A Strategy for Macrocyclic Ring Closure and Functionalization Aimed toward Split-Pool Syntheses

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Biologically active natural products frequently contain medium or large rings—erythromycin is a famous example. Many types of ring-closing reactions have been used in syntheses of such compounds.[1a] Typically, these reactions are optimized for efficiency by varying protecting groups, stereochemistry, and oxidation states of acyclic precursors and by varying reaction conditions.[1b] These ad hoc solutions are not practical when the split-pool strategy[2] is applied to simultaneous syntheses of millions of natural product-like compounds[3,4] containing macrocyclic structures. Likewise, applying the principles of macrocyclic stereocontrol to large collections of conformationally heterogeneous compounds is impractical. Achieving such syntheses, however, will likely result in many new biologically active compounds and will thus advance chemical genetics, where genetic-like screens using small molecules in place of mutations are used to explore biological processes.[5] We have initiated an effort aimed at split-pool syntheses of stereochemically and structurally diverse compounds. As a first step toward this goal, we report solution- and solid-phase reactions of designed acyclic compounds and of the resulting macrocycles that may be applicable to syntheses performed en masse.

Ring-closing reactions leading to six-membered rings often proceed with high effective molarities as a result of low-energy conformations that place the reacting termini in close proximity and with orientations suitable for bond formation. By introducing structural elements into acyclic precursors of macrocyclic rings that similarly result in conformations favorable to ring closure, high effective molarities may also be achieved.[6] One illustration of this strategy leading to 12-membered rings is shown in Scheme 1. By inserting planar, sp^2-hybridized two-atom (intra-annular) elements having trans geometry into alternating ring bonds of a fully sp^3-hybridized (saturated) six-membered ring, a hexagonally shaped 12-membered ring product free of trans-annular and torsional strain should result.[4,7] To maintain this idealized low-energy conformation, consideration must be given to the stereochemistry at ring carbons bearing substituents so as to avoid, among others, allylic ($A^{1,3}$) strain. Many permutations of this concept exist, and it has been applied successfully to the synthesis of structurally complex 10- and 14-membered rings (unpublished results of D.L. and S.L.S). Using the specific strategy in Scheme

Scheme 1
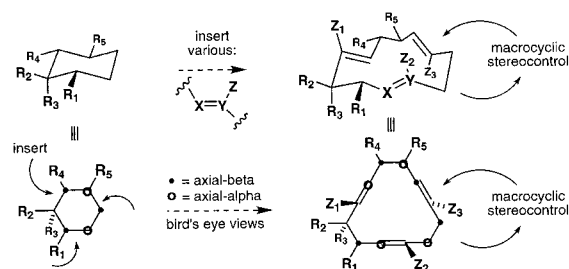
Scheme 2
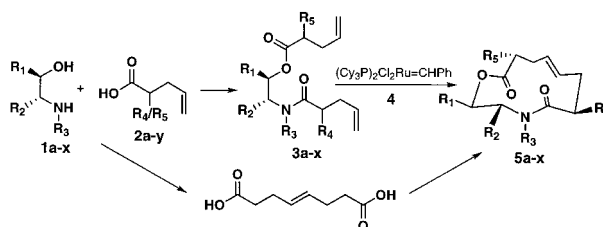
1, we have synthesized 12-membered-rings with hexagonal shapes in excellent yields using both sp^3−sp^3 carbon−carbon bond-forming[7] and imine (unpublished results of D.L. and S.L.S) bond-forming ring-closure reactions. In light of the extensive use of the olefin metathesis reaction as a means to effect[8] and study[9] macrocylization reactions, we elected to use the ring-closing metathesis (RCM) reaction for this study. Although RCM reactions[8] proceeded with variable yields, a systematic study of such reactions revealed illuminating trends that support the above conformation-based analysis. These results are described below.

The ring-closure substrates **3a**−**q** were prepared by simultaneous or sequential acylation of 1,2-amino alcohols **1a**−**j** with 4-pentenoic acid or its 2-substituted derivatives **2a**−**c** (EDC, DMAP, CH_2Cl_2) (Scheme 2), except for the precursor of **5l**, which was prepared from tartaric acid benzylidene acetal and 3-buten-1-ol. RCM reactions of **3a**−**s** were performed in the presence of the Grubbs' catalyst (**4**) (5−15 mol %) in CH_2Cl_2 (0.003−0.008 M, reflux, 24−50 h) to produce **5a**−**s** in moderate to excellent yields together with varying amounts of 24-membered cyclic dimers (Figure 1).[10] Alternatively, **5d** was obtained via a tandem inter- and intramolecular acylation of amino alcohol **1d** with *trans*-4-octenedioic acid (EDC, DMF) in 50% yield.[11]

RCM of precursors **3a**−**r** (identity of R_{1-5} substituents can be inferred by examination of products in Figure 1) provided macrocycles **5a**−**r**. X-ray crystallographic analyses showed that macrocycles **5a**−**g** adopt the idealized hexagonal conformations; **5h**−**m** are drawn in perspective based upon analogy. A deviation from ideality was seen in the crystal of **5n**, where the ester carbonyl rotates slightly, possibly to gain dipole-induced dipole stabilization of the eclipsing (relative to the ester carbonyl) $C\alpha$-methyl bond.[12] Anticipated deviations were observed in the crystals of **5o**−**p**, where the ester carbonyls rotate slightly to avoid

(1) (a) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 109−170. (b) Erythromycin synthesis including ring-closure studies: Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213, 3213−3215, 3215−321.

