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The Design of Dipeptide Helical Mimetics, Part I: the Synthesis of 1,6-Disubstituted Indanes

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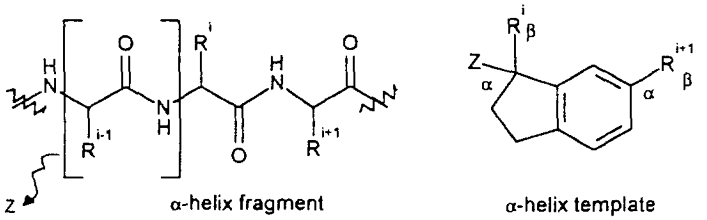
Abstract: The design and synthesis of conformationally restrained, non-peptide templates (1,6-disubstituted indanes) which allow the incorporation of two adjacent amino acid side-chains in an orientation similar to that found in alpha-helices is reported.

INTRODUCTION

Our interest in the rational design of non-peptide drug candidates (peptoids) for neuropeptide receptors, based on the structure of the endogenous neuropeptide has led us to devise a general design strategy (Scheme 1). As part of this strategy we are developing a family of 'rigid' templates with a range of physicochemical properties which mimic the common structural motifs found in proteins.[1] In these templates the α-β C-C bonds of at least two of the 'amino acid side chains' should overlay the corresponding bonds in the secondary peptide structure of interest (see Figs. 1 and 2 for example).



α-helix fragment

α-helix template

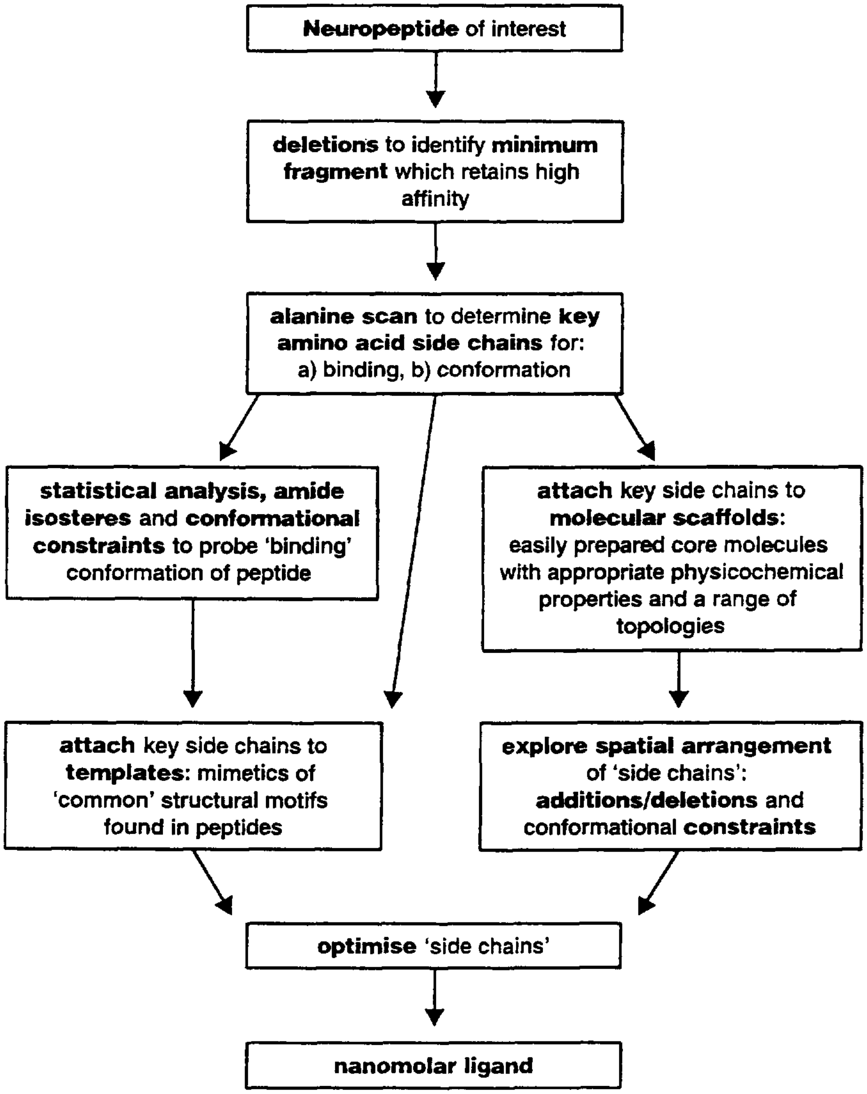
R^{i-1}, R^i, R^{i+1} = amino acid side-chains

Fig. 1. 1,6-disubstituted indanes as dipeptide helical mimetics

These templates should also meet the criteria outlined below if the goal of obtaining a non-peptide drug candidate is to be achieved:

i. relative ease of synthesis (< 8 steps from readily available starting materials containing 'key' amino acid side chains).

ii. contain functional groups which are not particularly susceptible to enzymatic degradation.



Scheme 1. A strategy for peptoid design

iii. contain sites for attachment of at least two amino acid side chains (ideally three, based on Ariens three ligand hypothesis[2]).

iv. molecular weight such that the 'addition' of three amino side-chains should not increase it >500 (to avoid potential bioavailability problems associated with high molecular weight and extraction into the bile).

v. log P (a measure of lipophilicity) such that the 'addition' of three amino acid side-chains should not increase it > 5 or decrease it < 0 (so that *in vivo* absorption and distribution are not adversely affected).

A suitable template can be selected based on the inferred binding conformation of the neuropeptide of interest, and coupled with key amino acid side chains identified from the alanine scanning step.[3] Such compounds can then be evaluated in an appropriate binding assay and high affinity ligands (IC_{50} < 100 nM) fed into our general strategy at the step entitled *optimise 'side chains'* (Scheme 1).

