Total Syntheses of Vancomycin and Eremomycin Aglycons**

David A. Evans,* Michael R. Wood, B. Wesley Trotter, Timothy I. Richardson, James C. Barrow, and Jeffrey L. Katz

Vancomycin, isolated in 1956 from *Streptomyces orientalis*,[1] is the prototypical member of a large family of antibiotics whose structures consist of an arylglycine-rich heptapeptide aglycon to which are appended an array of sugar residues. Structural diversity within this family of natural products is created by variation in the aglycon amino acid constituents and in the nature, position, and number of incorporated sugar residues.[2] Clinical applications of vancomycin to the treatment of Gram-positive bacterial infections and its efficacy against methicillin-resistant *Staphylococcus aureus* have established vancomycin as the antibiotic of last resort against infections by this deadly pathogen.[3] Recently, emergence of bacterial strains resistant to treatment by this family of antibiotics[4] has provided the stimulus for us and others[5] to develop reaction methodology and strategies relevant to the synthesis of the individual members of this family of natural products. In this communication we report the first syntheses of the vancomycin aglycon (**1**) and the eremomycin aglycon (**2**).[6]

The initial phase of our synthesis program in this area focused on the development of reactions critical to the synthesis of this family of target structures. Relevant methodology includes new asymmetric amino acid syntheses[7] and new macrocyclization reactions amenable to the construction of macrocyclic diaryl ether[8] and biaryl-containing[9] tripeptides. Application of this methodology to the synthesis of bis-dechlorovancomycin (orienticin C) aglycon has recently been reported.[10]

The most formidable synthesis challenges that the vancomycin skeleton presents are the three stereochemical elements of atropisomerism present in the structure as a consequence of hindered rotation in each of the cyclic tripeptide subunits. Our recent efforts have been directed toward the development of strategies for controlling these architectural features during the assemblage of the vancomycin skeleton. A detailed account of studies that have culminated in the current vancomycin synthesis is presented in the following communication.[11] These investigations have dictated both the general synthesis plan (Figure 1) and the strategy for controlling atropselectivity in each of the cyclic tripeptide subunits designated as M(2–4), M(4–6), and M(5–7).[12]

The amino acids required for the (4–7)-tetrapeptide were synthesized by our chiral auxiliary-based methodology.[7, 13] We envisioned two potential analogues of amino acid 6 (Figure 1, X = H, X = Cl) that could afford the desired M(4–6) chlorine atropisomer from either stereochemical outcome of an S_NAr-based macrocyclization given the versatility of the Sandmeyer reaction ($NO_2 \rightarrow H$, or $NO_2 \rightarrow Cl$). Preparation of the amino acids 6 commenced with (isothiocyanoacetyl)-oxazolidinone **3** (Scheme 1).[7c] Stannous triflate mediated aldol reaction of **3** with aldehyde **4a** or **4b**[14] proceeded with good diastereoselection (dr = 95:5) to afford the derived *syn* aldol adducts **5a** and **5b**. In subsequent manipulations of these adducts, the presence of the electrophilic halogen-containing nitroaromatic nucleus, particularly in the chlorinated series **4b**–**14b**, necessitated careful optimization of reaction parameters in order to minimize undesirable S_NAr-based fluoride displacement reactions. After Boc protection and transformation to the oxazolidinone in a one-pot sequence, selective removal of the chiral auxiliary was effected under carefully controlled conditions[15] to afford carboxylic acids **6a** and **6b**.

Peptide coupling of **6a** and **6b** with amino acid 7 (EDCI·HCl, HOBt, 4/1 CH_2Cl_2/DMF) provided dipeptides **7a** and **7b**. While endocyclic oxazolidinone cleavage of **7a** could be accomplished with LiOH (MeOH/H_2O), the corresponding transformation of chloro-containing **7b** was hampered by competing S_NAr-based displacement of the highly reactive aromatic fluoride on ring 6. Use of Li_2CO_3 in MeOH minimized this side reaction and provided **8b**, which was used in unpurified form after aqueous workup. Following Boc cleavage, coupling of **8a** and **8b** to amino acid 5 and subsequent protecting group exchange afforded tripeptides

