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Diphenylindane-Based Proteomimetics Reproduce the Projection of the *i*, *i*+3, *i*+4, and *i*+7 Residues on an α-Helix

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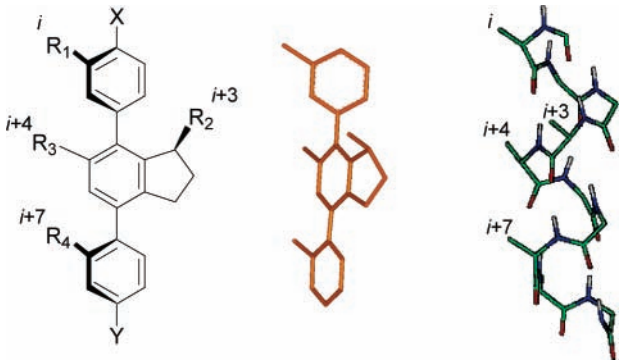
ABSTRACT



The design of a nonpeptidic scaffold based on 4,7-diphenyl-1,6-disubstituted indanes mimicking *i*, *i*+3, *i*+4, and *i*+7 residues of an α-helix has been described, and its synthesis has been accomplished. This strategy makes general approaches possible to helix mimetic scaffolds that could be targeted to different proteins by changing the nature of the substituents.

α-Helices are the most common protein secondary structure, accounting for over 40% of polypeptide amino acids in natural proteins.[1] The pharmaceutical potential for synthetic mimics of extended regions of α-helices is immense as they play pivotal roles in many protein−protein interfaces.[2,3] However, there have been only a few examples of such molecules. One approach to α-helix mimicry was reported by Kahne et al., who used a pentasaccharide scaffold to present multiple charged groups that bind the minor groove of DNA with selectivity over RNA.[4] *β*-Peptides have also been used to mimic α-helices by Gellman et al.[5] and a β^3-peptide having three residues on one face was introduced to block Hdm2 in the p53-Hdm2 interaction by Schepartz et al.[6] We have recently introduced a proteomimetic strategy based on a terphenyl scaffold that mimics the structure and recognition function of discontiguous stretches of an α-helix.[7−9] In this design, the terphenyl is expected to adopt a staggered conformation and closely reproduce the position and angular orientation of functionality on the surface of an α-helix. We have reported functionalized terphenyls as mimetics of the discontinuous binding epitopes of gp41,[6a] small muscle myosin light-chain kinase (smMLCK),[6b] and the helical Bak peptide binding to Bcl-xL.[7]

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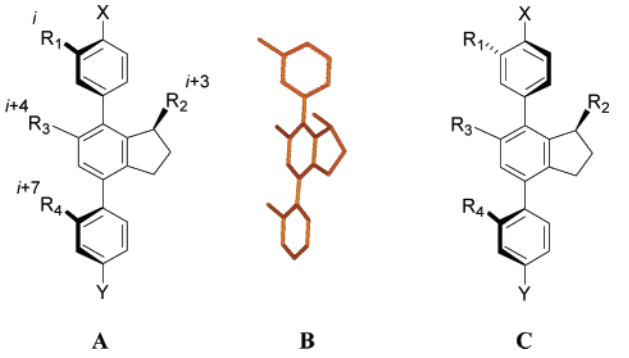

Figure 1. (A) 4,7-Diphenyl-1,6-disubstituted indanes. (B) Energy-minimized (MM2) tetramethyldiphenylindanes. (C) Atropisomer of **A**.

Our previous helix mimetics reproduced the *i*, *i*+4, and *i*+7 groups that project from one face of the helix and often make critical hydrophobic contacts to a target protein. However, in many helix/protein complexes, additional interactions come from residues flanking the hydrophobic face of the helix. For example, in the case of Bak and Bad peptides binding to Bcl-xL, important contacts are made by residues in the *i*, *i*+3, *i*+4, and *i*+7 positions (**V**GR**QL**AI**I**G and **Y**GR**EL**RR**M**, respectively).[10] The importance of *i*, *i*+3, *i*+4, and *i*+7 helical residues is also seen in the complex between the tumor suppressor p53 and its oncogenic regulatory protein Hdm-2.[11] p53 binds through a helical domain (16NET**F**SD**LW**KL**L**P27) with critical interactions being made to Hdm-2 by Phe19, Trp23, and Leu26 with additional contact from Leu22. The importance of the *i*+3 residue is demonstrated by a recent nanomolar level peptide-based inhibitor of Hdm-2 (Ac**Phe**MetAib**Pmp-6ClTrp**-GluAc3c-**Leu**NH2) which has a Pmp residue (a derivative of Tyr) adjacent to the central Trp.[12] Therefore, we report here the design and synthesis of a new synthetic scaffold which mimics *i*, *i*+3, *i*+4, and *i*+7 residues of the α-helices.

