



Oxidative Macrocyclizations for the Vancomycin Antibiotics. Unexpected Transannular Effects in the Thallium(III)-Mediated M(2-4) Macrocyclic Ring Closure

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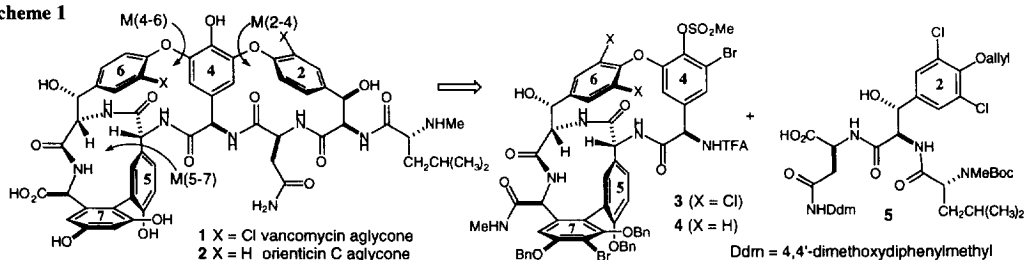
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Abstract: The course of the Tl(III)-mediated intramolecular oxidative macrocyclization of phenolic residues to provide the M(2-4) diarylether ring of the vancomycin antibiotics is remarkably sensitive to transannular effects across the M(4-6) ring, brought about by variations in the degree of ring-6 chlorination as well as the conformational bias imparted by the distal M(5-7) ring. The effect of structure on this reaction is documented.

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The members of the vancomycin class of glycopeptide antibiotics are important agents for the treatment of severe bacterial infections, particularly those caused by methicillin-resistant *Staphylococcus aureus*, and the basis of their activity has been of interest for some time.² The complex poly-macrocyclic architecture inherent in the vancomycin aglycone structures (**1**, **2**) renders them challenging targets for total synthesis, and many studies directed toward this goal have been reported.³ Our own efforts thus far have resulted in efficient syntheses of the required amino acid constituents,⁴ thallium(III)-mediated oxidative cyclizations to form the M(2-4)(4-6)⁵ bicyclic diarylether array,⁶ vanadium(V)-induced intramolecular biaryl construction to provide the strained M(5-7) ring,⁷ and application of the intramolecular S_NAr strategy to the M(2-4) ring closure.⁸ The successful integration of all of these methods has recently culminated in the synthesis of a M(4-6)(5-7) bicyclic synthon (**3**, **4**),^{9a} as well as the first total synthesis of orienticin C aglycone (**2**).^{9b} The purpose of this Letter is to report some key observations pertaining to our initial strategy of employing a late-stage thallium(III)-promoted oxidative cyclization to achieve the M(2-4) diarylether ring closure in the total synthesis of **2**. We have found that the oxidative cyclization is unexpectedly sensitive to subtle but important structural features of the substrates.

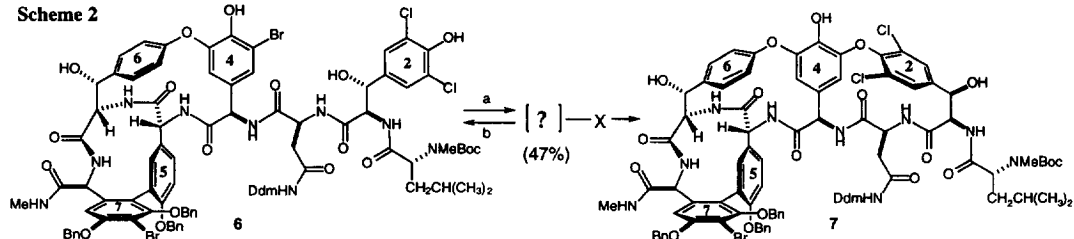
Scheme 1



In an initial convergent approach toward the synthesis of **2**, the *dehalogenated* M(4-6)(5-7) tetrapeptide fragment **4** was coupled to the tripeptide fragment **5** in anticipation of oxidative macrocyclization to provide the complete aglycone skeleton.^{10a} In the key reaction (Scheme 2), oxidation of heptapeptide **6** in analogy to previously optimized conditions (Tl(NO₃)₃·3H₂O, CH₂Cl₂/MeOH, 0 °C)⁶ cleanly afforded a less polar intermediate¹¹ which was then reduced *in situ* (CrCl₂, 0 °C) to provide returned starting material (**6**, 47%) instead of the desired polycyclic product **7**.

