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The Intramolecular Addition of Silylated Alkynes to Aldehydes: Methodology for the Construction of Cyclic Enediynes and Its Application to Dynemicin Analogs

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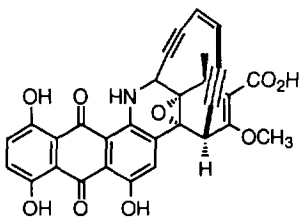
Abstract: Upon treatment with CsF, silylated alkynes react intramolecularly with aldehydes or iminium ions to form in one step in the presence of electrophilic trapping agents the cyclic enediyne ring system of dynemicin, with provision for the incorporation of various DNA recognition elements.

The emergence of the enediyne anti-tumor antibiotics as chemotherapeutic leads and reagents for nucleic acid modification has stimulated a great deal of research directed at their synthesis and molecular mode of action.[2-7] These compounds, which include dynemicin (**1**), calicheamicin, esperamicin, neocarzinostatin chromophore, kedarcidin chromophore, C-1027 chromophore and maduropeptin chromophore, exhibit pronounced cytotoxicity and exceptionally potent DNA cleaving ability.[2] These activities are proposed to arise from inducible cycloaromatization of their enediyne moiety to a diradical species[8] which abstracts hydrogens from proximate deoxyribosyl residues, leading to scission of the DNA sugar phosphate backbone.[9]



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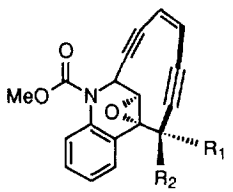
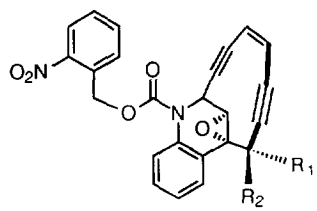


2a R_1=OH, R_2=H
2b R_1=H, R_2=OH

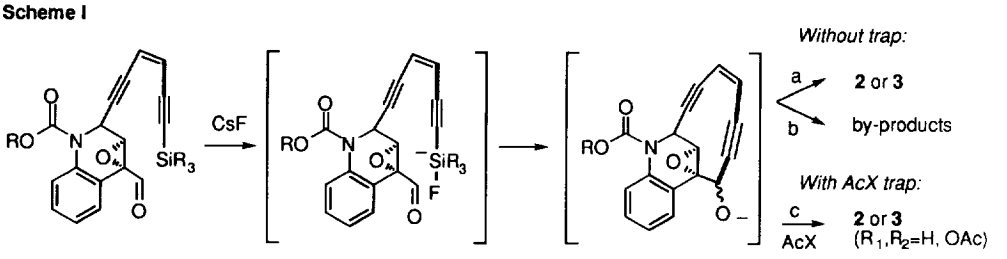


3a R_1=OH, R_2=H
3b R_1=H, R_2=OH

We recently reported the design and synthesis of the simplest functional analogs of dynemicin.[10,11] *These analogs, represented by enediynes **2a,b** and **3a,b** can be prepared in under 10 steps and upon activation exhibit DNA cleaving activity comparable to dynemicin itself.* Central to the successful synthesis of these analogs was the development in our laboratory of a method that allows for the fluoride induced *intramolecular* addition of a silyl-protected alkyne to an aldehyde, leading to the formation of the ten-membered ring (Scheme 1).[10-12] This procedure avoids the additional desilylation step and the use of strong base required to generate an alkynylide in an alternative procedure which, while successfully employed in the synthesis of cembranes[13] and some enediynes,[5] proved ineffective for the preparation of analogs **2** or **3**. While this *in situ* desilylation-condensation procedure has been extended by us[11] and others[14] to the construction of other enediyne systems, we subsequently found that the yield of this reaction could be substantially improved through the addition of acetic anhydride to the reaction mixture. The use of this

additive was prompted by the observation that when fluoride alone is used for the closure reaction, the nucleophilic oxygen of the initially formed product reacts further with the nitrogen protecting group of starting material or product. As a result, some carbonate by-products (path b) are formed along with degradation products derived from this unscheduled *triggering* of epoxide cleavage through nitrogen deprotection. The acetic anhydride thus serves to trap alkoxides as their acetates (path c), thereby preventing these secondary reactions. This initial observation from our laboratory suggested that this procedure could be used to simultaneously deprotect a terminal alkyne, construct the ten-membered enediyne ring system of a DNA cleaving device, and attach DNA recognition elements or their linkers to such cleaving devices *in one operation*. We report now that this one step procedure can indeed be conducted with mixed anhydrides, cyclic anhydrides, acid halides, and chloroformates, allowing for the attachment of groups commonly employed as linkers for minor groove binders.

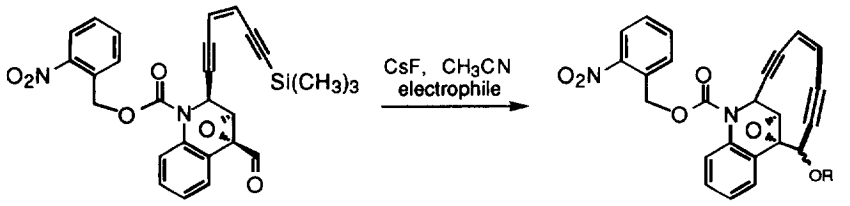
Scheme I



The preparation of aldehyde **4** (Table 1) has been previously reported.[11] To effect desilylative closure and oxygen trapping, cesium fluoride (3.5 equiv.) is added to a mixture of **4** (1 equiv.), acetic anhydride (2 equiv.), sodium bicarbonate (1.0 equiv.), and 4Å molecular sieves in acetonitrile solvent at room temperature under a nitrogen atmosphere. After 6 hours, the reaction mixture is filtered through a plug of silica and the effluent concentrated *in vacuo*. Purification of the residue by silica gel chromatography affords the cyclized acetate **5a** (2:1 mixture of epimers) in 83% yield. The remarkable effect of trapping agent on this process is indicated by comparison of this yield with that obtained in the absence of trapping agent (acetic anhydride): the alcohol corresponding to **5a**, namely **3**, is obtained in only 20% yield. It is noteworthy, however, that alcohol **3** can be obtained directly, if desired, in 84% yield through the use of trifluoroacetic anhydride as the trapping agent. In this case, the initially formed labile trifluoroacetate **5b** is readily hydrolyzed to the alcohol under the conditions of chromatographic purification.

