** is based on the analogy of a very similar prochiral 4-arylcyclohexanone deprotonation using the same base for the synthesis of pancratistatin,[6] and gives

the opposite absolute configuration required for the narurally occurring lycoranes. The assignment of absolute configuration was confirmed later, and clearly using the (-)-bis(α-methylbenzyl)amine would allow access to the natural enantiomers.

Exposure of **10** to $(PhIO)_n/TMSN_3$ in CH_2Cl_2 at -15° C rapidly produced **11** (95%) as a mixture of *trans*- and *cis*- diastereomers in a 3.5:1 ratio. It is important to use $(PhIO)_n$ that has been prepared and stored in a freezer for no more than three months, otherwise the β-azidonation reaction will not work in good yields. The deterioration of iodosylbenzene is caused by disproportionation to iodoxybenzene ($PhIO_2$) which is inactive with respect to the β-azidonation reaction.[10] The mixture of *cis*- and *trans*-**11** was reduced with lithium aluminum hydride to give **12** which was directly treated with NaH/TsCl to give **13**. While protection of the amine **13** as a carbamate derivative was preferable, we were unable to *N*-alkylate the carbamate, consequently the sulfonamide derivative was used. Phase transfer alkylation of **13** using 1,2-dibromoethane resulted in **14** (90%) ready for the cobalt mediated radical addition-dehydrogenation reaction.[7] Reduction of chloro(pyridine) bis(dimethylglyoximato) cobalt^{III} with $NaBH_4$/MeOH followed by addition of **14** proceeded cleanly to give **15** in excellent yield.

We had hoped that reductive removal of the sulfonamide from **15** followed by Pictet-Spengler cyclization of **16** would complete the synthesis of the lycorane core structure. While the first step to give **16** proceeded in good yield, the cyclization to give **17** was very poor (5%) and was complicated by β-elimination of the amine functionality followed by condensation-oxidation chemistry resulting in the biaryl adduct **18** as one of the products. Despite considerable experimentation we were unable to manipulate **16** in a satisfactory manner, consequently it was decided to prevent the β-elimination pathway through reduction of the carbonyl group. Removal of the triisopropylsilyl group from **15** to give **19** was accomplished with HF.pyridine/CH_2Cl_2. Reduction of **19** with $NaBH_4$/MeOH followed by acetylation resulted in **20**. Reductive removal of the sulfonamide group was achieved with sodium naphthalenide, and the resulting *sec*-amine was converted into the carbamate **21**. The carbamate **21** was subjected to the modified Bischler-Napieralski reaction conditions (Tf_2O/DMAP)[11] to give **22** (77%). The structure and absolute stereochemistry of **22** was confirmed by hydrolysis to the alcohol **23**, and conversion into the derived *p*-bromobenzoate **24** whose structure was elucidated by x-ray crystallography.[12] The alcohol **23** was also converted into the corresponding (R)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid ester (Mosher ester)[13] which exhibited a de of 87% by ^1H NMR.

Experimental

5-Bromo-1,3-benzodioxole 6. A solution of 1,3-benzodioxole (39.60 g, 0.32 mol) and *N*-bromosuccinimide (58.10 g, 0.33 mol) in chloroform (130 mL) was heated to reflux for 3.5 h, cooled to room temperature, filtered, and the solvent evaporated *in vacuo*. Distillation of the residue through a Vigreux column gave **6** (58.62 g, 90%) as a colorless oil; B.p. 78-83 °C/0.15 mmHg (Lit[14] 85-86 °C/10 mmHg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.97-6.94 (2H, m), 6.70 (1H, d, J = 9.0 Hz), 5.98 (2H, s).

