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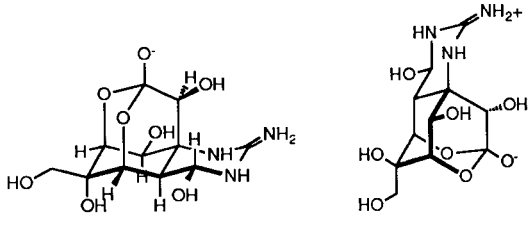
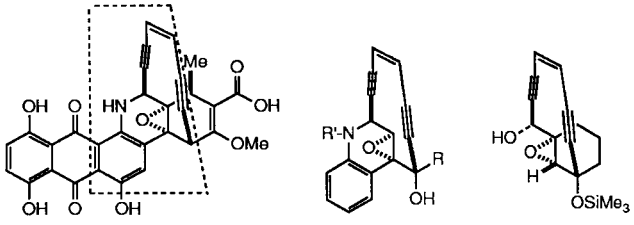
J. Heterocyclic Chem., **29**, 619 (1992).

Among many naturally occurring biotoxins, tetrodotoxin (**1**) and its analogues have particularly provided quite interesting problems to us for developing synthetic methodologies suitable to these specific targets as well as to others for general solution. The first topic deals with these unusual heterocyclic ring system of this toxin [1]. Dynemicin A (**2**), on the other hand, has been one of the leading compounds as enediyne class antitumor antibiotics [2], to which new methods are requested for syntheses. Some simplified enediyne compounds (**3**, **4**) were designed for examination toward bicyclo[7.3.1]-tridecenediyne ring system. Further approaches directed toward natural and unnatural enediyne compounds are to be discussed.



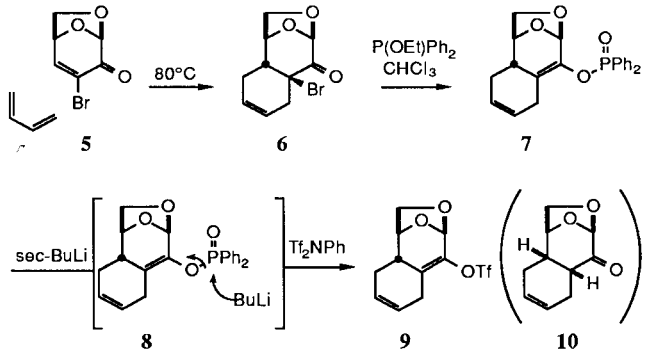
Tetrodotoxin 1



Dynemicin A (2) 3 4

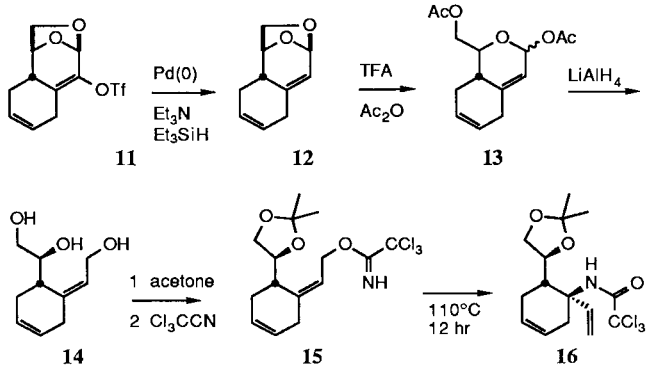
Tetrodotoxin.

The Diels-Alder strategy to a sugar derivative, bromolevoglucosenone **5** gave the adduct **6** [3]. A similar bromo-ketone (**24**, *vide infra*) was found, however, to be extremely unstable to enforce us converting it to vinyl phosphorus derivatives. The corresponding vinyl phosphate *via* the Perkov reaction was fairly stable. The phosphorus group in **7** was best cleaved by treatment with butyllithium from **8**, and protonation gave the *cis*-ketone **10**. Trapping of the enolate intermediate with *N*-phenyltrifluoromethane sulfonimide gave the vinyl triflate **9**.



