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Synthesis of the 'Enediyne' antibiotic esperamicin-A_1, and novel analogues for tumor targeting

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Abstract: Two strategies for the construction of the calicheamicin/esperamicin core structure are presented. The first is based upon the 2,3-Wittig ring contraction of a 13-membered macrocycle **3** (X = CH_2 or NCO_2Me). The aza 2,3-Wittig rearrangement of **3** (X = NCO_2Me) is of particular interest, as it can potentially lead to compound **6** in one operation. The objective in the second enediyne synthesis project is to obtain both enantiomers of the esperamicin A_1 aglycone (esperamicinone) via a highly concise route using the 3,4-cyclohexylidene derivative **17** of (-)-quinic acid as a common starting synthon.

The discovery of the "enediyne" antitumor antibiotics calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**) (Figure 1) has provided both new possibilities for the treatment of cancer, and a challenge to synthetic chemists to construct the highly strained bicyclo[7.3.1]tridecenediyne unit present as a common feature in the aglycone portion of each molecule. Already, the total synthesis of both molecules have been independently achieved by the Nicolaou and Danishefsky teams, and further work by other groups is leading in the same direction. In our laboratory, two distinct approaches to the synthesis of the aglycone portion of **1** and **2** are under study.

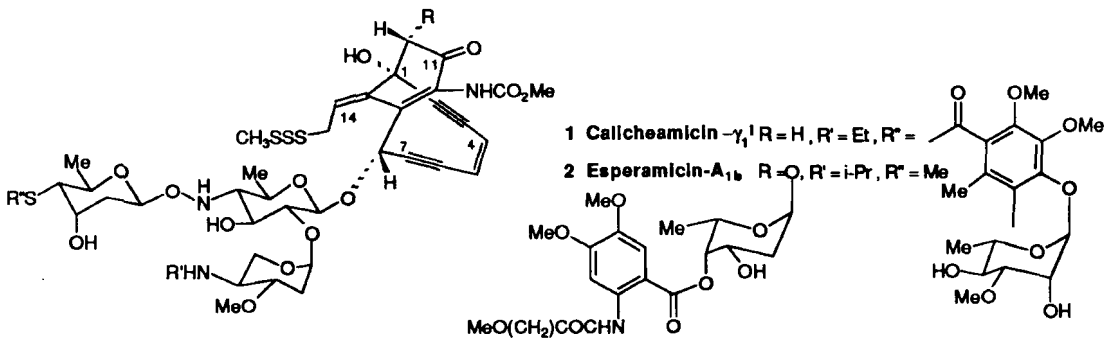


Figure 1

The first approach is based upon the idea of constructing a larger, readily accessible, and less strained, 13-membered enediyne which would undergo a 2,3-Wittig ring contraction to the strained 10-membered bicyclic system of the natural products (Figure 2).[1] Exploratory work to access the model compound **3** (X = CH_2) under 2,3-Wittig conditions revealed the incompatibility of the enediyne system in **4** with the organolithium base conditions employed (competing monoelectron transfer processes). However, the corresponding "dihydro" derivative of **3** (X = CH_2), lacking the $\Delta^{4,5}$ double bond did undergo efficient ring contraction, validating our strategy. Furthermore, when a suitable leaving group was

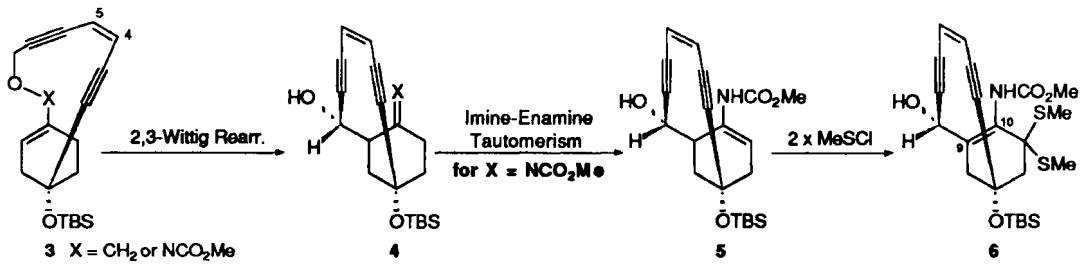


Figure 2

present at C-4 in the rearranged dihydro product, simple β-elimination under mild base conditions to give enediyne **4** could be effected. This bicyclic enediyne undergoes Bergman cyclization spontaneously at room temperature.