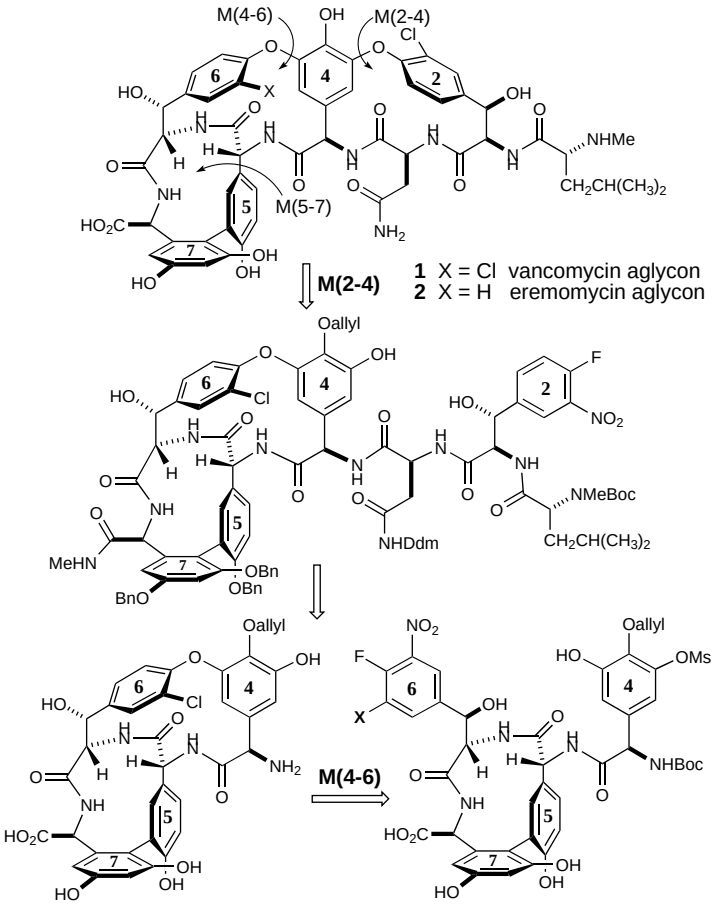


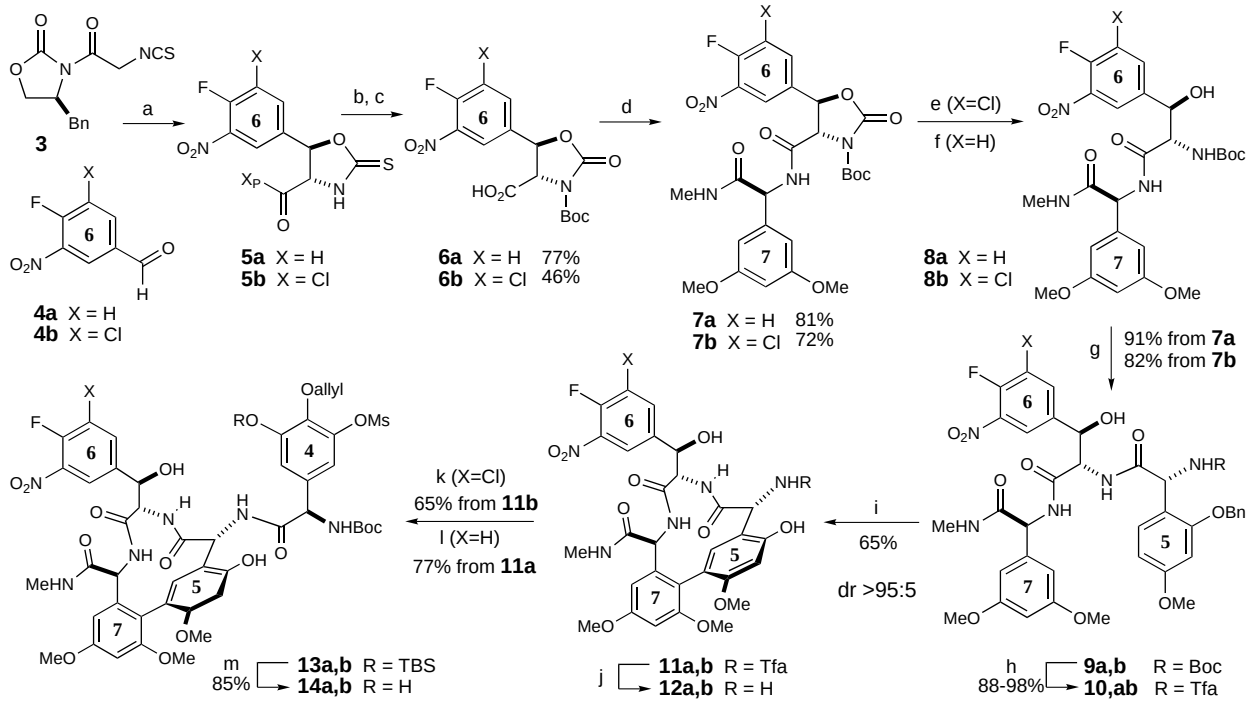
Figure 1. Assemblage strategy for vancomycin and eremomycin aglycons. See ref. [6] for abbreviations.

