
Separation of the undesired M(4–6) atropisomer was most conveniently achieved at this stage; the desired isomer was isolated in 69% yield.

The stereochemistry of 20 was confirmed by ROESY analysis (500 MHz).


Nonconventional Stereochemical Issues in the Design of the Synthesis of the Vancomycin Antibiotics: Challenges Imposed by Axial and Nonplanar Chiral Elements in the Heptapeptide Aglycons

David A. Evans,* Christopher J. Dinsmore, Paul S. Watson, Michael R. Wood, Timothy I. Richardson, B. Wesley Trotter, and Jeffrey L. Katz

In the preceding communication, we described the first syntheses of the heptapeptide aglycons of vancomycin (1a) and eremomycin (1b).[1] This contribution focuses on the development of stereoselective methods for the synthesis of the three stereochemical elements of atropisomerism present in vancomycin.[2] The design of a strategy for controlling these architectural features is one of the principal challenges presented by this family of natural products. As an aid in the ensuing discussion, a space-filling representation of the vancomycin aglycon, taken from the X-ray structure by Sheldrick et al.,[3] is provided (Figure 1).

The high barrier to rotation about the biaryl bond[4] in vancomycin introduces an element of axial chirality into the structure, while hindered rotation about the axes defined by the para-oriented CH(OH) and O-aryl substituents in ring 2 and ring 6 incorporates two examples of planar chirality. Collectively, these three features of the aglycon architecture present the significant challenge of controlling atropisomerism in the construction of each of the three macrocyclic tripeptide subunits designated as M(2–4), M(4–6), and M(5–7).[5] Hence, even with asymmetric syntheses of the amino acid constituents[6] and an assemblage strategy in hand,[7] one is still faced with the problem of producing the vancomycin aglycon skeleton as only one of eight possible atropodiastereomers.

The vancomycin aglycon skeleton (1a) consists of three interlocking cyclic tripeptides that collectively afford a conformationally rigid cup-shaped structure (Figure 1).[8] It is evident that the biaryl bond connecting amino acids 5 and 7 is the pivotal rigidifying amino acid crosslink. We therefore adopted the premise that macrocyclization model studies for the individual rings lacking the M(5–7) tripeptide subunit, while informative in identifying the local contributions to atropodiastereoselection, could prove unreliable stereochemical predictors for more complex cyclization substrates containing the M(5–7) fragment.

The construction of the M(5–7) tripeptide subunit[9] forms the basis of the synthesis plan. After the incorporation of an additional ortho benzoyloxy substituent on ring 5, high levels of kinetic atropodiastereoselection for the unnatural atropisomeric product M(R) were observed in the oxidative cyclization...
of tripeptides such as 2 (Scheme 1 a).[9, 10] This stereocchemical bias also extends to the more complex oxidative cyclization found in the orienticin C synthesis (Scheme 1 b).[7] A(1,3) strain[11] was implicated as the stereocchemical control element in these cyclizations when it was found that the diastereomeric tripeptide 6, containing the epimeric arylglycine in position 5, underwent a highly diastereoselective oxidative ring closure to the natural atropisomeric product 7 with S configuration.[10a] These observations reveal that the absolute stereochernistry of the substituent benzylic to ring 5 may be contrasted with the equilibration of the M(5–7) cyclic atropisomer to afford a 2:1 equilibrium ratio of atropisomers where the isolated in pure form and individually equilibrated at 100 °C to afford a 2:1 equilibrium ratio of atropisomers where the M(5–7) cyclic atropisomer found in the natural product is further enhanced (dr > 95:5) in the M(5–7) (4–6) bicyclic tetrapeptide (Scheme 2 c).[11]

The thermodynamic biaryl atropisomer bias in vancomycin is dictated by the global structure rather than by stereocchemical relationships proximal to the biaryl linkage (Scheme 2). For example, Jeffs et al. has isolated amino acid and aridicin.[12] Both atropisomers of the biaryl-containing diamino diacid, referred to as actinoidinic acid, have been isolated in pure form and individually equilibrated at 100 °C to afford a 2:1 equilibrium ratio of atropisomers where the R (unnatural) isomer is favored (Scheme 2 a). This result can be contrasted with the equilibration of the M(5–7) cyclic tripeptide 8(R) which now favors (dr = 89:11) the natural atropisomer 8(S) (Scheme 2 b).[10] The bias for the natural S atropdiastereomer found in the natural product is further enhanced (dr > 95:5) in these cyclizations when it was found that the diastereomeric subunit in our synthesis of orienticin C.[7] Our plan to implement a diastereoselective variant of this process for the construction of the M(4–6) subunit of vancomycin is shown in Scheme 3 a.