(2) (a) Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487−493. (b) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82−84.

(3) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565−8566.

(4) In this study, the term "natural product-like compounds" can most easily be related to the enterobactins, natural products having 12-membered rings and three unsaturation units (esters) that stabilize analogous hexagonal conformations.

(5) (a) Schreiber, S. L. *BioMed Chem.* **1998**, *6*, 1127−1152. (b) http://www-schreiber.chem.harvard.edu. (c) http://iccb.med.harvard.edu.

(6) By decreasing ring strain and transannular interactions, trigonal carbons in cyclization substrates can increase the effective molarities of ring-closing reactions that lead to medium rings, see: Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1974**, *96*, 1422−1427.

(7) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106−3213.

(8) For an early application, see: Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926−10927. For a recent review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(9) (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109. (b) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943.

(10) Schwab, P.; Grubbs, R. H.; Ziller, J. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(11) The *cis* isomer of **5d** was obtained from *cis*-4-octenedioic acid. The independent syntheses of both double bond isomers of **5d** prove unambiguously that the RCM reaction produces only the *trans* isomer. Nevertheless, NMR analyses suggest that several of the macrocycles exist as conformational isomers (ratios ∼3:1 to 6:1, see Supporting Information).
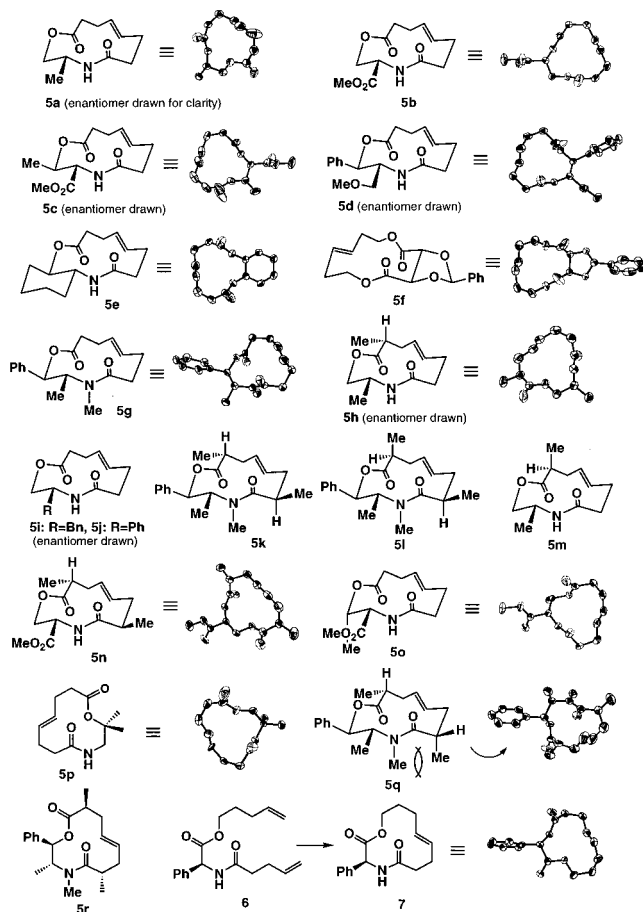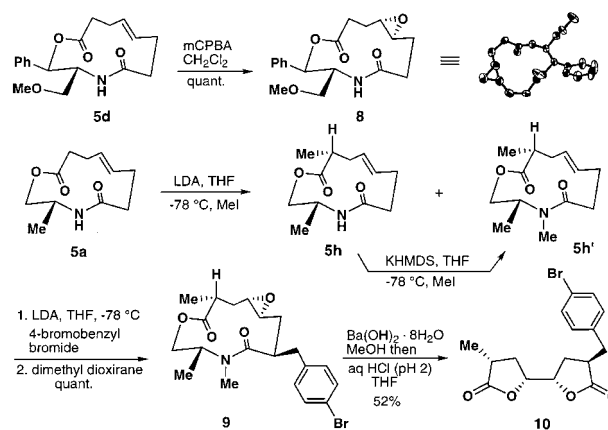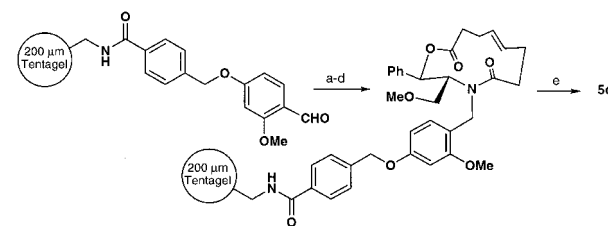
Figure 1. Reaction times and yields:[11] **5a** (120 h, 54%, 7% dimer); **5b** (24 h, 69%, 11% dimer); **5c** (50 h, 47%, 8.8% dimer); **5d** (16 h, 77%); **5e** (52 h, 53%, 14% dimer); **5f** (1 h, 85%); **5g** (24 h, 90%); **5h** (96 h, 84%, 2% dimer); **5i** (48 h, 61%, 9% dimer); **5j** (60 h, 80%, 10% dimer); **5k** (36 h, 98%); **5l** (22 h, 83%); **5m** (30 h, 75%); **5n** (30 h, 75%); **5o** (56 h, 50%, 22% dimer); **5p** (120 h, 10%); **5q** (30 h, 96%); **5r**, (60 h, 98%); **7** (90 h, 18%).

