ORGANIC LETTERS

2013
Vol. 15, No. 18
4892–4895

Synthesis of a Tetrasubstituted Tetrahydronaphthalene Scaffold for α-Helix Mimicry via a $MgBr_2$-Catalyzed Friedel–Crafts Epoxide Cycloalkylation

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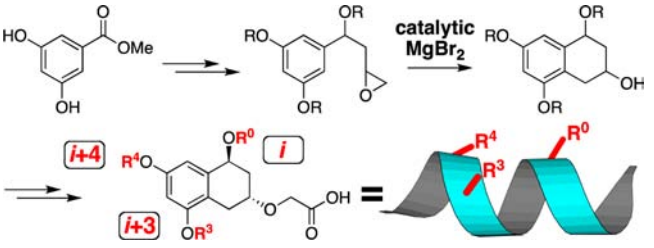
Received August 14, 2013

ABSTRACT



α-Helices are ubiquitous protein recognition elements that bind diverse biomolecular targets. The synthesis of a small molecule scaffold to present the side chains of an α-helix is described. The 1,3,5,7-tetrasubstituted 1,2,3,4-tetrahydronaphthalene scaffold, providing mimicry of the *i*, *i*+3, and *i*+4 positions of an α-helix, was synthesized using a novel $MgBr_2$-catalyzed Friedel–Crafts epoxide cycloalkylation as the key step. Each position may be differentiated via O-alkylation after scaffold synthesis, generating a diversity-oriented approach to readily synthesize proteomimetics for different targets.

α-Helices are fundamental protein secondary structure elements that are broadly utilized in biomolecular recognition.[1] Protein–protein, protein–DNA, and protein–RNA interactions employ α-helices as critical recognition epitopes. Inhibitors of α-helical protein interactions have considerable potential as therapeutics for a wide range of diseases.[2]

In α-helix-mediated recognition, the primary role of the α-helix is to organize the side chains for interaction with the target, with the protein typically undergoing a disorder-to-order transition. The protein backbone normally does not directly interact with the target molecule, instead primarily serving as a scaffold to organize side chains for target recognition. In view of its scaffolding role, the protein backbone could be replaced with an organic scaffold that can similarly present the equivalent protein side chain functionalities. In an α-helical proteomimetic approach, protein sequence information can be directly applied to inhibitor design, resulting in the rapid development of lead compounds.

A series of elegant α-helix proteomimetics for a range of biomedically important protein targets has been developed.[2,3] We sought to develop a novel scaffold for α-helical proteomimetics that would incorporate the following properties: (1) presentation of the side chains along one α-helical face over two helical turns; (2) strong conformational preferences in the scaffold while retaining sufficient flexibility to adapt to a broad range of protein interfaces; (3) rapid synthesis of target molecules from a universal scaffold; (4) facile incorporation of a wide range of functional groups via readily available compounds; (5) inclusion of a functionalizable handle to modulate electrostatics and solubility and to use as a linker for subsequent experiments; and (6) chirality to potentially increase target specificity.

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10.1021/ol402334j
Published on Web 09/09/2013

We identified a tetrasubstituted tetrahydronaphthalene as a promising scaffold for α-helix mimicry (Figure 1). In this scaffold, the oxygens are equivalent to the α carbon of the protein backbone, with side chains readily added to the scaffold as electrophiles in standard substitution chemistry. Moreover, this scaffold has two major ring conformations, allowing mimicry of both ideal and non-ideal α-helices.

The 1,3,5,7-oxygen-tetrasubstituted ring system of the scaffold has not previously been described. However, a straightforward synthesis from the inexpensive compound **1** or the commercially available compound **4** was envisioned. Grignard addition to the aldehyde **4**, followed by protection and epoxidation, yielded **7** as a precursor electrophile for synthesis of the bicyclic system (Scheme 1).

In the original approach to the 6,6-bicyclic system, an aryl-brominated variant of **7** was converted to a Grignard reagent in order to effect intramolecular nucleophilic addition to the epoxide. Despite good precedence for this reaction in model systems, that reaction proceeded poorly. However, surprisingly, product formation was observed after quenching the Grignard reagent. Those results were suggestive of an electrophilic aromatic substitution reaction with the epoxide mediated by Mg(II). Reaction of **7** with $MgBr_2 \cdot OEt_2$ (Scheme 2) resulted in the formation of the cycloalkylation products **8** and **9** as a mixture of diastereomers, proceeding effectively to generate the 6-endo products in CH_2Cl_2. The reaction proceeded poorly in coordinating solvents. Other Lewis acids ($AlCl_3$, $FeCl_3$, $ZnCl_2$) were also ineffective.

