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A Stereoselective Synthesis of 3-Substituted Hexahydroindeno[2,1-b]pyrroles via an Intramolecular Azomethine Ylide Cycloaddition

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Abstract: 3-Substituted hexahydroindeno[2,1-b]pyrroles were prepared in a stereoselective manner in high yield *via* an intramolecular azomethine ylide cycloaddition. Olefin geometry in the ylide precursor controlled the stereochemistry at the 3-position. © 1998 Elsevier Science Ltd. All rights reserved.

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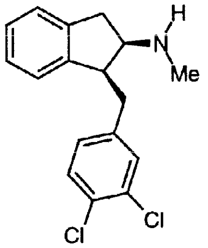
Aminoindanes have proven to be useful pharmacophores within medicinal chemistry, being present in a number of drug substances.[1,2] Out of a programme directed towards discovering new neuronal calcium antagonists, the substituted benzyl-2-aminoindane **1** was identified as a lead compound. In order to probe conformational preferences of the 3,4-dichlorobenzyl moiety we targeted the conformationally restrained hexahydro[2,1-b]indenopyrrole compounds **2** and **3** in which the conformation of the benzyl moiety is fixed in two distinct orientations.



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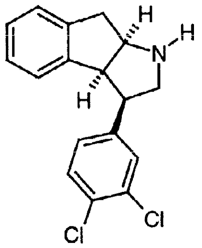

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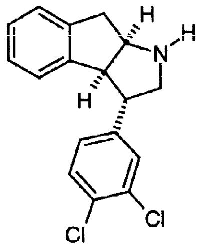

3

Our retro-synthetic analysis (Scheme 1) centred around a key intramolecular azomethine ylide cyclisation[3] in which olefin geometry could be used to control the relative stereochemistry of the dichlorophenyl moiety.[4]

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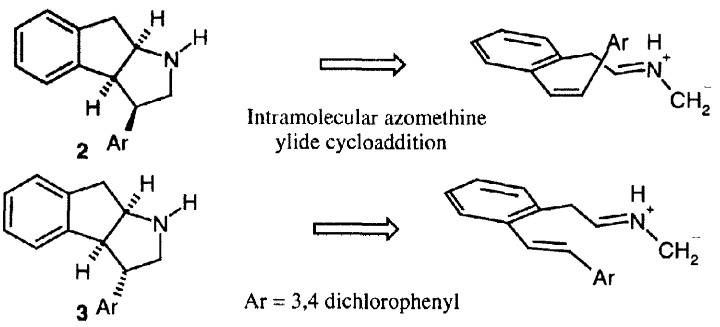
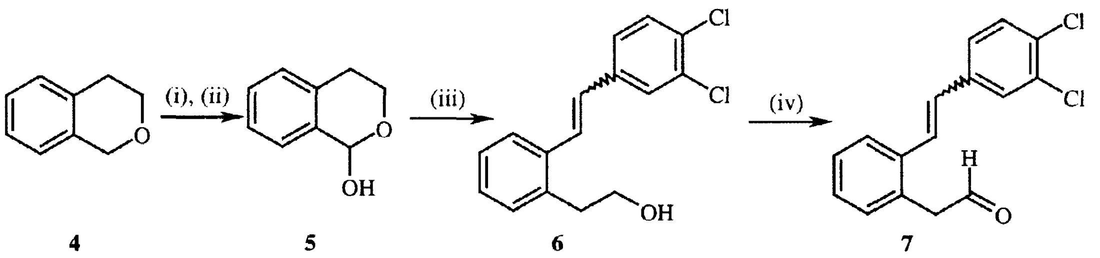


