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# Synthesis of the Orienticin C M(2-4) Macrocycle Utilizing a Nucleophilic Aromatic Substitution Strategy

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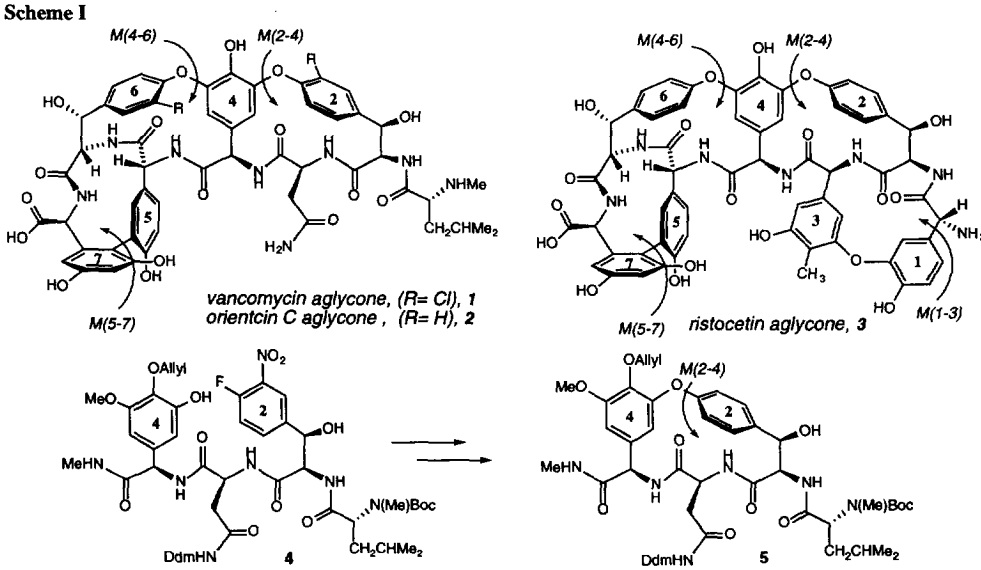
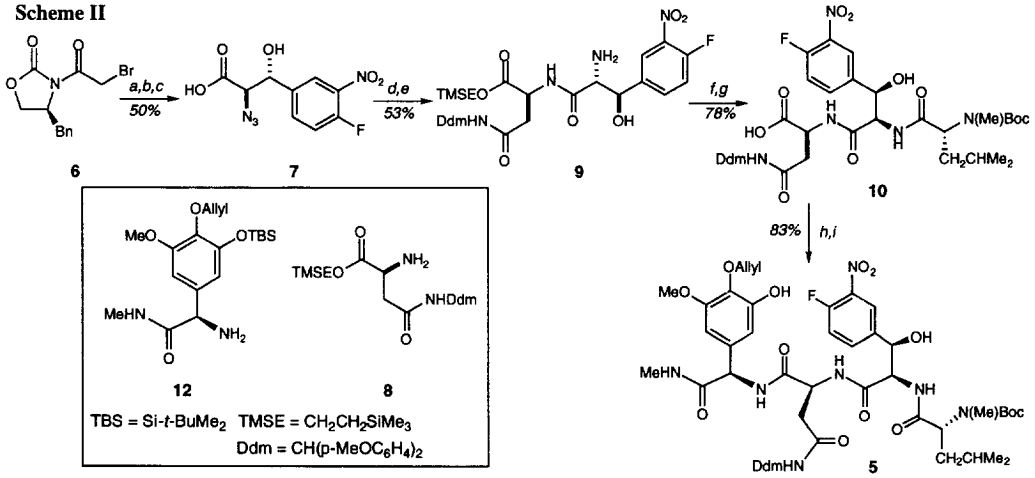
**Abstract:** The synthesis of the fully functionalized M(2-4) macrocyclic orienticin C subunit **5** is described utilizing a intramolecular nucleophilic aromatic substitution reaction.