8-(1,3-Benzodioxol-5-yl)-1,4-dioxaspiro[4.5]decan-8-ol 8. A stirred solution of **6** (10.58 g, 53 mmol) in Et_2O (120 mL) under nitrogen was cooled to -30 °C and treated dropwise with *n*-butyllithium (2.5 M in hexanes, 22 mL, 55 mmol). The mixture was stirred at -30 °C for 10 min and treated with a solution of **7**

(7.90 g, 51 mmol) in tetrahydrofuran (80 mL). The mixture was allowed to warm to room temperature, stirred for 2 h, and quenched with water (40 mL). The layers were separated and the aqueous layer extracted with dichloromethane (80 mL). The combined extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Chromatography of the residue over silica gel, eluting with 30:70 hexanes/Et_2O, gave **8** (11.24 g, 80%) as a white solid. M.p. 95-96 °C (Et_2O/hexanes). IR (film) 3440, 2923 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 2 Hz), 6.99 (1H, dd, J = 8, 2 Hz), 6.78 (1H, d, J = 8 Hz), 5.95 (2H, s), 4.04-3.94 (4H, m), 2.20-2.04 (4H, m), 1.83-1.78 (2H, m), 1.71-1.66 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.3, 142.8, 117.5, 108.3, 107.8, 105.7, 100.9, 72.3, 64.3, 64.2, 36.7, 30.7. HRMS found 278.1145, $C_{15}H_{18}O_5$ (M^+) requires 278.1154.

4-(1,3-Benzodioxol-5-yl)cyclohexanone 5 To a solution of **8** (8.42 g, 30.3 mmol) in pyridine (170 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (9.12 mL, 61 mmol) followed by $POCl_3$ (5.45 mL, 59 mmol) dropwise. The resultant orange solution was stirred at room temperature for 1 h, and at 80 °C for 90 min during which time the orange color darkened. The solution was recooled to 0 °C, and diluted carefully with EtOAc (200 mL) and H_2O (200 mL). The organic phase was washed with H_2O and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give **9** (7.64 g, 97%) as an orange-brown oil, which was routinely used without further purification. A pure sample of **9** could be isolated as a white solid by chromatography over silica gel, eluting with 65:35 hexanes/Et_2O. ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (1H, d, J = 2 Hz), 6.87 (1H, dd, J = 8, 2 Hz), 6.75 (1H, d, J = 8 Hz), 5.94 (2H, s), 5.89-5.87 (1H, m), 4.03 (4H, s), 2.64-2.59 (2H, m), 2.46 (2H, br s), 1.91 (2H, t, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.4, 135.9, 135.7, 120.5, 118.5, 107.8, 107.7, 105.8, 100.8, 64.4, 36.0, 31.3, 27.0. HRMS found 261.1129; $C_{15}H_{17}O_4$ (MH^+) requires 261.1127.

The crude oil from the above reaction was dissolved in 1:1 MeOH/tetrahydrofuran (150 mL) under nitrogen. Palladium (10% on carbon, 3.10 g, 2.9 mmol) was added and the nitrogen atmosphere replaced with hydrogen. The mixture was stirred for 20 h and filtered through a pad of Celite® and the solvent evaporated *in vacuo* to afford a brown oil which solidified on standing. Trituration with hot methanol gave a white solid, which was routinely used without further purification.

The solid was dissolved in a mixture of tetrahydrofuran, water and concentrated sulfuric acid (4:2:1, 210 mL). The mixture was stirred for 90 min, diluted with brine (150 mL) and extracted with Et_2O (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Chromatography of the residue over silica gel, eluting with 70:30 hexanes/Et_2O, gave **5** (4.95g, 75% over 3 steps) as a pale yellow solid. M.p. 99-101 °C (Et_2O/hexanes). IR (CH_2Cl_2) 2948, 1703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.77-6.68 (3H, m), 5.93 (2H, s), 2.95 (1H, tt, J = 12, 3.5 Hz), 2.51-2.46 (4H, m), 2.22-2.14 (2H, m), 1.95-1.80 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 147.7, 146.0, 138.7, 119.5, 108.3, 107.1, 100.9, 42.5, 42.3, 34.2; HRMS found 219.1020; $C_{13}H_{15}O_3$ (MH^+) requires 219.1021.