Scheme 1

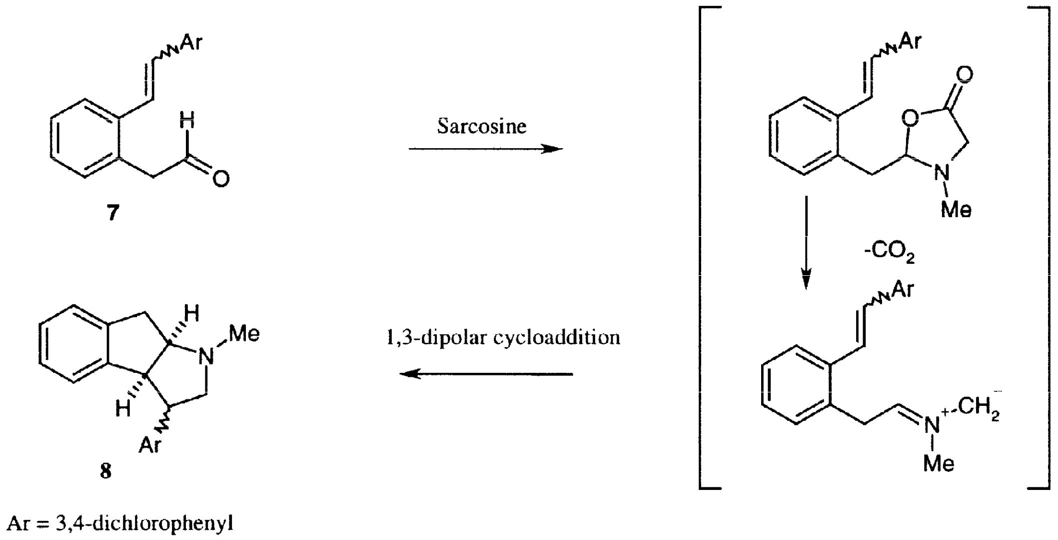
We envisaged that the required azomethine ylides could be generated *in situ* by reaction of the corresponding phenyl acetaldehyde with an amino acid such as glycine using a method similar to that employed by Joucla and Mortier.[5] The phenylacetaldehyde derivative appeared to be accessible *via* Wittig chemistry. Accordingly, lactol **5** was conveniently obtained by electrochemical oxidation of isochroman **4** in methanol followed by acid hydrolysis of the intermediate methyl acetal.[6] Treatment of this lactol with the triphenylphosphonium ylide derived from 3,4-dichlorobenzyl chloride under classical Wittig conditions afforded **6** as a 50:50 mixture of *E* and *Z* isomers (see Scheme 2). We decided to proceed with initial studies using this *E/Z* mixture of isomers in order to establish the viability of the intramolecular azomethine ylide cycloaddition.



Conditions : (i) MeOH, e$^-$, (70%), (ii) dil. HCl, THF (76%), (iii) n-BuLi, THF, 3,4-dichlorobenzyltriphenylphosphonium chloride (96%), (iv) Swern oxidation (27-40%)

Scheme 2

Oxidation of the primary alcohol to the corresponding aldehyde was carried out using Swern[7] conditions in modest yield (27-40%). Treatment of aldehyde **7** with glycine under Dean-Stark conditions failed to give any of the desired cycloadducts. We reasoned that the failure of this reaction may be due the presence of the acidic proton on the amine nitrogen which could render the closure of the carboxylic acid onto the imine reversible and hence prevent formation of the 1,3-dipole. In order to test this hypothesis we substituted glycine with the more widely used sarcosine (N-Me glycine)[8] as shown in Scheme 3.

