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Synthesis and Structure of Preorganized, C_3-Symmetric Trilactam Scaffolds with Convergently Oriented (*S*)-Acetylthiomethyl Appendages

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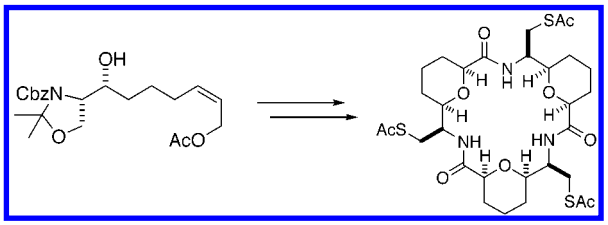
ABSTRACT



Efficient modular synthesis of conformationally preorganized, C_3-symmetric trilactams is reported. The allyl acetate cyclization substrate was synthesized in five steps from Garner's L-serine-derived aldehyde. After chiral ligand-mediated palladium cyclization, the resulting vinyl hydropyran was transformed into the orthogonally protected amino acids for iterative coupling. The final macrolactamization was accomplished using EDCI/HOBt or HATU/HOAt under high dilution conditions.

We have previously reported the synthesis, structural analysis, and cation binding efficacy of 18-membered, cyclic hydropyran oligolides with alternating ester and ether linkages.[1] The rigid, conformationally preorganized nature of these macrocycles allows for pendant functionality to be specifically spaced[2] and oriented for the attachment of biological recognition elements such as carbohydrates[3] or peptide chains. The potential for use of these macrocycles as templates has precipitated the need for a more robust framework utilizing amide bonds in place of the more labile ester bonds. Herein we discuss efforts toward the synthesis and characterization of this new class of macrocycles as a prelude to future template studies.

The C_3-symmetry of the targeted macrocyclic trilactams suggested a synthetic approach employing a hydropyran-based, protected amino acid module for trimerization and cyclization. As shown in Figure 1, it was envisioned that

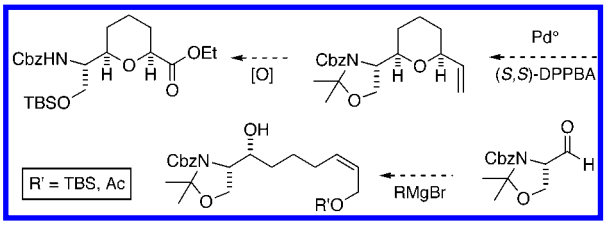


Figure 1. Hydropyran module synthetic strategy.

the individual hydropyran subunits could be derived from a stereoselective, palladium-mediated cyclization.[4,5]

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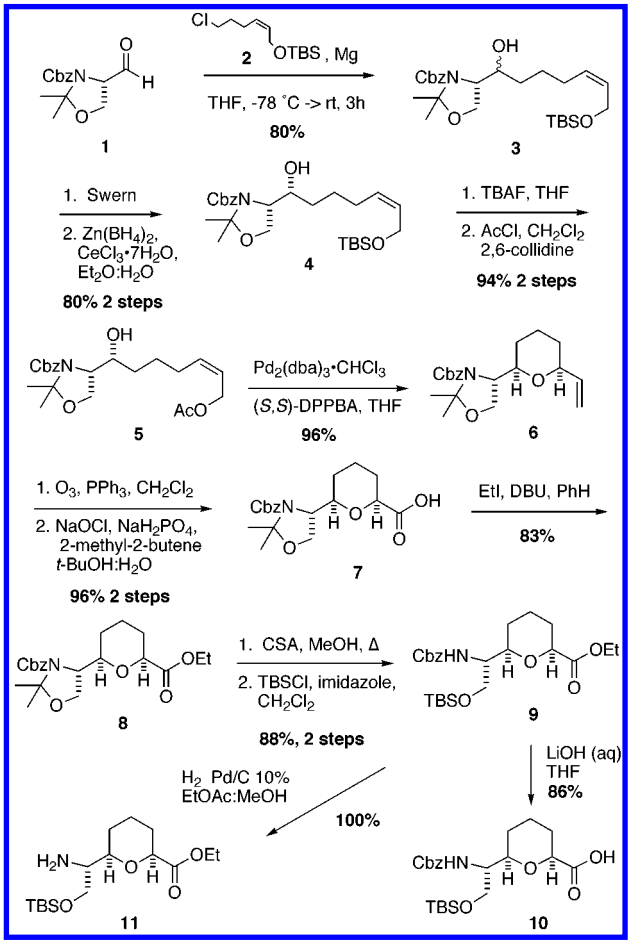
Scheme 1. Monomer Synthesis