5 6 7 8 9 10

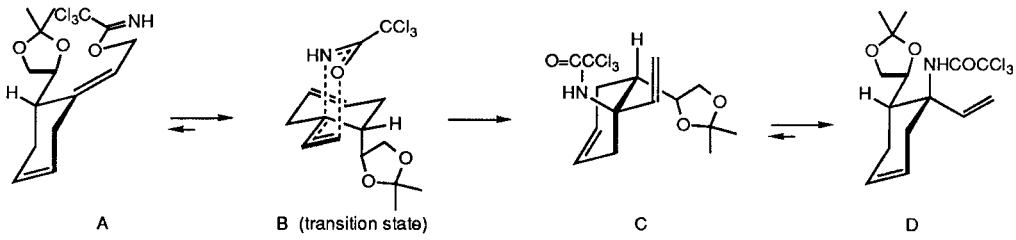
The triflate was convertible to the olefin **12**, which had been previously synthesized from the bromoketone **6** by two step reduction. The latter reaction involved a [3,3]-sigmatropic Overman rearrangement to the vinylamide **16** [4].



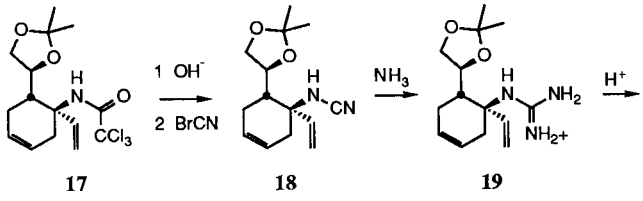
11 12 13 14 15 16

The following conformational analysis of the enforcing equilibrium between the imidates and the vinylamides explained the apparently unfavorable rearrangement of the nitrogen function into the more crowded position. A-strain [5] in **A** made the conformation of the substituent to axial at the transition state **B**. The rearranged **C** changed its conformation to the more stable one **D**.

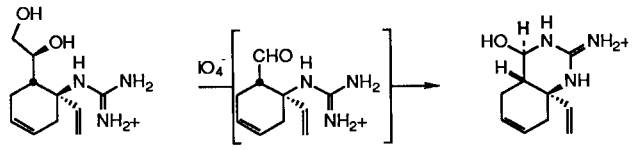
The guanidine formation **19** was manipulated on the amide **17** *via* the aminonitrile **18** and it was converted into the glycol **20**. Metaperiodate oxidation yielded the cyclic guanidine **22**.



A B (transition state) C D

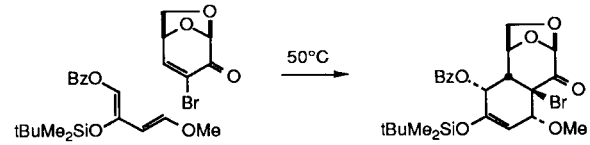


17 18 19

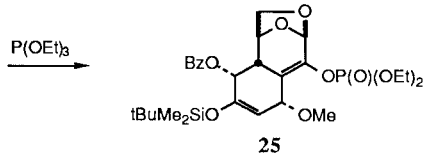


20 21 22

A similar cycloaddition with the oxygenated diene smoothly took place at 50°. Since the adduct bromoketone **24** was extremely unstable, it was converted into the phosphate **25**.

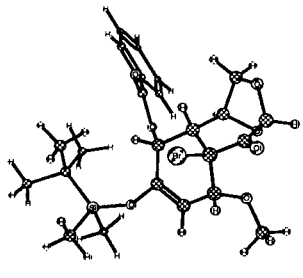


23 24

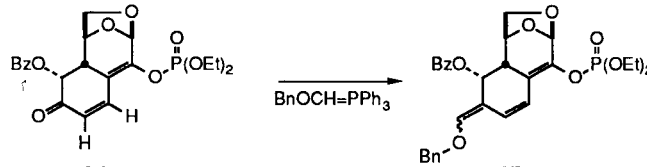


25

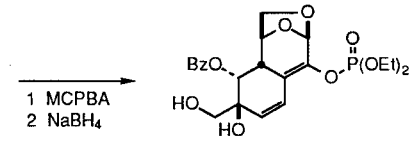
The conformation of the adduct **24a** was fairly strained because of the two substituents, benzoyloxy and methoxyl groups were to escape from the concave face of the *cis* ring system.



