Pergamon

Bioorganic & Medicinal Chemistry, Vol. 4, No. 1, pp. 33–42, 1996

0968-0896/96 $15.00 + 0.00

0968-0896(95)00169-7

The Design of Dipeptide Helical Mimetics: The Synthesis, Tachykinin Receptor Affinity and Conformational Analysis of 1,1,6-Trisubstituted Indanes[1]

David C. Horwell, William Howson, Giles S. Ratcliffe and Henriëtte M. G. Willems*
Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB, U.K.

Abstract—The design and synthesis of conformationally constrained, nonpeptide templates (1,1,6-trisubstituted indanes) which allow the incorporation of two adjacent amino acid side chains, plus a third binding group in an orientation similar to that found in alpha-helices are reported. Six racemic and two homochiral Phe–Phe and Trp–Phe mimetics were synthesised and evaluated in tachykinin receptor binding assays as molecular probes for the binding conformation of the endogenous peptides. Several were found to bind with micromolar affinity to the NK_1 and/or NK_3 receptor. The conformation of one of the homochiral indanes, (1*R*)-*N*-((*S*)-1-hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide, was analysed by X-ray crystallography and was found to be in an α-helix conformation.

Introduction

Peptides play a primary role in intercellular communication functioning, for example, as hormones, neurotransmitters and neuromodulators. Their use as therapeutic agents is limited because they are often unstable towards degrading enzymes, poorly absorbed from the gastro-intestinal tract and have potential for causing allergic reactions. The development of small nonpeptide ligands for neuropeptide receptors has, therefore, become a major goal of medicinal chemists over the last decade.

Our interest in the rational design of nonpeptide drug candidates for neuropeptide receptors, based on the structure of the endogenous neuropeptide itself (i.e., peptidomimetics) has lead us to devise a general strategy for their design.[1,2] As part of this strategy, we are developing a family of 'rigid' templates with a range of physicochemical properties which mimic part of the common structural motifs found in proteins.[3] In these templates the α–β C—C bonds of at least two of the appended 'amino acid side chains' should overlay the corresponding bonds in the secondary peptide structure of interest (e.g., α-helix, β-turn, β-sheet). These templates should also meet certain other criteria concerning their physicochemical properties if our goal of obtaining a nonpeptide drug candidate is to be achieved, in particular, templates should have a low molecular weight and be stable towards proteases.[4]

One of the common motifs of protein secondary structure is the α-helix. Several studies[5] have indicated that peptides, which are conformationally flexible in solution, can adopt an α-helical structure upon interaction with their target binding proteins. In these examples the amino-acid side chains of the alpha helices are cited to be important in the molecular recognition process.[5] These findings prompted our interest in the development of a template as an alpha helix mimetic.

Despite the prevalence of alpha helices there are no reports, apart from our earlier publications,[1,4,6] describing the synthesis of nonpeptide alpha helix mimetics mimicking two or three sequential amino acids, although Olson, et al. recently introduced an alpha helix spacer template,[7] mimicking two non-sequential amino acid residues lying alongside one face of the helix. Several groups have also described cyclic templates designed to initiate helical structure in appended peptide chains.[8]

The template we selected for our α-helix mimetics is a 1,1,6-trisubstituted indane (Fig. 1). This is a relatively rigid template, so the orientation in space of the substituents can be predicted. Molecular modelling indicates that a good overlay exists between the 1- and 6- substituents of the indane template and the Cα to Cβ bonds of the i and i+1 residues of an alpha helix. The second substituent at the 1-position of the indane overlays with the i−1 residue (labelled M). Six racemic dipeptide mimetics containing this template were prepared, as well as two homochiral compounds. These α-helix mimetics and four intermediates containing the indane skeleton were evaluated in binding assays for the tachykinin receptors to probe the binding conformation of their endogenous neuropeptides: substance P, neurokinin A and neurokinin B.

Chemistry

The synthesis of the racemic trisubstituted indanes is illustrated in Scheme 1. All mimetics were synthesised from a common intermediate: methyl

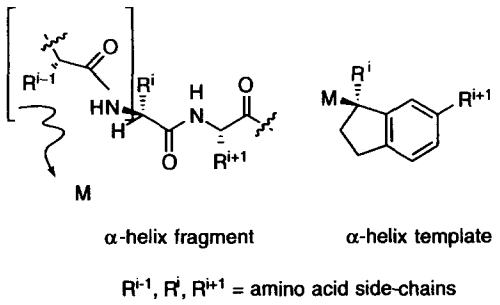
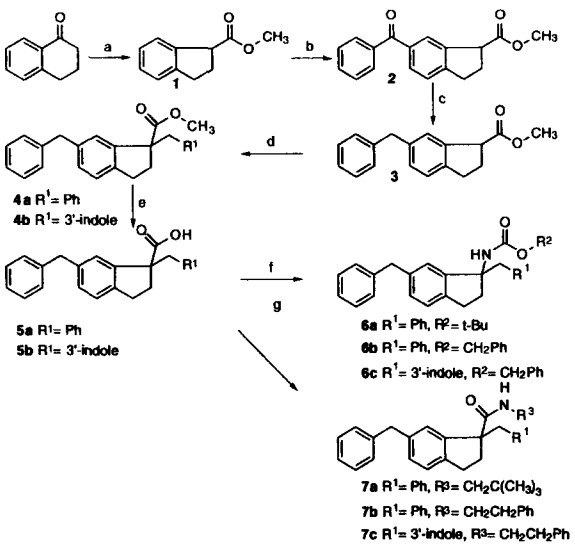


Figure 1. The indane template (right) mimicking an α-helix.

6-benzylindan-1-carboxylate (**3**). This methyl ester is prepared from the readily available α-tetralone, via a lead tetraacetate ($Pb(OAc)_4$) catalysed ring contraction to give **1**,[9] followed by a Friedel–Crafts acylation of the resulting ester[10] and subsequent hydrogenolysis of the aromatic carbonyl group. NOE experiments were carried out on compound **2**, obtained via the Friedel–Crafts acylation. These confirmed that the major product of the acylation was a 6-substituted indane. A small amount of 5-substituted indane was also formed (10–15%), but this could easily be separated from the desired product by column chromatography. The ester **3** was converted to its enolate and alkylated in good yields with either benzyl bromide to yield intermediate **4a** for the Phe–Phe mimetic series, or gramine methiodide, yielding the intermediate **4b** for the Trp–Phe mimetic series. The use of two equivalents of LHMDS in the enolate formation step was found to be essential in both cases. When one equivalent was used, no product was obtained and 60–80% of the starting material could be recovered. Basic hydrolysis of esters **4a** and **b** afforded their respective free acids in good to excellent yield.

Ester **5a** was subjected to a modified Curtius rearrangement using DPPA (diphenylphosphoryl azide) to yield the Boc–Phe–Phe mimetic **6a** in moderate yield. *t*-Butanol was added after formation of the intermediate isocyanate. The low yield of the rearrangement is probably due to the high stability of the isocyanate intermediate, since the yield dropped considerably when attempts were made to quench the isocyanate at temperatures below 120 °C. The Z–Phe–Phe mimetic **6b** was made in a similar manner from **5a** and benzyl alcohol. The phenylindolylmethyl acid **5b** was also subjected to a Curtius rearrangement yielding Z–Trp–Phe mimetic **6c** in a yield substantially lower than that reported for the Phe–Phe mimetic **6a**. Protection of the indole-N of **5b** as a *t*-butoxycarbamate greatly improved the yield of the Curtius rearrangement (from 15% to 55%). However, deprotection of the rearrangement product failed to give the desired **6c**.