(-)-(4*S*) 4-(1,3-Benzodioxol-5-yl)-1-triisopropylsilyl(oxy)cyclohexene 10. To a stirred suspension of (*R*,*R*)-bis-(α-methylbenzyl)amine hydrochloride (1.22 g, 4.66 mmol) in EtOAc (20 mL) was added 1 M NaOH (20 mL). The mixture was stirred for 15 min and the organic layer separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo* to afford the free amine which was dissolved in tetrahydrofuran (10 mL)

under nitrogen and cooled to -78 °C. *n*-Butyllithium (2.46 M in hexanes, 1.70 mL, 4.18 mmol) was added dropwise and the mixture stirred at -78 °C for 10 min, and allowed to warm to room temperature over 30 min and cooled to -78 °C. Lithium chloride (57 mg, 1.35 mmol) was suspended in tetrahydrofuran (20 mL), cooled to -78 °C and added to the lithium amide solution *via* cannula. Ketone **5** (0.607 g, 2.78 mmol) was added dropwise as a solution in tetrahydrofuran (5 mL). After 15 min, triisopropylsilyl trifluoromethanesulfonate (2.25 mL, 8.37 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 min and at room temperature for 30 min, then quenched with saturated aqueous $NaHCO_3$ (50 mL), Et_2O (50 mL) was added and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 50 mL), and the combined extracts were dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield a yellow oil. Chromatography over Florisil® eluting with 98:2 hexanes/Et_2O gave enantiomerically enriched **10** (1.00 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ -19.2 (c = 0.99, CH_2Cl_2). IR (film) 2943, 2866, 1668 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.68-6.64 (2H, m), 6.50 (1H, dd, *J* = 8, 1.5 Hz), 5.33 (2H, s), 4.97-4.95 (1H, m), 2.60-2.51 (1H, m), 2.26-2.03 (4H, m), 1.78-1.61 (2H, m), 1.15-1.13 (21H, m). ^{13}C NMR (75 MHz, C_6D_6) δ 150.9, 148.2, 146.3, 140.9, 120.0, 108.4, 107.7, 102.6, 100.7, 40.2, 32.7, 30.8, 30.6, 18.3, 13.0. HRMS found 375.2357; $C_{22}H_{35}O_3Si$ (MH^+) requires 375.2355.

(4*S*) 4-(1,3-Benzodioxol-5-yl)-3-(4-toluenesulfonamido)-1-triisopropylsilyl(oxy)cyclo hexene 13. To a mixture of **10** (1.47 g, 3.94 mmol) and iodosobenzene (1.04 g, 4.71 mmol) in dichloromethane (30 mL) under nitrogen, cooled to -15 °C, was added trimethylsilylazide (1.25 mL, 9.42 mmol). The mixture was stirred at -15 °C for 20 min and warmed to room temperature and the solvent evaporated *in vacuo*. Iodobenzene was removed by addition of toluene (20 mL) and concentration *in vacuo*, repeated 4 times to afford crude **11** (1.51 g) as a brown oil. The ratio of *trans:cis* diastereomers (3.5:1) was measured by integration of the signals at δ 4.99 (*trans*) and δ 5.18 (*cis*) in the ^1H NMR spectrum recorded in acetone-d_6.

The crude azide **11** was dissolved in Et_2O (30 mL) under nitrogen and treated with lithium aluminum hydride (0.154 g, 4.06 mmol). The mixture was stirred for 50 min, cooled to 0 °C, and quenched by dropwise addition of saturated aqueous Na_2SO_4 (0.5 mL). The mixture was stirred for a further 10 min, diluted with EtOAc (50 mL), dried (Na_2SO_4) and filtered through Celite®, washing the filter cake with further EtOAc (50 mL). Evaporation of the solvent *in vacuo* afforded crude amine **12** (1.08 g) as a yellow oil. The *ee*. was measured by dissolution of **12** (13 mg, 33 μmol) and (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (18.4 mg, 67 μmol) in benzene-d_6 (0.7 mL) and integration of the peaks at δ 5.04 and δ 5.12, (ee > 85%).

Sodium hydride (60% dispersion in mineral oil, 0.160 g, 4.0 mmol) was placed under nitrogen and washed with pentane (2 x 10 mL) then suspended in Et_2O (2 mL). The crude amine **12** was added as a solution in Et_2O (5 mL), followed by *p*-toluenesulfonyl chloride (0.80 g, 4.18 mmol) as a solution in Et_2O (10 mL). The mixture was stirred for 3 h, cooled to 0 °C, and quenched by dropwise addition of water (1 mL). After gas evolution had ceased, more water (10 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (2 x 25 mL), the combined extracts were washed with water (15 mL), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to afford a brown oil. Chromatography of the residue over Florisil®, eluting with 60:40 hexanes/Et_2O gave **13** as a mixture of *cis* -and *trans* -isomers (0.888 g, 60% over 3 steps) as a pale yellow solid which was alkylated immediately in the following step.

