

## SYNTHESIS OF THE VANCOMYCIN CDE RING SYSTEM

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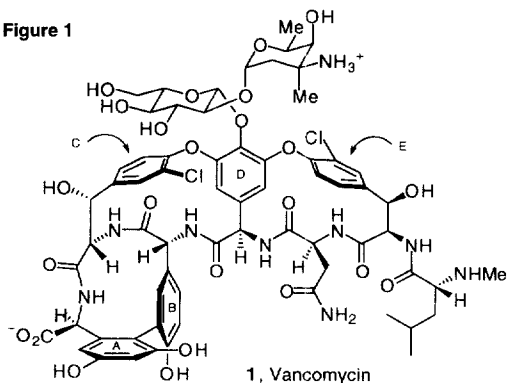
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**Abstract.** A first generation synthesis of **22** is described constituting the first disclosure of the preparation of an appropriately protected and fully functionalized vancomycin CDE ring system complete with the C and E ring monochloro substitution pattern. The approach, which is based on two aromatic nucleophilic substitution reactions for sequential CD and DE macrocyclization, provided the opportunity to define an indirect solution to the control of the CDE atropisomer stereochemistry through selective thermal equilibration of the DE versus unaltered CD ring system. Its success provides a rationale for a preferred order to the CD and DE ring system introductions. © 1998 Elsevier Science Ltd. All rights reserved.

Vancomycin (**1**, Fig. 1), which was isolated in 1956 from *Streptomyces orientalis*<sup>1</sup> and whose structure was secured 25 years later,<sup>2</sup> is the prototypical member of a class of clinically important glycopeptide antibiotics.<sup>3</sup> It is the therapeutic agent of choice for the treatment of methicillin-resistant *Staphylococcus aureus* and is routinely used against enterococci and bacterial infections in patients allergic to  $\beta$ -lactam antibiotics.<sup>4</sup> The structural complexity of vancomycin, the interest in defining its structural features responsible for inhibition of cell wall biosynthesis in sensitive bacteria,<sup>5</sup> and the emergence of clinical resistance<sup>6</sup> have provided renewed interest in the total synthesis of **1** and related agents.<sup>7,8</sup> Herein, we report a first generation synthesis of **22**, an appropriately protected and fully functionalized CDE ring system of vancomycin. The approach, which is based on two aromatic nucleophilic substitution reactions<sup>9,10</sup> for sequential CD and DE macrocyclization through formation of the biaryl ethers,<sup>11</sup> provided the opportunity to examine an indirect solution<sup>12</sup> to the control of the CDE atropisomer stereochemistry which suggests a preferred order to the CD and DE ring system introductions.

Figure 1



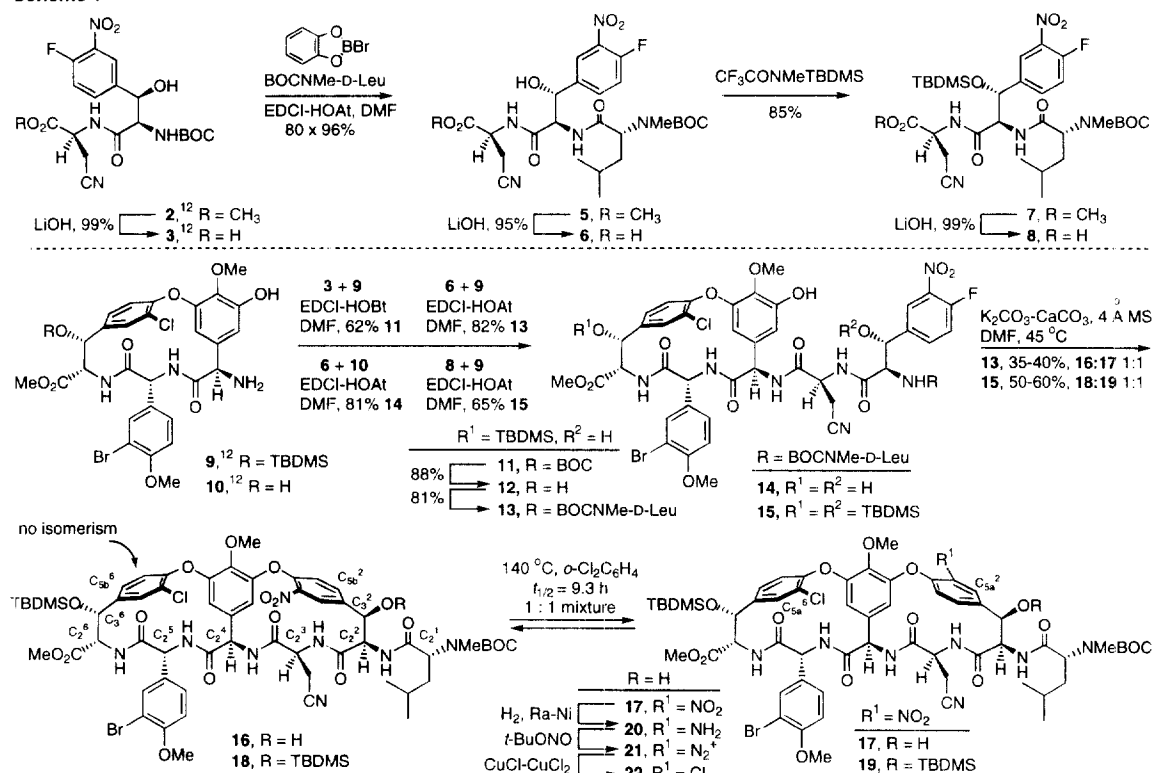
Coupling of **3**<sup>12</sup> with **9**<sup>12</sup> (EDCI-HOBt, DMF, 0 °C, 16 h, 62%) provided **11**, the first potential cyclization substrate (Scheme 1). Selective *N*-BOC deprotection effected by treatment of **11** with *B*-bromocatecholborane (5.5 equiv, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 88%) provided **12**, which was coupled with *D*-BOC-NMe-Leu (EDCI-HOBt, DMF, 4 °C, 16 h, 81%) to provide **13** and the second key cyclization substrate. Alternatively, **13** was prepared by introducing *N*-methyl-*D*-leucine onto **2**<sup>12</sup> requiring *N*-BOC deprotection (4 equiv *B*-bromocatecholborane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 80%) and coupling of the free amine **4** with *D*-