The acids **5** were also condensed with primary amines to give amides **7**. The dibenzyl acid **5a** was converted to its acid chloride and coupled to neopentylamine and phenethylamine to give **7a** and **7b** in good yield. In the case of indolylmethylbenzyl acid **5b** it was found that



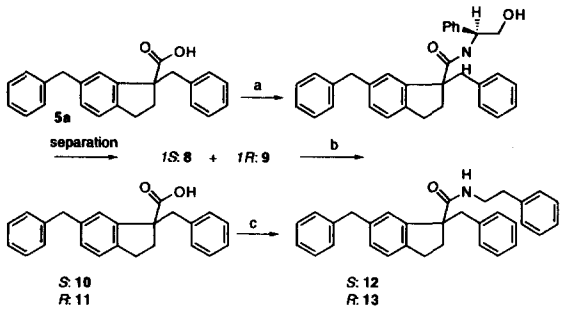
Scheme 1. The synthesis of the racemic α-helix mimetics.
Reagents and Conditions: (a) i. BF_3.etherate, MeOH, ii. $Pb(OAc)_4$ (43%); (b) i. $AlCl_3$, $MeNO_2$, ii. benzoyl chloride, reflux (70%); (c) H_2 (50 psi), 10% Pd on C, CF_3COOH, EtOH (88%).
For R_1 = Ph: (d) i. LHMDS, THF, −78 °C, ii. BnBr (88%); (e) NaOH, MeOH, reflux (88%); (f) i. DPPA, Et_3N, toluene, reflux, ii. R^2OH, 120 °C (39%, 24%); (g) i. $(COCl)_2$, CH_2Cl_2, ii. for R^3 = $CH_2C(CH_3)_3$; $(CH_3)_3CCH_2NH_2$, Et_3N (55%), for $R^3 = CH_2CH_2Ph$: $H_2NCH_2CH_2Ph.HCl$, Et_3N (79%).
For R^1 = 3'-indole: (d) i. LHMDS, THF, −78 °C, ii. gramine MeI, LHMDS (69%); (e) NaOH, MeOH, reflux (72%); (f) i. DPPA, Et_3N, toluene, reflux, ii. R^2OH, 120 °C (15%); (g) i. HBTU, ii. $H_2NCH_2CH_2Ph.HCl$, Et_3N (39%).

coupling aided by HBTU was a superior method than that mediated via the acid chloride.

For our homochiral preparation of the two isomers of Z–Phe–Phe mimetic **7b** (Scheme 2), racemic **5a** was derivatised with S-phenylglycinol and the resulting diastereomers **8** and **9** were easily separated by column chromatography. The amides were hydrolysed in moderate yield by refluxing in 2 M H_2SO_4/dioxane. The hydrolysis was found to be very slow, taking three days to go to completion. The resulting homochiral acids **10** and **11** were coupled to phenethylamine using the same procedure as used for the synthesis of **7b**, to give optically active **12** and **13**.

Results and Discussion

Computer modelling studies indicate a good overlay exists between the 1- and 6-substituents of the indane and the Cα to Cβ side chain bonds of the i and i+1 side chains of an α-helix. The second substituent at the 1-position of the indane overlays with the i−1 residue (labelled M in Figure 1). In fact, the two Cα and the two Cβ carbon atoms of adjacent (i, i+1) alpha helix side chains and the N-terminus nitrogen of the model template overlay with the corresponding positions in an alpha-helix with a root mean square (rms) deviation of 0.2 Å (Figure 2). Furthermore, the template skeleton does not extend beyond the space occupied by the α-helix. Of the two enantiomers of the template, only the *S*-isomer mimics the protein alpha helix (Figs 1 and



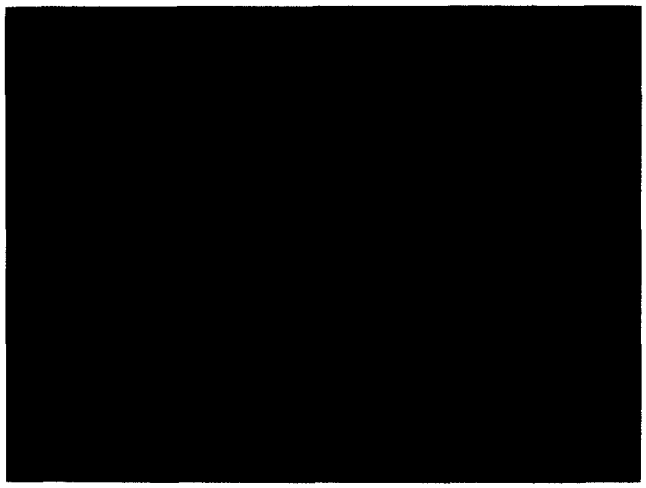
Scheme 2. The synthesis of the two homochiral α-helix mimetics. Reagents and Conditions: (a) i. $(COCl)_2$, CH_2Cl_2, ii. L-(+)-α-phenylglycinol, Et_3N (31% **8**, 34% **9**); (b) 2 M H_2SO_4, dioxane (58%); (c) i. $(COCl)_2$, CH_2Cl_2, ii. $PhCH_2CH_2NH_2$.HCl, Et_3N (75%).

2). Therefore, we prepared the individual enantiomers of one of the mimetics. The Z–Phe–Phe mimetic **7b** was chosen because of its ease of synthesis and relatively high affinity for the tachykinin NK_1 and NK_3 receptors. The absolute stereochemistry of optically active Z–Phe–Phe mimetics **12** and **13** was assigned from the stereochemistry of **9**. The latter was determined by X-ray analysis (Fig. 3) and found to be *R*. The stereochemistry of compounds **8**, **10**, and **11** also were assigned from this.

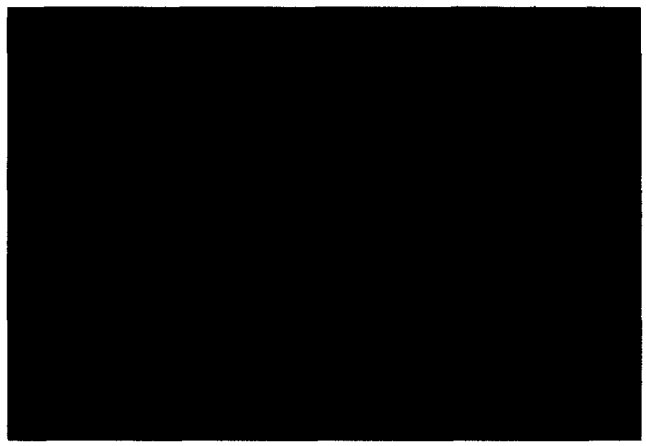
An overlay of the inverted structure of **9**, as determined by X-ray analysis, on a right handed alpha helix is shown in Figure 4. Inversion of the X-ray structure was carried out because **9** was shown to be the *R*-isomer, which does not mimic the protein alpha helix. Inverted **9** was fitted to a model alpha helix by overlaying the Cα atoms of the helix with the side chain attachment points of the indane (C9 and C15, Fig. 3) and the Cβ atoms with the first carbon atoms of the indane side chains (C1, C18, and C25, Fig. 3). The rms distance at these five points is 0.2 Å. This small rms distance shows that the 1,1,6-substituted indane template does indeed, at least in the solid phase, mimic an alpha helix, as was predicted by molecular modelling.