(3*R*,4*R*)-4-(1,3-Benzodioxol-5-yl)-N-(2-bromoethyl)-3-(4-toluenesulfonamido)-1-triisopropylsilyl(oxy)cyclohexene 14. Method 1. Sodium hydride (60% dispersion in mineral oil, 0.773 g, 19.3 mmol) was placed under nitrogen and washed with pentane (15 mL). Sulfonamide **13** (3.5:1 *trans:cis* mixture, 0.491 g, 0.90 mmol) was added as a solution in tetrahydrofuran (15 mL), followed by 1,2-dibromoethane (1.7 mL, 20 mmol). The mixture was heated at reflux for 14.5 h, cooled to 0 °C, and quenched by dropwise addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield a brown oil. Chromatography of the residue over Florisil®, eluting with 80:20 hexanes/Et_2O gave **14** (0.377 g, 64%) as a colorless oil. IR (film) 2943, 2866, 1659 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.52 (2H, d, J = 8 Hz), 6.70-6.67 (3H, m), 6.59 (1H, d, J = 8 Hz), 6.45 (1H, dd, J = 8, 1.5 Hz), 5.34-5.26 (2H, m), 4.86 (1H, br d, J = 9.5 Hz), 4.20 (1H, br s), 3.91-3.83 (1H, m), 3.67-3.58 (1H, m), 3.51-3.33 (2H, m), 2.28 (1H, td, J = 10.5, 3.5 Hz), 1.92 (3H, s), 2.01-1.90 (1H, m), 1.84-1.75 (1H, m), 1.53-1.47 (2H, m), 1.02-0.90 (21H, m). ^{13}C NMR (75 MHz, C_6D_6) δ 155.6, 148.3, 146.9, 142.9, 137.7, 136.5, 129.7, 121.3, 108.4, 108.0, 102.8, 100.9, 60.3, 46.3, 45.8, 31.5, 31.4, 30.1, 21.2, 18.2, 18.1, 12.8. HRMS found 650.1946, $C_{31}H_{45}BrNO_5SSi$ (MH^+) requires 650.1971.

Method 2. 50% NaOH (4 mL) was added to a vigorously stirred suspension of sulfonamide **13** (0.21 g, 0.38 mmol), *n*-Bu_4NI (28 mg, 0.08 mmol) and 1,2-dibromoethane (0.1 mL, 1.16 mmol) in dichloromethane (2 mL). After 5 h the mixture was diluted with water (30 mL) and extracted into EtOAc (2 x 15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a brown oil. Chromatography of the residue over Florisil®, eluting with 80:20 hexanes/Et_2O gave **14** as a mixture of diastereoisomers (0.224 g, 90%) as a colorless oil (3.5 : 1).

(-)-(1*R*,5*R*,6*R*)-7-Aza-5-(1,3-benzodioxol-5-yl)-7-(4-toluenesulfonyl)-2-triisopropyl silyl(oxy)bicyclo[4.3.0]non-2-ene 15. Chloro(pyridine)bis(dimethylglyoximato)cobalt (III) (0.334 g, 0.83 mmol) was suspended in methanol (10 mL) under nitrogen and treated with 10 M aqueous NaOH (250 μL, 2.50 mmol). The resulting brown solution was degassed by 5 freeze-pump-thaw cycles using argon. Sodium borohydride (63 mg, 1.66 mmol) was added, followed after 5 min by **14** (0.480 g, 0.74 mmol) as a solution in tetrahydrofuran (1.5 mL). The mixture was stirred for 90 min and the solvent was evaporated *in vacuo*. The brown residue was partitioned between brine (20 mL) and EtOAc (20 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a yellow oil. Chromatography over a short column of Florisil®, eluting with hexanes/Et_2O 50:50 gave **15** (0.374 g, 89%) as a white foam. M.p. 50-51 °C (hexanes/Et_2O). $[\alpha]_D^{25}$ -62.1 (c = 0.98, CH_2Cl_2). IR (CH_2Cl_2) 2943, 2866, 1670 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.68 (2H, d, J = 8 Hz), 6.97 (1H, d, J = 1.5 Hz), 6.81 (1H, dd, J = 8, 1.5 Hz), 6.74 (2H, d, J = 8 Hz), 6.70 (1H, d, J = 8 Hz), 5.34 (2H, s), 4.80 (1H, t, J = 4 Hz), 4.05 (1H, t, J = 6.5 Hz), 3.59 (1H, ddd, J = 11.5, 8.5, 3 Hz), 3.49 (1H, q, J = 5.5 Hz), 3.29-3.20 (1H, m), 2.57-2.49 (1H, m), 2.27-2.23 (1H, m), 2.16 (1H, dt, J = 17, 5 Hz), 1.89 (3H, s), 1.75-1.68 (1H, m), 1.25-1.20 (1H, m), 1.08-0.98 (21H, m). ^{13}C (75 MHz, C_6D_6) δ 149.5, 148.1, 146.6, 142.8, 137.0, 136.6, 129.6, 127.8, 121.7, 108.9, 108.3, 101.9, 100.8, 66.0, 47.6, 41.9, 41.3, 28.8, 26.7, 21.1, 18.2, 12.8. HRMS found 570.2713, $C_{31}H_{44}NO_5SSi$ (MH^+) requires 570.2709.

