Synthetic Studies on Cyclic Enediyne Antibiotic, Dynemicin A

A thesis presented

by

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to my wife Ariko

and son Shin

Contents:

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Abbreviations

Ac	acetyl
AcOEt	ethyl acetate
AcOH	acetic acid
Ac_2O	acetic anhydride
Bn	benzyl
Bu	butyl
BTAF	benzyltrimethylammonium fluoride
Boc	*tert*-butoxycarbonyl
calcd	calculated
conc.	concentrated
18-c-6	18-crown-6
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
dba	dibenzalacetone
DIBAL-H	diisobutylaluminum hydride
DEAD	diethyl azodicarboxylate
DMAP	dimethylaminopyridine
DMF	N,N-dimethylformamide
dmf	dimethyl fumarate
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Et_2O	diethyl ether
EtOH	ethyl alcohol
h	hour (s)
imid.	imidazole
LDA	lithium diisopropylamide
LAH	lithium aluminum hydride
LiHMDS	lithium hexamethyldisilazane
MCPBA	m-chloroperbenzoic acid
MEM	methoxylethylmethyl
MOM	methoxymethyl
MPM	methoxyphenylmethyl
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
NCS chr.	neocarzinostatin chromophore
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
PhH	benzene
P(*o*-tol)$_3$	*o*-toylphosphine
PMB	*p*-methoxybenzyl
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	t*ert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	trifurylphosphine
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetraproylammonium perruthenate
TPS	triphenylsilyl
TsCl	*p*-toluenesulfonyl chloride
TsOH	*p*-toluenesulfonic acid

Chapter 1

Introduction and Background

Introduction and Background

Discovery & Structure of cyclic enediyne antibiotics.

Neocarzinostatin (NCS) was isolated by Ishida and co-workers as a protein antitumor antibiotic in 1965,[1] which has been used in practical chemotherapy against cancer in Japan.[2] However, the active principle of NCS was recently found in non-proteinous component chromophore (NCS-chr.)[3] and its planner structure was elucidated by Seto and co-workers using the advanced NMR techniques in 1985.[4] The structure is completely novel and chemists including Seto suspected the structure[5] because the core structure of NCS-chr. contains two acetylenic bonds and one endo C-C double bond, one C-C exo double bond and one epoxide in one 9-membered ring. Such a highly strained structure is difficult to built by the plastic molecular model such as Dreiding Model. Complete structure including absolute configuration of NCS-chr was elucidated by A. G. Myers from the structure of degradation product which was formed via radical cycloaromatization induced by addition of methyl thioglycolate (**Figure 1-1**).[6] On the other hand, the apo-protein of NCS has 113 amino acids.[7] The role of apo-NCS was thought to stabilize the unstable NCS-chr. Quite recently, the 3-dimensional structures of apoprotein and the chromophore-protein complex were elucidated by means of X-ray crystallographic analysis and 2D-NMR methods.[8,9] These studies revealed that unstable enediyne core moiety was shielded by the amino acid residues of apo-protein.

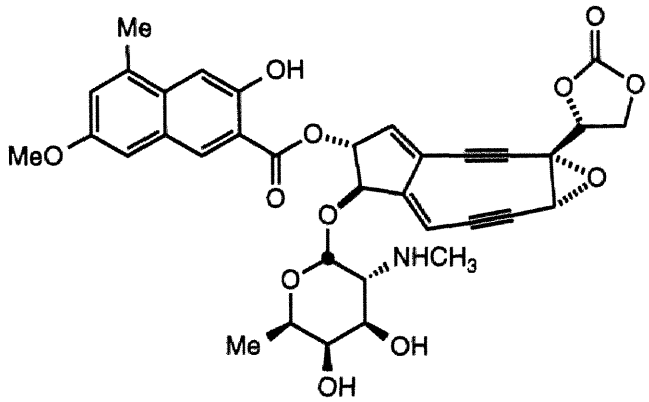
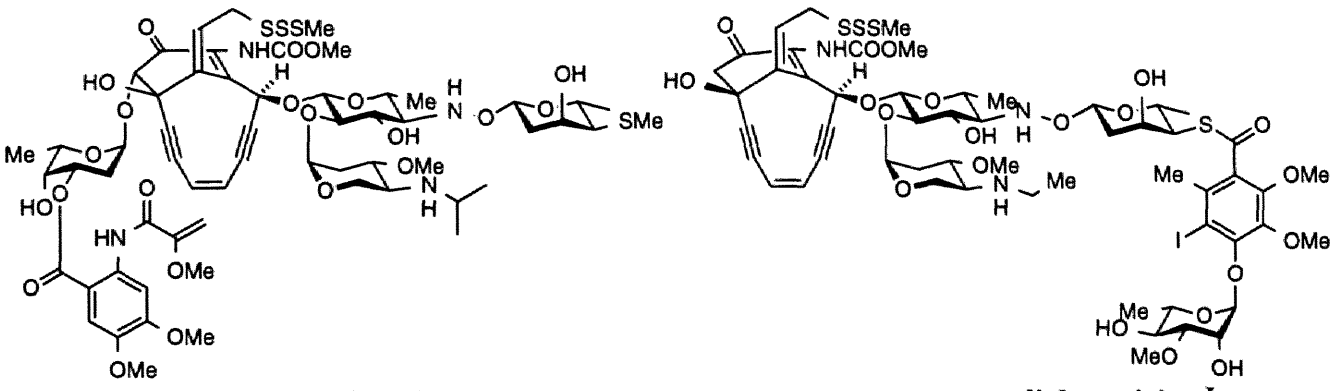


Figure 1-1. Structure of Neocarzinostatin chromophore.

In 1987, two groups of Bristol-Myers and Lederle independently reported the structures of a new class of potential antitumor antibiotics, esperamicin[10] and calicheamicin,[11] respectively. These antibiotics have a common aglycon which possesses a novel bicyclo[7,3,1]dienediyne system and show extraordinary powerful antitumor activity (eg. Esperamicin has activity more than about 10 times than CC-1065 which had been recognized as a most powerful antitumor antibiotics. Calicheamicin has activity 4000 times more than adriamycin which are used for chemotherapic treatment). These compounds also have an unique structures: 10-membered enediyne, trisulfide, bridgehead double bond, unique sugar and novel glycoside bond in oligosaccharide moiety. At the same time, fascinating mechanism for biological activity was proposed: DNA was cleaved by phenylene diradical *via* cycloaromatization (so-called Bergman reaction) in the enediyne moiety (*vide infra*).[12] In addition, esperamicin/calicheamicin cleaved the double strand DNA with highly sequence selective manner as with restriction enzymes. Particularly calicheamicin γ_1^I showed the preferential

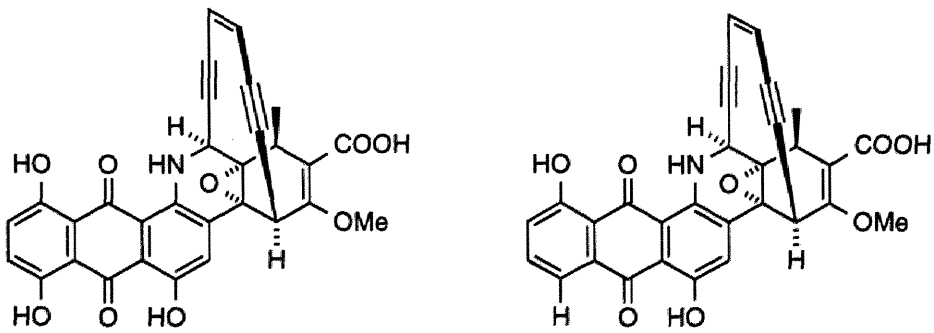
site-cleavage at the 5' C (3' to the adjacent thymidine) of 3'-TCCT/5'-AGGA sequence without exception.[13] This fact indicated that precise molecular recognition mechanism should be involved. Nowadays the sugar moiety of calicheamicin is believed to play a role as minor groove binder for the recognition of DNA sequence.[14]



esperamicin A_1 **calicheamicin γ^I_1**

Figure 1-2. Structures of esperamicin and calicheamicin.

In 1989, a new class of enediyne antibiotic, dynemicin A (**1-1**) was isolated from fermentation broth of *Micromonospora chersina* by M. Konishi and co-workers at research institute of Bristol-Myers in Tokyo.[15] In the next year, Shiomi *et al* at Institute of Microbial Chemistry in Tokyo reported the structure of deoxy-dynemicin A (**1-2**).[16] Although the structure of these antibiotics were determined by X-ray crystallographic analysis, the absolute stereochemistry was remained to be revealed.[14b] To solve this problem, docking experiments between dynemicin A and ds DNA using computer simulation were reported to assume plausible absolute configuration as shown in **Figure 1-3**.[17] These compounds can be considered to be hybrid antibiotics between two types of antitumor agents, anthracycline such as daunomycin and cyclic enediyne antibiotics such as esperamicin/calicheamicin. Although dynemicin A possesses potent cytotoxicity and *in vivo* antitumor activity and relatively weak acute toxicity, very low production by microorganism[18] prevents the further biological studies including its estimation for a practical cancer chemotherapy.[19] So that the supply of dynemicin A and its analogs by chemical synthesis has been highly desirable.



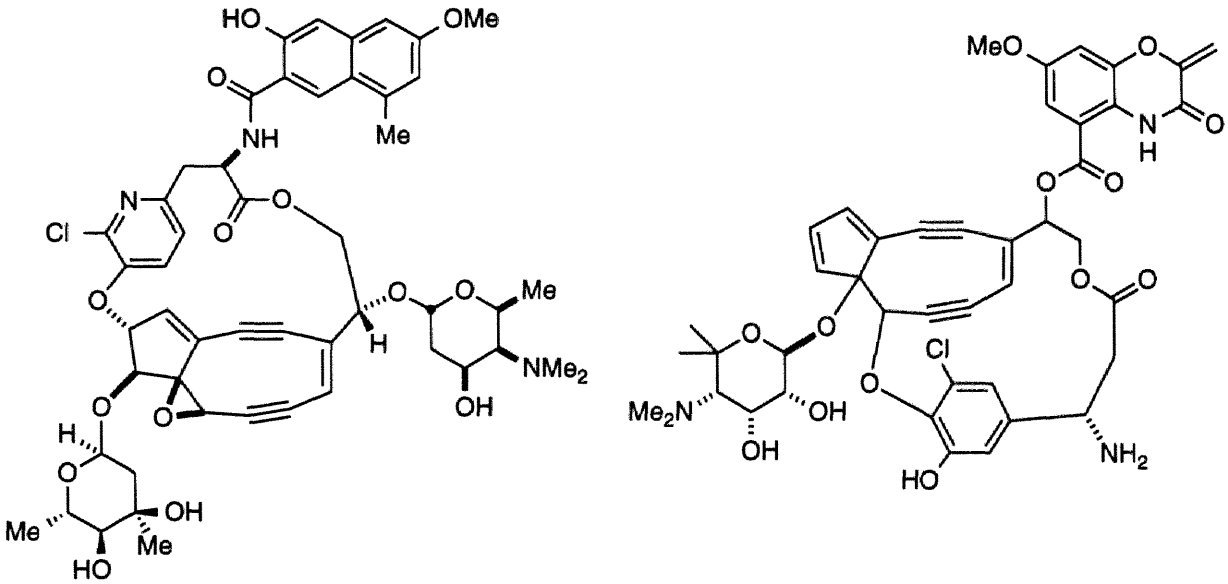
dynemicin A (1-1) **deoxy-dynemicin A (1-2)**

Figure 1-3. Structures of dynemicin A and deoxy-dynemicin A.

The special features of dynemicin A are followings. (i) Dynemicin A (**1-1**) has 1,4,6-trihydroxy-anthraquinone nucleus, the chromophore is identical or closely related to those of the

anthracycline group antibiotics. (ii) Dynemicin A exhibits broad and potent antimicrobial and cytotoxic activity comparable to those of the esperamicin family. (iii) Dynemicin A shows potent *in vivo* antitumor effect. (iv) Dynemicin A demonstrates *in vivo* antibacterial activity and relatively weak acute toxicity in mice. (v) Dynemicin A is therefore an interesting agent which warrants further biological evaluation and chemical and biological modification.

More recently, new type of chromoprotein antibiotics, kedarcidin[20] and C-1027[21] were reported. These chromophores have a similar carbon skeleton to NCS-chr., but different 9-membered enediyne system (**Figure 1-4**). Interestingly, the apo-protein of kedarcidin was found to have proteolytic activity to histones (protein component of nucleosome),[22] while the apo-protein of C-1027 shows binding affinity to DNA. Consequently, the whole systems of these complexes are regarded as naturally occurring supramolecules having efficient DNA cleaving activity.

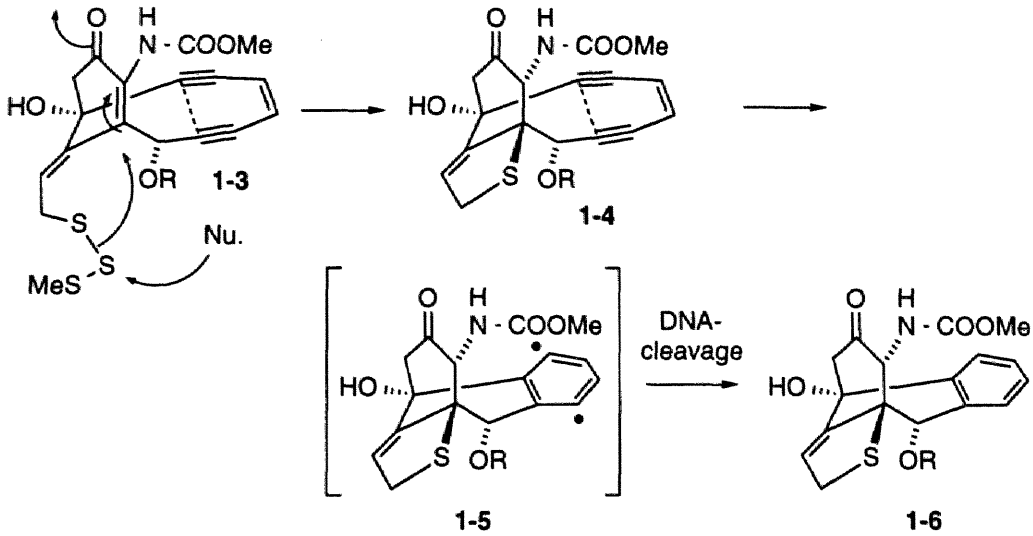


Kedarcidin chromophore **C-1027 chromophore**

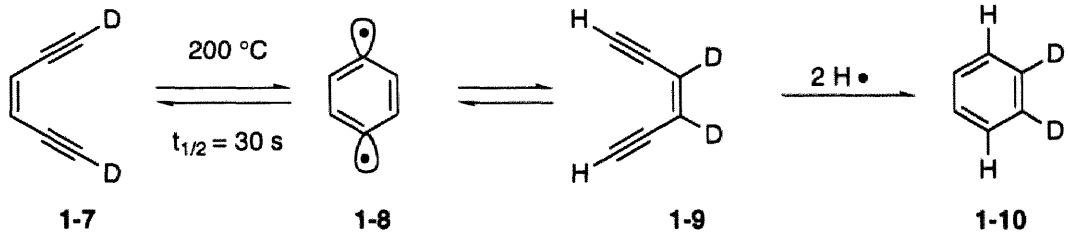
Figure 1-4. Structures of 9-membered enediyne antibiotics.

Action mechanism of enediyne antibiotics.

Esperamicin/calicheamicin: The mechanism of antitumor activities by esperamicin /calicheamicin was proposed at the same time when these structures were elucidated (**Scheme 1-1**).[23] Thiolate anion was generated by bio-reduction of trisulfide and then it attacked the bridgehead double bond to form the tricyclic compound (**1-4**).[24] During this reaction, strain of the enediyne moiety increased to undergo cycloaromatization, so-called Bergman reaction (**1-4** → **1-5**). Radical formation through Bergman reaction of acyclic enediyne compound usually requires high temperature (**Scheme 1-2**). Originally R. Bergman reported that, the deuterated acyclic enediyne (**1-7**) was in equilibrium at 200 °C with **1-9** *via* the diradical **1-8**, which abstracted the hydrogens to give the benzene-d_2 (**1-10**).[25] But these enediyne antibiotics proceeded Bergman reaction under physiological condition (at ca. 37 °C) because the 10-membered cyclic structure reduced the atomic distance of acetylenic group and the activation energy for Bergman reaction. Consequently, the natural products were inert under usual condition but under physiological condition (reductive condition or in the presence of nucleophiles such as thiol, amine, *etc.*) these antibiotics did express the activity.[26, 27]

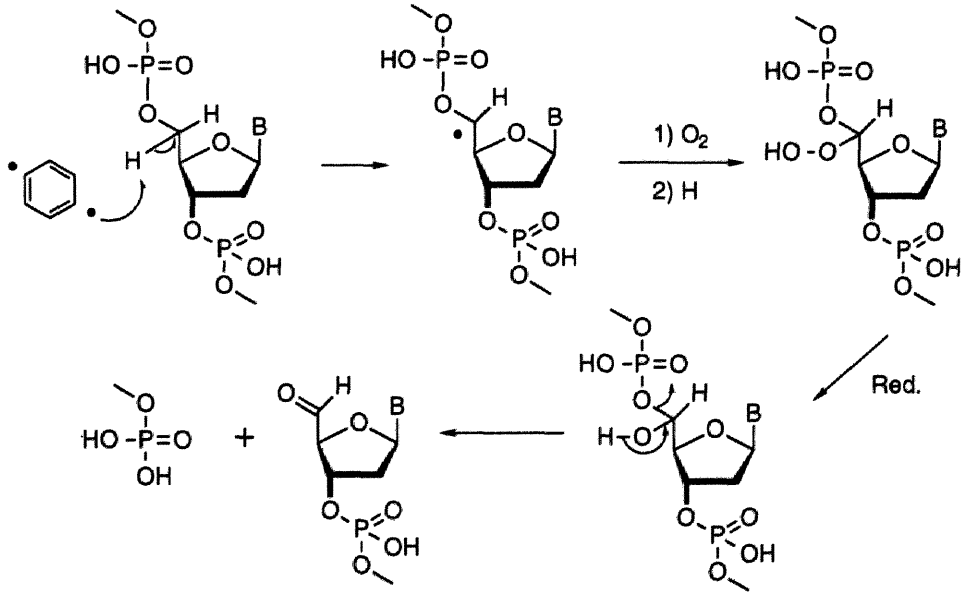


Scheme 1-1. Action mechanism of esperamicin/calicheamicin



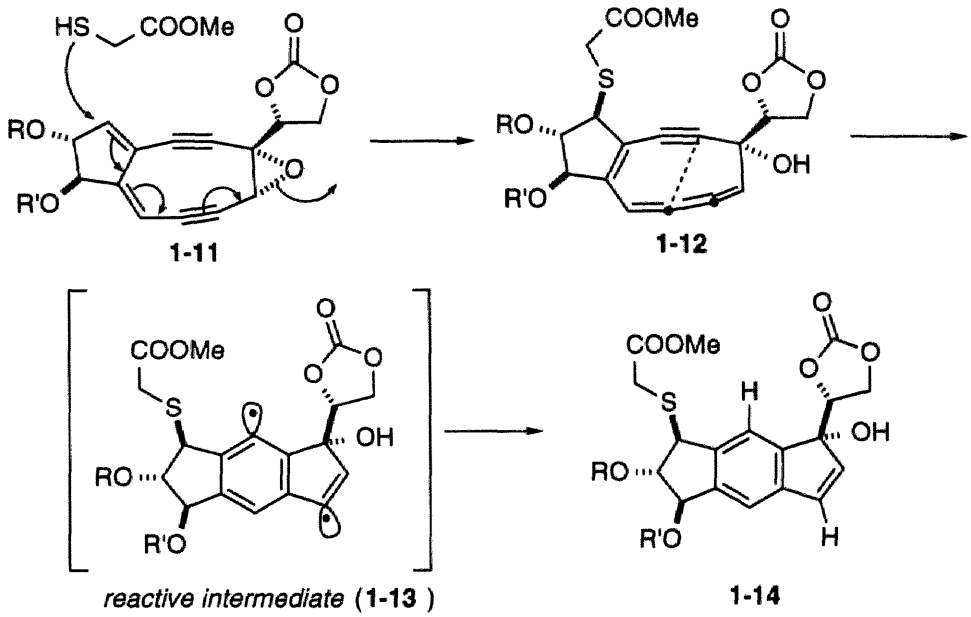
Scheme 1-2. Bergman reaction

It is worthwhile to note that the radical species were generated from Bergman as carbon radicals not as oxygen radicals. This point was marked contrast with another type of antitumor antibiotics such as bleomycin, daunomycin *etc.*, which were thought to generate oxygen radicals.[28] The phenylene diradicals directly could abstract hydrogen atoms from C-5' of deoxyribose in DNA (**Scheme 1-3**).[29] Since these two radicals abstracted the hydrogens from both chains of ds DNA at the same time, repairing enzymes can hardly work to result in inhibition of cell proliferation.



Scheme 1-3. DNA cleavage initiated by C-5' hydrogen atom abstraction

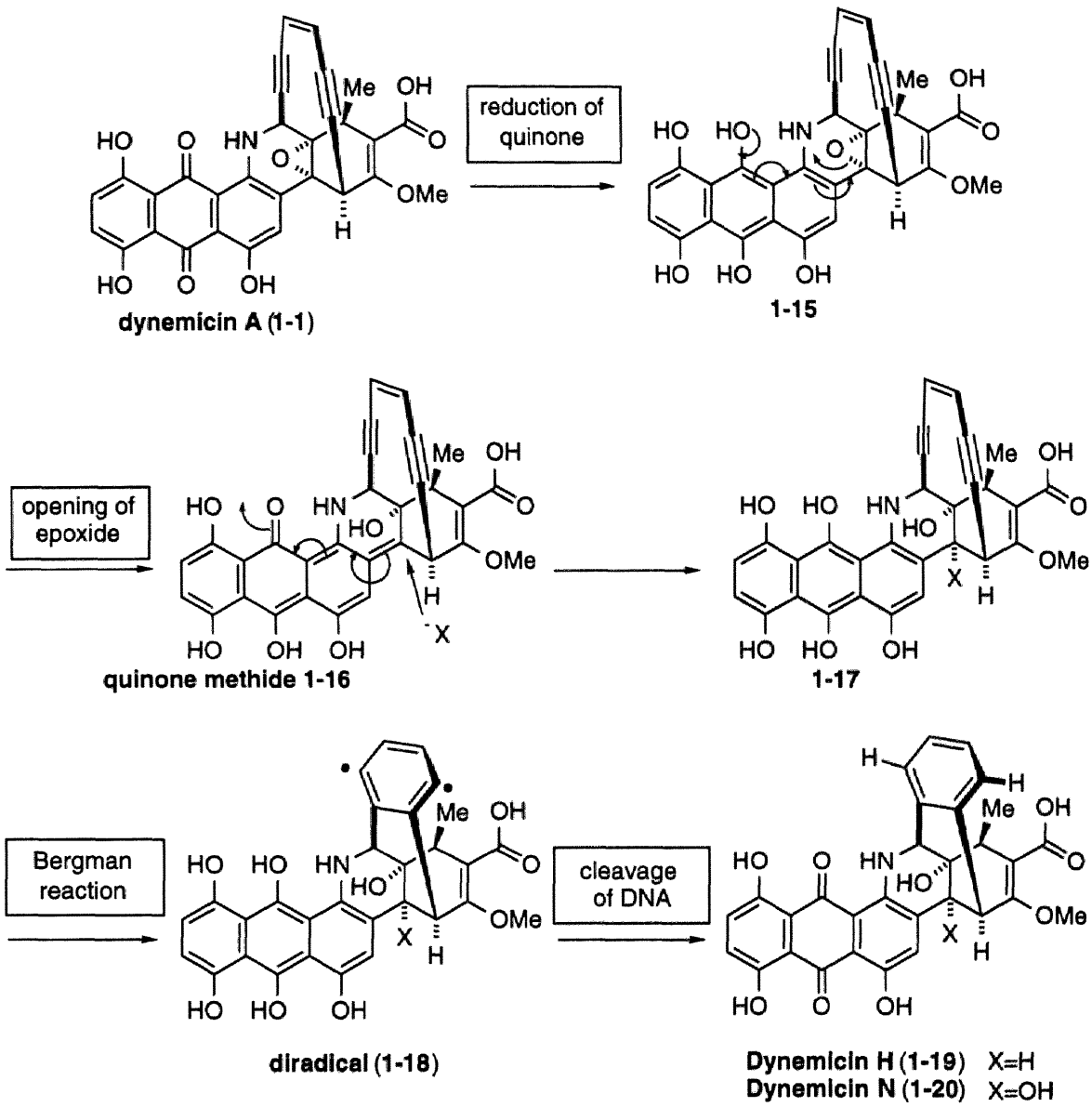
NCS-chr.: The mechanism of NCS-chr. was proposed by A. G. Myers as shown in **Scheme 1-4.** [5, 30] Thiol addition to **1-11** gave a highly unstable enyne cumulene intermediate **1-12**, which was cyclized to form diradical **1-13**. This radical **1-13** abstracted hydrogen atoms from deoxyribose of DNA. Myers elucidated the structure of degradation product **1-14** from its spectroscopic data and proposed the activation mechanism of NCS-chr. Finally he determined the complete structure including absolute configuration by means of chemical synthesis. Recently, a different mechanism of NCS-chr. was proposed by Saito and Hirama.[31]



Scheme 1-4. Action mechanism of NCS-chr.