The tachykinin receptor affinities of all the Phe–Phe and Trp–Phe mimetics synthesised were evaluated, as well as those of four intermediates containing the 1,1,6-substituted indane skeleton. The results are shown in Table 1. Albeit weak, selective binding to the NK_1 receptor was shown by compound **9** (NK_1 binding, $IC_{50} = 3.6$ μM). Compounds **7a** and **13** were found to be selective for the NK_3 receptor (NK_3 binding, $IC_{50} = 5.2$, 6.1 μM). Interestingly, compounds **7b**, **8**, and **12** show micromolar affinity for both the NK_1 and the NK_3 tachykinin receptor subtypes. None of the compounds synthesised displayed any affinity for the NK_2-receptor ($IC_{50} > 10$ μM).

The affinities obtained for the α-helix mimetics were compared to those of Boc–Phe–$PheNH_2$ and Z–Trp–$PheNH_2$, two N-protected dipeptides which had previously been shown to have a micromolar affinity for the NK_3 and NK_1/NK_2 tachykinin receptors, respectively.[11] All affinities are comparable to, but not



(a)



(b)

Figure 2. (a) An overlay of 1-*N*-acetyl-1,6-dibenzylindane (in red) with a model α-helix ($(Ala)_3PhePhe(Ala)_3$). The 1-*N*-acetyl-1,6-dibenzylindane has an energy of 3.5 kcals mol^{-1} above the lowest energy conformation and the rms distance is 0.2 Å. A cross-sectional view. (b) An overlay of 1-*N*-acetyl-1,6-dibenzylindane (in red) with a model α-helix ($(Ala)_3PhePhe(Ala)_3$). A side view.

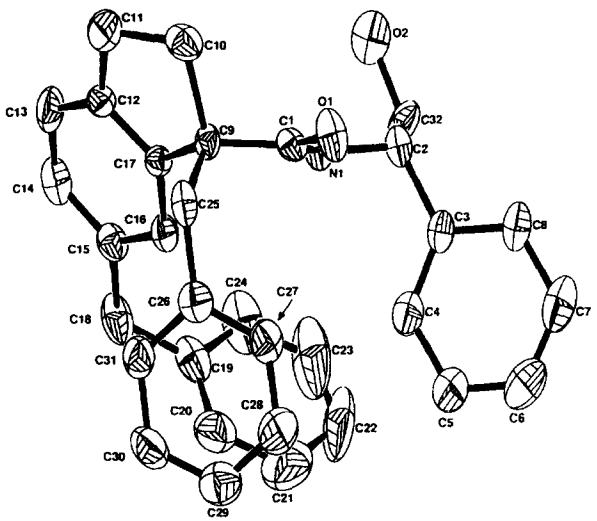


Figure 3. The structure of **9** as found by X-ray analysis.

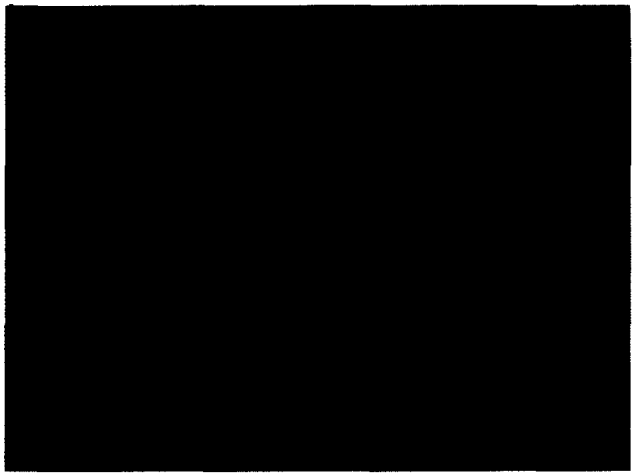


Figure 4. An overlay of an inverted X-ray diagram of (1*R*)-*N*-((*S*)-hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide **9** (in black) with a model α-helix ((Ala)$_4$PhePhe(Ala)$_4$).

better than those determined for the two dipeptide leads (the first two entries in Table 1). If a flexible dipeptide binds in the same conformation as its rigid mimetic, the binding affinity of the rigid mimetic is expected to be higher because of a more favourable entropy term.[12] The comparable affinities of the flexible N-protected dipeptides and the rigid mimetics would therefore suggest that the former do not bind in an α-helix conformation. Alternatively, it is possible that the amide bond in the dipeptides, which is not present in the α-helix mimetics, is important for binding. Further experiments are needed to establish which is most likely to be the case.

Conclusion

We have described the design of nonpeptide alpha helical mimetics and illustrated this with the synthesis of Boc–Phe–Phe, Z–Phe–Phe and Z–Trp–Phe mimetics. These were evaluated in tachykinin binding assays and several were shown to possess micromolar affinity for the NK_1 and/or NK_3 receptors. The two individual isomers of one of the Z–Phe–Phe mimetics were subsequently prepared and evaluated in the tachykinin binding assays. The *S*-isomer was found to have affinities comparable to the racemic Z–Phe–Phe mimetic **7b**. The *R*-isomer showed a decrease in NK_1 affinity. An X-ray structure of a key intermediate containing the 1,1,6-trisubstituted indane template was obtained, and confirmed the conformation of the template suggested by molecular modelling.

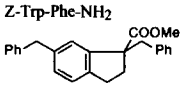
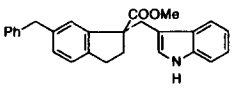
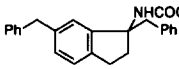
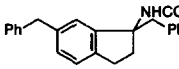
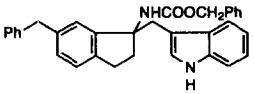
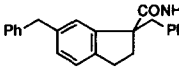
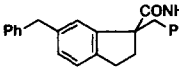
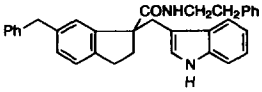
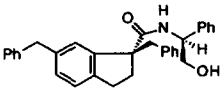
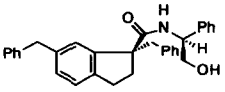
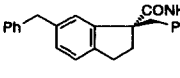
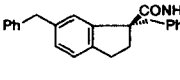
The Phe–Phe and Trp–Phe mimetics **7a**, **7b**, **8**, **9**, **12**, and **13** retained the same micromolar affinity as the parent dipeptides Boc–Phe–Phe–NH_2 and Z–Trp–Phe–NH_2. This has encouraged us to use template design to develop more potent mimetics of tachykinins and other neuropeptide targets. Further studies aimed at synthesising alpha helix mimetics containing a more polar template and the synthesis of small, polar beta turn mimetics are in progress and will be reported elsewhere.

