Synthesis and Conformational Properties of the M(4-6)(5-7) Bicyclic Tetrapeptide Common to the Vancomycin Antibiotics

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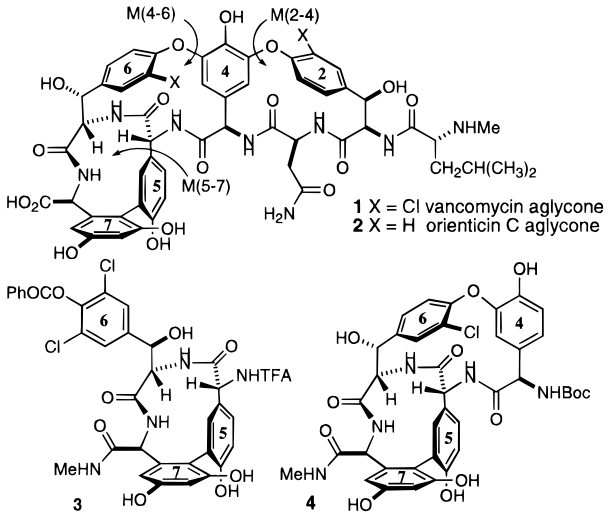
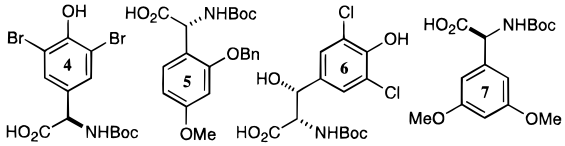
The vancomycin class of antibiotics, exemplified by vancomycin and orienticin C aglycons (**1**) and (**2**), is widely used in the treatment of infections due to methicillin-resistant *Staphylococcus aureus*.[1] The complexity of these structures, the interest in their mode of action,[2] and the emergence of bacterial strains resistant to treatment by this family of antibiotics[3] warrant development of reaction methodology and strategies for their synthesis.[4] In pursuit of this objective, we have developed the relevant asymmetric amino acid syntheses[5] and oxidative bond constructions for the synthesis of the biaryl ether-[6] and biaryl-containing[7] vancomycin-related cyclic tripeptide subunits. In a previous study, we also described the synthesis of the M(2-4)(4-6)[8] bicyclic hexapeptide that was essentially a biaryl bond construction away from the complete tricyclic heptapeptide. However, subsequent investigations have revealed the difficulties in integrating these methods into a synthesis of the tricyclic heptapeptide framework. The purpose of this paper is to describe the first synthesis and conformational analysis of a fully functionalized M(4-6)(5-7) bicyclic tetrapeptide (e.g., **3**).

With the exception of the chlorination pattern on the 6-position β-hydroxytyrosine constituent, all members of the vancomycin family share the M(4-6)(5-7) bicyclic tetrapeptide subunit **3**. Accordingly, our efforts have been directed toward the construction of this moiety followed by attachment of the *N*-terminal tripeptide and closure to the tricyclic heptapeptide related to the vancomycin aglycon. By inspection, there are two approaches to **3** that differ in the ordering of the macrocyclization events. Since prior studies[7] demonstrated that the M(5-7) tripeptide **4** exists as a mixture of biaryl atropisomers (89:11) as well as (5-6) amide isomers (*vide infra*) that complicate further development,[9] attention has been directed toward a synthesis where macrocycle assemblage follows the order M(4-6) → M(5-7).



Amino Acid Subunits. The 4-position amino acid was derived from commercially available D-4-hydroxyphenylglycine, while the remaining residues were synthesized using chiral imide enolate methodology previously developed for this purpose.[5] A differentially protected *o*-phenolic substituent on ring 5 was required to lower the oxidation potential sufficiently to induce *intramolecular* oxidative coupling. To suppress the lability of the *C*-terminal amino acid constituent, the decision was made to carry the carboxyl terminus through the synthesis as the *N*-methyl amide with the expectation that it might be selectively cleaved through a site-selective nitrosation/thermolysis[10] late in the synthesis. Preliminary experiments with derivatives of **3** and **4** suggested that this was a viable option.



