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Tetrahedron

I8 Graphical Abstract

New strategy for the synthesis of proaporphine and homoproaporphine-type alkaloids from a common intermediate

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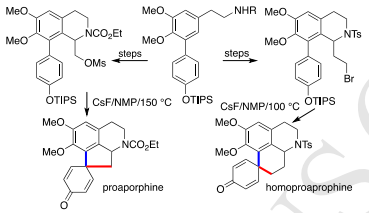

Pergamon

TETRAHEDRON

New strategy for the synthesis of proaporphine and homoproaporphine-type alkaloids from a common intermediate

Philip Magnus,* Kyle D. Marks and Alan Meis

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Abstract— Starting with 3-bromo-4,5-dimethoxybenzaldehyde **14**, it was coupled with the boronic anhydride **15** using standard Suzuki reaction conditions to give **16** (91%). The aldehyde **16** was exposed to classical nitro-aldol reaction conditions to give **17** (88%), and conjugatively reduced with DIBAL-H to give **18** (91%). Protection of the amine **18** as its *N*-carbamate derivative **19**, followed by condensation with glycol aldehyde dimer under acidic reaction conditions gave **20** (78%). Subsequent conversion of **20** into its mesylate derivative **21,** and exposure to CsF under aprotic reaction conditions gave **22** (81%). Deprotection of **22** gave (±)-stepharine **10** in 29% overall yield though 8 steps. A similar sequence of reaction conditions converted the amine **18** into the -NTs protected homoproaporphine adduct **28**.

Key words: alkaloids, Suzuki aryl-coupling, proaporphine, stepharine, homoproaporphine, Baldwins-rules.

1. Introduction

Recently, we reported a new strategy for the synthesis of morphinoid alkaloids,[1] and structurally related alkaloids, that makes use of the Suzuki aryl coupling reaction to form the crucial aryl-phenol bond as illustrated in figure 1 in blue. This approach has been successful when combined with *p*-phenolic alkylation (illustrated in red), to provide a concise synthesis of a number of alkaloids, and the results are summarized in figure 1. The Suzuki coupled product **1** (99%) was converted into its derived 1-ethoxy-2-bromoacetal derivative (ethylvinyl ether/Br_2/Et_3N) and treated with CsF in DMF at 130 °C to give the cross conjugated 2,5-cyclohexadienone **2** (96%) by intramolecular *C*-alkylation of the *insitu* generated phenolate.[2] Subsequent steps converted **2** into codeine **3**, thus illustrating the utility of this new strategy as an alternative to *o,p*-oxidative coupling of phenols.

Using the *o*-methoxy analogue of **1**, namely **4** (89%), provided **5** (85%) which was converted into salutaridine **6**.[3] The more highly substituted biaryl **7** (70%) gave access to **8** (76%), which in two steps was converted into cepharatine A **9**.[4] The formation of the crucial C-C bonds in high yields illustrate the advantage this strategy has over the conventional phenolic oxidation approach.

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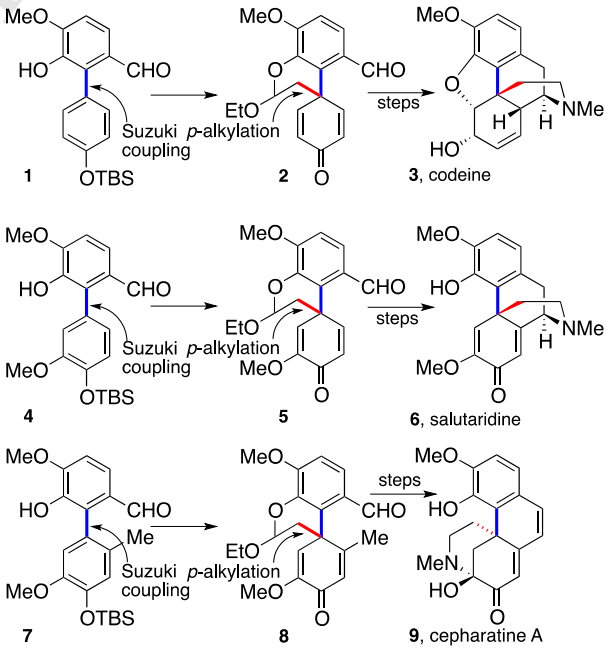
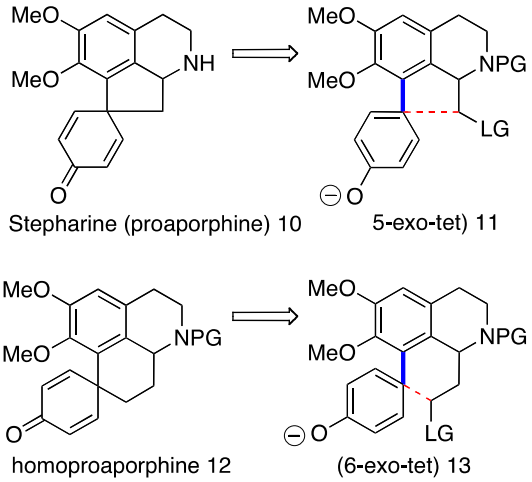


Figure 1. Strategy for the synthesis of codeine **3**, salutaridine **6**, and cepharatine **9**.



Scheme 1. Retrosynthesis for **10** and **12**.

