vancomycin. Synthetic **2** gave ^{1}H NMR, HPLC, and mass spectral data identical to a natural comparison sample (refs. [23] and [27]).

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[22] This assignment was confirmed by chemical correlation to a minor atropisomer corresponding to **16**.

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

[25] The stereochemistry of **20** was confirmed by ROESY analysis (500 MHz).

[26] D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, *J. Org. Chem.* **1997**, *62*, 4721–4736.

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[31] Vancomycin aglycon was prepared from vancomycin · HCl according to: R. Nagarajan, A. A. Schabel, *J. Chem. Soc. Chem. Comm.* **1988**, 1306–1307; see also F. J. Marshall, *J. Med. Chem.* **1965**, *8*, 18–24.

[32] Eremomycin aglycon was prepared from eremomycin · HOAc according to: G. F. Gause, M. G. Brazhnikova, N. N. Lomakina, T. F. Berdnikova, G. B. Fedorova, N. L. Tokareva, V. N. Borisova, G. Y. Batta, *J. Antibiotics* **1989**, *42*, 1790–1799.

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[**]

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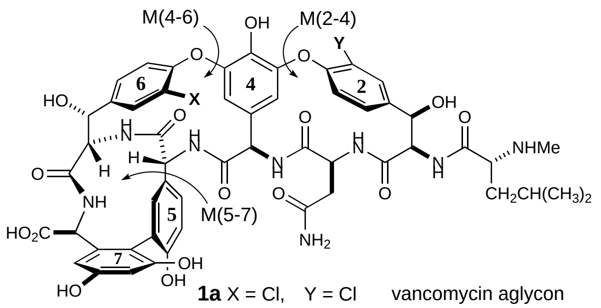
Paul S. Watson, Michael R. Wood,
Timothy I. Richardson, B. Wesley Trotter, and
Jeffrey L. Katz

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 development 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).



1a X = Cl, Y = Cl vancomycin aglycon
1b X = H, Y = Cl eremomycin aglycon
1c X = H, Y = H orienticin C aglycon

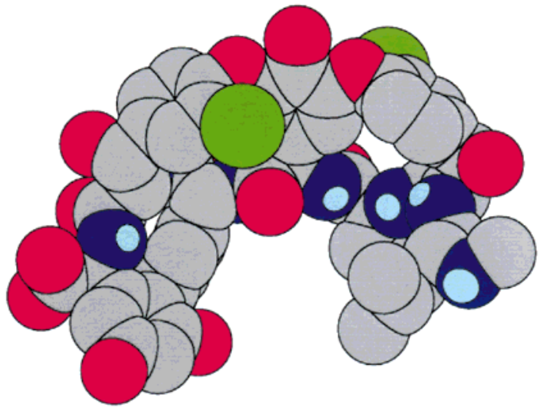


Figure 1. Space-filling representation of the vancomycin aglycon.[3b]

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 atropdiastereomers.

The vancomycin aglycon skeleton (**1a**) consists of three interlocking cyclic tripeptides that collectively afford a conformationally rigid cup-shaped structure (Figure 1).[3] 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 atropdiastereoselection, could prove unreliable stereochemical predictors for more complex cyclization substrates containing the M(5–7) fragment.

The construction of the M(5–7) biaryl subunit[8] forms the basis of the synthesis plan. After the incorporation of an additional *ortho* benzyloxy substituent on ring 5, high levels of kinetic atropdiastereoselection for the unnatural atropisomeric product **3(*R*)** were observed in the oxidative cyclization