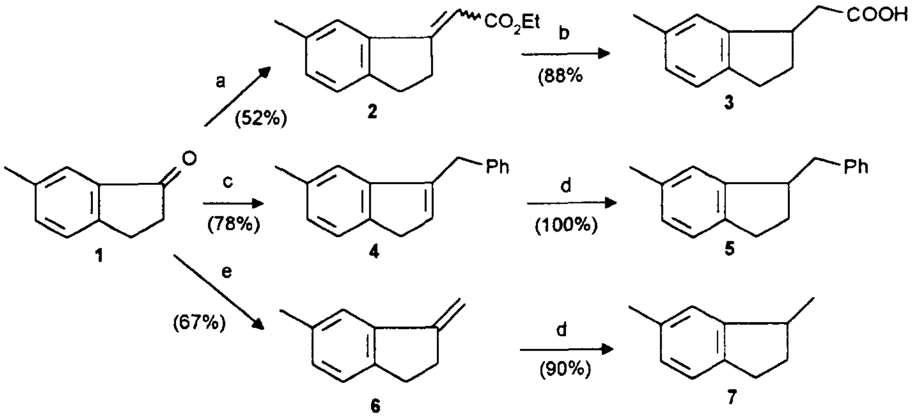
For the initial targets we chose mimetics of alpha helices since several studies[4] have indicated that peptides which are conformationally flexible in solution, for example a tetradecapeptide fibrinogen derivative and a 26-residue myosin light chain kinase derivative, adopt an alpha-helical structure upon interaction with their binding proteins, the enzyme thrombin and the regulatory protein calmodulin respectively. In these examples the amino acid side-chains of the alpha helices appear to be important in the molecular recognition process. The alpha helix of proteins was first described by Pauling in 1951[5] and is one of the most common secondary structural motifs found in proteins.[6] Despite the prevalence of alpha-helices there are no reports, apart from our earlier communication,[7] describing the synthesis of dipeptide helical mimetics, although several groups have described cyclic templates designed to initiate helical structure in attached peptides.[8]

Here we describe the design and synthesis of conformationally restrained, non-peptide templates which allow the incorporation of two adjacent amino acid side-chains in an orientation similar to that found in alpha-helix.

CHEMISTRY

The syntheses are described in Schemes 2 and 3.[9] The starting materials indicated on the schemes, 6-methyl indan-1-one[10] (**1**) and indan-1-one-6-carboxylic acid[11] (**8**) were prepared according to literature methods. The syntheses are designed to allow a wide variety of side-chains to be incorporated onto the bicyclic template by a Wittig, Grignard, or SN2 displacement reaction with the indanone carbonyl at C_1 (**1**, Scheme 2), with the aldehyde attached at C_6 (**14**, Scheme 3) or with the benzylic halide at C_6 (**18**, Scheme 3) respectively. In order to exemplify the methodology we selected three different R^i amino acid side-chains (see Fig. 1), CH_3 (Ala), CH_2Ph (Phe), CH_2COOH (Asp) (Scheme 2, compounds **3**,**5**,**7**) and six different R^{i+1} side-chains, CH_3 (Ala), CH_2CH_2COOH (Glu), CH_2OH (Ser), $CH_2CH(CH_3)_2$ (Leu), CH_2Ph (Phe), CH_2(3-indole) (Trp), (Scheme 3, compounds **12**,**13**,**15**,**17**,**19**).

In the first series of dipeptide mimetics, all 6-methylindanes, were synthesized from 6-methyl indan-1-one[10] (**1**) (Scheme 2). The Asp-Ala mimetic (**3**) was obtained by a Wittig reaction between (**1**) and ethyl 2-triphenylphosphoethanoate, subsequent reduction of the double bond and hydrolysis of the ethyl ester. Reaction of (**1**) with benzylmagnesium chloride, acid catalysed elimination of water and hydrogenation of the resulting olefin gave the Phe-Ala derivative (**5**). The Ala-Ala mimetic (**7**) was prepared in a similar manner to (**5**) , starting from (**1**) and methyl triphenylphoshonium bromide.

