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Olefin Metathesis in the Design and Synthesis of a Globally Constrained Grb2 SH2 Domain Inhibitor

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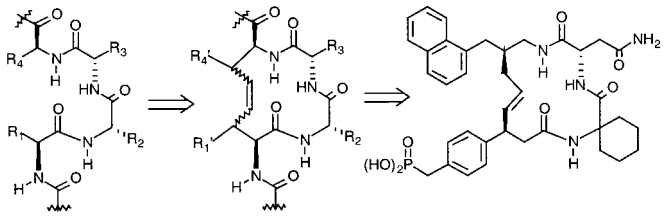
ABSTRACT



One drawback frequently associated with olefin metathesis-mediated peptide macrocyclization, the loss of side chain functionality at sites of ring closure, may be circumvented by incorporation of side chain functionality within the ring-closing olefin segments. This approach is demonstrated in the preparation of a macrocyclic Grb2 SH2 domain antagonist designed as a conformationally constrained β-bend mimic.

Restriction of conformational flexibility is an important peptidomimetic design consideration. Global constraint may be obtained by backbone cyclization either in a head-to-tail fashion or through amino acid residue side chains.[1] A modification of this latter approach can be achieved using the ruthenium-catalyzed ring-closing metathesis reaction of Grubbs.[2] However, one limitation of the use of this method is that the resulting macrocycle (**2**) frequently lacks side chain functionality at the sites of ring closure, originally present in the open chain parent (**1**) (Figure 1). Alternatively, incorporation of the side chain onto ring-closing segments could potentially allow macrocyclization without this type of loss (**3**).

In our ongoing effort to develop tyrosine-kinase dependent signal transduction inhibitors,[3] Grb2 SH2 domain binding antagonists are being prepared based on the naphthylpropyl-amide-containing tripeptide **4**.[4] Because binding of natural pTyr-containing ligands to Grb2 SH2 domains takes place in type-1 β-bend fashion,[5a] we envisioned that modification of **4** by incorporation within a macrocyclic structure could potentially increase affinity by introducing conformational constraints approximating those needed for binding. Since the pTyr phenyl phosphate group and the naphthyl ring are important for high affinity binding, the target macrocycle must include this side chain functionality at the sites of ring

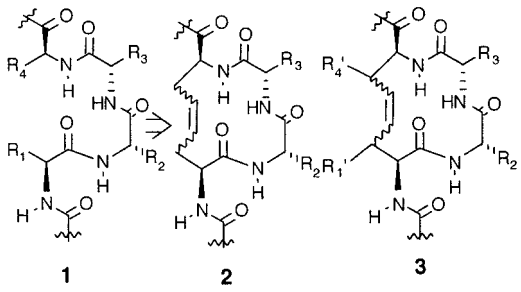


Figure 1. Macrocyclization with loss (**2**) and retention (**3**) of side chain functionality at the site of ring closure.

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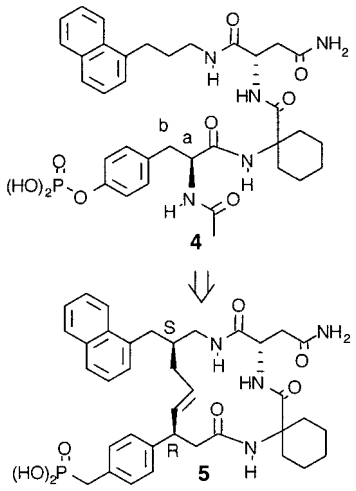


Figure 2. Macrocyclization protocol.

closure. Therefore, analogue **5** was designed (Figure 2), which exemplified the new type of macrocyclization shown by general structure **3** (Figure 1). (Note: replacement of the phosphate group in **4** with a phosphonate group in target **5** was done on the basis of the equivalent affinity of the two moieties in Grb2 SH2 domain assays.)[5b]

Synthetic Approach. On the basis of a retrosynthetic analysis leading to **5**, dipeptide **6** containing *tert*-butyl phosphonate was selected as the penultimate precursor to metathesis ring closure. The synthesis of **6** in turn required the synthesis of N- and C-terminal building blocks **7** and **8**, respectively, since the remaining residues were both commercially available in their N-Fmoc forms (Figure 3).

