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Reaction Discovery Employing Macrocycles: Transannular Cyclizations of Macrocyclic *Bis*-Lactams

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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 enroute to complex natural products.² As part of our studies, we considered preparation of macrocycles as substrates for reaction discovery³ and potential complexity-generating transannular cyclizations.^{4,5} In this communication, we report the preparation of 14-membered ring *bis*-lactams⁶ and their conversion to polycyclic frameworks by divergent, transannular reaction processes as well as preliminary computational studies to probe the reaction mechanism.

In order to access macrocyclic *bis*-lactam substrates, we utilized cyclodimerization of stereochemically well-defined homoallylic amino esters⁷ using Zr(IV)-catalyzed ester-amide exchange.⁸ Alloc-protected amino esters **1a–d** were prepared using asymmetric crotylation⁷ of the iminium species derived from condensation of allyl carbamate with aromatic aldehydes (Scheme 1). Subsequent alloc removal⁹ using a polymer-bound Pd(0) reagent (PS-PPh₃-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(Ot-Bu)₄-2-hydroxypyridine (HYP)⁸ as catalyst (Scheme 2). 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 hydroamidation¹¹ 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 base¹³ 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 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 Cs₂CO₃ as base showed no conversion, while NaOt-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 NaOt-Bu (20 mol %) (entry 5). Bases were also evaluated using THF as solvent; NaOt-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** were treated with NaOt-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 NaOt-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** while reaction in THF afforded **8d** exclusively in moderate yield. Transannular cyclization of both **3c** and **3d** also afforded slightly reduced diastereomeric ratios of the *bis*-cyclized products with diastereoselectivity of monocyclized products remaining high.

In order 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 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

Based on our experimental results, we propose an olefin isomerization-conjugate addition mechanism for the base-mediated transannular cyclization (Scheme 6).^{2b–c}, ¹⁶ ¹H 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 alpha 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 THF¹⁷ may be due to diminished acidity of the methylene hydrogens of **4** which bears a neighboring tertiary amide relative to those in macrolactam **3b**.

In order 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 calculations¹⁰ 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 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 endothermic¹⁰ 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.

In conclusion, macrocyclic *bis*-lactams have been efficiently synthesized by cyclodimerization of homoallylic amino ester monomers employing a Zr(IV)-catalyzed ester-amide 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Determination of Relative Stereochemistry.

Scheme 1.
Preparation of Homoallylic Amino Ester Monomers.

Scheme 2.
Synthesis of *Bis*-lactams via Cyclodimerization.

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 ₂ CO ₃	DMF	60 °C, 12 h	0%	-	-
4	NaOt-Bu	DMF	60 °C, 12 h	100%	0%	80% (5:1:1)
5 ^b	NaOt-Bu	DMF	60 °C, 24 h	64%	48% (>20:1)	9% (5:1:1)
6	NaOt-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%

Scheme 3.Base Evaluation for Transannular Cyclization.^a^aCombined yields of all the diastereomers. Diastereomer ratio determined by ¹H NMR integration. ^b0.20 equiv of base employed.

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)	—

Scheme 4.

Preparation of Bicyclic and Tricyclic Products.

^a Conditions: a) NaOt-Bu (2.0 equiv), DMA, 60 °C, 12 h; b) NaOt-Bu (2.0 equiv), THF, 60 °C, 24 h. ^b Diastereomeric ratios determined by ¹H NMR integration.

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

Scheme 5.

Kinetic Isotope Effect Experiments.

^a Determined by HPLC analysis. See Supporting Information for details.

Scheme 6.
Proposed Reaction Pathway.

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

Scheme 8.
Diastereoselective Alkylation.