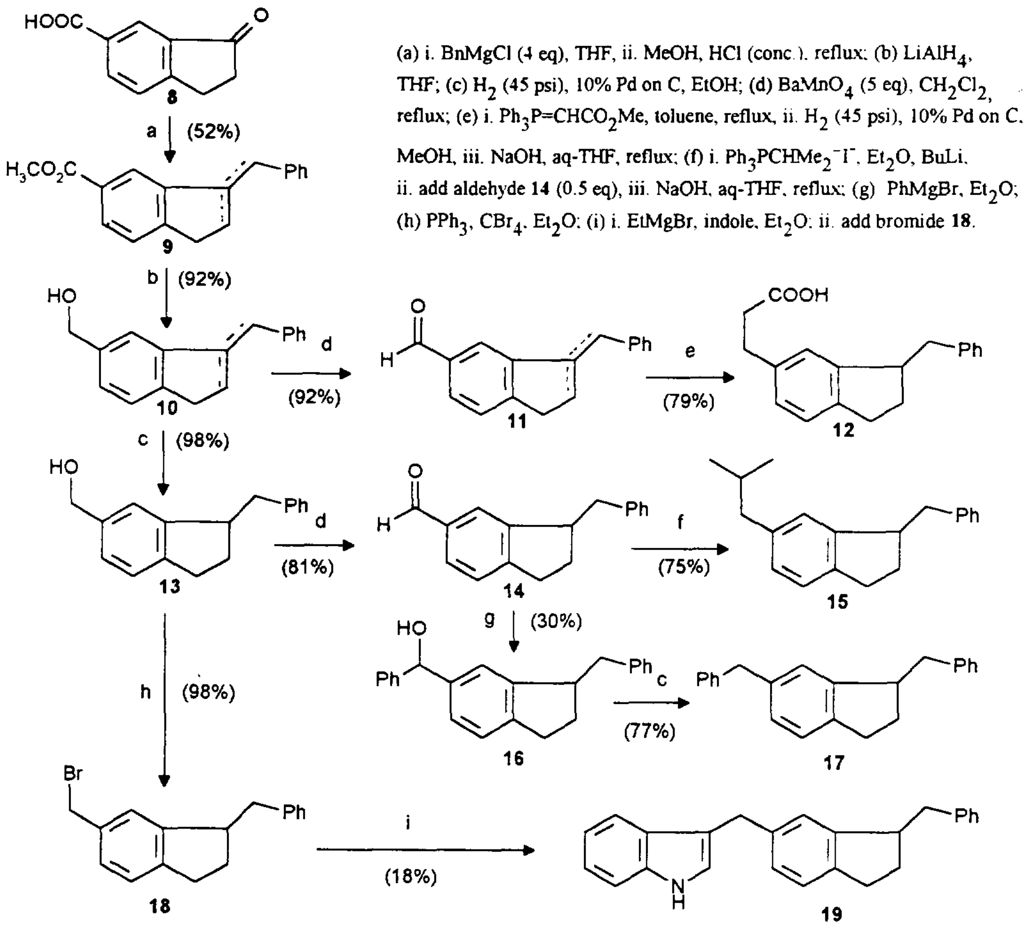


(a) $Ph_3P{=}CHCO_2Et$; (b) i. H_2 (45 psi), 10% Pd on C, MeOH; ii. NaOH, aq-THF; (c) i. $PhCH_2MgCl$ (5 eq), Et_2O; ii. MeOH, HCl (conc.), reflux; (d) H_2 (45 psi), 10% Pd on C, MeOH; (e) i. NaH, DMSO then $CH_3PPh_3^+Br^-$,DMSO; ii. add ketone **1**.

Scheme 2. Synthetic scheme for compounds **3,5,7**

The second series of dipeptide mimetics, all 1-benzylindanes, were synthesized from 6-carboxy-indanone[11] (**8**) (Scheme 3). Reacting (**8**) with benzylmagnesium chloride, followed by a tandem dehydration of the alcohol and esterification of the carboxylic acid led to the methyl ester (**9**) (a mixture of two regioisomers). Reduction of this ester with $LiAlH_4$ gave the alcohol (**10**) as a mixture of two regioisomers. Hydrogenation of the double bond yielded (**13**), the Phe-Ser mimetic, in good yield. Oxidation of (**10**) by $BaMnO_4$ resulted in aldehyde (**11**), as a mixture of two regioisomers, from which the Phe-Glu mimetic (**12**) was synthesised *via* a Wittig-reaction with methyl(triphenylphoshoranylidene)acetate, reduction of the double bond and hydrolysis of the resulting ester. The Phe-Ser mimetic (**13**) was a key intermediate for the synthesis of the Phe-Leu, Phe-Phe, Phe-Trp mimetics, compounds (**15**, **17**, **19**) respectively. Compound (**13**) was oxidised to the aldehyde (**14**) by $BaMnO_4$ in excellent yield. The Phe-Leu mimetic (**15**) was then obtained by a Wittig reaction on (**14**) followed by reduction of the double bond. Reaction of the aldehyde (**14**) with phenylmagnesium bromide followed by hydrogenolysis of the benzylic alcohol gave the Phe-Phe mimetic (**17**). The Phe-Trp mimetic was synthesised by reacting the alcohol (**13**) with carbon tetrabromide and triphenyl phosphine to give the bromide (**18**), followed by reaction with indole magnesium bromide.

Fig. 2. Orthogonal and sectional representations of the overlay of the Ala-Ala mimetic 7 (in green) with a model alpha-helix (in red)



(a) i. BnMgCl (4 eq), THF, ii. MeOH, HCl (conc.), reflux; (b) $LiAlH_4$, THF; (c) H_2 (45 psi), 10% Pd on C, EtOH; (d) $BaMnO_4$ (5 eq), CH_2Cl_2, reflux; (e) i. $Ph_3P{=}CHCO_2Me$, toluene, reflux, ii. H_2 (45 psi), 10% Pd on C, MeOH, iii. NaOH, aq-THF, reflux; (f) i. $Ph_3PCHMe_2{}^{+}I^{-}$, Et_2O, BuLi, ii. add aldehyde **14** (0.5 eq), iii. NaOH, aq-THF, reflux; (g) PhMgBr, Et_2O; (h) PPh_3, CBr_4, Et_2O; (i) i. EtMgBr, indole, Et_2O; ii. add bromide **18**.

Scheme 3. Synthetic scheme for compounds **12,13,15,17,19**

RESULT AND DISCUSSIONS

Examination of Dreiding molecular models indicated that the 1,6-substituents of an indane template overlaid closely the Cα and Cβ carbon atoms of adjacent (i, i+1) alpha-helix side-chains (Figure 1). This was subsequently confirmed with computer modelling (see experimental section) which indicated that the two Cα and the two Cβ carbon atoms of the lowest energy state of the S-enantiomer of the Ala-Ala mimetic (7) overlay with the corresponding positions in an alpha-helix with a root mean square (rms) deviation of 0.15 Angstroms (Figure 2). Furthermore, the indane template is orientated within the space occupied by the alpha-helix peptide backbone.

Having designed a suitable template a general synthesis was developed and illustrated with the preparation of eight dipeptide examples containing a wide range of amino acid side chains.

CONCLUSION

We have described the design of a dipeptide helical mimetic and illustrated its utility by the synthesis of eight dipeptide examples containing a wide range of side chains. At present this concept and template is being developed further with the synthesis of alpha-helix templates which mimic three amino-acid side chains and have polar linking groups. These will be reported shortly together with their binding affinity for an appropriate neuropeptide receptor.

EXPERIMENTAL SECTION

Computer molecular modelling

Computer molecular modelling was performed using the SYBIL programme (version 6.0), supplied by Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, Missouri 63144, USA. The lowest energy state of the (S)-enantiomer of compound (7) was found using a 1000 iterations of the RANDOMSEARCH algorithm. In this method an arbitrary starting point for geometry optimisation is found by the application of three random torsion angles to three of the rotatable bonds (including alicyclic rings). Geometry optimisation at each iteration was effected by minimisation of the energy (Tripos force field, no electrostatic charges) by MAXIMIN-II. Energy minimisation was terminated when the rms energy gradient fell below 0.02 kcalmol^{-1}A^{-1}. The lowest energy conformer found by this procedure was overlayed by the method of least squares with (Ala)$_8$ in an alpha-helix conformation (angles from the BIOPOLYMER library) and the rms fit calculated.

