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An Oligomer-Based Approach to Skeletal Diversity in Small-Molecule Synthesis

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The discovery of small molecules capable of modulating the functions of macromolecules in living systems is of central importance to the study of biology and the treatment of disease.[2] This process is being facilitated by methods to synthesize skeletally diverse small molecules efficiently.[3−14] Herein, we report a two-step process, involving the assembly of monomers and the rigidification of the resulting oligomers, that provides an alternative means to the assembly of widely varied molecular architectures.

Reactive oligomers are synthesized from readily accessible monomers and then subjected to a chemical transformation that causes them to transform into distinct three-dimensional shapes (Figure 1). This transformation serves a function analogous to the folding step in the production of the biologically active forms of proteins.[3,4] The enormous variety of three-dimensional shapes of natural proteins stems from their combinatorial synthesis in cells from ∼20 monomer building blocks. This observation hints at a capacity of the synthetic approach to yield many three-dimensional shapes of small molecules. Here, starting with only three simple monomers, we synthesized linear 2-mers and 3-mers that yielded 12 unique skeletons following ring-closing diene or eneyne metathesis.[15,16] 1,3-Diene products of the eneyne metatheses also served as substrates in a second skeletal diversification step using Diels−Alder reactions.

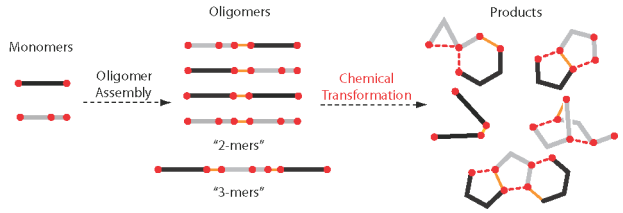
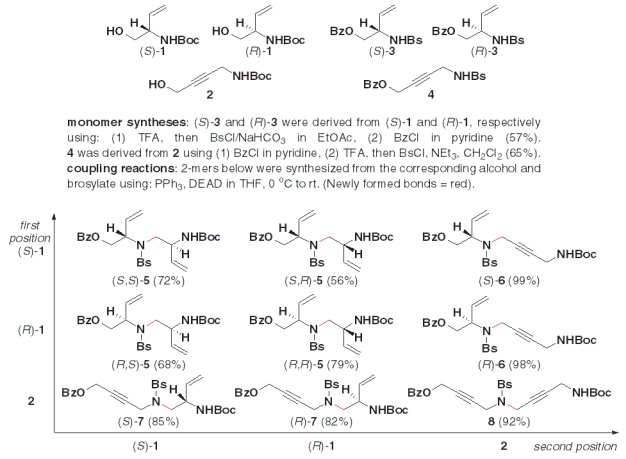


Figure 1. Schematic depiction of oligomer-based approach. Red circles indicate reactive groups, yellow lines indicate monomer attachment sites, and dashed red lines indicate newly formed covalent bonds.

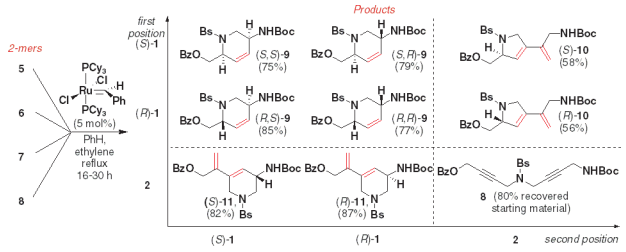
Monomers (*S*)-**1**, (*R*)-**1**, and **2** were readily synthesized[17] and converted into all nine possible 2-mer combinations **5**−**8** via intermediate sulfonamides (*S*)-**3**, (*R*)-**3**, and **4** (Scheme 1), whose structures are displayed in the scheme. The 4-bromobenzenesulfonyl (Bs) group was used both to modulate the pKa of the attached nitrogen to permit a Fukuyama−Mitsunobu coupling reaction,[18] and to introduce a handle for further derivatization of the aryl bromide. The benzoyl ester functions as a surrogate for a carboxypolystyrene solid support, which we plan to use in future studies.

Subjecting all stereoisomeric variants of **5**−**8** to the first generation Grubbs' catalyst in benzene under ethylene atmosphere at reflux provided eight products having three types of skeletons: disubstituted tetrahydropyridine, vinyl tetrahydropyridine, and dihydropyrrole (Scheme 2). The reactions of 2-mers **6** and **7**, yielding five- and six-membered heterocycles **10** and **11**, respectively, illustrate the key role of the order of coupling the "ene" and "yne"

Scheme 1



Scheme 2



monomers. Both diastereomeric combinations of 2-mers **6** yielded 2,5-disubstituted tetrahydropyridines **9** in good yields. Diyne **8** was unreactive toward the metathesis conditions.