Experimental

Computer molecular modelling

Computer molecular modelling was performed using the SYBYL program (Version 6.0) supplied by Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, Missouri 63144, U.S.A. The lowest energy

Table 1. Tachykinin binding data for the trisubstituted indanes

No. or name	Structure	NK_1[a] Binding (IC_{50}, uM)	NK NK_2[b] Binding (IC_{50}, uM)	NK_3[c] Binding (IC_{50}, uM)
Cam-3508	Boc-Phe-Phe-NH_2	>10	>10	1.6
Cam-104	Z-Trp-Phe-NH_2	5.2	3.1	>10
4a		3.0	>10	8.0
4b		>10	>10	>10
6a		>10	>10	>10
6b		>10	>10	>10
6c		>10	-	>10
7a		>10	>10	5.2
7b		2.4	>10	3.0
7c		>10	>10	>10
8		3.1	-	1.8
9		3.6	-	>10
12		5.1	-	3.2
13		>10	-	6.1

(a) Human IM-9 cells, ^{125}I-BH-SP.[11b] (b) Hamster urinary bladder, ^{125}I-NKA.[11a] (c) Human receptor expressed in stable CHO cells, ^{125}I-[MePhe7]-NKB.[11c]

state of the (*S*)-enantiomer of *N*-acetyl-1,6-dibenzylindane 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 kcal mol^{-1} A^{-1}. The lowest energy conformer found by this procedure was overlaid by the method of least squares with $(Ala)_4$ $PhePhe(Ala)_4$ in an alpha-helix conformation (angles from the BIOPOLYMER library). Both benzylgroups of the *N*-acetyl-1,6-dibenzylindane were subsequently rotated to overlay with the phenylalanine side chains of the alpha helix. In this conformation (shown in Figure 2) the indane has an energy of 3.5 kcal/mol above its lowest energy conformation and the rms distance is 0.2 Å.

X-ray Crystallography

Crystal structure determination was performed by the Crystallography Department at the School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K. A crystal of **9** with the approximate dimensions $0.3 \times 0.4 \times 0.2$ mm was prepared by recrystallisation from acetonitrile and subsequently used for the data collection.

Crystal data: $C_{32}H_{31}NO_2$, $M = 461.6$ monoclinic, $a = 9.857(1)$, $b = 9.702(1)$, $c = 14.131(3)$ Å, $\beta = 105.34(1)°$, $U = 1303.2$ Å^3, space group $P2_1$, $Z = 2$, $D_c = 1.18$ g cm^{-3}, $\mu(Mo-K_\alpha) = 0.70$ cm^{-1}, $F(000) = 492$. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leq \theta \leq 24°$. 2316 reflections were collected of which 1062 were unique with $I \geq 2\sigma(I)$. Data were corrected for Lorentz and polarisation, but not for absorption. The structure was solved by direct methods and refined using the SHELX[13] suite of programs. In the final least squares cycles, all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions, except in the instance of H1 and H2 (attached to N1 and O2, respectively), where the protons were located in an advanced Difference Fourier and refined at a distance of 0.96 Å from the relevant parent atoms.

Examination of the gross molecular packing revealed that the lattice was dominated by intermolecular hydrogen bonds through the oxygen atoms, yielding one dimensional linear polymers about the 2_1 screw axes. In particular, H2 of the molecule as presented bonds to O1 of the lattice neighbour generated via the operator $-x, 0.5 = y, -1 - z$. (H2–O1, 1.80 Å).

Final residuals after 12 cycles of least squares were $R = 0.0523$, $R_w = 0.0491$, for a weighting scheme of $w = 2.0667/[\sigma^2(F) + 0.000523(F)^2]$. Max. final shift/esd was 0.002. The max and min residual densities were 0.09 and -0.07 eÅ^{-3}, respectively. Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles and anisotropic temperature factors are available as supplementary data. The asymmetric unit is shown in Figure 3, along with the labelling scheme used.

Chemistry

Melting points were determined on a Reichert Thermometer hot stage microscope and are corrected. Solvents were evaporated using a Buchi rotary evaporator. IR spectra were recorded on a Perkin Elmer 1750 Fourier transform spectrometer. ^{1}H NMR spectra were recorded on a Brüker AM 300 spectrometer at 300 MHz and chemical shifts are reported in δ parts per million down field from tetramethylsilane. Chemical ionisation (CI) and electron ionisation (EI) mass spectra were determined on a Finnegan 4500 spectrometer at Parke–Davis, Ann Arbor, Michigan, U.S.A. or by the SERC mass spectroscopy service, Swansea, U.K. Elemental analysis indicated by the symbols of the elements were within ±0.4% of theoretical values and were performed by Medac Ltd., Dept. of Chemistry, Brunel University, Uxbridge, Middlesex, U.K. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 10 cm pathlength cell. Column chromatography was carried out under pressure (N_2) using Merck Kieselgel 60 for normal phase columns and LiChrom-prep®-RP-18 for reverse phase columns. Anhydrous solvents were purchased in septum capped bottles from Fluka Chemicals Ltd., Glossop, U.K. and dispensed by syringe.

Methyl 6-benzoylindan-1-carboxylate (2).[14] $AlCl_3$ (3.18 g, 0.02 mol) and $MeNO_2$ (dry; 40 mL) were placed in a 100 mL 2-necked flask. The flask was fitted with a condenser and a dropping funnel and flushed with N_2. Methyl indan-1-carboxylate (**1**)[9] (3.35 g, 0.019 mol) was dissolved in $MeNO_2$ (dry; 8 mL) and added in one go to the stirred $AlCl_3$-suspension. The mixture was cooled to 0 °C and a solution of benzoyl chloride (11.0 mL, 0.095 mol) in $MeNO_2$ (dry; 16 mL) was placed in the dropping funnel and added dropwise over 10 min. The reaction mixture was then heated to 45 °C for 4 h. After cooling the mixture was poured into ice water (150 mL). The resulting suspension was extracted with CH_2Cl_2 (3×120 mL). The combined organic layers were then washed with $NaHCO_3$ (aq, satd; 150 mL) and water (150 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane: Et_2O, 9:1) to give **2** as a yellow oil (3.70 g, 70%). IR(film) 2951, 1735, 1656, 1435, 1281 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 7.83 (1H, s), 7.79 (1H, d, $J = 7.0$ Hz), 7.7–7.2 (6H, m), 4.10 (1H, m), 3.73 (3H, s), 3.22 (1H, m), 3.03 (1H, m), 2.53 (2H, m); MS *m/z* (CI) 281 ($[M+H]^+$, 100%), 221 (15); found C, 76.82; H, 5.74; $C_{18}H_{16}O_3$ requires C, 77.12; H, 5.75.

Methyl 6-benzylindan-1-carboxylate (3). Methyl 6-benzoylindan-1-carboxylate (**2**) (400 mg, 1.43 mmol) was dissolved in ethanol (abs; 40 mL) and TFA (0.2 mL) was added. The solution was placed in a hydrogenation flask. The flask was flushed with N_2 for 5 min after which the catalyst, 10% Pd on C (150 mg), was added. The flask was filled with H_2 at 50 psi and the mixture shaken overnight at room temperature. The catalyst was removed by filtration through kieselguhr and the filtrate was concentrated in vacuo to give **3** as a pink oil (335 mg, 88%). IR(film) 3026, 2950, 1732, 1493, 1265, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.0 (8H, m), 4.02 (1H, m), 3.94 (2H, s), 3.69 (3H, s), 3.04 (1H, m), 2.87 (1H, m), 2.33 (2H, m); MS *m/z* (CI) 266 (M^+, 42%), 235 (6), 207 (100); Found C, 80.87; H, 6.85; $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81.

