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A Novel Approach to the Skeletons of the Ergot Alkaloids and Secoergolines

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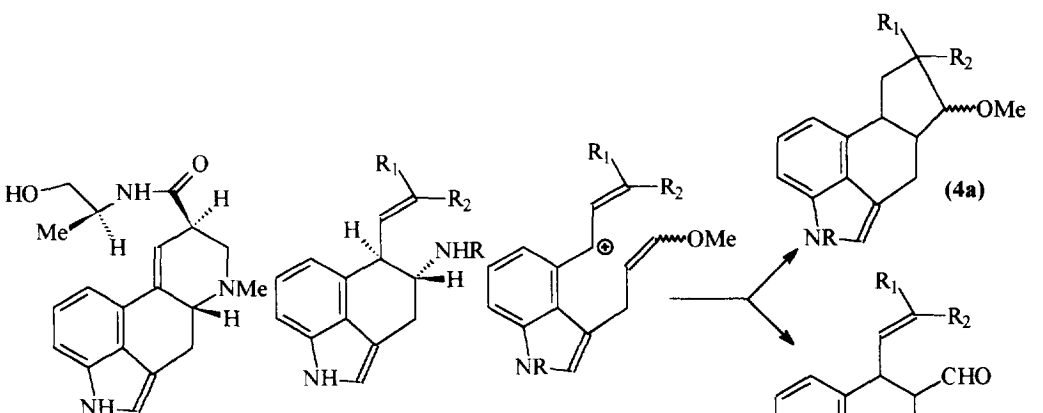
Abstract: An efficient eight-stage synthesis of N-benzenesulphonyl-3-(3'-methoxyprop-2'-en-1'-yl)-4-(1'-hydroxy-2'-trimethylsilylmethyl-prop-2'-en-1'-yl)-indoles from 4-carbomethoxyindole is described, together with the use of these benzylic alcohols for intramolecular cation-olefine cycloadditions that yield either a tetracyclic product (suitable for elaboration into ergot alkaloids) or a tricyclic product (suitable for elaboration into secoergolines) depending upon the reaction conditions.

INTRODUCTION

The ergot alkaloids from the fungus *Claviceps purpurea* were the main toxic agents responsible for the periodic outbreaks of ergotism in the Middle Ages [1], and crude extracts of the fungus were also used to 'quicken labour' from the 17th century onwards[2]. The somewhat dubious efficacy of this practice was investigated in the 20th century culminating in the discovery of the utility of ergometrine (**1**) as a vasoconstrictive agent used to stem post-partum haemorrhage[3]. The CNS activity of many of the compounds has also been evaluated and bromocriptine is an effective drug (a dopamine D2 agonist) used in the treatment of Parkinson's disease. The secoergolines, for example chanoclavine-I (**2**) are primarily of interest since they are biosynthetic intermediates *en route* to the ergot alkaloids[4], though the recent discovery that the N-propyl-analogue (**3**) (KSU-1415)[5] has potent CNS-stimulant activity (at dopaminergic neurones) provides a further incentive to synthesise this class of compounds.



(1)

(2) R_1=CH_2OH, R_2=Me, R=Me

(3) R_1=R_2=Me, R=propyl

(6)

FIG 1

A large number of partial and total syntheses of the ergot alkaloids and the secoergolines have been reported[6], but we were intrigued by the possibility of preparing the skeletons of both types of alkaloids via intermediates **(4a)** and **(4b)** produced by discrete cation-olefine cyclisations as shown in **FIG 1**. We had already demonstrated[7] that intramolecular cyclisations of the type shown were not only feasible but also practical in terms of scale and reproducibility. However, an attempt to prepare a suitable tetracyclic precursor of the ergot alkaloids using a similar reaction was unsuccessful[7]. In order to evaluate the approach shown in **FIG 1** it was necessary to devise a synthetic route to key 3,4-disubstituted indoles of general structure (**6**) which in turn were envisaged to arise from N-benzenesulphonyl-3-(3'-methoxyprop-2'-en-1'-yl)-4-formyl indole (**5**). The efficient, multigram synthesis of this latter compound from 4-carbomethoxyindole (**7**) is shown in **FIG 2**.

4-Carbomethoxyindole was prepared routinely on the 50 gram scale basically according to the literature method for 4-substituted indoles[8], which employs a reductive cyclisation of the Mannich reaction products of N,N-dimethylformamide with 1-substituted-2-methyl-3-nitrobenzenes. In our hands (and with our substrate) the reduction was very erratic with palladium on carbon, but the use of iron on silica[9] provided a method which was totally reproducible and high yielding (typically around 84% overall). The indole nitrogen was then protected by formation of the bezenesulphonyl amide (**8**) (aq. KOH, $PhSO_2Cl$ and $Bu_4N^+HSO_4^-$ in benzene) in yields of around 95%. Introduction of the requisite side-chain at C-3 was then acheived through a Heck-type reaction[10] between the 3-mercurichloride (**9**) and various allyl species. Mercuration at the 3-position of indoles is well known[11] and the formation of (**9**) was routinely accomplished on the 10 gram scale (in near quantitative yield) using mercuric acetate in in the presence of a catalytic quantity of perchloric acid, followed by addition of aqueous sodium chloride solution. The desired 3-propenyl derivative (**10**) was best prepared (and in excellent yield) using allyl bromide in conjunction with lithium tetrachloropalladate[12]