Chemistry

Melting points were determined with a Mettler FP80 or a Reichert Thermovar hotstage apparatus. Proton NMR spectra were recorded on a Bruker AM300 spectrometer; chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded with the compound either neat (oils and liquids) or as a Nujol mull on a sodium chloride disc on a Perkin-Elmer 1750 Fourier transform spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnegan 4500 or VG Analytical ZAB-E. Elemental analyses indicated by the symbols of the elements were within $\pm$ 0.4% of theoretical values and were determined by Medac Ltd., Uxbridge, U.K. Normal phase silica gel used for chromatography was Merck No. 9385 (230-400 mesh); reverse-phase silica gel used was Lichroprep RP-18 (230-400 mesh) both were supplied by E. Merck, A.G., Darmstadt, Germany. Anhydrous solvents were purchased in septum-capped bottles from Fluka Chemicals Ltd., Glossop, U.K. and dispensed by syringe. All other chemicals were purchased from Aldrich Chemical Co. Ltd., Gillingham, U.K. and were used without further purification, unless stated.

6-Methylindan-1-one[10](**1**)

To a solution of 3-(4-methylphenyl)propionic acid (2.0 g, 12 mmol) in CH_2Cl_2 (20 mL) was added a 2M solution of oxalyl chloride in CH_2Cl_2 (6.7 mL, 14 mmol). The solution was cooled to 0^oC and DMF (2 drops) added. The solution was stirred until the evolution of gas had stopped (1 h), then concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (300 mL) and cooled to 0^oC. $AlCl_3$ (1.7 g, 12 mmol) was then added over 15 min and the mixture stirred for 1 h. The reaction mixture was poured onto ice/water (400 mL) and the layers were separated. The water layer was extracted with Et_2O (4 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*, to give (**1**) as an off-white solid (1.7 g, 97%). mp 55-59°C; ν_{max}(film)/cm^{-1} 2925, 1708, 1492; ^{1}H NMR ($CDCl_3$): δ 7.55 (1H, s, aromatic), 7.40 (1H, d, J = 8 Hz, aromatic), 7.35 (1H, d, J = 8 Hz, aromatic), 3.09 (2H, t, J = 6 Hz, CH_2CO), 2.68 (2H, t, J = 6 Hz, $\underline{H_2}$CH_2CO), 2.40 (3H, s, $ArCH_3$).

Ethyl (6-Methylindan-1-ylidene)ethanoate (**2**, mixture of geometrical isomers).

(**1**) (0.5 g, 3.4 mmol) and ethyl 2-triphenylphosphoethanoate (5.9 g, 17 mmol) were placed in a flask that had been flushed with argon and fused at 140°C for 4 h. The mixture was cooled, poured into water (50 mL) and extracted with Et_2O (5 x 20 mL). The organic phase was washed with water (20 mL), brine (2 x 20 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica (eluent: hexane/Et_2O, 7:3), to give (**2**) as pale yellow crystals (0.41 g, 52%). mp 45-50 °C; ν_{max}(film)/cm^{-1} 2926, 1704, 1634; ^{1}H NMR ($CDCl_3$): δ 7.12 (1H, d, J = 8 Hz, aromatic), 6.95 (2H, m, aromatic), 3.55 (1H, q, J = 7 Hz, C$\underline{H}$), 2.82 (3H, m, $ArCH_2$, C$\underline{H}$'HPh), 2.38-2.55 (2H, m, CH'$\underline{H}$Ph, C$\underline{H}$'H), 2.33 (3H, s, $ArCH_3$), 1.75 (1H, m, CH'$\underline{H}$); MS found *m/e* 216.1150, $C_{14}H_{16}O_2$ requires 216.1150.

1-Carboxymethyl-6-methylindane (**3**)

A solution of (**2**) (200 mg, 0.9 mmol) in MeOH (20 mL) was placed in a 250 mL hydrogenation flask, which was then flushed with N_2 for 5 min. The catalyst, 10% Pd on C (50 mg), was added and the flask filled with H_2 at 45 psi and shaken for 30 min at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo*. The residue was dissolved in THF (9 mL) and a 10% NaOH solution (aq.; 1 mL) was added. The mixture was heated to reflux for 15 h, then cooled and diluted with water (20 mL). The layers were separated and the water layer extracted with Et_2O (3 x 20 mL). The organic phase was discarded and the aqueous phase acidified with 2 M HCl and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water and brine (both 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica (100% Et_2O), to give (**3**) as a white solid (168 mg, 88%). m.p. 105-107 °C; ν_{max}(film)/cm^{-1} 3700-2900 (br), 1707; ^{1}H NMR ($CDCl_3$): δ 7.12 (1H, d, J = 8 Hz, aromatic), 6.95 (2H, m, aromatic), 3.55 (1H, q, J = 7 Hz, C$\underline{H}$), 2.82 (3H, m, $ArCH_2$, C$\underline{H}$'HPh), 2.38-2.55 (2H, m, CH'$\underline{H}$Ph, C$\underline{H}$'H), 2.33 (3H, s, $ArCH_3$), 1.75 (1H, m, CH'$\underline{H}$); MS *m/e* (EI) 190 (M^+, 27%).

3-Benzyl-5-methylindene (**4**)

To a solution of (**1**) (1.0 g, 6.8 mmol) in Et_2O (dry; 25 mL) was added a 1 M solution of benzylmagnesium chloride in Et_2O (5 eq, 10.2 mL) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 15 h. The reaction mixture was quenched by careful addition of ice/water (20 mL), followed by 2M HCl (20 mL). The layers were separated and the water layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and HCl (conc.; 2 mL) added. The mixture was refluxed for 5 h, then cooled and poured into water (100 mL). The resulting mixture was extracted with Et_2O (5 x 10 mL). The organic phase was washed with 10% Na_2CO_3 (aq. sol.), water and brine (all 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography on silica (eluent : 100%

hexane), to give (**4**) as a colourless oil (1.10 g, 78%). ν_{max}(film)/cm^{-1} 3061, 3025, 2918, 1603; ^{1}H NMR (CDCl$_3$): δ 7.54-6.95 (8H, m, aromatics), 6.17 (1H, s, C=CH), 3.96 (2H, s, ArCH$_2$), 3.38 (2H, s, CH$_2$Ph), 2.46 (3H, m, CH$_3$); MS found *m/e* (EI) 220.1250, C$_{17}$H$_{16}$ requires 220.1252.