[*] Prof. D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz
Department of Chemistry & Chemical Biology, Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

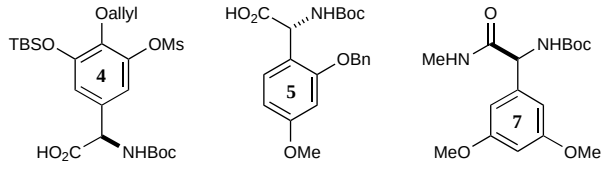
[**] Financial support has been provided by the National Institutes of Health (NIH).

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/98/3719-2700 $ 17.50+.50/0



Scheme 1. Synthesis of the M(5–7)-tetrapeptide. a) $Sn(OTf)_2$, *N*-ethylpiperidine, THF, −78 °C, then **4**; b) Boc_2O, DMAP, CH_2Cl_2, then 1:1 HCO_2H/30 % H_2O_2; c) 3.1 equiv LiOOH, −5 °C (X = Cl), 1.2 equiv LiOOH, −10 °C (X = H); d) amino acid 7, TFA, DMS, CH_2Cl_2, 0 °C, then **6**, EDCI · HCl, HOBt, CH_2Cl_2/DMF (X = Cl), THF (X = H), 0 °C; e) Li_2CO_3, MeOH, room temperature; f) LiOH, MeOH/H_2O; g) TFA, DMS, CH_2Cl_2, 0 °C, then amino acid 5, EDCI · HCl, HOBt, THF, 0 °C; h) TFA, DMS, CH_2Cl_2, 0 °C, then TFAA, 2,6-lutidine, CH_2Cl_2, room temperature; i) VOF_3, $BF_3 \cdot Et_2O$, $AgBF_4$, TFA/CH_2Cl_2, 0 °C, then $NaHB(OAc)_3$; j) $NaHCO_3$, MeOH, H_2O, room temperature, 6 d (X = Cl), 9–14 d (X = H); k) amino acid 4, HATU, HOAt, collidine, CH_2Cl_2/DMF, −20 °C, 16 h; l) isobutyl chloroformate, *N*-methylmorpholine, EtOAc, −10 → −5 °C, 30 min, then amino acid 4 in EtOAc/DMF, −20 °C → rt, 2 h; m) HF · pyridine, THF, room temperature, 1 h (X = Cl), TBAF, CH_2Cl_2, 0 °C, 15 min (X = H). See ref. [6] for abbreviations.