Methyl 1,6-dibenzylindan-1-carboxylate (4a). A 1 M solution of LHMDS in hexanes (2.45 mL, 2.0 equiv) and THF (dry; 20 mL) were placed in a 100 mL two-necked flask fitted with a dropping funnel, that had been flushed with argon. The solution was cooled to −78 °C and a solution of methyl 6-benzylindan-1-carboxylate (**3**) (320 mg, 1.2 mmol) in THF (dry; 4 mL) was added dropwise over 5 min via the dropping funnel. The solution was stirred for 45 min at −78 °C, then a solution of benzyl bromide (0.17 mL, 1.44 mmol, 1.2 equiv; dry) in THF (dry; 2.0 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C, then left to warm to room temperature and stirred for another 3 h. NH_4Cl (aq, satd; 25 mL) was added and the layers were separated. The water layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:ether, 9:1) to give **4a** as a colourless oil (378 mg, 88%). IR(film) 3027, 2949, 1728, 1494, 1237, 1198, 1171 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.0 (13H, m), 3.98 (2H, s), 3.67 (3H, s), 3.44 (1H, d, *J* = 13 Hz), 3.01 (1H, d, *J* = 13 Hz), 2.87 (1H, m), 2.57 (1H, m), 2.14 (2H, m); MS *m/z* (CI) 357 ($M+H^+$, 12%), 325 (11), 297 (100), 265 (55); Found C, 83.51; H, 6.84; $C_{25}H_{24}O_2 + 0.2\ H_2O$ requires C, 83.39; H, 6.83.

Methyl 6-benzyl-1-(3′-indolylmethyl)indan-1-carboxylate (4b). Gramine methiodide[15] (650 mg, 2.07 mmol) was placed in a solid addition device, which was then fitted on a 250 mL 3-necked flask. A dropping funnel and septum were fitted on the flask and it was flushed with argon. A 1 M solution of LHMDS in THF (3.8 mL, 2 equiv) and THF (dry; 25 mL) were placed in the flask. The solution was cooled to −78 °C and a solution of methyl 6-benzylindan-1-carboxylate (**3**) (500 mg, 1.88 mmol) in THF (dry; 14 mL) was added dropwise over 5 min. The solution was stirred for 45 min at −78 °C. The gramine methiodide was then added in 4 portions together with a 1 M solution of LHMDS in THF (2.8 mL, 1.5 equiv.). The mixture stirred for 30 min at −78 °C, followed by 45 min at room temperature. NH_4Cl (aq, satd; 30 mL) was added and the layers were separated. The water layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with $NaHCO_3$ (aq, satd, 30 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:EtOAc, 4:1) to give **4b** as a brown oil (510 mg, 69%). A small sample was further purified by reverse-phase column chromatography (methanol in water, 80→100%) to give a colourless glass. IR(film) 3420, 1722, 1238, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (1H, s, br), 7.47 (1H, d, *J* = 7.9 Hz), 7.3–6.9 (11H, m), 6.68 (1H, s), 3.96 (2H, s), 3.62 (3H, s), 3.57 (1H, d, *J* = 14.5 Hz), 3.19 (1H, d, *J* = 14.5 Hz), 2.92 (1H, m), 2.8–2.5 (2H, m), 2.19 (1H, m); MS *m/z* (CI) 396 ($M+H^+$, 28%), 336 (45), 265 (100), 130 (91); acc. mass: found 396.1964, $C_{27}H_{25}NO_2 + H^+$ requires 396.1964.

1,6-Dibenzylindan-1-carboxylic acid (5a). Methyl 1,6-dibenzylindan-1-carboxylate (**4a**) (146 mg, 0.41 mmol) was dissolved in methanol (15 mL). An aqueous 15% NaOH solution (2.5 mL) was added and the mixture was heated to reflux for 1 h. The methanol was evaporated off and the remaining oil taken up in water (10 mL). The mixture was acidified with 2 M HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:EtOAc, 4:1) to give **5a** as a colourless oil (125 mg, 89%). IR(film) 3500, 3027, 1698, 1494, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.4–7.0 (13H, m), 3.99 (2H, s), 3.48 (1H, d, *J* = 13 Hz), 3.05 (1H, d, *J* = 13 Hz), 2.93 (1H, m), 2.65 (2H, m), 2.19 (1H, m); MS *m/z* (CI) 360 ($M+NH_4+$, 10%), 343 ($M+H^+$, 5), 297 (42), 91 (100); found C, 82.58; H, 6.60; $C_{24}H_{22}O_2 + 0.42\ H_2O$ requires C, 82.36; H, 6.58.

6-Benzyl-1-(3′-indolylmethyl)indan-1-carboxylic acid (5b). Methyl 6-benzyl-1-(3′-indolylmethyl)indan-1-carboxylate (**4b**) (330 mg, 0.83 mmol) was dissolved in methanol (25 mL). An aqueous 15% NaOH solution (5.0 mL) was added and the mixture heated to reflux for 2 h. The methanol was evaporated off and the remaining oil taken up in water (20 mL). The mixture was acidified with 2 M HCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to give **5b** as an off-white foam (220 mg, 69%). Mp 57–58 °C; IR(film) 3425, 2932, 1694, 1256, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (1H, s, br), 7.50 (1H, d, *J* = 7.9 Hz), 7.4–6.9 (11H, m), 6.65 (1H, s), 3.98 (2H, s), 3.61 (1H, d, *J* = 14.6 Hz), 3.21 (1H, d, *J* = 14.6 Hz), 2.93 (1H, m), 2.7–2.5 (2H, m), 2.20 (1H, m); MS *m/z* (CI) 382 ($M+H^+$, 23%), 336 (17), 130 (91); found C, 81.55; H, 6.12; N, 3.58; $C_{26}H_{23}NO_2$ requires C, 81.86; H, 6.08; N, 3.67.

***N-tert*-Butoxycarbonyl-1,6-dibenzylindan-1-amine (6a).** A solution of 1,6-dibenzylindan-1-carboxylic acid (**5a**) (170 mg, 0.50 mmol) in toluene (dry; 15 mL) was

placed in a 100 mL 2-necked flask fitted with a condenser and septum. The flask was flushed with N_2 and triethylamine (0.069 mL, 0.50 mmol) and diphenylphosphoryl azide (0.108 mL, 0.50 mmol) were added. The mixture was heated to reflux for 1.5 h (until evolution of N_2 had stopped). *tert*-Butanol (dry; 3 mL) was added and the mixture was heated to reflux for another 48 h. An extra 2 mL of *tert*-butanol was added after 3, 20, and 26 h. The solvent was evaporated in vacuo and the residue taken up in CH_2Cl_2 (50 mL). The solution was washed with citric acid (aq, satd), H_2O, $NaHCO_3$ (aq, satd) and brine (all 15 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:ethyl acetate, 19:1) to give **6a** as a colourless oil (80 mg, 39%). IR(film) 3366, 2930, 1716, 1494, 1250, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.03 (10H, m, aromatics), 6.85 (2H, d, $J=7$ Hz), 6.67 (1H, s), 4.80 (1H, s, br), 3.88 (2H, s), 3.38 (1H, m, br), 3.09 (1H, m, br), 2.82 (1H, m), 2.58 (2H, m, br), 2.39 (1H, m), 1.44 (9H, s); MS *m/z* (CI) 414 ($M+H^+$, 3%), 322 (20), 297 (100); acc. mass: found 414.2433, $C_{28}H_{31}NO_2 + H^+$ requires 414.2433.