1-Benzyl-6-methylindane (**5**)

A solution of (**4**) (150 mg, 0.68 mmol) in MeOH (20 mL) was placed in a 250 mL hydrogenation flask, which was then flushed with N$_2$ for 5 min. The catalyst, 10% Pd on C (50 mg), was added and the flask filled with H$_2$ at 45 psi and shaken for 30 min at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica (100% n-pentane), to give (**5**) as a colourless oil (150 mg, 98%). ν_{max}(film)/cm^{-1} 3026, 2850, 1603; ^{1}H NMR (CDCl$_3$): δ 7.20 (5H, m, aromatic), 7.15 (1H, d, J = 8 Hz, aromatic), 6.95 (2H, *m*, aromatic), 3.44 (1H, m, CH), 3.14 (1H, dd, J = 5.3 and 13.5 Hz, C$\underline{H}$'HAr), 2.82 (2H, m, ArCH$_2$), 2.62 (1H, dd, J = 9.6 and 13.5 Hz, CH'$\underline{H}$Ar), 2.30 (3H, s, ArCH$_3$), 2.10 (1H, m, C$\underline{H}$'H), 1.75 (1H, m, CH'$\underline{H}$); MS found *m/e* 222.14100, C$_{17}$H$_{18}$ requires 222.14090.

6-Methyl-1-methyleneindane (**6**)

Sodium hydride (0.15 g; 60% dispersion in mineral oil) in DMSO (dry; 10 mL) was heated to 75^{0}C under an argon atmosphere until the evolution of gas stopped (30 min.). The solution was cooled to room temperature and methyl triphenylphosphonium bromide (1.21 g, 3.4 mmol) in warm DMSO (dry; 2 mL) was added. The mixture was stirred for 15 min. at room temperature. A solution of (**1**) (0.50 g, 3.4 mmol) in DMSO (dry; 1 mL) was added and the mixture stirred for 15 min., then poured into water (50 mL). The mixture was extracted with Et$_2$O (3 x 10 mL) and the organic phase was washed with water and brine (both 10 mL), dried (MgSO$_4$) and concentrated *in vacuo* at room temperature (volatile product!). The resulting oil was purified by column chromatography on silica (eluent: pentane, 100%), to give (**6**) as a colourless oil (330 mg, 67%). ν_{max}(film)/cm^{-1} 2922, 2851, 1641; ^{1}H NMR (CDCl$_3$): δ 7.29 (1H, s, aromatic), 7.13 (1H, d, J = 8 Hz, aromatic), 7.02 (1H, d, J = 8 Hz, aromatic), 5.4(1H, t, J = 2 Hz, C=C$\underline{H}$'H), 4.99 (1H, t, J = 2 Hz, C=CH'$\underline{H}$), 2.95, (2H, m, ArCH$_2$), 2.75 (2H, m, CH$_2$), 2.34 (3H, s, ArCH$_3$); MS found *m/e* 144.0939, C$_{11}$H$_{12}$ requires 144.0939.

1,6-Dimethylindane (7)

A solution of (6) (150 mg, 1.0 mmol) in MeOH (10 mL) was placed in a 250 mL hydrogenation flask, which was then flushed with N$_2$ for 5 min. The catalyst, 10% Pd on C (50 mg), was added and the flask filled with H$_2$ at 45 psi and shaken for 30 min at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate poured in water (100 mL) and extracted with n-pentane (3 x 20 mL). The combined organic layers were washed with water and brine (both 15 mL), dried (MgSO$_4$) and concentrated *in vacuo* at room temperature. The resulting oil (very volatile!) was purified by column chromatography on silica (100% n-pentane), to give (7) as a colourless oil (130 mg, 90%). ν_{max}(film)/cm^{-1} 3004, 1493, 1456; ^{1}H NMR (CDCl$_3$): δ 7.18 (1H, *d*, J = 7 Hz, aromatic), 7.09 (1H, s, aromatic), 7.03 (1H, d, J = 7 Hz, aromatic), 3.24 (1H, sextet, J = 7 Hz, CH), 2.92 (2H, m, ArCH$_2$), 2.42 (3H, s, ArCH$_3$), 2.38 (1H, m, C$\underline{H}$'H), 1.73 (1H, m, CH'$\underline{H}$), 1.36 (3H, d, J = 7 Hz, CHC$\underline{H}_3$); MS found *m/e* 146.1096, C$_{11}$H$_{14}$ requires 146.1096.

6-Carboxy-1-indanone[11] (**8**)

3-(4-Carboxyphenyl)propionic acid (3.0 g, 0.015 mole), aluminium chloride (10.5 g, 0.079 mole) and sodium chloride (0.90 g, 0.015 mole) were placed together in a 100 mL rb flask. The flask was shaken well to mix the solids, then fitted with a condenser. The mixture was fused for 1 h at 180 °C, cooled, and water/ice (75 mL) and 6M HCl (75 mL) were added in small portions, followed by EtOAc (150 mL). The layers were separated and the water layer extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with 2M HCl, water and brine (all 80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give (**8**) as a yellow solid (2.30 g, 87%). mp (crude material) 233-238°C, mp. lit. 256°C; ν_{max}(film)/cm^{-1} 3349, 1729 , 1675 , 1615; ^{1}H NMR (DMSO-d_6): δ 13.10 (1 H, s, COOH), 8.18 (1H, d, J = 8 Hz, aromatic), 8.10 (1H, s, aromatic), 7.70 (1H, d, J = 8 Hz, aromatic), 3.17 (2H, m, CH_2CO), 2.70 (2H, m, CH_2).