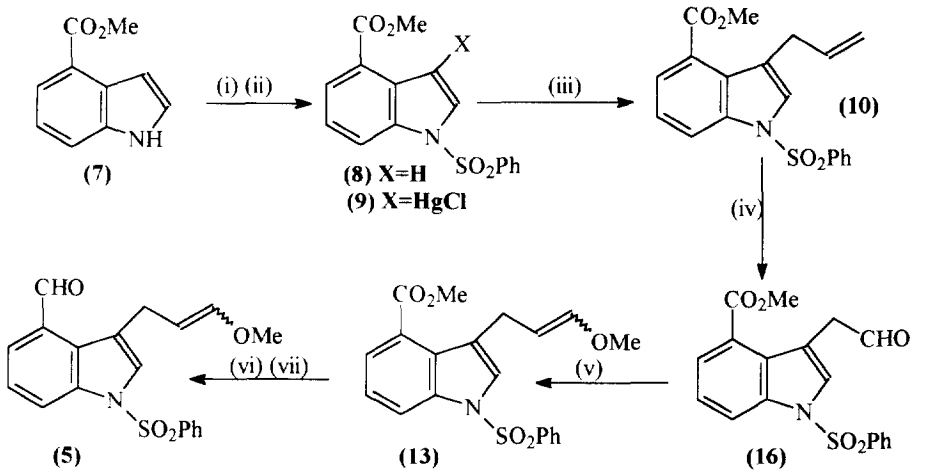


FIG 2 (i) $PhSO_2Cl$, 50% KOH, Bu_4NHSO_4, 95%; (ii) $Hg(OAc)_2$, AcOH, cat. $HClO_4$, then aq.NaCl, 99%; (iii) allyl bromide, Li_2PdCl_4, MeOH, 84%; (iv) OsO_4, NMO then $NaIO_4$, 81%; (v) $Ph_3PCHOMe.HCl$, *tert*-BuLi, 95%; (vi) Dibal-H; (vii) MnO_2, 84% overall.

A brief study was made of the scope of this palladium-catalysed reaction and a summary of the results is shown in **FIG 3**. Excellent results were obtained with acrolein and methyl acrylate in conjunction with palladium acetate, but perhaps the most intriguing result was the reaction between the 3-mercurichloride of N-benzensulphonylindole and allyl alcohol in the presence of lithium chloropalladate[13] to yield a mixture of the 3-propenylindole (60% isolated yield) and 3-formylethylindole (32%). This product mixture presumably reflects the competing reactions of dehydropalladation and dehydroxypalladation of a σ-alkyl palladium intermediate **(11)** **(FIG 3)**

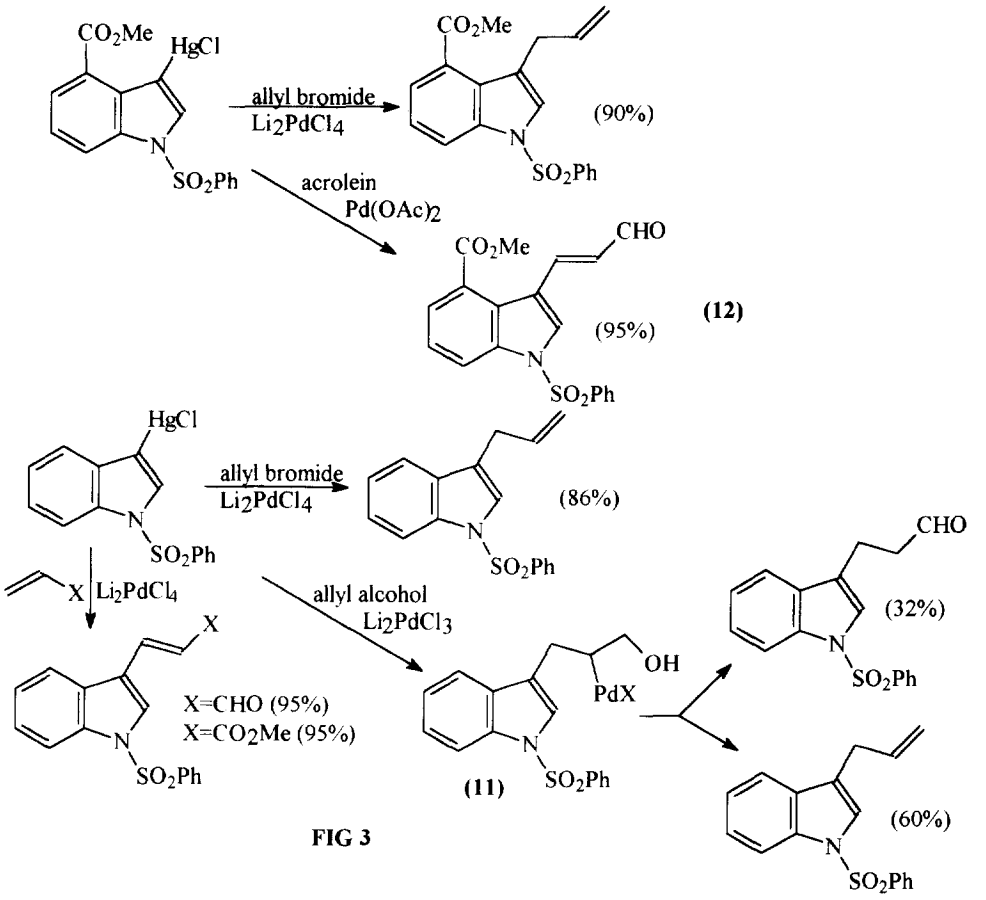
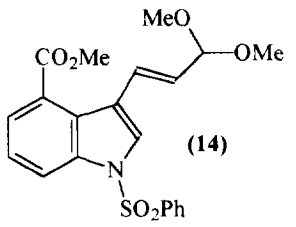
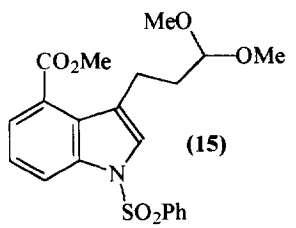


FIG 3

With quantities of aldehyde (**12**) in hand, an attempt was made to convert this directly into the desired enol ether (**13**). Reaction of (**12**) with hydroxylamine hydrochloride in conjunction with anhydrous K_2CO_3 in MeOH produced the dimethyl acetal (**14**)[14] (89% isolated yield) and hydrogenation (Pd/C in EtOAc) provided the saturated acetal (**15**) (85%). However, reaction of this with trimethylsilyl iodide in the presence of hexamethyldisilazane according to the method of Miller[15] produced at best a poor yield (ca 32%) of enol ether (**13**), and this approach was abandoned.