Dynemicin A: According to the previous studies on the action mechanism of esperamicin/calicheamicin and anthracycline antibiotics, the multi-step mechanism of DNA cleavage by dynemicin A was proposed as follows (**Scheme 1-5**):[32] (i) intercalation of anthraquinone moiety to double strand DNA, (ii) bio-reduction of quinone moiety to hydroquinone (**1-1** → **1-15**),[33] (iii) epoxide opening to quinone methide formation (**1-15**→ **1-16**),[32] (iv) nucleophilic attack of water or protonation to form sp^3 carbon which increase the strain of enediyne moiety (**1-16** → **1-17**), (v) Bergman cycloaromatization to generate phenylene diradical (**1-17** → **1-18**), (vi) to abstract hydrogen atoms from the sugar phosphate backbone of DNA (**1-18** →**1-19** or **1-20**)[34] and (vii) to cleave the DNA chain.

In fact, the aromatized dynemicin A derivatives such as dynemicin H, M, *etc.* were isolated from natural source and from acid treatment of dynemicin A.



Scheme 1-5. Proposed Action Mechanism of Dynemicin A

As mentioned above, enediyne antibiotics work as the molecule having a function of facile DNA-cleavage. In particular, calicheamicin γ_1^I acts as restriction enzymes. These compounds have 9 or 10-membered enediyne ring as cutting device, aromatic moiety as binding to DNA, sugar as recognition site for sequence selective cutting,[35] and trisulfide or epoxide as triggering system in the same molecule (**Figure 1-5**). For example, in dynemicin A the anthraquinone part plays a role of intercalation to DNA base pair, quinone and epoxide is a triggering system. The enediyne ring is indispensable part for generation of phenylene diradical by Bergman reaction and existence of epoxide ring forbids Bergman cycloaromatization.

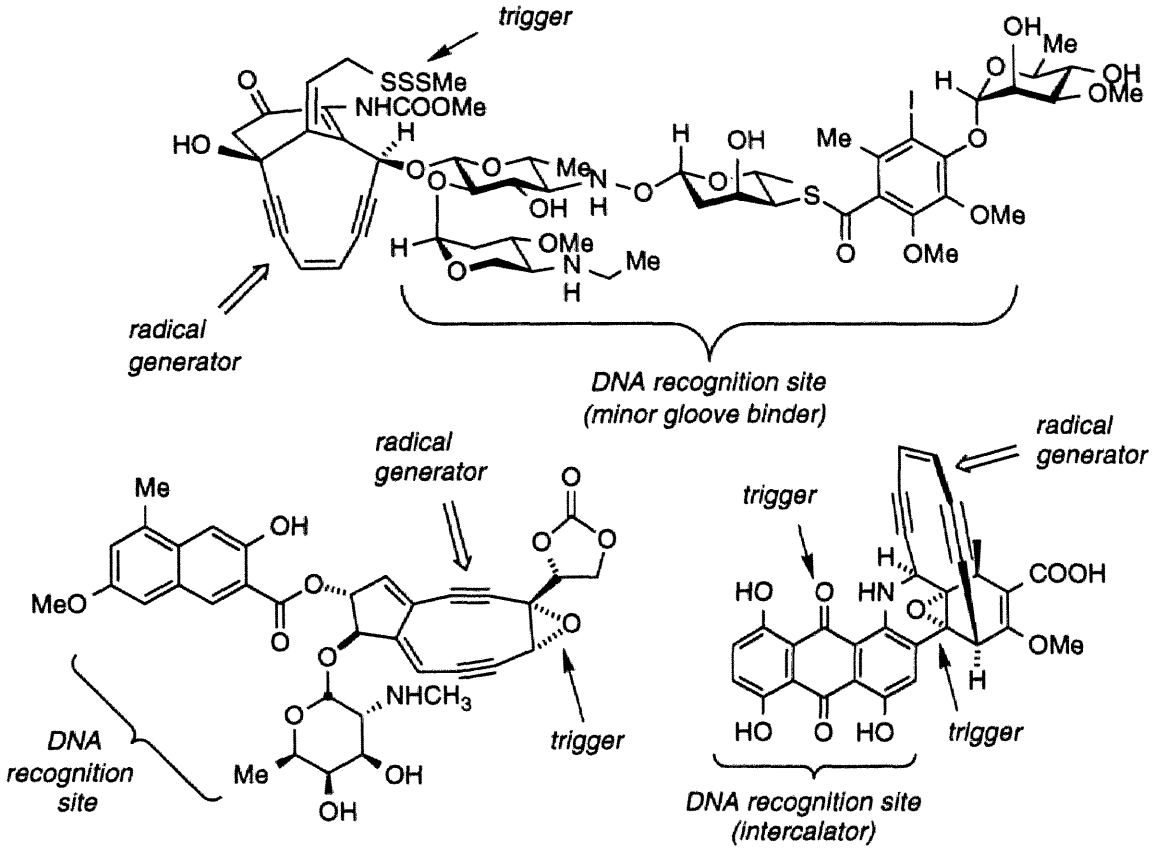


Figure 1-5. Functional Role of Enediyne Antibiotics.

I have been interested in the chemistry of these cyclic enediyne antibiotics, and felt a new field in natural product chemistry because of novel structures, potent biological activities, fascinating action mechanisms, precise recognition of DNA sequence and potentiality of creation of new type of DNA-cleaving molecule. I decided to start the synthetic studies on dynemicin A, including development of new reaction for the synthesis of dynemicin A, chemical syntheses of model compounds to explore biologically mimic structure, asymmetric synthesis, total synthesis, *etc.* [36]

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Discovery & structure of cyclic enediyne antibiotics

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Esperamicin/calicheamicin

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Kedarcidin and C-1027

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Action mechanism of enediyne antibiotics.

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Chapter 2

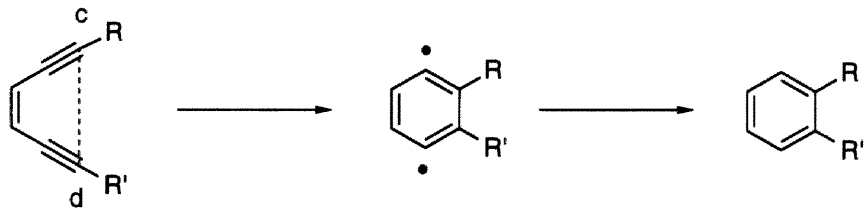
Molecular Design and Synthetic Plan of Dynemicin A Model Compounds

2-1.

Molecular Design of Dynemicin A Model Compound

Prediction of stability of enediyne compounds by molecular mechanics calculations

Recently, molecular mechanics calculations have been recognized as powerful tool for organic syntheses of complex molecules.[1] For example, the geometry of the stable conformer and the corresponding energy can be calculated, and we know the population of the conformer from the energy difference by Boltzmann equation. Based on the population, we can sometimes predict the selectivity in the diastereomeric reaction. In field of enediyne chemistry, Nicolaou and co-workers proposed that atomic distance (c-d distance) between two acetylenic atoms was correlated with the reactivity of Bergman reaction (**Scheme 2-1**).[2, 3] After calculations of many enediyne compounds and comparison with experimental data, critical range of c-d distance was found to be *3.31-3.20 Å*. The compounds with longer than 3.31 Å c-d value are known as stable compounds at 25 °C, while the compounds with shorter than 3.20 Å c-d values undergo spontaneous Bergman reaction at ambient temperatures. So that we might predict the reactivity to Bergman reaction by means of calculations of designed cyclic enediyne candidates before the actual synthesis. Although several exceptions have recently appeared,[4] c-d distances are convenient guide to predict the reactivities of Bergman reactions of designed enediyne candidates. We have used this guide for designing the model compounds and planning the synthetic route of model compounds of dynemicin A.

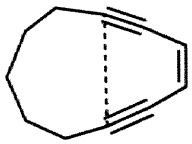
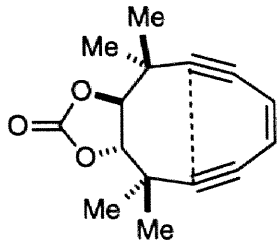
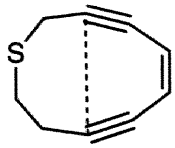
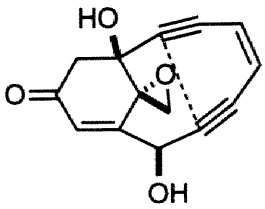
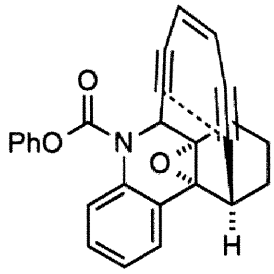
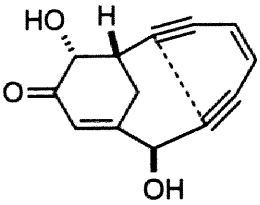
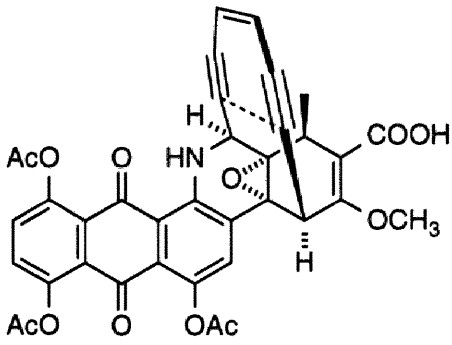
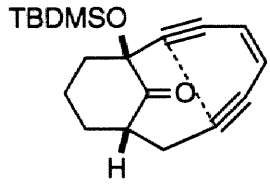


Scheme 2-1. Bergman reaction.

I calculated c-d distances of some enediyne compounds by MacroModel (MM2 force field) and Biograf (Dreiding II force field), and compared with experimental data from X-ray crystallographic analysis. The results are shown in **Table 2-1**. From this table, calculation using Biograf gave closer values to the results from X-ray crystallographic data. So that I have used Biograf in the following calculations of c-d distance.

As discussed above, molecular mechanics calculation can assist us to design the enediyne molecules. The distance of c-d predicted stability of enediyne structure. I used this method to estimate the stabilities of aftermentioned compounds.

Table 2-1.

Compound	Biograf	X-ray	Compound	Biograf	X-ray
	3.71 Å	3.66 Å [a]		3.45 Å	3.42 Å[f]
	3.48 Å	3.30 Å[b]			
	3.48 Å	3.44 Å[c]		3.48 Å	3.59 Å[g]
	3.46 Å	3.46 Å[d]		3.47 Å	3.54 Å[h]
	3.40 Å	3.39 Å[e]			

References: (a) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866-4868. Nicolaou, K. C.; Zuccarello, G, Reimer, C.; Estevez, V. A.; Dai, W.-M. *J. Am .Chem. Soc.* **1992**, *114*, 7360-7371. (b) Sakai, Y.; Nishiwaki, E.; Shibuya, M.; Kido, M. *Tetrahedron Lett.* **1991**, *32*, 4363-4366. (c) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 6890. (d) Schoenen, F. J.; Porco, J. A.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765-3768. (e) Magnus, P.; Fortt, S.; Oiterna, F.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986. (f) Nicolaou, K. C.; Sorensen, E.; Discordia, R.; Hwang, C.-K.; Minto, R. E.; Bharucha, K. N.; Bergman, R. G. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1044. (g) Nicolaou, K. C.; Hwang, C. K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (h) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

Molecular design of active mimic compound (Model A)

The first stage of this study aimed at exploring the biologically active mimic structure. Based on the proposed action mechanism of dynemicin A, the active mimic structure should contain 10-membered enediyne ring and epoxide at least. So that we designed bicyclo[7.3.1]-tridecendiyne system, **Model A** at first. In Chapter 3, the synthesis of the equivalent to **Model A** was described. The c-d distance of **Model A** was calculated to lead 3.50 Å, which suggested that **Model A** would be stable at ambient temperatures.

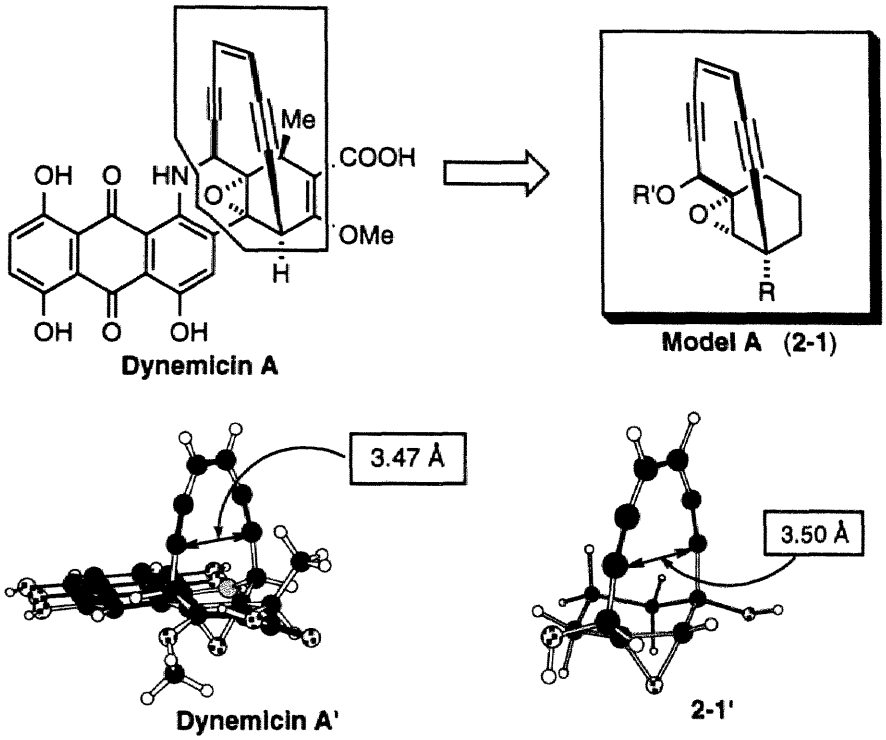
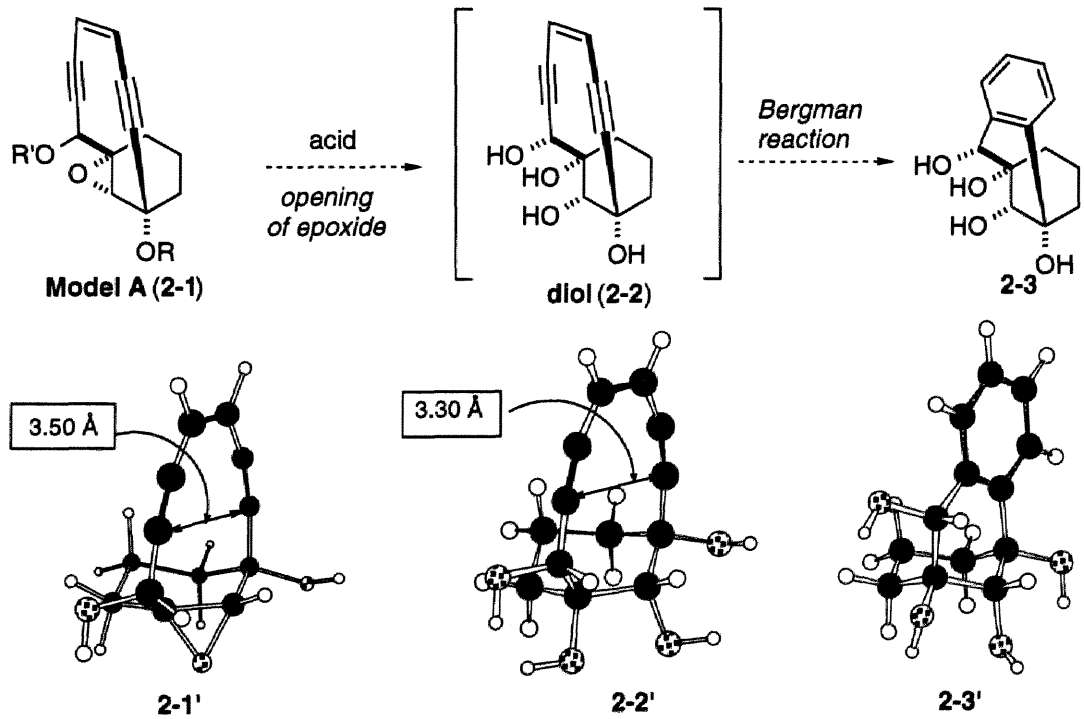


Figure 2-1. Simplification of dynemicin A.

I designed that trigger of **Model A** for Bergman reaction was opening of the epoxide **2-1**. I considered that acid treatment of **Model A** gave the diol **2-2**, which proceeded Bergman reaction spontaneously to give benzene derivative 2-3', because the c-d distance of the diol **2-2** was calculated to 3.30 Å by molecular mechanics calculation.



Scheme 2-2

Molecular design of active mimic compound (Model B)

As I described the detail result in Chapter 3, acid treatment of **Model A** afforded no Bergman product such as **2-3**. Consequently, I had to modify the structure of **Model A** or design the mimic structure again. After some consideration, **Model B** was designed as a new model compound, which had 10-membered enediyne ring, epoxide and aniline moieties. Connection of benzene ring to epoxide part was expected to facilitate regiospecific opening of epoxide.

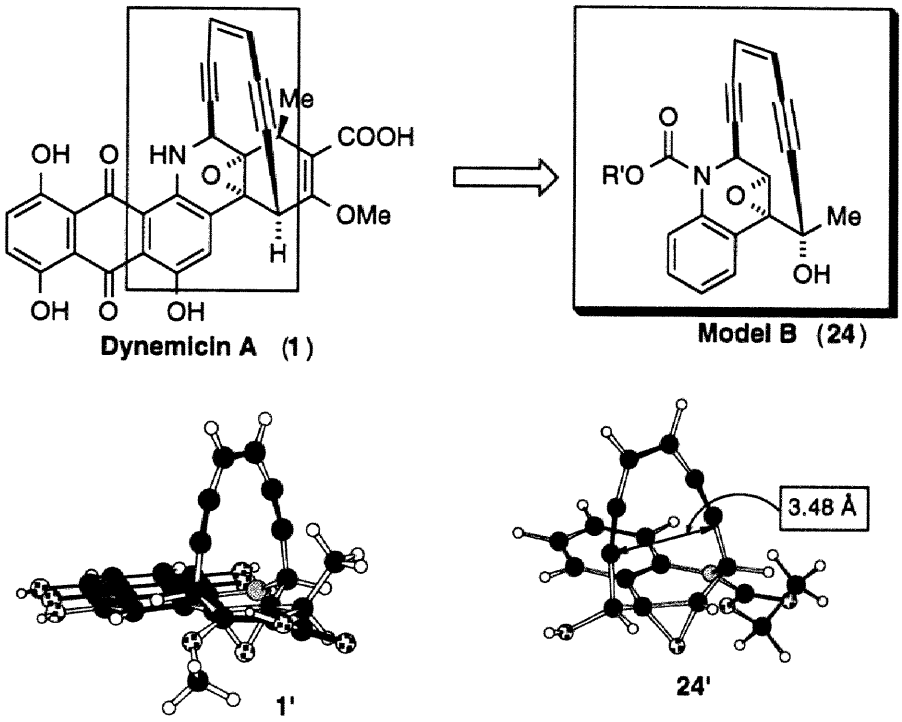
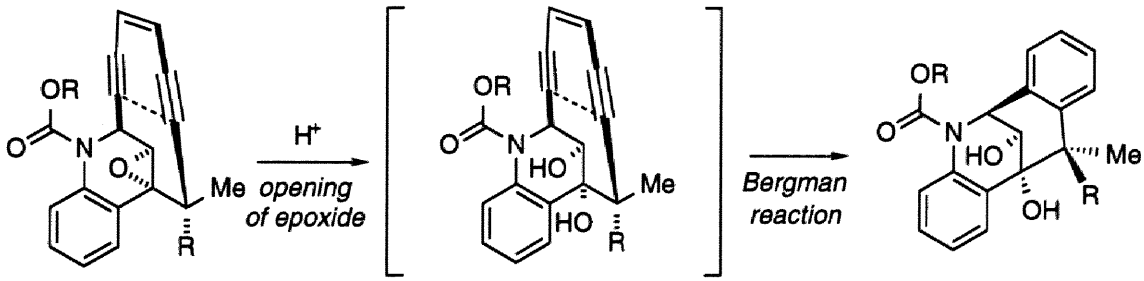


Figure 2-3.

Once the epoxide in **Model B** was opened, the cation was expected to be stabilized by benzene ring and captured by nucleophile such as water. The resultant diol **2-5** was anticipated to have the enough reactivity to Bergman reaction. This assumption was supported by molecular mechanics calculations. The c-d distance of diol **2-5** was 3.29 Å, which suggested that its Bergman reaction proceeded at room temperature to give **2-6**.



Scheme 2-3.

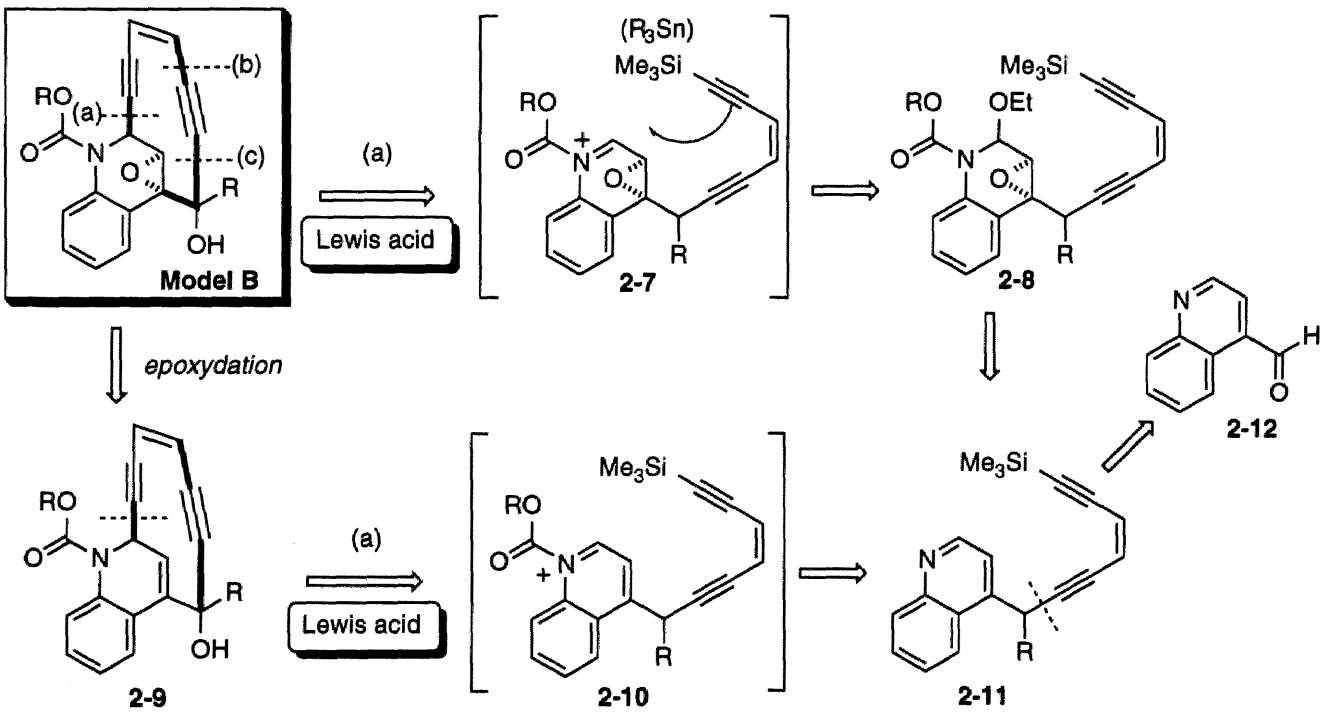
I described the efforts toward the synthesis of **Model B** in Chapter 4~7. In Chapter 7, the access to the more functionalized **Model B** was described. Finally, chiral synthesis of **Model B** was described in Chapter 8.

2-2

Synthetic Plan for Model Compound B

The most important step in the synthesis of **Model B** is a ring-closure of 10-membered enediyne ring, because the 10-membered enediyne moiety has a high strain and unstability. For the construction of 10-membered ring, I considered following three routes for disconnections at a, b and c position in **Model B** (**Scheme 2-4**).