Methyl 3-benzylindene-5-carboxylate (**9a**) and *methyl 1-benzylideneindan-6-carboxylate* (**9b**)

(**8**) (1.5 g, 8.5 mmol) was dissolved in THF (dry; 80 mL) and the solution cooled to 0 °C. Benzylmagnesium chloride in Et_2O (33.5 mL, 33.5 mmol; 1M) was added dropwise over 0.5 h and the resulting red suspension stirred overnight at room temperature. The reaction mixture was quenched by careful addition of ice/water (150 mL), followed by 2M HCl (10 mL). The resulting mixture was extracted with Et_2O (3 x 50 mL) and the organic phase then discarded. The basic aqueous phase was acidified with 2M HCl (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water and brine (both 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (50 mL) and conc. HCl (3.0 mL) added. The solution was heated to reflux overnight, cooled and poured into water (200 mL), giving a white precipitate. The mixture was extracted with Et_2O (4 x 50 mL) and the organic phase washed with 10% Na_2CO_3, water and brine (all 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica (eluent: hexane/Et_2O, 9:1, to give (**9**, mixture of two isomers) as a yellow solid (1.17 g, 52%). mp 272- 279°C; ν_{max}(film)/cm^{-1} 3025, 2951, 1719, 1602; ^{1}H NMR ($CDCl_3$): δ 8.25 (0.33H, s, aromatic b), 7.95 (0.66H, s, aromatic a), 7.91 (1H, d, J = 8 Hz, aromatic a+b), 7.45 (1H, d, J = 8 Hz, aromatic a+b), 7.42-7.21 (5H, m, aromatics), 7.15 (0.33H, s, C=CH b), 6.15 (0.66H, s, C=CH a), 3.90 (5H, m, $COOCH_3$ a + b and $ArCH_2$ a + b), 3.37 (1.33H, s, CH_2Ph a), 3.12 (0.66H, s, $C\underline{H}$'H b); MS *m*/*e* (EI) 264 (M^+, 66%).

3-Benzyl-5-(hydroxymethyl)indene (**10a**) and *1-benzylidene-6-(hydroxymethyl)indane* (**10b**)

A 250 mL three-necked flask fitted with a condenser and dropping funnel was flushed with N_2. THF (30 mL) and a 1M solution of $LiAlH_4$ in THF (5.0 mL) were placed in the flask and the solution was cooled to 0 °C. A solution of (**9**, mixture of isomers) (1.10 g, 4.2 mmol) in THF (20 mL) was placed in the dropping funnel and added dropwise to the $LiAlH_4$solution over 10 min. The mixture was allowed to warm up to room temperature and stirred for 2 h under N_2, then quenched by addition of 15% NaOH (aq; 0.5 mL), followed by water (1.5 mL). The mixture was stirred for 0.5 h, filtered through kieselguhr, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography on silica (eluent: hexane/Et_2O, 1:1) , to give (**10**, mixture of two isomers) as a yellow oil (0.8 g, 78%). ν_{max}(film)/cm^{-1} 3200-2800 (br), 1605, 1590. ^{1}H NMR ($CDCl_3$): δ 7.77-7.12 (8H, m, aromatics of a + b), 6.94 (0.33H, s, $C=C\underline{H}$ isomer b), 6.15 (0.66H, s, $C=C\underline{H}$ isomer a), 4.72 (0.66H, s, $ArC\underline{H}_2OH$ b), 4.70 (1.33H, s, $ArC\underline{H}_2OH$ a), 3.90 (2H, s, $ArCH_2$ a + b), 3.32 (1.33H, s, CH_2Ph a), 3.12 (0.66H, s, $C\underline{H}H$ b); MS found *m*/*e* (EI) 236.1200, $C_{17}H_{16}O$ requires 236.1201.

3-Benzyl-5-formylindene (**11a**) and *1-benzylidene-6-formylindane* (**11b**)

$BaMnO_4$ (0.64g, 2.5 mmol) was added to a solution of (**10**) (120 mg, 0.5 mmol) in CH_2Cl_2 (dry; 10 mL). The mixture was then heated at reflux overnight under N_2. After cooling the suspension was filtered through kieselguhr and concentrated *in vacuo*, to give (**11**, mixture of two isomers) as a colourless oil (107 mg, 92%). ν_{max}(film)/cm^{-1} 3026, 2834, 1696, 1606, 1572; ^1H NMR ($CDCl_3$): δ 10.05 (0.3 H, s, ArCHO a), 9.95 (0.7H, s, ArCHO b), 8.10 (0.3H, s, aromatic a), 7.82 (0.7H, s, aromatic b) 7.75 (0.7H, d, J = 8 Hz, aromatic b), 7.55 (0.7H, d, J = 8 Hz, aromatic b), 7.50-7.08 (5.6H, m, aromatics a + b), 7.05 (0.3H, s, C=CH a), 6.24 (0.7H, s, C=CH b), 3.91 (1.4H, s, br, $ArCH_2$ b), 3.38 (1.4H, s, br, CH_2 b), 3.15 (1.2H, m, $ArCH_2$ + $PhCH_2$ a); MS *m/e* (EI) 234 (M^+, 45%).

3-(1-Benzylindan-6-yl)propionic acid (**12**)

A solution of (**11**) (0.12 g, 0.5 mmol) and methyl(triphenylphosphoranylidene)acetate (0.83 g, 2.5 mmol) in toluene (dry; 10 mL) was heated at reflux for 15 h. The solvent was then removed *in vacuo* and the residue taken up in Et_2O (50 mL) and washed with water and brine (both 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. To a solution of the resulting yellow oil in THF (9 mL) was added 10% NaOH (1 mL). The mixture was heated to reflux for 15 h, then cooled and diluted with water (20 mL). The layers were separated and the water layer extracted with Et_2O (3 x 20 mL). The organic phase was discarded and the aqueous phase acidified with 2 M HCl and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water and brine (both 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica (100% Et_2O), to give (**12**) as a yellow gum (111 mg, 79%). ν_{max}(film)/cm^{-1} 3035, 1794, 1713 ; ^1H NMR ($CDCl_3$): δ 7.30-7.17 (5H, m, aromatics), 7.12 (1H, d, J = 8 Hz, aromatic), 6.98 (1H, d, J = 8 Hz, aromatic), 6.90 (1H, s, aromatic), 3.40 (1H, m, CH), 3.10 (1H, dd, J = 6 and 13 Hz, $C\underline{H}'HPh$), 2.90 (2H, t ,J = 8 Hz, $ArC\underline{H}_2CH_2COOH$), 2.85-2.64 (3H, m, $CH'\underline{H}Ph$ + $ArCH_2$), 2.62 (2H, t , J = 8 Hz, $ArCH_2C\underline{H}_2COOH$), 2.15 (1H, m, $C\underline{H}'H$), 1.75 (1H, m, $CH'\underline{H}$); MS *m/e* (EI) 280 (M^+, 5%).

