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Macrocycloadditions Leading to Conformationally Restricted Small Molecules

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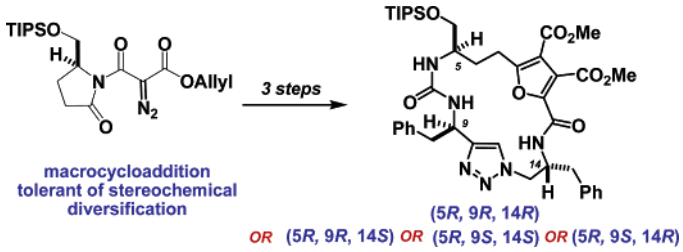
ABSTRACT



The Cu(I)-catalyzed cycloaddition of alkynes and azides (click reaction) provides a robust method for the construction of macrocyclic small molecules via an intramolecular macrocycloaddition. A three-subunit system has been used to explore the tolerance of this macrocycloaddition to variations of stereochemistries and substituents.

Restricting conformational freedom in small molecules[1] can lead to significant changes in assay performance, as was quantitated in a recent study using multidimensional screening.[2] For the class of compounds investigated, the presence of a macrocycle and the stereochemistry of substituents on the macrocycle were primary determinants of the observed global activity patterns. Elucidating these relationships is part of a larger effort to correlate chemical descriptors of small molecules to assay measurement outcomes.[3]

The preparation of macrocyclic compounds in library syntheses can be challenging, often requiring either the incorporation of conformational biasing elements or the empirical optimization of reaction conditions.[4] We initiated the current research with the idea that the substantial enthalpic gains associated with forming an aromatic triazole (ΔH_f = 60 kcal/mol) might provide a useful means for synthesizing macrocycles from substrates that vary in stereochemistry and substitution patterns.[5] We were also attracted to the mild conditions reported for the Cu-catalyzed cycloaddition of azides with alkynes (click reaction) that yields this functionality.[6] This strategy has previously proven successful in the head-to-tail cyclodimerization of peptides,[7] polysaccharides,[8] and carbohydrate/amino acid hybrids.[9] An

(1) (a) Burger, M. T.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 12697−12698 and references therein. (b) For a review in the context of peptides, see: Davies, J. S. *J. Pept. Sci.* **2003**, *9*, 471−501.

(2) Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F.; Patterson, N.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14740−14745.

(3) Schreiber, S. L. *Nat. Chem. Biol.* **2005**, *1*, 64−66.

(4) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1, 106480−10649 and references therein.

(5) Williams, C. I.; Whitehead, M. A. *THEOCHEM* **1997**, *393*, 9−24.

(6) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (c) Pérez-Balderas, F.; Ortega-Muñoz, O.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-Garciá, J.; Santoyo-Gonzáles, F. *Org. Lett.* **2003**, *5*, 1951−1954.

(7) (a) Punna, S.; Kuzelka, J.; Wang, O.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215−2220. (b) van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503−4506.

(8) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638−1639.

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application of this chemistry to small-molecule macrocycles as β-turn mimics has also been reported.[10]

We have now explored a macrocycloaddition strategy in a modular system that enables the facile variation of stereochemistries and substituents (Figure 1). Three subunits