Several 3-mers were then accessed from the 2-mers by deprotecting the Boc carbamates, introducing the *o*-nitrobenzenesulfonyl (Ns) groups, and applying the Fukuyama−Mitsunobu coupling reaction (Scheme 3a). This sequence provided **12**−**13** in 73−94% yields. Polyunsaturated 3-mers **12**−**13** afforded polycyclic products under the common metathesis conditions (Scheme 3b). Diastereomers (*S*,*R*)- and (*S*,*S*)-**12** afforded bicycles (*S*,*R*)- and (*S*,*S*)-**14** in 57 and 74% yields, respectively.[20]

Oligomer **13** underwent a cascade reaction to provide a tricyclic diene (**15**). We hypothesize that this compound results from consecutive ene−yne−yne ring-closing metathesis (**13** → **16**), spontaneous 6π-electrocyclic ring closure of an intermediate 1,3,5-triene (**16** → **17**), and sigmatropic 1,5-hydride shift (**17** → **15**)[21,22] (Scheme 4). During this remarkable process, three rings, three C−C bonds, and two stereocenters are formed in a single step. 3-Mer **13** and 2-mer **8** differ in the presence or absence of a terminal olefin-containing group; however, this difference is sufficient to convert an unreactive compound into a reactive one.

The 1,3-diene products of the oligomerization−skeletalization sequence are poised for a second round of skeletal diversification

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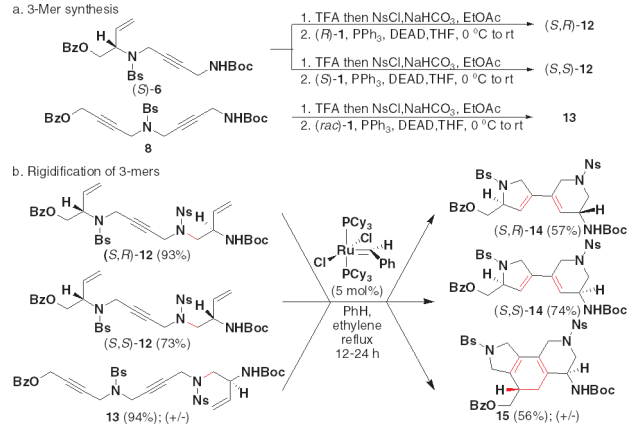
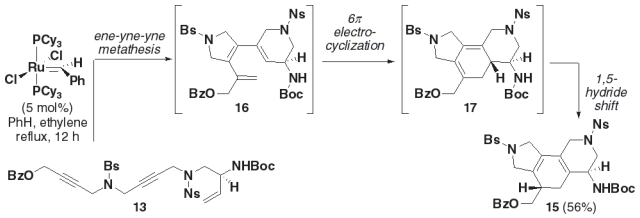
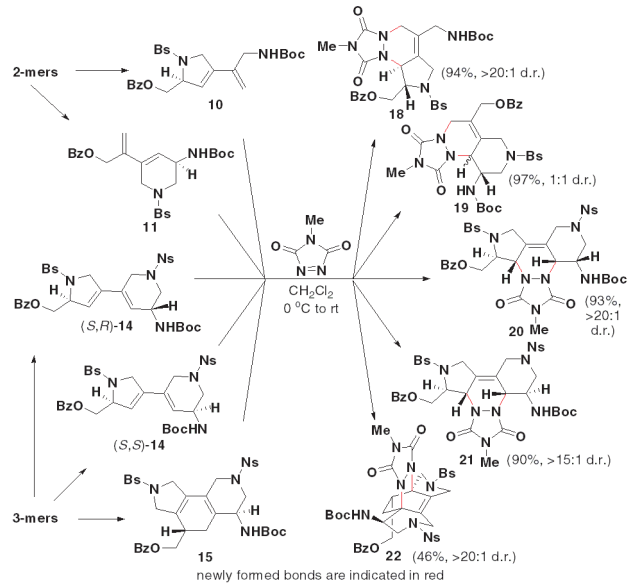
Scheme 3



Scheme 4



Scheme 5



using Diels−Alder cycloaddition reactions (Scheme 5). Thus, addition of 4-Me-1,2,4-triazoline-3,5-dione to dienes **10**, **11**, **14**, and **15** in CH_2Cl_2 at 0 °C provided complex polycycles **18**−**22** in 46−97% yields. The dienylic benzoyloxymethyl substituents in substrates **10** and **14** enforced excellent diastereofacial control, whereas the −NHBoc substituent provided virtually no directing effect.[23] This trend had the beneficial effect of affording both **20** and **21** in high diastereoselectivity irrespective of stereochemistry in the starting materials. Bridged pentacycle **22** was the only product isolated from the cycloaddition of diene **15**.

This initial report details the straightforward assembly of three monomers into diverse oligomers and the rigidification of these compounds into different molecular architectures. Future research will attempt to define additional chemical transformations capable of altering product structures and to annotate the resulting products using small-molecule screens. The discovery of a cascade annulation reaction of a linear ene-diyne illustrates the ability of the oligomerization/folding process to enable chemical discovery in addition to generating skeletally diverse small molecules.

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Supporting Information Available: Methods to perform experiments and to determine the constitution and stereochemistry of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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