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Stereoselective Synthesis of Precursors of the Macrolide Antibiotics *via* Reactions of Sulfur Ylides with Chiral Aldehydes

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Abstract: Reactions of stabilized sulfur ylides with chiral aldehydes provided epoxides with high stereoselectivity. The opening of the resulting epoxides with lithium dimethyl cuprate gave 2-methyl-3-hydroxy amides which represent potentially useful building blocks for the synthesis of macrolide natural products. These amides were transformed into chiral aldehydes, with a methyl group in the α-position, and were reacted, in a iterative process, with a sulfur ylide reagent to give, in high yield and stereoselectivity, the epoxides with the stereochemistry according to Felkin-Ahn control. Finally, opening of the epoxide with the Gilman reagent provided a compound with four stereocenters occurring in the macrolide-type of natural products.

Keywords: Macrolide antibiotics, sulphur ylides, epoxides.

Macrolides comprise a wide class of natural products with important biological activities produced by bacterial and marine sources.[1] The molecular structures of these compounds with the presence of multiple asymmetric centers and a macrocyclic lactone, together with their interesting biological properties as antibiotics or antitumor agents, has prompted intense research activity in chemistry and biology for two decades.[2] Efforts directed towards their synthesis have led to an impressive development of new asymmetric synthetic methodologies which are currently of general use in organic synthesis.[3] These asymmetric methods were designed specifically for the synthesis of subunits containing three or four stereocenters[4] (commonly named stereotriads and stereotetrads respectively) which are common structural motifs in these natural products. Our contributions to the chemistry of sulfur ylides as related to the carbohydrate field have found synthetic applications in the synthesis of C-furanoses and C-pyranoses[5] with biological activity, [6] and in the synthesis of useful building blocks by opening of epoxide rings with different nucleophiles in a regio- and stereoselective manner.[7] As a continuation of these studies, we envisioned the opening of oxirane rings with lithium dimethyl cuprate would provide a method for the synthesis of macrolide fragments. Therefore, despite many efficient solutions to overcome this synthetic problem having been reported so far, we wish to report our results on the stereoselective synthesis of tetrads of type A, by using sulfur ylides which react stereoselectively with chiral aldehydes to form epoxides. In particular, we describe the synthesis of fragment A, which occurs in the macrolides aplyronine A (C7-C10 fragment), a potent antitumor macrolide[8] and in streptovaricin U (C4-C7 fragment), an important ansamycin antibiotic.[9]

For this synthesis, the epoxyamide **1** was treated with lithium dimethyl cuprate to obtain alcohol **2**[10] in a 90% yield. Protection with TBSCl in DMF and reduction of the resulting silyl ether **3** with Super-hydride gave the alcohol **4**, which was oxidized under Swern conditions to the aldehyde **5** in 89% overall yield. Direct reduction of **3** to the aldehyde **5** with Red-Al was attempted, however elimination of the silyloxy ether occurred to produce the corresponding α,β-unsaturated aldehyde. On the other hand, the amide **8**, obtained by the same synthetic sequence from epoxyamide **6**, was reduced with DIBAL-H[11] to the aldehyde **5** in a 89% yield, but the steps to obtain **8** (condensation, opening and protection) were low yielding. The aldehyde **5** was reacted with sulfur ylide **9** to obtain the epoxyamide **10** and its (2*S*, 3*R*)-isomer in a 71% yield and high stereoselectivity

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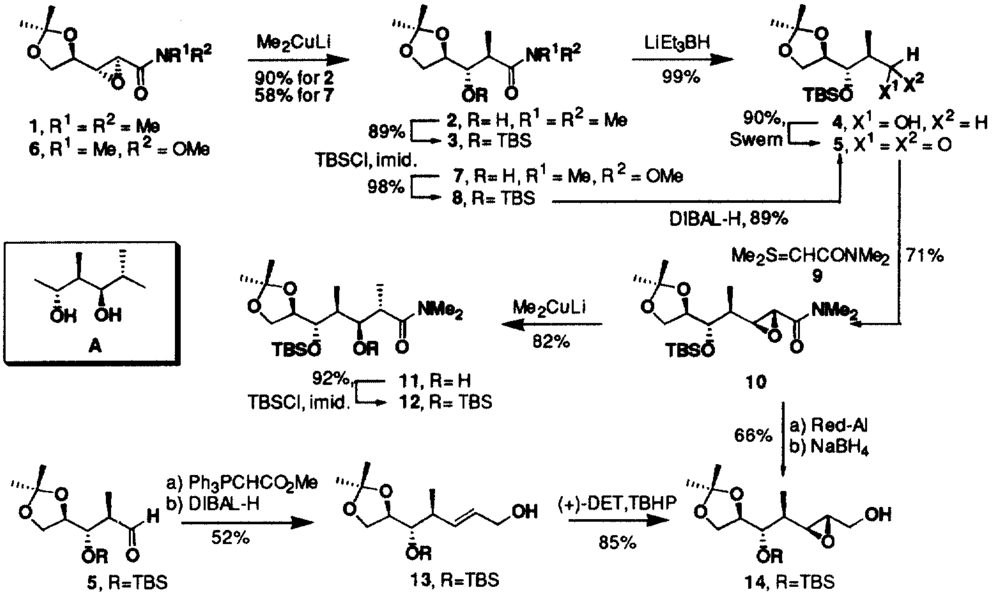
(85:15). These epoxides were separated by chromatography on silica gel and the major epoxide **10** treated with lithium dimethyl cuprate to obtain **11** which was protected as the silyl ether **12** in 75% overall yield (Scheme 1). The high stereoselectivity of epoxide **10** formation can be explained according to the Felkin-Ahn model[12] with many examples in the literature using other nucleophiles.[13] On the other hand, the stereochemistry at C-2 and C-3 of **10** was confirmed by correlation with **14** (See in scheme 1).



Scheme 1. *Stereoselective synthesis of tetrad containing product 12.*

In conclusion, we report a stereoselective synthesis of compound **12**[14] which contains four stereocenters using sulfur ylide reactions with chiral aldehydes. These reactions followed Felkin-Ahn control with the generation of two new stereocenters and the formation of an epoxide. In the present paper, this epoxide was used for the synthesis of macrolide building blocks, but other synthetic applications can be envisioned and further investigations are currently in progress.

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14. All new compounds exhibited satisfactory spectroscopic and analytical and/or accurate mass data.