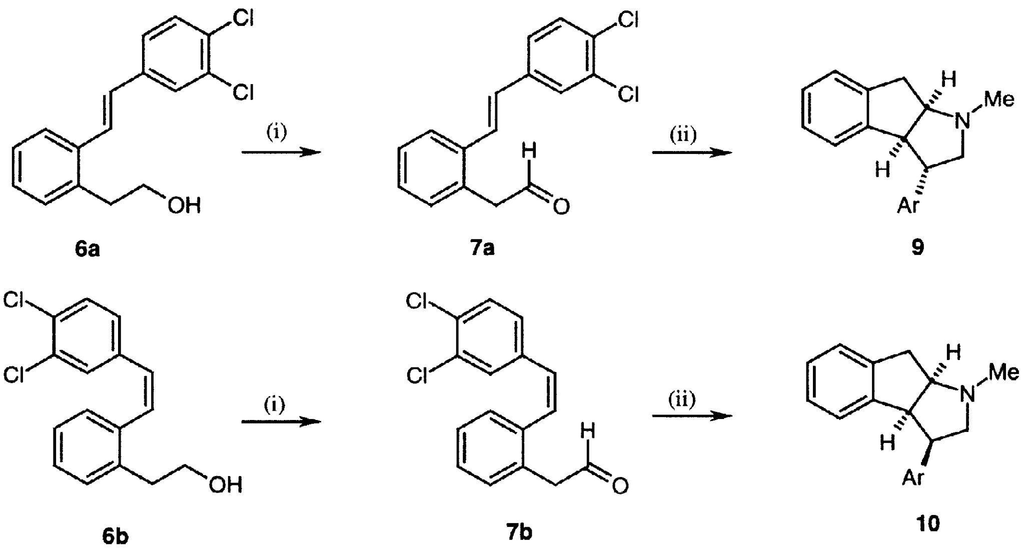


Scheme 3

Thus reacting aldehyde **7** with sarcosine under identical Dean-Stark conditions as before afforded the desired cycloadducts **8** in 70% yield as a 1:1 mixture of diastereomers. In order to demonstrate that alkene geometry would control the relative stereochemistry of the aryl substituent we required access to the individual *E* and *Z* isomers of aldehyde **7**. Altering the conditions of the Wittig coupling did not substantially shift the *E/Z* ratio away from 50:50 although it did prove possible to separate the *E/Z* isomers cleanly *via* preparative HPLC using a Dynamax60-A silica column and eluting with 2% *iso*-propanol in hexanes.

With the two pure alkenes in hand improvements to the Swern oxidation were sought. Pfitzner-Moffatt[9] conditions afforded the desired aldehydes **7a** and **7b** in high yield but it proved difficult to remove residual DCU at the end of the reaction. SO_3/pyridine[10] proved to be the reagent system of choice giving superior yields to the Swern oxidation with none of the purification problems associated with the use of DCC.

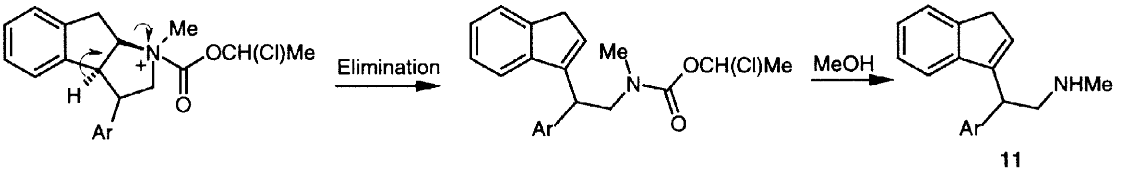
Repeating the azomethine ylide cycloaddition on the individual geometrical isomers **7a** and **7b**, afforded the desired cycloadducts **9** and **10** in yields of 73% and 81% respectively (Scheme 4). Assignment of the relative stereochemistry of the dichlorophenyl moiety was made by analogy with the uncyclised compound **1** in which a pronounced edge to face aromatic-aromatic interaction is observed in both ^1H and nOe difference nmr experiments. As expected, this effect was clearly visible in the cycloadduct **10** (shielded aromatic proton observed at δ 6.17) but not in **9** where such an aromatic-aromatic interaction is not possible due to the constraint of the pyrrolidine ring.



