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Reaction Discovery Employing Macrocycles: Transannular Cyclizations of Macrocyclic Bis-lactams

Chong Han,[†] Sathish Rangarajan,[†] Alicia C Voukides,[‡] Aaron B. Beeler,[†] Richard Johnson,[‡] and John A. Porco, Jr.*[,†]

Department of Chemistry and Center for Chemical Methodology and Library Development, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, and Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

porco@bu.edu

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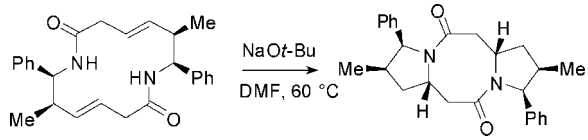
ABSTRACT



Macrocyclic bis-lactams have been synthesized by cyclodimerization of homoallylic amino esters employing a Zr(IV)-catalyzed ester-amide exchange protocol. Base-mediated transannular cyclizations have been identified to access both bicyclic [5-11] and tricyclic [5-8-5] frameworks in good yield and diastereoselectivity. Preliminary mechanistic studies support an olefin isomerization−intramolecular conjugate addition pathway.

Macrocyclic natural products often exhibit important biological activities and have thus inspired a number of studies involving diversity-oriented synthesis of macrocyclic frameworks.[1] Recent studies have also highlighted elegant examples of transannular cyclizations en route to complex natural products.[2] As part of our studies, we considered preparation of macrocycles as substrates for reaction discovery[3] and potential complexity-generating transannular cyclizations.[4,5] In this communication, we report the preparation of 14-membered ring bis-lactams[6] and their conversion to polycyclic frameworks by divergent, transannular reaction processes, as well as preliminary computational studies to probe the reaction mechanism.

To access macrocyclic bis-lactam substrates, we utilized cyclodimerization of stereochemically well-defined homoallylic amino esters[7] using Zr(IV)-catalyzed ester-amide exchange.[8] Alloc-protected amino esters **1a**−**d** were prepared

[†] Boston University.
[‡] University of New Hampshire.

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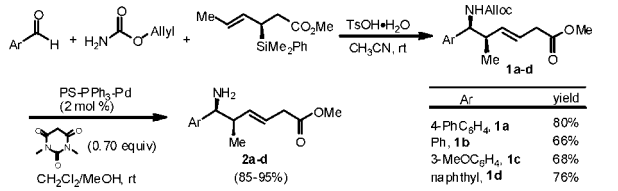
using asymmetric crotylation[7] of the iminium species derived from condensation of allyl carbamate with aromatic aldehydes (Scheme 1). Subsequent alloc removal[9] using a

Scheme 1. Preparation of Homoallylic Amino Ester Monomers

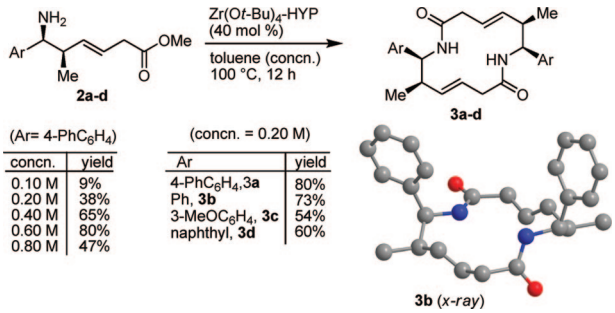


Ar	yield
4-PhC_6H_4, **1a**	80%
Ph, **1b**	66%
3-MeOC_6H_4, **1c**	68%
naphthyl, **1d**	76%

polymer-bound Pd(0) reagent (PS-PPh_3-Pd)[10] simplified product purification and afforded amino ester monomers **2a**−**d**.

As cyclodimerization of **2** involves consecutive intermolecular and intramolecular amidations, we anticipated that concentration may play an important role in reaction efficiency. Therefore, a range of concentrations (0.10−0.80 M) were examined for cyclodimerization of **2a** using Zr(O*t*-Bu)$_4$-2-hydroxypyridine (HYP)[8] as catalyst (Scheme 2).