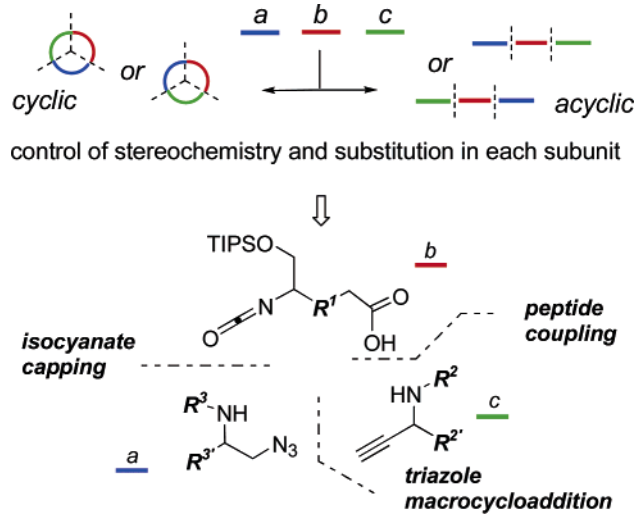


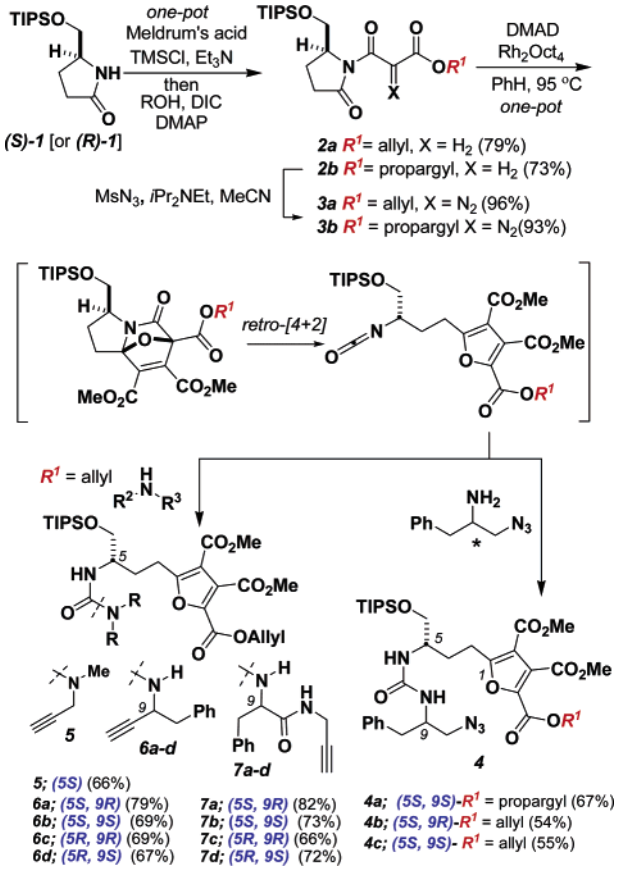
Figure 1. Three-subunit system for assembling macrocycles.

(**A**, **B**, and **C**) can be arranged to form two cyclic variants with the interchange of subunits **A** and **C**. Likewise, two acyclic variants can also be synthesized. **A** and **C** are interchangeable by virtue of their having amines as the reactive functionality. Orthogonal amine acceptors were incorporated into subunit **B** so that isocyanate trapping and peptide coupling reactions yield the acyclic triad.

Padwa and co-workers have reported reactions of isomünchnone dipoles with alkynes.[11] In these cases, decomposition of a diazoimide with Rh_2OAc_4 initiates a reaction cascade where the carbonyl ylide undergoes [3+2] cycloaddition to an alkyne to yield an indolizinone that then undergoes a [4+2] cycloreversion reaction releasing an isocyanate. This reaction provides a potentially efficient means to diversify subunit **B**.

To establish the stereochemistry in the subunit **B**, we began with the known pyrrolidinone **1** bearing a TIPS-protected hydroxymethyl group. This group serves to model a silylated macrobead solid support used commonly in our laboratory (Scheme 1).[12] We adapted a one-pot procedure to access β-imido esters by treatment of **1** first with Meldrum's acid in the presence of TMSCl and Et_3N and then with allyl alcohol, diisopropylcarbodiimide (DIC), and DMAP.[13] Diazo

Scheme 1. Preparation of the Central Sector



transfer afforded the α-diazo-β-imido esters **3a**,**b**. Treatment of **3a**,**b** with Rh_2Oct_4 resulted, presumably via an intermediate ylide, in a chemoselective cycloaddition with dimethylacetylene dicarboxylate without interference from the pendent alkene or alkyne substituents. Cycloreversion of these intermediates afforded the isocyanates that were converted to **4a**−**c** by the addition of (*S*)- or (*R*)-azidomethylphenylalanine.[14] Alternatively, the isocyanate was intercepted with: (1) *N*-methyl propargylamine to give **5**, (2) (*S*)- or (*R*)-2-aminophenyl butyne to give **6a**−**d**, or (3) the propargyl amide of (*S*)- or (*R*)-phenylalanine to yield **7a**−**d**.