Conditions: (i) SO_3/ pyridine, (ii) Sarcosine, toluene

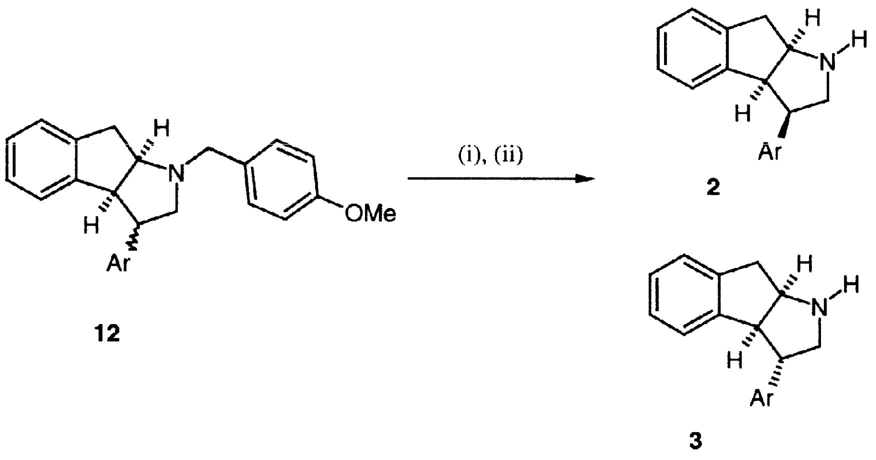
Scheme 4

Our final targets were in fact the N-H compounds **2** and **3** and accordingly cycloadducts **9** and **10** were treated with 1-chloroethyl chloroformate (ACE-Cl) in dichloromethane at reflux followed by heating in methanol at reflux in an attempt to effect N-demethylation.[11] The product from these reactions was **11** in each case, clearly arising due to a *trans* elimination as shown in Scheme 5.



Scheme 5

This problem was finally circumvented by carrying out the azomethine ylide cyclisation on **7** with 4-methoxybenzylglycine in 47% yield. Treatment of these N-benzyl analogues **12** with ACE-Cl at 0°C in the presence of Proton Sponge™ followed by methanol at reflux afforded the desired targets **2** and **3** which were readily separated via column chromatography.



Conditions: (i) ACE-Cl, Proton Sponge™, 0°C (ii) MeOH, reflux

Scheme 6

Experimental

Melting points were obtained on a Cambridge Instruments Galen III hot stage apparatus. Flash Chromatography[12] was carried out on Merck grade 60 silica gel (230-400 mesh) and reactions were monitored by TLC on Merck 60F-254 precoated silica gel on glass sheets. ^1H and ^{13}C nmr spectra were determined on a Bruker AC-250 or a Jeol GX-270 spectrometer. Chemical shifts are given in ppm relative to the residual non-deuterated solvent peak and J values are given in Hz. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR machine. Mass spectra (EI or CI) were recorded on a 7070E VG mass spectrometer and elemental analyses were carried out by the SmithKline Beecham Analytical Sciences Department. Commercially available anhydrous solvents (Aldrich) were used without further purification.

1-Methoxyisochroman[13]

Isochroman (13.4g, 100mmol) and tetrabutylammonium tetrafluoraborate (3.29g, 10mmol) were dissolved in methanol (100ml). Argon was slowly bubbled through this solution while two graphite electrodes were immersed into the solution. The system was then electrolysed for 26h at a current of 0.08A. The yellow solution was then concentrated *in vacuo* and the residue partioned between diethyl ether and water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was quickly passed down a short column of neutral alumina eluting with 20% diethyl ether in hexanes to afford the title compound (11.21g, 68%) as a yellow oil; ^1H NMR (250MHz, $CDCl_3$) 2.62 (1H, m), 3.05 (1H, m), 3.55 (3H, s), 3.92 (1H, ddd, J = 1, 6, 9 Hz), 4.14 (1H, m), 5.46 (1H, s), 7.13 (1H, m), 7.24 (3H, m).

Isochroman-1-ol (5)[6]

To a solution of 1-methoxyisochroman (11.0g, 67mmol) in THF (250ml) was added water (10ml) and 5N HCl (30ml). The solution was stirred at room temperature for 20 minutes then poured into saturated aq. sodium bicarbonate (400ml) and extracted with diethyl ether (3x100ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*. The resultant residue was purified by column chromatography on silica gel eluting with 30% ether in hexanes to afford the title compound **5** (6.88g, 68%) as white solid m.p. 69-72^{o}C; ^{1}H NMR (250MHz, $CDCl_3$) δ: 2.66 (1H, dd, J = 16, 3Hz), 2.98 (1H, m), 3.60 (1H, br. s), 3.98 (1H, m), 4.22 (1H, m), 5.95 (1H, s), 7.25 (4H, m).