24a



26 27



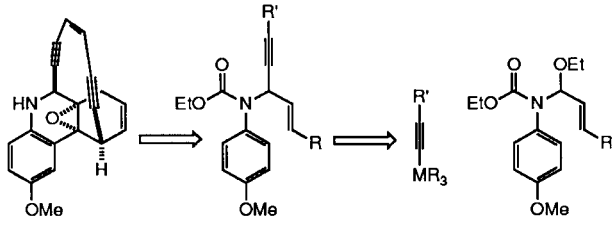
28

The eliminative hydrolysis of the silyl ether afforded the enone **26** which was homologated with the Wittig reagent to **27**. Further oxidation and reduction into **28** was the direction used toward completion of the cyclohexane ring of tetrodotoxin.

Enediyne

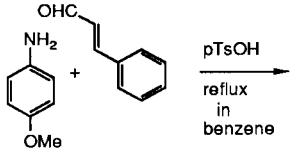
Dynemicin A (**2**), isolated from fermentation broth of *Micromonospora chersina* by M. Konishi and coworkers at the Research Institute of Bristol-Myers in Tokyo, possesses potent cytotoxicity and *in vivo* antitumor activity [2]. This compound **2** can be considered to be a hybrid antibiotic between two types of antitumor agents, anthracycline such as daunomycin and cyclic enediyne antibiotics such as esperamicin/calicheamicin. The multi-step mechanism of DNA cleavage by dynemicin A was proposed (i) to open the epoxide ring through bio-reduction of the quinone moiety, (ii) to facilitate Masamune-Bergman cycloaromatization to generate a phenylene diradical, (iii) to abstract hydrogen atoms from the sugar phosphate backbone of DNA and (iv) to cleave the DNA chain [6]. The enediyne ring is a necessary part for this cleavage.

Retrosynthesis of **2** suggested to us to consider the simplified model **29** containing the identical functional groups. The further simplified compound **30** was designed to explore the reaction for the acetylenic bond formation between **31** and **32**.

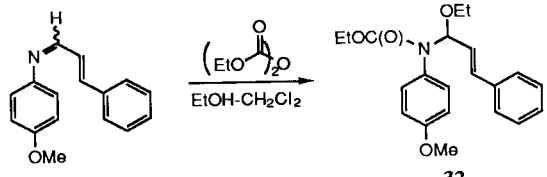


29 30 31 32

The Shiff base from the aniline and cinnamaldehyde was treated with diethyl pyrocarbonate to give the acyl amide **32**.

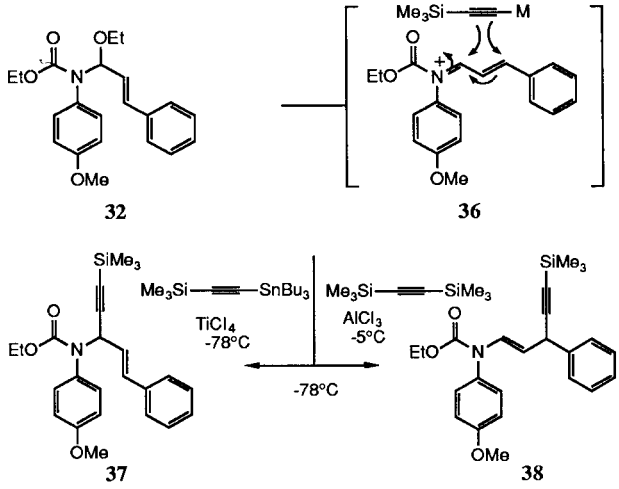


33 34



35 32

The acyliminium intermediate **36** was generated from the amide ether **32** by treatment with aluminum chloride. Several acetylenes shown in Table 1 were examined with various Lewis acids at low temperatures. The conjugated cation **36** was so designed that the intermediate would be stabilized to give higher yields of products **37** or **38**. All of the examples having trimethylsilylacetylene at one terminal afforded the unstable product of type **38**, the 1,4-addition product.