We next examined the ability of other dipoles to participate in the cycloaddition−cycloreversion sequence in an attempt to expand the diversity of subunit **B** (Scheme 2). Decomposition of the diazoimide **3a** in the presence of ethynyl tolyl sulfone and trapping with *N*-methyl propargylamine provided **8** as a single isomer in 76% yield. Methyl cyanoformate as a dipolarophile afforded oxazole **9** in 50% yield. Methyl propiolate is also an active participant, as reported previously.[11b]

We next turned our attention to the macrocycloaddition. Treatment of **4a** with CuI in THF afforded **9** efficiently, as judged by analysis of the reaction mixture by ^{1}H NMR, but in poor isolated yield (Scheme 3). The SFC-MS trace of the

(10) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, *70*, 9595−9598.
(11) (a) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820−829. (b) Padwa, A.; Hertzog, D. L. *Tetrahedron* **1993**, *49*, 2589−2600.
(12) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312−318.
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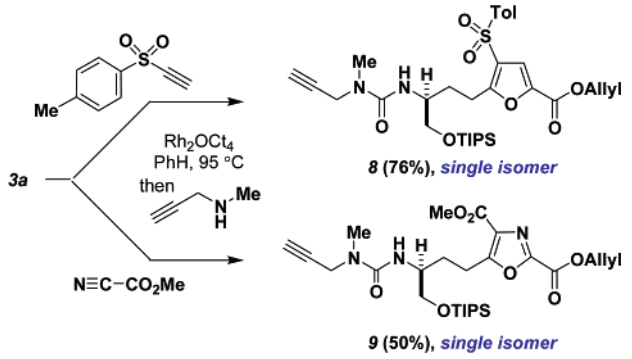
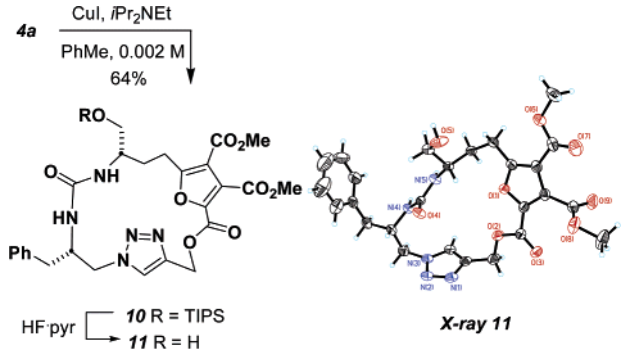
(14) Nantermet, P. G.; Selnick, H. G. *Tetrahedron Lett.* **2003**, *44*, 2401−2404.

Scheme 2. Expanding the Scope of the 3-CC Reaction



Cu(I)-catalyzed macrocycloaddition after 3 h was also exceptionally promising.[15] Product isolation, however, proved difficult, possibly because of the inclusion of Cu within the macrocycle. This was particularly problematic when the reaction was conducted in THF or in alcoholic/aqueous solvents using a variety of Cu(I) catalysts. Product recovery typically gave <20% yield. The use of polymer-bound cation scavengers failed to improve the recovery. Toluene proved optimal for the reactions, permitting simple product recovery after flash chromatography and a 64% yield of **10**.