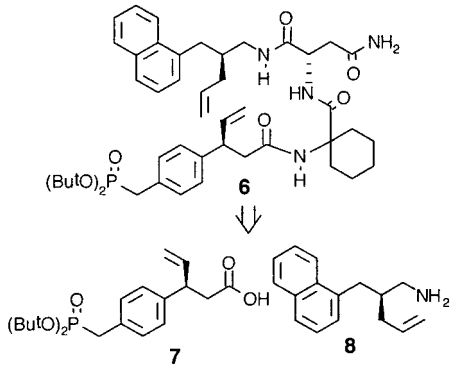
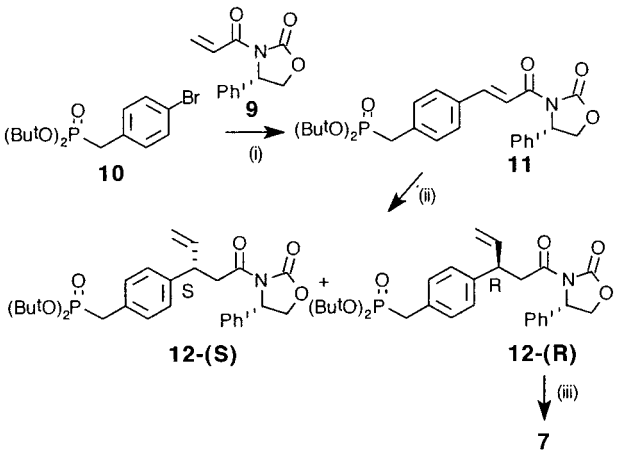


Figure 3. Synthetic targets for macrocyclization.

Preparation of N-terminal pTyr mimetic **7** proceeded from intermediate **11**, which was derived by palladium-catalyzed Heck reaction of known, chiral acrylamide **9** and *tert*-butyl protected 4-bromotoluyl phosphonate **10** in a manner similar to that outlined in our recent disclosure (Scheme 1).[6a] An

Scheme 1[a]



[a] Conditions: (i) Et_3N, $Pd(OAc)_2$, tri-*o*-tolylphosphine, reflux, (86% yield); (ii) vinylmagnesium bromide, PhSCu, Et_2O/THF, −40 °C (64% de in 67% yield); (iii) H_2O_2, 2 equiv of LiOH, THF/H_2O (81% yield).

important component of our synthetic approach was the subsequent introduction of β-vinyl functionality bearing the (*R*) configuration. Although 1,4-addition of vinylmagnesium bromide had been reported in the presence of a strong Lewis acid such as TMSCl,[6b] in our hands, solely the 1,2-addition product was obtained. To effect the desired 1,4-addition, a variety of reagents were investigated, including vinylmagnesium−CuI,[7a] vinylmagnesium−CuBr·Me_2S,[7b] and vinyllithium−CuI-Bu_3P[7c] complexes, as well as vinyllithium[7d] itself.

While none of these conditions yielded satisfactory results, it was found that vinylmagnesium−PhSCu complex[8] could provide desired product **12**-(*R*) with modest diastereoselectivity (64% de) in acceptable yield (67%). Separation of diastereomeric **12**-(*R*) and **12**-(*S*) products was achieved by silica gel chromatographic purification followed by crystallization, with hydrolysis of **12**-(*R*) to building block **7** then being achieved in good yield using standard conditions.[9]

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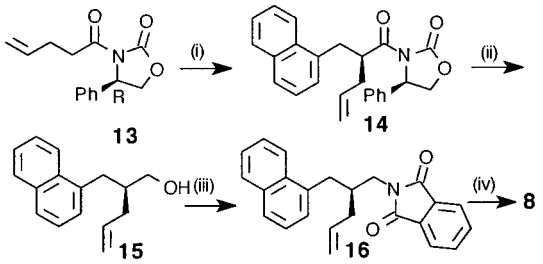
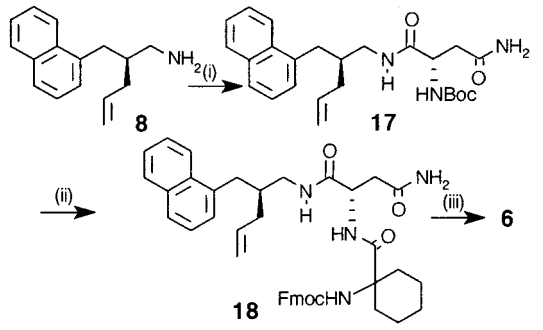
Similar to the syntheis of N-terminal pTyr mimetic **7**, stereoselective synthesis of C-terminal naphthylpropylamine **8** also utilized Evans' 4-phenyl-2-oxazolidinone chiral auxiliary (Scheme 2). Unlike the former synthesis, however, the (*R*)-(−)- rather than (*S*)-(+)-auxiliary was employed with a "reversed" addition of aryl functionality to alkenyl side chain. Therefore, acylation of commercially available Evans' oxazolidinone provided **13**. Subsequent alkylation of the lithium enolate with 1-(bromomethyl)naphthalene gave **14** in high yield as a single isolated diastereomer. With stereochemistry established, transformation to amine **8** was achieved in three steps: reduction to alcohol **15**; Mistunobu addition of phthalimide **16**; and finally hydrazine-mediated cleavage to **8** (66% yield for three steps). With N- and C-terminal units **7** and **8** in hand, respectively, construction of metathesis substrate **6** was achieved in straightforward fashion using standard coupling techniques (Scheme 3).

