Diastereoselective Total Synthesis of the Vancomycin Aglycon with Ordered Atropisomer Equilibrations

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Vancomycin (**1**) is the prototypical member of a class of clinically important glycopeptide antibiotics[1−3] enlisted as the drugs of last resort for the treatment of resistant bacterial infections or for patients allergic to β-lactam antibiotics.[4] The structural complexity of **1**, the interest in defining the structural features responsible for cell wall biosynthesis inhibition in sensitive bacteria,[5] and the emergence of clinical resistance[6] have generated considerable interest in **1** and related agents.[7−11] Complementary to recent efforts,[9,10] herein we detail a convergent total synthesis of the vancomycin aglycon (**2**) (Figure 1). Having established that the CD and DE ring systems are most effectively closed through the formation of the diaryl ether linkage[12] and having explored,[13] implemented,[14] and improved[15,16] methodology amenable to macrocyclization of the sensitive vancomycin CD and DE ring systems, we recently described an indirect strategy for controlling the three stereochemical elements of atropisomerism[14,15,17−19] and herein disclose methodology for the formation

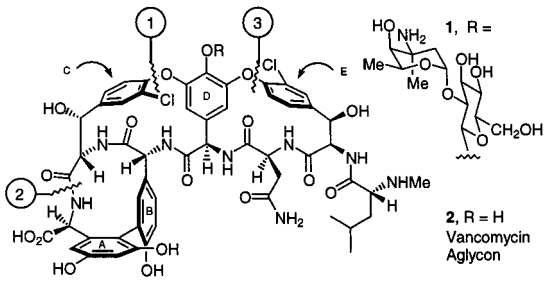
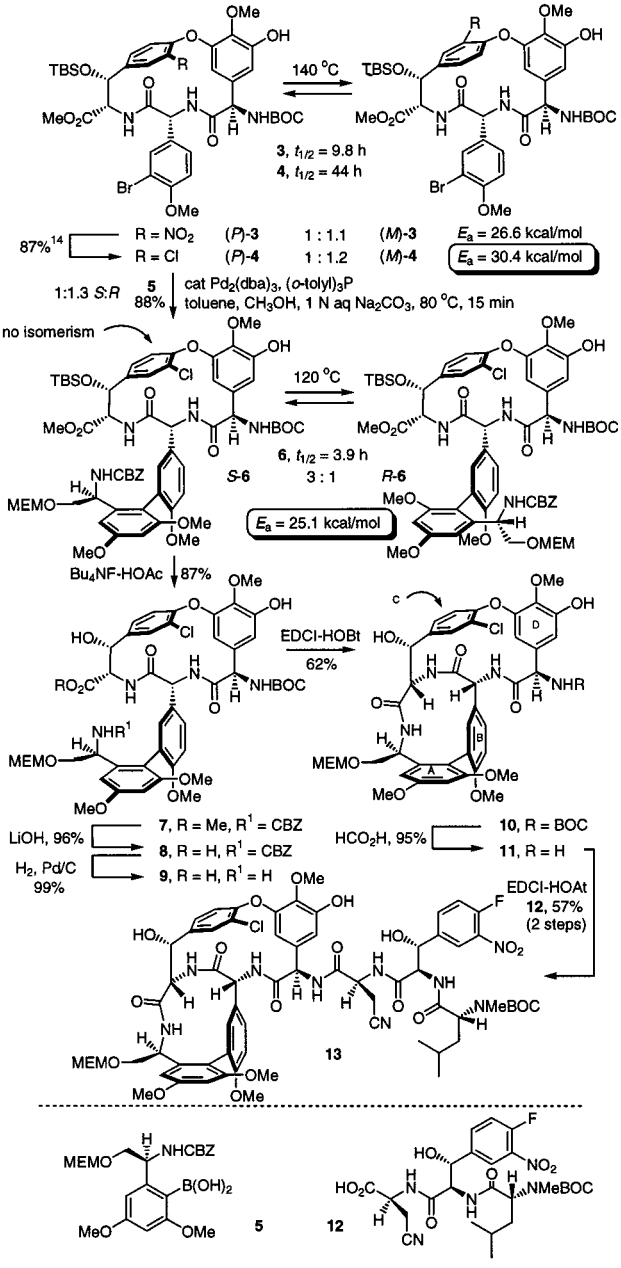


Figure 1.