Given the success of the strategy outlined in Figure 1, it was of interest to explore if this strategy could be applicable to other alkaloids that are also phenolic oxidation products, such as the proaporphine[5] stepharine **10**[6] and homoproaporphine type alkaloid **12**.[7] Plants of the genus *Stephania* that produce these types of compounds have been used for the treatment of medical ailments, and are widespread in the traditional medicine of Asia and Africa.[6] The proaporphine alkaloids were first described in Barton's 1957 work on phenolic oxidative couplings, several years before any members of the family had been isolated.[8]

The first synthesis of stepharine was reported in 1968 by Bernauer.[9] The most recent total synthesis of stepharine was in 2010 by Honda was accomplished nine steps with an overall yield of 29%.[10]

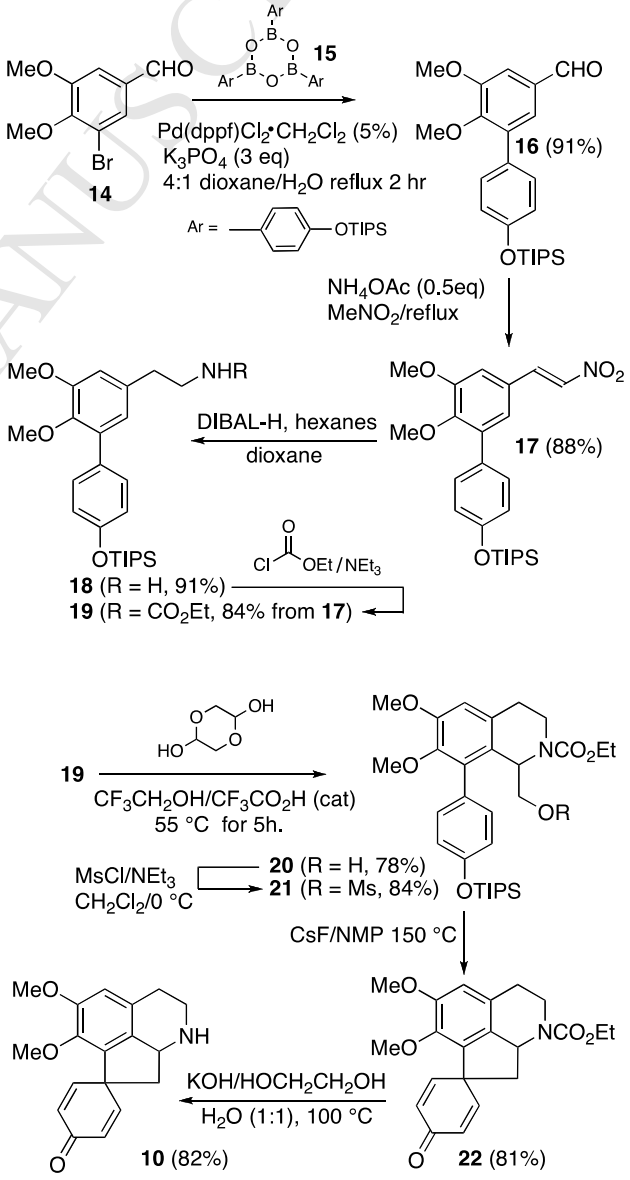
Scheme 1 outlines the retrosynthetic analysis for the compounds **10** and **12**. The blue biaryl bond in **11** will be made by an intermolecular Suzuki reaction, and a 5-exo-tet cyclization (favored, Baldwins rules)[11] forming the red bond should allow access to the cross-conjugated 2,5-cyclohexadienone **10**. Likewise, the blue bond in **13** can be formed using a Suzuki reaction, and a 6-exo-tet intramolecular alkylation (favored by Baldwins rules, red bond)[11] leads to the homoproaporphine skeleton **12**.

2. Results and discussion

The known[1] aryl boronate anhydride **15** was treated with **14** under standard Suzuki aryl coupling conditions to give **16** in 91% yield. The *O*-trisopropylsilyl ether (TIPS) derivative was the only phenolic silyl ether derivative that was stable to the subsequent reaction conditions.

Condensation of **16** with nitromethane under standard nitroaldol reaction conditions (Henry reaction conditions) converted **16** into **17** (88%) which was reduced using DIBAl-H[12] to the primary amine **18** (91%).

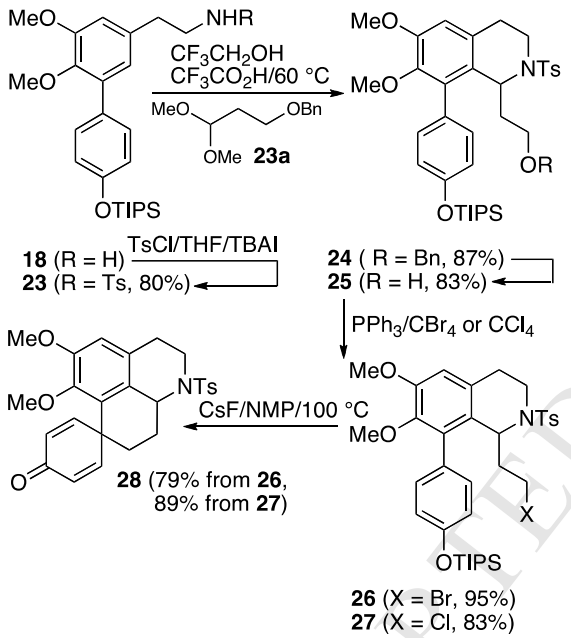
The amine **18** was converted into its carbamate derivative **19** (84%, two steps from **17**), and condensation with glycol aldehyde dimer in trifluoroethanol in the presence of trifluoroacetic acid gave **20** (78%, over the 2 steps). Activation of the primary hydroxyl group as its mesylate derivative **21** (84%) followed by exposure to CsF/NMP/150 °C/3.5 h gave **22** (81%). It should be noted that the more reactive triflate derivative of **20** gave small amounts of **22** (10%) but predominately elimination to the alkene.[13] Exposure of **22** to KOH/ethylene glycol at 100 °C gave (±)-stepharine **10** (82%).