***N*-Benzyloxycarbonyl-1,6-dibenzylindan-1-amine (6b).** A solution of 1,6-dibenzylindan-1-carboxylic acid (**5a**) (130 mg, 0.38 mmol) in toluene (dry; 10 mL) was placed in a 100 mL 2-necked flask fitted with a condenser and septum. The flask was flushed with N_2 and triethylamine (0.055 mL, 0.40 mmol) and diphenylphosphoryl azide (0.090 mL, 0.38 mmol) were added. The mixture was heated to reflux for 1.5 h (until evolution of N_2 had stopped). Benzylalcohol (0.062 mL, 0.57 mmol) was added and the mixture heated to reflux for another 48 h. The solvent was evaporated in vacuo and the residue taken up in CH_2Cl_2 (50 mL). The solution was washed with citric acid (aq, satd), water, $NaHCO_3$ (aq, satd) and brine (all 15 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:EtOAc, 5:1). The fraction containing the product was further purified by reverse-phase column chromatography (MeOH in water, 70→100%) to give **6b** as a colourless glass (40 mg, 24%). IR(film) 3340, 3028, 1723, 1494, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–6.95 (15H, m), 6.78 (2H, d, $J=7$ Hz), 6.65 (1H, s), 5.12 (2H, d, $J=12$ Hz), 5.09 (1H, d, $J=12$ Hz), 3.86 (2H, s), 3.38 (1H, m, br), 3.12 (1H, m, br), 2.79 (1H, m, br), 2.57 (2H, m, br), 2.36 (1H, m); MS *m/z* (CI) 448 ($M+H^+$, 7%), 356 (36), 312 (13), 297 (100); found C, 82.15; H, 6.67; N, 3.16; $C_{31}H_{29}NO_2 + 0.3\ H_2O$ requires C, 82.20; H, 6.59; N, 3.09.

***N*-Benzyloxycarbonyl-6-benzyl-1-(3′-indolylmethyl)-indan-1-amine (6c).** A solution of 6-benzyl-1-(3′-indolylmethyl)indan-1-carboxylic acid (**5b**) (610 mg, 1.60 mmol) in toluene (dry; 20 mL) was placed in a 100 mL 2-necked flask fitted with a condenser and septum. The flask was flushed with N_2 and triethylamine (0.25 mL, 1.76 mmol) and diphenylphosphoryl azide (0.38 mL, 1.76 mmol) were added. The mixture was heated to reflux for 2 h (until evolution of N_2 had stopped). Benzylalcohol (0.25 mL, 2.40 mmol) was added and the mixture was heated to reflux for another 24 h. The solvent was evaporated in vacuo and the residue taken up in CH_2Cl_2 (150 mL). The solution was washed with citric acid (aq, satd), water, $NaHCO_3$ (aq, satd) and brine (all 50 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, hexane:EtOAc, 5:1). The fraction containing the product was further purified by reverse-phase column chromatography (MeOH in water, 70→100%) to give **6c** as a colourless glass (123 mg, 15%). IR(film) 3419, 3348, 3029, 2917, 1712, 1494, 1232, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (1H, s, br), 7.39–6.95 (16H, m), 6.73 (1H, s), 6.32 (1H, s), 5.20 (1H, s), 5.09 (1H, d, $J=12$ Hz), 5.07 (1H, d, $J=12$ Hz), 3.83 (2H, s), 3.43 (1H, s, br), 3.30 (1H, d, $J=14$ Hz), 2.90 (1H, m), 2.7–2.5 (2H, m), 2.45 (1H, m); MS *m/z* (CI) 486 (M^+, 1%), 356 (59), 336 (100); found C, 80.57; H, 6.38; N, 5.35; $C_{33}H_{30}N_2O_2 + 0.3\ H_2O$ requires C, 80.56; H, 6.27; N, 5.69.

***N*-Neopentyl-1,6-dibenzylindan-1-carboxamide (7a).** 1,6-Dibenzylindan-1-carboxylic acid (**5a**) (270 mg, 0.79 mmol) was dissolved in toluene (dry; 25 mL) and placed in a 100 mL flask. Oxalyl chloride (0.21 mL, 2.37 mmol, 3 equiv) and DMF (dry; 0.3 mL) were added and the flask was fitted with a condenser closed with a drying tube. The solution was heated to 70 °C for 1 h, then concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (dry; 5 mL) and added dropwise to a solution of neopentylamine (0.092 mL, 0.79 mmol, 1 equiv) and triethylamine (0.164 mL, 1.19 mmol, 1.5 equiv) in CH_2Cl_2 (dry; 15 mL). The mixture was stirred at room temperature for 2 h, then concentrated in vacuo. The residue was taken up in 2 M HCl (15 mL) and the solution extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water and brine (both 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (hexane:EtOAc, 19:1) to give **7a** as a colourless oil (180 mg, 55%). IR (film) 3435, 2958, 1668, 1516 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.0 (10H, m), 6.92 (2H, d, $J=6.4$ Hz), 6.72 (1H, s), 5.47 (1H, s, br), 3.87 (2H, s), 3.50 (1H, d, $J=13$ Hz), 3.07 (2H, m + d, $J=13$ Hz), 2.83 (2H, m), 2.63 (1H, m), 2.35 (2H, m); MS *m/z* (CI) 412 ($M+H^+$, 100%), 320 (13), 297 (31), 91 (65); found C, 84.51; H, 8.16; N, 3.31; $C_{29}H_{33}NO$ requires C, 84.63; H, 8.08; N, 3.40.

***N*-Phenethyl-1,6-dibenzylindan-1-carboxamide (7b).** 1,6-Dibenzylindan-1-carboxylic acid (**5a**) (300 mg, 0.88 mmol) was dissolved in CH_2Cl_2 (dry; 25 mL) and placed in a 100 mL flask. Oxalyl chloride (0.23 mL, 2.63 mmol, 3 equiv.) and DMF (dry; 0.3 mL) were added and the flask was fitted with a condenser closed with a drying tube. The solution was heated to 44 °C for 1 h, then concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (dry; 2 mL) and added dropwise to a solution of phenethylamine hydrochloric

acid (140 mg, 0.88 mmol, 1 equiv) and triethylamine (0.306 mL, 2.2 mmol, 2.5 equiv) in CH_2Cl_2 (dry; 20 mL). The mixture was stirred at room temperature for 2 h, then concentrated in vacuo. The residue was taken up in 2 M HCl (20 mL) and the solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water and brine (both 20 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (hexane:EtOAc, 6:1) to give **7b** as a colourless oil (310 mg, 79%). IR(film) 3424, 3026, 2924, 1662, 1513, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–6.87 (17H, m), 6.64 (1H, s), 5.47 (1H, s, br), 3.80 (2H, dd, J=12 and 15 Hz), 3.58 (1H, m), 3.40 (1H, d, J=13 Hz), 3.31 (1H, m), 3.03 (1H, d, J=13 Hz), 2.67 (1H, m), 2.62 (2H, t, J=6 Hz), 2.57 (1H, m) 2.28 (2H, m); MS *m/z* (CI) 446 ($M+H^+$, 100%), 354 (16), 297 (35); found C, 85.94; H, 7.05; N, 3.21; $C_{32}H_{31}NO$ requires C, 86.25; H, 7.01; N, 3.14.