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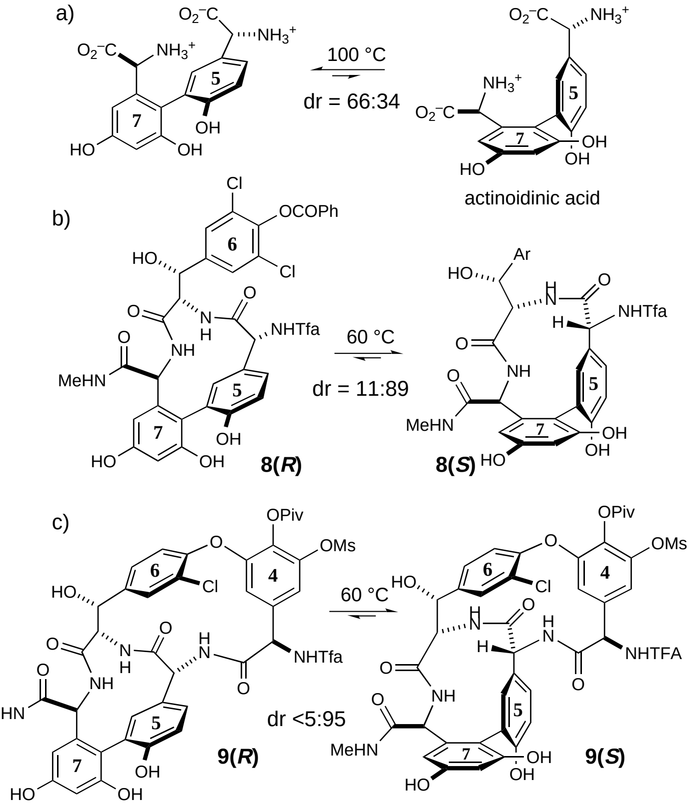
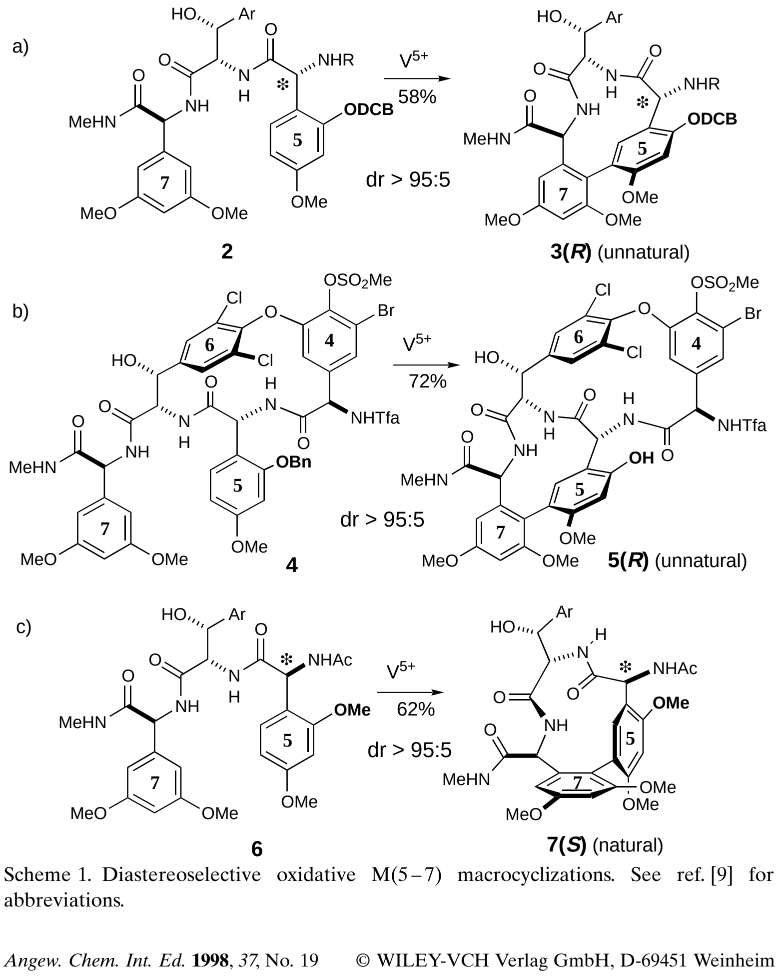
of tripeptides such as **2** (Scheme 1 a).[9, 10] This stereochemical bias also extends to the more complex oxidative cyclization found in the orienticin C synthesis (Scheme 1 b).[7] A(1,3) strain[11] was implicated as the stereochemical control element in these cyclizations when it was found that the 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.[10b] These observations reveal that the absolute stereochemistry of the substituent benzylic to ring 5 may be employed to control the absolute stereochemistry of the M(5–7) ring closure.