_E_-2-[2-(2-(3,4-Dichlorophenyl)vinyl)phenyl]ethanol (6a) and Z-2-[2-(2-(3,4-dichlorophenyl) vinyl)phenyl]ethanol (6b)

To a suspension of 3,4-dichlorobenzyltriphenylphosphonium chloride (28.36g, 62mmol) in dry THF (300ml) at 0°C under an atmosphere of argon was added n-butyllithium (39ml of a 1.6M solution in hexanes, 62mmol) dropwise. After 10 minutes a solution of isochroman-1-ol (4.71g, 31.4mmol) in dry THF (30ml) was added in one portion and the orange mixture was allowed to stir overnight at room temperature. The reaction mixture was then poured into water (1L) and extracted in diethyl ether (3x150ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with 30% diethyl ether in 60-80° petrol. Combination of appropriate fractions gave **6** as a colourless oil (8.92g, 97%). The geometric isomers were separated by preparative HPLC on a Dynamax60-A silica column eluting with 2% isopropanol in hexanes;^{1}H NMR (250MHz, $CDCl_3$) (*E*-isomer) δ: 1.43 (1H, t, J = 7 Hz), 3.07 (2H, t, J = 7 Hz), 3.88 (2H, q, J = 7 Hz), 6.90 (1H, d, J = 17 Hz), 7.23 - 7.46 (6H, m), 7.60 (2H, m); IR (neat) 3350, 3055, 2922, 1481, 1469, 1264, 1132, 1042, 736 cm^{-1} ; HRMS calcd. for $C_{16}H_{14}OCl_2$ 292.042171, found 292.043466;

^{1}H NMR (250MHz, $CDCl_3$) (Z-isomer) δ: 1.48 (1H, br s), 2.89 (2H, t, J = 7 Hz), 3.83 (2H, m), 6.51 (1H, d, J = 12 Hz), 6.85 (2H, m), 7.20 (6H, m); IR (neat) 3350, 3054, 2922, 1467, 1132, 1043, 761 cm^{-1}; HRMS calcd. for $C_{16}H_{14}OCl_2$ 292.042171, found 292.042606.

_E_-2-[2-(2-(3,4-Dichlorophenyl)vinyl)phenyl]acetaldehyde (7a)

To a solution of *E*-2[2-(2-(3,4-dichlorophenyl)vinyl)phenyl]ethanol (950mg, 3.2mmol) and triethylamine (4.45ml, 32mmol) in dry dimethyl sulfoxide (15ml) under argon was added a solution of sulfur trioxide-pyridine complex in DMSO (15ml). After 45 minutes the reaction mixture was acidified with 1N HCl then poured into water (250ml) and extracted with diethyl ether (3x50ml). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with 20% diethyl ether in 60-80° petrol to afford **7a** as a low melting point off white waxy solid (598mg, 63%); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.86 (2H, d, J = 3 Hz), 6.85 (1H, d, J = 17 Hz), 7.12 - 7.68 (8H, m), 9.73 (1H, t, J = 3 Hz); ^{13}C NMR (68MHz, $CDCl_3$) 48.6, 125.6, 126.4, 127.3, 128.3, 128.6, 129.3, 129.9, 130.6, 131.2, 131.5, 132.8, 136.7, 137.2, 198.8; IR (neat) 3063, 2922, 1722, 1481, 1469, 1132, 1028, 961, 754 cm^{-1}; HRMS calcd. for $C_{16}H_{12}OCl_2$ 290.026521, found 290.027498.

_Z_-2-[2-(2-(3,4-Dichlorophenyl)vinyl)phenyl]acetaldehyde (7b)

To a solution of Z-2-[2-(2-(3,4-dichlorophenyl)vinyl)phenyl]ethanol (890mg, 3mmol) and triethylamine (4.2ml, 30mmol) in dry dimethyl sulfoxide (15ml) under argon was added a solution of sulfur trioxide-pyridine complex (1.43g, 9mmol) in DMSO (15ml). After 45 min the reaction mixture was acidified with 1N HCl then poured into water (250ml) and extracted with diethyl ether (3x50ml). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with 20% diethyl ether in 60-80° petrol to afford **7b** as a yellow oil (445mg, 50%); ^{1}H NMR (250MHz, $CDCl_3$) δ: 3.68 (2H, d, J = 3 Hz), 6.48 (1H, d, J = 12 Hz), 6.68 (1H, d, 12 Hz), 6.90 (1H, dd, J = 8, 3 Hz), 7.21 (6H, m), 9.67 (1H, d, J = 3 Hz); IR (neat) 3063, 2922, 1722, 1467, 1132, 1028, 760 cm^{-1}; HRMS calcd. for $C_{16}H_{12}OCl_2$ 290.026521, found 290.027427.