Scheme 2. Synthesis of (±)-stepharine **10**.

In the sequence of reactions depicted in Scheme 3 for the synthesis of the homoproaporphine **12** it was found best to utilize the *N*-Ts derivative **23**.[14] When **23** was treated with the acetal **23a** in trifluoroethanol with trifluoroacetic acid at 60° C the tetrahydroisoquinoline **24** was isolated in 87% yield. Hydrogenolysis (Pd/C/ammonium formate/MeOH/50° C) gave **25**.

The alcohol **25** was converted into the bromide **26** (95%) and chloride **27** (83%) by treatment with $CBr_4/PPh_3/CH_2Cl_2$ and $CCl_4/PPh_3/CH_2Cl_2$ respectively. Exposure of the bromide **26** to CsF (3eq) in NMP (0.005 M) at 100-150 °C resulted in conversion into the cross-conjugated-2,5-cycloheaxadienone **28** in 79% yield (structure by X-ray). Under the same reaction conditions the chloride **27** gave **28** in 89% yield. Under more concentrated reaction conditions dimer formation (see experimental) became competitive.



Scheme 3. Synthesis of homoproaporphine **28**

3. Conclusion

The synthesis of the proaporphine alkaloid stepharine **10** proceeds in 8 steps with an overall yield of 29%, and the synthesis of the homoproaporphine derivative **28** proceeds in 8 steps with an overall yield of 31%**.**

The *p*-alkylation strategy provides a concise route to both proaporphine and homoproaporphine alkaloids that avoids phenolic oxidation.

4. Experimental Section

4.1 General

All reactions were carried out under an atmosphere of argon and only degassed when specified. Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrophotometer neat unless otherwise indicated. ^{1}H NMR spectra were recorded on a Varian spectrometer at 300 MHz, or 500 MHz, or 600 MHz in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded on a Varian spectrometer at 75 MHz or 125 MHz or 150 MHz in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Flash column chromatography was performed using EMD silica gel (particle size 0.040-0.063 □m 22 x 250 mm). Solvents and commercial reagents were purified in accordance with Armarego[15] or used without further purification.

4.2 Synthesis

*3-bromo-4,5-dimethoxybenzaldehyde **14***. To a stirred solution of vanillin (10.0 g, 66 mmol) in glacial acetic acid (100 mL) under argon was added bromine (3.7 mL, 72 mmol) over 5 min, and the mixture was stirred at room temperature for 3 h. The mixture was poured onto crushed ice (~200 g), and the solid was filtered, and dissolved in DMF (328 mL). To this solution was added K_3PO_4 (22.7 g, 164 mmol) followed by dropwise addition of iodomethane (4.5 mL, 72 mmol) over 10 min, and the mixture stirred overnight at room temperature. The mixture was transferred to a separatory funnel, diluted with water (300 mL), and extracted with *t*-butylmethyl ether (3 x 300 mL). The extracts were combined and washed with brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization of the residue from boiling hexanes gave **14**[16] (13.03 g, 81% yield) as white crystals. M.p. 59-60 °C. IR (thin film) 2945, 2836, 1692, 1587, 1566, 1486, 1281 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.85 (1H, s), 7.66 (1H, d, *J* = 2.0 Hz), 7.39 (1H, d, *J* = 2.0 Hz), 3.95 (3H, s), 3.93 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 189.86, 154.16, 151.78, 133.02, 128.78, 117.92, 110.04, 60.82, 56.23. HRMS calculated for $C_9H_9BrO_3$ (MH^+) 244.9813 and 246.9793 found 244.9815 and 246.9793.

Bromophenol (20 g, 116 mmol), triisopropylsilyl chloride (24.5 g, 127 mmol) and imidazole (19.7 g, 289 mmol) was added to 1,2-dichloroethane (200 mL), and the solution was heated at reflux for 3 h. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude oil was purified by flash chromatography over silica gel to give the title compound (38.03 g, 99%) as a clear oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 1.27-1.21 (3H, m), 1.08 (18H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.2, 114.7, 10.9, 5.6.

*Boronic Ester Trimer **15***. *n*-Butyl lithium (46 mL, 2.5 M in hexanes) was added dropwise to a stirred solution of (4-bromophenoxy)triisopropylsilane (14.5 g, 44 mmol) in THF (40 mL) at -78 °C under argon. The solution was allowed to stir for 0.5 h, and triisopropyl borane (53 mL, 229 mmol) was added to the solution dropwise at -78 °C. The solution was allowed to stir and warm to room temperature overnight. The reaction mixture was quenched by pouring it onto 10% aqueous $KHSO_4$ (60 mL), and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude solid was purified by flash chromatography giving **15** (11.2 g, 92%) as an oil that crystallized upon standing. IR (thin film) 2944, 2867, 1597, 1374, 1239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (6H, d, J = 8.4 Hz), 6.99 (6H, d, J = 8.8 Hz), 1.33-1.10 (63H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 137.4, 119.6, 17.9, 12.7. HRMS calculated for $C_{45}H_{75}B_3O_6Si_3$ (M^+) 828.5151, found 828.5166.