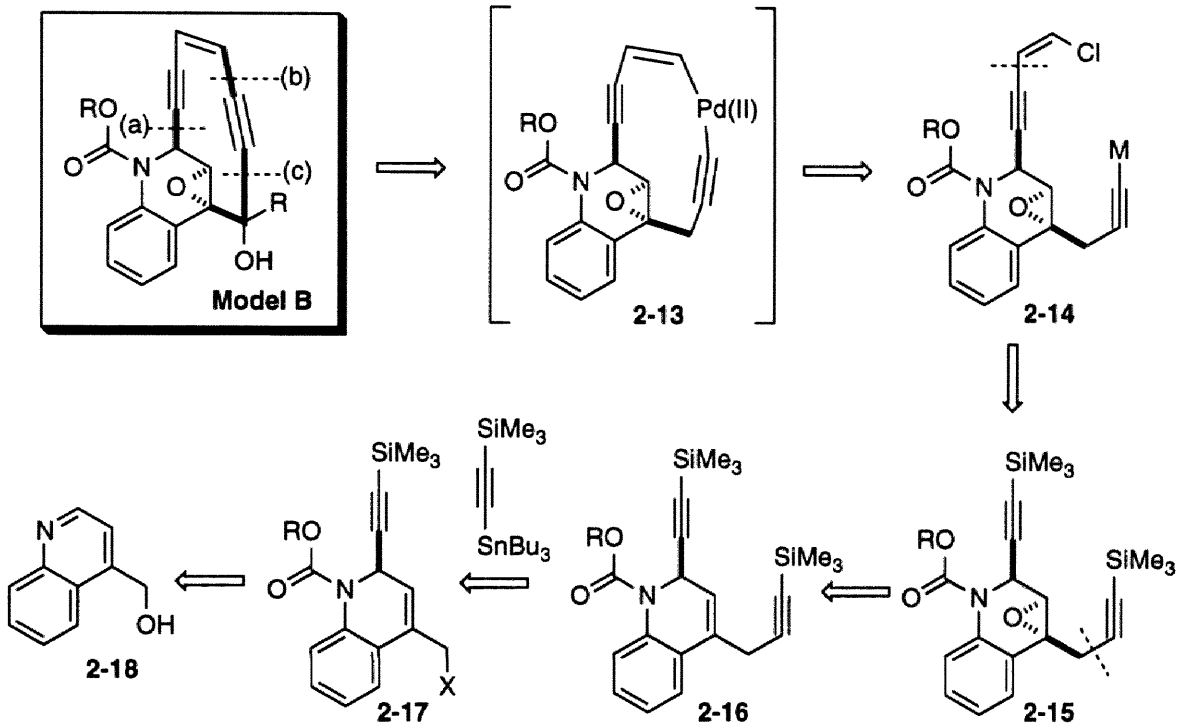
Route a (disconnection at a): The key reaction was intramolecular addition of silyl or tin acetylene to acyliminium cation **2-7**. As this type of reaction had not been reported, the development of the new reaction was necessary.[5] According to this plan, the precursor for cyclization was thought to be **2-8**. On the other hand, **2-9** was also plausible candidate as intermediate, an equivalent to **Model B**. For this intermediate **2-9**, the precursor was quinoline derivative **2-11**. Retrosynthesis of **2-8** and **2-11** led us to start from 4-quinolinecarboxaldehyde **2-12**. In the case of **2-11**, acyliminium cation **2-10** might be generated by treatment of **2-11** with chloroformate. In Chapter 4, the development of intermolecular reaction between silyl or tinacetylenes and acyliminium cations was described for this route.



Scheme 2-4. Retrosynthesis.

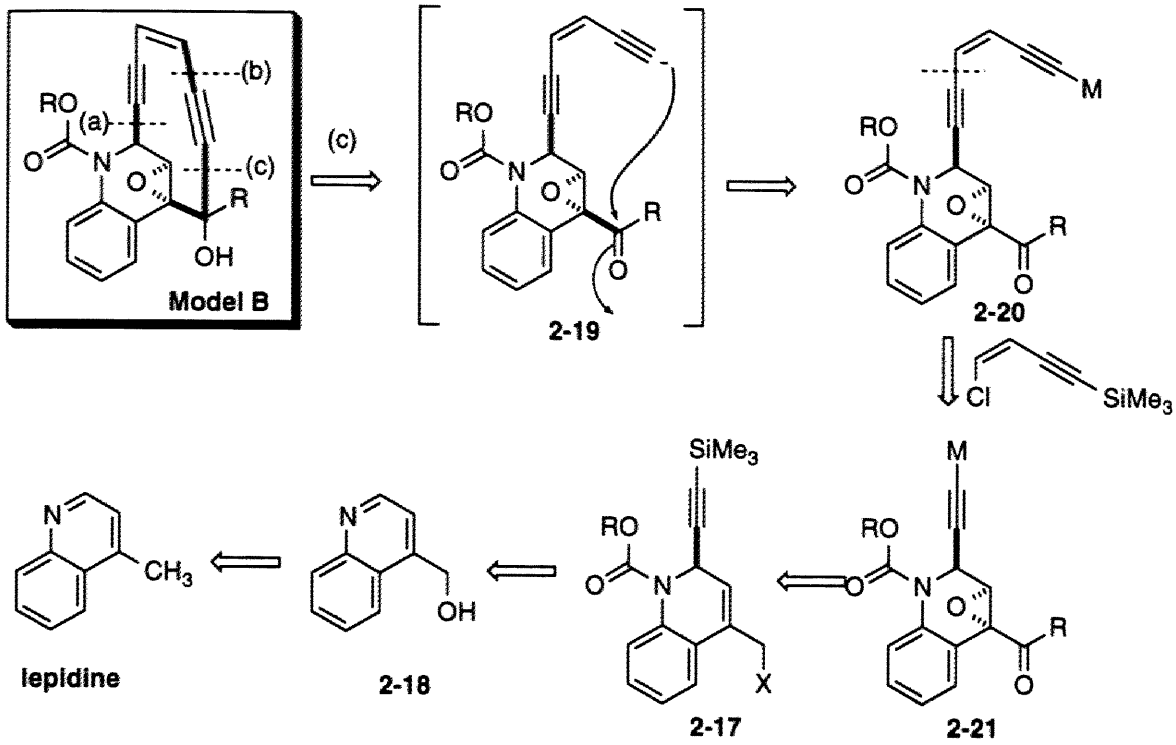
Route b (disconnection at b): The key cyclization was intramolecular palladium-mediated coupling under neutral condition.[6] For this coupling, following two Pd mediated reactions might be applied. (i) The palladium catalyzed coupling between terminal acetylene and vinyl chloride was known as Sonogashira's coupling,[7] in which CuI was used as a co-catalyst. (ii) The coupling reaction between tinacetylene and vinylhalide was known as Migita-Stille coupling[8] in which any co-catalyst was not required, but usually elevated temperature was necessary. The precursor for this cyclization

was bis-trimethylsilyl acetylene **2-15**, which would be synthesized through the palladium catalyzed coupling between the allyl derivative **2-17** and tinacetylene. There were little reports about such reaction in the literature. Consequently, I decided to develop the reaction for this C-C bond formation (in Chapter 6). The allyl intermediate was retrosynthesized into the quinoline compound **2-18** (**Scheme 2-5**). Introduction of acetylene to **2-18** would be realized by Yamaguchi's condition using magnesium acetylide and chloroformate.[9]



Scheme 2-5. Route b

Route c (disconnection at c): The key cyclization was intramolecular acetylide anion attack to carbonyl group. This method has been used to construct the enediyne ring in the synthesis of esperamicin/calicheamicin type compounds which were originally synthesized by Kende and Danishefsky independently.[10] The acetylide anion **2-19** can be generated by several methods such as deprotection of terminal acetylene with base, treatment of trimethylsilylacetylene with fluoride anion (Kuwajima and Nakamura's protocol),[11] *etc.* The precursor of this cyclization was an acyclic enediyne **2-20**, which was retrosynthesized into the epoxy carbonyl compound **2-21**. Stereoselective epoxidation of **2-17** could be controlled by axial like conformation of acetylene substituent (the conformation of **2-17** was described later). In Chapter 6, the synthesis of **Model B** by route was discussed.

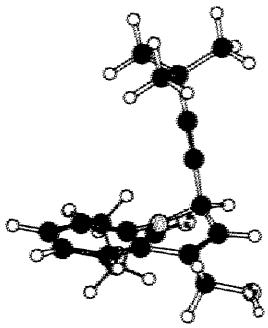


Scheme 2-6. Route c.

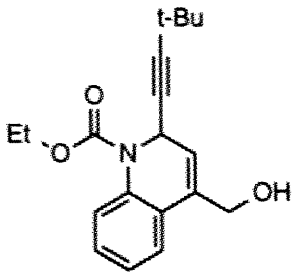
The common synthetic intermediate of **route b and c** was acetylene alcohol **2-17.** As discussed before, **2-17** might be synthesized from the quinoline derivative **2-18**, which was obtained by benzylic oxidation of commercially available 4-methylquinoline (lepidine).

Protective group of nitrogen atom.

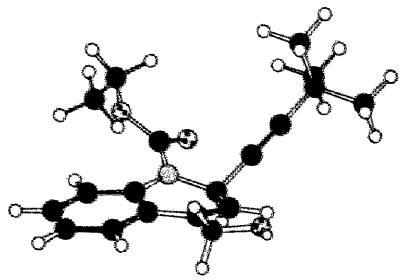
At this stage, I would like to mention the effect of protective group of nitrogen atom toward the preferential conformation. In the above desired intermediates (**2-14, 2-17, 2-20**), acetylene substituent occupies *pseudo*-axial position on 6-membered ring due to A-strain effect between amide bond and acetylene group.[12] This conformation may have a great advantage to critical cyclization process of 10-membered enediyne ring, because this axial conformation is similar to the conformation of desired cyclized product. This preferential conformation of **2-22** was supported by molecular mechanics calculation. As shown in Figure **2-4**, the axial conformer (**2-22 ax**) is 4.48 kcal/mol more stable than the equatorial conformer (**2-22 eq**), which suggests the **2-22 eq** being almost not present at rt. On the other hand, in the case of non protected amine (aniline) **2-23**, the conformation is not fixed. Molecular calculations gave that the energy difference between axial and equatorial conformers (**2-23 ax**. and **2-23 eq**.) was very small (ΔE = 0.22 kcal/mol), which indicated that both conformers existed at room temperature in the ratio 59:41.[13] Consequently, nitrogen atom of aniline should be protected by acyl group.



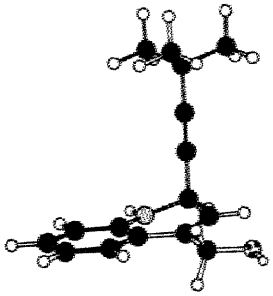
2-22 ax.
amine-axial
32.93 kcal/mol



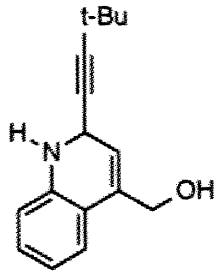
2-22
ΔE = 4.48 kcal/mol
axial : equatral = 99.9 : 0.1



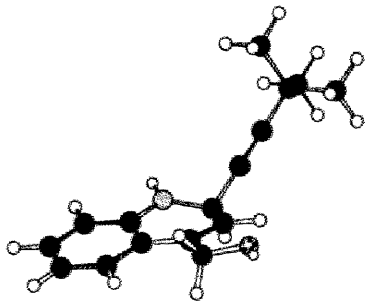
2-22 eq.
amide-equatorial
37.41 kcal/mol



2-23 ax.
amine-axial
10.29 kcal/mol



2-23
ΔE = 0.22 kcal/mol
axial : equatral = 59 : 41



2-23 eq.
amine-equatorial
10.51 kcal/mol

Figure 2-4

References & Notes

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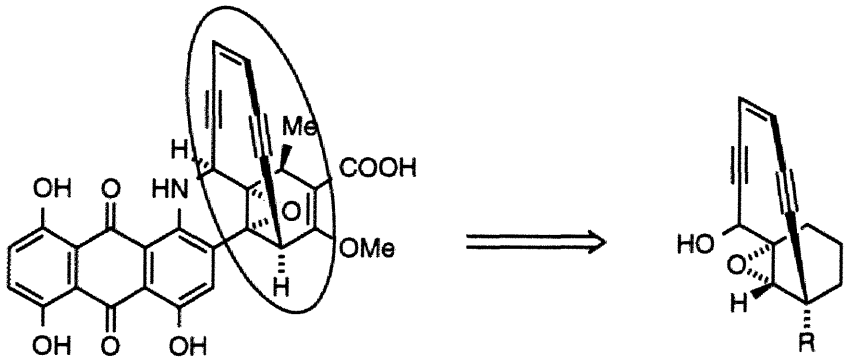
Chapter 3

Synthesis of Model Compound (Model A) having Epoxide and Cyclic Enediyne Moiety of Dynemicin A

Synthesis of Model Compound (Model A) having Epoxide and Cyclic Enediyne Moiety of Dynemicin A.

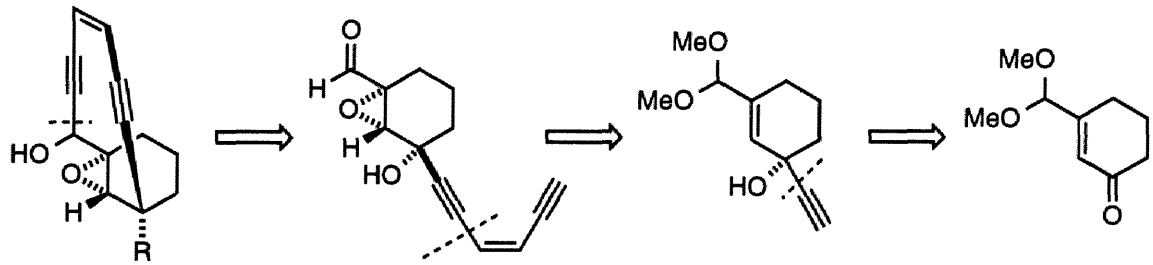
Model A compound have an epoxide as a trigger for Bergman reaction and 10-membered enediyne ring for radical formation via Bergman reaction. In this Chapter, I dealed with the following points: (i) a short synthetic route to construct bicyclo [7.3.1]-tridecenediyne system of **Model B**, and (ii) chemical behavior of synthesized **Model A** under acidic condition.



Dynemicin A (1) **Model A**

Figure 3-1. Simplification of dynemicin A into Model A

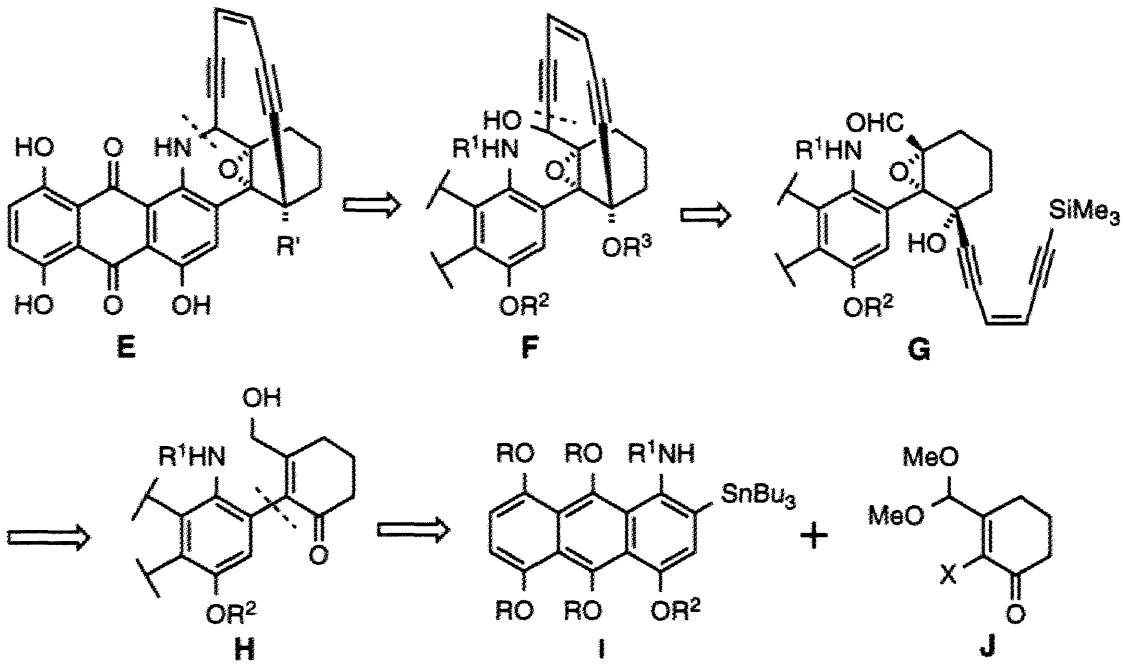
Synthetic plan for the **Model A** is shown in **Scheme 3-1**. Disconnection at the propargylic bond led us to the enediyne aldehyde **B** as a precursor for cyclization. This type of cyclization had been reported by A. S. Kende and S. J. Danishefsky independently.[1] Retrosynthetic analysis of **B** afforded the acetylene acetal **C**, which could be synthesized from the enone acetal **D**.



Model A **B** **C** **D**

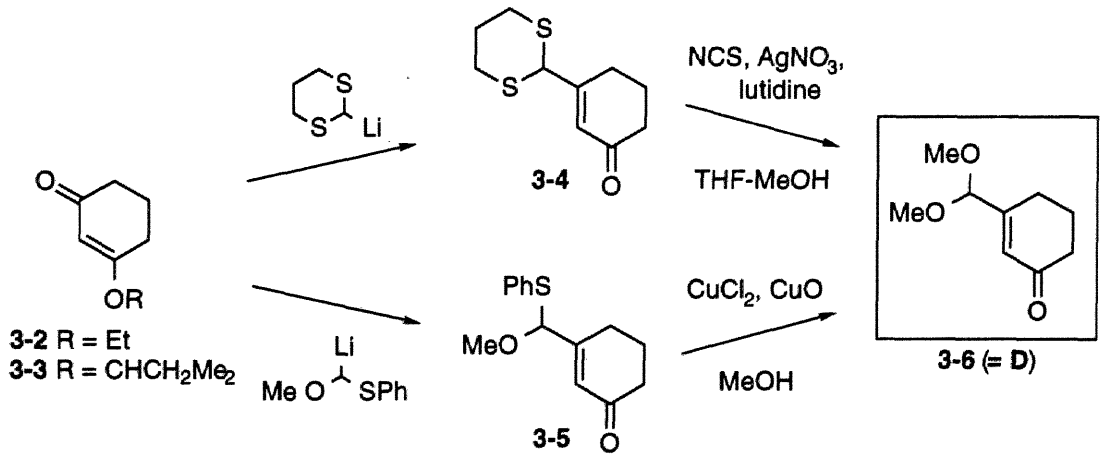
Scheme 3-1. Synthetic Plan for Model A

If the above plan could be realized, this plan will be extended to the following plan for the synthesis of the similar model to dynemicin A (**Scheme 3-2**). Retrosynthetic disconnection of the propargylic and acetylenic bonds in simplified model compound **E** afforded the aminoalcohol **F** and further the aminoaldehyde **G**. The precursor was analyzed as the enonealcohol **H**, from which the aromatic and aliphatic moieties were separated into **I** and **J**. The coupling reaction between **I** and **J** was described in Chapter 8.



Scheme 3-2

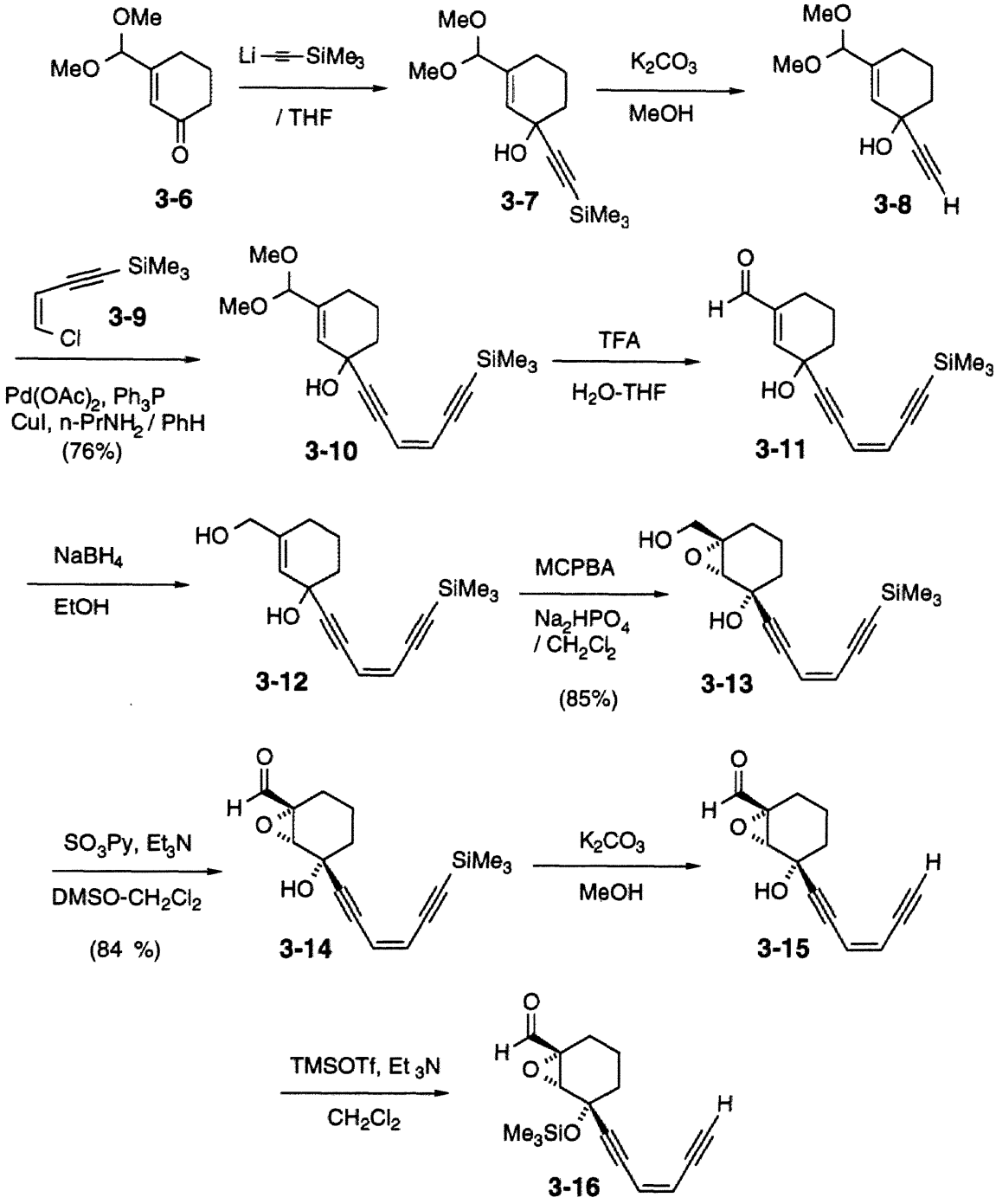
The synthesis started from preparation of starting material **D**. Since this enone acetal **D** had not been reported in the literature,[2] the following two methods were developed for the synthesis of **D**. 3-Alkyloxy-cyclohexenones (**3-2, 3-3**) were chosen as starting materials. Addition of lithio 1,3-dithiane to **3-2**, followed by hydrolysis gave **3-4**, which dithiane was converted into the dimethylacetal **3-6**. Alternatively, **3-3** was homologated with methoxymethyl thiophenylsulfide to afford the monothioacetal **3-5**, which was converted to the same enone acetal **3-6** under Mukaiyama's condition.[3] The resultant cyclohexenone acetal **3-6** (= **D**) is not only the starting material for **Model A**, but also a versatile and important synthetic intermediate for the synthesis of other natural products.[4]



Scheme 3-3

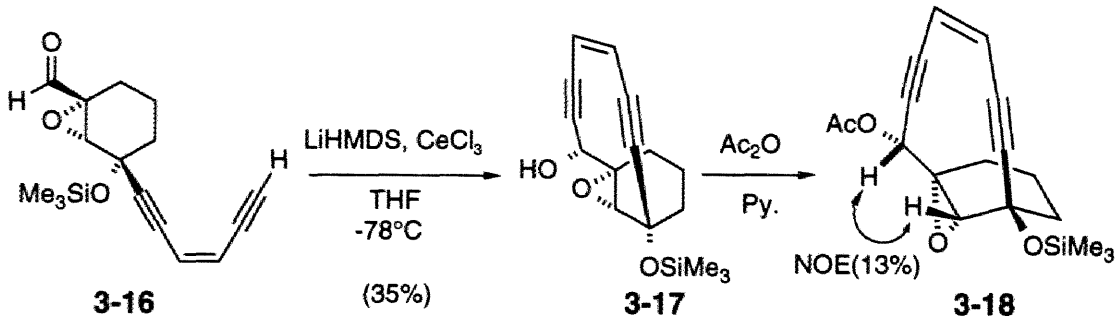
Lithium trimethylsilyl acetylide was added to **3-6** and the product **3-7** was desilylated to afford the propargyl alcohol **3-8**. Coupling between **3-8** and the (*Z*)-vinyl chloride **3-9**[1a] under Sonogashira's palladium condition (Pd-Cu catalyst)[5] afforded the acyclic enediyne **3-10**. Acid hydrolysis of the acetal **3-10** was followed by sodium borohydride reduction of the aldehyde to give the unstable diol **3-12**. Epoxidation of the allylic alcohol **3-12** with MCPBA at 5°C afforded the *syn* epoxide **3-13** whose

stereochemistry was assigned from Henbest rule at this moment. The epoxyalcohol **3-13** was oxidized with SO_3·Py -DMSO[6] to yield the epoxyaldehyde **3-14** in high yield (84%). Sequential desilylation from the silylacetylene **3-14** and silylation of the *tert*-alcohol in the aldehyde **3-15** furnished the cyclization precursor **3-16** (an equivalent to **B**).