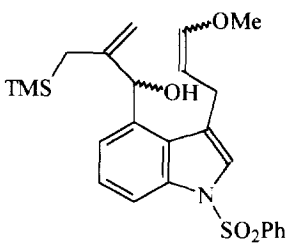
(14)



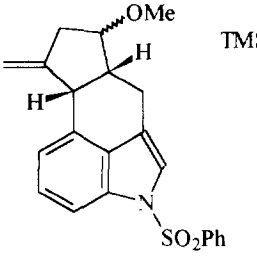
(15)

Oxidative cleavage of alkene (**10**) with osmium tetroxide in conjunction with N-methylmorpholine oxide followed by reaction of the resultant diol with sodium periodate, proceeded uneventfully and provided the desired aldehyde (**16**) in an overall yield of 81%. A Wittig reaction with methoxycarbonylmethylidene triphenylphosphorane (generated using two equivalents of *tert*-butyl lithium) yielded enol ether (**13**) (95% isolated yield). Finally, reduction of the ester group with DIBALH and oxidation of the resultant benzylic alcohol with manganese dioxide allowed obtention of the key aldehyde (**5**) (84% yield over two steps). The overall yield for this eight-step synthesis from 4-carbomethoxyindole was 48% and each stage was carried out on at least the 5 gram scale.

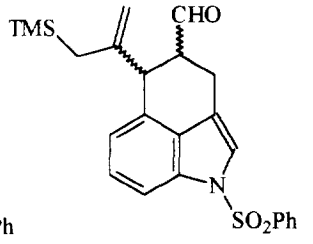
The requisite substrate (**6a**) for the cation-olefine reactions was generated by means of a Grignard reaction of compound (**5**) and 1-bromomagnesio-2-trimethylsilylmethyl-propene. This compound (isolated in 62% yield) was relatively unstable and was used for the cyclisation reactions after a rapid chromatographic purification. For the preparation of the potential tetracyclic precursor of the ergot alkaloids, (**6**) was added to a solution of $TiCl_4$ and N-methylaniline in DCM at -20° C and after one hour at this temperature, 1M HCl was added and the reaction mixture allowed to warm to room temperature. Work-up and purification provided a 56% isolated yield of two adducts (**17a** and **17b**) in a ratio of ca. 1:1[16]. Alternatively, if the temperature of the reaction was held below -20° C, a modest yield (ca 25%) of the tricyclic adduct (**18**) was obtained (together with a number of unidentified products, but none of **17a** and **17b**), and this has obvious potential as a precursor of secoergolines especially if the modified substrate (**6b**) can be prepared.



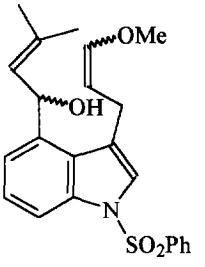
(**6a**)



(**17a**) β-OMe
(**17b**) α-OMe



(**18**)



(**6b**)

Whilst there is scope for optimisation of these cyclisation reactions, they have been carried out several times on a scale ranging from 0.1 to 0.35 gram. However, their preparative utility would be enhanced if the cyclisations were stereochemically defined, and our present efforts are directed towards the use of chiral enol ethers related to (**6a**) and to the use of chiral Lewis acids. In addition, we aim to synthesise and use compound (**6b**) for the preparation of a range of secoergolines.

Experimental section:

IR spectra were recorded using a Perkin Elmer 881 grating spectrometer, and samples were run as thin films or in solution using KBr plates. Low resolution and accurate mass data were recorded on a VG Analytical ZAB-IF mass spectrometer by the SERC mass spectrometry service at the University of Swansea. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker WM250 MHz or on a JEOL FX400 MHz spectrometer and *J* values are given in Hz. Flash chromatography was carried out using Sorbsil ^{TM} C60 silica gel (40-60 mesh). TLC was carried out using 0.25 mm film of silica gel containing a fluorescent indicator UV_{254} on plastic sheets. Melting points were determined on an Gallenkamp Electrothermal digital apparatus without correction.

8. N-benzenesulfonyl-4-carbomethoxy-indole

A mixture of the starting material **7** (4.375 g, 25 mmol), tetrabutyl ammonium hydrogen sulfate (0.815 g, 0.096 eq) and 50% potassium hydroxide (20 mL) in benzene (200 mL) was stirred vigorously for 5 minutes. A solution of benzenesulfonyl chloride (4.15 mL, 1.5 eq) in benzene (50 mL) was added dropwise to the reaction mixture which was then stirred for 1 h at room temperature. The red solution was then separated and the organic phase was washed exhaustively with water then dried with magnesium sulfate. The solvent was removed *in vacuo* giving a dark red oil. The pure compound was obtained by crystallization in absolute ethanol yielding a white solid (7.875 g, 95%) as the expected compound. M.p. = 150-151°C, (C = 61.02; H = 4.18; N = 4.41; $C_{16}H_{13}NO_4S$ requires C = 60.94; H = 4.16; N = 4.44); ν_{max} (nujol/cm^{-1}) 1725, 1287, 1173, 1108, 758; δ^{H} (400 MHz, $CDCl_3$) 8.22 [d, 1H, H_7] , 7.97 [d, 1H, H_5 , $^{3}J_{5,6} = {}^{3}J_{6,7} = 8.4$ Hz], 7.86 [cd, 2H, $H_{13} + H_{17}$], 7.70 [d, 1H, H_2] , 7.53 [t, 1H, H_{15}], 7.43 [ct, 2H, $H_{14} + H_{16}$, 7.38 to 7.34 [m, 2H, $H_3 + H_3$, $^{3}J_{13,14} = {}^{3}J_{16,17} = 7.3$ Hz]; δ^{C} (100 MHz, $CDCl_3$) C_{10} = 167.2, C_8 = 137.9, C_9 = 135.2, C_{15} = 134.0, C_{12} = 130.7, $C_{14} = C_{16}$ = 129.3, C_2 = 128.1, $C_{13} = C_{17}$ = 126.7, C_5 = 126.1, C_6 = 124.0, C_4 = 122.6, C_7 = 117.9, C_3 = 109.9, C_{11} = 52.0; Low Res. = 51, 77, 115, 143, 159, 174, 284, 315 (100%); Acc. Mass = 315.056 requires 315.0565.