*5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-carbaldehyde **16***. To a degassed mixture of 1,4-dioxane (100 mL) and water (25 mL) was added solid K_3PO_4 (16.1 g, 75.8 mmol), **14** (6.20 g, 25.3 mmol), and **15** (8.38 g, 10.1 mmol), followed by $Pd(dppf)Cl_2$•CH_2Cl_2 (0.103 g, 0.13 mmol). The solution turned black. The mixture was placed in an oil bath at 80 °C and stirred for 3 h. When the reaction was complete, as judged by TLC, the mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The extracts were combined, washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 0-15% EtOAc:hexanes) gave **16** as a white solid (8.60 g, 91%). Recrystallization from methanol gave white needles. M.p. 75-76 °C. IR (thin film) 2944, 2867, 2360, 1695, 1513, 1464, 1382, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.92 (1H, s), 7.47 (1H, d, J = 2.0 Hz), 7.44-7.40 (3H, m), 6.65 (2H, dt, J = 8.4, 2.0 Hz), 3.96 (3H, s), 3.64 (3H, s), 1.29 (3H, sep, J = 7.6 Hz), 1.12 (18H, d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.3, 155.9, 153.8, 151.9, 135.8, 132.3, 130.2, 129.6, 127.3, 119.8, 108.9, 60.5, 56.1, 17.9, 12.7. HRMS calculated for $C_{24}H_{34}O_4Si$ $(MH)^+$ 415.2305, found 415.2305.

*(E)-((2',3'-dimethoxy-5'-(2-nitrovinyl)-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane **17***. To a flame dried round bottom flask equipped with an oven dried Dean-Stark trap was added **16** (3.08 g, 7.4 mmol), nitromethane (56 mL), and ammonium acetate (0.43 g, 5.6 mmol). The mixture was heated at reflux overnight under an argon atmosphere. The flask was removed from the oil bath and allowed to cool to room temperature. The orange solution was concentrated *in vacuo*, and the resulting viscous orange oil was purified by column chromatography (SiO_2, 5% EtOAc:hexanes) to give **17** (3.00 g, 88%) as a viscous yellow oil that formed canary yellow crystals upon standing. M.p. 65-67 °C. IR (thin film) 2944, 2867, 1512, 1335, 1264. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (1H, d, J = 13.6 Hz), 7.56 (1H, d, J = 13.6 Hz), 7.38 (2H, d, J = 8.8 Hz), 7.17 (1H, d, J = 2.0 Hz), 7.01 (1H, d, J = 2.0 Hz), 6.95 (2H, d, J = 8.8 Hz), 3.94 (3H, s), 3.61 (3H, s), 1.28 (3H, sep, J = 7.2 Hz), 1.13, (18H, d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.9, 153.6, 150.1, 139.1, 136.5, 136.3, 130.1, 129.4, 125.6, 124.9, 119.8, 110.5, 60.6, 59.1, 17.9, 12.7. HRMS calculated for $C_{25}H_{35}NO_5Si$ $(M+Na)^+$ 480.2177, found 480.2175.

*2-(5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-yl)ethanamine **18***. To a flame dried round bottom flask under argon was added DIBAL-H (1 M in hexanes, 2.0 mL, 2.0 mmol), 1,4-dioxane (1 mL, dried over 4Å mol sieves) followed by dropwise addition of **17** (0.10 g, 0.2 mmol) as a solution in 1,4-dioxane (1 mL). The mixture was stirred for 1 h at room temperature, cooled to 0 °C, and quenched with ethyl acetate (2 mL), followed by addition of aqueous Rochelle's salt (3 mL). The solution was stirred at room temperature for 2 h, the organic layer separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were dried (Na_2SO_4), concentrated *in vacuo*, and the crude oil was purified by flash chromatography (SiO_2, 0-10% MeOH:DCM) to give **18** (0.085 g, 91%) as a clear viscous oil. IR (thin film) 2944, 2867, 1607, 1512, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (2H, d, J = 8.8 Hz), 6.91, (2H, d, J = 8.8 Hz), 6.77 (1H, d, J = 2.0 Hz), 6.72 (1H, d, J = 2.0 Hz), 3.88 (3H, s), 3.50 (3H, s), 3.03 (4H, brs), 2.71 (2H, t, J = 7.6 Hz), 1.28 (3H, sep, J = 8.0 Hz), 1.12 (18H, d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.3, 153.0, 144.9, 135.3, 134.8, 130.7, 130.2, 122.6, 119.6, 111.5, 60.3, 56.0, 43.0, 38.8, 17.9, 12.7. HRMS calculated for $C_{25}H_{39}NO_3Si$ $(M+Na)^+$ 452.2491 found 452.2584.