Scheme 3-4

For the cyclization, the lithium acetylide of **3-16** in the presence of $CeCl_3$[7] was the most effective to afford **3-17** (**Scheme 3-5**). The condition without $CeCl_3$ gave a mixture of **3-17** (in very low yield) and dimerized products. Stereochemistry of the alcohol **3-17** was assigned from the positive NOE between the epoxidic proton and propargylic proton in the corresponding acetate **3-18**. In this stage, the potential mimic compounds **3-17** and **3-18** of dynemicin A were obtained.



Scheme 3-5

In **Figure 3-2**, two cyclic enediyne antibiotics and our synthetic compound are compared. The product **3-18** possesses the bicyclo[7.3.1]-tridecendiyne system, and it is regarded as new esperamicin/ calicheamicin enediyne analog that contains a trigger of dynemicin A.

Epoxide opening induced by acid treatment did not afford the expected Bergman product, but isomerized allylic alcohol **3-19** which is an important analog of bicyclo[7.3.1]-tridecadiendiyne system as the esperamicin aglycon.

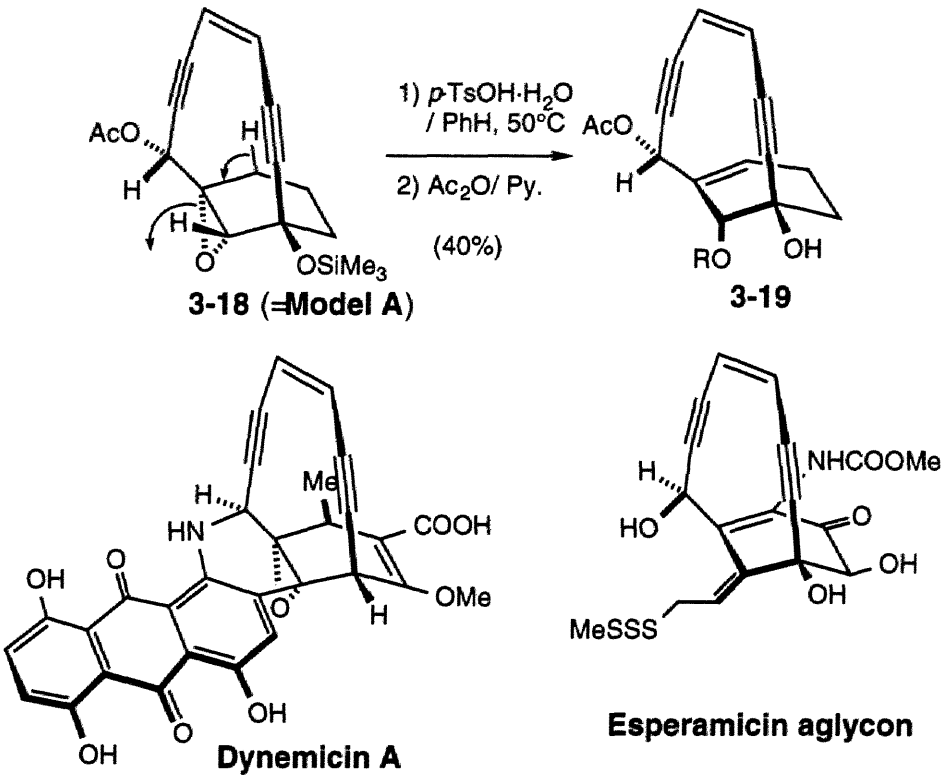
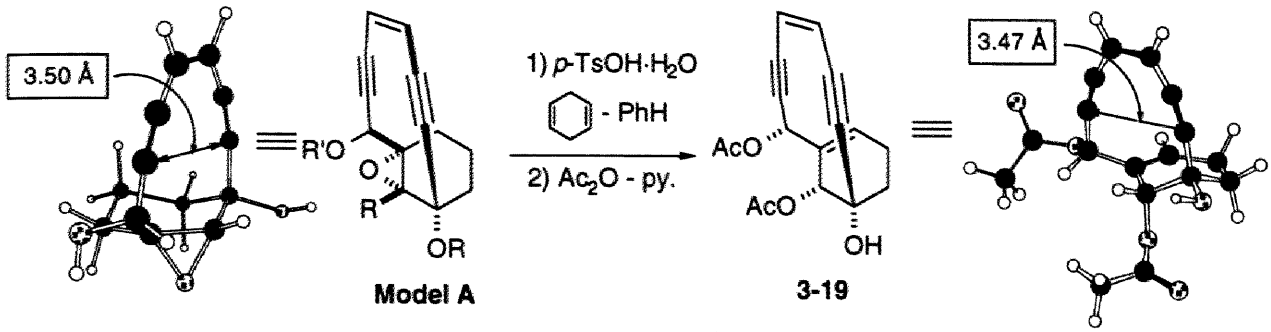


Figure 3-2

As mentioned earlier, **3-18** was inert toward Bergman reaction even under acidic reaction. The isomerized product **3-19** showed no reactivity to Bergman reaction because the bridgehead double bond inhibited Bergman reaction as esperamicin/calicheamicin. This fact was rationalized by molecular mechanics calculation (**Scheme 3-4**). The c-d distance of **3-19** was 3.47 Å, which suggested enough stable at ambient temperatures. One of the reasons that acid treatment of **3-18** did not give the diol, was due to the regiochemistry in opening of epoxide. Position of epoxide opening is different from the case of dynemicin A. The opening of the epoxide in dynemicin A occurred at benzylic position because of the stability of the generated cation. On the other hand, synthesized

Model A showed the different (opposite) regioselective opening of epoxide from the case of dynemicin A. Consequently, introduction of a substituent (R = aryl) to stabilize the cation formed by the opening epoxide was required to enforce the requisite diol formation.



Scheme 3-4

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Chapter 4

Silyl and Tin Acetylene as Nucleophile toward Acyliminium Cation

Silyl and Tin Acetylene as Nucleophile toward Acyliminium Cation

The C-C bond forming reaction between propargylic carbon and nitrogen in dynemicin A is important in the synthesis of dynemicin A (**Figure 4-1**).

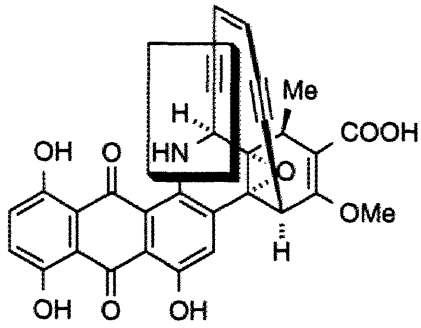
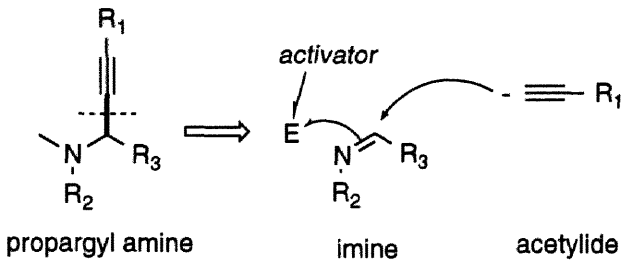


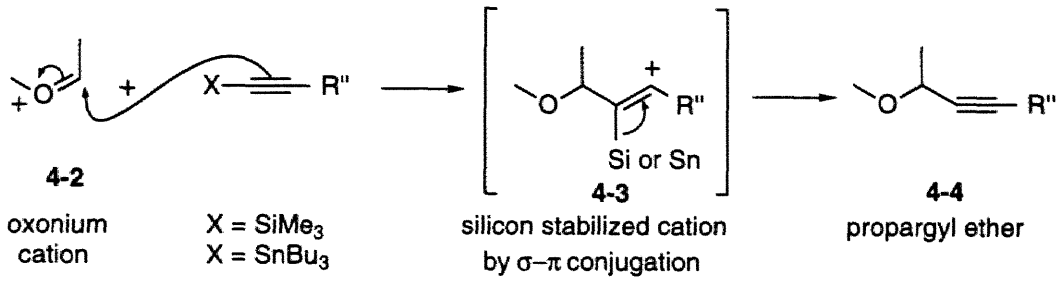
Figure 4-1. Dynemicin A

This type of process has been achieved by addition of metal acetylide to imine, in the presence of Lewis acid or acid chloride, which activates the imine to assist the addition of low nucleophilic metal (lithium, magnesium) acetylide (**Scheme 4-1**).[1]



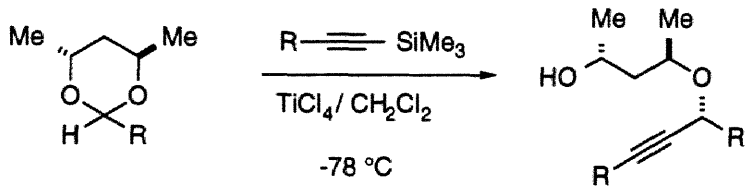
Scheme 4-1

On the other hand, silyl or tinacetylenes has been used as nucleophile towards cationic centers such as oxonium cation (**Scheme 4-2**). Namely, the oxonium cation **4-2** (eg. generated from acetal) reacted with silyl or tinacetylene to give the cation intermediate **4-3**, which was stabilized by σ–π conjugation of silicon or tin atom. Elimination of silicon from **4-3** afforded the product **4-4**. For example, W. S. Johnson reported that silylacetylene reacted with the chiral acetal in the presence of Lewis acid to give the chiral propargyl alcohol (eq. 1 in **Scheme 4-3**).[2] Nicolaou[3] and Isobe[4] independently reported C-glycosidation of glycals with silylacetylene in which an oxonium cation intermediates was formed *via* isomerization of the double bond (Ferrier type rearrangement) (eq. 2, 3). The high α–selectivity in this alkynylation was attributed to axial attack of silylacetylene to the oxonium cation. And in the same year, R. M. Williams reported alkynylation of bromo glycoside derivative with tinacetylene (eq. 4).[5] Mukaiyama simultaneously reported catalytic version of Johnson's type reaction.[6]

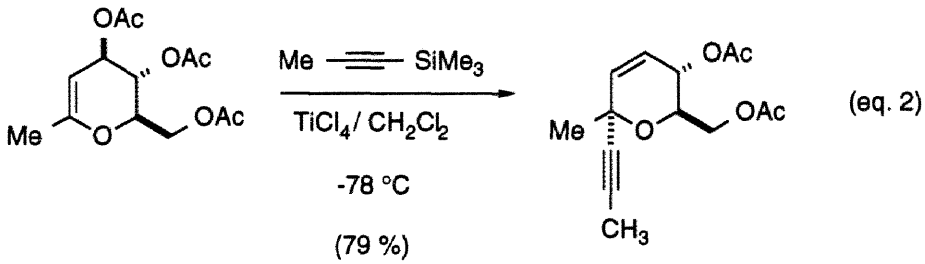


Scheme 4-2

W. S. Johnson (1983)

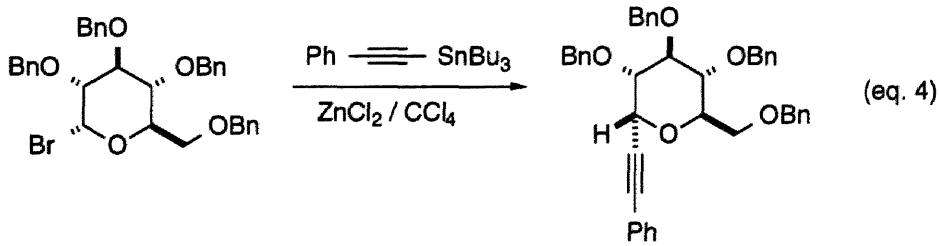


K. C. Nicolaou (1986)



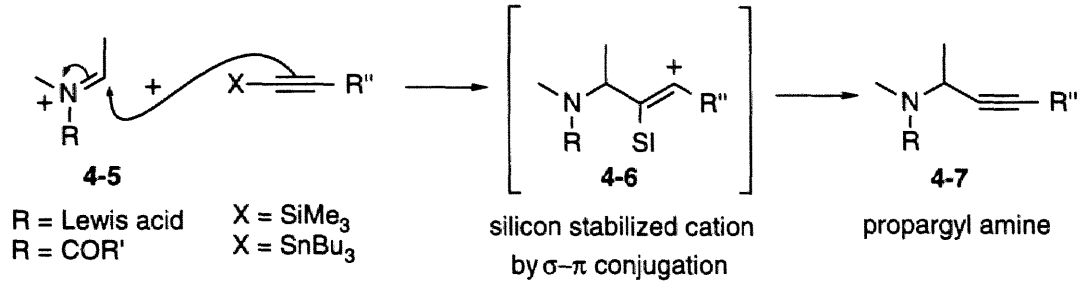
Isobe (1988)

R. M. Williams (1988)



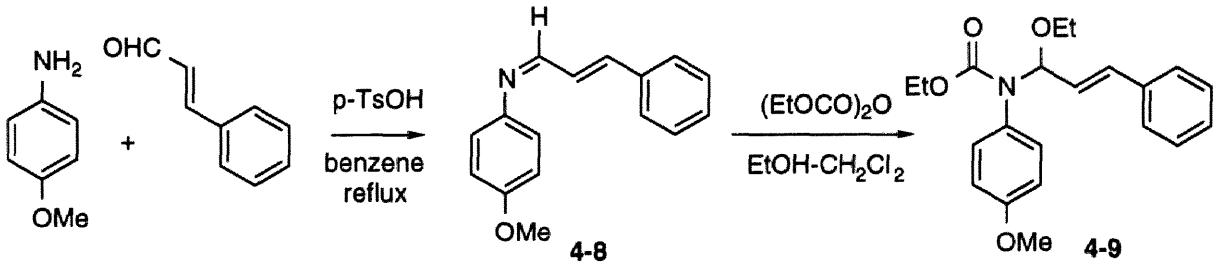
Scheme 4-3

Based on the above discussion, iminiun cation **4-5** was expected to have similar reactivities towards the silyl and tinacetylenes to the case of oxonium cation (**Scheme 4-4**). However, I found no report on the addition of silylacetylene to iminium cation in the literature. So that I embarked to study this type of reaction.



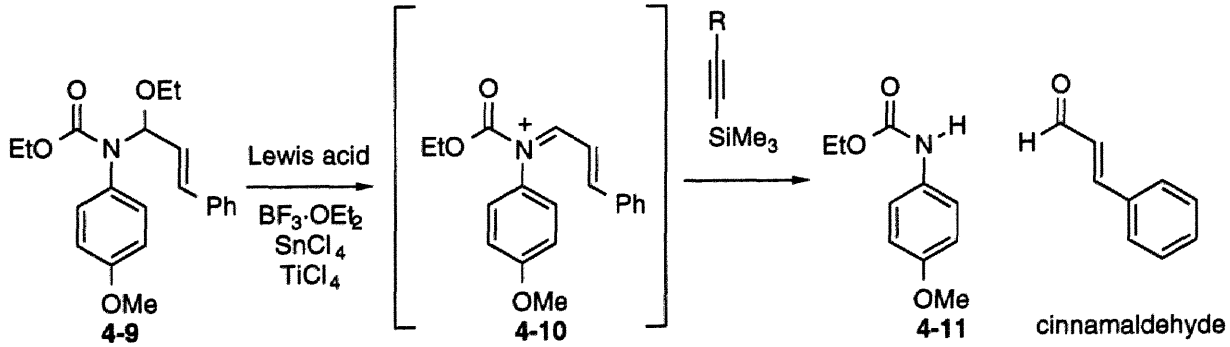
Scheme 4-4

In order to examine this reaction, I selected the imine **4-8** as a substrate which was easily prepared from *p*-anisidine and cinnamaldehyde in the presence of *p*-TsOH.[7] Initially I attempted the reaction of imine **4-8** and bis(trimethylsilyl)acetylene in the presence of various Lewis acids or chloroformates, but all attempts failed. After some consideration, α-alkoxycarbamate **4-9** was chosen for this study. The substrate **4-9** was also easily prepared from the imine **4-8** with diethyl pyrocarbonate.[8]



Scheme 4-5

Using α-ethoxycarbamate **4-9** as a substrate, I have examined the reaction conditions (Lewis acids) for displacement of acetylene. No displacement reaction with $BF_3{\cdot}OEt_2$, $SnCl_4$, $TiCl_4$ as Lewis acid, but hydrolysis to cinnamaldehyde and *N*-ethoxycarbonyl *p*-anisidine **4-11** occurred (**Scheme 4-6**). This result indicated that acyl iminium cation **4-10** was generated in these reaction conditions.[9] After some experiments, $AlCl_3$ was found to assist the addition of silylacetylene to acyl iminium cation.[10] But the product was not propargylic amine but unstable 1,4-adduct **4-12** (entry 1 in **Table 4-1**).

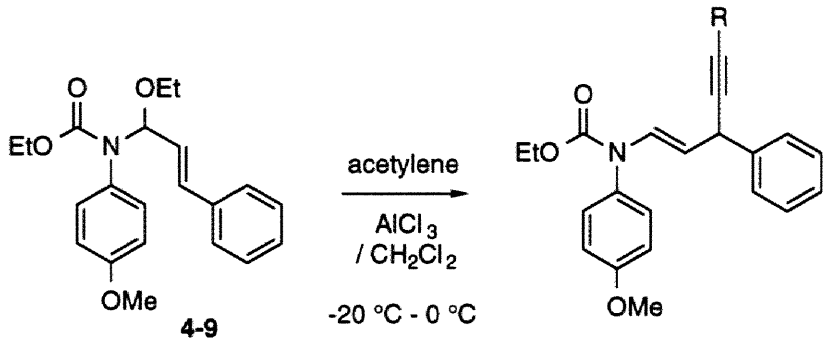


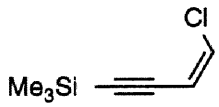
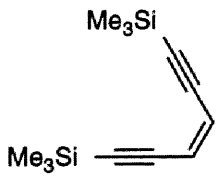
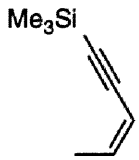
Scheme 4-6

For another silylacetylenes, the results are shown in **Table 4-1**. In entry 2, both TMS terminals were reactive. More complexed silylacetylenes in entry 3, 4, gave 1,4-adduct (**4-15**,[11] **4-16**[12]) in fair

yield. But phenylthioacetylene[13] gave complexed mixture even after exploring some conditions (entry 5).

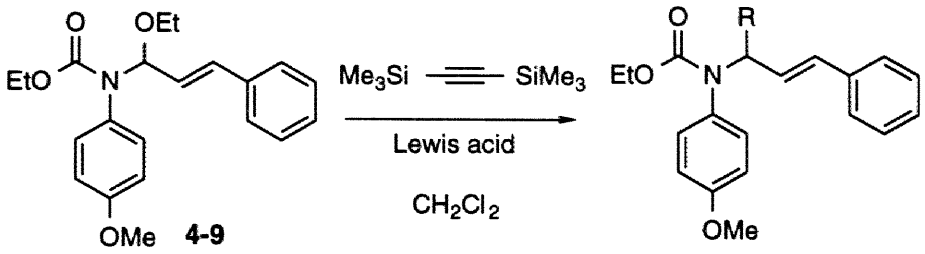
Table 4-1



entry	silylacetylene		product	yield (%)
1	Me_3Si—≡—$SiMe_3$	**4-12**	R = $SiMe_3$	40
2	Me_3Si—≡—≡—$SiMe_3$	**4-13**	—≡—$SiMe_3$	20
		4-14	—≡—)$_2$	20
3		**4-15**		45
4		**4-16**		31
5	Me_3Si—≡—SPh	**4-17**	—≡—SPh	0

Other aluminum Lewis acids examined in this reaction (**Table 4-2**) were $EtAlCl_2$ and Et_2AlCl, which gave the ethyl adduct **4-18** as a major product instead of ethynylated product **4-19** This result suggested that alane might act as a nucleophile. In fact, in the preliminary experiment, the alane gave **4-19** in low yield although the optimization of yield remained (entry 3).

Table 4-2

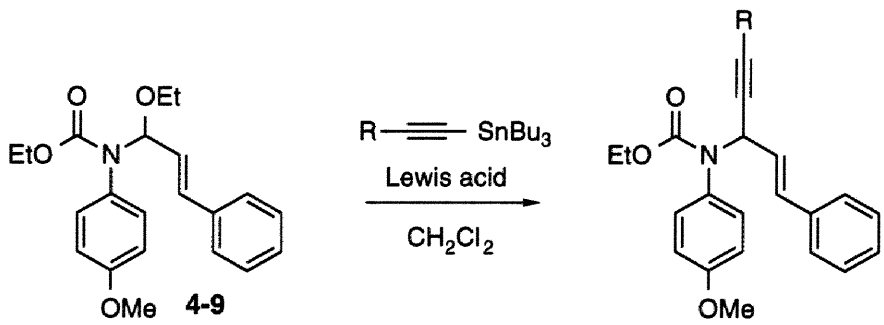


entry	Lewis acid (eq.)	temp.		product	yield
1	$EtAlCl_2$ (2.5)	-20 °C - rt	**4-18**	R = Et	51 %
2	Et_2AlCl (2.5)	-20 °C	**4-18**	R = Et	94 %
3	$Me_3Si{-}{\equiv}{-}AlEt_2$ (2.0)	-20 °C - 0 °C	**4-19**	$R = {\equiv}\text{-}SiMe_3$	14 %

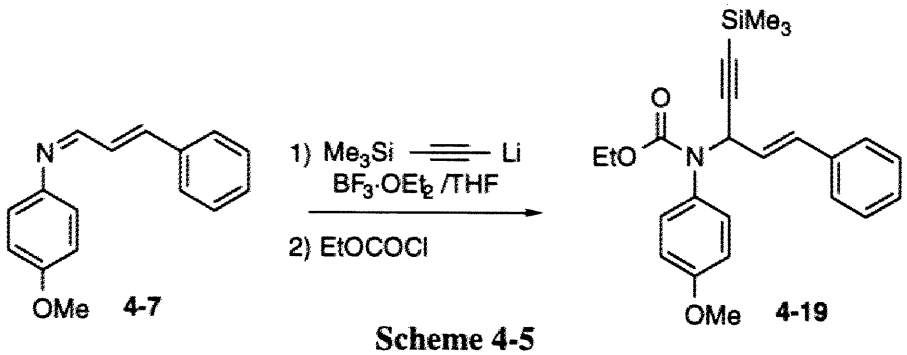
Tinacetylene

In general, tinacetylene has been known more reactive than corresponding silylacetylene.[14] So that I examined the reaction of tinacetylene to the same substrate **4-9** (**Table 4-3**). Surprisingly, the product was 1, 2-adduct exclusively. In contrast with silylacetylene described before, all the Lewis acids used here gave 1,2-adduct **4-19, 4-20**. The structure of **4-19** was confirmed by alternative synthesis shown in **Scheme 4-5**. The addition of acetylide did not occur without activation of imine by Lewis acid or acylating agent.