1-Benzyl-6-(hydroxymethyl)indane (**13**)

A solution of (**10**, mixture of isomers) (0.75g, 0.0032 mol) in EtOAc (50 mL) was placed in a 250 mL hydrogenation flask, which was then flushed with N_2 for 5 min. 10% Pd on charcoal (91 mg) was added and the flask was filled with H_2 at a pressure of 45 psi and shaken for 4 h. The catalyst was then removed by filtration through kieselguhr and the filtrate dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica (eluent: hexane/ Et_2O, 1:1), to give (**13**) as a white solid (550 mg, 72%). mp 175-177 ^{0}C; ν_{max}(film)/cm^{-1} 3300-2900(br), 1494, 1453, 1031; ^1H NMR ($CDCl_3$): δ 7.43-7.14 (8H, m, aromatics), 4.63 (2H, s, CH_2OH), 3.42 (1H, m, CH), 3.19 (1H, dd, J = 5.5 and 13.5 Hz, $CH'\underline{H}Ph$), 2.85 (2H, m, $ArCH_2$), 2.67 (1H, dd, J = 9.5 and 13.5 Hz, $C\underline{H}'HPh$), 2.16 (1H, m, $C\underline{H}'H$), 1.78 (1H, m, $CH'\underline{H}$); MS found *m/e* (EI) 256.1700, $C_{17}H_{18}O$ + NH_4^+ requires 256.1701.

1-Benzyl-6-formylindane (**14**)

$BaMnO_4$(0.73 g, 2.85 mmol) was added to a solution of (**13**) (140 mg, 0.59 mmol) in CH_2Cl_2 (10 mL). The mixture was then refluxed overnight under N_2. After cooling the suspension was filtered through kieselguhr and concentrated *in vacuo*, to give (**14**) as a yellow oil (130 mg, 95%). ν_{max}(film)/cm^{-1} 2922, 1696 , 1606, 1576; ^1H NMR ($CDCl_3$): δ 9.91 (1H, s, ArCHO), 7.66 (1H, s, aromatic), 7.60 (1H, s, aromatic) 7.33

(1H, d, J = 8 Hz, aromatic), 7.30-7.08 (5H, m, aromatics), 3.47 (1H, m, CH), 3.17 (1H, dd, J = 5.5 and 13.5 Hz, $\mathrm{CH'\underline{H}Ph}$), 2.85 (2H, m, $\mathrm{ArCH_2}$), 2.70 (1H, dd, J = 9.2 and 13.5 Hz, $\mathrm{C\underline{H}'HPh}$), 2.20 (1H, m, $\mathrm{C\underline{H}'H}$), 1.85 (1H, m, $\mathrm{CH'\underline{H}}$); MS found *m/e* 237.1279, $C_{17}H_{16}O + NH_4^+$ requires 237.1279.

1-Benzyl-6-isobutylindane (**15**)

To a suspension of isopropyl triphenylphosphonium iodide (0.5 g, 1.2 mmol) in Et_2O (20 mL) at 0°C under an argon atmosphere was added dropwise a 1.6 M solution of n-butyllithium in hexane (0.7 mL, 1.2 mmol). The mixture was stirred for 30 min. at room temperature. A solution of (**14**) (0.18 g, 0.77 mmol) in Et_2O (2 mL) was then added and the resulting yellow solution stirred overnight at room temperature. The mixture was filtered and the filtrate concentrated *in vacuo* at room temperature. The residue was dissolved in MeOH (10 mL) and placed in a 250 mL hydrogenation flask, which was then flushed with N_2 for 5 min. The catalyst, 10% Pd on C (50 mg), was added and the flask filled with H_2 at 45 psi and shaken for 45 min at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate poured in water (100 mL) and extracted with n-pentane (3 x 20 mL). The combined organic layers were washed with water and brine (both 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* at room temperature. The resulting oil (very volatile!) was purified by column chromatography on silica (100% n-pentane), to give (**15**) as a colourless oil (150 mg, 75%). ν_{max}(film)/cm^{-1} 3005, 1604, 1585, 1495; ^{1}H NMR ($CDCl_3$): δ 7.30-7.17 (m, 5H, aromatics), 7.10 (1H, d, J = 8 Hz, aromatic), 6.92 (1H, d, J = 8 Hz, aromatic), 6.86 (1H, s, aromatic), 3.39 (1H, m, CH), 3.11 (1H, dd, J = 5 and 14 Hz, $\mathrm{C\underline{H}'HPh}$), 2.83 (2H, m, $\mathrm{ArCH_2}$), 2.67 (1H, dd, J = 9 and 14 Hz, $\mathrm{CH'\underline{H}Ph}$), 2.42 (2H, d, J = 7 Hz, $\mathrm{CHC\underline{H}_2Ar}$), 2.12 (1H, m, $\mathrm{C\underline{H}'H}$), 1.73 (2H, m, $\mathrm{CH'\underline{H}}$ + $\mathrm{C\underline{H}(CH_3)_2}$), 0.89 (6H, d, J = 6 Hz, 2 x CH_3); MS *m/e* (EI) 264 (M$^+$, 8%).