*Ethyl (2-(5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-yl)ethyl)carbamate **19***. The crude amine **18** (theoretical 1.94 mmol) and diisopropylethylamine (0.877 g, 6.79 mmol) were dissolved in CH_2Cl_2 (100 mL) in a flame dried flask and cooled to 0 ºC. Ethyl chloroformate (0.629 g, 5.82 mmol) was added dropwise with stirring. The solution was allowed to warm to room temperature and stirred for 3 h. The mixture was diluted with ether, and the ether layer washed with saturated aqueous $NaHCO_3$, and brine. The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was

purified by silica gel flash chromatography to give **19** (0.823 g, 84% over two-steps from **17**) as a clear oil. IR (thin film) 3345, 2944, 2867, 1700, 1512 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.4 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 6.76 (1H, d, *J* = 2.0 Hz), 6.70 (1H, s), 4.73 (1H, s, brs), 4.11 (2H, dd, *J* = 14.0, 7.2 Hz), 3.88 (3H, s), 3.45 (2H, dd, *J* = 13.0, 6.4 Hz), 2.79 (2H, t, *J* = 14.0 Hz), 1.33-1.10 (24H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 155.4, 153.0, 145.0, 135.5, 134.5, 130.7, 130.2, 122.5, 119.6, 111.4, 60.7, 60.3, 55.9, 40.1, 63.0, 17.8, 14.6, 12.6. HRMS calculated for $C_{28}H_{43}NO_5Si$ (MH^+) 502.2983, found 502.2975.

Ethyl 1-(hydroxymethyl)-6,7-dimethoxy-8-(4-((triisopropylsilyl)oxy)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***20***. Carbamate **19** (0.10 g, 0.20 mmol) and glycolaldehyde dimer (0.018g, 0.15 mmol) were dissolved in 2,2,2-trifluoroethanol (0.5 mL), and trifluoroacetic acid (2 drops) added. The solution was heated to 55 °C, and allowed to stir for 5 h until the starting material was consumed as judged by LCMS. The crude mixture was concentrated *in vacuo* and purified by silica gel flash chromatography giving **20** (0.083 g, 78%). IR (thin film) 3447, 2943, 2867, 1684, 1512 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (2H, t, *J* = 7.2 Hz), 6.97 (2H, d, *J* = 7.6 Hz), 6.70 (1H, s), 5.21 (1H, m), 4.15 (2H, m), 3.86 (3H, s), 3.76-3.34 (6H, m), 2.88 (2H, d, *J* = 7.4 Hz), 1.33-1.11(24H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 151.8, 131.7, 131.1, 129.9, 124.7, 120.1, 119.7, 119.8, 118.8, 111.5, 71.1, 65.5, 61.5, 60.4, 55.8, 54.4, 39.7, 28.6, 28.1, 17.9, 14.6, 12.6. HRMS calculated for $C_{30}H_{45}NO_6Si$ (MNa^+) 566.2908, found 566.2911.

Ethyl 6,7-dimethoxy-1-(((methylsulfonyl)oxy)methyl)-8-(4-((triisopropylsilyl)oxy)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***21***. Alcohol **20** (0.205 g, 0.41 mmol) and dry triethylamine (0.041 g, 0.41 mmol) were added to a flame dried flask charged with CH_2Cl_2 (50 mL) and the mixture was cooled to 0 °C. Freshly distilled methanesulfonyl chloride (0.065 g, 0.61 mmol) was added to the solution dropwise. The mixture was allowed to stir at 0 ºC for 3 h until the staring material was consumed as shown by LCMS. The crude mixture was poured into a saturated aqueous $NaHCO_3$ and extracted with ether (3 x 50 mL). The ether extracts were washed with saturated aqueous NH_4Cl, brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography over neutral alumina to give **21** (0.214 g, 84%) as a clear oil. IR (thin film) 2934, 2867, 1701, 1511, 1176 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-6.96 (4H, m), 6.70 (1H, d, *J* = 0.8 Hz), 5.56-5.40 (1H, m), 4.17-4.02 (4H, m), 3.90-3.87 (4H, m), 3.41 (4H, m), 2.87 (2H, m), 2.64 (3H, d, *J* = 12.8 Hz), 1.31-1.11 (24H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 133.2, 131.9, 131.8, 131.5, 129.9, 127.6, 122.6, 120.3, 120.1, 120.0, 111.8, 105.0, 77.2, 69.0, 61.6, 60.4, 55.8, 50.9, 38.2, 37.1, 28.2, 17.9, 14.6, 12.6. HRMS calculated for $C_{31}H_{47}NO_8SiS$ (M^+) 621.2792, found 621.2783.

Ethyl 5' ,6'-dimethoxy-4-oxo-2',3',8',8a'-tetrahydro-1'H-spiro[cyclohexane-1,7'-cyclopenta[ij]isoquinoline]-2,5-diene-1'-carboxylate ***22***. Mesylate **21** (50 mg, 0.086 mmol) was dissolved in dry *N*-methylpyrrolidone (1.5 mL) and warmed to 100 ºC. Excess cesium fluoride (flamed dried under vacuum) was added to the solution and the mixture was heated to 150 ºC for 3.5 h until the starting material had been consumed as shown by LCMS. The solution was cooled to room temperature, poured into brine, extracted with ether (3 x 50 mL), and dried (Na_2SO_4). The extract was concentrated *in vacuo* and purified by flash chromatography on basic alumina to give **22** (28 mg, 88%). IR (thin film) 2948, 2932, 1694, 1664, 1282 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, dd, *J* = 10.0, 2.8 Hz), 6.85 (1H, dd, *J* = 9.8, 2.8 Hz), 6.71 (1H, s), 6.41 (1H, dd, *J* = 9.8, 1.6 Hz), 6.32 (1H, dd, *J* = 9.6, 2.8 Hz), 4.98 (1H, m), 4.24-4.16 (3H, m), 3.84 (3H, s), 3.63 (3H, s), 2.93-2.64 (4H, m), 2.33 (1H, dd, *J* = 12.4, 10.4 Hz), 1.30 (3H, t, *J* = 13.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 156.3, 152.8, 149.5, 144.8, 132.9, 132.1, 130.9, 125.3, 127.7, 115.5, 61.5, 60.9, 56.3, 55.0, 50.8, 49.7, 42.5, 28.7, 14.7. HRMS calculated for $C_{21}H_{23}NO_5$ (MH^+) 370.1649, found 370.1647.