Either illustrated stereochemical outcome (10a → 11 or 10b → 12) would provide access to the proper atropisomer with a chloro substituent in ring 6 given the versatility of the Sandmeyer reaction (NO2 → H or NO2 → Cl). This cyclization strategy was evaluated on tetrapeptides 13a and 13b (Scheme 3).[11] Macrocyclization of 13a with Na2CO3 (DMSO, room temperature, 66 h) afforded the undesired M(4–6) atropisomer 14 with 10:1 stereoselectivity (Scheme 3 b). NOE experiments established that the predominant product was the unnatural S isomer.[14] X-ray crystallographic analysis of the major atropisomeric aniline 15 verified this stereochemical assignment. The cyclization of chlorinated analogue 13b retained the stereochemical bias for the nitro substituent, forming the desired biaryl ether 16 with 5:1 atropdiastereoselection (Scheme 3 c). Transformation of 16 to the derived aniline, followed by diazotization and


reduction, afforded the M(4–6)(5–7) bicyclic monochloride 17, a pivotal intermediate for the synthesis of vancomycin.[11]

The last phase of the synthesis required the successful incorporation of the M(2–4) macrocycle into M(4–6)(5–7) bicyclic tetrapeptide intermediates. Accordingly, a detailed study of the stereochemical control elements that might influence the atropdiastereoselection of the chloro substituent on ring 2 was undertaken in the S_{Ar} cyclizations illustrated in Scheme 4. In simple tetrapeptides such as 18, macrocyclization (CsF, DMSO, 25 °C, 2.5 h) proceeds with low stereoselectivity (dr = 1.4:1) (Scheme 4a). Variation of solvent (DMSO or DMF) and cyclization promoters failed to significantly improve these results. It is evident from this and related investigations that there is a negligible stereochemical bias imparted by the amide backbone from amino acids 1–3 to the cyclization process.[15,16]

At the next level of architectural complexity, M(2–4) cyclizations on hexapeptide substrates containing the M(4–6) subunit were investigated. Cyclization (CsF, DMSO, 25 °C, 6 h) of 20 was weakly diastereoselective (dr = 2:1), favoring the desired R atropisomer (Scheme 4b).[14,17] A modest reduction in rate, relative to that of 18, was also observed. Conformational effects imposed by the M(4–6)(5–7) bicyclic tetrapeptide were then evaluated (Scheme 4c, d). Substrate 22, containing the unnatural M(5–7) configuration, cyclized with poor atropdiastereoselection (dr = 1.3:1). This selectivity is in fact similar to that observed in the cyclization of 20. In both 20 and 22, the 5–6 amide bonds adopt a trans rather than the cis configuration found in vancomycin.

We next investigated the impact of the natural M(5–7) biaryl atropisomer, which contains the cis 5–6 amide bond (substrates 24a–c, (Scheme 4d)). Cyclizations of 24a–c gave the desired M(2–4) atropisomer with good selectivity. It is noteworthy that the cyclization stereoselectivity of chlorine-containing 24b (dr = 7:1) is only marginally greater than that observed for its dechloro counterpart 24a (dr = 5:1). This observation establishes that the chloro substituent in ring 6 is not a dominant stereochemical determinant in the cyclization process. This point is confirmed in the cyclization of the monochloro atropisomer 24c that contains two of the three atropoisomeric relationships required for vancomycin (Scheme 4d). This cyclization, as predicted by the preceding analogies, also affords the desired disposition of the chloro substituent in ring 2, thus establishing all of the atropodiastereomeric relationships found in vancomycin. The natural M(5–7) biaryl configuration evidently imparts subtle steric and electronic effects which provide a kinetic bias for the desired M(2–4) cyclization.[18]
Collectively, the observations recorded herein have dictated the direction of the syntheses of both eremomycin and vancomycin that are described in the preceding communication.[1]

Keywords: antibiotics · atropisomerism · chirality · nucleophilic aromatic substitutions · vancomycin


[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).


The option of thermal atropisomer equilibration of the M(2–4) and M(4–6) macrocycles could be ascertained from 1H NOE data for protons on the nitro-containing aromatic ring; their positions are established relative to the benzylic hydroxyl-bearing stereocenters para to the diaryl ether linkage.


Similar observations have been made in monocyclic model systems.


The configuration of the M(4–6) and M(2–4) macrocycles could be ascertained from 1H NOE data for protons on the nitro-containing aromatic ring; their positions are established relative to the benzylic hydroxyl-bearing stereocenters para to the diaryl ether linkage.


Similar observations have been made in monocyclic model systems.


The option of thermal atropisomer equilibration of the M(2–4) and M(4–6) macrocycles could be ascertained from 1H NOE data for protons on the nitro-containing aromatic ring; their positions are established relative to the benzylic hydroxyl-bearing stereocenters para to the diaryl ether linkage.


Similar observations have been made in monocyclic model systems.


The option of thermal atropisomer equilibration of the M(2–4) and M(4–6) macrocycles could be ascertained from 1H NOE data for protons on the nitro-containing aromatic ring; their positions are established relative to the benzylic hydroxyl-bearing stereocenters para to the diaryl ether linkage.


Similar observations have been made in monocyclic model systems.


The option of thermal atropisomer equilibration of the M(2–4) and M(4–6) macrocycles could be ascertained from 1H NOE data for protons on the nitro-containing aromatic ring; their positions are established relative to the benzylic hydroxyl-bearing stereocenters para to the diaryl ether linkage.


Similar observations have been made in monocyclic model systems.
