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Synthesis of a new lactenediyne scaffold equipped with three handles

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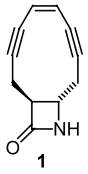
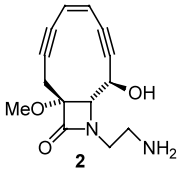
Abstract—A new lactenediyne scaffold endowed with three attachment points for substituents (handles) was synthesized. This scaffold was designed in order to be used to prepare libraries of compounds possessing a tethered nucleophile, an activating substituent, and DNA-complexing substructures.

Natural enediynes are among the most powerful antitumor compounds ever found.[1] Their structural complexity, however, makes the development of simpler analogues possessing a similar reactivity profile highly desirable.[2] In particular, the design of simple enediyne prodrugs provided with an easily controlled triggering mechanism is of paramount importance.

We[3–7] and others[8] have recently introduced a new family of artificial enediynes, called 'lactenediynes', and characterized by the fusion of a 10-membered enediyne moiety with a β-lactam. Among them, those with a *trans* fusion between carbons 3,4 of the lactam and carbons 8,9 of the enediyne ring (basic structure **1**) have emerged by now as the most promising, thanks to their exceptional thermal stability.[3,4,6,7]



1



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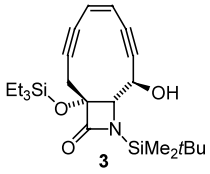

3

These compounds, compared to monocyclic 10-membered enediynes,[9] are strongly stabilized against Bergman cycloaromatization by the presence of the *trans* fused four-membered ring. While opening of the β-lactam does not occur at all under physiological conditions, we have already demonstrated that a tethered nucleophile may induce intramolecular opening of the azetidinone,[10] unlashing the reactivity of the enediyne moiety.[7] Actually, amine **2** was able to induce single breaks at concentrations as low as 4×10^{-5} M on plasmid DNA. Protection of the amine with an enzymatically removable protection can therefore be the correct answer to the quest for selective prodrug activation.

Improvements both in terms of overall activity and of double strand break percentages are however still needed. Toward this goal it seemed to us very important to have further attachment points (handles) where to attach suitable activating substituents (in order to modulate the rate of intramolecular β-lactam opening) as well as DNA-complexing substituents[11] (in order to increase the percentage of highly letal double strand breaks). Compound **2** possesses only two handles. Moreover, one of them is necessarily devoted to tether the nucleophile. Thus we wished to have in our hands a more versatile lactenediyne scaffold provided with three independent handles. This would allow us to prepare and evaluate a library of prodrugs by appending to the handles: (a) a tethered nucleophile; (b) an activating substituent; (c) a DNA-complexing substructure.

In this communication, we report the successful preparation of this new scaffold, represented by compound **3**. In it, the three interchangeable handles are represented by the two hydroxyl groups and by the azetidinone nitrogen, two of which are protected.

The general synthetic scheme (Scheme 1)[12] followed that employed for the synthesis of **2**.[6,7] The key intermediate was therefore alcohol **10**. Its preparation encompassed construction of a 4-stiryl azetidinone through a Staudinger reaction, stereoselective propar-

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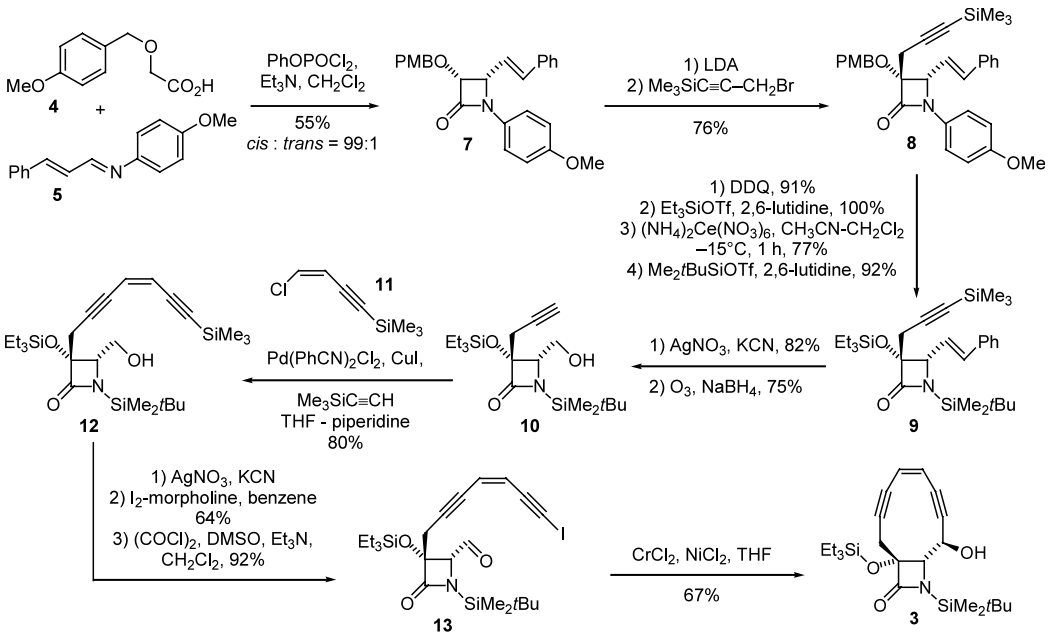