***N*-Phenethyl-6-benzyl-1-(3′-indolylmethyl)indan-1-carboxamide (7c).** To a solution of 6-benzyl-1-(3′-indolylmethyl)indan-1-carboxylic acid (**5b**) (130 mg, 0.34 mmol) in DMF (dry; 3 mL) was added triethylamine (0.096 mL, 0.68 mmol) and HBTU (130 mg, 0.34 mmol). The mixture was stirred for 10 min at room temperature. A solution of phenethylamine hydrochloric acid salt (55 mg, 0.34 mmol) and triethylamine (0.048 mL, 0.34 mmol) in DMF (dry; 2 mL) was added and the mixture was stirred for 2 h at room temperature, then concentrated in vacuo. The residue was taken up in EtOAc (80 mL) and washed with NaCl (aq, satd), 1 M HCl, water, $NaHCO_3$ (aq, satd) and 10% aqueous NaCl (all 20 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by reverse-phase column chromatography (MeOH in water, 70→100%) to give **7c** as a off-white solid (65 mg, 39%). Mp 40–42 °C; IR(film) 3419, 3216, 2924, 1645, 1516, 1455, 1341 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (1H, s, br), 7.41–6.82 (16H, m), 6.70 (1H, s), 6.46 (1H, s), 5.45 (1H, s), 3.74 (1H, d, J=12 Hz), 3.72 (1H, d, J=12 Hz), 3.52 (1H, m), 3.41 (1H, d, J=14 Hz), 3.37 (2H, m), 2.69 (2H, m), 2.62 (2H, m), 2.38 (1H, m), 2.12 (1H, m); MS *m/z* (CI) 485 ($M+H^+$, 100%), 355 (22), 336 (6), 130 (45); acc. mass: found 485.2593, $C_{34}H_{32}N_2O+H^+$ requires 485.2593; Found C, 83.08; H, 6.80; N, 5.53; $C_{34}H_{32}N_2O+0.4\ H_2O$ requires C, 83.02; H, 6.72; N, 5.70.

***N*-Hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide (8 and 9).** 1,6-Dibenzylindan-1-carboxylic acid (**5a**) (325 mg, 0.95 mmol) was dissolved in CH_2Cl_2 (dry; 15 mL) and placed in a 100 mL flask. Oxalyl chloride (0.25 mL, 2.85 mmol, 3 equiv) and DMF (dry; 0.3 mL) were added and the flask closed with a drying tube. The solution was stirred for 1.25 h at room temperature, then concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (dry; 2 mL) and added dropwise to a solution of L-(+)-α-phenylglycinol (143 mg, 1.05 mmol, 1.1 equiv) and triethylamine (0.20 mL, 1.42 mmol, 1.5 equiv) in CH_2Cl_2 (dry; 16 mL). The mixture was stirred at room temperature for 3 h, then 2 M HCl (20 mL) was added and the layers separated. The water layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water and brine (both 20 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (hexane:EtOAc, 2:1) to give 137 mg (31%) **8** as a colourless oil and 150 mg (34%) **9** as white cubic crystals (recrystallised from CH_3CN).

(1*S*)-*N*-((*S*)-1-hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide (8). R_f 0.61 (hexane:EtOAc, 1:1); $[\alpha]_D^{20}$ −4.8° (*c* 1.4; MeOH); IR (film) 3409, 3040, 2907, 1645, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.10 (13H, m), 6.99 (2H, dd, J=1.6 and 7.2 Hz), 6.90 (2H, dd, J=1.6 and 7.2 Hz), 6.77 (1H, s), 6.16 (1H, d, J=7.0 Hz), 4.98 (1H, m), 3.89 (2H, s), 3.66 (2H, m), 3.46 (1H, d, J=13 Hz), 3.08 (1H, d, J=13 Hz), 2.77 (1H, m), 2.58 (1H, m), 2.35 (2H, m) MS *m/z* (CI) 462 ($M+H^+$, 75%), 444 (11), 430 (15), 297 (53), 91 (100); acc. mass: found 462.2433, $C_{32}H_{31}NO_2$ requires 462.2433.

(1*R*)-*N*-((*S*)-1-Hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide (9). R_f 0.37 (hexane:EtOAc, 1:1); mp 126–127 °C; $[\alpha]_D^{20}$ −46.4° (*c* 0.97; MeOH). IR(film) 3411, 3028, 2923, 1645, 1494, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–6.99 (15H, m), 6.85 (2H, d, J=8.0 Hz), 6.72 (1H, s), 6.18 (1H, d, J=7.0 Hz), 5.00 (1H, m), 3.86 (2H, s), 3.68 (2H, m), 3.40 (1H, d, J=13 Hz), 3.06 (1H, d, J=13 Hz), 2.82 (1H, m), 2.64 (1H, m), 2.40 (1H, m), 2.32 (1H, m); MS *m/z* (CI) 462 ($M+H^+$, 100%), 444 (12), 430 (8), 370 (7), 297 (28); found C, 83.14; H, 6.82; N, 3.03; $C_{32}H_{31}NO_2$ requires C, 83.26; H, 6.77; N, 3.03.

(*S*)-1,6-Dibenzylindan-1-carboxylic acid (10). (1*S*, 1′*S*)-*N*-(1-Hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide (**8**) (230 mg, 0.50 mmol) was dissolved in dioxane (10 mL) and 2 M H_2SO_4 (aq; 10 mL) was added. The solution was heated to reflux for 2 days, then left to cool. Water (20 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, CH_2Cl_2:Et_2O, 9:1) to give **10** as a colourless oil (58 mg, 30%). $[\alpha]_D^{20}$ 47.2° (*c* 1.0; MeOH); IR (film) 3454, 3034, 2925, 1698, 1494, 1283, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.00 (13H, m), 3.98 (2H, s), 3.46 (1H, d, J=13 Hz), 3.05 (1H, d, J=13 Hz), 2.90 (1H, m), 2.64–2.52 (2H, m), 2.07 (1H, m).

(*R*)-1,6-Dibenzylindan-1-carboxylic acid (11). (1*R*, 1′*S*)-*N*-(1-Hydroxymethylbenzyl)-1,6-dibenzylindan-1-carboxamide (**9**) (275 mg, 0.60 mmol) was dissolved in dioxane (10 mL) and 2 M H_2SO_4 (aq; 10 mL) was added. The solution was heated to reflux for 3 days, then left to cool. Water (20 mL) was added and the resulting suspension extracted with CH_2Cl_2 (3 × 20

mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting brown oil was purified by column chromatography (eluent, CH_2Cl_2:Et_2O, 9:1) to give **11** as a colourless oil (120 mg, 58%). $[\alpha]_D^{20}$ −46.1° (*c* 1.0; MeOH); IR (film) 3500, 3027, 1698, 1494, 1282, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.00 (13H, m), 3.98 (2H, s), 3.46 (1H, d, $J=13$ Hz), 3.05 (1H, d, $J=13$ Hz), 2.93 (1H, m), 2.65–2.52 (2H, m), 2.07 (1H, m).

