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Efficient and Stereoselective Access to the Polyol Fragment C9−C16 of Ansamycin Antibiotics

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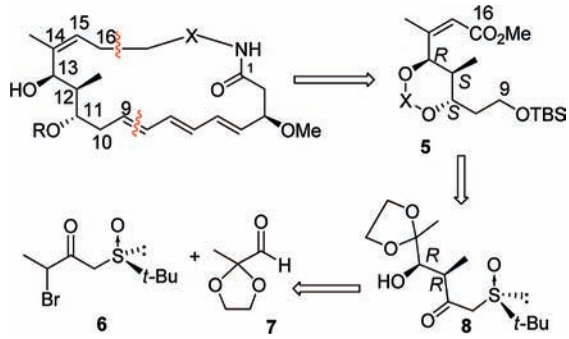
ABSTRACT



Efficient synthesis of the fragment C9−C16 bearing the *anti,syn* stereotriad of ansamycin antibiotics is described. Key steps for controlling the configuration of the three stereogenic centers involve a stereoselective Reformatsky-type reaction followed by a diastereoselective reduction of a *β*-ketosulfoxide.

Isolation from microbial sources (*Streptomycines* generally) and structure elucidation of an important class of complex macrolactam antibiotics, the ansamycins (mycotrienins),[1] has been reported in the last two decades. These secondary metabolites are very attractive because of their powerful biological activity, for example, antibacterial, antifungal, or antitumor properties. The ansamycin class of natural products includes mycotrienins (or ansatrienins) I (**1a**) and II (**2a**),[2] trienomycin A (**3a**),[3] cytotrienin A (**2b**),[4] and thiazinotrienomycin (**4a**)[5] (Figure 1). More recently, quinotrierixin (**1a** with a SCH_3 on the quinone ring), demethyltrienomycins A and B, and demethyltrienomycinol (without a methyl at C14) were isolated from the culture broth of *Streptomyces* species

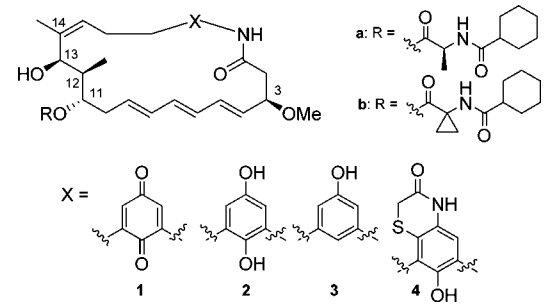


Figure 1. Members of the triene−ansamycins group.

(1) Wrona, I. E.; Agouridas, J.; Panek, J.S. C. R. *Chimie* **2008**, *11*, 1483.
(2) Sugita, M.; Hiramoto, S.; Ando, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 799, and references cited therein.
(3) (a) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Omura, S. *J. Antibiot.* **1989**, *42*, 479. (b) Blagg, B. S.J.; Peng, W. *Org. Synth.* **2006**, *8*, 965.
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PAE37 and were found to have cytocidal activity against HeLa cells.[6] All these compounds are characterized by a 21-membered cyclic lactam including a (*E*,*E*,*E*)-triene and four chiral centers. A series of SAR studies were performed to screen the most active part of the triene ansamycins. These results indicate that the stereotriad C11−C13, the CH_3 group at C14, and the OCH_3 group at C3 are essential.[6,7]

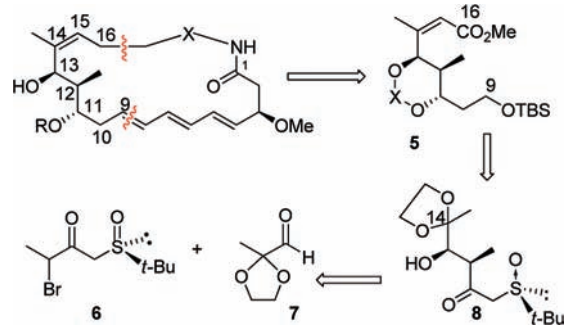
Absolute and relative stereochemistry of the stereogenic centers of these ansamycins have been determined or assigned by Smith and co-workers through careful degradative and spectroscopic methods.[8] To date, only Smith, Panek, and very recently Hayashi have reported the total synthesis of trienomycin,[9] mycotrienin,[10] thiazinotrienomycin,[11] and cytotrienin A[4b] as well as the macrocyclic core of cytotrienin.[12] More recently, Kirschning *et al.* reported a multigram scale synthesis of the ansatrienol derivative.[13]

In relation with a program devoted to asymmetric synthesis mediated by sulfoxides,[14] we have recently described a highly stereoselective Reformatsky-type reaction of chiral non racemic α-bromo-α′-sulfinyl ketones with aldehydes in the presence of SmI_2.[15]

In this paper, we describe the synthesis of the C9−C16 unit **5** of ansamycins bearing the *anti*,*syn* stereotriad C11−C13.