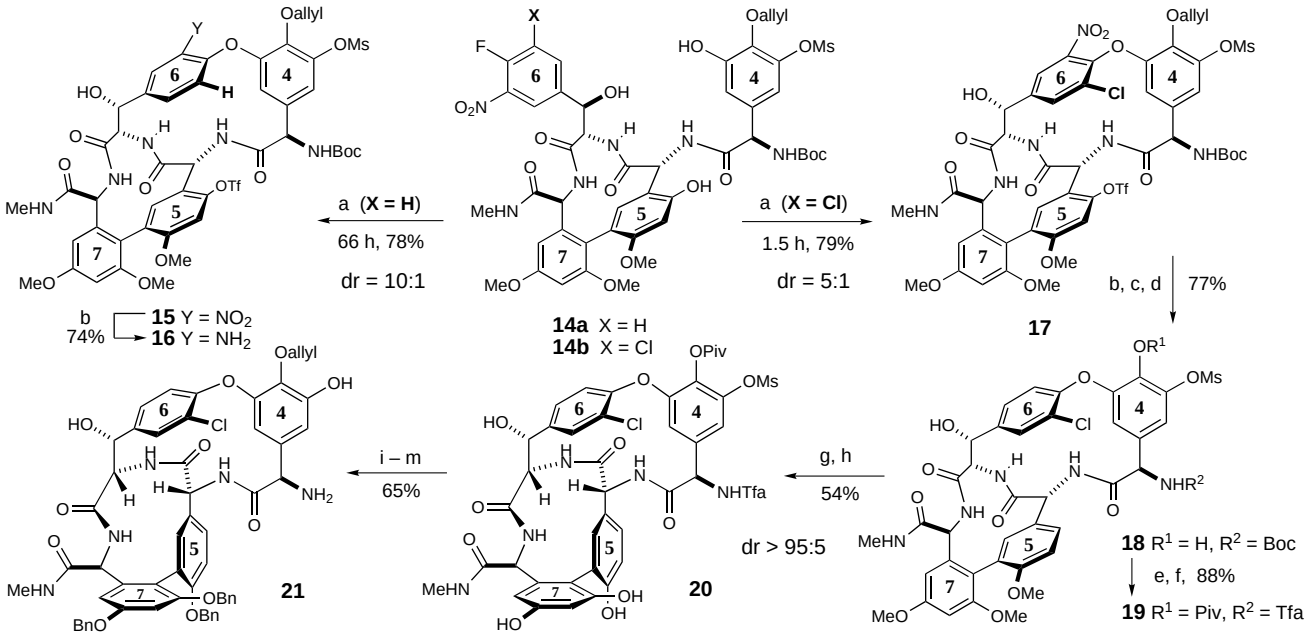


10a and **10b** in excellent overall yield for the hydrolysis and coupling events (see Scheme 1).

Oxidative cyclization of **10a** and **10b** according to our previously reported conditions (VOF_3)[9, 10] provided the M(5–7) cyclic tripeptides **11a** and **11b** as their unnatural *R* atropisomers (dr > 95:5). The reductive quench for this oxidation was modified to employ $NaBH(OAc)_3$ in place of zinc dust to avoid the unwanted reduction of the nitro group in ring 6. As noted previously, the desired cleavage of the aryl benzyl ether in ring 5 was also observed under the reaction conditions.[9, 10] We also investigated the analogous oxidative cyclizations of more conventional amino acid 7 ester analogues of tripeptide **10**. However, these substrates exhibited significant levels of epimerization of the C-terminal amino acid residue during the cyclization process, a side reaction that was suppressed through use of the illustrated *N*-methyl amides.

In preparation for incorporating amino acid 4 into the M(5–7) tripeptide **12**, removal of the trifluoroacetamide protecting group in **11** was accomplished by treatment with $NaHCO_3$ in MeOH/H_2O. These conditions effected conversion into amines **12** with no detectable aromatic fluoride displacement for either **12a** or **12b** by HPLC. Coupling[16] of **12** and amino acid 4 provided tetrapeptides **13**. As a prelude to M(4–6) macrocyclization, silyl deprotection of the phenolic hydroxyl in ring 4 was accomplished for **13a** under basic conditions (TBAF, THF), while acidic deprotection conditions (HF · pyridine) proved necessary for substrate **13b**.[17]

Atropisomer control during the construction of the M(4–6) macrocycle has posed a major challenge to the development of a successful vancomycin synthesis. In conjunction with evaluating potential strategies for achieving the proper disposition of the chloro substituent in ring 6, substrates **14a** and **14b** were examined with respect to the diastereoselectivity of their individual cyclization processes (Scheme 2). Optimal conditions for intramolecular S_NAr cyclization (Na_2CO_3, DMSO, room temperature),[18] when applied in the dechloro series starting from **14a**, provided the *undesired* nitro atropisomer (dr = 10:1); in situ derivatization of the phenolic hyxdoxy group in ring 5 afforded **15**. Reduction of the nitro group in **15** provided the major atropisomer **16** as a crystalline aniline whose structure was established by X-ray analysis.[19, 20] These results led to the speculation that the analogue **14b** with a chloro substituent in ring 6 might also cyclize with the same stereochemical outcome (**14b** → **17**) if the stereochemical bias for the nitro group were maintained. In the event, cyclization of **14b** afforded the desired atropisomer **17** as a 5:1 mixture of atropdiastereomers in 79 % yield (Scheme 2). The enhanced electrophilicity of **14b** was evident in the striking rate difference for the two cyclizations (**14a**: 66 h; **14b**: 1.5 h). More remarkable was the fact that **14b**