BOC-NMe-Leu (EDCI–HOAt, DMF, 5 °C, 12 h, 96%). Ester hydrolysis (2 equiv LiOH, 2:1 *t*-BuOH–H<sub>2</sub>O, 0 °C, 0.75 h, 95%) and coupling of **6** with **9**<sup>12</sup> (EDCI–HOAt, DMF, 0–5 °C, 10 h, 75–82%) provided **13** directly. A third substrate **14** that bears both a CD and DE free alcohol was prepared by coupling **6** with **10**<sup>12</sup> (EDCI–HOAt, DMF, and 5 °C, 81%). The fourth and the most successful substrate **15**, which protects both CD and DE alcohols as TBDMS ethers, was prepared by TBDMS protection of **6** (CF<sub>3</sub>CONMeTBDMS, CH<sub>3</sub>CN, 55 °C, 85%), ester hydrolysis (1.1 equiv LiOH, 2:1 *t*-BuOH–H<sub>2</sub>O, 0 °C, 99%), and direct coupling of **8** with **9**<sup>12</sup> (EDCI–HOAt, DMF, 5 °C, 65%).

Initial studies with **11**–**13** revealed that cyclization of the more advanced intermediate **13** was cleaner than **11** and was examined in detail. Macrocyclization was effected by treatment with K<sub>2</sub>CO<sub>3</sub>–CaCO<sub>3</sub><sup>12</sup> (5.0 equiv–7.5 equiv, 2 wt equiv 4 Å MS, 0.008 M DMF, 40 °C, 12–36 h) providing a 1:1 mixture of the two atropisomer products **16** and **17** (35–40%) along with an epimer of **13**, which failed to cyclize.<sup>13</sup> The closure of **13** was found to be slower and less effective than that of the DE ring system itself<sup>12</sup> and similar transannular effects derived from the fused CD ring system have been implicated in the studies of Evans.<sup>14</sup> The assignment of the DE atropisomer stereochemistry was derived from 2-D <sup>1</sup>H NMR with the observation of strong diagnostic NOE's between C<sub>5a</sub><sup>2</sup>-H/C<sub>3</sub><sup>2</sup>-H(s) and C<sub>5a</sub><sup>2</sup>-H/C<sub>2</sub><sup>2</sup>-H(m) for the desired atropisomer **17**, and between C<sub>5b</sub><sup>2</sup>-H/C<sub>3</sub><sup>2</sup>-H(s) and C<sub>5b</sub><sup>2</sup>-H/C<sub>2</sub><sup>2</sup>-H(s) for **16**. The maintenance of the CD atropisomer stereochemistry was confirmed by observation of C<sub>5a</sub><sup>6</sup>-H/C<sub>3</sub><sup>6</sup> and C<sub>2</sub><sup>6</sup>-H as well as C<sub>5b</sub><sup>6</sup>-H/SiCH<sub>3</sub> NOE's with both **16** and **17**. A variety of cyclization conditions were examined including K<sub>2</sub>CO<sub>3</sub>–CaCO<sub>3</sub> (DMSO), which resulted in more competitive or exclusive substrate epimerization,<sup>13</sup> and CsF (DMF or DMSO, 0–25 °C) which resulted in OTBDMS deprotection and CD retro Aldol ring cleavage under conditions where no DE macrocyclization was detected. This stands in interesting contrast to the report of Evans where an analogous DE ring closure was effectively accomplished without retro Aldol or epimerization with CsF (DMSO) on a substrate incorporating the AB ring system.<sup>8a</sup> Preliminary efforts to promote the macrocyclization of the free alcohol **14** with CsF (DMF or DMSO, 0–25 °C) similarly led to CD retro Aldol ring cleavage under conditions where no DE macrocyclization was detected. Since thermal atropisomerism also promotes retro Aldol of the CD, but not DE, ring systems on substrates bearing a free C<sub>3</sub><sup>6</sup> and C<sub>3</sub><sup>2</sup> alcohol,<sup>15</sup> the approach enlisting **14** was not further investigated and focused efforts on the development of macrocyclization conditions that permit maintenance of the