The thermodynamic biaryl atropisomer bias in vancomycin is dictated by the global structure rather than by stereochemical relationships proximal to the biaryl linkage (Scheme 2). For example, Jeffs et al. has isolated amino acid components from the controlled hydrolysis of vancomycin 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 the M(5–7) (4–6) bicyclic tetrapeptide (Scheme 2 c).[1]

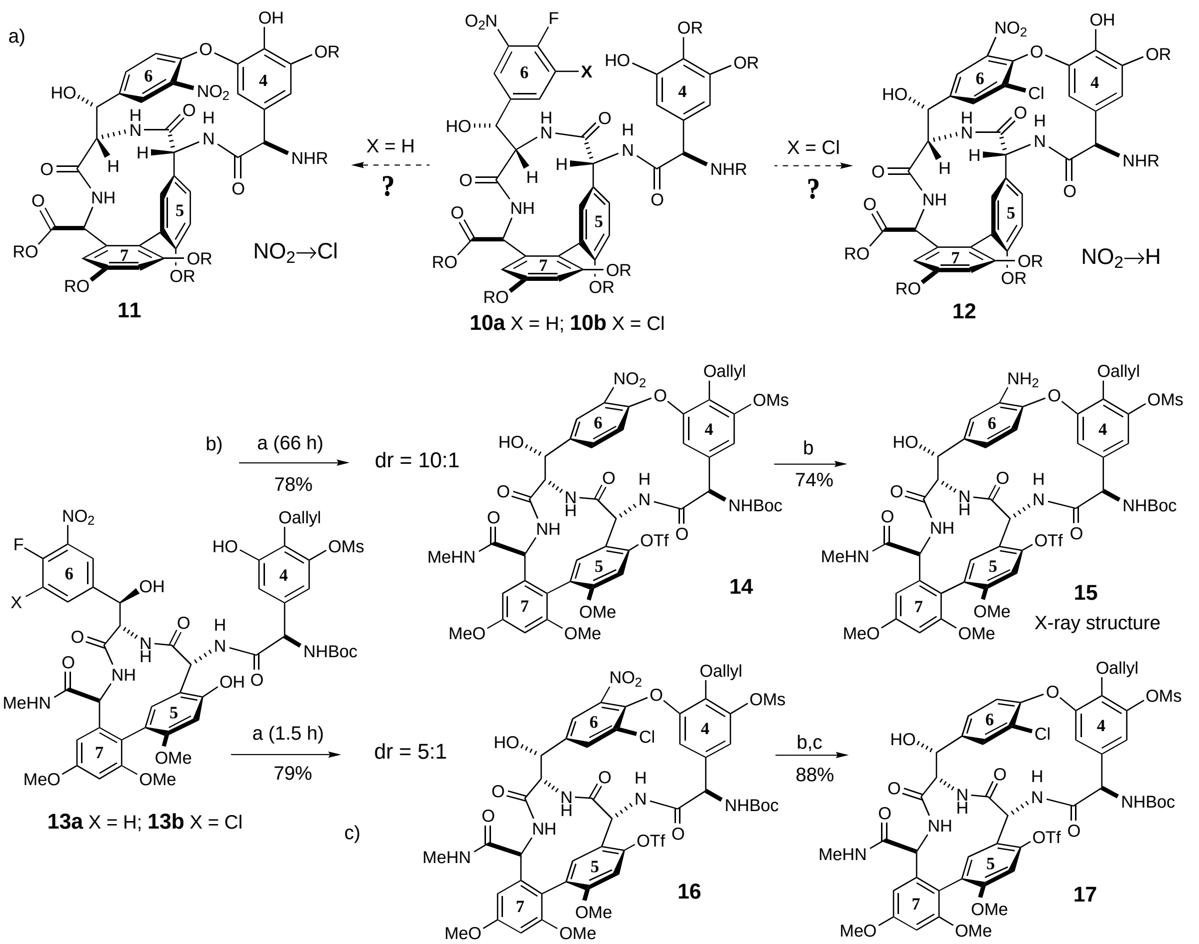


Scheme 2. Biaryl equilibration of the M(5–7) macrocycle. See ref. [9] for abbreviations.