More recently, this project has evolved toward a study of a new "aza" version of the 2,3-Wittig rearrangement. Applied to compound **3** (X = NCO_2Me) (Figure 3), ring contraction would ultimately lead to the enamine intermediate **5**, which, on *in situ* reaction with two equivalents of MeSCl, would provide access to the $\Delta^{9,10}$ double bond isomerized product **6**. Thus, in essentially one operation, the C-10 urethane unit, the bridgehead double bond, and the C-11 keto functionality (in its protected dithioketal form) could be correctly positioned in compound **6**. To implement this strategy, the dihydro macrocycle **10** was prepared from the dilithio derivative of 1,5-hexadiyne and the monoketal **7** of cyclohexan-1,4-dione. N-Carboxymethylation of this intermediate has proven to be unexpectedly difficult. However, the N-acetyl and N-trifluoroacetyl derivatives **11** and **12** can be prepared in good yield. It is clear from the isolation of dimer **13** that in the reaction of acetamide **11** with LiTMP both amide enolate formation and deprotonation at the C-8 propargyl center occurs . Furthermore, in this reaction, and the reaction of trifluoroacetamide **12**, the *in situ* generated anion at C-8 fragments via a β-elimination process producing an aldehyde intermediate (cf. **14**), rather than through the desired 2,3-Wittig pathway. However, this may not pose a problem, as condensation of the enamine and aldehyde components in **14** under basic conditions can similarily lead to formation of the desired 10-membered bicyclic enediyne system. Experimentally, treatment of aldehyde **14** with NaH results (for the moment) in preferential formation of the decarbonylated product **15**.

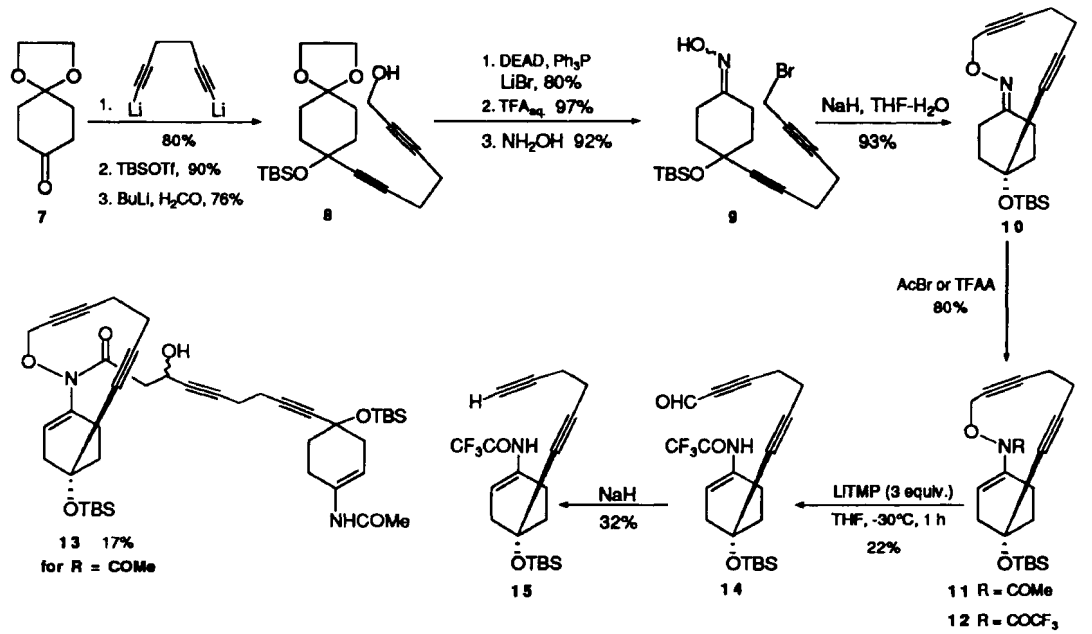
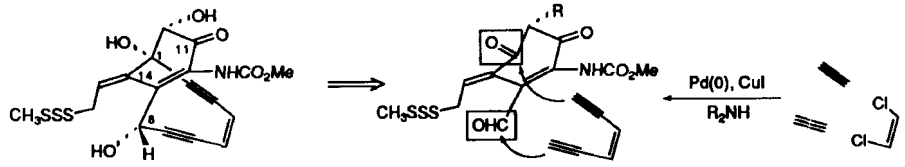