9. N-benzenesulfonyl-4-carbomethoxy-3(chloromercurio)-indole

A mixture of N-benzenesulfonyl-4-carbomethoxy-indole **8** (3.15 g, 10 mmol), mercuric acetate (3.18 g, 1 eq), 70% perchloric acid (1 drop) in acetic acid (200 mL) was stirred for 24 h at room temperature. The suspension was then poured into a 10% solution of sodium chloride (1L). The resulting suspension was stirred for 5 min. The precipitate was suction filtered, washed with water and dried *in vacuo* until constant weight yielding (5.44 g, 99%) of a white solid. M.p.= 248-250°C; (Found: C = 34.88; H = 2.26; N = 2.56, $C_{16}H_{12}NO_4SHgCl$ requires C = 34.85; H = 2.20; N = 2.54); ν_{max} (nujol/cm^{-1}) 1703, 1318, 1158, 760, 733; δ^{H} (250 MHz, $CDCl_3$) 8.28 [d, 1H, H_7], 7.98 [cd, 2H, $H_{13} + H_{17}$], 7.86 [m, 2H, $H_5 + H_2$] , 7.71 [t, 1H, H_6], 7.59 [t, 2H, $H_{14} + H_{16}$.], 7.35 [t, 1H, H_{15}] , 3.93 [s, 3H, H_{11}].

10. N-benzenesulfonyl-4-carbomethoxy-3-propenylindole

A mixture of **9** (2.2 g, 4 mmol) and allyl bromide (3.46 mL, 10 eq) in methanol (100 mL) was stirred at room temperature under argon. A solution of lithium tetrachloropalladate in methanol (0.1 M, 2 mL) was added to the reaction mixture. The suspension was stirred at room temperature for 24 h. The resulting solution was filtered through a pad of Celite which was washed with methanol. The filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel with EtOAc-petrol (2:8) as eluent afforded (1.529 g, 84%) of a yellow solid as the expected compound. M.p. 102-103°C; ν_{max} (nujol/cm^{-1}) 1722, 1310, 1272, 1163, 1090, 1041, 756, 725, 687; (C = 64.19, H = 4.83, N = 3.96; $C_{19}H_{17}NO_4S$ requires C = 64.21, H = 4.83, N = 3.94); δ^H (250 MHz, $CDCl_3$) 8.19 [d, 1H, H_7], 7.84 [d, 2H, H_{13} + H_{17}], 7.63 [d, 1H, H_5], 7.52 to 7.48 [m, 2H, H_{15} + H_2], 7.41 [t, 2H, H_{14} + H_{16}], 7.30 [t, 1H, H_6], 5.95 [tt, 1H, H_{19}], 5.07 [complex d, 1H, H_{20cis}], 4.98 [complex d, 1H, $H_{20trans}$, $^3J_{19,20cis}$ = 10.2 Hz - $^3J_{19,20trans}$ = 16.8 Hz], 3.89 [s, 3H, H_{11}], 3.53 [d, 2H, H_{18}, $^3J_{18,19}$ = 6.23 Hz]; δ^C (100 MHz, $CDCl_3$) C_{10} = 167.9, C_8 = 137.8, C_{12} = 136.3, C_{19} = 135.8, C_{15} = 133.9, C_{14} = C_{16} = 129.3, C_4 = 128.0, C_{13} = C_{17} = 126.6, C_2 = 126.1, C_9 = 125.6, C_7 = 125.2, C_6 = 123.8, C_3 = 121.5, C_5 = 117.0, C_{20} = 116.3, C_{11} = 52.2, C_{18} = 31.3; Acc. Mass = 454.916 requires 455.0732.

16. N-benzenesulfonyl-3-formylmethyl-4-carbomethoxy-indole

To a solution of **10** (2.27 g, 5 mmol) and N-methylmorpholine-N-oxide (1.05 g, 1.8 eq) in a mixture of 3:1 THF / water at 0°C under nitrogen was added a solution of osmium tetraoxide (2 mL, 50 mg/mL in *t*-BuOH). The reaction was stirred 30min at this temperature and left stirring 18h at RT. Aqueous sodium metabisulfite was then added and the mixture was stirred 5min. THF was removed *in vacuo* and the residue was partitionned between EtOAc and water. After three extractions of the aqueous phase, the combined organic phases were dried with Na_2SO_4 and the solvent removed *in vacuo* after filtration. The crude diol was dissolved in a mixture of 3:1 THF/water and sodium periodate (4.28 g, 4 eq) was added. The mixture was stirred for 24 h. After completion (TLC), the THF was removed, salt was added and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed i*n vacuo* yielding 84% of a pale yellow oil. ν_{max} (DCM/cm^{-1}) 1727, 1602, 1450, 1420, 1379, 1272, 1176, 1069, 1044, 913, 759, 728, 687; (C = 60.34, H = 4.80, N = 3.50; $C_{18}H_{15}NO_5S$ requires C = 60.50, H = 4.23, N = 3.92); δ^H (400 MHz, $CDCl_3$) 9.77 [s, 1H, H_{19}], 8.21 [d, 1H, H_7], 7.87 [dd, 2H, H_{13} + H_{17}, $^3J_{13,14}$ = 7.4 Hz - $^4J_{13,15}$ = 1.5 Hz], 7.80 [d, 1H, H_5, $^3J_{5,6}$ = 7.6 Hz], 7.62 [s, 1H, H_2], 7.54 [m, 1H, H_{15}], 7.43 [t, 2H, H_{14} + H_{16}] - 7.34 [t, 1H, H_6], [s, 2H, H_{18}], [s, 3H, H_{11}]; δ^C (100 MHz, $CDCl_3$) C_{19} = 198.9, C_{10} = 167.3, C_8 = 137.6, C_9 = 136.2, C_{15} = 134.1, C_{14} = C_{16} = 129.3, C_2 = 128.1, C_{13} = C_{17} =126.7, C_5 = 126.2, C_4 = 124.7, C_6 = 124.0, C_7 = 117.6, C_3 = 114.4, C_{18} = 60.3, C_{11} = 52.2; Low Res. (CI) = 78, 94, 144, 160, 176, 190, 218, 268, 303, 333, 344, 375; Acc. Mass (CI) = 375.1015 requires 375.1015.