Scheme 1. Diastereoselective oxidative M(5–7) macrocyclizations. See ref. [9] for abbreviations.

S_NAr macrocyclizations of phenolic substrates now constitute a reliable method for the construction of macrocyclic diaryl ether containing tripeptides.[13] This reaction has recently been employed in the construction of the M(2–4) 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 ($NO_2 \rightarrow H$ or $NO_2 \rightarrow Cl$). This cyclization strategy was evaluated on tetrapeptides **13a** and **13b** (Scheme 3).[1] Macrocyclization of **13a** with Na_2CO_3 (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



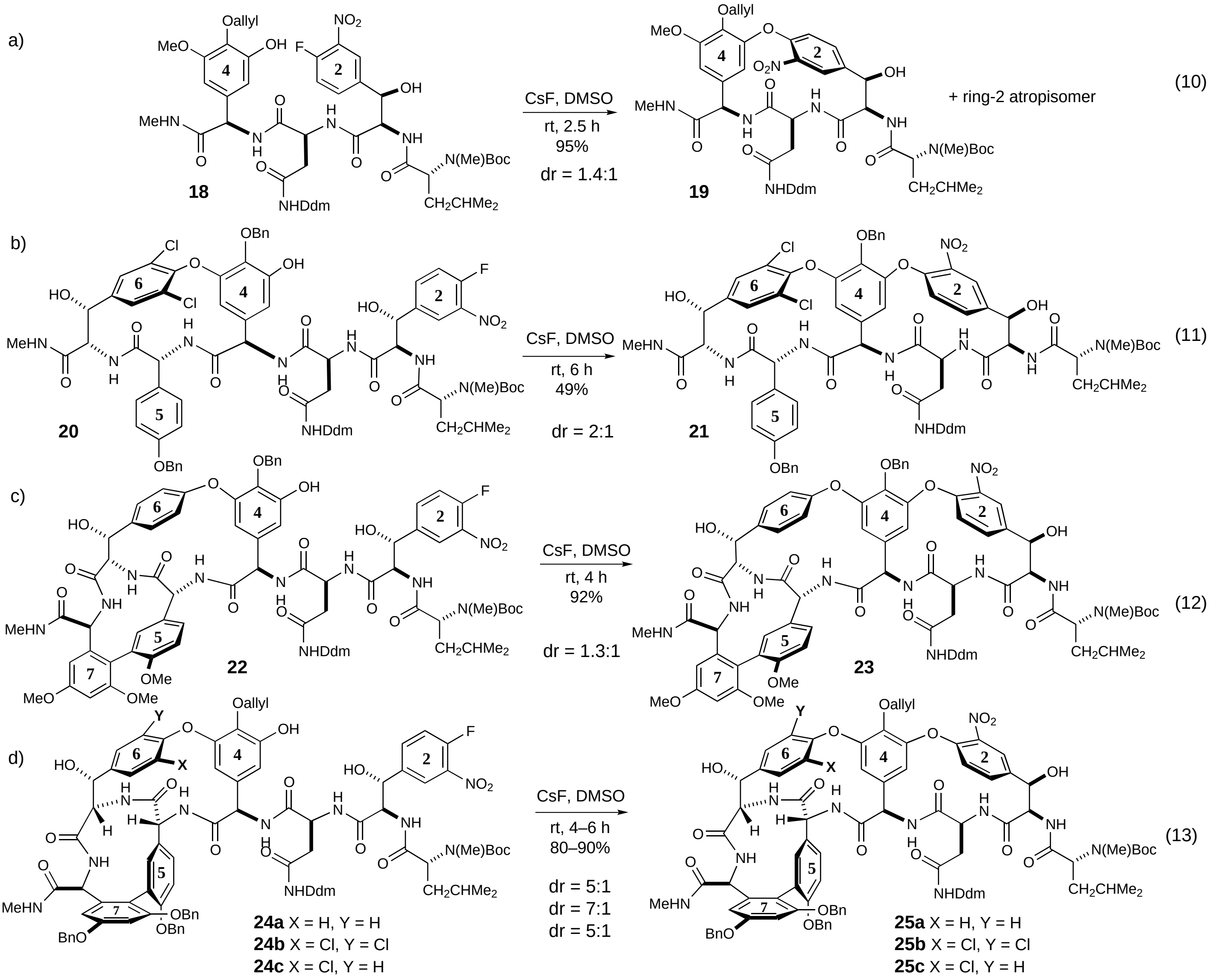
Scheme 3. Diastereoselective S_NAr-based M(4–6) macrocyclizations. a) Na_2CO_3, DMSO, room temperature, then Tf_2NPh, 1 h; b) Zn°, HOAc, EtOH, 40°C; c) $NaNO_2$, H_3PO_2, cat. Cu_2O, THF/H_2O, 0°C, 1 h. See ref. [9] for abbreviations.