32 36

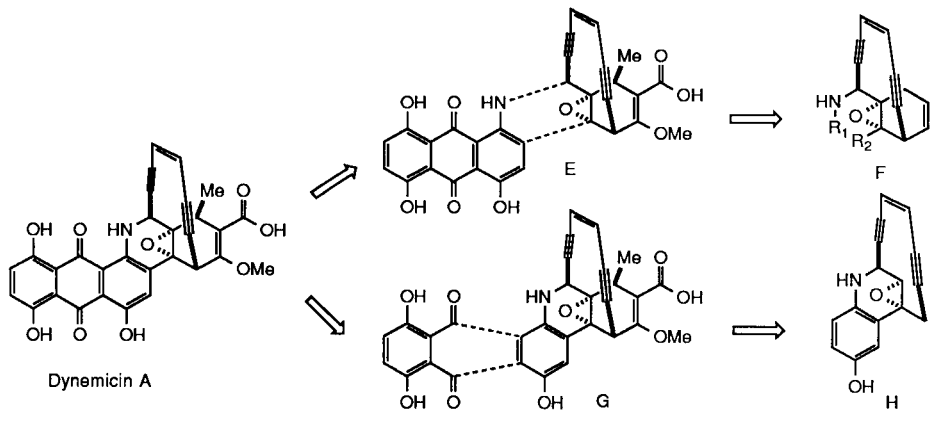
37 38

The results are summarized in Table 1 [7]. Silylacetylene gave mainly the conjugate addition products with aluminum chloride. On the other hand, the tin acetylene gave the 1,2-adducts with titanium tetrachloride at -78°.

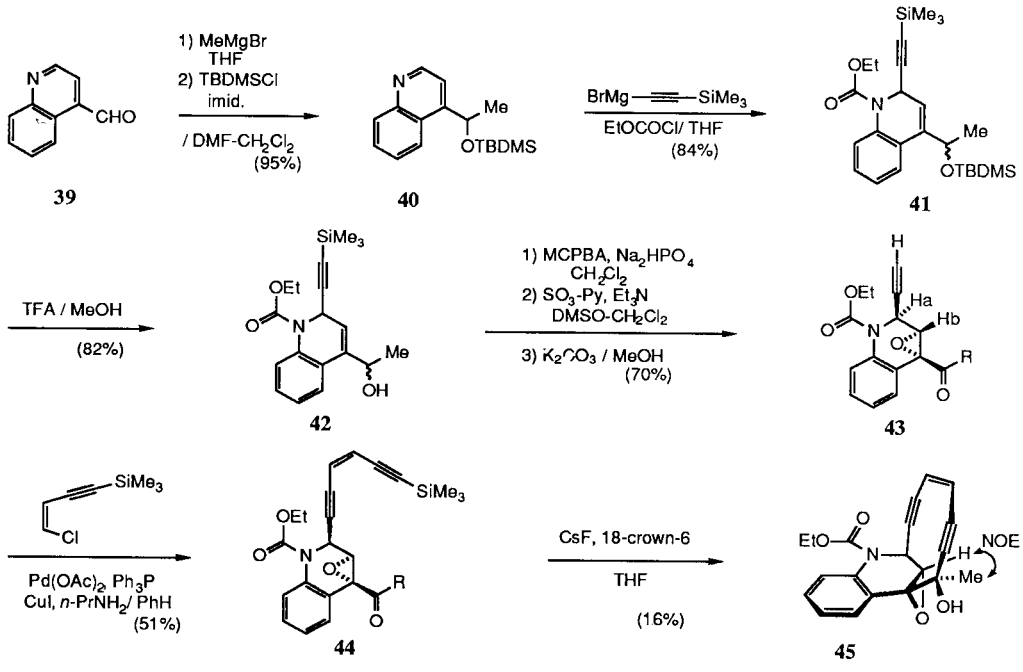
Table 1

R^1	R^2	Temp (°C)	Lewis Acid (equiv.)	Yield (%)	Product Type **37** : **38**	
$SiMe_3$	$SiMe_3$	-20 to 0	$AlCl_3$ (2.5)	40	0	10
$SnBu_3$	Ph	-78 to -20	BF_3-OEt_2 (2.0)	47	10	0
$SnBu_3$	Ph	-78 to -20	$SnCl_4$ (1.5)	51	10	0
$SnBu_3$	$SiMe_3$	-78 to -20	$TiCl_4$ (1.5)	81	10	0