C<sub>3</sub><sup>6</sup> OTBDMS protecting group. In addition, studies with the DE ring system<sup>12</sup> indicated that a macrocyclization substrate bearing a TBDMS ether cyclized more rapidly than the corresponding alcohol. Consistent with this, macrocyclization of **15** with K<sub>2</sub>CO<sub>3</sub>–CaCO<sub>3</sub> (5 equiv–7.5 equiv, 2 wt equiv 4 Å MS, 0.004 M DMF, 45 °C, 48 h) cleanly provided a 1:1 mixture of **18** and **19** (50–60%) without TBDMS deprotection, and without significant competitive epimerization. Both 2-D <sup>1</sup>H NMR and chemical correlation of **16** with **18** and **17** with **19** effected by silylation of **16/17** (TBDMSOTf) established the atropisomer assignments.<sup>16</sup>

Access to **16** provided the opportunity to examine the thermal atropisomerism of the CDE ring system.<sup>15</sup> We recently disclosed that both the CD and DE ring system atropisomers may be thermally equilibrated.<sup>12,15</sup> Moreover, the rates were sufficiently different that the selective isomerization of the DE ring

Scheme 1



system ( $E_a = 15.3$  kcal/mol) in the presence of the CD ring system ( $E_a = 26.6$  kcal/mol) could be anticipated. Thus, thermal equilibration of **16** cleanly provided a 1:1 mixture of the DE atropisomers **16** and **17** under conditions where the stereochemistry of the CD ring system remained unaltered (140 °C, *o*-Cl<sub>2</sub>C<sub>6</sub>H<sub>4</sub>,  $t_{1/2} = 9.3$  h or DMSO,  $t_{1/2} = 3.1$  h).<sup>15</sup> This confirmed that the two products are atropisomers and not diastereomers derived from an inadvertent epimerization under the cyclization conditions, and allowed isomerization of the undesired atropisomer **16** to **17**.

Reduction of the nitro group of **17** (0.3 wt equiv Ra-Ni, H<sub>2</sub>, CH<sub>3</sub>OH, -20 °C, 1–2 h), diazotization (1.3 equiv *t*-BuONO, 1.3 equiv HBF<sub>4</sub>, CH<sub>3</sub>CN, 0 °C, 1.5 h) and Sandmeyer substitution (50 equiv CuCl, 60 equiv CuCl<sub>2</sub>, CH<sub>3</sub>CN–H<sub>2</sub>O, 0 °C, 4 h, 50%) provided the fully functionalized vancomycin CDE ring system **22** without competitive reduction or detectable loss of the natural atropisomer stereochemistry. Continued improvements in this approach to **22** which define a preferred order to the CD and DE macrocyclization reactions and its extension to the preparation of the vancomycin aglycon and related agents are in progress and will be reported in due course.

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- Consistent with a tentative assignment that this occurs at the central phenylglycine site, the largest distinguishing features in the  $^1\text{H}$  NMR of the epimerized substrate were localized to  $\text{C}_2^4\text{-H}$  and the two aromatic protons. Preparation of the substrates bearing the unnatural D-configuration at the  $\beta$ -cyanoalanine or 2(*S*) configuration at the  $\beta$ -hydroxy-(4-fluoro-3-nitro)phenylalanine residues confirmed that epimerization had not occurred at these sites. Resubjection of the epimerized substrate to the reaction conditions failed to provide a cyclization product and afforded recovered starting material.
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- The  $\text{C}_2^3$  epimer of **15** closed even more effectively (90%) and provided exclusively the unnatural DE atropisomer stereochemistry.