Approaches to the Synthesis of the Vancomycin Antibiotics. Synthesis of Orienticin C (Bis-dechlorovancomycin) Aglycon

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In the preceding paper, we described the synthesis of the vancomycin-related M(4-6)(5-7) bicyclic subunit 3 (Scheme 1). Herein we describe the first synthesis of the vancomycin-related heptapeptide nucleus and the transformation of this intermediate to orienticin C (bis-dechlorovancomycin) aglycon 2.

Our original strategy for the construction of the biaryl ether-containing rings was based on a successful study that demonstrated that these macrocycles, in the absence of the biaryl-containing M(4-6)(5-7) bicycle, could be constructed through a Ti(III)-mediated oxidative cyclization. In the current plan, the N-terminal tripeptide 4 incorporating the 4,4′-dimethoxydiphenylmethyl (Ddm)-protected asparagine was employed for the construction of the final M(2-4) macrocyclic subunit. The selection of this protecting group was predicated on its favorable impact on epimerization during the fragment coupling, on suppression of the aspartate-iso-aspartate rearrangement, and on protection of this residue during selective derivatization of the N-methyl amide at the end of the synthesis. Given the complexity of these natural products, orienticin C aglycon 2 was chosen as our initial target.

Deprotection of the Boc-protected bicyclic tetrapeptide 3 (30% TFA, DMS, CH2Cl2, 0 °C) and fragment coupling with the N-terminal tripeptide 4 was carried out under standard conditions (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), THF, 0 °C) to afford heptapeptide 5 in excellent yield with no detectable epimerization (Scheme 1). Removal of the ring-2 allyl ether provided 6, which was cyclized under the optimized conditions developed for the M(2-4)(4-6) bicycle (Tl(NO3)3•3H2O, 30:1 CH2Cl2/MeOH, rt; 21°C, 1 min). The resulting aryllithium intermediate was trapped by 20% of a recyclable dehalogenated material. This bicyclic tricyclic intermediate was then coupled with the protected N-terminal CrCl3, 0 °C) to provide the desired tricycle 7 in approximately 20% yield as an inseparable mixture with two other unidentifiable byproducts. In spite of an extensive reevaluation of this methodology, no improvement in yield for this critical transformation could be achieved. We conclude that the enhanced rigidity of the biaryl-containing M(4-6)(5-7) bicycle, in comparison to that of the M(4-6) monocyclic counterpart employed in the model studies, could be responsible for the failure of this transformation. A detailed investigation of this reaction will be published elsewhere.

Rather than proceeding with a standard cyclization step, other diaryl ether-forming macrocyclization strategies were considered. On the basis of the existing precedent provided by Beugelmans, Rao, and Boger, the nitroaromatic-based S₈-Ar methodology was evaluated. Accordingly, the refunctionalization of bicyclic tetrapeptide 3 to phenol 8 was undertaken (Scheme 2). Protection of the ring-4 phenol as its derived allyl ether and subsequent deprotonation of the six amido and alcoholic hydrogens with MeMgCl (18 equiv, THF/Et2O, 0 °C) was followed by lithium–iodine exchange (t-BuLi, −78 °C, 1 min). The resulting aryllithium intermediate was trapped with (EtO)3B (−78 °C → −20 °C, 40 min) and oxidized (HOAc, H2O2, −20 °C → rt, 2 h) to provide 9 in 53% yield accompanied by 20% of a recyclable dehalogenated material. This bicyclic intermediate was then coupled with the protected N-terminal.

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tripeptide 9, previously prepared in conjunction with our recently reported model study on the construction of the M(2-4) monocyte.11 Surprisingly, the peptide coupling of 8 with 9 was more sensitive than the corresponding 3→4 union. Specifically, use of the newly developed 1-hydroxy-7-azabenzotriazole (HOAt) acyl transfer catalyst,12 rather than HOBt, was required to suppress epimerization in the carbodiimide-mediated fragment coupling. Cyclization of heptapeptide 10 under the previously reported conditions11 (CsF, DMF, rt) was very sluggish. Fortunately, when the reaction was carried out in DMSO (CsF, rt, 6 h), the desired product 11 was obtained in 90% yield as a 7:1 mixture of isomers favoring illustrated ring-2 nitro atropisomer. The stereochemical outcome of this transformation has important implications for the eventual synthesis of vancomycin, since the NO2 → Cl transformation can be employed to introduce the ring-2 chlorine into the vancomycin skeleton with the requisite stereochemistry.

In pursuit of orienticin C aglycon, removal of the nitro group was effected by reduction to the aniline (Zn, HOAc, EtOH, 40 °C) followed by in situ diazotization13 (NaNO2, H3PO2, CuO2, THF/H2O, 0 °C) to afford 12 in 85% overall yield. The N-methyl amide masking the carboxyl terminus was then cleaved through a selective nitrosation (N2O4, NaOAc, CH2Cl2/CH3CN, 0 °C) to afford 13 (85%, two steps); (b) MeMgCl, 0 °C, TFA, DMS, CH2Cl2, rt. (g) N2O4, NaOAc, CH2Cl2/CH3CN, 0 °C; (h) H2O2, LiOH, THF/H2O, 0 °C (46%, two steps); (i) Pd(PPh3)4, morpholine, THF, rt; (j) 10% Pd/C, H2 100 psi, MeOH, rt; (k) TFA, DMS, CH2Cl2, rt. to provide acid 13. We have found that this strategy for masking base-sensitive carboxylates to be general,17 and the mild activation/hydrolysis conditions render this an attractive option in synthetic planning. Deallylation of 13 (Pd(PPh3)4), morpholine, THF, rt) followed by hydrogenolysis of the benzyl ethers and the aryl chlorines (H2, 100 psi, Pd/C, MeOH, rt, 24 h) and extended (11 h, rt) TFA-mediated removal of the Boc and Ddm groups cleanly afforded orienticin C aglycone whose 1H NMR, HPLC, and mass spectra were identical to a comparison sample.18

In addition to the recently reported X-ray structures of ureidobalhimycin and vancomycin,19 this synthesis confirms the structural assignment of this class of natural products and provides important precedents for the synthesis of other members of this family of antibiotics.

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Supporting Information Available: Characterization data for all compounds (10 pages). See any current masthead page for ordering and Internet access instructions.

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