Scheme 2. Synthesis of the M(4–6)(5–7) bicyclic tetrapeptide. a) Na_2CO_3, DMSO, room temperature, 66 h (X = H), 1.5 h (X = Cl), then Tf_2NPh, 1 h; b) Zn^0, HOAc, EtOH, 40 °C; c) $NaNO_2$, H_3PO_2, cat. Cu_2O, THF/H_2O, 0 °C, 1 h; d) [Pd(dppf)Cl_2]·CH_2Cl_2, Et_3N, HCO_2H, DMF, 75 °C; e) PivCl, Et_3N, THF, room temperature; f) TFA, DMS, CH_2Cl_2, 0 °C, then TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C to room temperature; g) $AlBr_3$, then EtSH, 0 °C; h) MeOH, 55 °C; i) BnBr, Cs_2CO_3, Bu_4NI, DMF, 0 °C; j) LiSEt, THF, 0 °C; k) allyl-Br, Cs_2CO_3, DMF, 0 °C; l) LDA, THF, −78 °C; m) LiOH, THF/H_2O/MeOH, 0 °C. See ref. [6] for abbreviations.

cyclized at an appreciable rate upon dissolution in DMSO and other polar, aprotic solvents *without added base*. Bicyclic peptide **17** was submitted to reduction (Zn, HOAc, EtOH, 40 °C) and diazotization/reduction ($NaNO_2$, H_3PO_2, Cu_2O, THF/H_2O, 0 °C),[21] to give the desired monochloride in 88% yield. NOE experiments confirmed that the major atropisomer possessed the desired *R* configuration.[22] Palladium-catalyzed reduction of **17** removed both the extraneous aryl triflate on ring 5 and the phenolic allyl protecting group on ring 4 (Scheme 2),[23] affording phenol **18** in 87% yield.[24] Protecting group adjustment (**18** → **19**) and cleavage of the phenolic methyl ethers ($AlBr_3$/CH_2Cl_2, EtSH, 0 °C) was followed by M(5–7) atropisomerization (MeOH, 55 °C, 24 h) to give the bicyclic peptide **20**, which possesses the desired *S* biaryl configuration (dr > 95:5). It is noteworthy that **20** and its analogue without a chloro substitutent in ring 6, which comprise the M(5–7) aglycon subunits common to every member of the vancomycin family, contain the 5–6 *cis*-amide found in vancomycin.[25] In preparation for the final peptide coupling, the triphenol was benzylated, the phenolic hydroxy group in ring 4 was transformed to its allyl ether, and the mesylate and trifluoroacetamide protecting groups were removed to provide free amine **21**.

