

Synthesis of macrocyclic lactam/lactone derivatives having antimicrobial activity

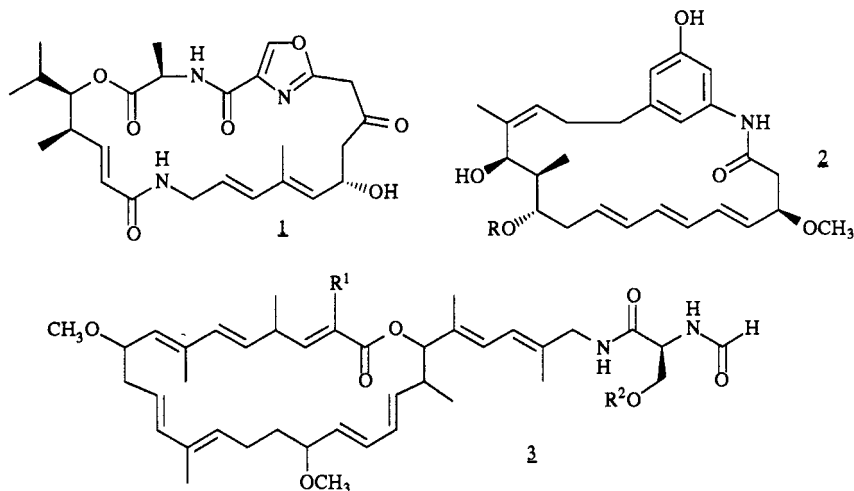
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Abstract: A number of new synthetic methods have been developed that are applicable to several types of antibiotics possessing macrocyclic lactone or lactam structures. These methods have permitted the synthesis of several key subunits of these compounds, and progress has been made on the total synthesis of some of these antibiotics. The type A streptogramin antibiotics have served as a special focus of these efforts. In addition, a combination of microbiological and chemical methods have been investigated for the direct modification of the naturally occurring antibiotics.

Included among macrocyclic compounds of current biomedical interest are the streptogramin antibiotics (1), the trienomycins (2), and the iejimalides (3). These compounds occur naturally as highly functionalized macrocyclic lactam or lactone systems. Madumycin I (1) is a representative member of the type A streptogramin series which comprises several antibiotics having wide-ranging applications. The trienomycins (2) and the iejimalides (3) show potent cytotoxicity in a variety of assays.



The rich structural diversity of these compounds and their important biological activity has prompted us to use them as platforms for the development of new synthetic methods that may ultimately be applied to the total synthesis of these compounds and various analogues for further biomedical investigations. Considerable progress has been made in these efforts. In this brief paper, our results will be exemplified by our most recent progress on the synthesis of the streptogramin antibiotics. A more comprehensive description of our earlier work in this area has been published previously (4).

Our basic strategy for the synthesis of the streptogramin antibiotics is shown for madumycin (Fig. 1). A number of new methods have been developed for the synthesis of the individual subunits shown in this strategy. Considerable attention was initially devoted to the types of functionalized 1,3-dienes and polyenes seen in 1 - 3, and a number of methods were investigated, especially through use of various palladium-catalyzed reactions and new phosphonate reagents (5). Stereoselective routes were developed for the unsaturated acid subunit seen on the left of Fig. 1 through use of asymmetric aldol condensations and other approaches (6). A rhodium-catalyzed reaction of diazocarbonyl compounds with nitriles was developed for the synthesis of 4-carboxy-1,3-oxazole derivatives as seen in all of the type A streptogramin antibiotics (7). Titanium- and zirconium-catalyzed lactamization reactions were also investigated which

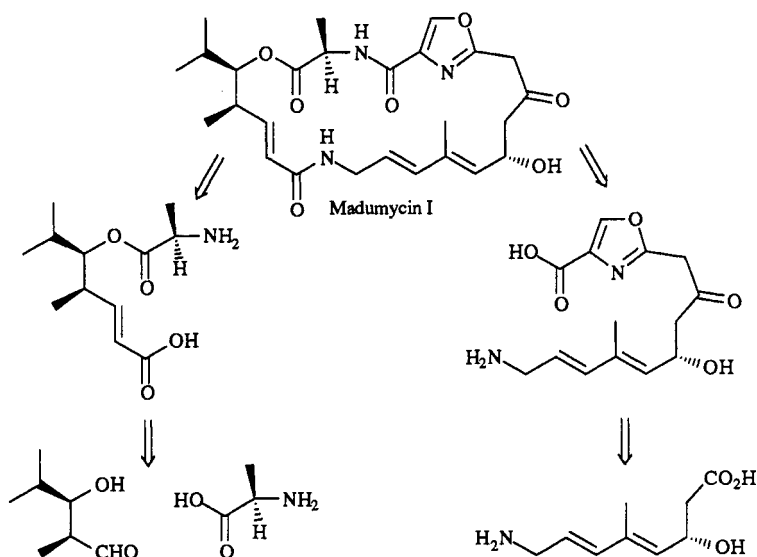


Fig.1. Strategy for the synthesis of madumycin I

may be applicable to the macrocyclization step that will be required at the end of the synthesis (8). With these several new methods in hand, we have now made considerable progress in implementing this basic strategy for the synthesis of the streptogramin antibiotics. These and related methods are also being applied in the synthesis of the trienomycins and the iejimalides.