Scheme 2. Synthesis of Bis-lactams via Cyclodimerization



(Ar= 4-PhC_6H_4)

concn.	yield
0.10 M	9%
0.20 M	38%
0.40 M	65%
0.60 M	80%
0.80 M	47%

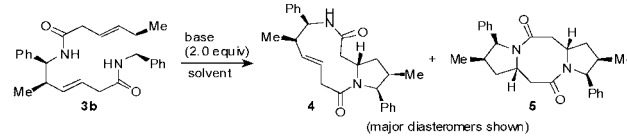
(concn. = 0.20 M)

Ar	yield
4-PhC_6H_4,**3a**	80%
Ph, **3b**	73%
3-MeOC_6H_4, **3c**	54%
naphthyl, **3d**	60%

Based on these studies, an optimal concentration for production of 14-membered bis-macrolactam **3a** was found to be 0.60 M. Macrocyclic bis-lactams **3b**−**d** were also prepared in moderate to good yield using the optimized conditions. The structure and stereochemistry of bis-lactam **3b** was confirmed by single X-ray crystal structure analysis (one conformer shown).[10]

With the target macrolactams in hand, we focused on reaction discovery to identify complexity-generating transannular cyclizations. Initial attempted intramolecular hydroamidation[11] of bis-lactam **3b** utilizing carbophilic late-transition-metal catalysts including Pd(II), Ag(I), Pt(II), Au(I), and Au(III)[12] failed to afford any cyclized products. After reaction screening, use of NaH as base[13] in DMF at 60 °C was found to provide tricyclic [5-8-5] product **5** (dr = 5:1:1) (Scheme 3, entry 1). Reaction at room temperature

Scheme 3. Base Evaluation for Transannular Cyclization



entry	base	solvent	conditions	convn	yield **4** (dr)[a]	yield **5** (dr)[a]
1	NaH	DMF	60 °C, 12 h	95%	<5% (>20:1)	70% (5:1:1)
2	NaH	DMF	rt, 48 h	0%	-	-
3	Cs_2CO_3	DMF	60 °C, 12 h	0%	-	-
4	NaO*t*-Bu	DMF	60 °C, 12 h	100%	0%	80% (5:1:1)
5[b]	NaO*t*-Bu	DMF	60 °C, 24 h	64%	48% (>20:1)	9% (5:1:1)
6	NaO*t*-Bu	THF	60 °C, 24 h	75%	70% (>20:1)	0%
7	LiHMDS	THF	60 °C, 24 h	0%	-	-
8	NaHMDS	THF	60 °C, 24 h	33%	31% (>20:1)	0%

[a] Combined yields of all the diastereomers. Diastereomer ratio determined by ^{1}H NMR integration. [b] 0.20 equiv of base employed.

using NaH gave no conversion, indicating a high activation energy for transannular cyclization (Scheme 3, entry 2). Further optimization was conducted by evaluating different bases and solvents. When DMF was used as the solvent, use of Cs_2CO_3 as base showed no conversion, whereas NaO*t*-Bu afforded full conversion (entries 3 and 4). It is noteworthy that a 64% conversion to a mixture of **4** and **5** could be obtained using a catalytic amount of NaO*t*-Bu (20 mol %) (entry 5). Bases were also evaluated using THF as solvent; NaO*t*-Bu yielded bicyclic product **4** (dr >20:1) exclusively in 70% yield (entry 6).

The relative stereochemistries of **4** and **5** were determined using NOE studies (Figure 1).[10] Furthermore, a single X-ray crystal structure for major diastereomer **5** was obtained to fully support the structure and stereochemical assignment.[10] In order to understand the potential for epimerization, either compound **5** or an inseparable mixture of diastereomers **6** and **7** was treated with NaO*t*-Bu in DMF at 60 °C, which resulted in an approximate 5:1:1 diastereomeric ratio of **5**:**6**:**7**, indicating a reversible, thermodynamically controlled cyclization process.

We also probed the effect of aryl substitution in the transannular cyclization process (Scheme 4). Reaction of bis-lactam **3c** with NaO*t*-Bu in DMA (condition a) afforded approximately a 1:1 mixture of monocyclized product **8c** and bis-cyclized product **9c**. The corresponding reaction of **3c** in THF (condition b) afforded exclusively **8c**, albeit in low yield. Reaction of **3d** using DMA as solvent afforded a 1:4 mixture of **8d** and tricyclic product **9d**, and reaction in THF afforded **8d** exclusively in moderate yield. Transannular

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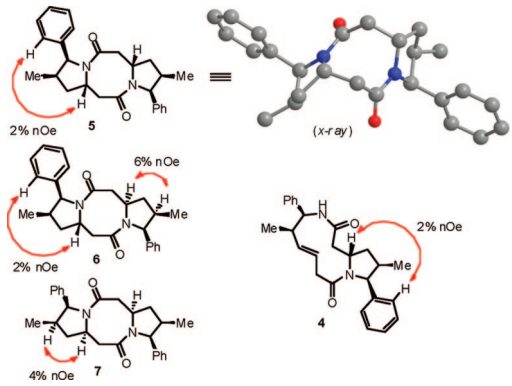
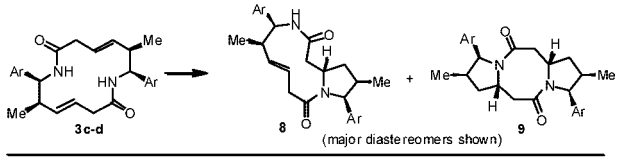