Scheme 2[a]



[a] Conditions: (i) (a) LiHMDS, THF; (b) 1-bromomethylnaphthalene, (88% yield); (ii) $LiAlH_4$, THF, −78 °C to rt (100% yield); (iii) DEAD, PPh_3, phthalimide, THF (73% yield); (iv) EtOH, H_2O, $N_2H_4 \cdot H_2O$ (91% yield).

Scheme 3[a]

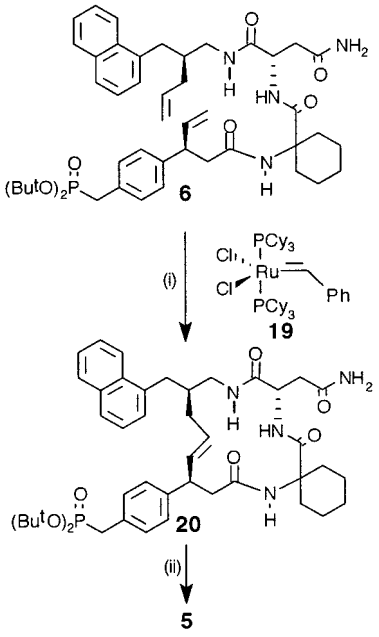


[a] Conditions: (i) (a) HOBt, DIPCDI (95% yield); (ii) (a) TFA-CH_2Cl_2; (b) $NaHCO_3$; (c) Fmoc-1-amino-cyclohexanecarboxylic acid, HOBt, DIPCDI (70% yield); (iii) (a) piperidine in CH_3CN (86% yield); (b) **7**, HOBt, DIPCDI (67% yield).

N-Boc-protected asparagine amide **17**, obtained by condensation of **8** with commercially available N-Boc asparagine, was deprotected and coupled with commercially available N-Fmoc 1-aminocyclohexane carboxylic acid to provide dipeptide amide **18**. Removal of Fmoc protection, followed by HOBt active ester coupling with pTyr mimetic **7**, gave penultimate intermediate **6** in good yield.

Ruthenium-containing catalyst **19** has enjoyed widespread utility in olefin metathesis, including the formation of peptide bend mimetics.[2,10] Accordingly, by subjecting **6** to olefin metathesis in the presence of **19** in CH_2Cl_2 at reflux under argon, ring-closed product **20** was obtained in good yield predominantly as the *trans* isomer (Scheme 4). Although chromatographic separation of minor amounts of *cis* contamination proved difficult at this stage, following TFA-mediated cleavage of *tert*-butyl phosphonate protection, pure final product **5** could be obtained in 60% yield using reverse-phase HPLC chromatography.

Scheme 4[a]



[a] Conditions: (i) Grubbs' catalyst (**19**), CH_2Cl_2, reflux, 60 h (67% yield); (ii) TFA/H_2O/trimethylsilane, 1 h (60% yield).

As demonstrated herein, olefin metathesis-induced macrocyclization of pseudotripeptide precursor can be achieved with full functionality incorporated into the C- and N-terminal alkene moieties, so as to afford ring-constrained peptidomimetics bearing complete side chain functionality present in the parent open chain peptide. Utilization of Grubbs' olefin metathesis reaction in this fashion, may prove

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useful for the preparation of constrained analogues in a variety of contexts.

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Supporting Information Available: Synthetic procedures and spectral characterization for compounds **5**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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