The unexpected failure of **6** to undergo the desired biarylether construction prompted an investigation into the role of the structural features which differ from those of previously reported model studies.^{6,12} Of these, the absence of ring-6 aryl halogens (substituents which had been present in all of the previous Tl(III)-mediated cyclizations), as well as the presence of the M(5-7) biaryl portion (absent in all previous studies), were thought to be the most likely structural elements contributing to the unfortunate lack of cyclization.

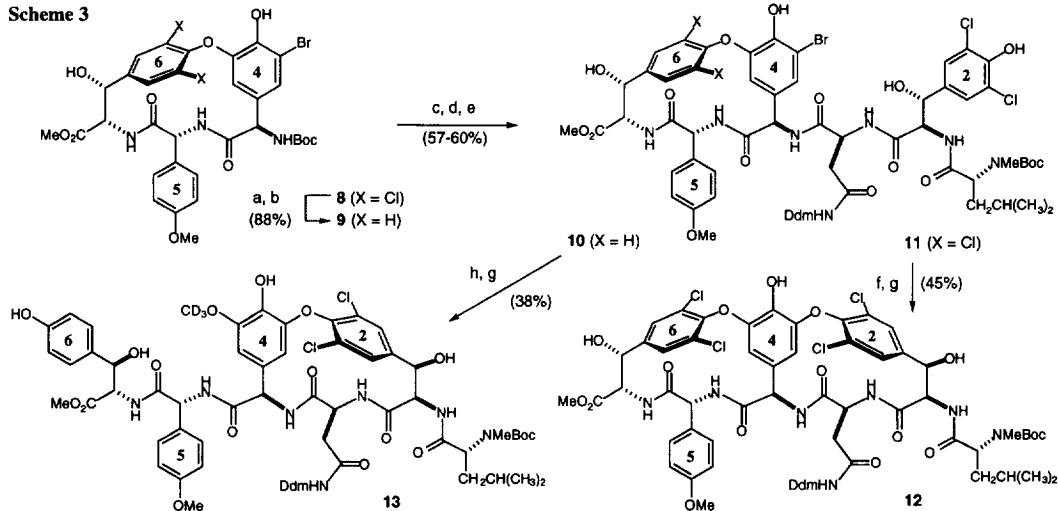
Scheme 2



(a) $\text{Tl}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, 30:1 CH_2Cl_2 : MeOH , 0 °C, 0.5 h. (b) CrCl_2 , 0 °C, 15 min.

A model study was designed to define the importance of these structural modifications (Scheme 3). The M(4-6) tripeptide fragment **8**, prepared in analogy to earlier work,⁶ was dehalogenated and brominated to give **9**. Both macrocycles were coupled with tripeptide **5**, and deprotected to provide the model substrates **10** (dehalogenated) and **11** (ring-6 dichloride) in good yield. As expected, thallium(III) oxidation of **11** ($\text{Tl}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 0 °C) provided a less polar intermediate quinol methyl ether, which was reduced *in situ* (CrCl_2 , 0 °C) to provide the M(2-4)(4-6) bicyclic hexapeptide **12** in 45% yield. When the oxidation-reduction protocol was applied to *dehalogenated* **10**, the only isolated material was **13** (38%), surprisingly derived from M(2-4) cyclization and M(4-6) ring-cleavage.¹³ Thus, the presence of chlorine atoms on ring-6 is essential for a successful oxidative M(2-4) cyclization onto a preexisting M(4-6) template.