Scheme 3. Optimizing the Macrocycloaddition of an ABC Triad

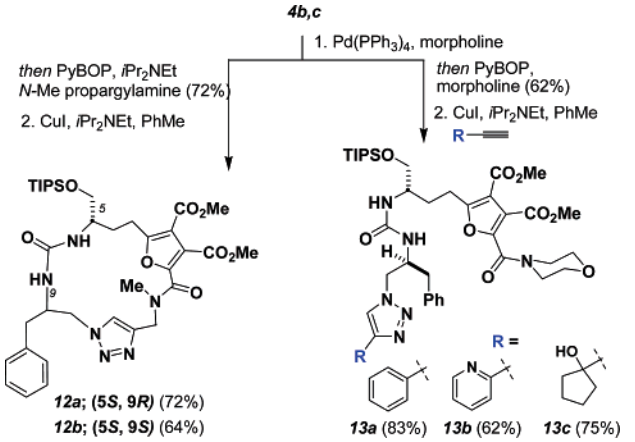


Deprotection of **4b** or **4c** gave acids that were coupled to *N*-methyl propargylamine or to morpholine, the latter of which cannot participate in a subsequent macrocyclization reaction (Scheme 4). Phoshine-liganded palladium deprotected the allyl ester without noticeable interference by the resident azide. The macrocycloaddition conditions afforded both diastereomers of the **ABC** macrocycles **12a**,**b** in comparable isolated yields. The acyclic **ABC** constructs **13a**−**d** were produced in good yield by acyclic coupling with a variety of terminal alkynes.

In the examples above, the stereochemistry within the macrocycles (**12a**,**b**) was largely indeterminant of the macrocycloaddition outcome. Thus, we next examined stereo-

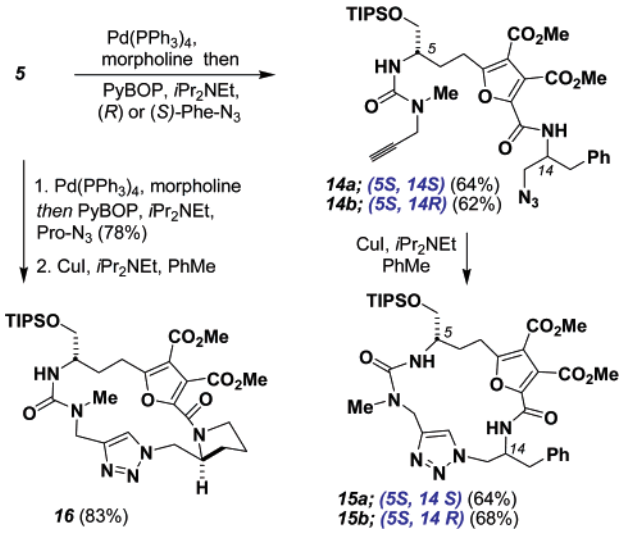
(15) For examples, see Supporting Information. SFC = supercritical fluid chromatography.

Scheme 4. Partitioning between Acyclic and Cyclic Products



chemical influences within other subunits. We first synthesized three **CBA** triads using related chemistry (Scheme 5). Deprotection of **5** and coupling with (*S*)- or (*R*)-azidomethylphenylalanine gave the macrocycloaddition precursors **14a**,**b**. Exposure individually of the diastereomers to catalytic CuI in toluene gave the (5*S*,14*S*) and (5*S*,14*R*) macrocycles (**15a**,**b**) in nearly equivalent yields (64% and 68%, respectively). We also note that proline can be incorporated into the 17-membered macrocycles with similar efficiency (**16**).[16]