Table 4-3

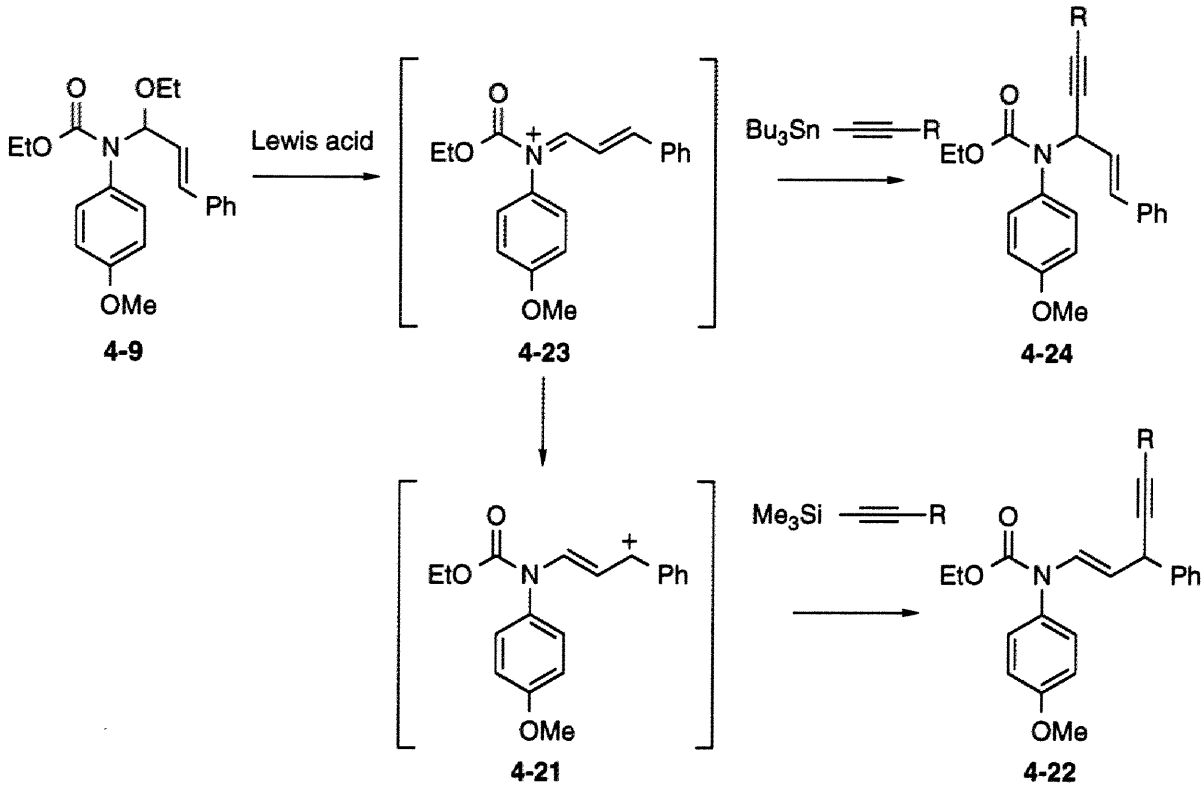


entry	tin acetylene	Lewis acid (eq)	product	yield
1	R = Ph	$BF_3{\cdot}OEt_2$ (1)	**4-20**	47 %
2	R = Ph	$TiCl_4$ (1.5)	**4-20**	27
3	R = Ph	$SnCl_4$ (1.5)	**4-20**	51
4	$R = SiMe_3$	$TiCl_4$ (1.5)	**4-19**	81



Scheme 4-5

In summary, silylacetylene was added to α-ethoxycarbamate **4-9** to give 1,4-adduct **4-22**, while tinacetylene reacted to give desired 1,2-adduct **4-24**, exclusively (**Scheme 4-6**). The difference of regioselectivities between silylacetylene and tinacetylene might be rationalized as follows. Treatment of α-ethoxycarbamate **4-9** with Lewis acid formed acyliminium cation **4-23** as initial intermediate, which might be isomerized to more stable benzylic cation **4-21**. Tinacetylene immediately reacted with **4-23** to give **4-24** because of high reactivity of tinacetylene. On the other hand, less reactive silylacetylene reacted with more stable cation intermediate **4-21** after the isomerization was competed. In the next stage, this reaction was applied to the cyclic α-alkoxycarbamate which was similar structure to the part of dynemicin A.

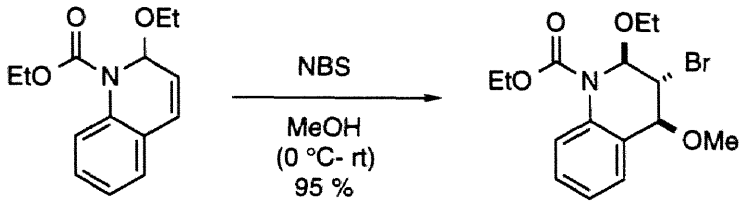


Scheme 4-6

Cyclic α-alkoxycarbamate

Initially I chose EEDQ **4-25** (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) as a cyclic substrate for this purpose. EEDQ is commercial available for peptide condensing reagent. After some experiment, EEDQ itself was found to be not suitable substrate for current reaction. Since the epoxidation of EEDQ **4-25** with MCPBA did not give the epoxide, while the bromohydrin **26** was

synthesized from **4-25** with NBS in methanol. The results of the coupling reaction using **4-26** and tin and silylacetylene was shown in **Table 4-4**.

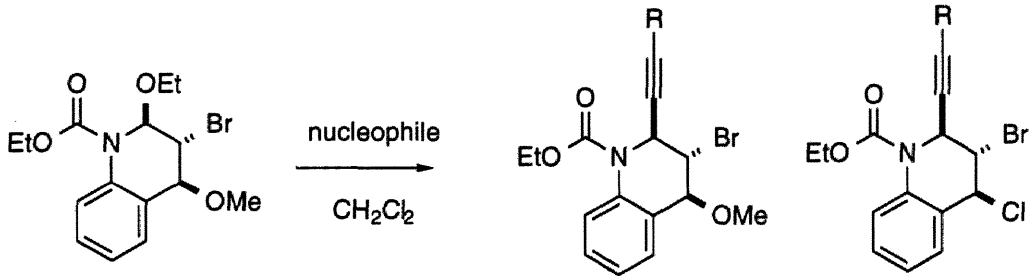


EEDQ (4-25) **4-26**

Scheme 4-7

Both tin and silylacetylenes were added to give the ethynylated products (**4-27**, **4-28**). The yields of the products were not good. In the case of $AlCl_3$, the problem in this substrate was that unstable benzylic OMe was replaced with Cl under the condition. More reactive tinacetylene in the presence of milder Lewis acid $BF_3{\cdot}OEt_2$ gave only **4-28a**.

Table 4-4



4-26 **4-27a** **4-28a** **4-27b** **4-28b**

entry	nucleophile	Lewis acid	temp.		R	yiels of **a**	yiels of **b**
1	$Me_3Si{\equiv}SiMe_3$	$AlCl_3$	-20 °C - 0 °C	**4-27**	$SiMe_3$	16 %	23 %
2	$Ph{\equiv}SnBu_3$	$BF_3{\cdot}OEt_2$	-20 °C - rt	**4-28**	Ph	23 %	0 %

Above model studies provided promising method toward the introduction of acetylenic group in enediyne antitumor antibiotics such as dynemicin A. But in this reaction the following problems were revealed during this studies. (i) Tinacetylenes was unstable under acidic condition. In particular, tinacetylene of conjugated enediyne was found to be difficult to prepare. (ii) This reaction was difficult to apply acid sensitive substrate. Dynemicin A has an epoxide connected to benzene ring. So that this epoxide may be extremely unstable under acidic conditions. Thus this reaction may be difficult to apply the enediyne ring closure.

References & Notes

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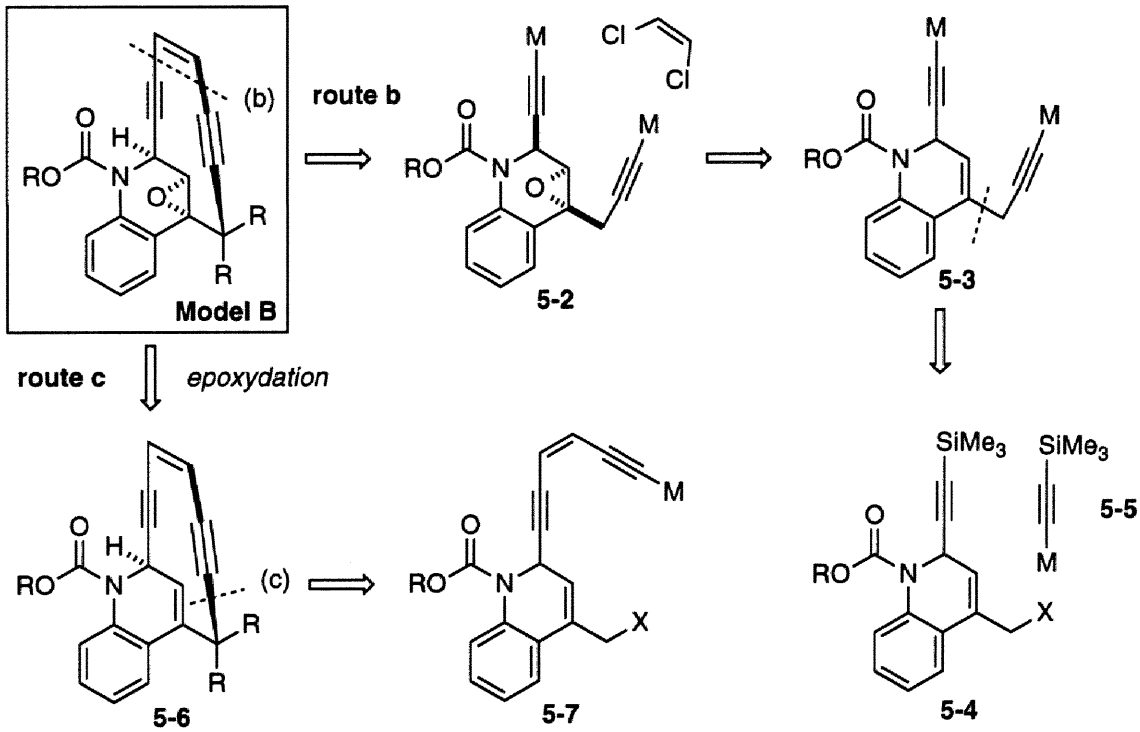
Chapter 5

Palladium Catalyzed Coupling Between Allyl Derivatives and Tinacetylenes

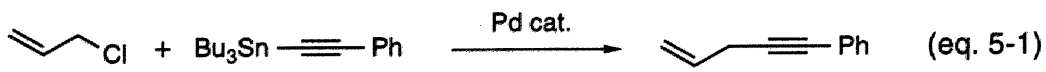
Palladium Catalyzed Coupling Between Allyl Derivatives and Tinacetylenes

Retrosynthetic analysis of model compound B (**Model B**) submitted some possible routes as discussed in Chapter 2. One of these was to disconnect at the vinyl position of enediyne (**route b**). Another one was to disconnect the propargyl bond (**route c in Scheme 5-1**). **Route b** included palladium catalyzed cyclization (double coupling or stepwise coupling) between bisacetylenic compound **5-2** and *cis*-dichloroethylene. The bisacetylenic compound **5-2** was prepared by coupling between allyl derivative **5-4** and acetylene **5-5** . On the other hand, **route c** included the cyclization by means of intramolecular coupling between allyl derivative and acetylide anion. This type of process has been achieved by using alkali metal acetylide with allyl halide.[1, 2] But due to the extremely unstability of the substrate and the product under basic conditions, a new milder C-C bond forming reaction became to be highly desirable.[3] Consequently we decided to use palladium catalyst in order to overcome this problem under essentially neutral condition.

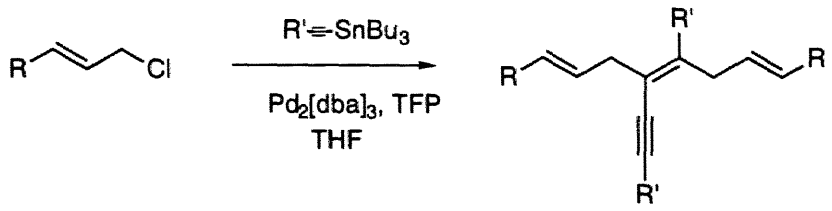


Scheme 5-1. Synthetic plan for Model B using palladium catalyst

The palladium-catalyzed allylic substitution reaction by various nucleophiles has been thoroughly studied and has received wide applications in organic synthesis.[4] Although there are also many reports on the coupling reactions of allylic derivatives with organotin compounds (e.g. vinyl, allyl, aryl),[5, 6] to our knowledge a little report on the coupling reaction with tinacetylenes was found in the literature. Migita and Kosugi reported the first example in which allylic chloride was coupled with phenyltin acetylene to give the non-conjugated eneyne in 32 % (eq. 5-1).[5a]

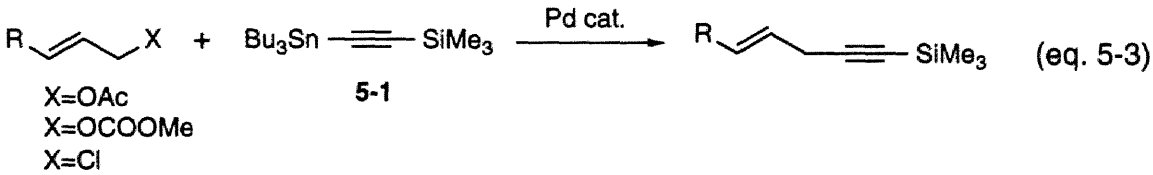


Recently Farina and co-workers reported that Pd catalyzed coupling of allylic chlorides with tin acetylene did not give expected 1-ene-4-yne compounds but gave unprecedented products (eq. 5-2).[7]



(eq. 5-2)

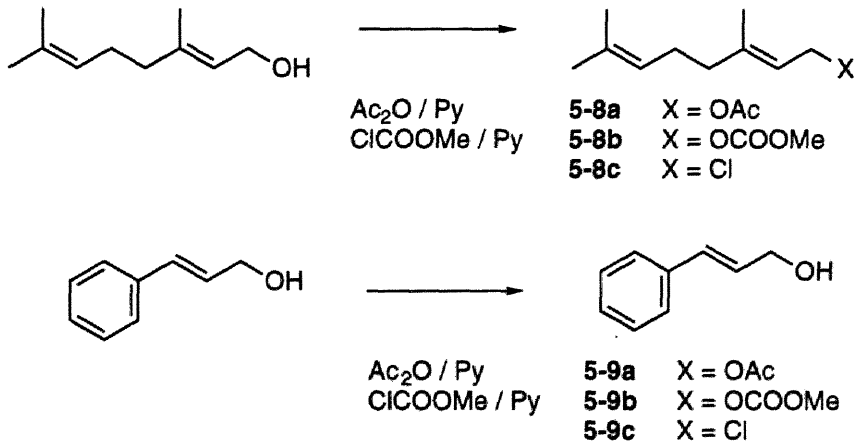
I describe herein a normal coupling reaction of allylic derivatives (acetate, carbonate, chloride) with tin acetylene to give 1-ene-4-yne system (eq.5-3). Tributylstannyl (trimethylsilyl) ethyne (**5-1**)[8] was chosen as tinacetylene because the silylacetylene in the products is readily accessible for conversion to a variety of substituents by the acetylide or Pd-catalyzed coupling with suitable electrophiles.



(eq. 5-3)

Synthesis of Substrates

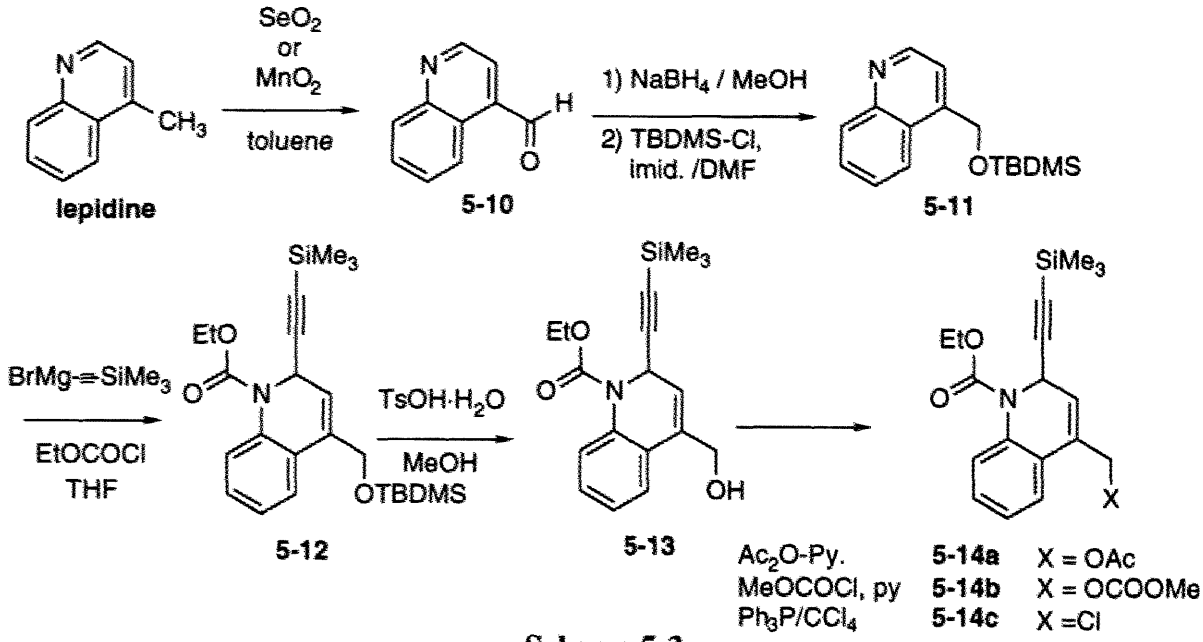
The allyl derivatives tested here as substrates for this examination were prepared as followings. Geranyl and cinnamyl derivatives (acetate **5-8a**, **5-9a**, carbonate **5-8b**, **5-9b**, chloride **5-8c**, **5-9c**) were commercially available or prepared from corresponding alcohols by standard methods as shown in **Scheme 5-2**.



Scheme 5-2

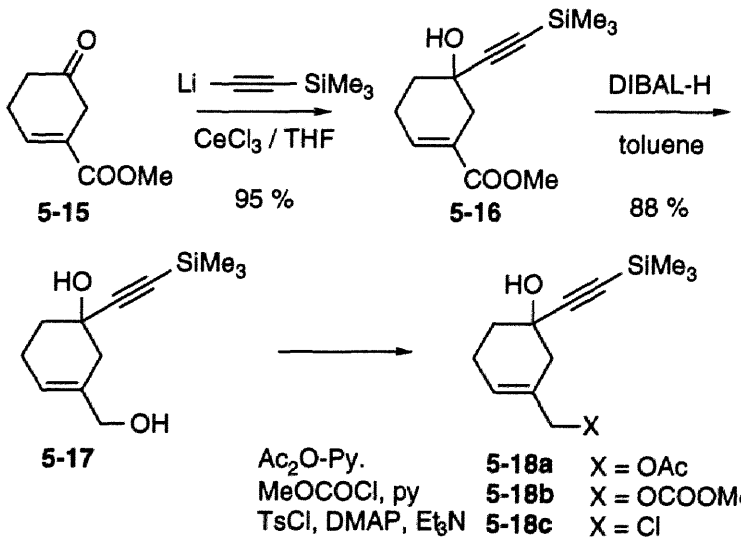
The substrates for the synthesis of dynemicin A were synthesized from lepidine (4-methylquinoline) (**Scheme 5-3**). Lepidine was oxidized with SeO_2 or activated MnO_2 to give 4-quinolinecarboxaldehyde (cinchonaldehyde) **5-10**,[9] which was reduced to alcohol with $NaBH_4$. After protection of the resultant alcohol, acetylenic group was introduced under Yamaguchi's condition[10] to

afford **5-12**. Treatment of resulting **5-12** with acid in MeOH gave alcohol **5-13**, which was converted into following three allylic derivatives (**5-14a**, **5-14b**, **5-14c** [11]) by standard methods.



Scheme 5-3

Another substrate **5-18** was synthesized from **5-16**, which was obtained by the reaction of ketoester **15** with lithium acetylide in the presence of $CeCl_3$. (This process was developed by Mr. S. Shibuya in our laboratory)[12] Reduction of the ester **5-16** with DIBAL-H gave the alcohol **5-17**, which was common intermediate for substrates such as acetate, carbonate and chloride. Acetate **5-18a** and methylcarbonate **5-18b** were prepared by standard methods. Chlorination of the allylic alcohol **5-17** was effected with TsCl-DMAP[13] to give **5-18c**.



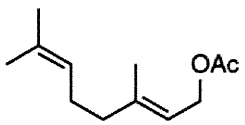
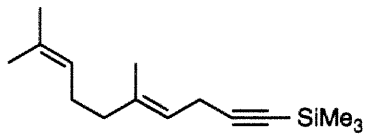
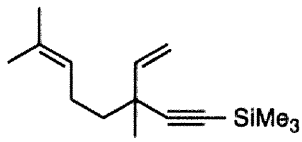
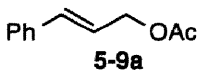
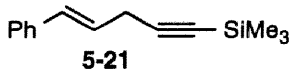
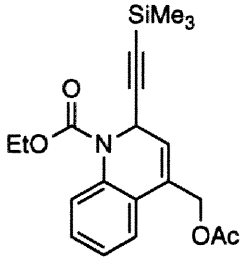
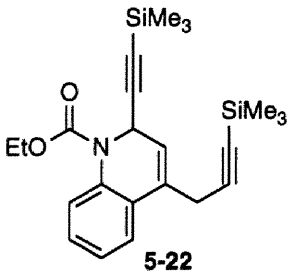
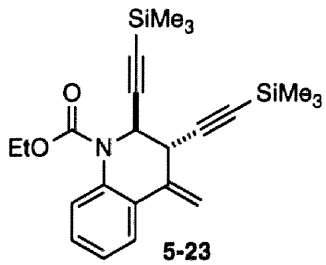
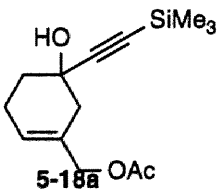
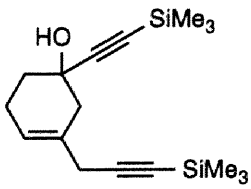
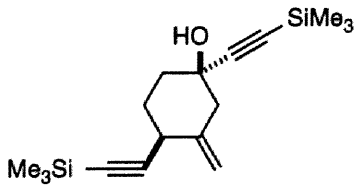
Scheme 5-4

I started to explore the reaction conditions including the solvents, palladium reagents, ligands, ratio of ligand to Pd, and found that every substrates could be converted to 1-ene-4-yne compounds under appropriate conditions.

Allyl acetates

Usually allyl acetates have not been used in the coupling with organotin compounds because of its low reactivities.[14] However, geranyl and cinnamyl acetates (**5-8a**, **5-9a**) were coupled with **5-1** to give the desired product (**5-19**, **5-21**) under mild condition (entry 1, 2 in **Table 5-1**) in which using *N*-methyl pyrrolidone (NMP) as a solvent was essential. Recently Stille reported that allyl acetates were coupled with organotin compounds (alkyl, vinyl- and aryltins) under ligandless condition ($Pd[dba]_2$, LiCl/DMF).[15] No reaction with tinacetylene **5-1** as coupling partner occurred under such condition. Although stereochemistry of transposed products **5-23** and **5-25** obtained as single stereoisomer could not be determined, *trans*-acetylene substituents were deduced from the mechanistic point of view as shown in **Table 5-1**.

Table 5-1. Palladium-catalyzed coupling of allyl acetates with tinacetylene 5-1

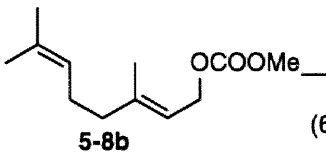
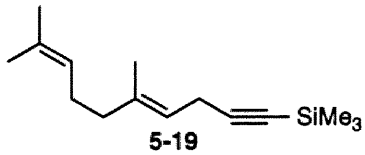
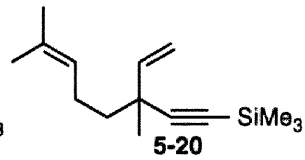
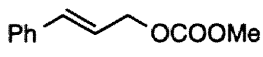
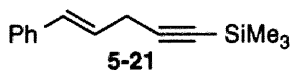
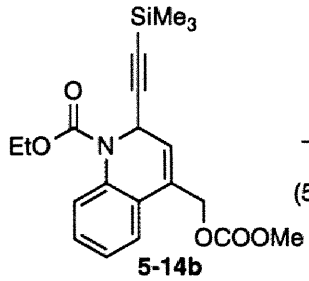
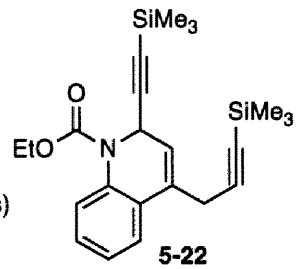
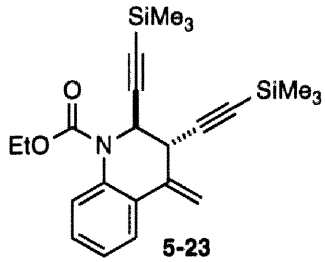
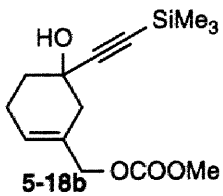
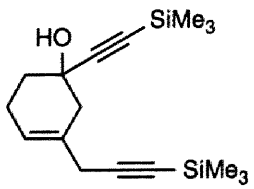
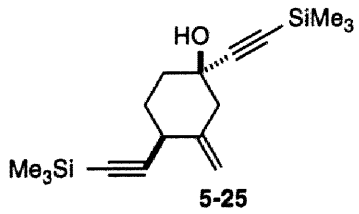
entry	substrate	condition [a]	product [b]	yield (ratio)[d]
1	 **5-8a**	**5-1**, **A** (80 °C, 42 h)	 **5-19**  **5-20**	57 (15:1)
2	 **5-9a**	**5-1**, **A** (50 °C, 48 h)	 **5-21**	87
3	 **5-14a**	**5-1**, **A** (80 °C, 2 days)	 **5-22**  **5-23**	27 [c] (7:1)
4	 **5-18a**	**5-1**, **A** (80 °C, 40 h)	 **5-24**  **5-25**	47

[a] **condition A**: **5-1** (1.1eq.), $Pd_2[dba]_3{\cdot}CHCl_3$.(3 mol %), Ph_3P(12 mol %) / NMP. [b] Isolated yield. [c] Starting material was recovered. [d] Determined by ^1H NMR.