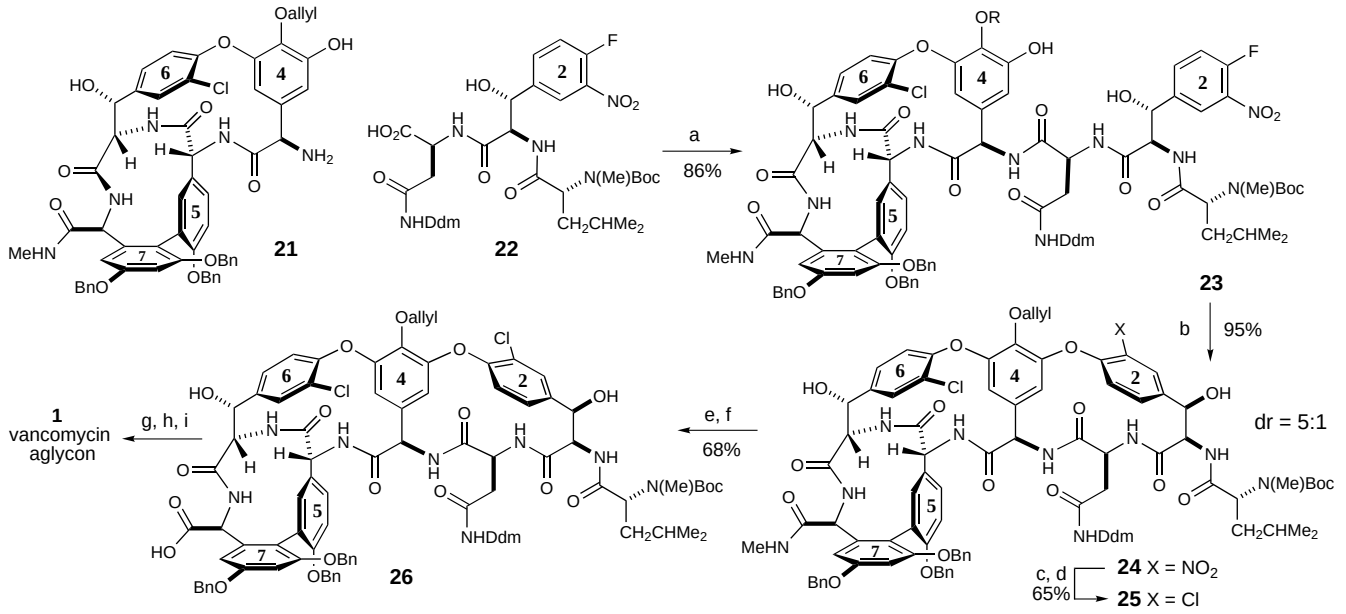
The completion of the aglycon synthesis is summarized in Scheme 3. Coupling of **21** and tripeptide **22**[10b] (EDCI·HCl, HOAt, THF, 0 °C) afforded heptapeptide **23** in 86% yield with no detectable epimerization (Scheme 3). Under optimal conditions (CsF, DMSO, room temperature, 5 h), intramolecular S_NAr cyclization provided the fully assembled tricyclic core of vancomycin as a 5:1 mixture of M(2–4) atropisomers favoring the desired *R* configuration **24** (95% yield). The mixture of nitro atropisomers was reduced (Zn, AcOH, EtOH, 40 °C) to provide two diastereomeric anilines which were separated by silica gel chromatography, affording a single atropisomer in 80% yield. Sandmeyer transformation[26] to the protected vancomycin aglycon **25** proceeded in 81% yield.

Deprotection of **25** to vancomycin aglycon (**1**) followed the sequence developed for the synthesis of orienticin C.[10b] The *N*-methyl amide moiety at the carboxyl terminus was removed by selective nitrosation in the presence of seven other amidic functional groups (N_2O_4, NaOAc, CH_2Cl_2, MeCN, 0 °C) followed by treatment with lithium hydrogen peroxide to give **26** in 68% yield.[27] Superficially, this transformation appears improbable in view of the other competing nitrosation sites; however, the steric effects associated with amide nitrosation have been documented.[28] Subsequent deprotection of allyl ether **26** ([$Pd(PPh_3)_4$], morpholine, THF, 0 °C) proceeded in 62% yield. Benzyl deprotection in the presence of the aryl chlorides was achieved using transfer hydrogenation conditions (Pd/C, 1,4-cyclohexadiene, EtOH, room temperature, 70% yield).[29] Final deprotection of the acid-labile nitrogen-protecting groups (Boc, Ddm) was effected through prolonged exposure to trifluroacetic acid (TFA/CH_2Cl_2, 3/1, DMS, 83% yield) to afford vancomycin aglycon (**1**), which proved identical (^{1}H NMR, COSY, HPLC, MS, [α]) to a natural sample.[30, 31]

The route detailed here provides vancomycin aglycon (**1**) in 40 steps (longest linear sequence) from 3,5-dimethoxybenzyl alcohol (amino acid 7). Eremomycin aglycon (**2**)[32] was also successfully synthesized through an identical strategy. These syntheses provide diastereoselective solutions to each of the biaryl ether and biaryl macrocycles and define a convergent assemblage process which can be extended to a variety of natural and unnatural analogues in the vancomycin series.

Received: August 17, 1998 [Z12295IE]
German version: *Angew. Chem.* **1998**, *110*, 2864–2868

  1433-7851/98/3719-2702 $ 17.50+.50/0



Scheme 3. Assemblage of the vancomycin aglycon. a) EDCI, HOAt, THF, 0 °C; b) CsF, DMSO, room temperature; c) Zn^0, HOAc, EtOH, 40 °C; d) HBF_4, *t*BuONO, MeCN, then CuCl, $CuCl_2$, H_2O; e) N_2O_4, NaOAc, CH_2Cl_2/CH_3CN, 0 °C; f) H_2O_2, LiOH, THF/H_2O; g) $[Pd(PPh_3)_4]$, morpholine, THF; h) 10 % Pd/C, 1,4-cyclohexadiene, EtOH, room temperature; i) TFA, DMS, CH_2Cl_2, 0 °C to room temperature. See ref. [6] for abbreviations.