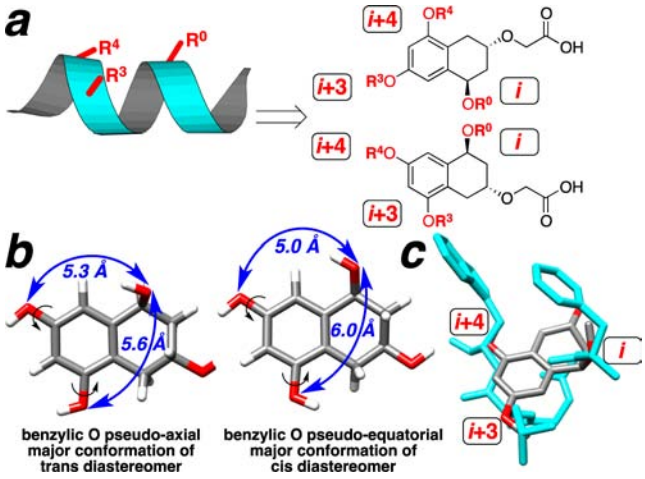

Figure 1. (a) A tetrahydronaphthalene scaffold to mimic the *i*, *i*+3, and *i*+4 residues over 2 turns of an α-helix. The O is designed to be equivalent to the Cα on the protein. (b) Scaffold ($R^0 = R^3 = R^4 = H$) structure, with the major ring conformations of the trans and cis diastereomers shown. O−O distances in the proteomimetic are nearly identical to the Cα−Cα distances in a canonical α-helix: the benzylic O, when in a pseudoaxial conformation, is 5.2−5.8 Å from the phenolic oxygens. When the benzylic O is in a pseudoequatorial conformation, the corresponding distances are 4.9−6.1 Å, similar to those found in the nonideal α-helices often observed in recognition α-helices. Rotation about the C−O bonds provides flexibility in binding to different helical interfaces at a modest cost in conformational entropy. (c) Overlay of the trans scaffold (gray, $R^0 = R^3 = R^4 = Me$) with residues 19−23 of the p53 activation domain (cyan; backbone and Phe19, Leu22, and Trp23 side chains shown).[4] All chiral compounds synthesized herein are racemates.

Friedel−Crafts epoxide cycloalkylation reactions have previously been described using several strong Lewis acid catalysts, including $SnCl_4$, BF_3, and $TiCl_4$, as well as a recent major advance using $AuCl_3$.[5] These reactions all generated the 6-endo products. In our case, the use of $SnCl_4$ or BF_3 resulted in decomposition of the starting material and $AuCl_3$ was cost-prohibitive on a preparative scale. The $MgBr_2$-catalyzed Friedel−Crafts epoxide

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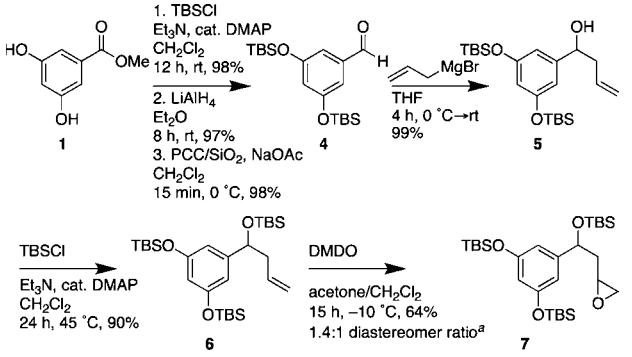
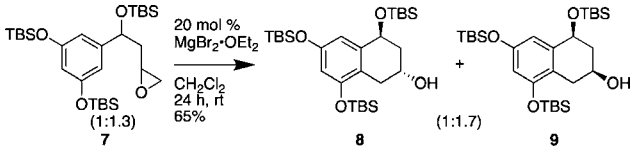
Scheme 1. Synthesis of the Cycloalkylation Precursor **7**



[a] This transformation was alternatively accomplished via mCPBA, Et_2O, 48 h, rt, 32% (1:1.3 diastereomer ratio).