Figure 1. Determination of relative stereochemistry.

cyclization of both **3c** and **3d** also afforded slightly reduced diastereomeric ratios of the bis-cyclized products with

Scheme 4. Preparation of Bicyclic and Tricyclic Products



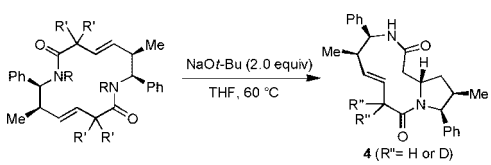
Ar	condition[a]	yield **8** (dr)[b]	yield **9** (dr)[b]
3-MeOPh, **3c**	a	**8c**, 33% (>20:1)	**9c**, 27% (3.6:1.6:1)
	b	**8c**, 20% (>20:1)	—
naphthyl, **3d**	a	**8d**, 18% (>20:1)	**9d**, 69% (3.2:1.4:1)
	b	**8d**, 41% (>20:1)	—

[a] Conditions: (a) NaO*t*-Bu (2.0 equiv), DMA, 60 °C, 12 h; (b) NaO*t*-Bu (2.0 equiv), THF, 60 °C, 24 h. [b] Diastereomeric ratios determined by ^{1}H NMR integration.

diastereoselectivity of monocyclized products remaining high.

To probe the reaction mechanism, we performed kinetic isotope effect experiments employing **3b** and deuterated substrates **10** and **11** (Scheme 5). A significant kinetic isotope

Scheme 5. Kinetic Isotope Effect Experiments



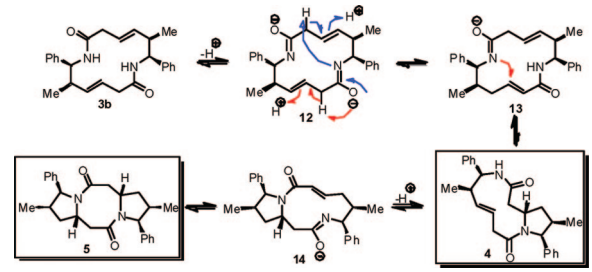
	substrate	rate constant[a]	k_{rel}
3b	R= H, R'= H	k_1= 0.0455 mM/min	2.3
10	R= H, R'= D	k_2= 0.0201 mM/min	1.0
11	R= D, R'= H	k_3= 0.0423 mM/min	2.1

[a] Determined by HPLC analysis. See Supporting Information for details.

effect (k_1/k_2= 2.3) was observed when methylene-deuterated substrate **10** was utilized in comparison to **3b** to afford monocyclized product **4**.[14] These results suggest that the rate-determining step for production of **4** likely involves methylene deprotonation.[15]

On the basis of our experimental results, we propose an olefin isomerization−conjugate addition mechanism for the base-mediated transannular cyclization (Scheme 6).[2b,c,16] ^{1}H

Scheme 6. Proposed Reaction Pathway



NMR studies indicate that the initial step is likely deprotonation of bis-lactam **3b**, generating anionic species **12**.[10] Proton transfer may occur at the α position (red) or transannularly (blue) to afford olefin-isomerized intermediate **13**. Subsequent conjugate addition affords the bicyclic product **4**. The bicyclic product may undergo further deprotonation−isomerization to afford intermediate **14**, which may be followed by conjugate addition to provide **5**. In contrast to use of DMF as solvent, we speculate that the absence of a second cyclization in the less polar solvent THF[17] may be due to diminished acidity of the methylene hydrogens of **4**, which bears a neighboring tertiary amide relative to those in macrolactam **3b**.

To understand the stereochemical outcome of the reaction, we carried out computational studies based on our proposed mechanism. The studies included conformational searches and M052X density functional calculations[10] on bis-lactam **3b**, key proposed intermediates (**15**, **17**, and **18**), cyclized products (**4**−**7**, **16**), and transition states. Scheme 7 summarizes relative energies for neutral species. Enone conjugation is endothermic, consistent with our failure to isolate conjugated intermediates. The two cyclization steps define an energy cascade with the experimentally observed products of lowest energy as might be expected for an equilibrium process.