Our principal goal in this study was to develop general approaches to helix mimetic scaffolds that could be targeted to different proteins by changing the nature of the substituents. This is exactly analogous to the natural use of α-helices as common scaffolds for mediating protein−protein interactions with selectivity being imparted by modifications in the shape and charge characteristics of the side-chain residues. Our approach to mimicking the *i*, *i*+3, *i*+4, and *i*+7 groups on a helix involves combining the terphenyl strategy (*i*, *i*+4, *i*+7) with a 1,6-disubstituted indane that had previously been reported to reproduce the angular projection of adjacent residues (*i* and *i*+1) on the helix.[13] As shown in Figure 1B, MM2 calculations on tetramethyl-substituted 4,7-diphenylindanes reveal that a conformation with aryl−aryl torsion angles of 67° and 62° closely reproduces the position and angular projection of the *i*, *i*+3, *i*+4, and *i*+7 groups.

Superimposition of the four CH_3−C bonds on the indane with *i*, *i*+3, *i*+4, and *i*+7 CH_3−C groups on an all-Ala helix shows a good matching with an rms difference of 0.92 Å (Figure 2B).

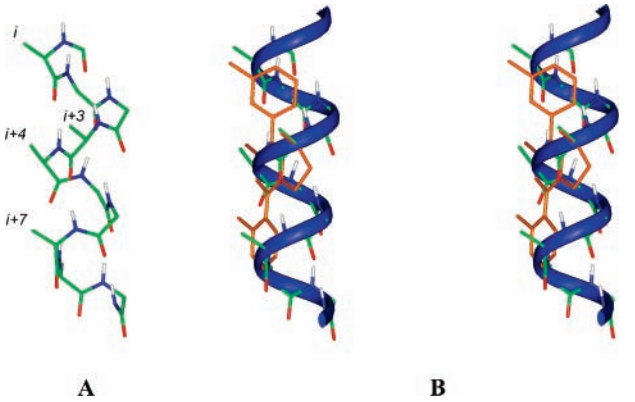

Figure 2. (A) Poly-Ala α-helix with *i*, *i*+3, *i*+4, and *i*+7 groups. (B) Stereoview of rms difference (0.92 Å) overlay of α-helix and tetramethyldiphenylindane.

The synthesis of 4,7-diphenyl-1,6-disubstituted indanes began with indanone **1**, which was prepared from *o*-cresol by treatment with chloropropionyl chloride, subsequent Fries rearrangement and Friedel−Crafts reaction, and methylation of the 7-hydroxyindanone.[14] Reaction of ketone **1** with *i*-propylmagnesium bromide in the presence of cerium chloride and subsequent elimination gave the indene which was catalytically hydrogenated to the key 7-methoxy-2,6-disubstituted indane, **2** (Scheme 1). Suzuki coupling between the boronic acid **4**, which was derived from **3** after NBS bromination of **2**, and triflate **5** containing the *i*+4 binding side chain gave 1,4,6-trisubstituted indane, **6**. The next coupling, which would establish the *i*+1 binding group, with an extremely hindered triflate **7** was explored using original and modified Suzuki and Stille coupling methods.

Although many useful coupling methods have been recently developed for sterically hindered and less-reactive aryl halides, there is no efficient Suzuki method for 2,6-disubstituted triflates. Although a coupled product could not be obtained by Suzuki-type reactions, the modified Stille condition involving a Pd/Cu cocatalyst and harsh reaction conditions gave the desired compound **9** in a very low yield (<20%) (Scheme 2).[15] The yield could be improved to 71% by a prolonged dropwise addition of the aryltributyltin **8** as a dilute solution in DMF. To our best knowledge, **7** is one

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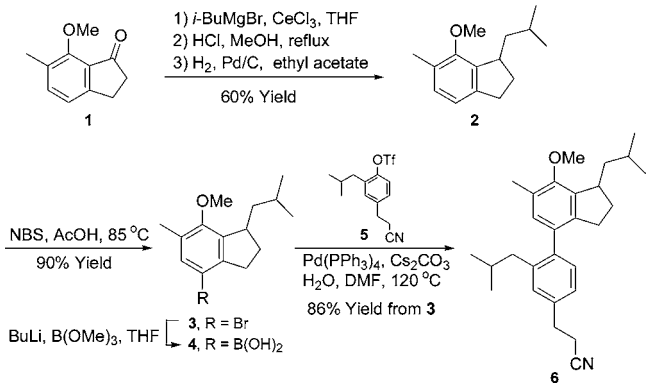
Scheme 1. Synthesis of 4-Phenylindane **6**