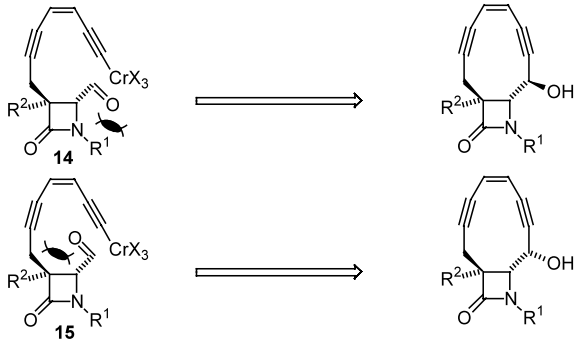
Scheme 1.

gylation, and chemoselective ozonolysis of the double bond. The main problem turned out to be the correct choice of protecting groups. After considerable investigation, we found that the PMB (*p*-methoxybenzyl) and anisyl group were well suited for a Staudinger condensation[13] and for the subsequent stereoselective propargylation to give **8** (*cis*:*trans* = 200:1). However, the oxidative removal of the *p*-methoxyphenyl group from nitrogen was more difficult than expected. For example, treatment of **8** with CAN proceeded quite sluggishly, giving the desired product with unsatisfactory yields.[13] The same behaviour was encountered also on more advanced synthetic intermediates. Also removal at the final lactenediyne stage was therefore anticipated to be troublesome and we decided to get rid of this group at an early stage. In order to achieve good yields in its oxidative removal, it was necessary to substitute the PMB group with a different protection. The anisyl removal gave poor yields also when performed on the unprotected tertiary alcohol. Among several protecting groups tested, triethylsilyl was found to be the best.[14]

Although the change of both protecting groups involved four additional steps, the overall yield of transformation of **8** into **9** was good (64%). Chemoselective ozonolysis of the double bond in the presence of the triple one[15] followed by reduction gave alcohol **10**. Construction of the acyclic enediyne through a Castro–Stephens–Sonogashira reaction[16] (best yields were obtained by the 'sacrificial alkyne' method)[4] was followed by the two-step iodination of the terminal triple bond and Swern oxidation to give aldehyde **12**. The stage was set for the final Nozaki cyclization, which took place in good yields and with excellent stereoselectivity (only one diastereoisomer detected). The configuration of **3** was unambiguously established on the basis of the high (9.1 Hz.) H_9–H_{10} coupling constant. It is interesting to note that cyclization of the analogue of **13** lacking the Et_3SiO group gave the 9,10-*cis* epimer instead as major adduct in 86:14 ratio. As previously suggested by us,[6] the stereoselectivity in the cyclization depends on the preferred formyl conformation (Scheme 2): **14** will give the 9,10-*trans* isomer, while **15** will form the 9,10-*cis* one. The steric encumbrance of the $SiMe_2tBu$ groups disfavours the 'outside' conformation **14** with the aldehydic oxygen directed toward it; on the other hand the presence of an R^2 group different from hydrogen is expected to disfavour the 'inside' conformation **15** that points the oxygen toward the silyloxy group. The result obtained in this work clearly indicates that when both R^1 and R^2 are bulky, the control by R^2 is definitely more important and conformation **14**, leading to 9,10-*trans* product, prevails.

Preliminary deprotection experiments have shown that the N-$SiMe_2tBu$ group could be smoothly cleaved with HF without affecting the triethylsilyl group.

Work directed toward the synthesis of lactenediyne libraries from this scaffold are in progress and structure–activity results will be published in due course.



Scheme 2.

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12. All compounds shown in Scheme 1 were prepared in racemic form. They have been fully characterized by ^{1}H and ^{13}C NMR, IR, GC–MS (when feasible) and elemental analysis (in some cases).
13. Acid **4** (mp 50.8–51.8°C) was prepared in 88% yield from 4-methoxybenzyl alcohol by treatment with NaH and then Br-CH_2-CO_2H in DMF–THF.
14. Among the various protection tested, only the acetyl group gave yields comparable with triethylsilyl. However, the latter was better suited for our aims.
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