In order to explore the biologically active mimic of dynemicin A (**2**), retrosynthetic simplification gave various interesting compounds. A biosynthetic information may separate the molecule as **E**, which led us to have the simplest bicyclo[7.3.1]-ring system such as **F** [8]. Alternatively the aromatic part should be attached to the model to provide **H**. In both cases, the key reaction would be the acetylenic bond formation.



Dynemicin A

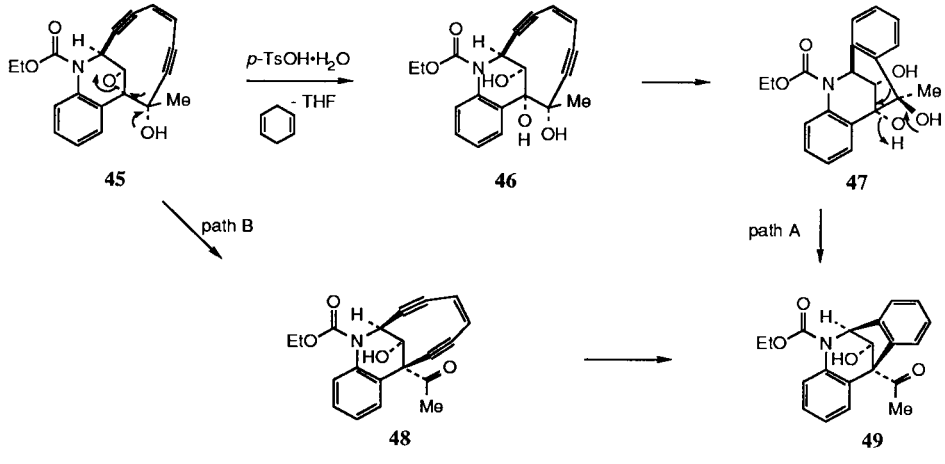


39 40 41 42 43 44 45

The target molecule **II** was selected as bicyclo[7.3.1]-compound **45** [9]. The precursor **43** (R = H) was difficult to make from the corresponding alcohol. The starting quinoline aldehyde **39**, that was prepared in about 50% yield from commercially available lepidine after selenium dioxide oxidation, was reacted with methylmagnesium bromide and the resulting alcohol was silylated to provide **40**. Manipulation of the acetylenic and the epoxidic moieties provided the precursor **44**, which was cyclized with fluoride to give **45**. Wender recently synthesized a similar compound [10].

The cycloaromatization of **45** was achieved under acidic condition to cleave the epoxide ring and to diminish the strain to the macro ring system. We first expected that the epoxide opening of **45** might afford **47** *via* **46** through Bergman cycloaromatization. But the product which was obtained, in fact, from **45** with *p*-toluenesulfonic acid in the presence of cyclohexa-1,4-diene in THF solvent was the methyl ketone **49**, instead. Nicolaou reported similar rearrangement [11].

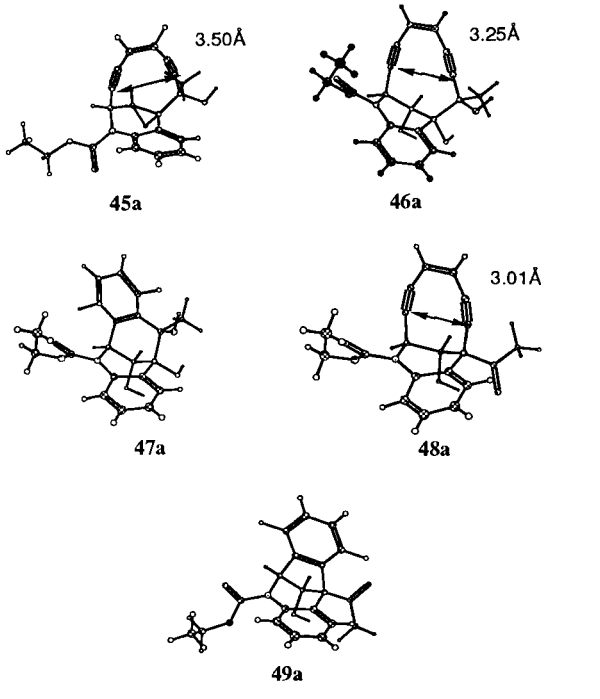
This aromatized compound **49** may come from the 1,2-glycol **47** *via* pinacol-pinacolone rearrangement of