The vancomycin family of glycopeptide antibiotics, as represented by vancomycin (**1**), orienticin C (**2**), and ristocetin (**3**), are widely employed in the treatment of severe staphylococcal infections.[2] The complex molecular architecture contained within these internally cross-linked peptide natural products makes them formidable targets for total synthesis, and a number of studies have been launched with the long-term objective of achieving this goal.[3] In prior research in this area, we have addressed the successful development of auxiliary-controlled enantioselective syntheses of all of the amino acid constituents,[4] the biomimetic thallium(III) mediated oxidative cyclization to form the M(2-4) and M(4-6) diaryl ether macrocycles,[5] and the vanadium(V) promoted M(5-7) biaryl construction.[6] The purpose of this Letter is to describe the synthesis of the *fully functionalized* M(2-4) macrocyclic ether subunit of orienticin C **5** from the seco tetrapeptide precursor **4** *via* an intramolecular nucleophilic aromatic substitution strategy precedented by Hobbs and Still for thioether-containing vancomycin models[7] and more recently investigated by both Beugelmans[8] and Rao.[9] This study was motivated by our unexpected failure in the application of previously developed Tl(III) methodology to the construction of the final M(2-4) macrocyclic ring from the preformed M(5-7)-M(4-6) bicyclic orienticin precursor.

**Scheme I**



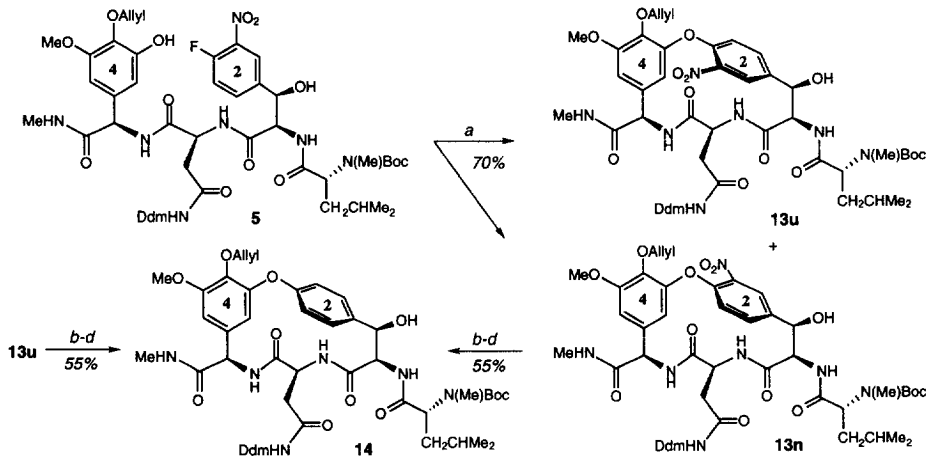
**Scheme II**




a) $Bu_2BOTf$, $Et_3N$, $Et_2O$, -78 °C→23 °C, 4-fluoro-3-nitrobenzaldehyde, $Et_2O$, -78 °C. b) TMGA, $CH_2Cl_2$, 0 °C. c) LiOH, $H_2O_2$, THF, $H_20$, 0 °C. d) **8**, DMF, EDC, HOBT, 0 °C. e) $Ph_3P$, THF, $H_2O$, 23 °C. f) *D-N*-Boc-*N*-methylleucine, EDC, HOBT, THF, 0 °C. g) TBAF, DMF, 0 °C. h) **12**, EDC, HOBT, THF, 0 °C. i) TBAF, $CH_2Cl_2$, 0 °C.

The synthesis of the required tetrapeptide **5** is shown in Scheme II. The *anti*-4-fluoro-3-nitro-β-hydroxy-α-azido acid **7** was prepared using standard imide enolate methodology.[4] Reaction of the boron enolate of chiral imide **6** with 4-fluoro-3-nitrobenzaldehyde provided the aldol adduct with greater than 95:5 diastereoselectivity in 76% yield. Displacement of the resulting bromide with tetramethyl guanidinium azide (TMGA)[10] followed by hydrolysis[11] of the chiral auxiliary provided **7** in 50% overall yield. Coupling of azido acid **7** with the suitably protected-L-asparagine derivative **8**[12] and reduction of the resulting azide with triphenylphosphine afforded dipeptide **9**. Treatment of dipeptide **9** with EDC, HOBT and D-*N*-Boc-*N*-methylleucine in THF at 0 °C followed by cleavage of the ester with TBAF afforded tripeptide **10** in 78% yield for the two steps. Incorporation of the final amino acid **12**[13] (EDC, HOBT, THF, 0 °C, 89%) followed by fluoride-induced removal of the *tert*-butyldimethylsilyl protecting group (TBAF, $CH_2Cl_2$, 0 °C, 93%) provided the cyclization precursor **5**.

