Oxidative Coupling of Arylglycine-Containing Peptides. A Biomimetic Approach to the Synthesis of the Macro cyclic Actinoidinic-Containing Vancomycin Subunit

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The vancomycin class of glycopeptide antibiotics is widely used in the treatment of infections due to methicillin-resistant Staphylococcus aureus and in bacterial infections in patients allergic to β-lactam-derived antibiotics. The structural complexity of these molecules, as well as interest in their specific mode of action,2 has rendered them attractive targets for total synthesis. Although no synthesis of any member of this family of natural products has yet been achieved, efforts from a number of groups3 have led to the preparation of functionally simplified analogs of the M(4-6) and M(2-4) diaryl ether-containing macrocyclic subunits. In addition, several multistep syntheses of the diaryl diamino diacid actinoidinic acid have been achieved; however, the incorporation of this diaryl-containing subunit into the M(5-7) tripeptide macrocycle has not been reported. As a continuation of our efforts directed toward the development of a biomimetic approach to the synthesis of vancomycin,4 we report our successful investigations on an oxidative coupling approach to the M(5-7) tripeptide macrocycle, a structural subunit common to all members of this family of antibiotics.

In a series of unsuccessful investigations, we found that linear tripeptides related to 2 (Scheme 1) containing a single para oxygen substituent on the 5-arylglycine could not be induced to undergo intramolecular oxidative coupling under a wide range of condi tions. The products of these errant oxidations were the intermolecular dimeric biaryl coupling products resulting from the union of the 7-arylglycine residues. This observation led to the strategy wherein a temporarily installed alkoxy residue was incorporated into the 5-arylglycine to facilitate intramolecular oxidative coupling.

The linear tripeptide substrates 2a and 2b were assembled by standard peptide coupling of the requisite amino acids, which were prepared according to previously described methodology from this laboratory.5a-c Initial investigations focused on model tripeptide 2a, containing an undifferentiated 5-arylglycine OP substituent. A variety of oxidants (Tl(TFA)3, FeCl3, VOCl3, CoF3, Pt anode) failed to induce cyclization, providing either recovered starting material, ring-7 oxidized products, or decomposition. However, the use of VO2+BF4− as TFA6 followed by the addition of excess activated zinc was highly successful, affording an 81% yield of macrocycle 3 as a single atropisomer with the "unnatural" biaryl configuration.7 The addition of BF4−OEt2 was found to be critical in preventing competitive attack of oxygen nucleophiles on the putative ring-7 radical cation,8 while the zinc reduction step was necessary to quench the radical cation derived from 3, which is also prone to nucleophilic attack.9 The use of Mn(acac)3 in place of VO2+ under the same conditions met with modest success, providing 3 in 42% yield.

It is likely that the sense of atropodiastereoselectivity in this reaction is a result of A(1,3) strain conformational constraints within the 5-arylglycine moiety in both 2 and in the cyclization product 3. Partial thermal atropisomerization of 3→4 possessing the "natural" configuration10 (3:6:1 ratio) was accomplished in DMSO at 160 °C for 9 h. The reequilibration of the minor atropisomer 4 in DMSO-d6 resulted in a 2:1 mixture of 3a:4a along with other unidentified products. Although the equilibration experiments were complicated by accompanying decomposition, we believe that the equilibrium ratio slightly favors the "unnatural" atropisomer. Ironically, the added ortho phenolic oxygen substituent (OP), incorporated into the 5-arylglycine residue to establish the viability of the oxidative cyclization, seems responsible for providing both a kinetic and a thermodynamic bias for the undesired M(5-7) atropisomer.

Tripeptide 2b was then assembled with the acid-stable, removable 3,4-dichlorobenzyl (DCB) protecting group in antic

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(10) (a) Ag(I) was also added to sequester traces of chloride ion, present in commercial TFA. (b) In the absence of BF4−OEt2, clean conversion to 3 was observed. (c) Quench with aqueous NaCl instead of Zn gave 30% yield of 3a. Tripeptide 2b proved to be more sensitive to the presence of adventitious water than 2a. In the reaction of 2b under the same oxidation conditions as for 2a, half of the isolated material was comprised of 3a.
Communications to the Editor


DMSO 160 °C, 9h
isolated ratio 78:22

\[ \text{Scheme I} \]

- (a) VOF₃, BF₃·OEt₂, AgBF₄, TFA, 0 °C, then Zn.
- (b) VOF₃, BF₃·OEt₂, TFA, TFAA, CH₂Cl₂, 0 °C, then Zn.
- (c) Pd black, H₂, sonication.
- (d) PhNTf₂, Et₃N.
- (e) [1,1'-bis(diphenylphosphino)ferrocene]PdCl₂·CH₂Cl₂, Et₃N, HO₂CH.
- (f) AlBr₃, EtSH.

The rather slow rate of interconversion \( \left( t_{1/2} = 1.5 \text{ h at } 50 °C \right) \) without detectable decomposition. The measured barrier for this atropisomerization is 21 kcal/mol. Based on our NMR studies, the conformation of 10 is very similar to the M(5-7) vancomycin subunit, including the preference for the cis amide linkage between amino acid residues 5 and 6.

These results, in conjunction with earlier studies from this laboratory, demonstrate for the first time the feasibility of pursuing a total synthesis of vancomycin and related antibiotics via biomimetic oxidative coupling strategies.

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Supplementary Material Available: Detailed experimental procedures for the syntheses of 2a and 2b as well as all transformations in Scheme I; characterization data for all compounds; NOE data for 3, 4, 8, and 10; and kinetic data for the isomerization of 9 (16 pages). Ordering information is given on any current masthead page.