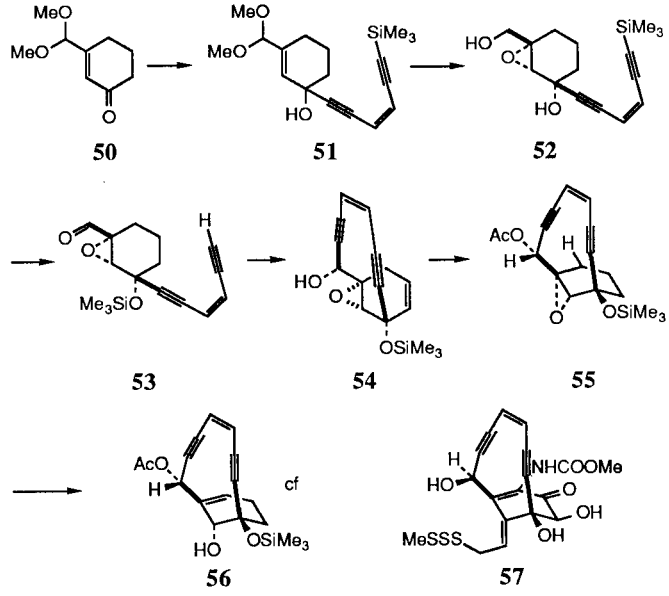
45 46 47 48 49

the hypothetical intermediate **46** (path A). The enediyne **46** showed cycloaromatization to **47**. The same product **49** could alternatively be considered as another Bergman cycloaromatization through **48**, a pinacol-pinacolone type rearrangement product with concomitant epoxide opening as shown above (path B). The rearrangement in the latter case, however, has to be associated with ring-shrinking process against the strained 10-membered enediyne system into 9-membered one in **48**. To assist in solving the mechanistic questions, some molecular mechanics calculations [12] were considered and the results are indicated above in the form to clarify their conformations (**45a**-**49a**). Molecular mechanics calculations of the epoxide **45** concluded its conformation as shown in **45a**, which showed the distance between the 1,6-acetylenic carbons to be 3.50Å. The values on the other enediynes **46a** and **48a** were 3.25Å and 3.01Å, respectively. These products have shorter distances than the original **45a** to allow the cycloaromatization at ordinal temperature [13]. The cycloaromatization of **46a** should give **47a**, which could rearrange with phenyl group migration into **49**.

The possible conformations of the above molecules with calculated distances of the 1,6-acetylenic carbons



An alternative model compound **F** was also studied [8]. Lithium trimethylsilyl acetylide was added to **50** and the product was desilylated to produce the propargyl alcohol, which was coupled with the (Z)-vinyl chloride under palladium coupling to afford the acyclic enediyne **51**. Acid hydrolysis of the acetal was followed by sodium borohydride reduction of the aldehyde and further epoxidation of the allylic alcohol afforded the *syn* epoxide **52** whose stereochemistry was assigned from the Henbest rule at this moment. The epoxyalcolhol **52** was oxidized with the sulfur trioxide-pyridine activated DMSO to yield the corresponding epoxyaldehyde. Sequential desilyation from the silylacetylene and silylation of the *tert*-alcohol afforded the cyclization precursor **53**. For the cyclization, the lithium acetylide fo **53** in the presence of ceric chloride [14] was the most effective to afford **54**.