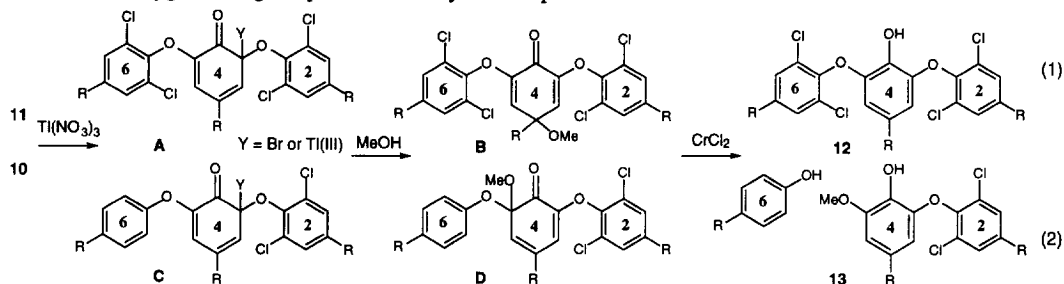
Scheme 3



(a) Pd/C , H_2 , $i\text{-Pr}_2\text{EtN}$, MeOH , 25 °C, 2 h. (b) Br_2 , NaOAc , HOAc , CH_2Cl_2 , 0 °C, 10 min. (c) TFA , DMS , CH_2Cl_2 , 0 °C, 2 h. (d) **5**, EDC , HOBT , THF , 0 °C, 2 h. (e) $\text{Pd}(\text{PPh}_3)_4$, morpholine, THF , 0 °C, 2 h. (f) $\text{Tl}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, 30:1 CH_2Cl_2 : MeOH , 0 °C, 1 h. (g) CrCl_2 , 0 °C, 15 min. (h) $\text{Tl}(\text{NO}_3)_3$, 3Å sieves, 30:1 CH_2Cl_2 : $d_4\text{-MeOH}$, 0 °C, 20 min.

The mechanistic construct illustrated below (eq 1, 2) provides a reasonable explanation for why chlorination on ring-6 is important to the outcome of the oxidative transformation. In their respective reactions, the model substrates **11** and **10** may be converted to initial ring-4 *ortho*-thallated intermediates which undergo nucleophilic

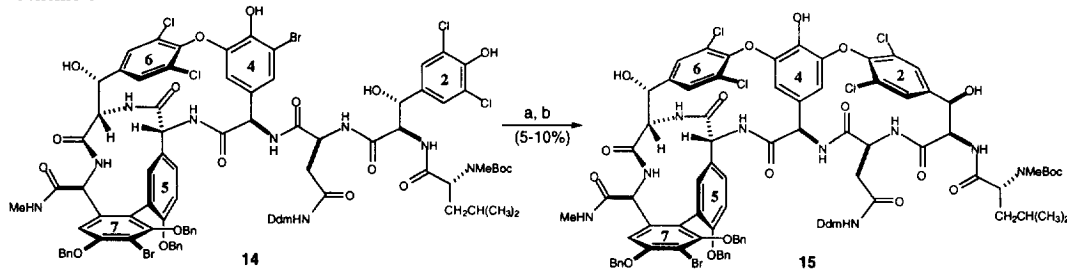
attack by the ring-2 phenol to produce **A** (eq 1) and **C** (eq 2), respectively. In the next step, the positional selectivity in the attack of ring-4 by methanol (**A**→**B** and **C**→**D**) likely differs for the two substrates, where the regiochemical outcome is directed by steric hindrance from the neighboring chloro-substituents. In the desired reaction path (eq 1), intermediate *para*-quinol methyl ether **B** is reductively aromatized with loss of MeOH to provide bicyclic product **12**, while in the undesired path (eq 2) an *ortho*-quinol methyl ether **D** is reductively cleaved at the M(4-6) oxygen linkage to provide monocyclic compound **13**.