a steric clash between the carbonyl and substituents attached to the carbon bearing the ring oxygen of the ester. A predicted alteration in ring conformation is seen in the crystal of **5q**, where a conformation is adopted that avoids allylic ($A^{1,3}$)-strain involving the N-methylated amide unit. A similar conformation is predicted for **5r**, which contains the same stereochemical arrangement of nearby amide substituents. The ability to anticipate the consequences of ring substituents and their stereochemistries on ring conformation should be vitally important in efforts to functionalize en masse ring products synthesized by split-pool methods.

To explore the effect of moving an unsaturation unit (ester, amide, olefin) out of register on the efficiency of ring closure, the cyclization of **6** was compared to its reference, **3j**. Although **3j** and **6** differ as substrates in ways beyond the strategic placement of unsaturation units, the low yield (18%) observed in the cyclization of the nonideal substrate **6** to **7** stands in contrast to the cyclization of the idealized substrate **3j** to **5j** (80%). This comparison supports the basic premise of our strategy—that conformational analysis can be used to rationally juxtapose the reactive termini of acyclic precursors to macrocycles.

Structural diversity of products in split-pool syntheses can be achieved by rational alteration of stereochemistry (as alluded to in the current conformational model), by judicious selection of building blocks, and by the use of bifurcating reaction pathways that produce different backbone scaffolds. To illustrate the latter strategy, we turned our attention to functionalization reactions

(12) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035−5041.

Scheme 3

Scheme 4[a]

[a] (a) Trimethyl orthoformate, 2-amino-3-methoxy-1-phenyl-1-propanol; (b) NaBH$_3$CN, MeOH, 1% AcOH; (c) EDC, DMAP, Et$_3$N, DMF, 4-pentenoic acid; (d) **4**, CH$_2$Cl$_2$; (e) 10% TFA, CH$_2$Cl$_2$.

under macrocyclic stereocontrol and to ring permutation reactions (Scheme 3).[13] Epoxidation of **5d** (mCPBA, 0 °C), provided a single epoxide **8**, which adopts the idealized conformation in the solid state, in quantitative yield. Alkylation of **5a** (LDA, −78 °C, MeI) proceeded with complete stereochemical control, yielding **5h** and **5h′** in varying ratios (1:1 to 1:6) (stereochemistry assigned by independent synthesis; see Figure 1). Selective N-methylation of **5h** to **5h′** (KHMDS, MeI, −78 °C to room temperature) followed by benzylation (LDA, −78 °C, 4-bromobenzyl bromide) and epoxidation (DMDO) resulted in **9** stereoselectively. Hydrolysis (Ba(OH)$_2$·8H$_2$O, MeOH) of the ester moiety of **8** followed by acidification (aqueous HCl, pH 2) provided the bislactone **10** (52%), a compound whose backbone scaffold differs dramatically from the originating macrolide.

Finally, to demonstrate feasibility of performing the RCM reaction sequence on a solid support[14] appropriate for a bead arraying and compound distributing system developed by our colleagues at the ICCB (L. Walling and R. King, unpublished results), a traceless linker was used to synthesize **5d** with excellent purity following cleavage with 10% TFA (Scheme 4). This outcome bodes well for future split-pool syntheses.

These studies illustrate strategies and conformational principles relevant to the goal of synthesizing stereochemically complex macrocycles and macrocyle-derived compounds en masse and in few steps. Although the comparative analysis in this study used primarily the RCM reaction, it is likely that other ring-closing reactions can be identified that proceed with higher efficiency.

Supporting Information Available: Experimental details (PDF). An X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA992658M

(13) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.

(14) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9609−9614.