(3*RS*, 3a*RS*, 8a*SR*)-1-Methyl-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (9)
A mixture of *E*-2-[2-(2-(3,4-dichlorophenyl)-vinyl)-phenyl]acetaldehyde (600mg, 2mmol) and sarcosine (356mg, 4mmol) in toluene (25ml) was heated at reflux over night under argon using a Dean-Stark trap. On cooling, the toluene was removed *in vacuo* and the residue subjected to column chromatography on silica gel eluting with 4% ethanol in chloroform to afford **9** as a white solid (530mg, 81%) which was converted to the HCl salt and crystallised as a white solid m.p. 246 - 249°C dec. (from methanol-diethyl ether); ^{1}H NMR (free base, 270 MHz, $CDCl_3$) δ: 2.44 (3H, s), 2.45 (1H, m), 3.03 (2H, m), 3.30 (3H, m), 3.76 (1H, m), 7.07 - 7.27 (5H, m), 7.45 (2H, m); ^{13}C NMR (68MHz, $CDCl_3$) δ: 36.9, 40.2, 51.7, 58.3, 66.0, 70.7, 123.8, 125.4, 126.9, 127.0, 127.2, 129.7, 130.4, 130.5, 132.5, 141.1, 144.0, 145.9.; IR ($CHCl_3$) 3000, 2950, 2840, 1472, 1132, 754 cm^{-1}; MS: m/z (EI$^+$) 317 M$^+$;$C_{18}H_{17}NCl_2$.HCl requires C 60.95, H 5.12, N 3.95; found C 60.80, H 5.11, N 3.96.

(3*SR*, 3a*RS*, 8a*SR*)- 1-Methyl-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (10)
A mixture of Z-2-[2-(3,4-dichlorophenyl)vinyl)phenyl]acetaldehyde (420mg, 1.4mmol) and sarcosine (256mg, 2.8mmol) in toluene (25ml) was heated at reflux overnight under argon using a Dean-Stark trap. On cooling, the toluene was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with 4% ethanol in chloroform to afford **10** as a white solid (335mg, 73%) which was converted to the HCl salt and crystallised as a white solid m.p. >255°C dec. (from methanol-diethyl ether); ^{1}H NMR (freebase, 270MHz, $CDCl_3$) δ: 2.43 (3H, s), 2.86 (2H, m), 3.01 (2H, m), 3.30 (1H, m), 3.66 (1H, m), 4.12 (1H, dd, J = 7, 7 Hz), 6.17 (1H, d, J = 7 Hz), 6.82 (2H, m), 7.09 (4H, m); ^{13}C NMR (68MHz, $CDCl_3$) δ: 36.0, 40.0, 46.5, 54.9, 64.0, 70.0, 124.5, 125.6, 126.3, 126.4, 128.5, 129.3, 129.5, 130.9, 131.2, 141.8, 142.7, 143.6; IR ($CHCl_3$) 2995, 2950, 1472, 1132, 756 cm^{-1}; MS: m/z (EI$^+$) 317 M$^+$; $C_{18}H_{17}NCl_2$.HCl requires C 60.95, H 5.12, N 3.95; found C 60.85, H 5.00, N 3.66.

Attempted demethylation of 10 with 1-chloroethylchloroformate.
To a solution of (3*SR*, 3a*RS*, 8a*SR*)- 1-Methyl-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (270mg, 0.8mmol) and proton sponge™ (257mg, 1.2mmol) in 1,2-dichloroethane (15ml) under argon was added 1-chloroethylchloroformate (130ul, 1.2mmol) and the mixture heated at reflux for 2h. The reaction mixture was then evaporated to dryness and the residue heated at reflux in methanol (15ml) for 1h. After removal of the methanol *in vacuo* the residue was partioned between aq. potassium carbonate and diethyl ether. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with 5% ethanol in chloroform to afford **(11)** as a yellow oil (190mg, 70%); ^{1}H NMR ($CDCl_3$) 2.48 (3H, s), 3.03 (1H, dd, J = 7, 12Hz), 3.23 (1H, dd, J = 6, 12Hz), 3.45 (2H, s), 4.16 (1H, t, J = 7Hz), 6.40 (1H, s), 7.16 (4H, m), 7.35 (2H, m), 7.45 (1H, m); IR (neat) 3366, 3072, 3011, 2959, 1480, 1130, 783 cm^{-1} ; HRMS calcd. for $C_{17}H_{15}NCl_2$ 303.058155, found 303.058450.