13. 3-(N-benzenesulfonyl-4'-carbomethoxy-ind-3'-yl)-1-methoxy-1-propene

A solution of *tert*-BuLi (2.21 mL, 1.73 M in pentane) was slowly added to a suspension of the phosphonium salt (1.43 g, 2.5 eq) in THF (dry, 80 mL) at -78°C under nitrogen.The mixture was left stirring 1h at this temperature,left warming up to room temperature and stirred for a further hour (clear red solution). To this solution was then added a solution of **16** (668 mg, 1.87 mmol) in THF (dry, 5 mL) at -78°C under nitrogen. The reaction was stirred 15 min. at this temperature and left warming up to room temperature and was stirred for a further 1h30. The reaction was quenched with a solution of saturated ammonium chloride and diluted with EtOAc. The organic phase was washed with saturated bicarbonate, brine and was dried with sodium sulfate. Purification by column chromatography with DCM as eluent afforded 684 mg of a pale orange gum as the expected compound (95% yield). ν_{max} (DCM/cm^{-1}) 3057, 2951, 1721, 1682, 1450, 1438, 1372, 1267, 1175, 1105, 1044, 705, 687; (C = 62.32, H = 5.02, N = 3.35; $C_{20}H_{19}NO_5S$ requires C = 62.32, H = 4.97, N = 3.63); δ^H (250 MHz, $CDCl_3$) 8.19 [d, 1H, H_5], 7.86 [d, 2H, H_{13} + H_{17}], 7.63 [d, 1H, H_7], 7.58 to 7.40 [m, 4H, H_2 + H_{14} + H_{15} + H_{16}] -7.32 [t, 1H, H_6], 6.35 [d, 1H, $H_{20trans}$, $^3J_{19,20trans}$ = 12.6 Hz], 6.02 [d, 1H, H_{20cis}, $^3J_{19,20cis}$ = 6.2 Hz], 4.84 [m, 1H, $H_{19trans}$], 4.52 [m, 1H, H_{19cis}], 3.91 [s, 3H, H_{11}], 3.54 [s, 3H, $H_{21trans}$], 3.61 [s, 3H, H_{21cis}], 3.51 [d, 2H, H_{18cis}] - 3.40 [d, 2H, $H_{18trans}$, $^3J_{18,19trans}$ = 6.5 Hz - $^3J_{18,19cis}$ = 6.7 Hz]; δ^C (100 MHz, $CDCl_3$) C_{10} = 168.0, $C_{20trans}$ = 148.8, C_{20cis} = 147.4, C_8 = 138.0, C_9 = 136.4, C_{15} = 133.8, C_{14} = C_{16} = 129.2, C_{13} = C_{17} = 126.6, C_2 = 125.7, C_5 = 125.0, C_6 = 123.7, C_4 = 123.6, C_3 = 123.5, C_7 = 177.0, C_{19cis} = 103.4, $C_{19trans}$ = 100.1, C_{21cis} = 59.6, $C_{21trans}$ = 56.0, C_{11} = 52.2, $C_{18trans}$ = 25.6, C_{18cis} = 22.0; Low Res. = 385, 371, 328, 315, 245, 231, 212, 188, 170, 156, 128, 77; Acc.Mass = 385.0984 requires 385.0984

5. 3-(N-benzenesulfonyl-4'-carboxaldehyde-ind-3'-yl)-1-methoxy-1-propene

DIBAL (1 M in toluene, 5.34 mL, 3 eq) was added dropwise to a solution of starting material (684 mg, 1.78 mmol) in DCM (dry, 100 mL) under nitrogen at -78°C. The reaction was completed after 45min. (TLC). 2 mL of water were added at -78°C to quench the reaction. The reaction mixture was then left warming up to room temperature. The aluminium salts were filtered through a sintered funnel. The solid residue was washed several times with DCM. The solvent was removed in vacuo and the crude colorless oil was used directly in the following reaction. The crude alcohol (99% pure) was dissolved in DCM and MnO_2 (1.55 g, 10 eq) was added. The mixture was left stirring for 48h. TLC shown only one spot of the oxidized compound. Filtration on a celite pad afforded 467 mg of the nearly pure compound (overall yield for reduction-oxidation: 81%) as a pale yellow oil. ν_{max} (DCM/cm^{-1}) 1687, 1658, 1651, 1450, 1379, 1250, 1186, 756, 725, 688; (C = 64.24, H = 5.11, N = 3.17, $C_{19}H_{17}NO_4S$ requires C = 64.21, H = 4.82, N = 3.94), δ^H (400 MHz, $CDCl_3$) 10.51 [s, 1H, H_{10cis}], 10.44 [s, 1H, $H_{10trans}$], 8.26 [d, 1H, H_{5trans}], 8.24 [d, 1H, H_{5cis}], 7.85 [2d, 2H, H_{13} + H_{17}], 7.95 to 7.12 [m, 5H, H_2 + H_7 + H_{14} + H_{15} + H_{16}], 6.34 [d, 1H, $H_{20trans}$], 6.07 [d, 1H, H_{20cis}], 4.93 [m, 1H, $H_{19trans}$], 4.52 [m, 1H, H_{19cis},