Scheme 1



of the 12-membered biaryl AB ring system. Thus, two aromatic nucleophilic substitution macrocyclizations of the 16-membered diaryl ethers were enlisted for sequential CD and DE ring

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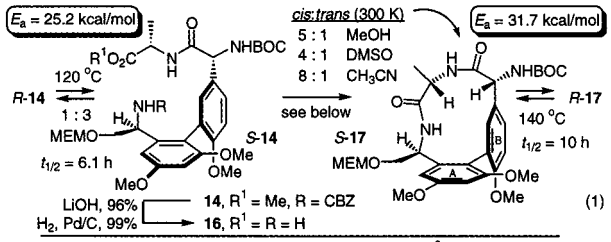
formations, an effective macrolactamization was developed for closure of the 12-membered biaryl AB ring system, and the defined order of CD, AB, and DE ring closures permitted selective thermal atropisomerism of the newly formed ring systems or their immediate precursors. This order permitted the recycling of the undesired atropisomers and provided a solution to the control of the stereochemistry funneling all synthetic material into the one of eight atropdiastereomers characterizing the natural product. The key to the recognition of this order was the establishment of the thermodynamic parameters of atropisomerism: DE ring system (E_a = 21.1−23.6 kcal/mol) < AB biaryl precursor[20] (E_a = 25.1 kcal/mol) < CD ring system (E_a = 30.4 kcal/mol).[14,15,17−19]

Preparation of **3** (4 steps from starting amino acids), equilibration and recycling of the unnatural atropisomer *M*-**3**, and conversion to *P*-**4** was accomplished as disclosed (Scheme 1).[14,15] Both the ease of isomerization and thermodynamic ratio of the atropisomers were more favorable with **3** versus **4** such that the former was enlisted for equilibration while conversion to the latter enhanced the thermodynamic stability of the CD ring system throughout the synthesis. Suzuki biaryl coupling of **4** with **5** (0.3 equiv of $Pd_2(dba)_3$, 1.5 equiv of (*o*-tolyl)$_3$P, toluene/CH_3OH/1 N aqueous Na_2CO_3 10/3/1, 80 °C, 15 min)[21] provided a 1:1.3 mixture of *S*:*R* **6** in superb yield (88%). Analogous to observations made with a model AB precursor (eq 1), thermal equilibration of the

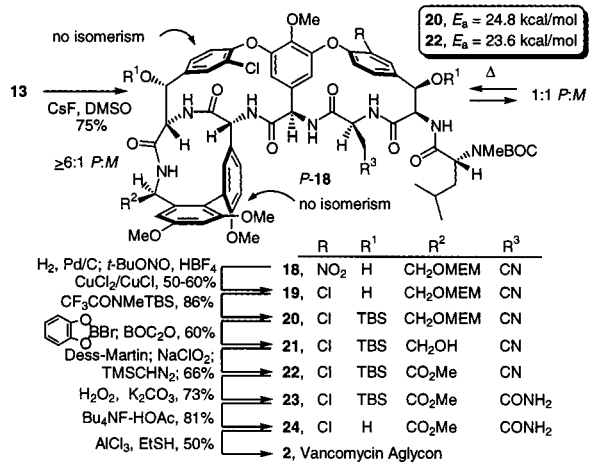


reagents	conditions (30 min, 25 °C)	% yield **17**
HATU/*i*-Pr$_2$NEt, 1.5/1.5 equiv	0.001 M DMF	91%
HATU/DMAP, 2.0/3.0 equiv	0.001 M DMF	90%
EDCI/HOAt, 3.0/3.0 equiv	0.004 M 20% DMF-CH_2Cl_2	75%
EDCI/HOBt, 3.0/3.0 equiv	0.002 M DMF (4.5 h)	60%
PyBOP/DMAP, 2.0/3.0 equiv	0.001 M DMF	91%