Transition state searching for the conjugate addition steps posed a greater challenge. In macrocyclic rings, there are few systematic methods to simultaneously search both

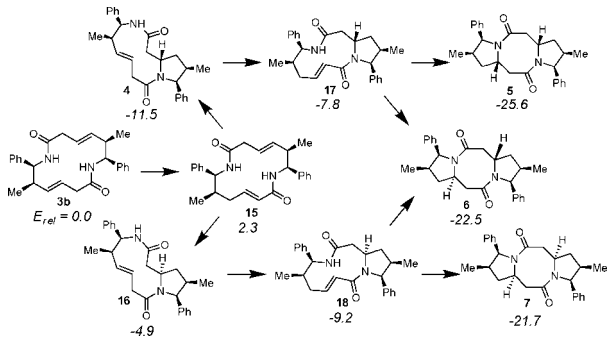
(14) Approximately 20% deuteration remained at R″ when the reactions were quenched by addition of H_2O.

(15) For related examples of kinetic isotope effects in enolate chemistry, see: (a) Held, G.; Xie, L. *Microchem. J.* **1997**, *55*, 261. (b) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605.

(16) Johnson, S. J. *J. Org. Chem.* **1995**, *60*, 8089.

(17) For solvent effects on acidities of the α-hydrogens of amides, see: Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.

Scheme 7. DFT Relative Energies (kcal/mol) for Neutral Species



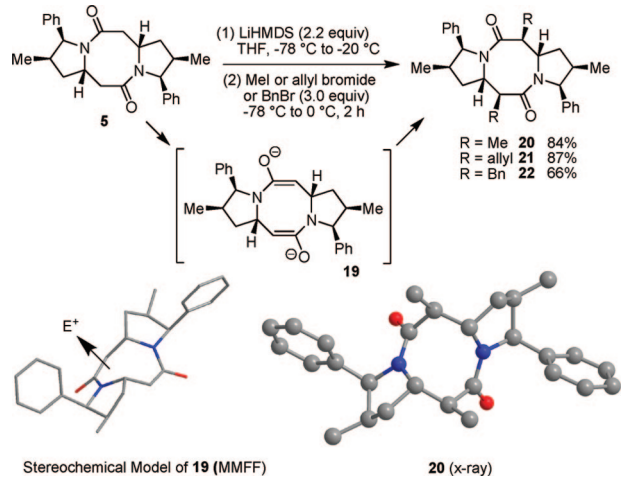
conformations and transition states.[18] Transition state conformational searches were carried out by Monte Carlo methods, with a constrained length (1.9 Å) for the nascent transannular bond. The 50−100 candidate structures of lowest energy were further optimized with the AM1 method, followed by single point HF/3-21G calculation. Finally, the lowest energy collection of structures was subjected to M052X/6-31G(d) optimization and frequency analysis.[10] The predicted transition state energy barriers of 6−15 kcal/mol are consistent with the facile nature of these reactions. Each anionic cyclization step is endothermic[10] and as a consequence, the product distribution is thermodynamically controlled consistent with the relative energies shown in Scheme 7.

Further functionalization of the tricyclic core structure of **5** was conducted in an effort to generate further complexity. Stereoselective bis-alkylations were achieved in good yield by treatment of **5** with LiHMDS at −78 °C and subsequent quenching with alkyl halides (Scheme 8) to afford alkylated products (**20**−**22**) as single diastereomers. Stereoselectivity may be derived by approach of the electrophile from the convex face of the dienolate intermediate **19**. The structure and stereochemistry of bis-alkylated product **20** was confirmed by single crystal X-ray analysis.[10]

In conclusion, macrocyclic bis-lactams have been efficiently synthesized by cyclodimerization of homoallylic amino ester monomers employing Zr(IV)-catalyzed esteramide exchange. Reaction discovery has led to the identification of transannular cyclizations to provide bicyclic [5-11] or tricyclic [5-8-5] frameworks in good yield and diastereoselectivity. Diastereoselective C-alkylation was developed to further elaborate structures. Preliminary mechanistic studies including computational analyses support an olefin isomerization−intramolecular conjugate addition pathway. Further studies involving reaction discovery of macrocyclic frameworks are in progress and will be reported in due course.

(18) For discussions of transition state conformational searches, see: (a) Wolfe, S.; Buckley, A. V.; Weinberg, N. *Can. J. Chem.* **2001**, *79*, 1284. (b) Baldwin, J. E.; Raghavan, A. S.; Hess, B. A., Jr.; Smentek, L. *J. Am. Chem. Soc.* **2006**, *128*, 14854. (c) Koslover, E. F.; Wales, D. J. *J. Chem. Phys.* **2007**, *127*, 1341.

Scheme 8. Diastereoselective Alkylation



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Supporting Information Available: Experimental procedures and characterization data for all new compounds and summary energetics for stationary points from density functional calculations. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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