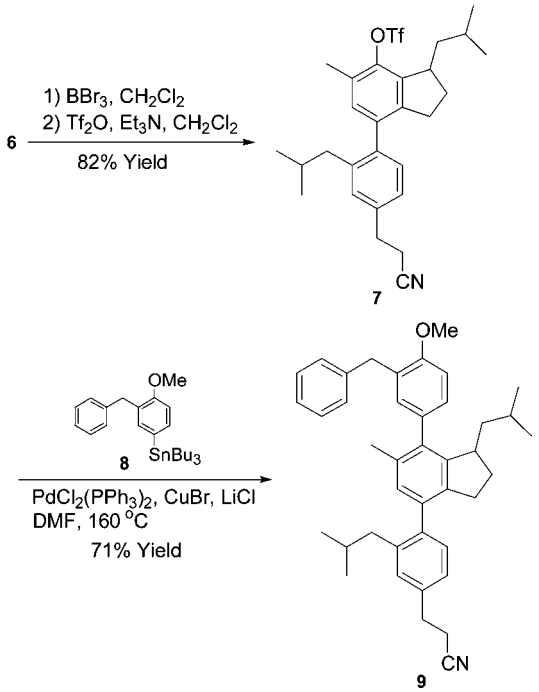


of the most sterically hindered triflates to undergo this reaction with a good yield.

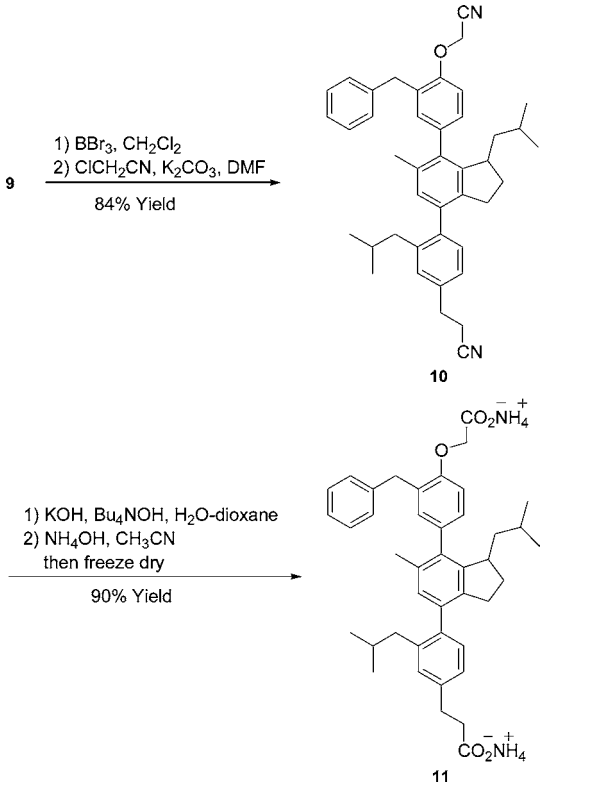
The final steps to the helix mimetic involved demethylation and a subsequent alkylation of the hydroxyl group with a solubility modulating substituent affording dicyanide **10**. Hydrolysis of the terminal cyano groups furnished **11** having carboxyl groups on both ends of the terphenyl backbone (Scheme 3). The resulting acid groups were converted into their corresponding ammonium salts to increase the solubility in aqueous solution.

The ^{1}H NMR of **9** displayed two diastereomeric peaks for the benzylic methine proton because the bulky substituents of the indane cause atropisomerism from the high rotational barrier for the top ring. Figure 3 illustrates a coalescence at 66 °C for the diastereomeric peaks. Peak separation ($\Delta\nu$) was 46.5 Hz at 25 °C, and the rotational barrier was

Scheme 2. Synthesis of 4,7-Diphenylindane **9**



Scheme 3. Preparation of Dicarboxy-4,7-diphenylindane **11**



calculated by Eyring absolute rate theory to be 16.8 kcal mol^{-1}. This value reveals that the diastereomeric compounds (Figure 1A,C) are readily interconvertible at room temperature and should not present a significant issue in binding to a protein target.

In conclusion, the design and synthesis of a helix mimetic scaffold mimicking *i*, *i*+3, *i*+4, and *i*+7 residues and based

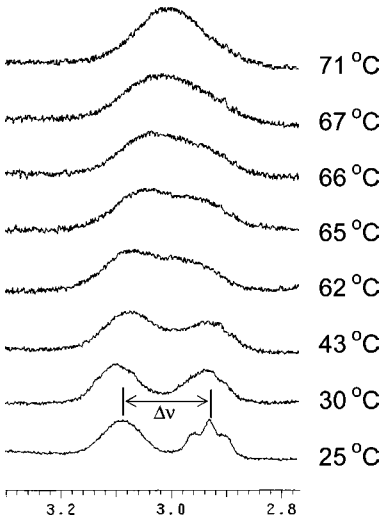


Figure 3. Variable-temperature ^{1}H NMR spectrum of benzylic methine resonance of **9** in CD_3CN. Compound **9** can exist as two diastereomers.

on 4,7-diphenyl-1,6-disubstituted indanes have been successfully completed. Binding studies against various target proteins are under investigation.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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