Allyl carbonates

Methyl carbonates could be substrates for this coupling reaction under the same reaction condition as the case of allyl acetate in the presence of LiCl (**Table 5-2**).[16] In contrast to allyl acetates, NMP was not essential solvent in case of allyl carbonate. While methyl carbonates proceeded the coupling under phosphineless condition (see in allyl chloride), more functionalized substrates gave unsatisfied results (entry 3 and 4).

Table 5-2. Palladium-catalyzed coupling of allyl carbonates with tinacetylene 5-1

entry	substrate	condition [a]	product	yield [b] (ratio)
1	 **5-8b**	**5-1**, **B** (60 °C, 7 h)	 **5-19** +  **5-20**	66
2	 **5-9b**	**5-1**, **A** (50 °C, 44 h)	 **5-21**	43
3	 **5-14b**	**5-1**, **A** (55 °C, 5 days)	 **5-22** +  **5-23**	23[c] (30:1)
4	 **5-18b**	**5-1**, **B** (65 °C, 18 h)	 **5-24** +  **5-25**	24

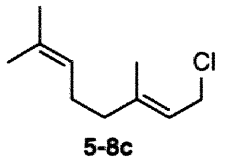
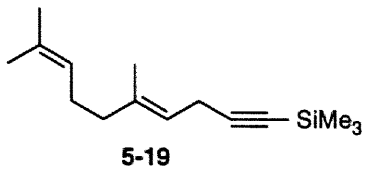
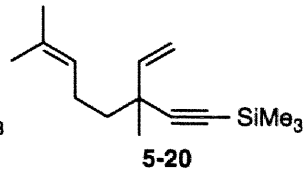
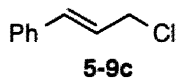
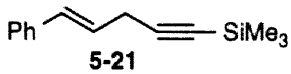
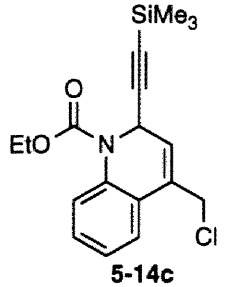
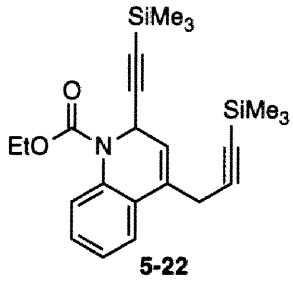
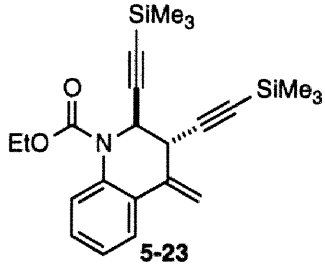
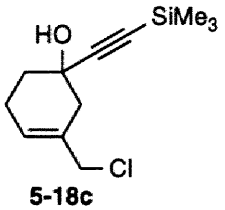
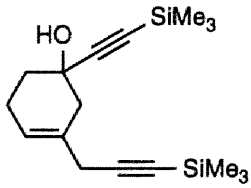
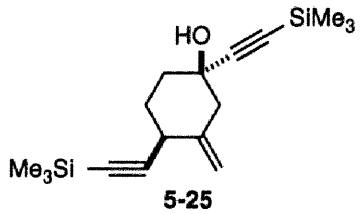
[a] **condition A**: **5-1** (1.1 eq.), $Pd_2[dba]_3{\cdot}CHCl_3$ (3 mol %), PPh_3 (12 mol %), LiCl (2 eq.) / NMP. **condition B**: **5-1** (1.1 eq.), $Pd_2[dba]_3{\cdot}CHCl_3$ (3 mol %), dimethylfumarate (20 mol %), LiCl (2 eq.)/ benzene. [b] Isolated yield. [c] Determined by 1H NMR.

Allyl Chlorides

Allyl chlorides were more reactive than the corresponding acetates and carbonates (**Table 5-3**). Phosphineless condition using dimethylfumarate (dmf) and benzene as solvent was found to be more efficient for all substrates. In particular this phosphineless condition (**condition B**) brought about reduction in reaction time. Even functionalized substrates **5-14c** and **5-18c** gave the best results under the phosphine-less condition (entry 3, 4). **Condition B** is modified Kurosawa's protocol;[17] In the absence of phosphine ligand, electron deficient olefin such as dimethylfumarate accelerates reductive elimination on catalytic cycle. .

Although we examined the corresponding allyl phosphates (X = $OPO(OEt)_2$) under various conditions, all substrates gave only low yields.

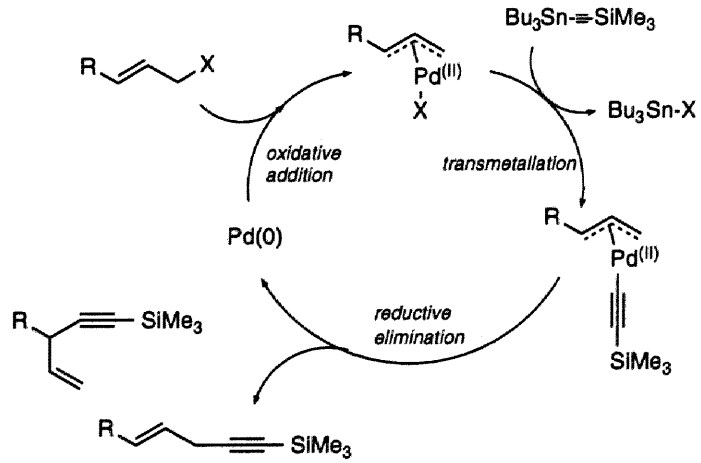
Table 5-3. Palladium-catalyzed coupling of allyl chlorides with tinacetylene 5-1

entry	substrate	condition [a]	product [b]	yield (ratio)[c]
1	 **5-8c**	**5-1** **A** (80 °C, 42 h) **B** (60 °C, 11 h)	 **5-19**  **5-20**	61 (8:1) 70 (17:1)
2	 **5-9c**	**5-1** **A** (50 °C, 48 h) **B** (60 °C, 4.5 h)	 **5-21**	55 60
3	 **5-14c**	**5-1** **B** (80 °C, 2 days)	 **5-22**  **5-23**	63 (16:1)
4	 **5-18c**	**5-1** **B** (80 °C, 40 h)	 **5-24**  **5-25**	83 (22:1)

[a] **condition A**: **5-1** (1.1eq.), $Pd_2[dba]_3{\cdot}CHCl_3$ (3 mol %), Ph_3P (12mol%) / NMP. **condition B**: **5-1** (1.1eq.), $Pd_2[dba]_3{\cdot}CHCl_3$. (3 mol %), dimethylfumarate (20 mol %) / benzene. [b] Isolated yield. [c] Determined by ^1H NMR.

Mechanism

The proposed mechanism of this reaction is shown in **Scheme 5-5.** The presence of π-allyl Pd complex intermediate was supported by obtaining the allylic transposed products **5-20, 5-23, 5-25.** In the intramolecular version of this coupling, it is anticipated that palladium catalyst could act as a template to assemble the end of molecule through an oxidative addition and coordination of the tinacetylene, and reductive elimination could generate carbon-carbon bond *via* pseudo Pd-mediated ring contraction.



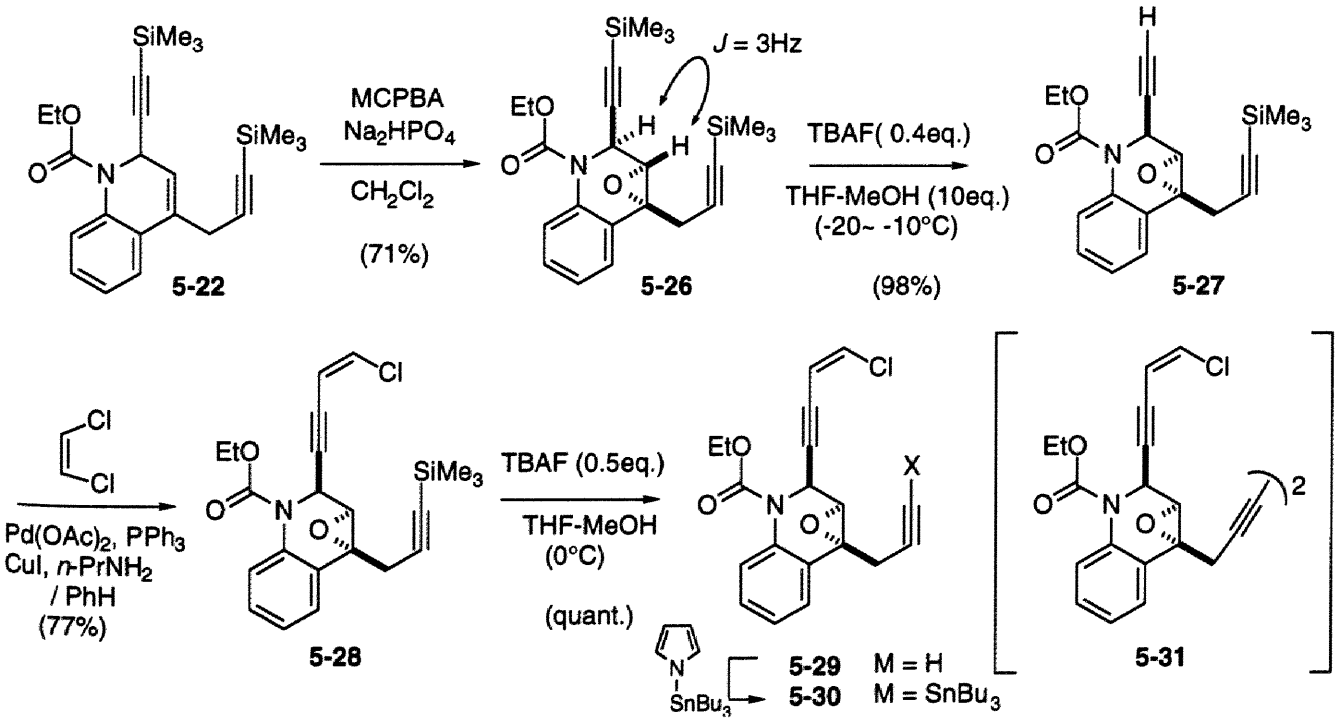
Scheme 5-5. Catalytic cycle

Approaches to Cyclic Enediyne Compound

With the bisacetylenic compound (an equivalent to **5-3** in **Scheme 5-1**) in hand, transformations to the precursor for cyclization were examined. In **route b**, I adopted the stepwise coupling with (*Z*)-dichloroethylene.

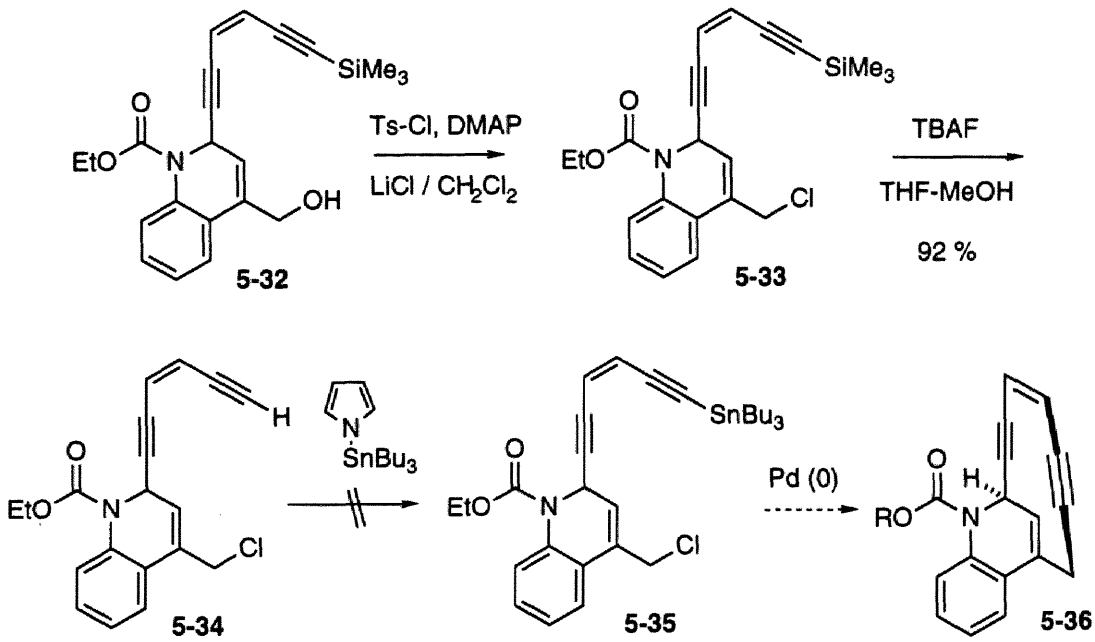
The olefin in **5-22** was epoxidized with MCPBA to afford **5-26** as a single stereoisomer, whose stereochemistry was deduced to have *anti*-epoxide to acetylene substituent (**Scheme 5-6**). Coupling constant between the propargylic and epoxide protons was 3 Hz indicating *anti* stereochemistry. This assumption was supported by molecular mechanics calculations (*anti*- and *syn*-epoxide gave J = 3.9 and 8.5 Hz, respectively). Control element of this selectivity was steric hindrance of pseudo-axial acetylenic group. Next problem was a regioselective desilylation of one of the two trimethylsilylacetylenes in **5-26** for stepwise Pd coupling with (*Z*)-dichloroethylene. We found that limited use of TBAF (0.4-0.5 eq.) at -20 ~ -10 °C gave **5-27** in 98 % yield. This high selectivity was presumably due to the acyl group connected to the propargylic carbon, which electron withdrawing property activated the Si-C(sp) bond. This remarkable high selectivity was first example to my knowledge, although the mono-desilylation of bis-trimethylsilylacetylene compound with $NaBH(OMe)_3$ was recently reported (60 %).[18, 19] Terminal acetylene of **5-27** was coupled with (*Z*)-dichloroethylene under Sonogashira's condition to give an eneyne **5-28** which was further desilylated at 0°C to furnish **5-29**, the precursor for cyclization.

All attempts to cyclize **5-29** by using Pd-CuI catalyst failed.[20, 21] The only isolated product was dimer **5-31**. To avoid this dimerization, **5-29** was converted to tinacetylene **5-30** by using *N*-tributyltin-pyrrole.[22] Even in the case of tinacetylene **5-30**, cyclization product was not obtained. Therefore I abandoned the **route b** for synthesis of **Model B.**



Scheme 5-6

In **route c**, on the other hand, the precursor **5-34** for the cyclization was synthesized from acyclic enediyne **5-32** as shown in **Scheme 5-7**. (The synthesis of **5-32** is described in Chapter 6) Chlorination of alcohol in **5-32** was effected with TsCl, DMAP to give **5-33**, which was successively desilylated with TBAF in the presence of MeOH in good yield. However, stannylation of terminal acetylene in the enediyne **5-34** was found to be difficult because of the extreme unstability of the product **5-35**. Tinacetylene **5-35** might be very acid-sensitive judging from the fast protodesilylation of **5-35** on the silica gel plate. So that I have not tried the cyclization by palladium catalyst using **5-35** as a substrate.



Scheme 5-7

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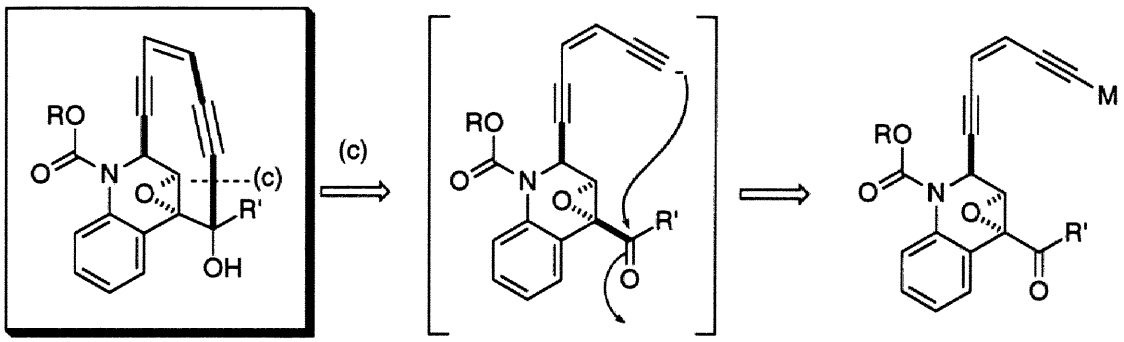
Chapter 6

Synthesis of Simple Model Compound of Dynemicin A

Synthesis of Simple Model Compound of Dynemicin A

Until previous Chapter, the synthesis of **Model B** had not been achieved yet, even if some reactions were developed. In this Chapter, I described the successful synthesis of **Model B** by means of an intramolecular addition of an enediyne acetylide to the carbonyl group (**Scheme 6-1**).



Model B **6-2** **6-3**

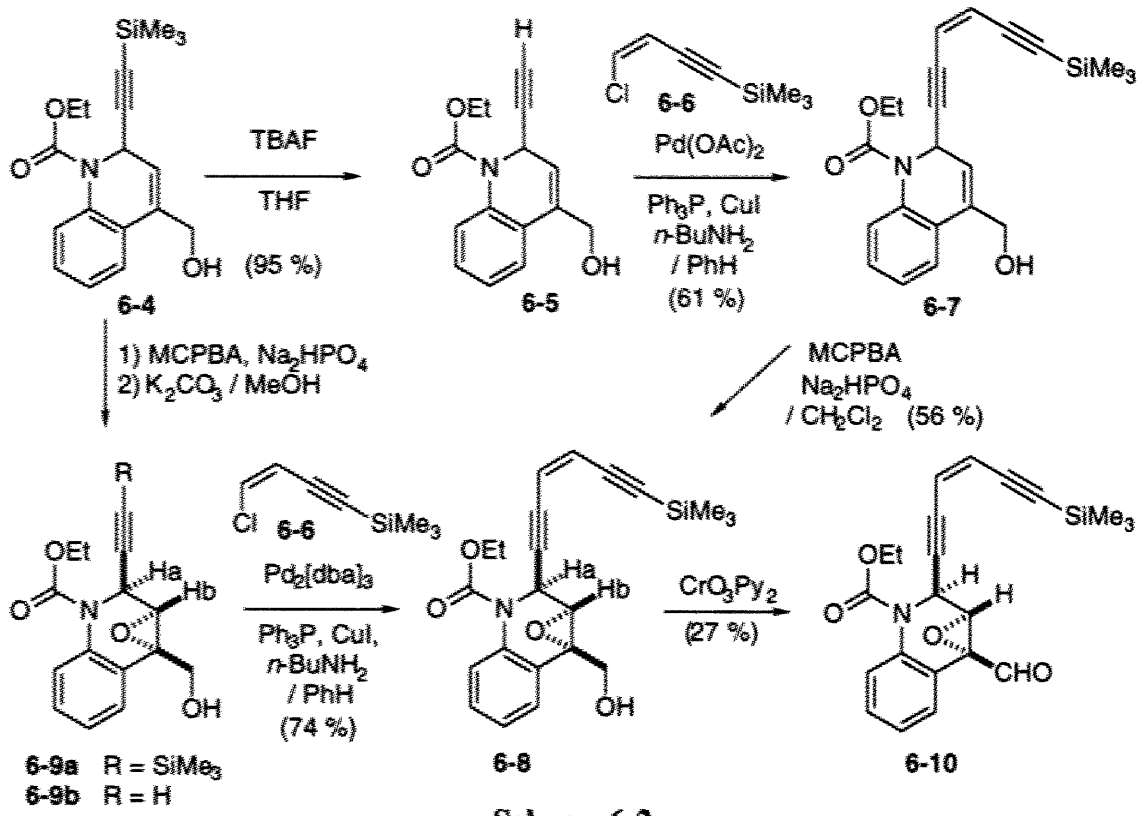
Scheme 6-1

Synthesis of the epoxyaldehyde as a precursor for cyclization

The synthesis started from the common intermediate **6-4** which was prepared in Chapter 5. After desilylation of the silylacetylene in **6-4**, the resultant acetylene **6-5** was coupled with (*Z*)-vinyl chloride **6-6**[1] to give the unstable acyclic enediyne **6-7** in 61 % yield. Epoxidation of the allylic alcohol was effected with MCPBA in the presence of Na_2HPO_4 to give the epoxy alcohol **6-8** as a single stereoisomer. The stereochemistry of the epoxide was assumed as *anti* to acetylenic substituent because acetylene group occupied at pseudo-axial position. This conformation was supported from its ^{1}H NMR data (observed, $J_{a\text{-}b}$ = 3 Hz) to have good harmony with one of the calculated values *anti* ($J_{a\text{-}b}$ = 3.9 Hz) but not with *syn* (J = 8.5 Hz). Consequently, the reagent MCPBA approached from the opposite face to acetylene group, gave the *anti*-epoxide **6-8**.

Alternative route to avoid through the unstable intermediate **6-7** was explored. Epoxydation followed by desilylation of **6-4**, gave the epoxy alcohol **6-9b**, which was coupled with the (*Z*)-vinyl chloride **6-6** under Sonogashira's condition to give the same epoxyalcohol **6-8**. In reality, the epoxy aldehyde intermediate **6-10** was extremely difficult to obtain from the epoxyalcohol **6-8** by oxidation under various conditions; PCC, PDC, Collins oxidation, SO_3·Py-DMSO, Swern oxidation,[2] TPAP,[3] *etc.* (Wender independently reported the oxidation of a similar epoxyalcohol **6-8** with Dess-Martin reagent [4] gave the desired epoxy aldehyde in fair yield.)[5]

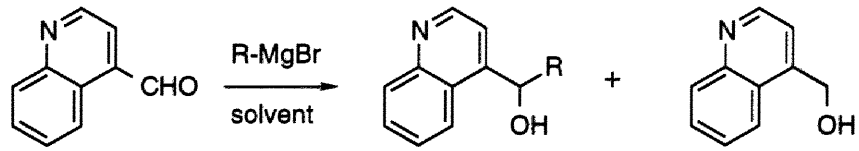
These findings prompted us to continue the same intramolecular cyclization using a higher homologue, such as **6-3** (R' = Me) which was expected more stable.



Scheme 6-2

Synthesis of epoxyketone as a precursor for cyclization

The synthesis of homologue **6-12** started from the addition of MeMgBr to 4-quinoline carboxaldehyde **6-11**. On the other hand, addition of ethyl Grignard reagent (EtMgBr) gave the mixture of desired ethyl adduct **6-13** and reduction product **6-14** (**Table 6-1**). Addition of cerium chloride [6] did not improve the yield of **6-13** although ether was superior solvent over THF.



