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

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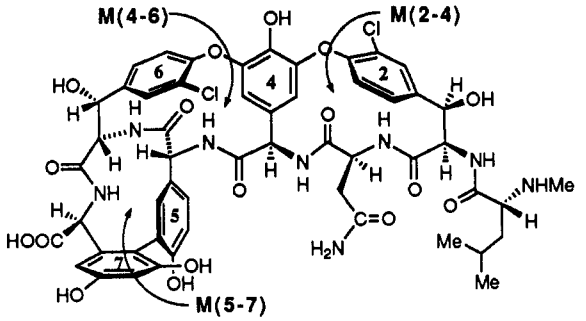
The vancomycin class of glycopeptide antibiotics is widely used in the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and in bacterial infections in patients allergic to β-lactam-derived antibiotics. The structural complexity of these molecules, as well as interest in their 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 groups[3] have led to the preparation of functionally simplified analogs of the M(4–6)[4] and M(2–4) diaryl ether-containing macrocyclic subunits. In addition, several multistep syntheses of the biaryl diamino diacid actinoidinic acid have been achieved;[5] however, the incorporation of this biaryl-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,[6] 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.



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In a series of unsuccessful investigations, we found that linear tripeptides related to **2** (Scheme I) containing a single para oxygen substituent on the 5-arylglycine could not be induced to undergo intramolecular oxidative coupling under a wide range of conditions.[7] 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.[5b,6,8] Initial investigations focused on model tripeptide **2a**, containing an undifferentiated 5-arylglycine OP substituent. A variety of oxidants ($Tl(TFA)_3$, $FeCl_3$, $VOCl_3$, CoF_3, Pt anode) failed to induce cyclization, providing either recovered starting material, ring-7 oxidized products, or decomposition. However, the use of $VOF_3/BF_3{\cdot}OEt_2$ (7/15 equiv) in TFA[9a] 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.[10] The addition of $BF_3{\cdot}OEt_2$ was found to be critical in preventing competitive attack of oxygen nucleophiles on the putative ring-7 radical cation,[9b] while the zinc reduction step was necessary to quench the radical cation derived from **3**, which is also prone to nucleophilic attack.[9c] The use of $Mn(acac)_3$ in place of VOF_3 under the same conditions met with modest success, providing **3** in 42% yield.

It is likely that the sense of atropdiastereoselectivity 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" configuration[10] (3.6:1 ratio) was accomplished in DMSO at 160 °C for 9 h. The reequilibration of the minor atropisomer **4** in DMSO-d_6 resulted in a 2:1 mixture of **3**:**4** 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-

(1) (a) National Institutes of Health Postdoctoral Fellow. (b) National Science Foundation Predoctoral Fellow.

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(4) It is proposed that each macrocycle within the vancomycin framework be identified as M(*X* – *Y*) where *X* and *Y* are the numbers of the oxidatively linked aromatic amino acid residues contained within that macrocycle. According to the usual convention, the amino acid constituents in vancomycin are numbered consecutively from the amino terminus.

(5) (a) Morrissey, M. M. Ph.D. Thesis, Harvard University, 1986. (b) Evans, D. A., Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, M. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189–1192. (c) Rama Rao, A. V.; Chakraborty, T. K.; Joshi, S. P. *Tetrahedron Lett.* **1992**, *33*, 4055–4048.

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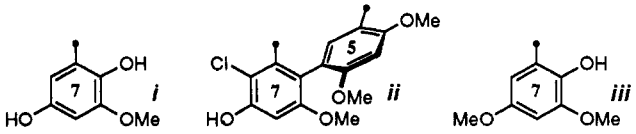
(9) (a) Ag(I) was also added to sequester traces of chloride ion, present in commercial TFA. (b) In the absence of $BF_3{\cdot}OEt_2$, clean conversion to *i* was observed. (c) Quench with aqueous NaCl instead of Zn gave 30% yield of *ii*. (d) Tripeptide **2b** proved to be more sensitive to the presence 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 *iii*.



(10) The stereochemistry was unambiguously determined by ^1H NMR NOE analysis, as described in the Supplementary Material. Diagnostic evidence includes the presence and/or absence of intraresidue NOEs between the $C_\alpha H$ and adjacent ArH protons for residues 5 and 7. NOE experiments also indicate that biaryls of "unnatural" configuration possess 5,6-trans/6,7-trans amide linkages, while those with the "natural" configuration prefer 5,6-cis/6,7-trans geometry.