$^3J_{19,20trans}$ = 12.7 Hz - $^3J_{19,20cis}$ = 6.1 Hz], 3.66 [s, 3H, H_{21cis}], 3.66 [d, 2H, H_{18cis}], 3.56 [s, 3H, $H_{21trans}$], 3.56 [d, 2H, $H_{18trans}$]; Acc.Mass (CI) = 373.1222 requires 373.1222

12. 3-(N-benzenesulfonyl-4'-carbomethoxy-ind-3'yl)-acrolein

Palladium acetate (0.449 g, 1 eq) was added to a solution of starting material **9** (1.1 g, 2 mmol) and acrolein (1.4 mL, 10 eq) in dry acetonitrile (30 mL) under nitrogen at 0°C. The reaction mixture was left stirring at room temperature overnight. The mixture was then filtered through a silica pad which was washed several times with ethyl acetate. The solvent was removed *in vacuo* giving a bright yellow solid. Purification by column chromatography with DCM as eluent afforded the pure compound as a pale yellow solid (95% yield). M.p.= 172-173°C; (C = 61.81; H = 4.09; N = 3.76; $C_{19}H_{15}NO_5S$ requires C = 61.78; H = 4.09; N = 3.79); ν_{max} (nujol/cm^{-1}) 1726, 1681, 1258, 1158, 1019, 867, 765, 725, 671; δ^H (250 MHz, $CDCl_3$) 9.71 [d, 1H, H_{20}], 8.20 [dd, 2H, H_7 + H_{18}], 8.07 [s, 1H, H_2], 7.91 [2d, 3H, H_5 + H_{13} +H_{17}], 7.61 [m,1H, H_{15}], 7.50 [m, 2H, H_{14} +H_{16}] - 7.42 [t, 1H, H_6], 6.57 [dd, 1H, H_{19}], 3.93 [s, 3H, H_{11}, $^3J_{19,20}$ = 7.87 Hz - $^3J_{18,19}$ = 7.98 Hz]; δ^C (100 MHz, $CDCl_3$) C_{20} = 193.5, C_{10} = 167.1, C_{18} = 146.2, C_8 = 137.4, C_9 = 136.2, C_{15} = 134.5, C_{14} = C_{16} = 129.6, C_{19} = 128.6, C_2 = 127.5, C_5 = 127.0, C_{13} = C_{17} = 126.9, C_6 = 124.7, C_3 = 118.8, C_7 = 117.7, C_{11} = 52.3; Low Res. = 75, 86, 99, 125, 154, 210, 279, 325, 341, 355, 369

14. 3-(N-benzenesulfonyl-4'-carbomethoxy-ind-3'-yl)-acrolein dimethylacetal

To a mixture of starting material **12** (800 mg, 2.16 mmol) and hydroxylamine hydrochloride (304 mg, 2 eq) in methanol (50 mL), was added (232 mg, 1 eq) of anhydrous sodium carbonate at 0-5°C. After stirring for 1h30, the reaction was completed (TLC) and the solvent is removed in vacuo. The crude white solid was purified by column chromatography with petrol-EtOAc (9:1)as eluent affording 93% of the pure compound as a pale orange oil. ν_{max} (DCM/cm^{-1}) 3424, 2991, 2832, 1724, 1602, 1444, 1420, 1376, 1269, 1179, 1046, 971, 911, 734, 705, 686; δ^H (250 MHz, $CDCl_3$) 8.20 [dd, 1H, H_7, $^3J_{5,6}$ = 8.4 Hz - $^4J_{5,7}$ = 1.1 Hz], 7.87 [cd, 2H, H_{13} + H_{17}, $^3J_{13,14}$ = 6.9 Hz] 7.80 [s, 1H, H_2], 7.73 [dd, 1H, H_5], 7.55 to 7.27 [m, 4H, H_6 + H_{14} + H_{15} + H_{16}], 7.04 [dt, 1H, H_{18}, $^3J_{18,19}$ = 15.9 Hz - $^4J_{18,20}$ = 1.1 Hz], 5.95 [dd, 1H, H_{19}, $^3J_{19,20}$ = 5.0 Hz], 4.96 [dd, 1H, H_{20}], 3.92 [s, 3H, H_{11}], 3.41 [s, 6H, H_{21}]; δ^C (100 MHz, $CDCl_3$) C_{10} = 167.6, C_8 = 137.7, C_9 = 135.9, C_{15} = 134.2, C_{14} = C_{16} = 129.4, C_{13} = C_{17} = 126.8, C_{19} = 126.5, C_{18} = 126.4, C_5 = 125.9, C_2 = 125.1, C_6 = 124.2, C_4 = 120.8, C_7 = 117.2, C_{20} = 102.8, C_{21} = 52.9, C_{11} = 52.1

15. 3-(N-benzenesulfonyl-4'-carbomethoxy-ind-3'-yl)-propanal dimethylacetal

10% palladium on charcoal (17 mg, cat.) was added to a solution of starting material **14** (250 mg, 0.6 mmol) in ethyl acetate. The reaction flask was purged three times with hydrogen and left under a hydrogen