reduction, afforded the M(4–6)(5–7) bicyclic monochloride **17**, a pivotal intermediate for the synthesis of vancomycin.[1]

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_NAr 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 atropisomeric 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 atropdiastereomeric 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]



Scheme 4. Diastereoselective S_NAr-based M(2–4) macrocyclizations. See ref. [9] for abbreviations.

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]

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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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[8] For model studies directed toward the construction of the M(5–7) biaryl linkage see: a) K. C. Nicolaou, X.-J. Chu, J. M. Ramanjulu, S. Natarajan, S. Bräse, F. Rübsam, C. N. C. Boddy, *Angew. Chem.* **1997**, *109*, 1551–1552; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1539–1540; b) K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy, *Chem. Commun.* **1997**, 1899–1900.

[9] Abbreviations: Tfa: trifluoroacetyl; TFA: trifluoroacetic acid; DMSO: dimethyl sulfoxide; Boc: *tert*-butoxycarbonyl; NOE: nuclear Overhauser effect; Tf: trifluoromethanesulfonyl; Ms: methanesulfonyl; Ac:acetyl; Ddm: 4,4Õdimethoxydiphenylmethyl; Bn: benzyl; DCB: 3,4-dichlorobenzyl; Piv: pivaloyl.

[10] a) D. A. Evans, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, *J. Am. Chem. Soc.* **1993**, *115*, 6426–6427; b) D. A. Evans, C. J. Dinsmore, *Tetrahedron Lett.* **1993**, *34*, 6029–6032.

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

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[16] Similar observations have been made in monocyclic model systems. a) D. L. Boger, R. M. Borzilleri, S. Nukui, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091–3096; b) D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, *J. Org. Chem.* **1997**, *62*, 4721–4736.

[17] A related cyclization (K_2CO_3/$CaCO_3$, DMF, 45 °C) proceeding with negligible atropselectivity has recently been reported: D. L. Boger, R. T. Beresis, O. Loiseleur, J. H. Wu, S. L. Castle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 721–724.

[18] The option of thermal atropisomer equilibration of the M(2–4) and M(4–6) rings is also possible. Boger et al. have begun to explore these processes: D. L. Boger, O. Loiseleur, S. L. Castle, R. T. Beresis, J. H. Wu, , *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3199–3202. See also ref. [16b].