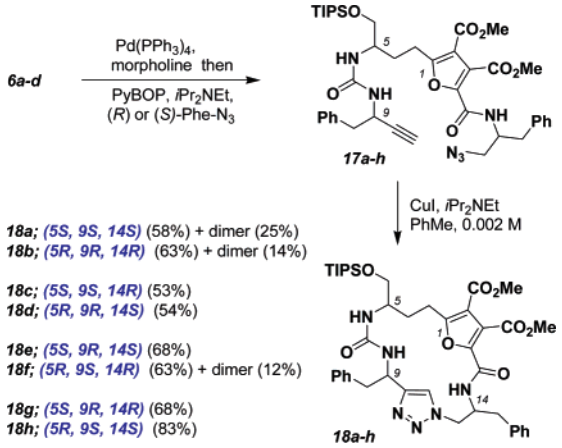
Scheme 5. Inverted CBA Triad



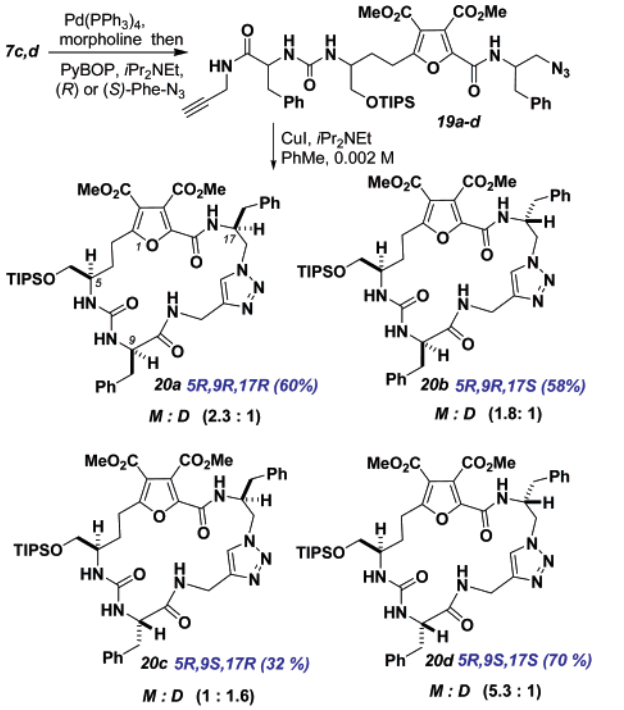
Beginning with **6a**−**d**, we also constructed a complete set of diastereomeric macrocycloaddition precursors (**17a**−**h**) to examine whether this approach would tolerate all three subunits bearing stereogenic centers (Scheme 6). All stereoisomers of the acyclic azidoalkynes were shown to participate in the macrocycloaddition reaction affording the macrocycles

(16) Incorporation of two proline residues into macrocyclic triazoles has recently been reported: Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919−922.

Scheme 6. 17-Membered Macrocycles



Scheme 7. 21-Membered Macrocycles



18a−**h** in fair to good isolated yields. The incorporation of a third stereogenic center appears to facilitate the formation of a cyclodimer in some cases, albeit in low yield.

Previous reports had alerted us to the potential of a confounding cyclodimer formation,[10] so we were pleasantly surprised by the relatively small amounts of cyclodimer produced in the macrocycloadditions reported in this study. For example, no cyclodimer was detected in reactions yielding macrocycles having only one or two stereocenters. To determine whether this result is specific to the 17-membered macrocycles, we prepared an analogous series of lengthened acyclic precursors **19a**−**d** (Scheme 7). Macrocycloaddition of these compounds produced the 21-membered monomer **20a**−**d** in all cases; however, significant amounts of the cyclodimer were observed. This cyclodimerization predominates in the reaction of the (5*R*,9*S*,17*R*) stereotriad (**20c**).

The Cu(I)-catalyzed macrocycloaddition of alkynes with azides appears to provide a reliable path for the synthesis of macrocyclic triazoles. We have been sufficiently encouraged by the results reported herein, especially with respect to the macrocycloadditions' tolerance to variations in stereochemistries and substituents, that we are initiating an expanded research effort. The effort will include experiments to determine whether control of site−site interactions in solid-phase synthesis can be used to decrease further the yield of cyclodimers while increasing the yield of the target macrocycles. Such a capability will be especially important in expanded efforts, for example, to synthesize 21-membered macrocycles (Scheme 7).

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Supporting Information Available: Characterization data for all new compounds and X-ray crystallographic files for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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