(*S*)-*N*-Phenethyl-1,6-dibenzylindan-1-carboxamide (12). (*S*)-1,6-Dibenzylindan-1-carboxylic acid (**10**) (58 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (dry; 5 mL) and placed in a 50 mL flask. Oxalyl chloride (0.046 mL, 0.51 mmol, 3 equiv) and DMF (dry; 0.1 mL) were added and the flask was fitted with a condenser closed with a drying tube. The solution was heated to 44 °C for 1 h, then concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (dry; 2 mL) and added dropwise to a solution of phenethylamine hydrochloric acid (33 mg, 0.20 mmol, 1.2 equiv) and triethylamine (0.060 mL, 0.43 mmol, 2.5 equiv) in CH_2Cl_2 (dry; 5 mL). The mixture was stirred at room temperature for 3 h. 2 M HCl (10 mL) was added and the solution extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water and brine (both 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (hexane:EtOAc, 6:1) to give **12** as a colourless oil (57 mg, 75%). $[\alpha]_D^{20}$ −23.1° (*c* 1.0; MeOH); IR (film) 3420, 3026, 2923, 1661, 1515, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–6.87 (17H, m), 6.64 (1H, s), 5.30 (1H, s, br), 3.80 (2H, dd, $J=12$ and 15 Hz), 3.58 (1H, m), 3.40 (1H, d, $J=13$ Hz), 3.32 (1H, m), 3.05 (1H, d, $J=13$ Hz), 2.69 (1H, m), 2.62 (2H, t, $J=6$ Hz), 2.57 (1H, m) 2.28 (2H, m); MS *m/z* (CI) 446 ($M+H^+$, 100%); found C, 85.25; H, 7.23; N, 2.93; $C_{32}H_{31}NO + 0.3\ H_2O$ requires C, 85.22; H, 7.06; N, 3.11.

(*R*)-*N*-Phenethyl-1,6-dibenzylindan-1-carboxamide (13). (*R*)-1,6-Dibenzylindan-1-carboxylic acid (**11**) (102 mg, 0.30 mmol) was dissolved in CH_2Cl_2 (dry; 8 mL) and placed in a 100 mL flask. Oxalyl chloride (0.079 mL, 0.90 mmol, 3 equiv) and DMF (dry; 0.1 mL) were added and the flask was fitted with a condenser closed with a drying tube. The solution was heated to 44 °C for 1 h, then concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (dry; 2 mL) and added dropwise to a solution of phenethylamine hydrochloric acid (55 mg, 0.34 mmol, 1.2 equiv) and triethylamine (0.104 mL, 0.75 mmol, 2.5 equiv) in CH_2Cl_2 (dry; 8 mL). The mixture was stirred at room temperature for 4 h. 2 M HCl (15 mL) was added and the solution extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water and brine (both 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (hexane:EtOAc, 6:1) to give **13** as a colourless oil (80 mg, 60%). $[\alpha]_D^{20}$ 26.0° (*c* 1.0; MeOH); IR (film) 3424, 3026, 2924, 1662, 1513, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–6.87 (17H, m), 6.64 (1H, s), 5.30 (1H, s, br), 3.80 (2H, dd, $J=12$ and 15 Hz), 3.58 (1H, m,), 3.40 (1H, d, $J=13$ Hz), 3.31 (1H, m), 3.03 (1H, d, $J=13$ Hz), 2.67 (1H, m), 2.62 (2H, t, $J=6$ Hz), 2.57 (1H, m) 2.28 (2H, m); MS *m/z* (CI) 446 ($M+H^+$, 100%); found C, 85.89; H, 7.01; N, 3.10; $C_{32}H_{31}NO$ requires C, 86.25; H, 7.01; N, 3.14.

References

1. A preliminary account of this work has already been published: Horwell, D. C.; Howson, W.; Ratcliffe, G.; Willems, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2825.

2. Horwell, D. C.; Howson, W.; Rees, D. C. *Drug Design & Discovery* **1994**, *12*, 63.

3. See the following review articles: (a) Hölzemann, G. *Kontakte (Darmstadt)* **1991**, *1*, 3. (b) Hölzemann, G. *Kontakte (Darmstadt)* **1991**, *1*, 55. (c) Ball, J. B.; Alewood, P. F. *J. Mol. Recognition* **1990**, *3*, 55. (d) Farmer, P. S. In *Drug Design*, Ariens, E. J., Ed.; Academic: London, 1980; Vol. X, pp 119–143.

4. Horwell, D. C.; Howson, W.; Nolan, W. P.; Ratcliffe, G. S.; Rees, D. C.; Willems, H. M. G. *Tetrahedron* **1995**, *51*, 203.

5. (a) Ikura, M.; Clore, M. G.; Gronenborn, A. M.; Zhu, G.; Klee, C. B.; Bax, A. *Science* **1992**, *256*, 632. (b) Martin, P. D.; Robertson, W.; Turk, D.; Huber, R.; Bode, W.; Edwards, B. F. P. *J. Biol. Chem.* **1992**, *267*, 7911.

6. Nolan, W. P. ; Ratcliffe, G. S.; Rees, D. C. *Tetrahedron Lett.* **1992**, *33*, 6879.

7. Olson, G.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039.

8. (a) Kemp, D. S.; Curran, T. P. *Tetrahedron Lett.* **1988**, *29*, 4931. (b) Kemp, D. S.; Curran, T. P. *Tetrahedron Lett.* **1988**, *29*, 4935. (c) Müller, K.; Obrecht, D.; Knierzinger, A.; Stankovic, C.; Spiegler, C.; Bannworth, W.; Trzeciak, A.; Englert, G.; Labhardt, A. M.; Schönhölzer, P. In *Perspectives in Medicinal Chemistry*; Testa, B.; Kyburz, F.; Fuhrer, W.; Giger, R., Eds.; VCH: Basel; 1993; pp 513–531.

9. Nongrum, F. M.; Myrboh, B. *Synthesis*, **1987**, 845.

10. Aono, T.; Araki, Y.; Imanishi, M.; Noguchi, S. *Chem. Pharm. Bull.* **1978**, *26*, 1153.

11. (a) Boyle, S.; Guard, S.; Hodgson, J.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; Watling, K. J.; Woodruff, G. N. *Bioorg. Med. Chem.* **1994**, *2*, 101. (b) Boyle, S.; Guard, S.; Higginbottom, M.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J.; Woodruff, G. N. *Bioorg. Med. Chem.* **1994**, *2*, 357. (c) Boden, P.; Eden, J. M.; Hodgson, J.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A. T.; Meecham, K.; Pritchard, M. C.; Raphy, J.; Ratcliffe, G. S.; Suman-Chauhan, N.; Woodruff, G. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1679.

12. Kollman, P. A. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1995; 5th Edition, Vol. 1, pp 399–416.

13. (a) Sheldrick, G. M. SHELX86, a computer program for crystal structure determination, University of Göttingen, 1986. (b) Sheldrick, G. M. SHELX76, a computer program

for crystal structure determination, University of Cambridge, 1976.

14. Compound **2** has been synthesised previously. See Haas, G.; Rossi, A. *Ger. Offen.* 2 505 106, 1975; *Chem. Abs.* **1976**, *84*, 105276g.

15. Geissman, T. A.; Armen, A. *J. Am. Chem. Soc.* **1952**, *74*, 3916.

(*Received in U.S.A.* 28 *March* 1995; *accepted* 21 *September* 1995)