The entire right-hand portion of madumycin I has been obtained as shown in Fig. 2 in a form (9) suitable for further transformation into the antibiotic (9). One key step is an Evans-type asymmetric aldol condensation of the aldehyde 4 to obtain the adduct 5 under conditions developed by Thornton (10). The bromomethyloxazole 7 is obtained through our $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of $\text{N}_2\text{C}(\text{CO}_2\text{Et})\text{CHO}$ with bro-

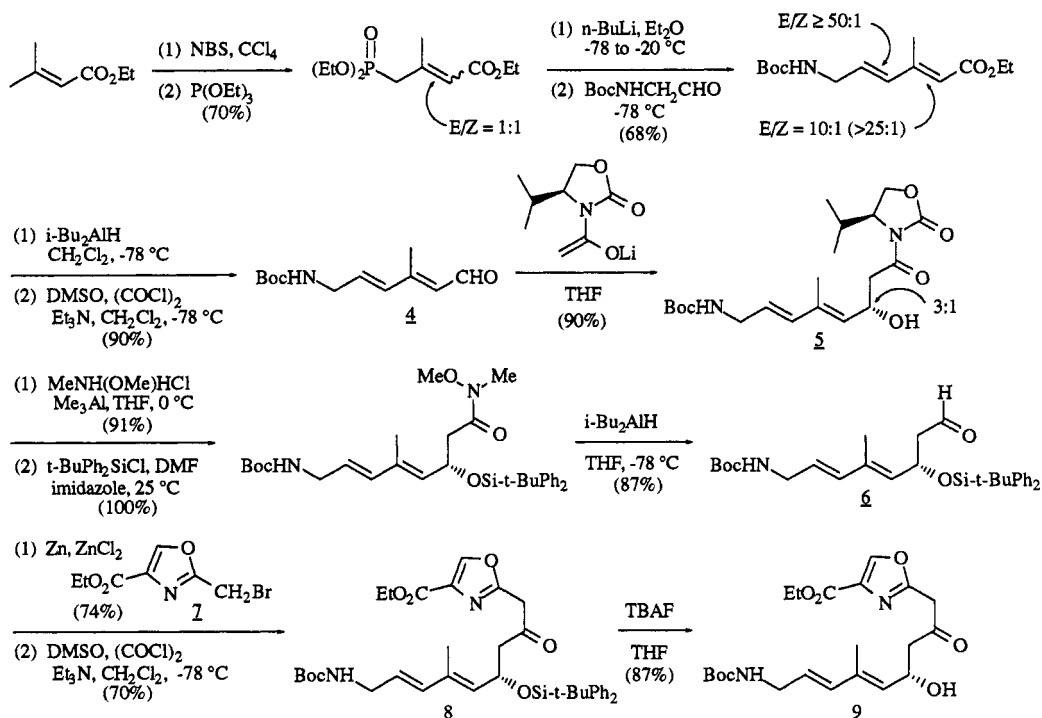


Fig. 2. Synthesis of the right-hand portion of the type A streptogramin antibiotics

moacetonitrile (7). A modified Reformatsky reaction of 7 with the aldehyde 6 provides the adduct 8 which upon further simple manipulations provides the major streptogramin subunit 9.

With both the left-hand and the right-hand portions of madumycin I available, studies have now begun to join the two subunits. The results of a model study are depicted in Fig. 3. The model carboxylic acid portion (10) is again obtained through use of our previously described oxazole chemistry (7). The previously obtained left-hand subunit 11 (6) is coupled with a protected D-alanine derivative to give the aminoester 12. Removal of the *N*-Boc group and coupling with the model acid subunit 10 followed by Swern oxidation (11) provides the madumycin model compound 13.