(1*R*,5*R*,6*R*)-7-Aza-5-(1,3-benzodioxol-5-yl)-2-triisopropylsilyl(oxy)bicyclo[4.3.0] non-2-ene 16. A stock solution of sodium naphthalenide in THF (1.5 M, 0.5 mL, 0.75 mmol) was added dropwise over 5 min to a solution of sulfonamide **15** (80 mg, 0.15 mmol) in THF (2 mL) at -78 °C under argon. The black suspension formed was stirred for a further 5 min, then quenched by addition of water (2 mL) to give a frozen pale yellow solid which melted on warming to room temperature. The layers were separated and the aqueous layer extracted into EtOAc (10 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a brown oil. Chromatography of the residue over Florisil®, gradient eluting with EtOAc to MeOH gave **16** (0.054 g, 90%) as a colorless oil. Used directly.

(1*R*,5*R*,6*R*)-7-Aza-5-(1,3-benzodioxol-5-yl)-7-(4-toluenesulfonyl)bicyclo[4.3.0]non-2-one 19. To a solution of **15** (175 mg, 0.308 mmol) in dichloromethane at 0 °C under argon was added HF-pyridine complex (60%, 1 mL). After 30 min the mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted into EtOAc (2 x 10 mL). The combined extracts were washed with 0.5 M HCl (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give **19** as a 3.5:1 mixture of diastereoisomers (126 mg, 99%) as a white foam. IR (CH_2Cl_2) 1705, 1490, 1345, 1250, 1160, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.0 Hz), 7.18 (2H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 6.66-6.62 (2H, m), 5.93 (2H, s), 4.19 (1H, dd, *J* = 9.5, 7.0 Hz), 3.55-3.41 (2H, m), 2.87 (1H, dt, *J* = 12.5, 3.5 Hz), 2.57 (1H, dd, *J* = 12.5, 4.5 Hz), 2.52-2.34 (2H, m), 2.38 (3H, s), 2.18 (1H, dt, *J* = 12.5, 4.5 Hz), 2.08-1.87 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 146.3, 143.4, 135.1, 134.9, 129.5, 127.2, 121.1, 108.1, 108.0, 100.8, 67.0, 63.0, 51.8, 46.2, 44.2, 37.2, 28.7, 28.4, 21.4. HRMS found 414.1365, $C_{22}H_{24}NO_5S$ (MH^+) requires 414.1375.