Figure 3



Esperamicinone 16 **Figure 4**

In the second enediyne synthesis project our objective has been to obtain both enantiomers of the esperamicin A1 aglycone (esperamicinone **16**) via a highly concise route using the 3,4-cyclohexylidene derivative **17** of (-)-quinic acid as a common starting synthon. This work was inspired from the information illustrated in Figure 4. Through a series of simple steps compound **17** (Figure 5) was converted to the alcohols **18** and **19**. Dess-Martin oxidation of alcohol **18** provides (-)-**21**, whereas, ketal isomerization in **19** and oxidation of the hydroxyl group in **20** gives (+)-**21**. The presence of the *cis* ketal moiety in **21** guarantees introduction of the acetylene function and subsequent construction of the enediyne system on the opposite face of the molecule. At this point the ester group in **22** was reduced and reoxidized giving aldehyde **23** in high yield. Cyclization of the C-desilylated derivative of **23** under KHMDS conditions proved efficient. However, subsequent attempts to effect O_1-TBS deprotection revealed the facility of the reverse reaction wherein the cyclized enediyne **24** is reconverted to the ring opened aldehyde form. Elaboration of ketone **26** was thus made using the O_8-methyl enediyne **25**. Rather than explore conditions for activation of the C-13 methylene center in **26**, with regards construction of the allylic trisulfide system, we decided to study introduction of the urethane unit at C-10. Substitution of this center by a nitrogen substituent using $Ph_2S{=}NH$ gave aziridine **27**. It is also noteworthy that during this transformation migration of the O_1-TBS group to the adjacent C-12 hydroxyl group occured. Aziridine **27** was readily converted to its carbamate derivative **28**, in preparation for aziridine ring opening. At present, our efforts are being directed towards obtaining the α,β-unsaturated ketone **29** from this N-carbomethoxylated aziridine intermediate.