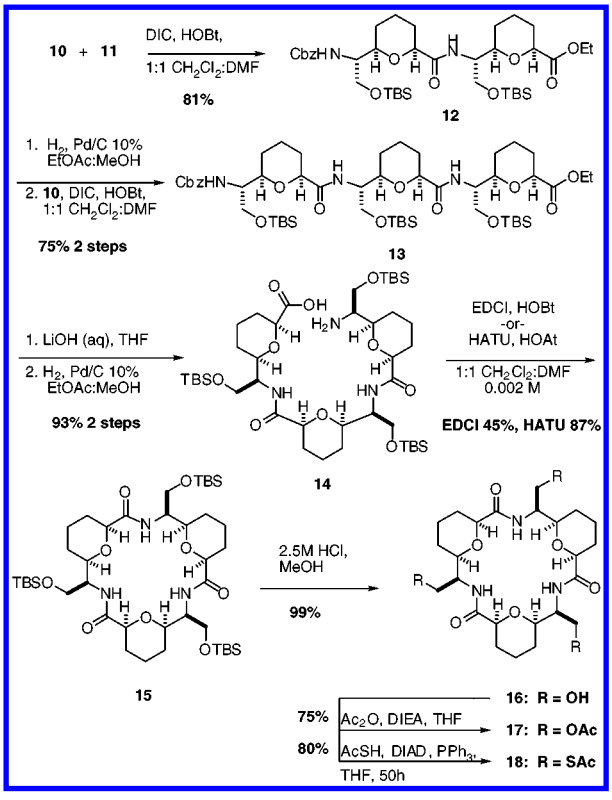
As detailed in Scheme 1, the cyclization substrate would arise from Grignard addition of the TBS derivative of 6-chlorohex-2-en-1-ol (**2**)[6] to *N*-Cbz-protected Garner's aldehyde (**1**), which is readily available from L-serine in four steps.[7] There is precedence for stereoselective addition to Garner's aldehyde with reactive nucleophiles, such as vinylmagnesium bromide or vinyllithium, via Felkin−Ahn preferred attack to produce the desired *erythro* alcohol.[8] Unfortunately, less reactive nucleophiles, such as the Grignard reagent prepared from **2**, react with little stereoselectivity, giving the resulting alcohol as an inseparable mixture of diastereomers (1:1, determined by HPLC). The desired alcohol diastereomer **4** was stereoselectively produced via Swern oxidation followed by chelation-controlled (*anti*-Felkin−Ahn) reduction under modified Luche conditions.[9] Using a procedure developed and optimized specifically for this reaction, $Zn(BH_4)_2$[10] with $CeCl_3$ gave the desired *erythro* alcohol in excellent yield. Deprotection of the silyl ether with TBAF followed by selective monoacylation of the primary alcohol yielded the allylic acetate cyclization substrate **5**. Cyclization utilized $Pd_2(dba)_3$ (1.3 mol %) with Trost's chiral (*S*,*S*)-*N*-[2,(2′-diphenylphosphino)benzamido cyclohexyl] (2′-diphenyl-phosphino) benzamide ligand [(*S*,*S*)-DPPBA (5.3 mol %)] to produce **6** (96%) as a single diastereomer.[5] With the third stereocenter in place, oxidative cleavage of the vinyl group produced the corresponding aldehyde, which was oxidized under mild conditions with sodium hypochlorite to afford the *N*-Cbz-protected amino acid **7**.

The monomer unit synthesis was completed by protection of the acid as the ethyl ester followed by deprotection of the dimethyl *N*,*O*-acetal with catalytic CSA in methanol. The resulting hydroxymethyl side chain was protected as the TBS ether to provide **9**.