(1*R*,2*S*,5*R*,6*R*)-7-Aza-2-acetoxy-5-(1,3-benzodioxol-5-yl)-7-(4-toluenesulfonyl) bicyclo[4.3.0] nonane 20. Sodium borohydride (140 mg, 3.68 mmol) was added to a stirred solution of **19** (126 mg, 0.31 mmol) in wet methanol (3 mL) at 0 °C under argon. After 2 h the mixture was quenched with water (3 mL), and extracted into EtOAc (3 x 10 mL). The combined extracts were washed with brine (10 mL) dried ($MgSO_4$) and the solvent evaporated *in vacuo* to a white foam. The crude alcohol was immediately dissolved in dichloromethane (2 mL) cooled to 0 °C, and 4-*N*,*N*-dimethylaminopyridine (5 mg, catalytic), pyridine (1 mL) and acetic anhydride (1 mL) were added, and the mixture stirred for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted into EtOAc (2 x 10 mL). The combined extracts were washed with 0.5 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give a white foam. Chromatography over silica gel, eluting with pentane/Et_2O 50:50 to 25:75 gave **20** as a 3.5:1 mixture of diastereoisomers (125 mg, 90%) as a colorless oil. IR (CH_2Cl_2) 1730, 1245, 1160, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.0 Hz), 7.14 (2H, d, *J* = 8.0 Hz), 6.66 (1H, d, *J* = 8.5 Hz), 6.57-6.56 (2H, m), 5.91 (2H, s), 5.07 (1H, dt, *J* = 11.0, 5.5 Hz), 3.94 (1H, dd, *J* = 10.5, 6.0 Hz), 3.58-3.42 (2H, m), 2.37 (3H, s), 2.33-2.22 (1H, m), 2.14-1.76 (6H, m), 2.00 (3H, s), 1.64-1.42 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 147.3, 146.1, 142.9, 2 x 135.9, 129.2, 127.2, 121.2, 108.1, 100.7, 71.2, 65.7, 45.5, 44.7, 42.1, 29.4, 25.9, 23.8, 21.4, 21.1. HRMS found 458.1642, $C_{24}H_{28}NO_6S$ (MH^+) requires 458.1637.

(+)-(1*R*,2*S*,5*R*,6*R*)-7-Aza-2-acetoxy-5-(1,3-benzodioxol-5-yl)-7-(carbomethoxy) bicyclo[4.3.0]nonane 21. A stock solution of sodium naphthalenide in THF (1.5 M, 1 mL, 1.5 mmol) was added dropwise over 5 min to a solution of **20** (125 mg, 0.27 mmol) in THF (2 mL) at -78 °C under argon. The black suspension formed was stirred for a further 5 min, then quenched by addition of water (2 mL) to give a pale yellow solid which melted on warming to room temperature. The mixture was extracted into EtOAc (3 x 15 mL), and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a brown oil. The crude amine was dissolved in dichloromethane (3 mL), cooled to 0 °C, and pyridine (1 mL) and methyl chloroformate (1 mL) were added. The mixture slowly turned purple. After 1 h the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and the solvent evaporated *in vacuo* to give a brown oil. Chromatography over silica gel, eluting with pentane/EtOAc 50:50 to 25:75 gave **21** (44 mg, 60%) as a white foam, plus the pyrrolidine diastereomer (14.5 mg, 20%). $[\alpha]_D^{25}$ +24.8 (c = 1.05, CH_2Cl_2). IR (CH_2Cl_2) 1730, 1700, 1695, 1685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 8.0 Hz), 6.64 (1H, s), 6.55 (1H, d, *J* = 8.0 Hz), 5.89 (2H, s), 5.14 (1H, dt, *J* = 11.0, 5.5 Hz), 3.90 (1H, dd, *J* = 10.5, 6.0 Hz), 3.58-3.43 (2H, m), 3.08 (3H, s), 2.71-2.60 (1H, m), 2.35 (1H, dt, *J* = 11.5, 3.5 Hz), 2.15-2.03 (1H, m), 2.06 (3H, s), 2.00-1.88 (2H, m), 1.86-1.79 (1H, m) and 1.72-1.59 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.3, 147.4, 145.9, 136.9, 121.2, 107.8, 107.8, 100.7, 71.5, 62.8, 51.6, 45.0, 44.2, 41.9, 28.5, 26.1, 22.3, 21.2. HRMS found 362.1608, $C_{19}H_{24}NO_6$ (MH^+) requires 362.1604.