Keywords: antibiotics · eremomycin · natural products · total synthesis · vancomycin

[1] M. H. McCormick, W. M. Stark, G. E. Pittenger, R. C. Pittenger, G. M. McGuire, *Antibiot. Annu.* **1955 – 56**, 606 – 611.

[2] For a comprehensive discussion of the vancomycin antibiotics see: *Glycopeptide Antibiotics* (Ed.: R. Nagarajan), Marcel Dekker, New York, **1994**.

[3] a) D. H. Williams, *Natl. Prod. Reports* **1996**, 469 – 477; b) M. Foldes, R. Munro, T. C. Sorrell, S. Shankar, M. Toohey, *J. Antimicrob. Chemother.* **1983**, *11*, 21 – 26.

[4] a) S. Tabaqchali, *Lancet*, **1997**, *350*, 1644 – 1645; b) R. C. Moellering, *Clinical Infectious Diseases* **1998**, *26*, 1196 – 1199; c) C. T. Walsh, S. L. Fisher, I.-S. Park, M. Prahalad, Z. Wu, *Chem. Biol.* **1996**, *3*, 21 – 28, and references therein.

[5] For reviews on methodology relevant to the synthesis of the vancomycin aglycon structure see: a) D. A. Evans, K. D. DeVries in ref. [2], pp. 63 – 103; b) A. V. Rama Rao, M. K. Gurjar, K. L. Reddy, A. S. Rao, *Chem. Rev.* **1995**, *95*, 2135 – 2168; c) J. Zhu, *Synlett*. **1997**, 133 – 144; d) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889 – 917.

[6] Abbreviations: dr: diastereomer ratio; X_p: (4*S*)-4-(phenylmethyl)-2-oxazolidinone; Tfa: trifluoroacetyl TFA: trifluoroacetic acid; Boc: *tert*-butoxycarbonyl; NOE: nuclear Overhauser effect; Tf: trifluoromethanesulfonyl; Ms: methanesulfonyl; Bn: benzyl; Piv: pivaloyl; Ddm: 4,4′dimethoxydiphenylmethyl; EDCI · HCl: 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride; HOBt: 1-hydroxybenzotriazole; DMAP: 4-dimethylaminopyridine; DMS: dimethylsulfide; TFAA: trifluoroacetic anhydride; HATU: *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOAt: 7-aza-1-hydroxybenzotriazole; LDA: lithium diisopropylamide; dppf: 1,1′-bis(diphenylphosphanyl)ferrocene.

[7] a) D. A. Evans, D. A. Evrard, S. D. Rychnovsky, T. Früh, W. G. Wittingham, K. M. DeVries, *Tetrahedron Lett.* **1992**, *33*, 1189 – 1192; b) D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011 – 4030; c) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1987**, *109*, 7151 – 7157.

[8] a) D. A. Evans, J. A. Ellman, K. M. DeVries, *J. Am. Chem. Soc.* **1989**, *111*, 8912 – 8914; b) D. A. Evans, C. J. Dinsmore, A. M. Ratz,*Tetrahedron Lett.* **1997**, *38*, 3189 – 3192; c) D. A. Evans, P. S. Watson, *Tetrahedron Lett.* **1996**, *37*, 3251 – 3254.

[9] 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.

[10] For the synthesis of orienticin C aglycon see: a) D. A. Evans, C. J. Dinsmore, A. M. Ratz, D. A. Evrard, J. C. Barrow, *J. Am. Chem. Soc.* **1997**, *119*, 3417 – 3418; b) D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, J. A. Ellman, S. D. Rychnovsky, J. Lacour, *J. Am. Chem. Soc.* **1997**, *119*, 3419 – 3420.

[11] D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz, *Angew. Chem.* **1998**, *111*, 2868 – 2872; *Angew. Chem. Int. Ed.* **1998**, *37*, 2704 – 2708.

[12] 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 cross-link between aryl groups of residues X and Y. Bicyclic moieties will be identified as M(W – Y)(X – Z).

[13] Amino acid 4 was derived from (*R*)-*para*-hydroxy-phenylglycine.