atmosphere for 18h. After completion, the reaction flask was degassed to eliminate all the hydrogen and then the reaction mixture was filtered through a silica pad. The pad was rinsed thoroughly with ethyl acetate and the solvent of the combined fractions was removed *in vacuo* giving 212 mg of the crude (99% pure) compound as a pale yellow oil. ν_{max} (DCM/cm^{-1}) 3431, 2951, 1725, 1653, 1601, 1446, 1374, 1285, 1176, 1091, 757, 729, 686; (C = 60.39, H = 5.32, N = 3.62; $C_{21}H_{23}NO_6S$ requires C = 60.42, H = 5.55, N = 3.36); δ^H (400 MHz, $CDCl_3$) 8.19 [d, 1H, H_7, $^3J_{5,6}$ = 8.3 Hz], 7.84 [d, 2H, H_{13} + H_{17}], 7.63 [d, 1H, H_5], 7.54 to 7.27 [m, 5H, H_2 + H_6 + H_{14} + H_{15} + H_{16}], 4.36 [t, 1H, H_{20}, $^3J_{19,20}$ = 5.7 Hz], 3.92 [s, 3H, H_{11}], 3.32 [s, 6H, H_{21}], 2.84 [t, 2H, H_{18}, $^3J_{18,19}$ = 7.18 Hz], 1.86 [dt, 2H, H_{19}]; δ^C (100 MHz, $CDCl_3$) C_{10} = 167.9, C_8 = 137.7, C_9 = 136.2, C_{15} = 133.8, C_{14} = C_{16} = 129.2, C_{12} = 128.0, C_{13} = C_{17} = 126.5, C_2= 125.3, C_5 = 125.2, C_6 = 127.3, C_4 = 122.7, C_7 = 116.9, C_{20} = 103.8, C_{21} = 52.7, C_{11} = 52.1, C_{19} = 32.1, C_{18} = 22.2; Low. res.= 417, 385, 354, 328, 276, 244, 212, 188, 75; Acc. Mass = 417.1246 requires 417.1246.

6a. N-Benzenesulfonyl, 3-(3'-methoxyprop-2'-enyl)-4-(1'-hydroxy-2'-trimethylsilyl-prop-2'-enyl)-indole

Magnesium turnings (55 mg, 20 eq) were stirred overnight with a crystal of iodine under argon. Then a solution of 2-bromoallylsilane (0.38 mL, 1.8 eq) in dry THF (3 mL) was slowly added to the activated magnesium. When the Grignard reagent started to form, 2 ml of dry THF were added. The reaction was left stirring at room temperature for 2h. Then 1.5 mL of the Grignard solution were transfered to an other flask to which was added a solution of the aldehyde (100 mg, 0.28 mmol) in 4 mL dry THF. The reaction was left stirring at room temperature for a further 3h. A saturated aqueous solution of ammonium chloride was added to the reaction mixture and the aqueous phase was extracted with ether. The combined organic phases were dried with anhydrous sodium sulfate and the solvent was removed *in vacuo*. Purification was achieved by a quick filtration on silica gel with ether-petrol (1:1) as eluent. This gave 82 mg of a pale yellow oil (62%) as the expected compound. ν_{max} (nujol/cm^{-1}) 1733, 1298, 1162, 1150, 1185, 1177, 1140, 1091, 1047, 850, 742, 720, 684; δ^H (400 MHz, $CDCl_3$) 7.98 to 7.79 [m, 3H, H_7 + H_{15} + H_{19}], 7.54 to 7.28 [m, 6H, H_5 + H_6 + H_{16} + H_{17} + H_{18} + H_2], 6.32 [d, 1H, $H_{23trans}$, $^3J_{22,23trans}$ = 12.6 Hz], 6.13 [d, 1H, H_{23cis}, $^3J_{22,23cis}$ = 5.8 Hz - $^3J_{10,25cis}$ = 5.3 Hz - 5.65 [d, 1H, H_{10cis}], 5.59 [d,1H, $H_{10trans}$, $^3J_{10,25trans}$= 4.5 Hz], 5.11 [s, 1H, H_{12a}], 4.99 [qt, 1H, $H_{22trans}$], 4.93 [s, 1H, H_{12b}], 4.66 [q, 1H, H_{22cis}], 3.60 [s, 3H, H_{24cis}], 3.56 [s, 3H, $H_{24trans}$], 2.08 [d, 1H, H_{25cis}], 2.00 [d, 1H, $H_{25trans}$], 1.62 [d, 1H, H_{13a}], 1.17 [d, 1H, H_{13b}, $^2J_{13a,b}$ = 14.2 Hz]; δ^C (100 MHz, $CDCl_3$) C_{23} = 149.1, C_{11} = 147.8, C_8 = 137.2, C_9 = 134.8, C_{18} = 133.7, C_{17} = C_{19} = 129.1, C_{16} = C_{20} = 126.7, C_2 = 1214.6, C_5 = 124.3, C_{15} = 124.1, C_4 = 123.1, C_6 = 122.1, C_7 = 113.6, C_{12} = 108.8, C_3 = 103.1, C_{22} = 99.8, C_{10} = 73.3, C_{24} = 56.2, C_{21} = 25.6, C_{13} = 23.9, C_{14} = -1.3.