6-11 **6-12** R = Me **6-13** R = Et **6-14**

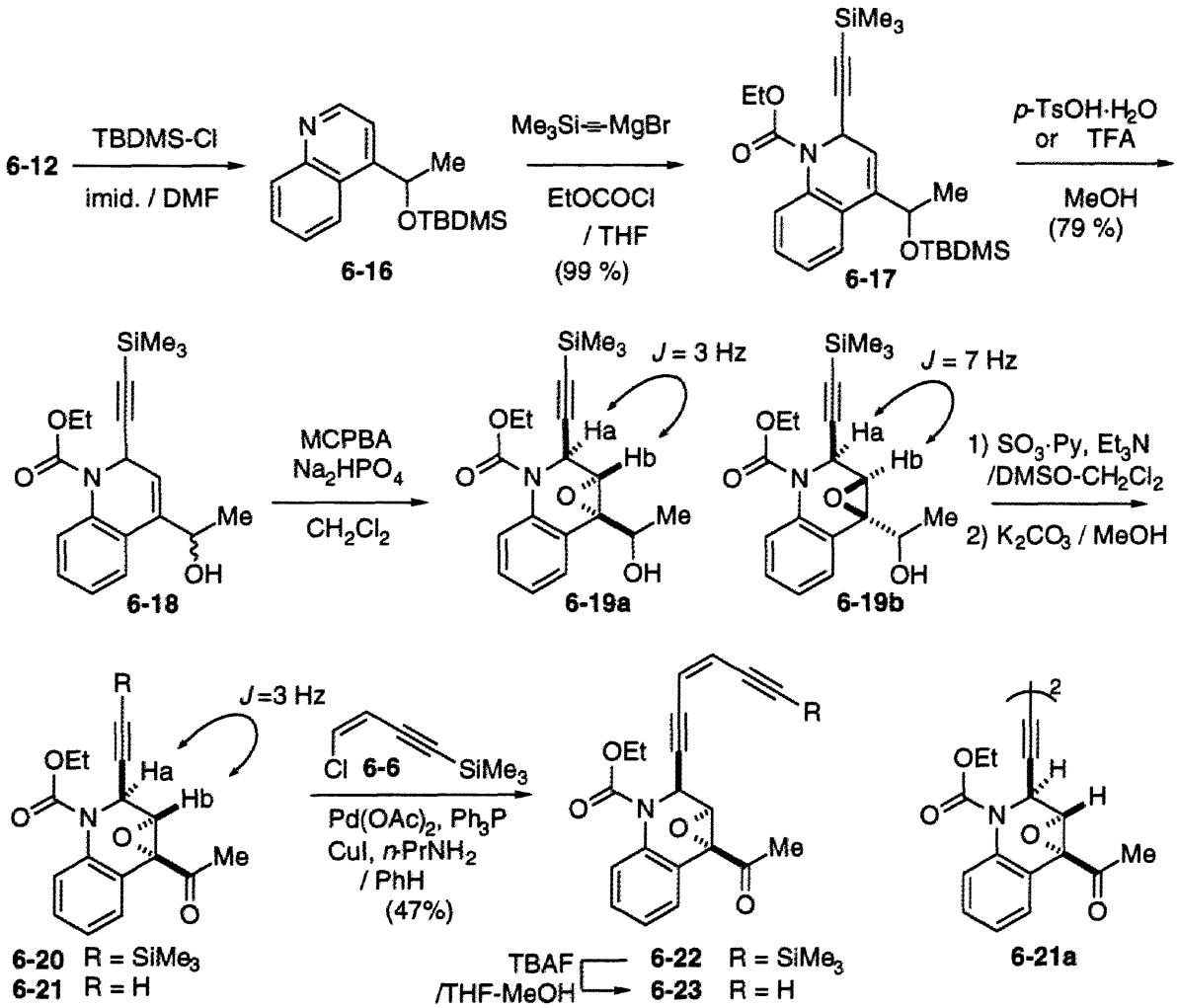
Scheme 6-3

Table 6-1

entry	reagent	solvent	product		6-14
1	MeMgBr	THF	**6-12**	75 %	0
2	EtMgBr	THF	**6-13**	34	43
3	EtMgBr	Et_2O	**6-13**	77	12

After protection of alcohol **6-12** as TBDMS ether, magnesium acetylide of trimethylsilyl acetylene was added to the quinoline nucleus by Yamaguchi's procedure to afford **6-17** in high yield. The diastereoselectivity of this reaction was about 2:1 by ^1H NMR. Selective desilylation of TBDMS ether under acidic condition followed by epoxidation with MCPBA, gave the mixture of epoxy

alcohols **6-19** which included at least 3 epoxyalcohols, two of which were **6-19a** and **6-19b**. These structure was elucidated from the coupling constant between propargylic and epoxidic protons: $J_{a\text{-}b}$ value between propargylic and epoxidic protons of major **6-19a** was 3 Hz, that of **6-19b** was 7 Hz. These $J_{a\text{-}b}$ values were good agreement with the calculated values of corresponding diastereomers (J_{calcd} = 3.9, 8.5 Hz, respectively). Oxidation of the mixture **6-19** with SO_3Py-DMSO [7] followed by desilylation, gave the single epoxyketone **6-20** as a stable crystalline compound (Mp. 114.5-116 °C). The acyclic enediyne **6-22** was constructed by Sonogashira's coupling between acetylene **6-21** and vinyl chloride **6-6** in about 50 % yield. The reason of relative low yields in this reaction was the competitive formation of dimer **6-21a** of acetylene **6-21.**

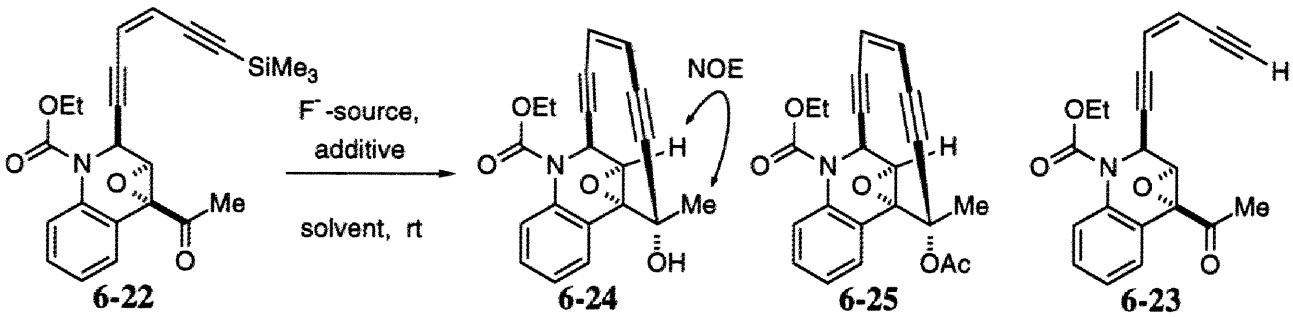


Scheme 6-4

Cyclization of 10-membered enediyne ring

Initial attempts to cyclize **6-23** by generation of acetylide using base (LDA, LiHMDS) failed, because of the competitive enolate formation at the methylketone. In fact the quenching experiment with D_2O afforded the products which were deuterated at methyl ketone and terminal acetylene. In order to avoid this competitive deprotonation, we decided to use fluoride anion for selective acetylide generation from trimethylsilylacetylene under essentially neutral condition, which had been developed by Kuwajima and Nakamura.[8] In the case of KF and LiF, cyclization did not occur even in the presence of appropriate crown ether (18-crown-6, 12-crown-4). After some experiment, CsF was

found to be effective source for this cyclization in the presence of crown ether.[9] The cyclization product **6-24** obtained here was largely single isomer (>95:5, by ^{1}H NMR analysis) about the new stereogenic center, which was assigned by NOE data observed between the methyl group and the epoxy proton. The representative results of examination of reaction condition are shown in **Table 6-2** (This optimization was performed by Mr. Akira Ino in our laboratory.). Although all attempts could not dramatically improve the yield of **6-24**, surprisingly *tert*-acetate **6-25** was obtained in the use of excess CsF (entry 4). The structure of acetate **6-25** was confirmed by conversion of **6-24** to **6-25** (Ac_2O-Py, 43 %). Origin of the acetyl group was assumed to be methyl ketone, although the mechanism has not been clear yet. Another fluoride anion source such as tetrabutylammonium fluoride (TBAF), benzyltrimethylammonium fluoride (BTAF) gave only desilylated product **6-23** (entry 6, 7).



Scheme 6-5

Table 6-2.

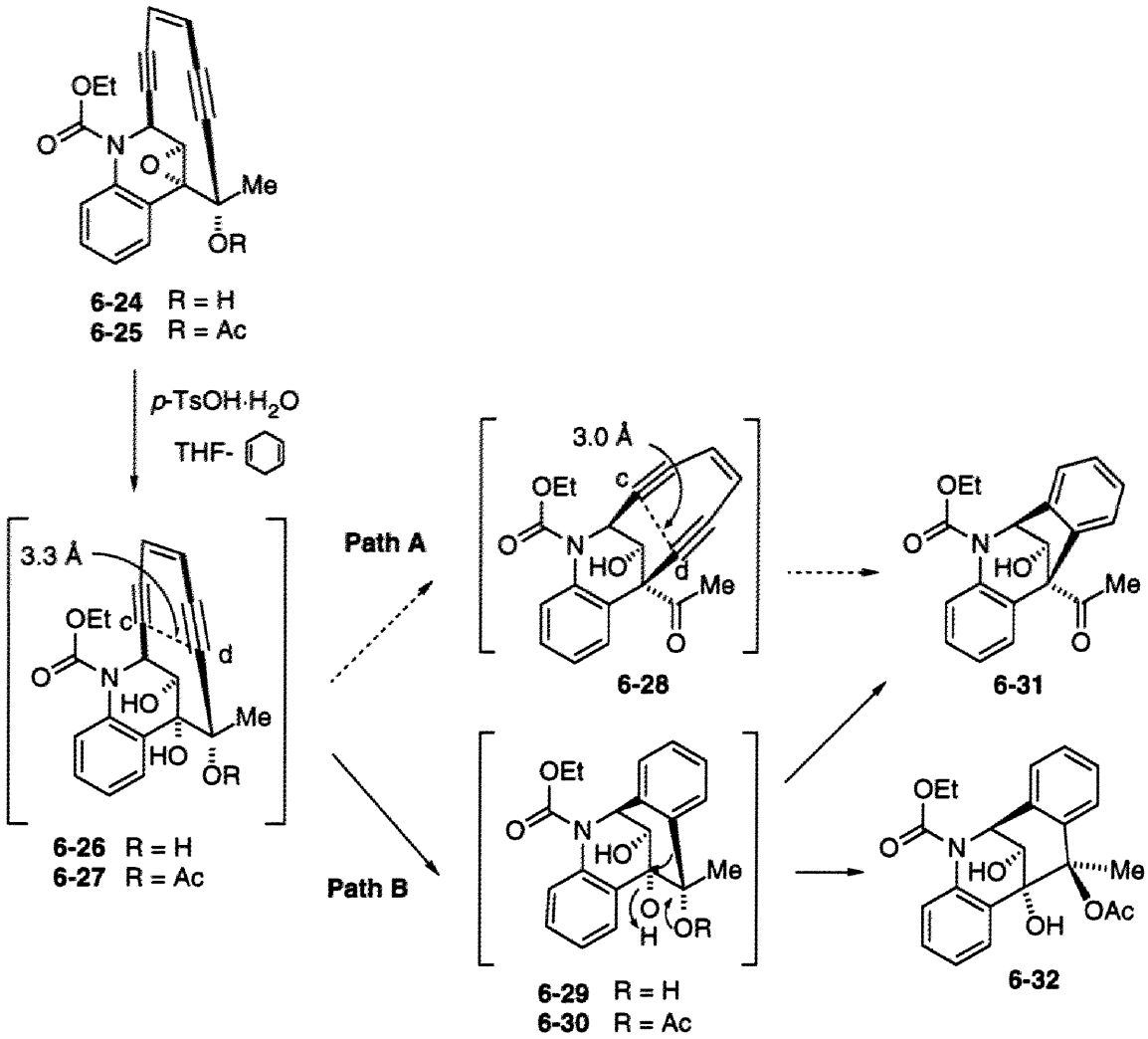
entry	F -sourse (equiv)	18-crown-6 equiv.	solvent	**6-24** (%)	**6-25** (%)	**6-23** (%)	**6-22** (%)
1	CsF (0.1)	0.1	THF	16	0	20	23
2	CsF (0.2)	0.1	THF	20	0	21	0
3	CsF (1.0)	1.0	THF	15	0	-	-
4	CsF (2.0)	1.5	THF	7	10	8	2
5	CsF (0.1)	0.0	MeCN	0	0	52	0
6	TBAF (1.1)	0.0	THF	2	0	24	0
7	BTAF (1.2)	0.0	THF	0	0	48	0

Bergman reaction

Acid treatment of **6-23** in the presence of 1,4-cyclohexadiene gave a benzene derivative as expected through Bergman cycloaromatization (**Scheme 6-6**). The product, however, was not the triol **6-29**, but the ketone **6-31** judging from the Me signal in ^{1}H NMR (δ 2.51 ppm). This fact suggested that pinacol-pinacolone rearrangement occurred before or after Bergman reaction.[10] As described in Chapter 2, the c-d distance of the intermediate **6-26** was assumed to be 3.3 Å by molecular mechanics calculation, and the distance of pinacol-pinacolone rearrangement product **6-28** was 3.0 Å. These two intermediates **6-26** and **6-28** have short enough c-d distances to proceed Bergman cycloaromatization

under the conditions. It is unlikely that **Path A** was operative due to the low migration aptitude of acetylenic group[11, 12], and involvement of the more strained 9-membered enediyne **6-28.**

This speculation was supported by the fact that the *tert*-acetate **6-25** underwent Bergman reaction to afford **6-32**. This fact indicated that the intermediate **6-27** retained enough ability to undergo cycloaromatization at room temperature. From above discussion, I concluded that **Path B** is more plausible than **Path A**.



Scheme 6-6

DNA-cleaving activity

The synthetic enediynes (**6-24**, **6-25** and **6-33**) were subjected to examine DNA cleaving activity although we did not expect much activity because of triggering device locked by stable *N*-protective group.[13] Surprisingly, **6-24**, **6-25** and **6-33** showed considerable cleaving activities toward supercoiled DNA (form I) to nicked DNA (form II) under neutral condition (**Figure 6-1**). This activity was comparable with that of K. C. Nicolaou's model compound, which was more active in basic media. The mechanism for DNA cleavage of the synthesized enediyne **6-24**, **6-25** and **6-33** may not involve oxidative cleavage of DNA by carbon radicals produced from Bergman reaction, because **6-33** was stable in buffer solution (pH 7.4). Anyway these are the first examples to exhibit DNA cleavage activity with such compounds having stable *N*-protective group such as ethoxy and phenyl carbamate.[14]

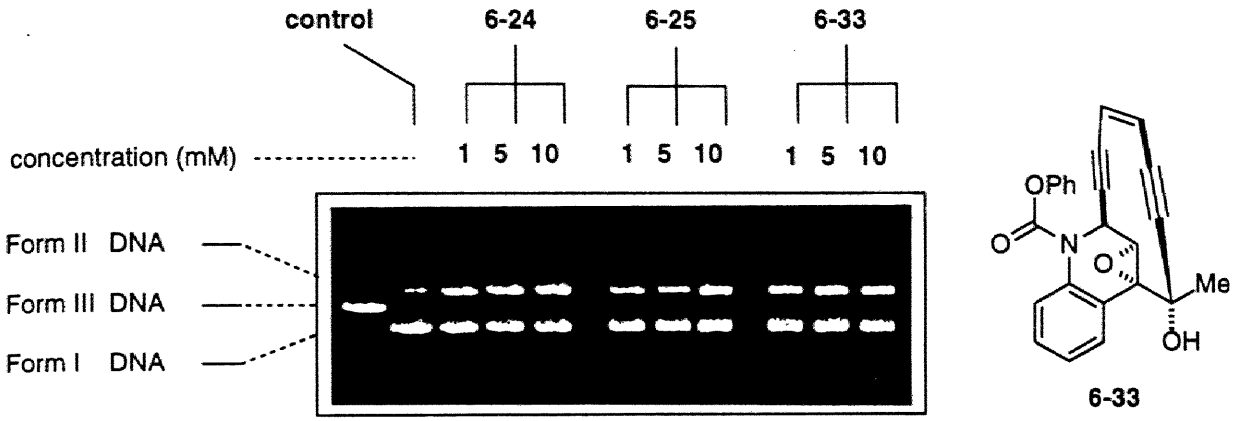


Figure 6-1. DNA cleaving activity Agarose gel electrophoretic patterns of ethidium bromide stained ΦX174 DNA (90 % form I) after treatment with model compounds in phosphate buffer (pH 7.4) at 37 °C for 18 h.

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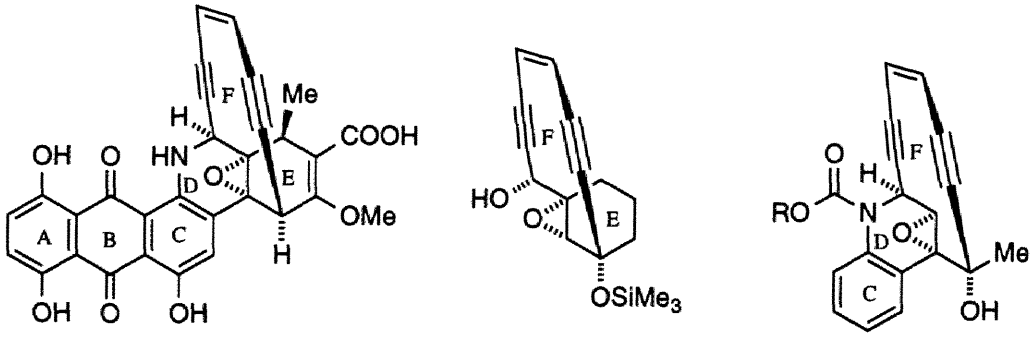
Chapter 7

New Quinoline Synthesis for C, D and E Rings in Dynemicin A

New Quinoline Synthesis for C, D and E Rings in Dynemicin A

This chapter dealed with the synthesis of important intermediates **7-2** and **7-3** for new variants of **Model A** and **Model B** (**Scheme 7-1**). Compound **7-2** contains C, D and substituted E rings in dynemicin A. Several quinoline derivatives without substituents on E ring have been reported in the synthesis of enediyne compounds related to dynemicin A by Nicolaou's group.[1]

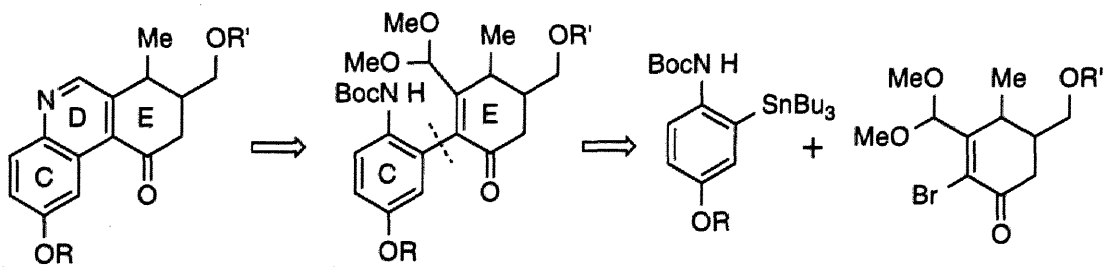


Dynemicin A **Model A** **Model B**

Figure 7-1

Synthetic plan

The basic retrosynthesis of **7-2** is outlined in **Scheme 7-1**. Compound **7-3** was expected to be produced by palladium catalyzed coupling (so called Migita-Stille coupling)[2] between an aryltin compound **7-4** (contains C ring) and an α-bromocyclohexenone derivative **7-5** (contains E ring). Compound **7-3** is a potentially useful intermediate for the aryl substituted **Model A** according to the previously described plan. Acid treatment of **7-3** would provide the cyclization product **7-2**. Compound **7-2** would be convertible to a compound as **Model B** having cyclic enediyne ring according to the previously reported methods. Palladium catalyzed coupling reaction between vinylhalides and aryltin compounds has been known more difficult than the coupling with vinyltins.[3] In addition, α-haloenone usually exhibits low reactivity in oxidative addition of Pd(0).[4] We started from the examination of the cross-coupling between simple aryltins and α-bromoenone compound.



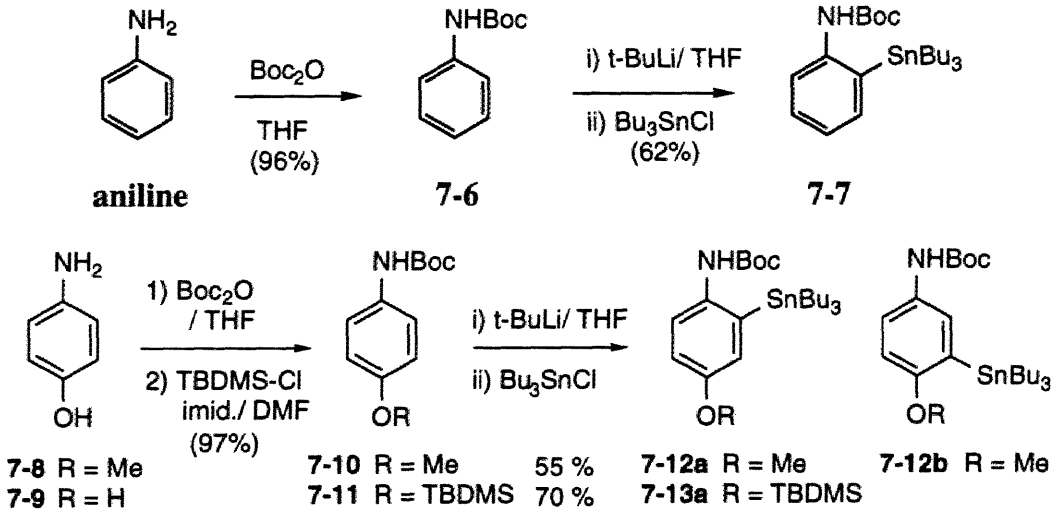
7-2 **7-3** **7-4** **7-5**

Scheme 7-1. Retrosynthetic analysis

Preparation of coupling partners (aryltin and α-bromoenone).

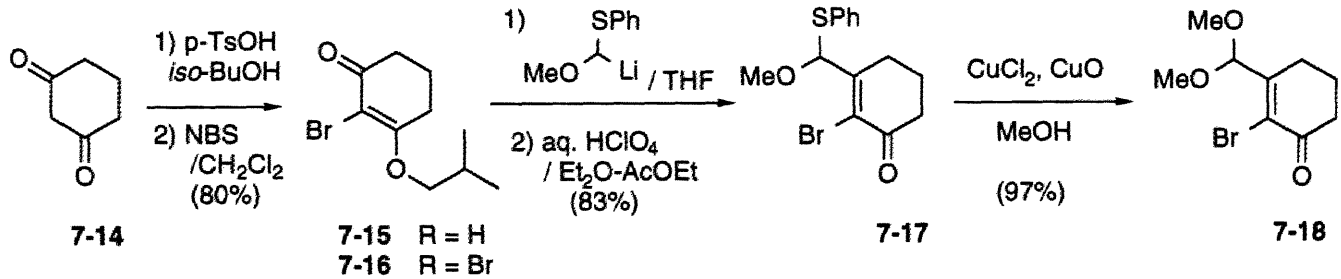
Aryltin **7-7** as coupling counterpart was prepared from *ortho* lithiation and stannylation of the *N*-Boc aniline **7-6**.[5] In the case of *N*-Boc anisidine **7-8**, however, the selectivity of lithiation was not

good (**7-12a**:**7-12b** = 5.5:1).[6] To improve the regioselectivity, TBDMS-ether **7-11** was employed for protection of the phenol group because the low chelation ability of bulky silylether.[7] In this case, the stannylated compound **7-13a** was largely obtained.



Scheme 7-2. Preparations of aryltin compounds

On the other hand, simple α-bromocyclohexenone **7-18** was prepared from 1,3-cyclohexanedione **7-14** according to Horiguchi and Kuwajima's procedure.[8] Namely, β-isobutyloxycyclohexanone **7-15** was brominated with NBS[9] to give **7-16**, which was homologated with lithio methoxymethyl phenylsulfide[10] and acid treatment. The resulting mono thioacetal **7-17** under Mukaiyama's condition ($CuCl_2$-CuO)[11] afforded the bromo acetal **7-18**.



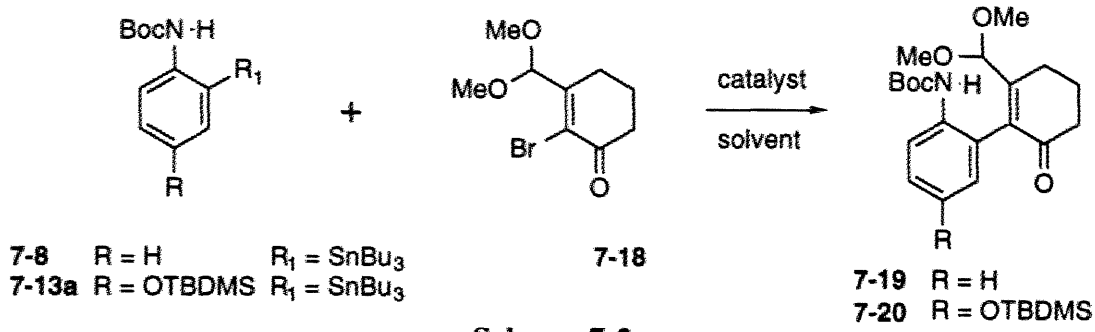
Scheme 7-3

Coupling of C and E rings

The conditions of palladium catalyzed coupling between vinylbromide **7-18** and its coupling partners **7-7, 7-13a** were examined. Representative results are listed in **Table 7-1**. I found that combination of P(*o*-tol)$_3$ as a phosphine ligand and NMP (*N*-methyl-2-pyrrolidone) as a solvent gave good result (entry 4). Combination of Ph_3P and toluene showed poor reproducibility even under higher reaction temperatures (entry 1, 2). Other attempts such as using TFP (trifurylphosphine) or conditions without ligand[12] failed to improve the yields.

Recently, Johnson and co-workers reported that α-iodoenones and organotin compounds underwent palladium catalyzed coupling with highly toxic triphenylarsine as a ligand to palladium in the presence of CuI.[13] They also described that α-bromoenone is inferior substrate (yields were less than 20 %). On the other hand, our result indicated that α-bromoenone is enough reactive toward this type of palladium catalyzed coupling using non-toxic P(*o*-tol)$_3$ in the absence of CuI. Although the

coupling using **7-13a** as a substrate diminished the yield of product **7-20**, using toluene as a solvent improved the yield (entry 5, 6). The same tendency was observed in the reactions between **7-13a** and other substituted α-bromoenones (*vide infra*).