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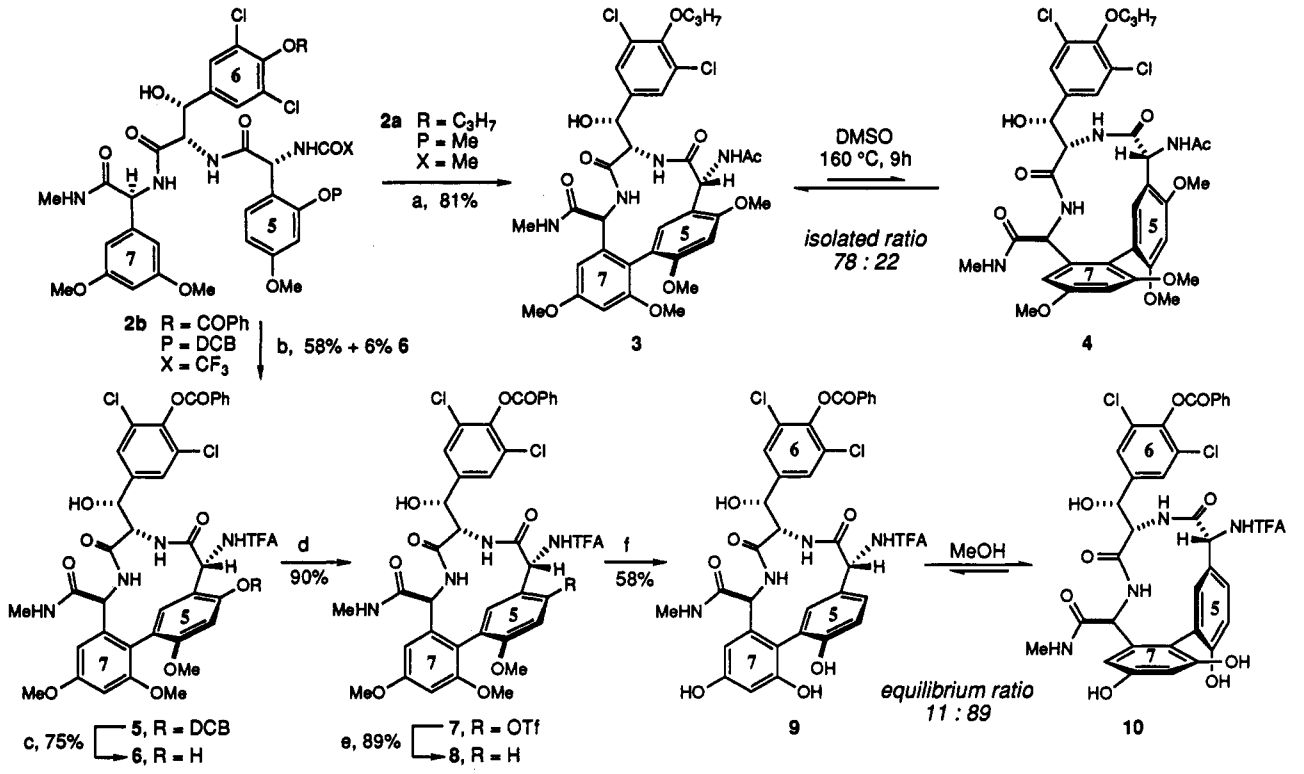
Scheme I[a]



[a] (a) VOF_3, $BF_3{\cdot}OEt_2$, $AgBF_4$, TFA, 0 °C, then Zn. (b) VOF_3, $BF_3{\cdot}OEt_2$, TFA, TFAA, CH_2Cl_2, 0 °C, then Zn. (c) Pd black, H_2, sonication. (d) $PhNTf_2$, Et_3N. (e) [1,1′-bis(diphenylphosphino)ferrocene]$PdCl_2{\cdot}CH_2Cl_2$, Et_3N, HO_2CH. (f) $AlBr_3$, EtSH.

ipation of the projected selective excision of the ring-5 ortho phenolic substituent after cyclization. Under slightly modified conditions[9d] employing a TFA/TFAA solvent mixture, the VOF_3-induced cyclization afforded a 58% yield of **5** accompanied by 6% of debenzylated **6**, each of which was isolated as a single atropisomer. Sonication-assisted hydrogenolysis of **5** with palladium black afforded phenol **6**, which was converted to the derived triflate **7** in 68% yield for the two steps. Reduction of this hindered triflate with Pd(II) and triethylammonium formate (DMF, 110 °C, 45 min) gave **8** in 89% yield.[10-12] Demethylation with aluminum tribromide in ethanethiol[13] (25 °C, 1 h) afforded a 58% yield of the phenolic M(5–7) macrocycle **9**, along with 19% of the related debenzoyl analog of **9**. In the final crucial step, atropisomerization of **9** in methanol proceeded at room temperature to give a 11:89 equilibrium mixture favoring the "natural" atropisomer **10**.[10] The rather slow rate of interconversion ($t_{1/2}$ = 29 h at 23 °C) could be increased on warming ($t_{1/2}$ = 1.5 h at 50 °C) 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,[6] 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.

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(12) Competing hydrodechlorination of ring-6 was avoided in this sequence of reactions.

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