Synthesis of M(4-6)(5-7) Bicycle. Sequential peptide coupling from the *N*-methyl amide of the 7-position amino acid was accomplished using conventional conditions (1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), THF, 0 °C → room temperature (rt)) to provide tetrapeptide **5** in good overall yield (Scheme 1). Thallium trinitrate-mediated oxidative cyclization[6] afforded the M(4-6) macrocycle **6** in 54−70% yield. The ring-4 phenol was protected as the acid-stable mesylate to raise the oxidation potential of ring 4 relative to rings 5 and 7 and to differentially protect this phenol for the selective functionalization of ring 4 later in the synthesis. Oxidative cyclization of **6**[7a] afforded the highly strained bicyclic tetrapeptide **8** in 72% yield with 97:3 kinetic selectivity for the *R* (unnatural) atropisomer.[11] Independent experiments indicated that the expected ring-5 benzyl ether in **7** is conveniently cleaved under the reaction conditions, and reaction times were adjusted to effect both steps in one chemical operation. The ring-5 phenol was then excised by conversion of **8** to the derived triflate followed by reductive cleavage[12] to give **9** in 86% overall yield. Removal of the methyl ether protecting groups was followed by atropisomer-

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(4) For reviews of synthetic approaches, see: (a) Evans, D. A.; DeVries, K. D. In *Glycopeptide Antibiotics*; Nagarajan, R., Ed.; Marcel Dekker, Inc.: New York; 1994; pp. 63−103. (b) Rama Rao, A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2168.

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

(6) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912−8914.

(7) (a) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426−6427. (b) Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *34*, 6029−6032.

(8) 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 crosslink between aryl groups of residues *X* and *Y*. Bicyclic moieties will be identified as M(*X*-*Y*)(*Y*-*Z*).

(9) None of the unnatural biaryl atropisomer has been detected in any of the vancomycin glycopeptides, and there is only one example, the antibiotic UK69542, that exhibits 5,6-amide *cis*/*trans*-isomerization, but only in DMSO. Skelton, N. J.; Williams, D. H.; Rance, M. J.; Ruddock, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 3757−3765.

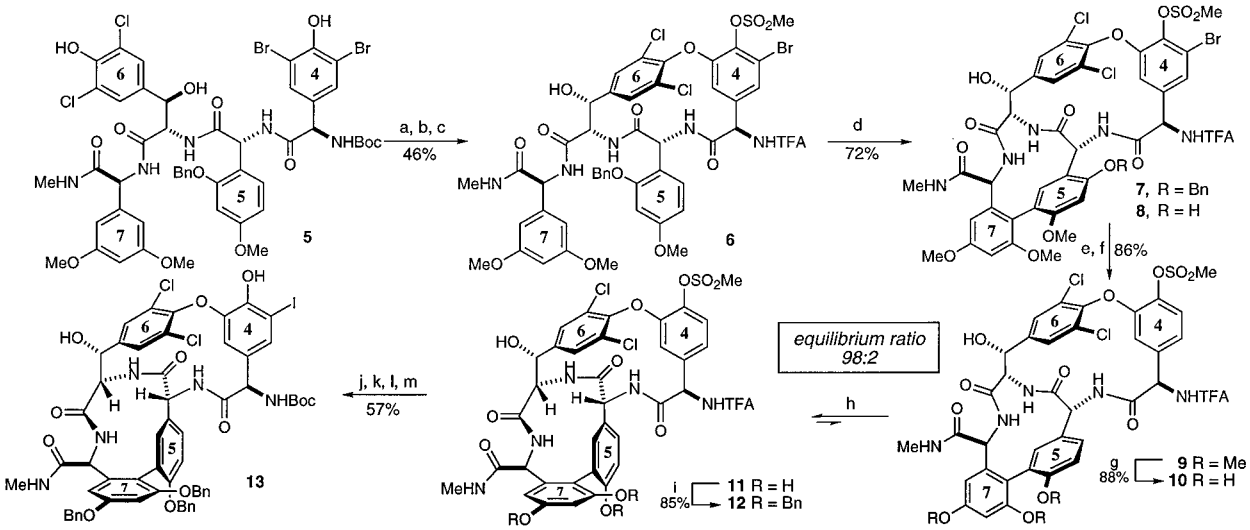
(10) (a) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6008−6010, 6011−6014, 6014−6021. (b) Garcia, J.; Gonzalez, J.; Segura, R.; Vilarrasa, J. *Tetrahedron* **1984**, *40*, 3121−3127.

(11) The selectivity for the *R* (unnatural) atropisomer has previously been demonstrated to be the result of an A(1,3) interaction between the ring-5 *o*-oxygen substituent and the proximal stereogenic center (ref 7b).

(12) Cacci, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541−5544.