separable atropdiastereomers under conditions where the CD atropisomer was stable provided an equilibrium 3:1 ratio of *S*:*R* **6** in which the natural isomer predominated.[20] The minor, unnatural *R*-**6** was recycled through the use of this thermal equilibration. Silyl ether deprotection under conditions that suppress retro aldol cleavage of the CD ring system (4 equiv of Bu_4NF, 4.8 equiv of HOAc, THF, 25 °C, 10 h, 87%),[14] methyl ester hydrolysis (2 equiv of LiOH, THF, 0 °C, 2 h, 96%), and NCBZ deprotection (H_2, cat 10% Pd/C, EtOAc/EtOH 2.5/1, 25 °C, 7.5 h, 99%) provided **9**. By enlisting conditions developed with the model tripeptide **14**[21] (eq 1), macrolactamization was effected by treatment with EDCI/HOBt (5 equiv/5 equiv, CH_2Cl_2/DMF 5/1, 0.002 M, 0 °C, 16 h) to provide **10** (62%) possessing the natural vancomycin ABCD atropisomer stereochemistry (45% from **4** and 21% overall from constituent subunits). Of the methods examined (eq 1), the EDCI/HOBt conditions proved most effective with **9**.

Selective NBOC deprotection of **10** (HCO_2H−$CHCl_3$ 1:1, 25 °C, 5 h, 95%) followed by coupling of **11** with **12**[14] (2 equiv of

Scheme 2



EDCI, 2 equiv of HOAt, THF, 0 °C, 30 min, 57% from **10**) provided **13** and set the stage for DE macrocyclization. Diaryl ether formation proceeded cleanly upon treatment with CsF (6 equiv, DMSO, 25 °C, 23 h, 75%) to provide a ≥6:1 mixture of *P*:*M* **18** with the natural DE atropisomer predominating (Scheme 2).[15] This preferential generation of the natural stereochemistry was first disclosed by Evans[8,9] with closely related substrates (5:1) but contrasts with observations described by Nicolaou[10] (1:3) where the unnatural atropisomer predominated with an alternative substrate and mode of closure. Notably, thermal atropisomerism of **20** could be conducted without affecting the AB or CD atropisomer stereochemistry analogous to our prior observations with **22**,[19,20] and those conducted with **20** and **22** were much cleaner than attempts with **18** due to suppressed competing retro aldol reactions.[19] Sandmeyer substitution with introduction of the E-ring chloride was accomplished without loss of the DE atropisomer stereochemistry (H_2, 10% Pd/C, EtOAc, 25 °C, 3 h; 1.5 equiv of *t*-BuONO, 1.5 equiv of HBF_4, CH_3CN, 0 °C, 10 min; 60 equiv of $CuCl_2$, 50 equiv of CuCl, H_2O−CH_3CN, 25 °C, 1 h, 50−60% overall).[14] TBS protection of the secondary alcohols (60 equiv of $CF_3CONMeTBS$, CH_3CN, 50 °C, 22 h; aqueous citric acid, 25 °C, 13 h, 86%),[19] MEM ether deprotection (5.9 equiv of *B*-Br catecholborane, CH_2Cl_2, 0 °C, 2 h; 3.9 equiv of Boc_2O, 4.6 equiv of $NaHCO_3$, 2:1 dioxane/H_2O, 25 °C, 2.5 h, 60% for 2 steps), and two-step alcohol oxidation (3.7 equiv of Dess−Martin periodinane, CH_2Cl_2, 0 °C, 15 min then 25 °C, 1 h; 9 equiv of $NaClO_2$, 0.7 M NaH_2PO_4, isobutene/*t*-BuOH 1/4, 25 °C, 20 min), followed by methyl ester formation ($TMSCHN_2$, C_6H_6/CH_3OH 4/1, 25 °C, 45 min) provided **22** (66%, 3 steps), which was identical to material derived from natural vancomycin.[19] The final three steps in the conversion of **22** to **2** followed our disclosed sequence,[19] and significantly, the final step involved clean cleavage of the methyl ester, four methyl ethers, and NBoc deprotection.

The longest linear synthetic sequence entailed the preparation and incorporation of the central amino acid[14,22] (31 steps), and the convergent assemblage of **2** from the seven amino acid subunits required 26 steps (0.5−1.0% overall). Given the modular nature of the synthesis and its reliable control of the atropisomer stereochemistry, it is especially suited for the preparation of analogues, and such studies are in progress.

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Supporting Information Available: Characterization of **5**−**24**, **2** and details of the preparations of **5** and **14** are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Details may be found in the Supporting Information. The natural AB atropisomers within the ABCD and ABCDE ring systems are also the thermodynamically most stable (≥95:5) ensuring that DE equilibration does not affect the set AB stereochemistry.[19]

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