5',6'-dimethoxy-2',3',8',8a'-tetrahydro-1'H-spiro[cyclohexane-1,7'-cyclopenta[ij] isoquinoline]-2,5-dien-4-one (stepharine) ***10***. The cyclized product **22** (5 mg, 0.014 mmol) and potassium hydroxide (100 mg, 1.78 mmol) were dissolved in a mixture of water (1.5 mL) and ethylene glycol (1.5 mL) and heated to 100 ºC. The solution was allowed to stir for 12 h. The crude mixture was diluted with chloroform and washed with water and brine. The organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using preparative TLC to give (±)-stepharine **10** (3.3 mg, 82%)**.** Spectra matching literature values. IR (thin film) 3584, 2923, 1662, 1490, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, d, *J* = 10.0 Hz), 6.89 (1H, d, *J* = 9.2 Hz), 6.64 (1H, s), 6.41 (1H, d, *J* = 10.0 Hz), 6.29 (1H, d, *J* = 10.0 Hz), 4.33 (1H, m), 3.81 (3H, s), 3.60 (3H, s), 3.51 (1H, m), 3.21-3.08 (1H, m), 3.16 (1H, m), 2.85-2.74 (2H, m), 2.45-2.39 (1H, m), 2.27-2.23 (1H, m). HRMS calculated for $C_{18}H_{19}NO_3$ (MH^+) 298.1438, found 298.1434.

N-(2-(5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-yl)ethyl)-4-methylbenzenesulfonamide ***23***. To a stirred solution of **18** (0.69 g, 1.6 mmol) in THF (5 mL) under argon was added water (15 mL) followed by *p*-toluenesulfonyl chloride (0.37 g, 1.9 mmol) and tetrabutylammonium iodide (spatula tip). The solution was stirred at room temperature for 6 h then transferred to a separatory funnel and extracted with ethyl acetate

(3 x 20 mL). The organic fractions were combined, washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 5-10% EtOAc:hexanes) gave **23** (0.751 g, 80%) as an off white solid. M.p. 99-100 ºC. IR (thin film) 2944, 2866, 1512, 1262 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (2H, d, *J* = 8.4 Hz), 7.36 (2H, d, *J* = 8.4 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 6.59 (2H, d, *J* = 4.8 Hz), 4.39 (1H, t, *J* = 6.0 Hz), 3.84 (3H, s), 3.51 (3H, s), 3.24 (2H, q, *J* = 6.8 Hz), 2.74 (2H, t, *J* = 6.8 Hz), 2.41 (3H, s), 1.27 (3H, sep, *J* = 6.8 Hz), 1.13 (18H, d, *J* = 6.8Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm □□□□□□□□□□□□□□□□□□□□□□, 143.4, 136.9, 135.7, 133.2, 130.5, 130.2, 129.7, 127.1, 122.4, 119.6, 111.3, 60.3, 55.9, 44.1, 35.6, 21.5, 17.9, 12.7. HRMS calculated for $C_{32}H_{45}NO_5SSi$ $(M)^+$ 583.2788 found 583.2795.

1-(2-(benzyloxy)ethyl)-6,7-dimethoxy-2-tosyl-8-(4-((triisopropylsilyl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinoline ***24***. To a flame dried round bottom flask under argon was added **23** (0.732 g, 1.25 mmol), 2,2,2,-trifluoroethanol (15 mL), **23a** (0.395 g, 1.88 mmol), and trifluoroacetic acid (0.14 mL, 1.88 mmol). The mixture was heated in an oil bath at 60 ºC and stirred for 24 h (reaction monitored by LCMS or ^1H NMR). The mixture was cooled to room temperature, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (SiO_2, 5-10% EtOAc:hexanes) to give **24** (0.794 g, 87%) as a clear viscous oil. IR (thin film) 2944, 2866, 1511, 1464, 1262 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.60 (2H, d, *J* = 8.0 Hz), 7.32-6.95 (11H, comp), 6.51 (1H, s), 4.87 (1H, dd, *J* = 10.4, 4.0 Hz), 4.22 (2H, s), 3.80 (4H, comp), 3.53 (1H, m), 3.42 (3H, s), 3.26 (1H, td, *J* = 9.2, 5.2 Hz), 3.04 (1H, m), 2.81 (1H, m), 2.70 (1H, m), 2.34 (3H, s), 1.73 (2H, m), 1.30 (3H, sep, *J* = 7.6 Hz), 1.14 (18H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.4, 151.4, 145.3, 143.0, 138.5, 137.3, 134.2, 131.8, 130.2, 129.2, 128.8, 128.2, 127.4, 127.3,120.1, 120.0, 111.7, 72.6, 67.7, 60.4, 55.7, 51.2, 38.8, 35.2, 27.0, 21.5, 17.9, 12.6. HRMS calculated for $C_{42}H_{55}NO_6SSi$ $(M+Na)^+$ 752.3412 found 752.3389.