1-Benzyl-6-(α-hydroxybenzyl)indane (**16**)

A 100 mL three-necked flask was fitted with condenser and dropping funnel and flushed with N_2. Et_2O (10 mL) and a 3.0 M solution of PhMgBr in Et_2O (1.5 mL) were placed in the flask and a solution of (**14**) (200mg, 0.85 mmol) in Et_2O (dry; 5 mL) was added dropwise over 20 min via the dropping funnel. The reaction mixture was stirred for 3 h at room temperature then quenched by adding NH_4Cl (aq. sat.; 2 mL) followed by water (20 mL) and Et_2O (20 mL). The layers were separated and the water layer extracted with ether (2 x 25 mL). The combined organic layers were washed with 2M HCl (15 mL), water (15 mL) and 10% NaCl (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica (eluent: hexane/EtOAc, 19:1), to give (**16**) as a colourless oil (80 mg, 30%). ν_{max}(film)/cm^{-1} 3385, 3026, 2928, 2850, 1602; ^{1}H NMR ($CDCl_3$): δ 7.44 (13H, m, aromatics), 5.80 (1H, d, J = 4.3 Hz, $\mathrm{C\underline{H}OH}$), 3.41 (1H, m, CH), 3.14 (1H, dd, J = 4.8 and 13.5 Hz, $\mathrm{CH'\underline{H}Ph}$), 3.0-2.5 (3H, m, $\mathrm{ArCH_2}$ + $\mathrm{C\underline{H}'HPh}$), 2.19 (1H, m, $\mathrm{C\underline{H}'H}$), 1.80 (1H, m, $\mathrm{CH'\underline{H}}$); MS found *m/e* (CI) found 315.1740, $C_{23}H_{22}O + H^+$ requires 315.1749.

1,6-Dibenzylindane (**17**)

A solution of (**16**) (75 mg, 0.24 mmol) in EtOH (95%; 25 mL) was placed in a 250 mL hydrogenation flask, which was then flushed with N_2 for 5 min. Palladium on charcoal (10%)(25 mg) was added and the flask filled with H_2 at 45 psi and shaken for 19.5 h at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* and dried by evaporation with toluene. The resulting brown oil was purified by column chromatography on silica (eluent: hexane/Et_2O, 9:1), to give

(**17**) as a colourless oil (50 mg, 70%). ν_{max}(film)/cm^{-1} 3026, 2924, 1602; ^{1}H NMR (CDCl$_3$): δ 7.29-7.01 (13H, m, aromatics), 3.92 (2H, s, PhCH$_2$Ph), 3.49 (1H, m, CH), 3.12 (1H, m, CH'$\underline{H}$Ph), 2.88-2.59 (3H, m, ArCH$_2$ + C$\underline{H}$'HPh), 2.07 (1H, m, C$\underline{H}$'H), 1.84 (1H, m, CH'$\underline{H}$); MS found *m/e* (CI) 299.1800, $C_{23}H_{22}$ + H$^+$ requires 299.1800.

1-Benzyl-6-(bromomethyl)indane (**18**)

Carbon tetrabromide (0.50 g, 1.5 mmol) and triphenyl phosphine (0.40 g, 1.5 mmol) were put in a 100 mL two-necked flask together with Et$_2$O (dry; 10 mL) and stirred for 10 min at room temperature. A solution of (**13**) (300 mg, 1.26 mmol) in ether (dry; 5 mL) was then added dropwise via the dropping funnel and the reaction mixture stirred for 3 h at room temperature.. The precipitate was then filtered off through kieselguhr and the filtrate concentrated *in vacuo*. The resulting brown oil was purified by column chromatography on silica (eluent: hexane/EtOAc, 19:1), to give (**18**) as a yellow oil (373 mg, 98%). ν_{max}(film)/cm^{-1} 3026, 2929, 1602, 1495; ^{1}H NMR (CDCl$_3$): δ 7.28-7.01 (8H, m, aromatics), 4.47 (2H, s, CH$_2$Br), 3.44 (1H, m, CH), 3.15 (1H, m, CH$\underline{H}$'Ph), 2.91-2.57 (3H, m, ArCH$_2$, C$\underline{H}$'HPh), 2.16 (1H, m, C$\underline{H}$'H), 1.79 (1H, m, CH'$\underline{H}$); MS *m/e* (CI) 302, 300 ([M+H]$^+$, 6%).

1-Benzyl-6-(3-indolylmethyl)indane (**19**)

A 3M solution of ethylmagnesium bromide in Et$_2$O (0.22 mL, 0.66 mmol) was placed in a 100 mL three-necked flask, fitted with a condenser and dropping funnel and flushed with N$_2$. A solution of indole (64 mg, 0.55 mol) in toluene (1 mL) was placed in the dropping funnel and added slowly to the solution while stirring. The mixture was heated to 60 °C for 30 min and cooled to 0 °C. A solution of (**18**) (150 mg, 0.50 mmol) in toluene (1.2 mL) was added dropwise. The reaction mixture was then stirred for 5 h at 0°C, followed by 72 h at 20°C. The reaction mixture was quenched by addition of ice/water (10 mL) and 6M HCl (5 mL). Et$_2$O (10 mL) was added and the layers were separated. The water layer was extracted with Et$_2$O (2 x 10 mL), the combined organic layers washed with water and brine (both 10 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The resulting red-brown oil was purified by column chromatography on silica (eluent: hexane/EtOAc, 19:1). The high running fractions (R_f= 0.55 , 0.39) did not contain any product. All lower running fractions were concentrated *in vacuo* to give a red solid. This was purified by reverse phase column chromatography (40% →90% MeOH in water), to give (**19**) as a yellow gum (55 mg, 18%). ν_{max}(film)/cm^{-1} 3420, 2919, 1455, 1090; ^{1}H NMR (CDCl$_3$): δ 7.92 (1H, s,br, NH indole), 7.55-7.00 (12H, m, aromatics), 6.86 (1H, s, H2 indole), 4.05 (2H, s, CH$_2$indole), 3.51 (1H, m, CH), 3.11 (1H, dd, J = 5.6 & 13.5 Hz, CH'$\underline{H}$Ph), 2-2.5.916 (3H, m, ArCH$_2$ + C$\underline{H}$'HPh), 2.12 (1H, m, C$\underline{H}$'H), 1.75 (1H, m, CH'$\underline{H}$); MS found *m/e* (EI) 338.1909, $C_{25}H_{23}N$ + H$^+$ requires 338.1909.

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