17a, 17b. CYCLOADDUCT

N-methyl aniline (2 eq) was added to a solution of $TiCl_4$ (1M in DCM, 1.8 eq) at 0°C under argon. The solution was left stirring for 30 min. To this mixture was added a solution of the precursor (84 mg, 0.22 mmol) in 4 mL dry DCM at -20°C. After 1 h, ether and HCl 1M were added to the reaction mixture at -20°C. The mixture was then left warming up to room temperature. The ether phase was separated and the aqueous phase wasextracted with DCM. The combined organic phases were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by chromatography on silica gel with ether-pentane (1:1) as eluent gave the expected compound in 56% yield as an epimeric mixture. ν_{max} (DCM/cm^{-1}) 2933, 2254, 1451, 1434, 1377, 1363, 1180, 1114, 1092; (C = 69.74, H = 5.65, N = 3.50, $C_{22}H_{21}NO_3S$ requires C = 69.63, H = 5.58, N = 3.69); δ^H (400 MHz, $CDCl_3$) 7.90 to 7.84 [m, 2H, H_{19} + H_{23}], 7.78 to 7.74 [m, 1H, H_{13}], 7.53 to 7.45 [m, 1H, H_{21}], 7.44 to 7.37 [m, 3H, H_{20} + H_{22} + $H_{11}{}^B$], 7.31 to 7.24 [m, 1H, H_{12}], 7.19 [s, 1H, H_2], 7.11 [d, 1H, $H_{11}{}^A$], 5.47 [cd, 1H, $H_{16\alpha}{}^b$], 5.10 [cd, 1H, $H_{16\beta}{}^b$, $^2J_{16\alpha,\beta}{}^b$ = 2.56 Hz], 4.95 [d, 1H, $H_{16\alpha}{}^a$], 4.81 [d, 1H, $H_{16\beta}{}^a$], $^2J_{16\alpha,\beta}{}^b$ = 1.84 Hz], 3.91 [bd d, 1H, $H_9{}^A$], 3.67 [m, 1H, $H_6{}^B$], 3.52 [m, 1H, $H_6{}^A$], 3.48 [bd d, 1H, $H_9{}^B$], 3.41 [s, 3H, $H_{17}{}^B$] - 3.29 [s, 3H, $H_{17}{}^A$], 3.23 [dd, 1H, $H_{4\alpha}{}^B$], 3.01 [dd, 1H, $H_{7\alpha}{}^B$], 2.78 [m, 1H, $H_{4\alpha}{}^A$], 2.73 [m, 1H, $H_{7\alpha}{}^A$], 2.57 [m, 1H, $H_5{}^A$], 2.48 [m, 1H, $H_{4\beta}{}^B$], 2.46 [m, 1H, $H_{4\beta}{}^A$], 2.42 [m, 1H, $H_{7\beta}{}^A$], 2.38 [m, 1H, $H_{7\beta}{}^B$], 2.10 [m, 1H, $H_5{}^B$]; δ^C (100 MHz, $CDCl_3$) C_8 = 149.9, C_{14} = 146.0, C_{15} = 138.5, C_{21} = 133.6, C_{18} = 130.8, C_{20} = C_{22} = 129.2, C_{10} = 128.7, C_{19} = C_{23} = 126.7, C_{12} = 125.4, $C_{11}{}^A$ = 121.7, C_3 = 120.8, C_2 = 119.6, $C_{11}{}^B$ = 118.2, C_{13} = 111.5, $C_{16}{}^A$ = 109.0, $C_{16}{}^B$ = 108.0, $C_6{}^A$ = 83.4, $C_6{}^B$ = 82.2, $C_{17}{}^B$ = 57.6, $C_{17}{}^A$ = 56.7, $C_5{}^B$ = 50.8, $C_9{}^B$ = 45.5, $C_9{}^A$ = 44.8, $C_5{}^A$ = 44.1, $C_7{}^B$ = 39.6, $C_7{}^A$ = 36.6, $C_4{}^B$ = 26.1, $C_4{}^A$ = 21.1; Low Res (CI) = 397, 380, 302, 268, 240, 232, 215, 177, 160, 125, 108, 91 78; Acc. Mass (CI) = 397.1586 requires 397.1586.

18. Intermediate from cyclization reaction

The procedure is the same as for the preparation of compound **17** except that the temperature was held at -40°. This was the main product in this reaction (≈ 25%) among three other fractions that were separated but could not be identified. δ^H (400 MHz, $CDCl_3$) 9.40 [s, 1H, H_6], 7.74 to 7.63 [m, 3H, H_{19} + H_{23} + H_{13}], 7.39 to 7.05 [m, 6H, H_2 + H_{14} + H_{15} + H_{20} + H_{21} + H_{22}], 4.63 [s, 1H, $H_{9\alpha}$], 3.84 [s, 1H, $H_{9\beta}$], 3.80 [d, 1H, H_7, $^3J_{5,6}$ < 1 Hz], 2.99 [d, 1H, $H_{4\alpha}$ $^2J_{4\alpha\beta}$ = 16 Hz], 2.84 to 2.80 [m, 2H, H_5 + $H_{4\beta}$], 1.59 [d, 1H, $H_{10\alpha}$], 1.43 [d, 1H, $H_{10\beta}$] - $^2J_{10\alpha\beta}$ = 14 Hz], δ^C (100 MHz, $CDCl_3$) C_6 = 204.3, C_8 = 148.2, C_{16} = 139.5, C_{21} = 134.6, C_{17} = 132.2, C_{20} = C_{22} = 130.3, C_{19} = C_{23} = 127.8, C_{14} = 126.8, C_{13} = 122.8, C_2 = 121.4, C_3 = 119.2, C_9 = 113.5, C_{15} = 112.8, C_7 = 50.6, C_5 = 46.7, C_{10} = 26.8, C_4 = 20.1, C_{11} = 0.1, Acc. Mass ($H^{(+)}$) = 438.1559 requires 438.1559, (CI) = 455.1825 requires 455.1825.

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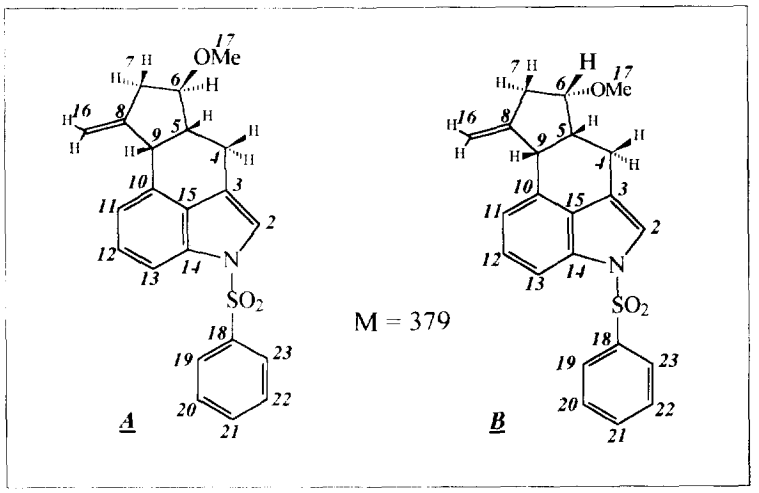
16. Although these compounds could not be separated, discrete signals were observed for each of the hydrogens of both molecules (see experimental section) probably reflecting their discrete conformations.



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