Total Synthesis of Vancomycin Aglycon—Part 1: Synthesis of Amino Acids 4–7 and Construction of the AB-COD Ring Skeleton

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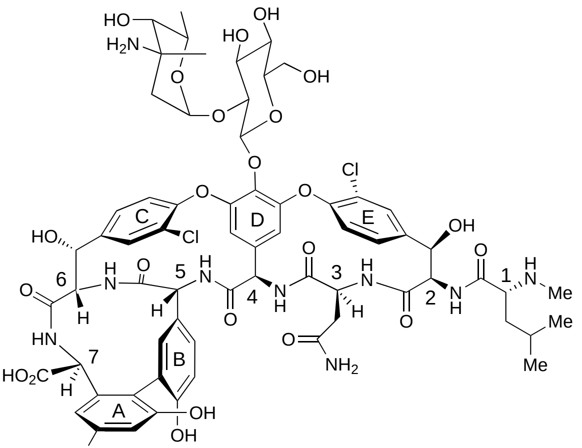
Nareshkumar F. Jain, Robert Hughes,
Michael E. Solomon, Joshi M. Ramanjulu,
Christopher N. C. Boddy, and Masaru Takayanagi

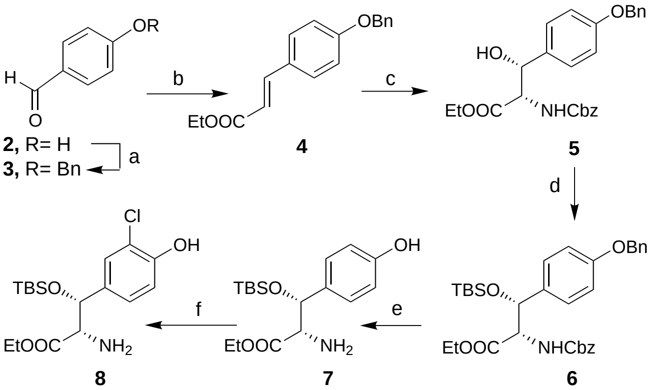
Vancomycin (**1**, Figure 1) is a clinically effective antibiotic used in cases of severe bacterial infections caused by several drug resistant pathogens.[1] Its medical importance and intriguing mode of action[2] coupled with its unusual molecular architecture[3] has fascinated synthetic chemists for some time.[4] Having established a number of new synthetic technologies and strategies aimed at this structural type,[5] we have recently focused our efforts on the total synthesis of **1**.[6] In this and the following communication,[7] we wish to report our progress and findings in the field, beginning with the stereoselective synthesis of amino acids 4–7 (compounds **8**, **22**, **27**, and **32**), the biaryl ring system (**35**), and the construction of the AB-COD skeleton (**46a**) of vancomycin.



1 Vancomycin

Figure 1. Molecular structure of vancomycin (**1**). The amino acids are labeled with numbers, and the aromatic rings with capital letters.

Scheme 1 outlines the synthesis of amino acid 6 in its protected form **8**. Thus, benzylation of 4-hydroxybenzaldehyde (**2**) with BnBr under basic conditions (98% yield), followed by olefination with the anion of $(EtO)_2(O)PCH_2$-COOEt, furnished α,β-unsaturated ethyl ester **4** (95% yield) via compound **3**. Asymmetric aminohydroxylation (AA) according to the Sharpless protocol[8] gave directly the Cbz derivative (**5**) of the desired amino alcohol in 45% yield and



Scheme 1. Reagents and conditions: a) K_2CO_3 (1.5 equiv), BnBr (1.0 equiv), KI (0.1 equiv), DMF, 25 °C, 12 h, 98%; b) $(EtO)_2(O)PCH_2$-COOEt (1.1 equiv), KOH (1.5 equiv), THF, 25 °C, 12 h, 95%; c) NaOH (3.0 equiv), $BnOCONH_2$ (3.1 equiv), *t*BuOCl (3.0 equiv), $(DHQD)_2AQN$ (0.05 equiv), $K_2[OsO_2(OH)_4]$ (0.04 equiv), *n*PrOH:H_2O (1:1), 25 °C, 12 h, 45% (87% *ee*); d) TBSOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, 98%; e) H_2, $Pd(OH)_2/C$ (0.01 equiv), MeOH, 0.5 h, 95%; f) SO_2Cl_2 (1.0 equiv), Et_2O (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, 80%. Bn = benzyl; Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl. TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.

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