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Analogues of Bleomycin: Synthesis of Conformationally Rigid Methylvalerates

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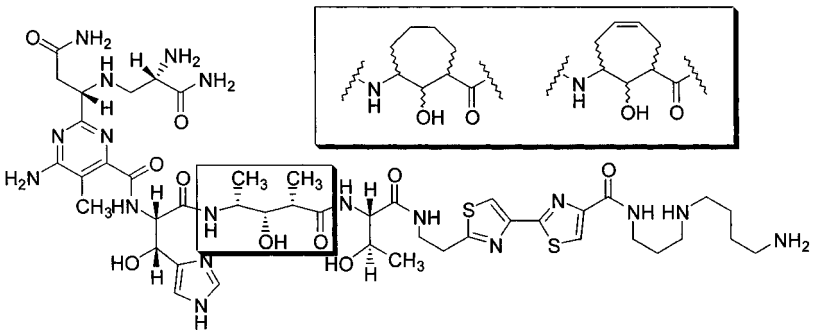
ABSTRACT



Several conformationally rigid analogues of the methylvalerate subunit contained within the linker domain of the antitumor antibiotic bleomycin have been prepared. These compounds have been protected in a fashion suitable for the solid-phase synthesis of bleomycin. Bleomycin congeners containing these analogues should facilitate a more detailed understanding of the nature of the conformational bend that the methylvalerate moiety is thought to impart to the natural product.

The study of peptides containing unnatural β and γ amino acids has been the topic of several recent investigations.[1,2] It has been shown that short peptides composed of β or γ amino acids have well-defined secondary structures, even in relatively polar solvents. Secondary structural predispositions of molecules composed entirely or in part of β or γ amino acid constituents are actually precedented in nature. For example, β-hydroxy-γ-amino acids are a class of amino acids that can be found as structural components of a number of natural products having interesting biochemical and biological properties.[3] Among these are the bleomycin group antibiotics (Figure 1) whose synthesis[4] and mechanism of action[5] have been studied intensively for more than 30 years. Until recently, the role of the linker domain of bleomycin was poorly understood. Recent studies[6] have suggested that

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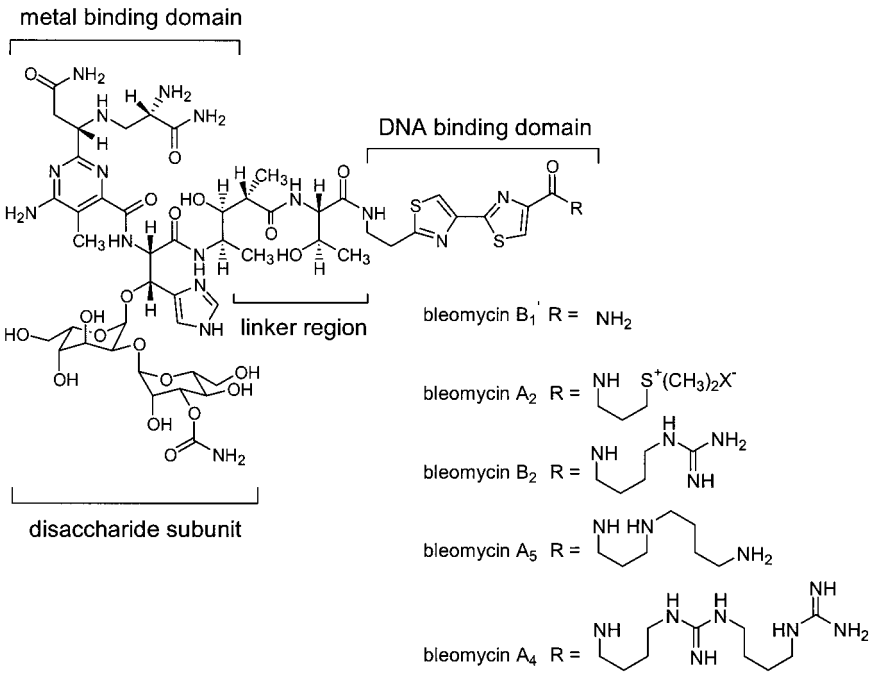


Figure 1. Structure and functional domains of the bleomycin group antibiotics.

the (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (methylvalerate) and *S*-threonine moieties are important for the activity of bleomycin and that they impart a characteristic secondary structure to bleomycin that has a marked effect on the efficiency with which the agent is able to cleave DNA. On the basis of these findings, a set of conformationally rigid methylvalerate analogues has been designed that should facilitate an understanding of the secondary structure imposed by the linker region of bleomycin (Figure 2). These analogues can also be used to construct resin-bound combinatorial libraries of BLM analogues, based on our solid-phase methodology for the synthesis of deglycobleomycins.[7] Scheme 1 details the strategy used for the synthesis of methylvalerate analogues **1**−**8**, as exemplified by the syntheses of **1** and **3**. Boc-protected *R*-allylglycine was converted to the respective Weinreb amide.[8] Reduction of **9** was achieved readily by treatment with lithium aluminum hydride.[9] Due to the well-documented configurational instability of N^{α}-Boc amino-aldehydes,[10] **10** was not stored for longer than 2−3 days at −20 °C. Condensation of **10** with the acyloxazolidinone **11**[11] at −78 °C in the presence of dibutylborontriflate and Hunig's base[12] permitted synthesis of the aldol product **12** in 48% yield. Using Grubbs' catalyst, bis(tricyclohexylphosphine)-benzylidene ruthenium(IV) dichloride,[13] ring closure gave the conformationally constrained intermediate **13**. From this intermediate two routes were pursued. First, the chiral auxiliary could be removed using LiOOH,[6c] followed by conversion of the amine protective moiety from Boc to Fmoc to permit utilization of this amino acid analogue (**3**) in solid-phase bleomycin synthesis. Alternatively, hydrogenation of endocyclic olefin **13** over 5% Pt/C effected conversion to saturated analogue **14**. Removal of the chiral auxiliary from **14**, and conversion of the amine protecting group from Boc to Fmoc, provided analogue **1** in 9% overall yield. It was found that representative derivatives could be utilized readily in the solid-phase synthesis of deglycoBLM analogues.