Scheme 2. $MgBr_2$-Catalyzed Friedel–Crafts Cycloalkylation



cycloalkylation is a practical alternative approach using inexpensive, nontoxic reagents and mild conditions, allowing product formation with sensitive starting materials.[6]

We briefly investigated the scope of this reaction in the attempted synthesis of alternative scaffolds (Scheme 3). Not surprisingly, no product formation was observed with the contracted compound **10**, similar to results in model compounds with $SnCl_4$.[5a,b] However, the homologated compound **11**, synthesized via the cascade approach of Lubell to generate homoallylic ketones,[7] underwent cycloalkylation to yield the expected 6-exo (Baldwin) product, albeit in poor yield. We also examined this reaction in a related simpler compound **34**, which proceeded readily.

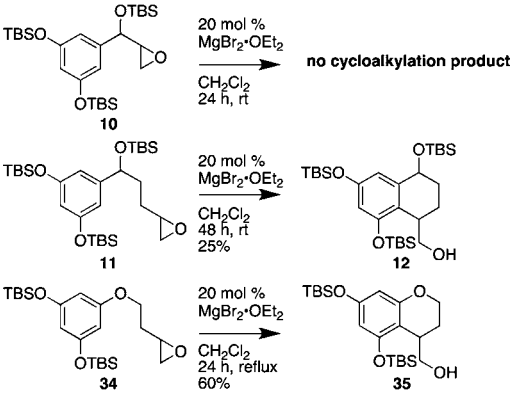
The bromohydrin (e.g., **13**) was the major side product in these reactions.[8] The cycloalkylation reaction mechanism could potentially involve direct Lewis acid activation of the epoxide, as observed previously, or could alternatively proceed via attack on the bromohydrin or its alkoxide. In order to investigate this possibility, the isolated bromohydrin **13** was subjected to reaction conditions, using $MgBr_2$, or alternatively using EtMgBr to generate the magnesium alkoxide (Scheme 4). In both conditions, no product formation was observed, consistent with Lewis acid activation of the epoxide as the reaction mechanism.

(6) Ueki and Kitazume (ref 5e) observed a 3% yield of Friedel–Crafts epoxide cycloalkylation product with $MgBr_2$ using difluorovinyl epoxides in the only identified precedent for this reaction.

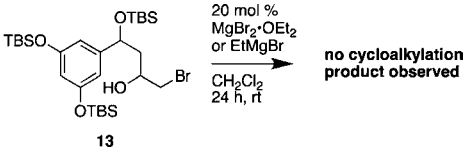
(7) Hansford, K. A.; Dettwiler, J. E.; Lubell, W. D. *Org. Lett.* **2003**, *5*, 4887–4890.

(8) The isolated bromohydrin **13** was readily converted to the starting material epoxide **7** (1:1 mixture of diastereomers) in quantitative yield with NaH.

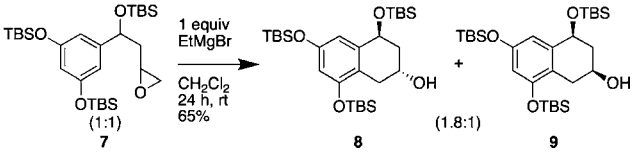
Scheme 3. Brief Analysis of the Scope of $MgBr_2$-Catalyzed Friedel–Crafts Cycloalkylation Reactions



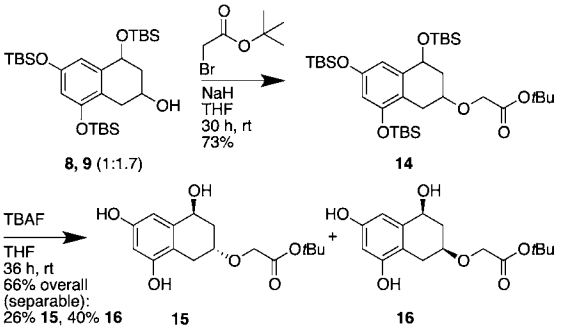
Scheme 4. Examination of One Possible Mechanism of $MgBr_2$-Catalyzed Cycloalkylation Reaction via the Bromohydrin