S0002-7863(96)04419-8 CCC: $14.00

Scheme 1[a]

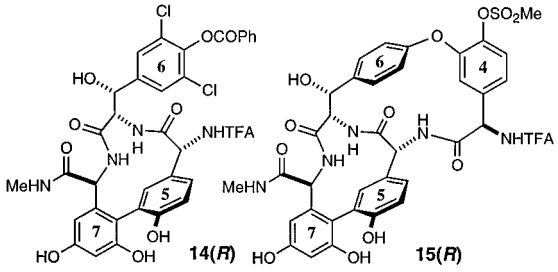


[a] Reagents and conditions: (a) $Tl(NO_3)_3 \cdot 3H_2O$, pyridine, THF/MeOH, 0 °C, then $CrCl_2$, THF/MeOH, 0 °C; (b) $MeSO_2Cl$, *i*-Pr_2NEt, THF, 0 °C; (c) TFA, DMS, CH_2Cl_2, then TFAA, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) VOF_3, $BF_3 \cdot OEt_2$, $AgBF_4$, TFA, 0 °C, then Zn; (e) $PhNTf_2$, K_2CO_3, DMF, 0 °C; (f) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Et_3N, HCO_2H, DMF, 75 °C; (g) $AlBr_3$, NaI, $ClCH_2CH_2Cl$; (h) MeOH, 55 °C, 96 h; (i) BnBr, Cs_2CO_3, Bu_4NI, DMF, 0 °C; (j) $NaBH_4$, EtOH, 0 °C; (k) MeMgCl, THF, 0 °C; (l) Boc_2O, $NaHCO_3$, dioxane/H_2O, rt; (m) NIS, DMF, rt.

ization (MeOH, 55 °C, 55 h) which afforded **11** as a single isomer as judged by ^1H NMR analysis.

Bicyclic tetrapeptide **11**, as the desired *S* (natural) atropisomer, was further modified in anticipation of eventual fragment coupling and final M(2-4) macrocyclization.[13] The ring-4 halogen, lost during removal of the ring-5 triflate, was selectively reinstalled, and a set of protecting groups suitable for the final stages of the synthesis was incorporated. Thus, reprotection of the three phenols as their derived benzyl ethers, achieved without detectable epimerization, afforded bicyclic intermediate **12**. Subsequent reductive removal of the trifluoroacetamide with $NaBH_4$ provided the intermediate amine in 78% yield. Finally, removal of the mesylate and reprotection of the amine as its *tert*-butyl carbamate now allowed for selective iodination of ring 4 with *N*-iodosuccinimide in DMF to afford **13** in 57% overall yield from **12**. This represents the first synthesis of an appropriately functionalized M(4-6)(5-7) vancomycin bicycle which could, in principle, serve as an intermediate in the synthesis of any member of this family of natural products.

Conformational Properties. On the basis of the method of synthesis, the preceding route provides access to both biaryl atropisomers **10** and **11** (Scheme 1). In a series of closely related biaryl-containing cyclic peptides, we have determined the conformational properties and activation parameters for the unnatural → natural, *R* → *S*, atropisomerization (Figure 1). Comparison of the kinetic and equilibrium data on the unnatural atropisomers of peptides **14**[7] and **15** reveals the profound influence of the M(4-6) macrocyclic ring on the M(5-7) macrocycle conformation. The data indicate that the presence of the M(4-6) macrocycle reinforces both the stability of the *S* biaryl atropisomer (>98:2) and the bias for the *cis*-configuration of the (5-6) amide bond that is found in the vancomycin structure. The differences in the rates of atropisomerization are significant. The longer half-life for the isomerization of **15** appears to be derived largely from the entropy of activation for the process which requires a more complex set of bond reorganizations.[14]



property	14 (*R*)→(*S*)	15 (*R*)→(*S*)
biaryl equilibrium ratio	89:11	>98:2
5-6 amide *cis-trans* ratio	78:22	>98:2
E_a, kcal/mol	20.8	21.5
$\Delta H^{\neq}$, kcal/mol	20.3	20.8
$\Delta S^{\neq}$, eu	-13.6	-16.0
$t_{1/2}$ (23 °C), h	29	230

Figure 1. Comparison of conformational equilibria and barriers for biaryl atropisomerization in MeOH.

The integration of this M(4-6)(5-7) bicyclic tetrapeptide into the orienticin C aglycon is presented in the following paper.[13]

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Supporting Information Available: Characterization data for all compounds, NOE data for **9**, **12**, and **15**, and kinetic data for the isomerization to **15** (7 pages). See any current masthead page for ordering and Internet access instructions.

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