2-(6,7-dimethoxy-2-tosyl-8-(4-((triisopropylsilyl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanol ***25***. To flame dried round bottom flask under argon was added methanol (20 mL), **24** (0.396 g, 0.54 mmol), ammonium formate (0.171 g, 2.71 mmol) and 10% palladium on carbon (0.30 g). The mixture was heated in an oil bath at 50 ºC for 6 h until the reaction was complete, as judged by TLC. The mixture was filtered through a pad of Celite, washed with copious amounts of methanol, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 5-20% EtOAc:hexanes) to give **25** (0.287 g, 83%) as a white solid. Recrystallization from methanol afforded white crystals. M.p. 105-107 ºC. IR (thin film) 3545, 2944, 2866, 2361, 2340, 1606, 1511, 1464, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ□ppm 7.53 (2H, d, *J* = 7.6 Hz), 7.18 (2H, d, *J* = 8.2 Hz), 7.12 (1H, d, *J* = 7.6 Hz), 6.99 (2H, d, *J* = 8.2 Hz), 6.86 (1H, d, *J* = 7.2 Hz), 6.53 (1H, s), 4.83 (1H, dd, *J* = 8.4, 8.0 Hz), 3.81 (3H, s), 3.60 (3H, m), 3.42 (1H, m), 3.41 (3H, s), 2.78 (2H, m), 2.37 (3H, s), 2.19 (1H, t, *J* = 7.6 Hz), 1.68 (2H, m), 1.31 (3H, sep, *J* = 7.6 Hz), 1.14 (18H, d, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.6, 151.5, 145.4, 143.3, 136.3, 134.2, 131.4, 130.4, 129.4, 129.2, 128.3, 127.7, 127.3, 120.1, 119.9, 111.5, 60.5, 59.0, 55.7, 51.1, 40.5, 39.0, 27.3, 21.5, 17.9, 12.6. HRMS calculated for $C_{35}H_{49}NO_6SSi$ $(M+H)^+$ 640.3128 found 640.3107.

1-(2-bromoethyl)-6,7-dimethoxy-2-tosyl-8-(4-((triisopropylsilyl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinoline ***26***. To a flame dried round bottom flask under argon was added dry CH_2Cl_2 (25 mL), **25** (0.613 g, 0.96 mmol) and carbon tetrabromide (0.636 g, 1.92 mmol). The flask was placed in an ice bath and triphenylphosphine (0.502 g, 1.92 mmol) was added. The ice bath was removed and the reaction was stirred at room temperature for 3 h (monitored by TLC). The mixture was diluted with ether (100 mL) and filtered. The filtrate was concentrated *in vacuo* and the crude material purified by flash chromatography (SiO_2, 10% EtOAc:hexanes) to give **26** (0.641 g, 95%) as a white solid which was recrystallized from methanol to give white crystals. M.p. 112-113 ºC. IR (thin film) 2944, 2866, 1512, 1463, 1262 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.62 (2H, d, *J* = 8.0 Hz), 7.19 (2H, d, *J* = 8.0 Hz), 7.10 (1H, m), 7.01-6.98 (3H, m), 6.49 (1H, s), 4.80 (1H, dd, *J* = 10.4, 3.2 Hz), 3.81 (4H, comp), 3.48 (1H, ddd, *J* = 15.6, 10.0, 5.6 Hz), 3.42 (3H, s), 3.14 (1H, td, *J* = 10.0, 4.4 Hz), 2.77 (2H, m), 2.67 (1H, dt, *J* = 16.4, 5.2 Hz), 2.37 (3H, s), 2.02 (1H, m), 1.87 (1H, m), 1.30 (3H, sep, *J* = 6.8 Hz), 1.14 (18H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ□ppm 155.5, 151.7, 145.4, 143.3, 137.0, 134.3, 131.6, 130.1, 129.4, 128.8, 127.7, 127.3, 127.1, 120.3, 120.0, 111.7, 105.0, 60.5, 55.7, 52.9, 39.0, 28.8, 27.0, 21.5, 17.9, 12.7. HRMS calculated for $C_{35}H_{48}BrNO_5SSi$ $(M+Na)^+$ 724.2098 and 726.2084 found 724.2068 and 726.2069.

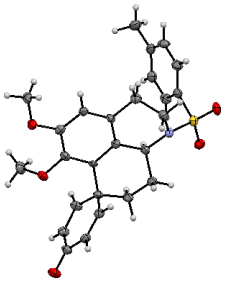
1-(2-chloroethyl)-6,7-dimethoxy-2-tosyl-8-(4-((triisopropylsilyl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinoline ***27***. To a flame dried round bottom flask under argon was added dry CH_2Cl_2 (5 mL), **25** (0.104 g, 0.16 mmol) and carbon tetrachloride (0.075 g, 0.49 mmol). The flask was placed in an ice bath and triphenylphosphine (0.128 g, 0.49 mmol) was added. The ice bath was removed and the reaction mixture was stirred at room temperature for 5 h (monitored by TLC). The mixture was diluted with ether (30 mL), filtered, and the filtrate concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 10% EtOAc:hexanes) to give **27**

