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Kinetic and Thermodynamic Atropdiastereoselection in the Synthesis of the M(5-7) Tripeptide Portion of Vancomycin

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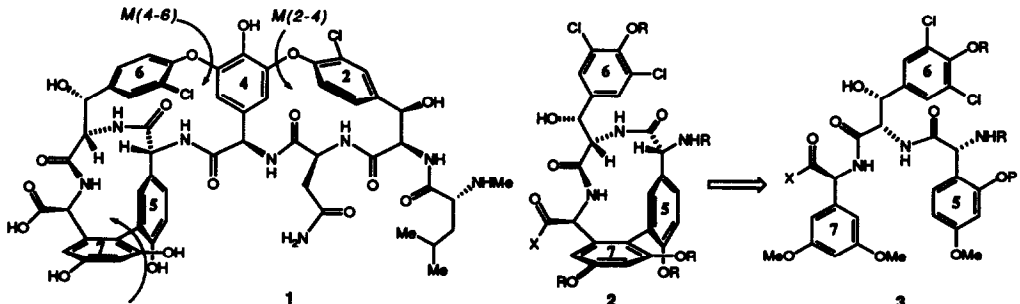
Abstract: The C_α stereochemistry of the position-5 arylglycine plays a pivotal role in determining the kinetic atropdiastereoselection in the oxidative biaryl cyclization reaction, the key step in a biomimetic strategy directed toward the synthesis of the M(5-7) vancomycin fragment. The equilibrium ratio of biaryl and amide conformations within this 12-membered macrocycle is significantly influenced by interaction of this same center with adjacent substituents.

Various members of the vancomycin class of glycopeptide antibiotics continue to be widely employed in the treatment of infections caused by methicillin-resistent *Staphylococcus aureus*, and the basis of their expressed antibiotic activity has been the subject of intense scrutiny.[1] In addition, the complex architecture inherent in the vancomycin structure (1) makes it a challenging target for total synthesis. To date, some progress has been made towards the development of a viable synthesis plan for this family of natural products;[2,3] however, no completed syntheses of any member of the vancomycin family have yet appeared. The purpose of this Letter is to provide important examples of kinetic and thermodynamic atropdiastereoselection in the formation and equilibration of the M(5-7) tripeptide macrocycle 2 and related structures.

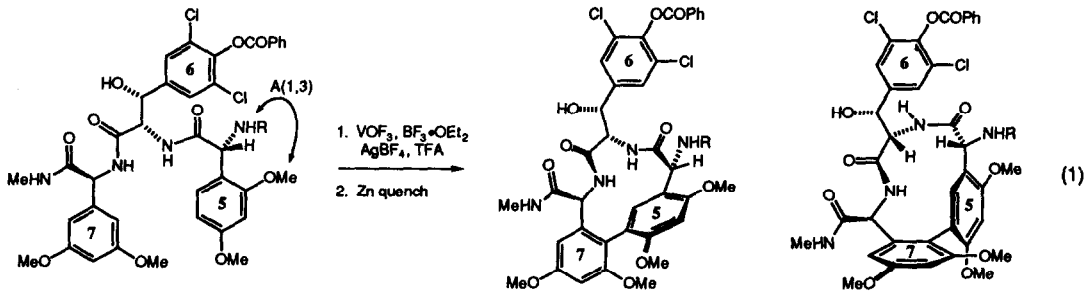
Scheme 1



Our laboratory has been pursuing a biomimetic approach to the synthesis of the vancomycin skeleton which places a premium on the development of the pivotal phenolic coupling events leading to the construction of the M(2-4) and M(4-6), macrocyclic subunits.[3a] In addition, we recently communicated the results of a convergent approach to the biaryl-containing M(5-7) tripeptide macrocycle 2, a subunit common to all members of this family of natural products.[3c] Macrocyclization of the linear tripeptide 3 was achieved in good yield by intramolecular oxidative biaryl coupling employing VOF_3. Subsequent excision of the position-5 arylglycine "OP" substituent, followed by biaryl atropisomerization, afforded the appropriately functionalized framework 2 as the atropdiastereomer required for the vancomycin skeleton. In conjunction with the biaryl bond construction, we

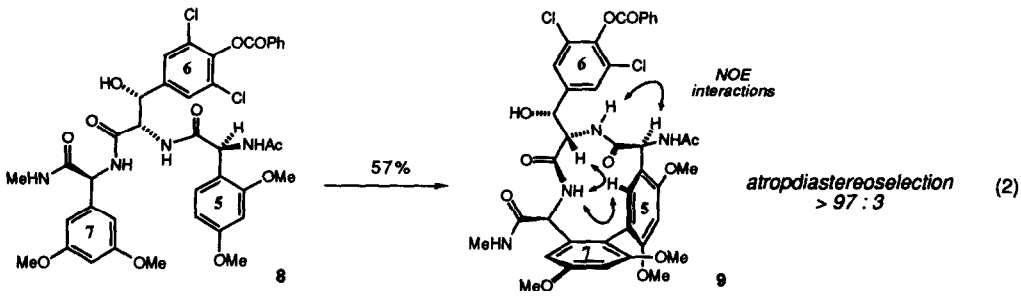
noted that the "OP" substituent, while required for the cyclization, is apparently responsible for providing a kinetic preference for the biaryl atropisomer with the "unnatural" configuration. Isomerization experiments suggested that its presence imparts a thermodynamic bias against the desired "natural" biaryl atropisomer. In the following discussion we provide data which confirm that the intraresidue interaction between the "OP" substituent and C_α stereocenter of the position-5 arylglycine governs the kinetic cyclization atropdiastereoselectivity and contributes to thermodynamic control of biaryl and amide conformations.

