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The Synthesis of 1,6-Disubstituted Indanes which Mimic the Orientation of Amino Acid Side-Chains in a Protein Alpha-Helix Motif.

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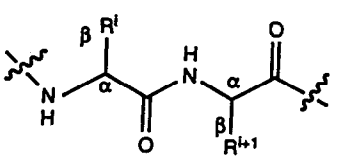
Abstract. We utilize a 1,6-disubstituted indane as a template onto which two amino acid side-chains are appended in an orientation which mimics that found in a protein alpha-helix motif.

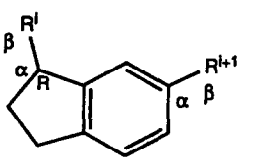
The protein alpha-helix was first described by Pauling in 1951[1] and is now known to be one of the most common secondary structural motifs in proteins.[2]

The design and synthesis of compounds which mimic the conformations of the common secondary structural motifs of proteins is the subject of several publications most of which describe beta-turn mimetics.[3] Despite the prevalence of alpha-helices we are not aware of any reports describing the synthesis of non-peptide alpha-helix mimetics, although two groups have described cyclic templates designed to initiate helical structures in attached peptides[4]. Our interest was stimulated in this area because two recently published studies indicate that peptides which are conformationally flexible in solution (a tetradecapeptide fibrinogen derivative and a 26-residue myosin light chain kinase derivative) adopt an alpha-helical structure upon interaction with their respective binding proteins (the enzyme thrombin and the regulatory protein calmodulin).[5,6] In these examples the amino acid side-chains of the alpha helices appear to be important in the molecular recognition of the binding interaction. This leads us to propose that non-peptide templates onto which amino acid side-chains are attached in a conformation which mimics that found in an alpha-helix may be useful probes to investigate the conformation of peptide ligands when bound to their receptor proteins.



α-helix fragment

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



α-helix template

Our aim therefore was to design and synthesise conformationally restrained, non-peptide molecules which allow the incorporation of two adjacent amino acid side-chains in an orientation similar to that found in an alpha-helix. With the aid of molecular modelling we selected a 1,6-disubstituted indane skeleton as a template. Examination of Dreiding molecular models indicated that the 1,6-substituents overlay closely with the Cα and Cß carbon atoms of adjacent (i,i+1) alpha-helix side-chains. This was subsequently supported with computer modelling[7] (see figure) which indicates that the two Cα and the two Cß carbon atoms of the Phe-Glu mimetic (4) overlay with the corresponding residues in an α-helix with a root mean square (rms) deviation of 0.18Å. Furthermore, the indane moiety is orientated within the space occupied by the α-helix peptide backbone.

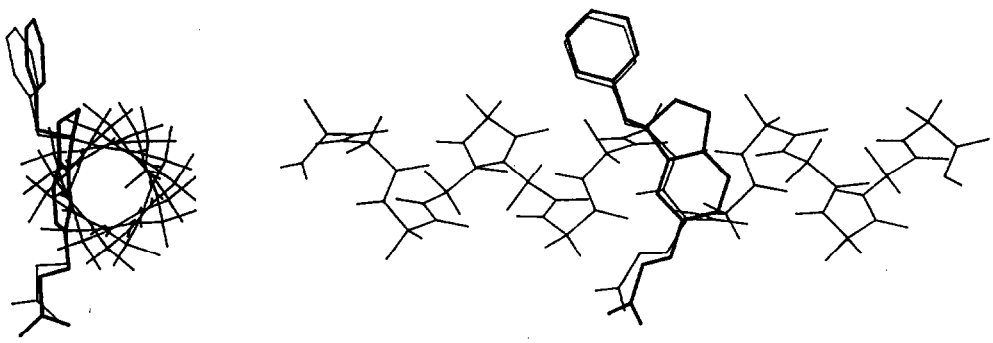
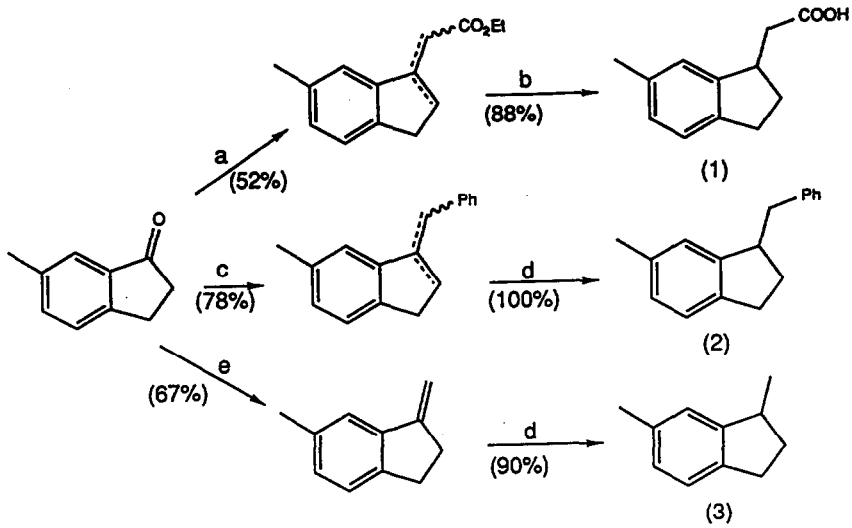