(0.088 g, 83%) as a white solid which was recrystallized from methanol to give white crystals. M.p. 115-118 ºC. IR (thin film) 2944, 2867, 1606, 1511, 1464, 1339,1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (2H, d, *J* = 8.4 Hz), 7.24 (1H, d, *J* = 7.2 Hz), 7.19 (2H, d, *J* = 8.0 Hz), 7.10 (1H, d, *J* = 9.2 Hz), 7.01 (3H, m), 6.50 (1H, s), 4.77 (1H, dd, *J* = 10.4, 3.2 Hz), 3.73 (4H, comp), 3.49 (1H, ddd, *J* = 15.2, 10.0, 5.6 Hz), 3.42 (3H, s), 3.27 (1H, ddd, *J* = 10.8, 9.6, 4.8 Hz), 2.96 (1H, m), 2.80 (1H, m), 2.68 (1H, dt, *J* = 15.2, 4.0 Hz), 2.30 (3H, s), 1.92 (1H, m), 1.78 (1H, m), 1.31 (3H, sep, *J* = 7.6 Hz), 1.14 (18H, d, *J* = 7.6 Hz). ^{13} C NMR (100 MHz, $CDCl_3$) δ ppm 155.5, 151.6, 145.4, 143.3, 137.0, 134.3, 131.6, 130.1, 129.4, 128.8, 127.7, 127.3, 127.2, 120.2, 120.0, 111.7, 60.5, 55.7, 51.8, 41.0, 39.0, 38.5, 27.0, 21.5, 17.9, 12.7. HRMS calculated for $C_{35}H_{48}ClNO_5SSi$ $(M+Na)^+$ 680.2603 found 680.2579.

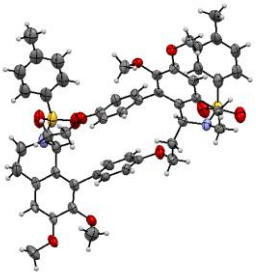
5,6-dimethoxy-1-tosyl-1,2,3,8,9,9a-hexahydrospiro[benzo[de]quinoline-7,1'-cyclohexa[2,5]dien]-4'-one ***28***. Flame dried cesium fluoride (32 mg, 0.21 mmol) in a round bottom flask, was placed in an oil bath at 100 ºC. A solution of **26** (50 mg, 0.071 mmol) in distilled *N*-methylpyrrolidone (14 mL) was cannulated under a nitrogen atmosphere into the flask containing cesium fluoride and the resulting suspension was stirred at 100 ºC for 2 h (reaction monitored by LCMS). The flask was removed from the oil bath, allowed to cool to room temperature, and transferred to a separatory funnel. Water was added (30 mL) and the mixture was extracted with toluene (4 x 30 mL). The organic fractions were combined, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified via column chromatography (SiO_2, 20% EtOAc:hexanes) to give **28** (26.2 mg, 79%) as a white solid. Crystals suitable for X-ray diffraction were grown via slow diffusion of hexanes into EtOAc. M.p. 174-175 ºC. IR (thin film) 2939, 2360, 2340, 1659, 1620, 1597, 1477, 1337, 1316. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (2H, d, *J* = 8.0 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 7.02 (1H, dd, *J* = 10.0, 3.2 Hz), 6.92 (1H, dd, *J* = 10.0, 3.2 Hz), 6.52 (1H, s), 6.32 (1H, dd, *J* = 10.0, 2.0 Hz), 6.22 (1H, dd, *J* = 10.0, 2.0 Hz), 4.50 (1H, dd, *J* = 11.6, 4.0 Hz), 3.97 (1H, dt, *J* = 13.6, 4.0 Hz), 3.76 (3H, s), 3.58 (3H, s), 3.15 (1H, ddd, *J* = 14.0, 11.6, 2.8 Hz), 2.59 (1H, dq, *J* = 12.8, 3.2 Hz), 2.48 (1H, dt, *J* = 15.6, 2.8 Hz), 2.42 (3H, s), 2.33 (1H, ddd, *J* = 15.2, 11.2, 4.0 Hz), 2.20 (1H, td, *J* = 14.0, 2.8 Hz), 1.99 (1H, m), 1.79 (1H, ddd, *J* = 14.0, 4.4, 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 186.0, 156.5, 153.5, 151.4, 143.6, 137.5, 131.4, 129.9, 129.1, 127.2, 126.4, 126.3, 124.4, 112.1, 105.0, 60.9, 55.6, 54.8, 43.7, 42.7, 35.7, 30.2, 29.3, 21.5. HRMS calculated $C_{26}H_{27}NO_5S$ $(M+H)^+$ 466.1688 found 466.1685.

Under more dilute reaction conditions the dimer **28a** (structure by X-ray) was isolated in modest yields.

4.3 Crystallography



ORTEP representation of **28** (CCDC 1055666)



ORTEP representation of dimer **28a**. (CCDC 1055667)

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There are no conflicting interests with any commercial organisations in this research.

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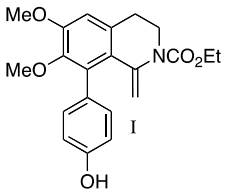
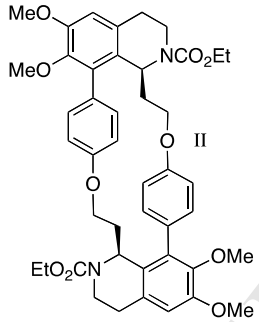
13. The alkene product from elimination of the triflate precursor has the structure **I**.



I

14. The *N*-CO_2Et derivative of **25** (as its mesylate) gave the dimer **II** (structure by X-ray) as one of the products when treated with CsF/DMF/120 °C.



II

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