(+)-(3a*R*,3*S*,12b*R*,12c*R*)-3-Acetoxy-1, 2, 3a, 4, 5, 12b, 12c-octahydro-3H-1,3-dioxolo-[4,5j]pyrrolo[3.2.1-de]phenanthridine 22. Trifluoromethanesulfonic anhydride (0.074 mL, 0.44 mmol) was added to a cold (0 °C) solution of **21** (32 mg, 0.087 mmol) and 4-*N*,*N*-dimethylaminopyridine (33 mg, 0.27 mmol) in dichloromethane (2 mL) under argon. The resultant yellow suspension was heated to reflux for 2 h, then allowed to cool to room temperature. Saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (10 mL) were added, and the aqueous phase extracted with EtOAc (10 mL). The combined extracts were washed with 0.5 M HCl (5 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a yellow solid. Chromatography over silica gel, gradient eluting with pentane/EtOAc (25:75) to EtOAc/MeOH (99:1) gave **22** (22 mg, 77%) as a white solid. M.p. 191-193 °C (dec). $[\alpha]_D^{25}$ +97.7 (c = 1.02, CH_2Cl_2). IR (CH_2Cl_2) 1730, 1700, 1695, 1685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 8.0 Hz), 6.64 (1H, s), 6.55 (1H, d, *J* = 8.0 Hz), 5.89 (2H, s), 5.14 (1H, dt, *J* = 11.0, 5.5 Hz), 3.90 (1H, dd, *J* = 10.5, 6.0 Hz), 3.58-3.43 (2H, m), 3.08 (3H, s), 2.71-2.60 (1H, m), 2.35 (1H, dt, *J* = 11.5, 3.5 Hz), 2.15-2.03 (1H, m), 2.06 (3H, s), 2.00-1.88 (2H, m), 1.86-1.79 (1H, m), 1.72-1.59 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.3, 147.4, 145.9, 136.9, 121.2, 107.8, 107.8, 100.7, 71.5, 62.8, 51.6, 45.0, 44.2, 41.9, 28.5, 26.1, 22.3, 21.2. HRMS found 362.1608, $C_{19}H_{24}NO_6$ (MH^+) requires 362.1604.

(3a*R*,3*S*,12b*R*,12c*R*)-3-(4-Bromobenzoyloxy)-1, 2, 3a, 4, 5, 12b, 12c-octahydro-3H-1,3-dioxolo-[4,5j]pyrrolo[3.2.1-de]phenanthridine 24. Sodium methoxide in MeOH (0.67 M, 1 mL, 0.67 mmol) was added to a solution of **22** (11 mg, 0.03 mmol) in tetrahydrofuran (1 mL) at 25 °C under argon. After 3 h the mixture was quenched by addition of saturated aqueous NH_4Cl (2 mL) and extracted into EtOAc (3

x 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give a white solid. The crude alcohol **23** was dissolved in dichloromethane (1 mL) under argon, and 4-*N,N*-dimethylaminopyridine (5 mg, 0.04 mmol), pyridine (1 mL) and 4-bromobenzoyl chloride (15 mg, 0.07 mmol) were added. The mixture was heated at reflux for 6 h, allowed to cool to room temperature, and quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted into EtOAc (3 x 10 mL). The combined extracts were washed successively with 1 M HCl (15 mL), water (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (5 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give a white solid. Purification through a short pad of silica (EtOAc eluant) gave **24** (15 mg, 92%) as white crystalline solid. M.p. 254-256 °C (EtOAc, dec). IR (CH_2Cl_2) 2920, 1710, 1640, 1265, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.5 Hz), 7.6 (2H, d, J = 8.5 Hz), 7.46 (1H, s), 6.66 (1H, s), 6.01 (2H, s), 5.49 (1H, ddd, J = 11.0, 6.0, 4.5 Hz), 4.23 (1H, ddd, J = 12.0, 5.0, 3.5 Hz), 3.65 (1H, dd, J = 12.5, 8.5 Hz), 3.39-3.29 (1H, m), 2.98-2.92 (1H, m), 2.89 (1H, dd, J = 12.5, 5.0 Hz), 2.25 (1H, app. t, J = 13.0, 5.0 Hz), 2.12-1.90 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 163.3, 150.4, 146.6, 137.2, 131.9 (x2), 131.1 (x2), 128.8, 128.4, 125.1, 108.6, 103.6, 101.5, 71.3, 60.8, 45.8, 41.0, 37.9, 26.3, 25.8, 21.4. HRMS found 470.0599 [^{79}Br] (MH^+), $C_{23}H_{21}{}^{79}BrNO_5$ requires 470.0603.

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