[14] Compound **4b** was prepared by the chlorination of **4a**: F. D. March, W. B. Farnham, D. J. Sam, B. E. Smart, *J. Am. Chem. Soc.* **1982**, *104*, 4680 – 4682. 4-Fluoro-3-nitrobenzaldehyde (**4a**) was prepared from 4-fluorobenzaldehyde: F. Michael, D. Noffz, *Chem. Ber.* **1957**, *90*, 1586 – 1589. Dr. S. Rubenstein is acknowledged for the preparation of this material.

[15] Alternate conditions and reagents were plagued by competitive endocyclic oxazolidinone hydrolysis and/or undesired nucleophilic displacement of the fluoride. D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141 – 6144.

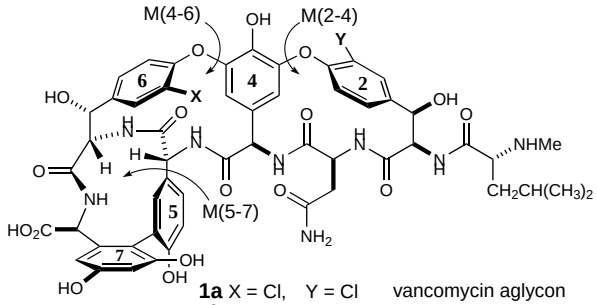
[16] HATU-mediated peptide coupling: L. A. Carpino, A. El-Fahan, C. A. Minor, F Albericio, *J. Chem. Soc. Chem. Commun.* **1994**, 201 – 203.

[17] The removal of the TBS protecting group highlighted the significant reactivity difference between the chloro and des-chloro substrates. Treatment of **13b** with TBAF resulted in immediate M(4 – 6) cyclization with reduced diastereoselection. See also ref. [24].

[18] Studies of the cyclization of **14a** revealed that the observed atropselectivity depended significantly on the base used, varying from 4:1 (KF) to 10:1 (Na_2CO_3) in favor of the unnatural atropisomer. It was further observed that cyclization of substrates in which the *meta*-phenols of amino acid 4 were *both* unmasked proceeded with negligible selectivity under a variety of conditions, necessitating the synthesis of a fully differentiated triphenol.

[19] Following diazotization/reduction of aniline **16**, eremomycin aglycon (**2**) was synthesized by a route analogous to that presented for

vancomycin. Synthetic **2** gave ^{1}H NMR, HPLC, and mass spectral data identical to a natural comparison sample (refs. [23] and [27]).
[20] We thank Mr. Kevin Campos for determining the X-ray structure of this intermediate.
[21] H. J. Shine, S. E. Rhee, *J. Am. Chem. Soc.* **1986**, *108*, 1000 – 1006.
[22] This assignment was confirmed by chemical correlation to a minor atropisomer corresponding to **16**.
[23] S. Cacci, P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1986**, *27*, 5541 – 5544.
[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.
[27] D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535 – 4538.
[28] J. Garcia, J. Gonzalez, R. Segura, J. Vilarrasa, *Tetrahedron* **1984**, *40*, 3121 – 3127.
[29] A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, J. Meienhofer, *J. Org. Chem.* **1978**, *43*, 4194 – 4196.
[30] We thank Dr. Bret Huff of Eli Lilly & Company for generous samples of vancomycin · HCl and eremomcyin · HOAc.
[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.



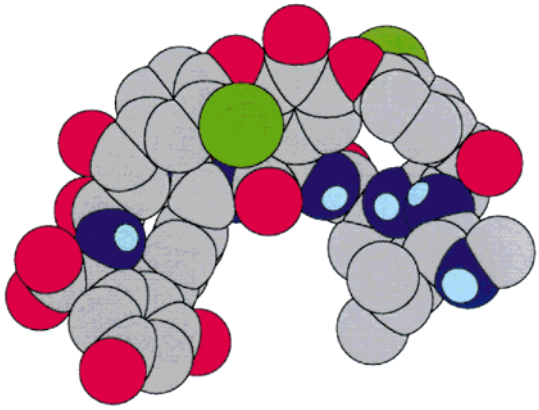


Figure 1. Space-filling representation of the vancomycin aglycon.[3b]

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 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).

[*] Prof. D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz
Department of Chemistry & Chemical Biology, Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

[**] Financial support has been provided by the National Institutes of Health (NIH).

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

  1433-7851/98/3719-2704 $ 17.50+.50/0