With the protected monomer in hand, saponification of the ethyl ester or hydrogenolysis of the benzyl carbamate gave the primary coupling partners, acid **10** and amine **11**, respectively. In early experiments, the methyl ester was employed as the carboxyl protecting group, but the free amine undergoes competing cyclization to the bicyclic [3.3.1] lactam under the peptide coupling conditions. The ethyl ester proved hindered enough to effectively prevent this deleterious side reaction.

Standard peptide bond formation using diisopropylcarbodiimide (DIC) with stoichiometric 1-hydroxybenzotriazole (HOBt) effected coupling, affording **12** in good yield (Scheme 2). Hydrogenolysis followed by coupling to another

Scheme 2. Iterative Coupling Sequence



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equivalent of **10** afforded pseudotrimer **13**. At this point, the carboxyl terminus was deprotected, followed by hydrogenolysis to yield the macrolactamization substrate, amino acid **14**.

Macrolactamization to **15** proceeded under high dilution conditions (0.002 M) in 1:1 CH_2Cl_2/DMF with either 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide (EDCI) and HOBt or *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt)[11] over a period of 16−60 h. HATU/HOAt couplings required significantly reduced reaction times and were generally higher yielding.

Deprotection of the siloxymethyl side chains with methanolic HCl afforded triol **16** as a waxy solid. Preparation of the triacetate derivative **17** yielded a crystalline compound (mp 198−201 °C) for structural confirmation by X-ray diffraction (Figure 2). The 18-membered core favors an open, nearly planar macrocycle with the acetoxymethyl side chains pointing nearly perpendicular to the mean core plane (Figure 2b). A best fit least-squares approximation places the cavity defining heteroatoms (O1, O5, O9, N1, N2, N3) as coplanar to within 0.13 Å. These attributes parallel those of the related ester analogues,[1] suggesting that the preorganized nature of the triester and triamide families is comparable.

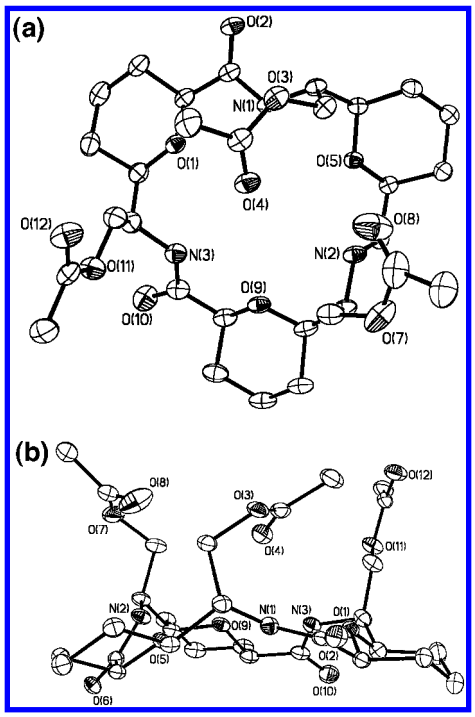

Figure 2. ORTEP 40% ellipsoid crystal structure of macrocyclic triacetate **17**: (a) top view, (b) edge view.

There was initial concern that the carbonyl oxygens in the macrocycle would react with the activated hydroxymethyl side chains during the Mitsunobu transformation. Such a reaction would result in the formation of trioxazoline derivatives. Although a successful test reaction was performed on the monomer, it was feared that the macrocyclic cabonyls could have a more reactive orientation as a result of conformational constraints. From the crystal stucture it is apparent that the opposite is true. The degree to which the carbonyl oxygens are pointing downward and away from the hydroxymethyl side chains was reassuring. The Mitsunobu reaction converting **16** to **18** proceeded cleanly in THF on all three of the template side chains to yield the trithiol triacetate as the exclusive product (80%) upon extended reaction times.

In summary, a new class of C_3-symmetric macrotrilactams has been synthesized in high yield from readily available precursors. The synthetic route displays the utility of palladium-mediated cyclizations for stereoselective synthesis of functionalized hydropyrans. Successful introduction of ester and protected thiol functionality in the convergently oriented appendages presages the utilization of these macrocycles as scaffolds and catalysts.

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Supporting Information Available: Experimental procedures and spectral data for compounds **3**−**13**, **15**−**18**, and crystallographic data for compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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