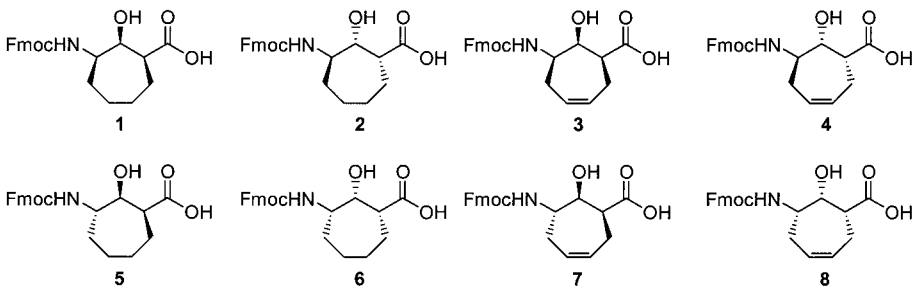
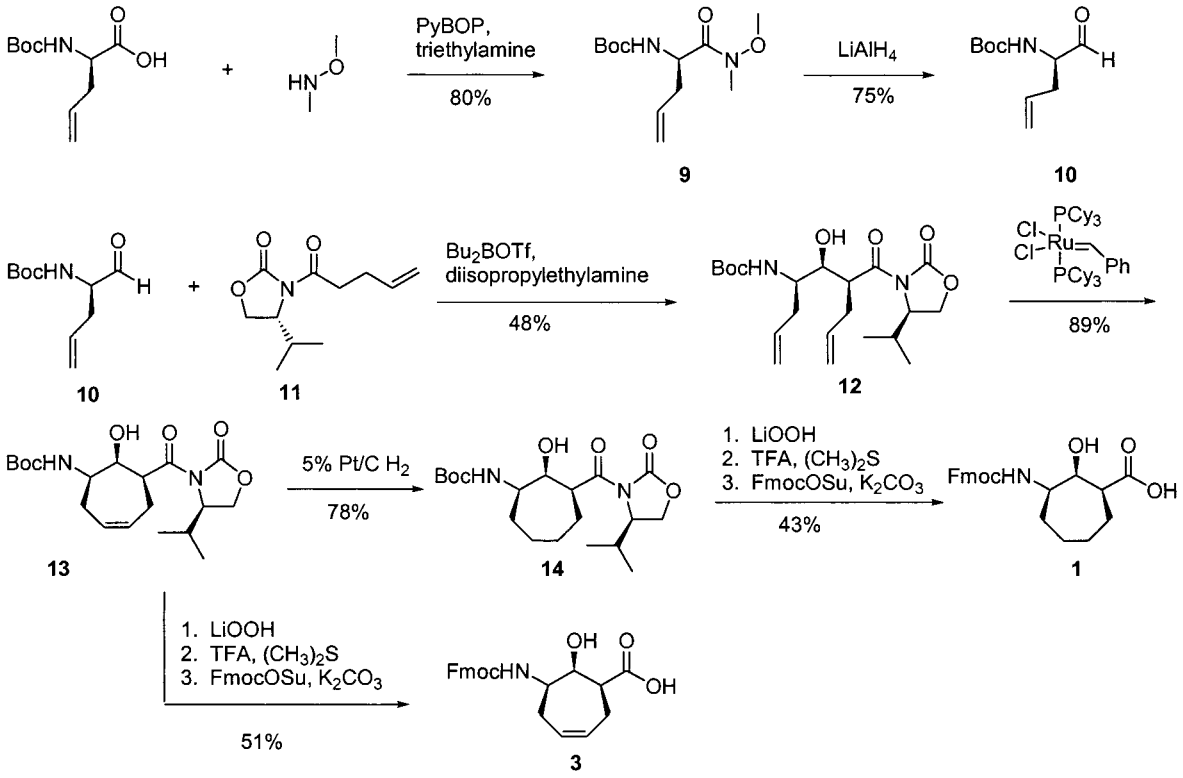


Figure 2. Conformationally rigid methylvalerate analogues synthesized for incorporation into bleomycin congeners.

Scheme 1. Synthesis of Conformationally Constrained Methylvalerate Analogues



Analysis of the conformations of **1**−**8** in the context of an analysis of the conformation of the methylvalerate moiety in bleomycin[6] suggested that **2** has a conformational bias most closely approximating that of the natural product. In fact, the synthesis of a deglycobleomycin A_5 analogue that incorporated **2** within the structure afforded a species capable of relaxing supercoiled plasmid DNA in the presence of Fe^{2+} + O_2, albeit less effectively than deglycoBLM A_5 (data not shown).

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Supporting Information Available: Experimental procedures and full characterization for the compounds shown in Scheme 1 including ^{1}H NMR, optical rotary, and low- and high-resolution mass spectrometry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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