Scheme 5. EtMgBr-Mediated Friedel–Crafts Cycloalkylation

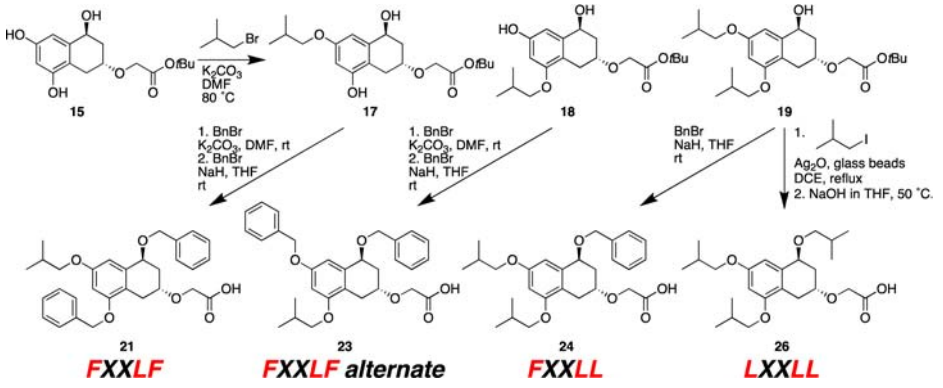


Scheme 6. Synthesis of General Scaffolds for α-Helix Mimicry



Interestingly, EtMgBr also effectively mediated the epoxide cycloalkylation (Scheme 5), producing **8** and **9** with the trans diastereomer **8** as the major product (dr 1.8:1 **8**:**9**),

Scheme 7. Partial Alkylation to Differentiate the Scaffolds and the Positions on the α-Helix Mimic[a]



[a] Synthesis of the cis diastereomers is described in the Supporting Information. All compounds are racemates.

in contrast to the $MgBr_2$-catalyzed reaction which generated the cis diastereomer as the major product (dr 1:1.7). Analysis of starting material and product as a function of time under EtMgBr reaction conditions revealed an increase in dr of both the starting material and product over time, suggesting epimerization as the basis for the change in the diastereomer ratio. This reaction was critically dependent on noncoordinating solvents (CH_2Cl_2 and DCE), and with Grignard reagents prepared in Et_2O yielding cycloalkylation product, but with no desired product formation observed for Grignard reagents prepared in THF.

Scaffold synthesis proceeded readily from the mixture of **8** and **9** (Scheme 6), via alcohol modification to form **14** as a mixture of diastereomers. A carboxylate was incorporated to specifically modulate electrostatics and solubility and as a handle for further conjugation. Subjection of **14** to global deprotection with TBAF yielded two alternative general scaffolds for α-helix mimicry, **15** and **16**, which were separable. 2-D NMR analysis (Supporting Information) allowed assignment of the relative stereochemistry of both compounds and revealed that in **15** the benzylic O is predominantly in a pseudoaxial conformation, whereas in **16** the benzylic O is in a pseudoequatorial conformation (Figure 1b). The difference in the major conformations of **15** and **16** suggests that each scaffold will present attached side chains with alternative geometries, as desired.

A primary goal of this work is the synthesis of a general scaffold for α-helix mimicry that could be rapidly converted to α-helix mimics of a variety of biological targets. In order to demonstrate the ready functionalization of the general scaffold, we sought to synthesize small molecules that could be mimics of a series of short linear motifs that bind their target via short α-helices. Our initial targets were the FXXLF motif present in the androgen receptor coactivator; the FXXLL motif present in transcription activation domains such as NF-κB p65; and the LXXLL motif of the estrogen receptor coactivator.[3g,k,p,s,t,x,z,9]

The synthesis of small molecules to mimic each of these short linear motifs proceeded readily in two to three steps from the general scaffold, generating four lead compounds for three different targets in eight total steps (Scheme 7). In addition, the analogous compounds derived from the cis diastereomer of the general scaffold were similarly synthesized (Supporting Information).

The incorporation of side chain equivalents in the final steps of the synthesis, combined with the use of simple alkylation chemistry and the wide availability of diverse electrophiles, suggests the expeditious application of this approach to a broad range of diverse targets. In addition, lead optimization should proceed readily using electrophiles to represent unnatural amino acids. Our efforts in the application of this strategy to control protein−protein interactions will be reported in due course.

Acknowledgment. We thank the NIH (RR17716) and the University of Delaware for funding. We thank Gasirat Tririya for preliminary work in the development of alternative approaches. We thank Anil Pandey for experimental assistance. We thank Professor Barry Trost (Stanford) for helpful discussion.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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