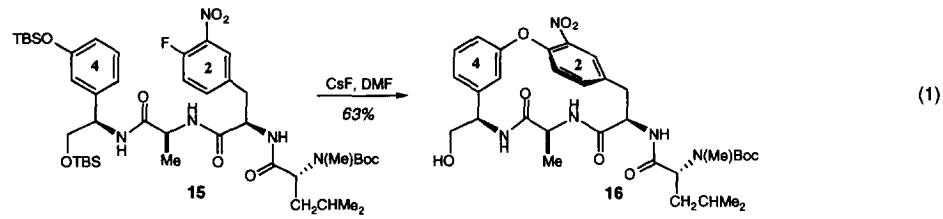
**Scheme III**




a) CsF, DMF, 23 °C. b) $SnCl_2$, EtOH, 40 °C. c) $BF_3$-$Et_2O$, *t*-BuONO, $CH_2Cl_2$, 0 °C. d) $Bu_3SnH$, THF, 23 °C.

Treatment of tetrapeptide **5** under several different basic conditions ($K_2CO_3$, DMF; $Cs_2CO_3$, DMF; $K_2CO_3$, 18-crown-6, THF) failed to promote the desired cyclization. However, the use of CsF, conditions recently reported by Beugelmans,[14] (3 equiv, DMF, 0.008M, 23 °C, 48 h) led to atropdiastereomers **13u** (unnatural configuration) and **13n** (natural configuration), in a 1.7:1 ratio in 70% yield (Scheme III). The stereochemical assignments of **13u** and **13n** are based on NOESY experiments and confirmed by independent conversion of the individual atropdiastereomers to the common M(2-4) macrocycle **14**. This overall transformation was accomplished using a stannous chloride reduction to the aniline ($SnCl_2$, EtOH, 40 °C, 7h), diazotization[15] followed by $Bu_3SnH$ reduction of the unpurified diazonium salt.[16] There are two potential concerns associated with base catalyzed cyclizations of this type: (a), epimerization of the stereogenic center associated with the 4-arylglycine residue; (b), dehydration or retroaldol degradation of the 2-hydroxyphenylalanine. The preceding experiments establish that neither of these side reactions are an impediment to the desired macrocyclization.

Beugelmans has recently reported the related cyclization of simplified tetrapeptide analog **15** (Eq 1).[14] Interestingly, this less functionalized system exhibited complete atropdiastereoselection favoring the natural conformation under the CsF/DMF conditions. Tetrapeptide **5** contains several major structural differences that could be responsible for its significantly lower level of atropdiastereoselectivity. Studies to ascertain the discrete control elements for the high level of selectivity that model **15** exhibits are ongoing in this laboratory. Since completion of this study, Boger reported a study comparable to the present investigation (Eq 2).[17] The diastereoselectivities observed in the cyclization of tripeptide **17** are in line with our observations which indicate that negligible atropdiastereoselection is observed in these $S_NAr$ cyclizations. We thus conclude that this family of cyclizations do not yet provide an unequivocal solution to the atropdiastereomer issue in the vancomycin skeleton.

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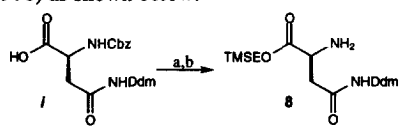
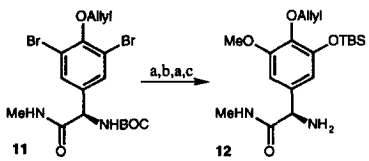
12. Amino acid **8** (Ddm = (4, 4'-dimethoxydiphenyl)methyl) was prepared from *i* (Konig, W.; Geiger, R. *Chem. Ber. 103*, 2041-2051, **1970**) as shown below.




*I* **8**

a) TMSE, DCC, DMAP, DMF, $CH_2Cl_2$, 0 °C, 77% b) $H_2$, Pd/C, EtOAc, EtOH, 90%

13. Amino acid **12** was prepared from the previously described **11** (Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912-8914) as shown below.




**11** **12**

a) *i*-PrMgCl, THF, 0 °C, *n*-BuLi, THF, -78 °C, $B(OMe)_3$, 0 °C, $H_2O_2$, 0 °C - 23 °C, 57% b) MeI, $Cs_2CO_3$, DMF, 0 °C, 93%
a) 64% c) 2,6-lutidine, TBSOTf, $CH_2Cl_2$, 0 °C, 93%

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