The observation of distinctly different results in the oxidative reactions of heptapeptide **6** and model compound **10**, which differ only in the presence or absence of the M(5-7) biaryl portion, suggest that there might also be conformational issues that play a significant role in dictating the course of the reaction. Whereas **10** cyclized at M(2-4) and then ring-opened at M(4-6), **6** failed to cyclize at all. The difference is perhaps due to an unfavorable constraint within the M(4-6) ring induced by the presence of the M(5-7)-enforced *cis*-amide bond linking residues 5 and 6,^{9a} a feature which may influence the rate of intramolecular cyclization onto ring-4. It was our hope at this stage that the retarding effect of the conformation within **6** could be overcome by the reinstallation of ring-6 halogens, enabling cyclization in analogy to the successful transformation **11**→**12**.

The heptapeptide test substrate **14** was derived from the union of **3** and **5**.^{10b} The usual oxidation-reduction protocol (Scheme 4) required higher temperature and longer reaction time than was necessary in earlier instances (23 °C, 1.5 h). In contrast to the case of dechlorinated **6**, substrate **14** provided a complex mixture of products which included the desired fully-functionalized aglycone derivative **15** (5-10%) along with recovered starting material (10-20%). The important role of the ring-6 chlorines in the transformation is again indicated. In addition, direct comparison of the reaction of **14** to the more successful cyclization of hexapeptide **10** provides further evidence that *systems possessing the M(5-7) biaryl-containing macrocycle suffer from a conformational bias which undermines the efficiency of the M(2-4) oxidative cyclization onto a preexisting M(4-6) template*.

Scheme 4



(a) $\text{Ti}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$, 30:1 CH_2Cl_2 : MeOH, 23 °C, 1.5 h. (b) CrCl_2 , 0 °C, 15 min.

Based on these results, it appears that thallium(III)-promoted oxidation chemistry at arylglycine-4 for the M(2-4) macrocyclization is remarkably sensitive to transannular effects across the M(4-6) ring, brought about by variations in ring-6 chlorination as well as conformational change imparted by the more distal M(5-7) ring. These

limitations should have considerable impact on the design of synthetic approaches to the vancomycin aglycones, since partial ring-6 chlorination as well as M(5-7) ring installation are necessary components of any strategy. Current synthetic efforts are focused on alternative cyclization sequences in the overall assembly.

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- (1) (a) NIH Postdoctoral Fellow; (b) DOD and Division of Organic Chemistry (ACS) predoctoral fellow.
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- (5) The seven amino acid residues are numbered consecutively, starting from the amino terminus. The M(X-Y) nomenclature refers to the macrocycle containing an oxidative crosslink between aryl groups of residues X and Y. Bicyclic moieties will be identified as M(X-Y)(Y-Z).
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- (10) (a) Fragment **4** was deprotected, brominated, coupled with **5**, and deprotected to provide **6** using the following reactions: i) MeMgBr, THF, 0 °C, 70%; ii) Br₂, NaOAc, AcOH, 23 °C, 86%; iii) NaBH₄, EtOH, 0 °C; iv) **5**, EDC, HOBt, THF, 0 °C, 47% two steps; v) Pd(PPh₃)₄, morpholine, THF, 0 °C, 81%. (b) For **3**→**14**: i) NaBH₄, EtOH, 0 °C, 78%; ii) MeMgBr, THF, 0 °C, 93%; iii) Br₂, NaOAc, AcOH, 23 °C, 97%; iv) **5**, EDC, HOBt, THF, 0 °C, 93%; v) Pd(PPh₃)₄, morpholine, THF, 0 °C, 92%.
- (11) We speculate that this unstable intermediate is a spirocyclic oxazoline derived from intramolecular oxidative attack of the ring-3 amide oxygen onto ring-4. The use of isopropanol as solvent resulted in the same intermediate, as judged by tlc on silica gel.
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- (13) In the reaction of **10**, partial decomposition was alleviated by using more anhydrous conditions [Ti(NO₃)₃ dried *in vacuo* with P₂O₅; 3Å sieves]. Deuterated solvent was employed to assay for epimerization (*d*-incorporation) at the arylglycine-4 α-position *via* quinone methide formation; none was observed.

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