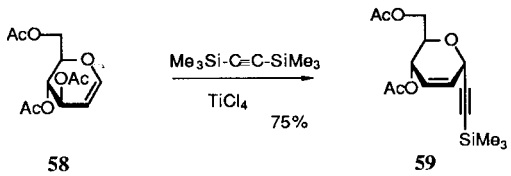


We have developed several methodologies useful for the acetylenic bond formation which might result in the cyclization of this 10-membered ring. They are (i) a short route to construct bicyclo [7.3.1]tridecenediyne system that is included in dynemicin A and (ii) acidic transformation of **55** with opening the epoxide into **56**, esperamicin/calicheamicin type ring system.

The product **55** possesses the bicyclo[7.3.1]tridecendiyne system, and it was regarded as a new esperamicin/calicheamicin enediyne analogue that contained a trigger of dynemicin A. The epoxide **55** was converted to the allylic alcohol **56** by heating in the presence of acid, and the product was isolated as its acetate in 40% overall yield. Thus, **56** can be considered as an important analogue of bicyclo[7.3.1]-tridecadiendiyne system as the esperamicin aglycon **57**.

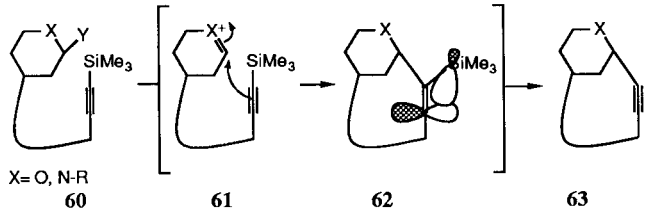
The acetylenic bond formation with silyl or tin acetylenes was originally studied during the course of okadaic acid, a marine polyether toxin [15]. The key reaction was found with the glucal **58**, when treated

with Lewis acid, the trimethylsilylacetylene afforded **59** as an axial adduct.

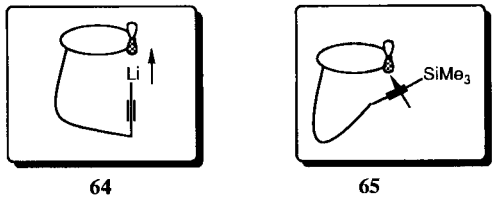


58 59

The mechanism might involve a stabilization of the *sigma-pi* conjugation by the silyl group as **62**. The general scheme as shown in the following figure involves the acetal or aminal functional group in the starting material **60**. The cationic intermediate **61** caused by Lewis acid could be attacked to give the product **63** as adduct. The direction of the nucleophile acetylene, if this might be true, may not be **64** but **65**, in which pi-electrons start to participate instead of the electrons in a shorter *sp* orbital.