The VOF_3-promoted cyclization of tripeptide **4** was explored in our model studies for the M(5-7) synthesis (eq 1). As described for similar derivatives,[3c] the unnatural atropisomer **5a** was produced to the exclusion of the desired atropisomer **5b**. However, the related substrate **6** with a modified position-5 nitrogen protecting group afforded diminished stereoselectivity. Presumably, the carbamate group of **6** underwent rapid conversion to the corresponding ammonium ion in the strongly acidic reaction medium prior to cyclization to give a mixture of **7a** and **7b**. This point was confirmed by the analogous cyclization of the free amine derived from **6** which provided the same result. The biaryl configurations and amide conformations for **5a** and **7a,b** were deduced from ^1H NMR NOE analyses in d_6-DMSO.[4] It is significant that the amide bonds connecting residues 5-6 and 6-7 in the unnatural biaryls **5a** and **7a** are both *trans*, while the corresponding linkages in the natural biaryl **7b** (and *N*-acylated derivatives) are 5,6-*cis* and 6,7-*trans* as found in the natural products.



(1)

4 (R = Ac) *62%, atropdiastereoselection > 97 : 3* **5a : 5b**(R = Ac)
6 (R = Boc) *46%, atropdiastereoselection 84 : 16* **7a : 7b**(R = H)

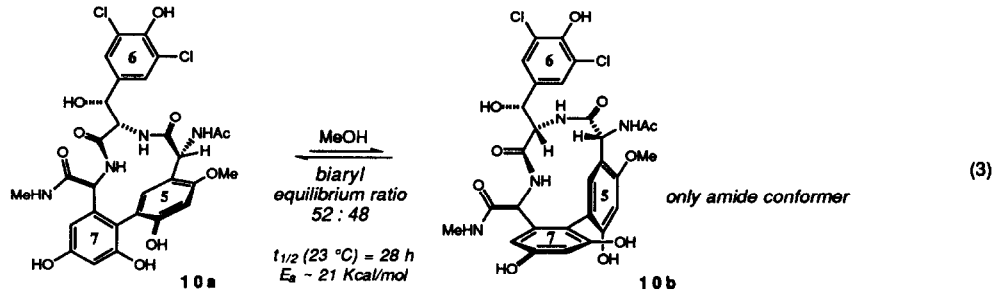


(2)

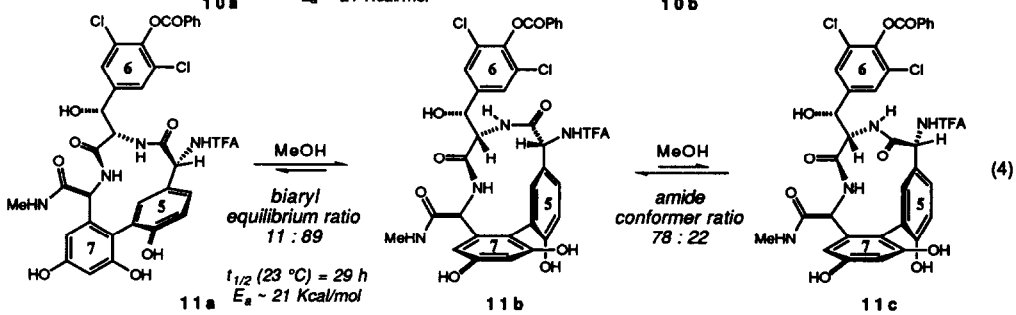
The sense of asymmetric induction in these cyclizations is probably controlled by the A(1,3) strain[5] between the ring-5 *ortho* methoxy group and the adjacent C_α stereocenter. Although the mechanistic details of the oxidation remain unclear,[6] inspection of models reveals that if the low energy *syn*-coplanar orientation of the Ar-OMe and C_α-H bonds is maintained throughout the C-C bond construction and rearomatization steps, the biaryl of unnatural configuration would be the kinetically formed product. Apparently, a reduction in the magnitude of the destabilizing A(1,3) interaction (NHAc↔OMe in **4** vs NH_3^+↔OMe in **6**) allows the residue-5 conformation leading to the natural biaryl to be accessed.