Figure. Orthogonal representations of the overlay of 4 (in bold) with a model alpha-helix ($(Ala)_8$-Phe-Glu-$(Ala)_6$) showing the Phe and Glu side-chains.

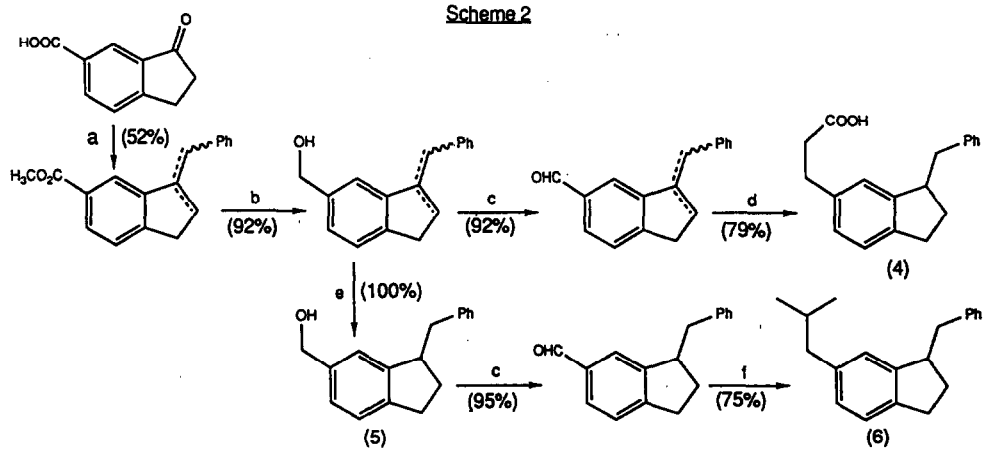
The syntheses are described in schemes 1 and 2.[8] The starting materials indicated on the schemes, 6-methyl indan-1-one[9] and indan-1-one-6-carboxylic acid[10] were prepared according to literature methods. The syntheses are designed to allow a wide variety of side-chains to be incorporated onto the bicyclic template by Wittig or Grignard reaction with the indanone carbonyl at C_1 (Scheme 1) or with the aldehyde attached at C_6 (Scheme 2). In order to exemplify the methodology we selected three different R^1 amino acid side-chains, CH_3 (Ala), CH_2Ph (Phe), CH_2COOH (Asp) (Scheme 1, compounds 1 - 3) and four different R^{i+1} side-chains, CH_3 (Ala), CH_2CH_2COOH (Glu), CH_2OH (Ser), $CH_2CH(CH_3)_2$ (Leu)(Scheme 2, compounds 4 - 6). All of these correspond to amino acids which are found in alpha-helices.[2]

Scheme 1



Reagents a) $Ph_3P = CHCO_2Et$, 140°, 4h; b) i) H_2 (45 psi), 10% Pd-C, MeOH, 20°; ii) NaOH, aq-THF, reflux 15h; c) i) $PhCH_2MgCl$ (5 equiv.), Et_2O, 0°-20°, 15h; ii) MeOH, cHCl, reflux, 5h; d) H_2 (45 psi), 10% Pd-C, MeOH, 20°; e) i) form Wittig reagent : NaH, DMSO, 75°, 30 min then $CH_3PPh_3^+Br^-$, DMSO, 20°; ii) add ketone (1 equiv.), 20°, 15h.