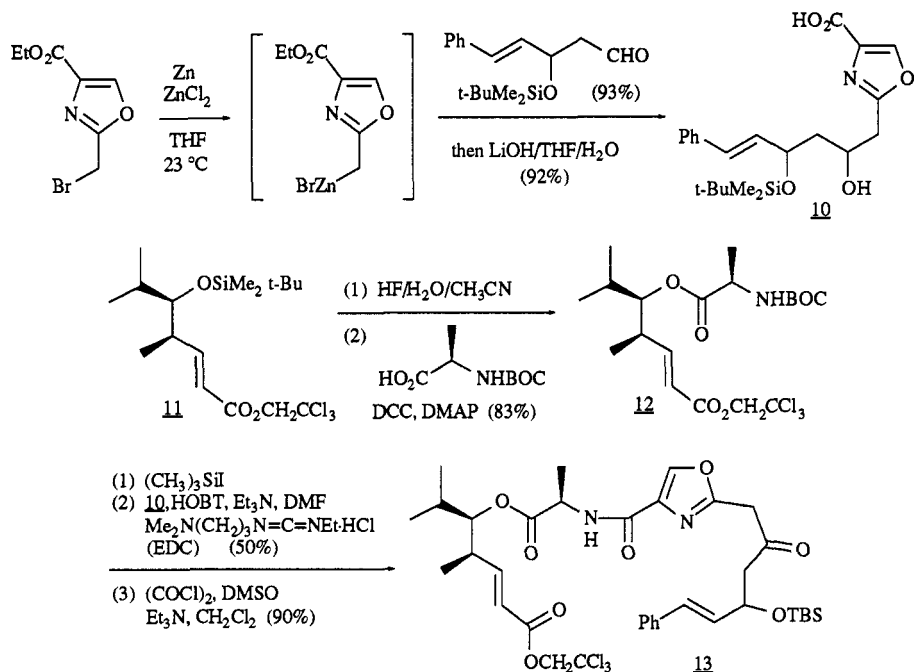


Fig. 3. Model study for streptogramin subunit assembly

The initial attempts at effecting the amide coupling of 10 and 12 have proceeded in only modest yields, but after improved conditions are found, the coupling will be extended to appropriate derivatives of the acid subunit 8 as proposed in Fig. 4. A key remaining step will be the cyclization of madumycin pre-

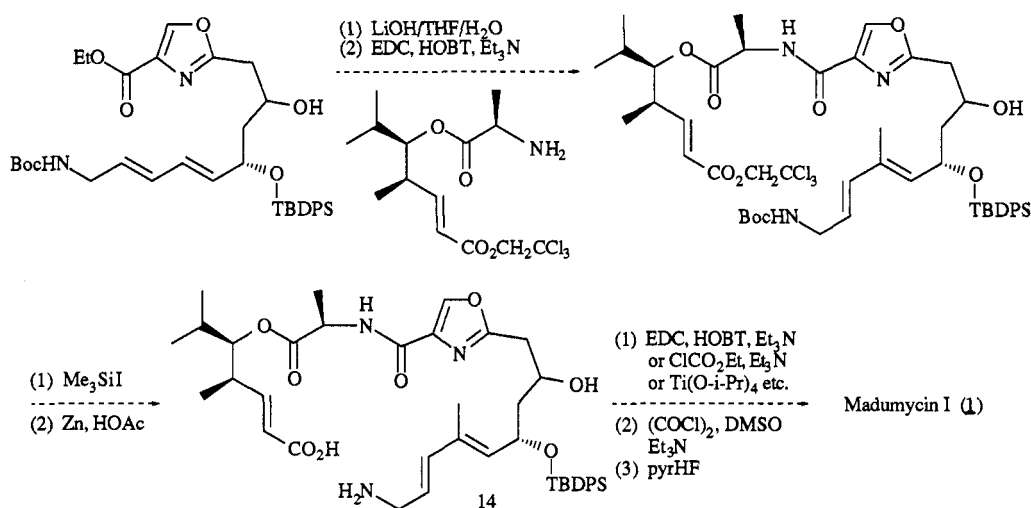


Fig. 4. Proposed completion of the synthesis of madumycin I

cursor 14. Determination of appropriate conditions will doubtless require detailed experimentation. Many variations of this end game can be envisioned, including different protecting group schemes and different orders of forming the ester and amide linkages of the macrocyclic system.

In addition to these approaches to the total synthesis of macrocyclic antibiotics, we are investigating their direct modification by a combination of chemical, enzymatic, and microbiological methods for the purpose of obtaining modified compounds for use in further biological studies. For example, we have investigated the bacterial strain *Actinoplanes utahensis* which is resistant to virginiamycin M₁, another of the type A streptogramin antibiotics. Upon exposure to a growing culture of *A. utahensis*, virginiamycin M₁ is converted into several inactive derivatives, two of which have been isolated and characterized as compounds in which the pentadienyl alcohol portion of the structure has been modified (12). On the other hand, direct chemical modification of the streptogramin antibiotic system has provided a number of new derivatives that retain strong antibiotic activity. These compounds are being studied from the point of view of developing antibiotics having improved therapeutic properties and also with the aim of using them as probes of the biological mechanism of action of these macrocyclic compounds.

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