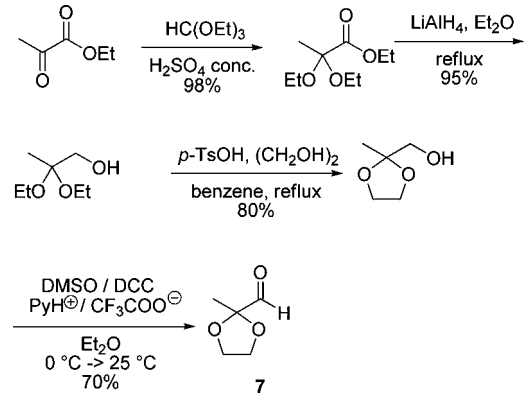
One synthetic key issue of the ansamycin is the stereocontrol of the stereotriad C11−C13. Using our Reformatsky-type reaction between α-bromo-α′-sulfinyl ketone **6** and the aldehyde **7** as well as the well-established DIBALH or Lewis acid/DIBALH diastereoselective reduction[16] of the corresponding *β*-keto sulfoxide **8**, we report a highly stereoselective access to the stereotriad (Scheme 1). To facilitate

Scheme 1. Retrosynthesis toward the C9−C16 Unit **5** of Ansamycin



elucidation of mechanism of action of ansamycins, the development of a methodology allowing the synthesis of some stereoisomers of the stereotriad is highly important. With our methodology, four diastereomers of the stereotriad could be easily accessible depending on the absolute configuration of the sulfinyl moiety.

Scheme 2. Synthesis of the Aldehyde **7**



The synthesis of the aldehyde **7**[17] depicted in Scheme 2 began with the formation of the diethyl acetal of ethyl pyruvate in the presence of triethyl orthoformate in concentrated sulfuric acid. Reduction of the ester moiety with $LiAlH_4$ followed by transacetalization in the presence of diethylene glycol afforded the dioxolane derivative which was then submitted to a Moffatt-type oxidation to give the aldehyde **7** in 52% overall yield.

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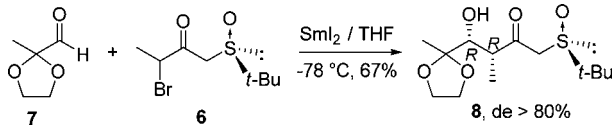
We applied our SmI_2-promoted Reformatsky-type reaction between α-bromo-α′-*tert*-butylsulfinyl ketone **6** synthesized as previously reported[15a] and the aldehyde **7**, and we obtained the Reformatsky adduct **8** in excellent *syn* diastereoselectivity[18] and good yield (Scheme 3).

Scheme 3. Reformatsky-Type Reaction between **6** and **7**



To confirm the absolute configuration of the major stereoadduct, after chromatographic separation and crystallization, suitable crystals were obtained and the structure (3*R*,4*R*)-**8** was determined by X-ray analysis (Figure 2).

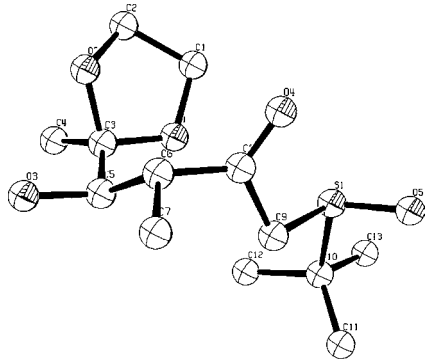


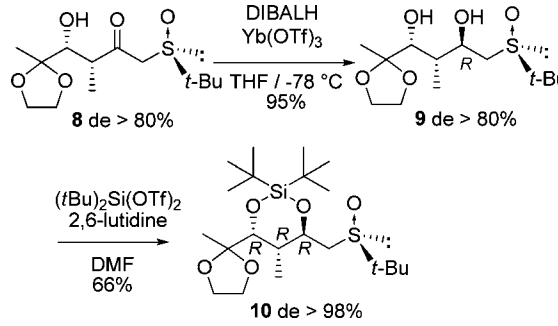
Figure 2. ORTEP plot of (3*R*,4*R*)-**8**. Hydrogen atoms are omitted for clarity.

In order to obtain the (2*R*,3*R*,4*R*,*RS*) stereotriad of ansamycins, we performed the diastereoselective reduction of **8** with DIBALH in the presence of $Yb(OTf)_3$ followed by protection of the resulting 1,3-diols by a silylated bridge[19] giving after flash chromatography the enantiopure (2*R*,3*R*,4*R*,*RS*)-**10** [$[\alpha]^{20}_D = +34.8$ (*c* 0.45, $CHCl_3$)] whose stereochemical assignment was controlled by NOESY experiments (Scheme 4).

It should be pointed out that the stereoisomer (2*S*,3*R*,4*R*,*RS*) was easily obtained by reduction with DIBALH only, and both diastereomers (2*R*,3*S*,4*S*,*SS*) and (2*S*,3*S*,4*S*,*SS*) could be efficiently synthesized using the enantiomer (*S*) of the sulfinyl moiety.