To test the extent of stereocontrol exerted by the position-5 arylglycine on kinetic atropdiastereoselectivity, tripeptide **8**, containing the enantiomeric position-5 arylglycine moiety, was subjected to the same reaction (eq 2). As predicted, complete reversal of selectivity ensued to give biaryl **9**, an epimer of the natural biaryl **5b**. NOE analysis revealed that the amide linkages possess the 5,6-*trans*/6,7-*trans* geometries.

The influence of the 5-arylglycine "OP" substituent on thermodynamic atropdiastereoselection was determined by comparing the equilibrium ratios of the phenolic derivatives **10a** and **11a** (eq 3 and 4).[7] Although the half-lives and activation barriers for the isomerizations are essentially the same,[8] the presence of the ring-5 methoxy group (**10a,b**) results in a biaryl equilibrium ratio favoring the unnatural isomer. In the absence of the methoxy group (**11a,b**) the natural biaryl is preferred, and exists as a mixture of amide conformers (**11b,c**).[9] These observations can be explained by closer analysis of the residue-5 conformations in each species, shown in Scheme 2.[10] Compound **10** slightly favors unnatural atropisomer **10a'** to minimize A(1,3) strain, and avoids *trans* amide **10c'** for the same reason. Since **11a',b',c'** do not suffer these destabilizing interactions, the atropisomer composition is dominated by some other effect, such as transannular steric repulsion between the CONHMe and ring-5 aryl groups in the unnatural biaryl.



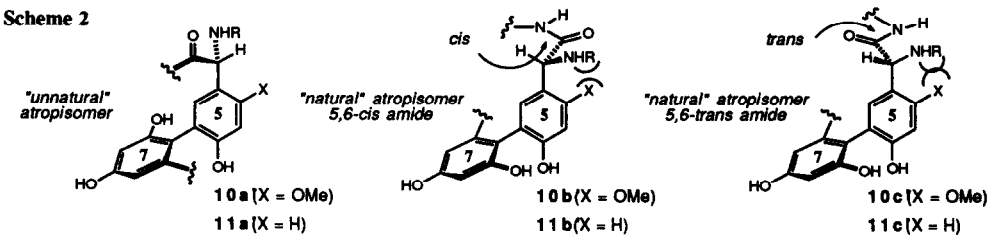
(3)



(4)

It should be noted that none of the unnatural biaryl atropisomer has been detected in any of the vancomycin glycopeptides,[1] and all but one have the 5,6-amide in exclusively the *cis* orientation.[11] In light of the results described here, it is apparent that the rigidity imparted by the M(4-6) scaffold must have a significant role in the biaryl and amide conformational populations in the M(5-7) fragments of these antibiotics.

Scheme 2



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(†) National Institutes of Health Postdoctoral Fellow.

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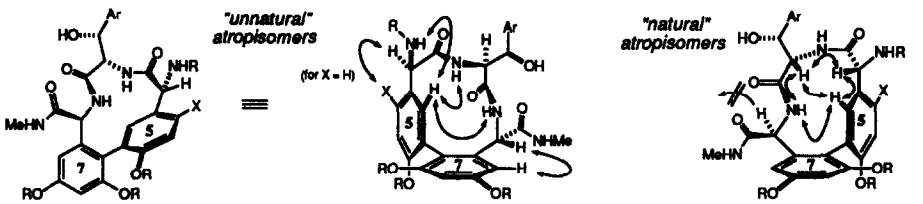
(4) Typical NOE interactions observed for this family of derivatives are shown below:



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(7) (a) Biaryl **10a** was prepared by demethylation ($AlBr_3$/EtSH, 25 °C, 1 h, 38%, ref 7b) of a derivative of **5a** where $Ar_6OCOPh = Ar_6OC_3H_7$. The position of the remaining ArO*Me* group is assigned based on: *i* an NOE interaction which locates it on ring-5. *ii* its NMR chemical shift (the two *upfield* methyl groups were removed). *iii* the similar E_a values for eq 3 and 4. Biaryl **11a** was prepared as described in ref 3c. (b) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275-4277.

(8) (a) Determined by 300 MHz NMR analysis, including integration of the NH*Me* resonances. The values given are for the reactions **10a/11a→10b/11b,c**, not the reverse process. (b) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, 9, 219-235.

(9) The assignment of **11c** as the 5,6-*trans* amide was based on ^1H NMR experiments which showed: *i* solvent dependence on **11b/11c** ratio (3.5:1 MeOH, 8:1 DMSO). *ii* saturation transfer from **11b** to **11c**. *iii* signal coalescence on warming a thermally stable permethylated derivative of **11b,c**. *iv* large downfield shifts of $C_\alpha H$ signals for **11c**, consistent with similar observations by Williams (ref 11). That the only significant structural difference between **10b** (*cis*) and **11b,c** is the ring-5 OMe group is good circumstantial evidence.

(10) The structures drawn in Scheme 2 are derived from the inspection of models.

(11) The antibiotic UK69542, which contains a ring-5 sulfate, was found to exhibit 5,6-amide *cis/trans* isomerization in DMSO, similar to the **11b/11c** equilibrium. Skelton, N. J.; Williams, D. H.; Rance, M. J.; Ruddock, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 3757-3765.

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