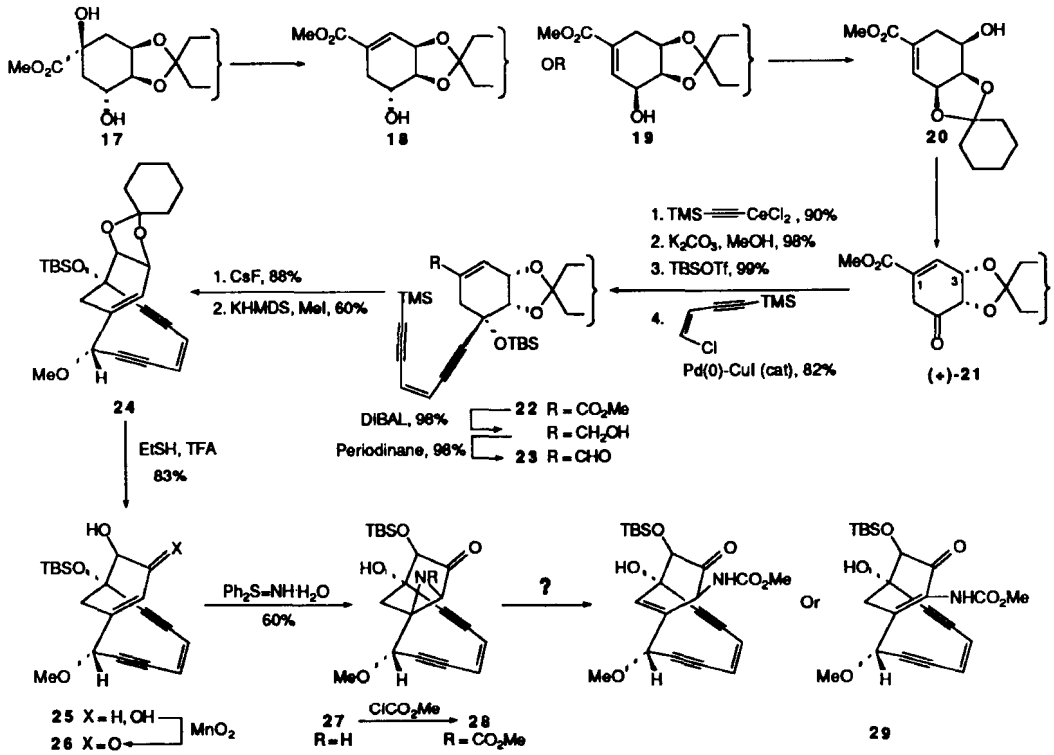


Figure 5

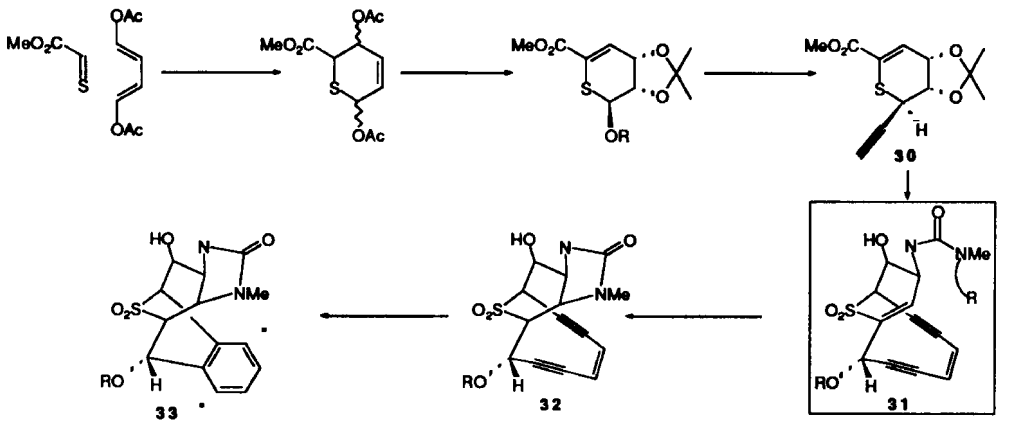


Figure 6

The experience gained during this enantioselective approach to esperamicinone from (-)-quinic acid is also being put to use to achieve the synthesis of the novel esperamicin analog **31** from the thioshikimic acid derivative **30** (Figure 6). Kirby *et al.*[2] have recently shown that the thioshikimic acid system can rapidly be assembled via a thio Diels-Alder reaction. In compound **31**, it is anticipated that the sulfone group at C-13 will activate the bridgehead double bond with respect to Michael addition of the nitrogen atom of the urethane group attached to the C-11 hydroxyl group. It is noteworthy that in compound **31**, R represents a tumor vectoring device (monoclonal antibody, ...), and activation of the molecule toward formation of the cyclic urethane **32** and subsequent Bergman cyclization to **33** will be achieved by cleavage of the tethering arm joining the urethane nitrogen to this vectoring device.

References:

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