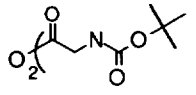
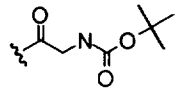
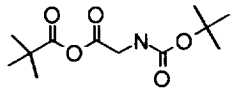
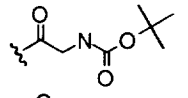
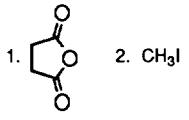
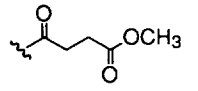
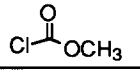
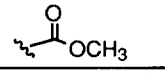
In addition to simple acylations, this procedure can also be used with more functionalized anhydrides (entry 3), allowing for the attachment of amino acid or peptidyl DNA recognition elements to the DNA cleaving subunit. For some applications of these cleaving agents, the use of symmetrical anhydrides (entries 1-3) would not be economical since one half of the anhydride functions only as a leaving group. For these purposes, a mixed anhydride (entry 4) has been found to be effective, giving the acylated product with loss of pivalate. Cyclic anhydrides (entry 5) can also be used. In this case, however, due to the acid lability of the epoxide, the initially formed carboxylate is alkylated with methyl iodide to provide the cyclized product (**5d**), possessing a differentiated diester for linking various DNA recognition elements. Both aliphatic and aromatic acid chlorides (entries 6 and 7) can also be used as trapping agents in this procedure, affording esters in good yield. Finally, the use of chloroformates (entry 8) allows for the preparation of mixed carbonates. Attempts to form ethers through the use of alkyl halides as trapping agents has not been effective thus far.

In a further investigation of the scope of this process, we explored whether closure could be realized with an iminium ion in place of the aldehyde (Scheme 2). This process would furnish an amide linkage, which would be less easily hydrolyzed in the aqueous environment necessary for DNA cleavage studies. Such methodology would thus allow the attachment of the N-terminus of peptides and proteins that recognize



4 5a-f

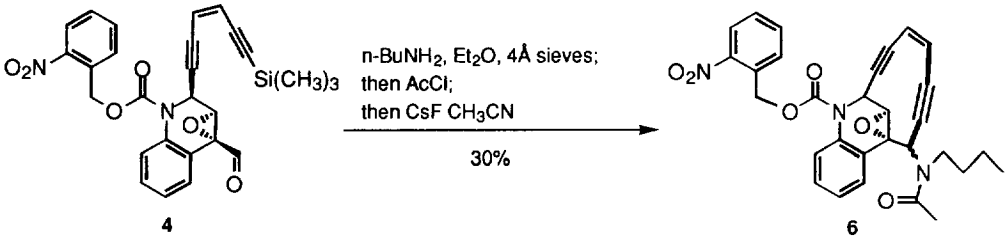
Table 1. Electrophiles used in the CsF-mediated cyclization reaction

entry	electrophile	product	R=	percent yield (β:α)
1	Ac_2O	**5a**	Ac	83 (2:1)
2	$(CF_3CO)_2O$	**5b**	$COCF_3$[a]	
		3	H[b]	84 (2:1)
3		**5c**		41 (2:1)
4		**5c**		51 (2:1)
5		**5d**		43 (3:1)
6	AcCl	**5a**	Ac	67 (2:1)
7	BzCl	**5e**	Bz	75 (2:1)
8		**5f**		51(2:1)

[a]observed in the ^1H NMR of crude reaction mixture after removal of solvent
[b]isolated yield after chromatography on silica

DNA. For this purpose, the imine of aldehyde **4** was prepared quantitatively by stirring it with butylamine in Et_2O over 4Å molecular sieves. Although the imine was usually not isolated because of its sensitivity, it was characterized by ^1H and ^{13}C NMR and IR spectroscopy. Treatment of the imine with an acid chloride followed by CsF resulted in the formation of the desired amide **6**.

Scheme 2



4 6

In summary, an intramolecular desilylative condensation has been developed for the combined deprotective cyclization and functionalization of the ten-membered enediyne ring of dynemicin analogs. This

method employs mild conditions and furnishes ester- and carbonate-substituted enediynes in moderate (43%) to good (84%) yields in one step from an acyclic silyl-protected alkyne precursor. Alternatively, the use of trifluoroacetic anhydride as the trapping agent gives the unfunctionalized alcohol **3** directly, due to the lability of the trifluoroacetate **5b** towards chromatography on silica. The condensation can also be accomplished with the iminium salt of aldehyde **4** to produce an analog with a substituent attached via a hydrolytically more stable amide linkage. Experiments with these analogs indicate that their DNA cleaving ability is not affected by the linker introduced in this procedure. Studies are currently underway to utilize this methodology for the attachment of DNA recognition elements to the photoactivatable dynemicin analog **3** .

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