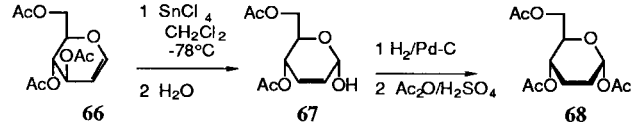


60 61 62 63

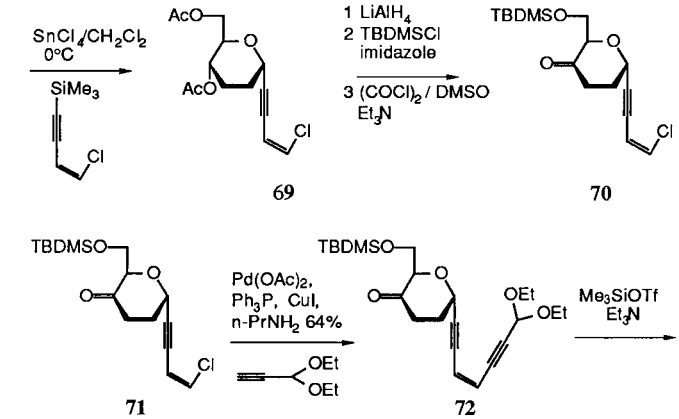


64 65

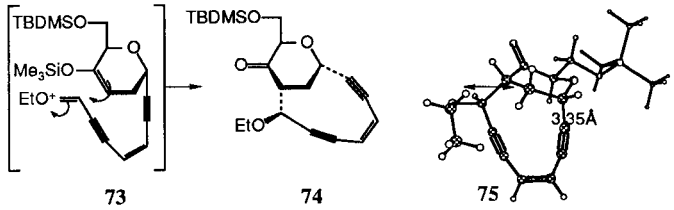
A convenient oxabicyclo[7.3.1]tridecane system was planned to be synthesized from D-glucal *via* *C*-glycosidation. The tri-*O*-acetyl-D-glucal **66** was hydrolyzed and the reduction product **68** was treated with the chlorovinyl-trimethylsilylacetylene in the presence of tin tetrachloride. The glycosidated product was further converted into **71** and acetal acetylene was coupled to afford **72** as the precursor of carbocyclization. The acetal was treated with TMS triflate [16] to prompt the enolization **73** to produce a product, which we believe to be a cyclized product **74** only because of the facts judging from the loss of ethoxy group and acetal proton in its nmr spectrum and appearance of H at δ 4.95 ppm. Its possible cycloaromatization is currently under investigation. The distance between the two acetylenic carbons as shown in **75** was calculated to be 3.35Å.



66 67 68



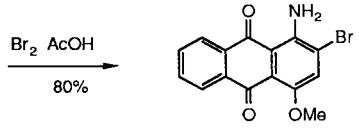
69 70 71 72



73 74 75

The studies toward total synthesis of dynemicin A has progressed to the significant step. Celliton Fast Pink B **76** is a famous dispersion dye, which was selected as the starting material to dynemicin A (**2**). Protection of the phenol and bromination gave **78**. The basisity of the amino group in these systems, **76** through **78**, was high enough to react with the activated carboxylic acid [17]. Its intramolecular Heck-type cyclization with palladium gave the pentacyclic compound **81** [18]. Epoxidation and two step oxidation gave **83**.

76 77



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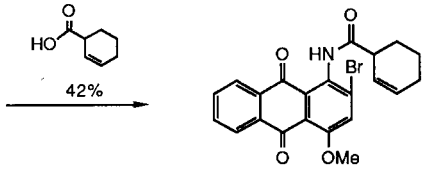

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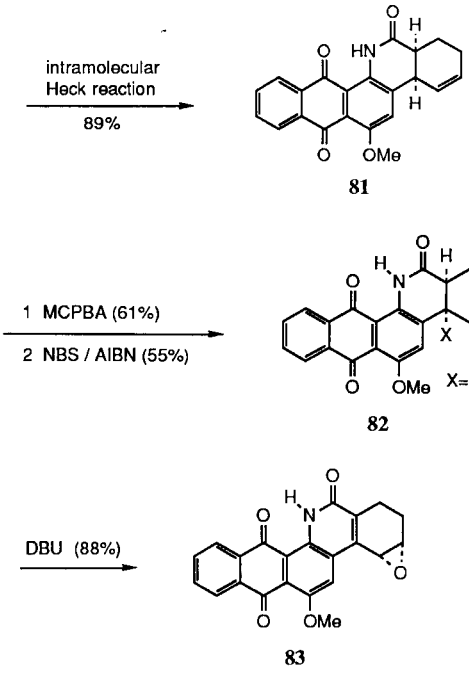
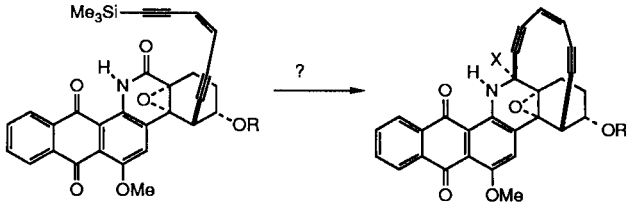


The key step for acetylenic bond introduction was achieved with the opening of the epoxide ring in **83**. The final enediyne ring formation to **85** is to be awaited under the condition investigated above. Schreiber also reported the studies on dynemicin A [19].



Studies on the acetylenic bond formation and their application to form the bicyclo[7.3.1]tridecane system are still in great progress. Heteroconjugate addition strategy was shown to be useful for the asymmetric synthesis with L-valinol as a chiral template [20]. These methodologies are to be applied for the synthesis of enediyne class antitumor antibiotic synthesis.

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