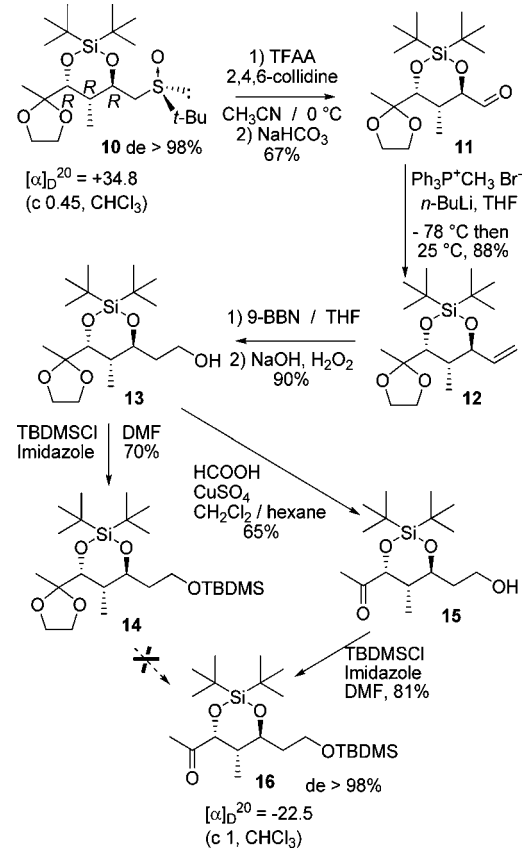
Treatment of the enantiopure compound **10** under Pummerer conditions[20] afforded after flash chromatography the

Scheme 4. Obtaining the *Syn-Anti* Stereotriad



aldehyde **11**, which was then submitted to a Wittig reaction with $Ph_3P{=}CH_2$ in THF to give the corresponding olefin **12** in 88% yield. Further regioselective hydroboration of **12** with 9-BBN in THF followed by treatment with NaOH and H_2O_2 afforded the alcohol **13** in 90% yield which was protected as a silylated ether **14** (Scheme 5).

Scheme 5. Synthesis of the Methyl Ketone **16**



In order to obtain the methyl ketone **16** which will be transformed into the vinylic ester **5**, we had to perform a selective deprotection of the dioxolane **14** in the presence of the silylene bridge. The first attempt using PPTS in acetone and water afforded only the deprotection of the TBDMS

(18) Determined by proton NMR analysis of the product on the basis of our previous results.[15]

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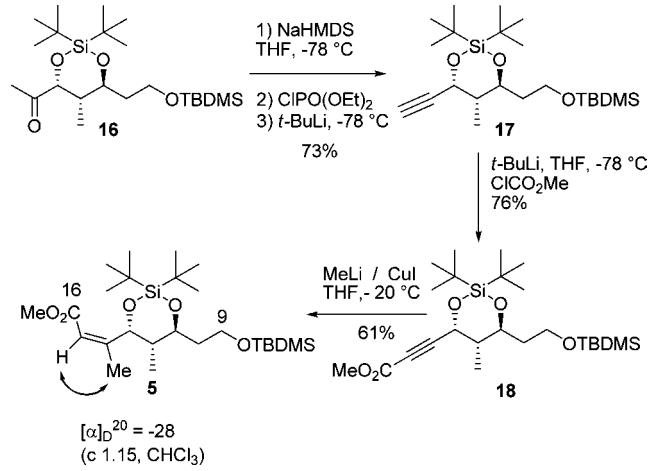
ether. Therefore, we tried the deprotection on the free alcohol **13** with PPTS in acetone/water at reflux or with acetic acid/water at room temperature, but no reaction occurred. Nevertheless, more acidic conditions such as *p*-toluenesulfonic acid in water at room temperature or use of CAN[21] led to the deprotection of the dioxolane as well as the deprotection of the silylated bridge. Finally, formic acid in presence of $CuSO_4$[22] in a mixture of CH_2Cl_2 and hexane (1/1) afforded the methyl ketone **15** in 65% yield whose primary alcohol was then silylated to give **16** (Scheme 5).

Starting from the methyl ketone **16**, we used the Smith[8b] procedure to obtain the methyl-substituted double bond with *Z* selectivity. The kinetic enolate of **16** was obtained by treatment with sodium bis(trimethylsilyl)amide and trapped with diethyl chlorophosphate to give the corresponding enol phosphate. Elimination induced by *t*-BuLi provided the terminal alkyne **17** in 73% yield. Treatment of **17** with *t*-BuLi and methyl chloroformiate afforded **18**. Finally, methyl cuprate (Me_2CuLi) addition was performed in THF at −20 °C giving in 61% yield the desired *Z* olefin **5**. The stereochemistry of the double bond was controlled by NOESY experiments considering the interaction between H15 and the adjacent methyl group (Scheme 6).

In conclusion, our strategy based on the stereoselective Reformatsky-type reaction followed by the reduction of *β*-ketosulfoxides has been exemplified by the enantiopure synthesis of the stereotriad C11−C13 of ansamycin antibiotics. The asymmetric synthesis of C9−C16 fragment **5** has been achieved in 11 steps and an overall yield of 6%. Total synthesis of trienomycinol **3** (with R = H) is currently underway in our laboratory.

Scheme 6. Synthesis of the *Z* Olefin **5**



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Supporting Information Available: Experimental procedures and data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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