(3*RS*, 3a*RS*, 8a*SR*) and (3*SR*, 3a*RS*, 8a*SR*)-1-(4-Methoxybenzyl)- 3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (12)
A mixture of *E* and Z-2-[2-(2-(3,4-dichlorophenyl)vinyl)phenyl]acetaldehyde **7** (1.46g, 5mmol) and 4-methoxy-benzylglycine (1.5g, 8.3mmol) in toluene (50ml) was heated at reflux for 6h under argon using a Dean-Stark trap. On cooling, the toluene was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with 1% ethanol in chloroform to afford the title compounds as a yellow oil (1.0g, 47%); MS: m/z (AP$^+$) 424 M$^+$.

(3*RS*, 3a*RS*, 8a*SR*)-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (2)
and
(3*SR*, 3a*RS*, 8a*SR*)-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (3)

To a solution of (3*RS*, 3a*RS*, 8a*SR*) and (3*SR*, 3a*RS* 8a*SR*)-1-(4-methoxybenzyl)-3-(3,4-dichlorophenyl)-1,2,3,3a,8,8a-hexahydro-1-azacyclopenta[a]indene (809mg, 1.9mmol) in dichloromethane at 0°C under argon was added proton sponge™ (413mg, 1.9mmol) followed by 1-chloroethylchloroformate (0.405ml, 3.9mmol). After 30 minutes, the volatile fractions were removed *in vacuo*. The residue was taken up in methanol (50ml) and heated at reflux for 30 minutes. On cooling, the methanol was removed *in vacuo* to afford a mixture of the two diastereomers which were readily separated by column chromatography on silica gel eluting with a gradient of 5-7% ethanol in chloroform. The faster eluting diastereomer (260mg, 45%), was converted to the HCl salt and crystallised to afford **(2)** as a white crystalline solid m.p. 222-224°C (from methanol ether); ^{1}H NMR (270 MHz, DMSO-d^6) δ: 3.41 (5H, m), 4.06 (1H, m), 4.70 (1H, m), 7.05 (1H, d, J = 7Hz), 7.23 (3H, m), 7.51 (1H, dd, J = 1,7 Hz), 7.68 (1H, d, J = 7Hz), 7.87 (1H, d, J = 1Hz), 9.83 (2H, br.s); ^{13}C NMR (68 MHz, DMSO-d^6) δ: 35.1, 49.5, 51.7, 56.0, 62.3, 123.7, 125.0, 127.3, 127.8, 128.4, 129.8, 129.9, 130.8, 131.4, 139.7, 140.7, 142.1.; IR ($CHCl_3$, free base) 3305, 3068, 3019, 2923, 1474, 1132,751 cm^{-1}.; HRMS calcd. for $C_{17}H_{15}NCl_2$ 303.0579, found 303.0581. Similarly the slower eluting diastereomer (198mg, 34%) afforded **(3)** as a white crystalline solid m.p. 201-202°C; ^{1}H NMR (270MHz, DMSO-d^6) δ: 3.09 (1H, t , J = 10Hz), 3.95 (1H, m), 4.30 (1H, t, J = 7Hz), 4.65 (1H, m), 5.91 (1H, d, J = 8Hz), 6.90 (1H, t, J = 7Hz), 7.18 (2H, m), 7.26 (1H, d, J = 7Hz), 7.45 (1H, d, J = 1Hz), 7.58 (1H, d, J = 7Hz), 9.48 (2H, br. s); ^{13}C NMR (68MHz, DMSO-d^6) δ:39.3, 45.4, 45.5, 52.4, 61.1, 124.4, 125.4, 126.1, 127.7, 129.0, 129.7, 130.1, 130.5, 130.9, 136.9, 138.3, 141.8.; IR ($CHCl_3$, free base) 3305, 3072, 3019, 2930, 1472, 1131, 750 cm^{-1}; HRMS calcd. for $C_{17}H_{15}NCl_2$ 303.0579, found 303.0584.

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