Scheme 2



Reagents a) i) $PhCH_2MgCl$ (4 equiv.), THF, 0°-20°, 15h; ii) MeOH, cHCl, reflux, 15h; b) i-Bu_2AlH-hexane (2 equiv.), THF, -78°-20°; c) $BaMnO_4$ (5 equiv.), CH_2Cl_2, reflux, 15h; d) i) $Ph_3P = CHCO_2Me$, PhMe, reflux, 15h; ii) H_2 (45 psi), 10% Pd-C, MeOH, 20°, iii) NaOH, aq-THF, reflux, 15h; e) H_2 (45 psi), 10% Pd-C, MeOH, 20°; f) i) form Wittig reagent : $Ph_3PCHMe_2^+I^-$, Et_2O, BuLi, 0°-20°, 30 min; ii) add aldehyde (0.5 equiv.), 20°, 15h; iii) as e).

In summary we report synthetic methodology for the construction of a conformationally restrained non-peptide which we believe to be the first template designed to mimic the orientation of two adjacent amino acid side-chains of a protein alpha-helix motif. This methodology has been exemplified by the incorporation of side-chains corresponding to Ala, Phe, Asp, Glu, Ser and Leu.

Further studies aimed at synthesising templates which mimic two or three amino acid side-chains are in progress and will be reported subsequently, together with their receptor/enzyme binding affinity.

Acknowledgements

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7. Computer molecular modelling was performed using the SYBIL programme, supplied by Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, Missouri 63144, USA. The lowest energy state of the R-enantiomer of compound **4** found using the RANDOMSEARCH option is 2.8 kcal.mol^{-1} lower than the energy of the conformation overlayed with $(Ala)_8$-Phe-Glu-$(Ala)_6$ in an alpha-helix conformation.
8. All compounds are racemates. Selected data for key compounds : Compound (1) NMR δ (300 MHz, $CDCl_3$) 1.75 (1H, m), 2.33 (3H, s), 2.46 (2H, m), 2.8 (3H, m), 3.55 (1H, m), 6.95 (1H, d, J = 8), 6.99 (1H, s), 7.12 (1H, d, J = 8); MS (m/e) EI 190 (27%, M^+); mp 105-107°. Compound (2) NMR δ (300 MHz, $CDCl_3$) 1.75 (1H, m), 2.1 (1H, m), 2.30 (2H, s), 2.62 (1H, dd J = 13, 10), 2.8 (2H,m), 3.14 (1H, dd, J = 12, 5), 3.4 (1H, m), 6.94 (2H, m), 7.15 (1H, d, J = 8), 7.2 (5H, s); MS (m/e) EI found 222.1410, $C_{17}H_{18}$ requires 222.1409. Compound (4) NMR δ (300 MHz, $CDCl_3$) 1.8 (1H, m), 2.15 (1H, m), 2.62 (2H, m), 2.7 (3H, m), 2.9 (2H, m), 3.10 (1H, dd, J = 13, 6), 3.40 (1H, m), 6.90 (1H, s), 6.98 (1H, d, J = 8), 7.12 (1 H, d, J = 8), 7.25 (5 H, m); MS (m/e) EI 280 (5%, M^+). Compound (5) NMR δ (300 MHz, $CDCl_3$) 1.78 (1H, m), 2.17 (1H, m), 2.67 (1H, dd, J = 13, 9), 2.8 (2H, m), 3.16 (1H, dd, J = 13, 5), 3.4 (1H, m), 4.63 (2H, s), 7.2 (8H, m); MS (m/e) found 256.1700, $C_{17}H_{18}O$ requires 256.1701.
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