7-8 R = H R_1 = $SnBu_3$
7-13a R = OTBDMS R_1 = $SnBu_3$

7-18

7-19 R = H
7-20 R = OTBDMS

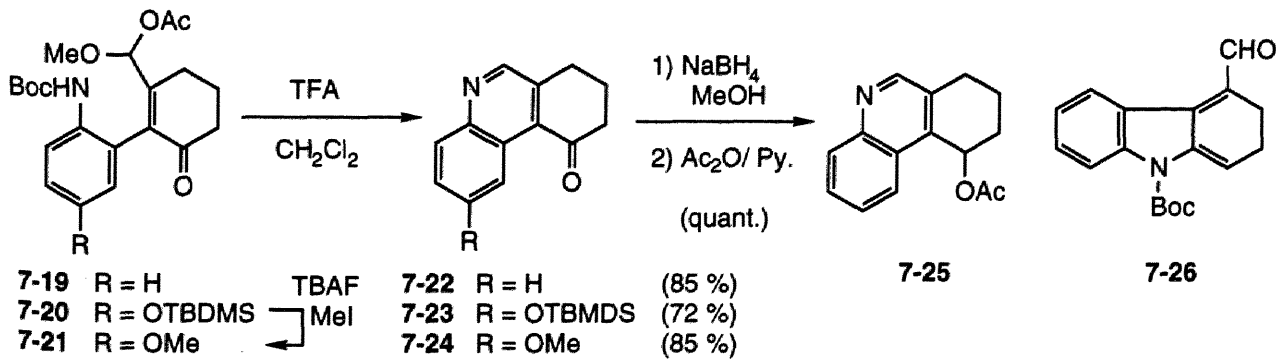
Scheme 7-2

Table 7-1. Palladium catalyzed coupling of α-bromoenone 7-18 with aryltins

entry	aryl tin	catalyst	solvent	temp, time	product	yield (%)
1	**7-8**	$Pd[Ph_3P]_4$	toluene	110 °C, 17 h	**7-19**	45
2	**7-8**	$PdCl_2[Ph_3P]_2$	toluene	110 °C, 6 h	**7-19**	46
3	**7-8**	$Pd(OAc)_2$, P(*o*-tol)$_3$	NMP	60-70 °C, 12 h	**7-19**	48
4	**7-8**	$Pd_2[dba]_3 \cdot CHCl_3$, P(*o*-tol)$_3$	NMP	60-70 °C, 2 h	**7-19**	78
5	**7-13a**	$Pd_2[dba]_3 \cdot CHCl_3$, P(*o*-tol)$_3$	NMP	60-70 °C, 2.5 h	**7-20**	51
6	**7-13a**	$Pd_2[dba]_3 \cdot CHCl_3$, P(*o*-tol)$_3$	toluene	80 °C, 2 h	**7-20**	70

Quinoline Ring Formation

The acetal **7-19** cyclized into the quinoline **7-22** by treatment with TFA in CH_2Cl_2 (**Scheme 7-3**). A side product of this reaction was unstable *N*-Boc aldehyde **7-26**. The ketone **7-22** was further reduced with $NaBH_4$ and acetylated to the acetate **7-25** which was identical to the spectroscopic data with one of the Nicolaou's intermediates.[14] On the other hand, the two protected phenols **7-20** and **7-21** were also converted into the corresponding quinoline derivatives **7-23** and **2-24**, respectively. Methyl ether **7-21** was prepared from the silyl ether **7-20** in one step (MeI in the presence of TBAF).



7-19 R = H
7-20 R = OTBDMS
7-21 R = OMe

7-22 R = H (85 %)
7-23 R = OTBMDS (72 %)
7-24 R = OMe (85 %)

7-25

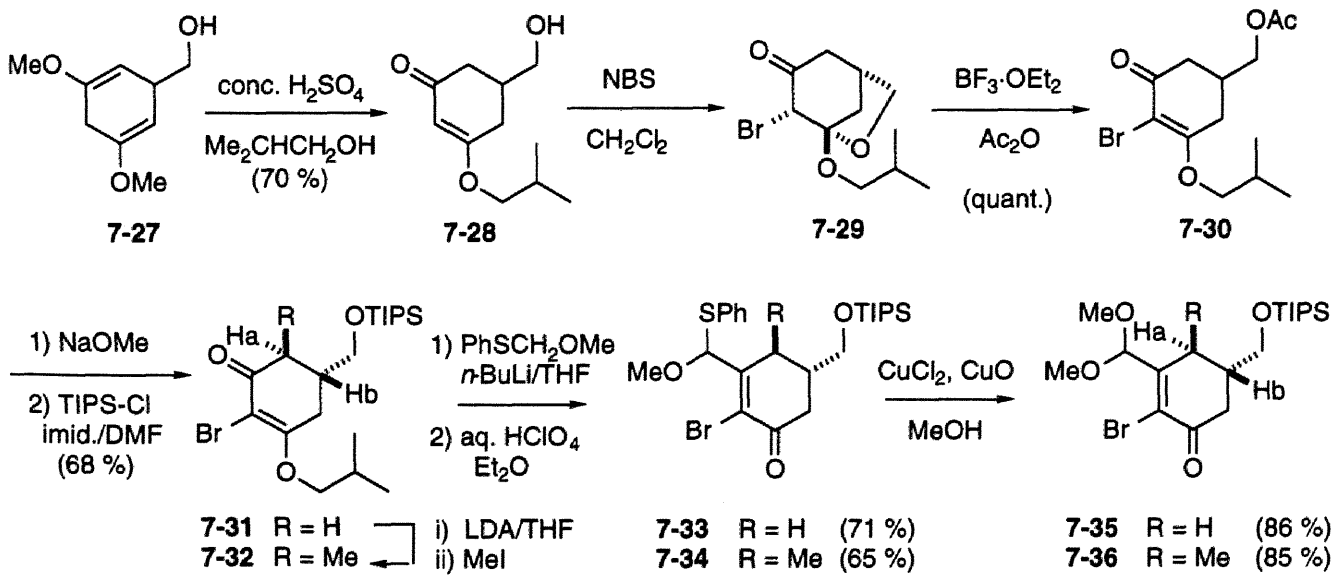
7-26

Scheme 7-3. Quinoline syntheses

Two carbon chains are necessary for the synthesis of E ring synthon for compounds **7-2** and **7-3**. For this purpose, the functionalized α-bromoenone **7-36** was designed. Its synthesis started from the vinyl ether **7-27** prepared from gallic acid (3,4,5-trimethoxybenzoic acid) in two steps [15] Birch reduction and $LiAlH_4$ reduction. Solvolysis of **7-27** in isobutanol gave **7-28**. I initially attempted the next bromination with the TBDMS-ether of **7-28**, but found this reaction being too slow to obtain the α-bromoenone such as **7-31** in a preparative scale. I examined the alternative route which employs direct treatment of **7-28** with NBS to afford bicyclic acetal **7-29**, and subsequent acetolysis to the enone acetate **7-30** with $BF_3{\cdot}OEt_2$ in acetic anhydride.[16] The protective group in **7-30** was converted to TIPS ether **7-31** in two steps.

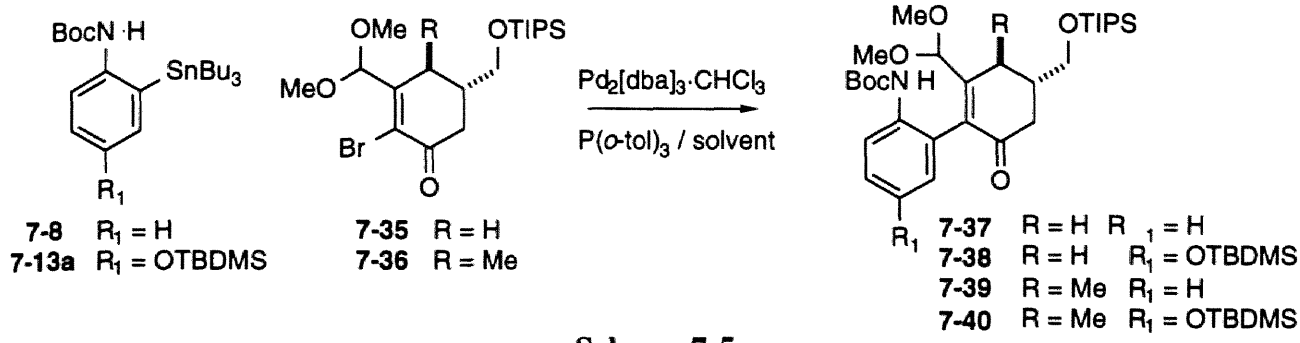
Methylation of **7-31** with MeI/LDA at -78 °C (Stork-Danheiser condition)[17] afforded at least 3 products and the thermodynamically stable product (**7-32**) was obtained by crystallization from hexane. The *trans* stereochemistry of **7-32** was determined by the coupling constant ($J_{a\text{-}b}$ = 10 Hz) in its ^1H NMR.

Homologation of **7-31** with methoxymethyl phenylsulfide was followed by acid treatment to give monothioacetal **7-33**. Copper catalyzed methanolysis of **7-33** under Mukaiyama's condition yielded dimethylacetal **7-35**. The homolog **7-36** was synthesized from **7-32** in the same way. The small coupling constant ($J_{a\text{-}b}$ = 2 Hz) of the *trans* stereochemistry in **7-36** will be discussed later.



Scheme 7-4

The palladium catalyzed coupling reaction between the two aryltin compounds (**7-8** and **7-13a**) and the two homologous α-bromoenones (**7-35** and **7-36**) underwent as described before to afford the corresponding products (**Table 7-2**). In the case of TBDMS analog (**7-13a**), toluene was superior over NMP as a solvent (entry 2, 3).



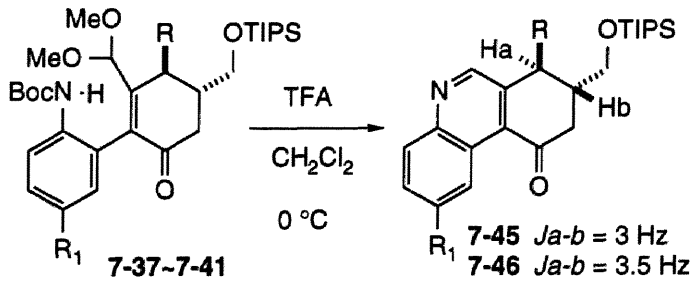
Scheme 7-5

Table 7-2. Palladium catalyzed coupling reaction between α-bromoenones with aryltins

entry	aryl tin	bromide	solvent	temp, time	product	yield (%)
1	**7-8**	**7-35**	NMP	85 °C, 1 h	**7-37**	80
2	**7-13a**	**7-35**	NMP	85 °C, 75 min	**7-38**	48
3	**7-13a**	**7-35**	toluene	80 °C, 40 min	**7-38**	70
4	**7-8**	**7-36**	NMP	70 °C, 70 min	**7-39**	82
5	**7-13a**	**7-36**	toluene	80 °C, 2 h	**7-40**	48

The ^{1}H NMR spectra of all products in **Table 7-2** suggested that these products consist of mixtures of two compounds (ca. 1:1). This was due to the restricted rotational isomers. Acid hydrolysis of the mixture of isomers (**7-37~7-41**) gave the corresponding single cyclization products (**7-42 ~ 7-46**). The methyl ether **7-41** prepared from **7-38** in the same manner to the synthesis of **7-24**, was transformed to **7-44.**

Table 7-3. Quinoline synthesis



entry	substrate			product	yield (%)
1	**7-37**	R = H	R_1 = H	**7-42**	89
2	**7-38**	R = H	R_1 = OTBDMS	**7-43**	88
3	**7-41**	R = H	R_1 = OMe	**7-44**	84
4	**7-39**	R = Me	R_1 = H	**7-45**	92
5	**7-40**	R = Me	R_1 = OTBDMS	**7-46**	77

In the ^{1}H NMR spectra, *J* a-b of **7-36** was 2 Hz which was remarkable contrast with 10 Hz for **7-32**. The difference of the coupling constant between **7-32** and **7-36** is rationalized by the conformational change of cyclohexenone ring, that is, methyl and hydroxymethyl substituents occupy di-*equatorial* position in **7-32**, while steric hindrance between Me group and dimethylacetal group in **7-36** gave di-*axial* conformer (**7-36b**). This assumption was supported by molecular mechanics calculations using MacroModel (MM2 force field).[18, 19] Calculated coupling constant (*J* a-b = 1.8 Hz) for more stable conformer (**7-36b**) is in good agreement with the experimental value (**Figure 7-2**). The corresponding coupling constants (*J* a-b) of **7-45** and **7-46** were also small (3 and 3.5 Hz, respectively) which indicated these two compounds to have a similar conformation to **7-36b** about the cyclohexenone ring. This was also supported by the molecular mechanics calculations (see below).

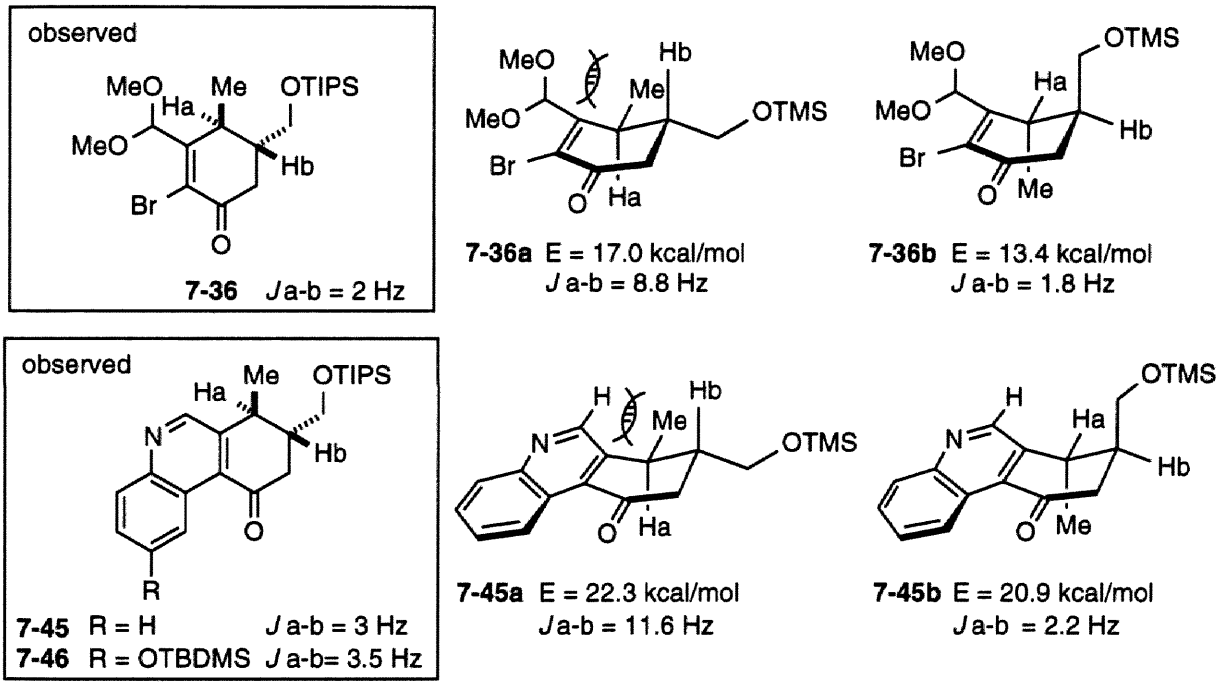


Figure 7-2

In summary, the construction of C, D and E ring of dynemicin A was investigated, in particular compound **7-46** has a fully functionalized carbon atoms on E ring without acetylenic group. This study provided a promising method toward a wide variety of dynemicin A model compounds.

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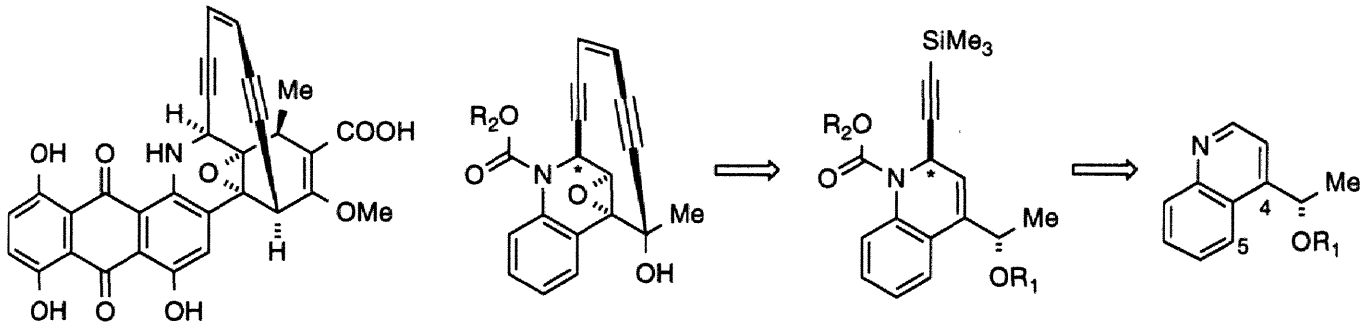
Chapter 8

Chiral Synthesis of Dynemicin A Model Compound

Chiral Synthesis of Dynemicin A model Compound

The absolute stereochemistry of naturally occurring dynemicin A has not been determined yet, even though the relative stereochemistry was determined by X-ray crystallographic analysis. Some docking studies between dynemicin A and double strand DNA by using computer graphics, proposed the absolute stereochemistry of dynemicin A as shown in **Scheme 8-1**.[1] In order to obtain the information about its absolute stereochemistry and to estimate the difference of biological activities between both enantiomers, chiral synthesis of the model compound was required.[2] In this Chapter, I described the asymmetric synthesis of both enantiomer of **Model B** by novel remote asymmetric induction as key step.



dynemicin A **Model B** **8-2** **8-3**

Scheme 8-1

Outline of racemic synthesis of **Model B** is shown in **Scheme 8-1**, which analyzed that all asymmetric centers in **Model B** were induced from the asymmetric center (*) of propargylic position. Namely, epoxide was introduced to the opposite side to axially oriented acetylene group, and *tert*-alcohol was controlled in the cyclization. I planned stereoselective introduction of acetylene group induced by the stereogenic center at side chain of **8-3**.[3] In the previous synthesis of *racemic* **Model B**, magnesium acetylide was introduced into quinoline **8-3** (R_1 = TBDMS) with ethyl chloroformate at 0 °C. The diastereoselectivity was about 1:2 (by ^1H NMR analysis). I considered that this selectivity might be explained by the preferential addition of magnesium acetylide from the less hindered side of quinoline plane (the opposite side to bulky silylether) in the most stable conformer (rotamer). The most stable conformation was expected to that shown in **Figure 8-1**, due to the severe steric interaction between the protons at peri position (C-5) and side chain at C-4.[4] This proposed conformation might be supported by following NMR studies. The following compounds (**8-11**, **8-22a** and **8-22b**) showed strong NOE enhancement between benzylic proton and the proton at C-5, while only weak or no NOE were observed between benzylic proton and the proton at C-3. Furthermore, molecular mechanics calculations (using MacroModel, MM2 force field) were performed to search the stable conformation of simplified compound (*t*-butylether **8-4**). The energy difference between two stable conformers (**8-4a**, **8-4b**) was calculated to give 3.4 kcal/mol, which indicated that the population of desired conformer **8-4a** was over 99 %. These studies suggested that preferential conformation of **8-3** at least in ground state was shown in **Figure 8-1**.[5]

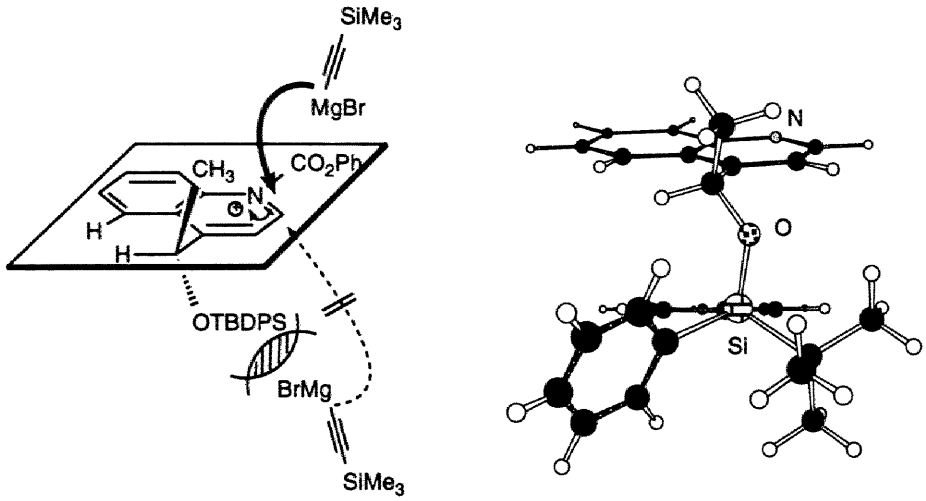
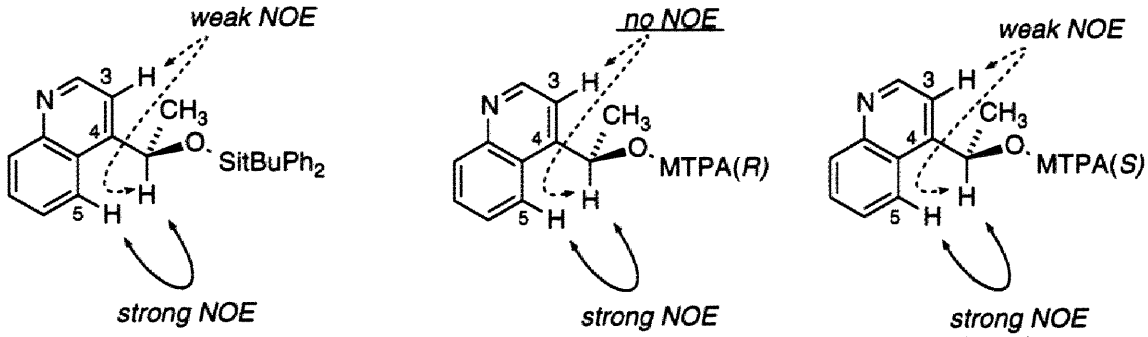
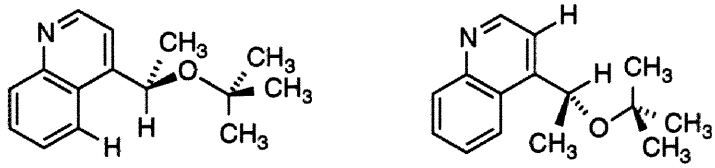


Figure 8-1



8-11 **8-22 a** **8-22 b**

Figure 8-2



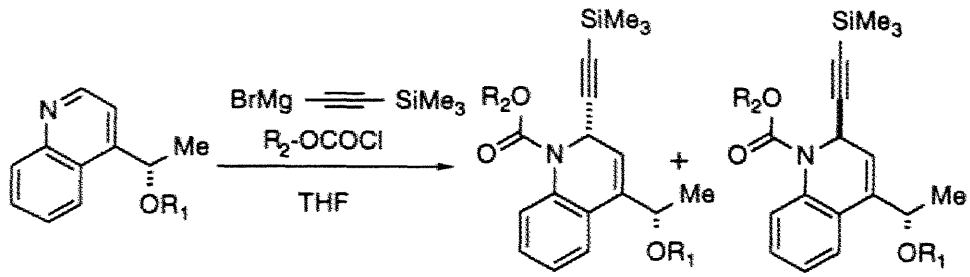
8-4a **8-4b**

53.02 kcal/mol (99.7 %) 56.40 kcal/mol (0.3 %)

Figure 8-3

Based on above discussion, larger protective group for hydroxy group was expected to increase the selectivity. If the selectivity could be improved, synthetic route of chiral **Model B** would be simplified. So that we started to search the best condition for this remote asymmetric induction. Representative results of the selectivity under different size of R_1 and different type of R_2 at different temperatures using racemic compounds (**8-5 ~ 8-8**) are shown in **Table 8-1** (This optimization was performed by Miss Kazuyo Obi in our laboratory). Combination in entry 7 comprising TBDPS as protective group in the substrate, phenyl carbamate and low reaction temperature (-78 °C) gave the highest ratio (1:13 by ^{1}H NMR analysis). To keep the reproducible high selectivity in this reaction, the stirring time (at -78 °C) before the addition of phenyl chloroformate to the solution of **8-8** and magnesium acetylide was found to be important. If the time was less than 30 min, the selectivity decreased to about 1:8. Stirring over 2 h at -78 °C was required for keeping high selectivity (1:13).

Anti- stereochemistry of major product was determined by X-ray crystallographic analysis of alcohol **8-14** which was derived from **8-13** (**Scheme 8-3**).[6] The ORTEP drawing of **8-14** is shown in **Figure 8-4** .

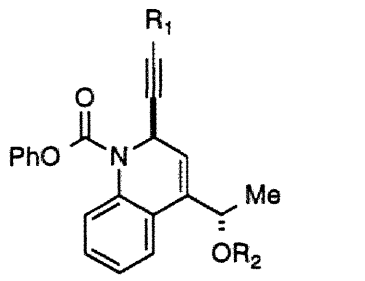


8-5 ~ 8-11 ***syn*** ***anti***

Scheme 8-2

Table 8-1

	substrate				products		
entry		R_1	R_2	temp (°C)		yield (%)	***syn* : *anti***
1	**8-5**	MOM	Me	0	**8-9**	65	1 : 1.1
2	**8-6**	PMB	Me	0	**8-10**	85	1 : 1.3
3	**8-7**	TES	Me	0	**8-11**	63	1 : 1.5
4	**8-8**	TBDPS	Me	0	**8-12**	85	1 : 2.3
5	**8-8**	TBDPS	Ph	0	**8-13**	100	1 : 4.9
6	**8-8**	TBDPS	Ph	-20	**8-13**	100	1 : 5.6
7	**8-8**	TBDPS	Ph	-78	**8-13**	87	1 : 13



a, b → **8-13** R_1 = $SiMe_3$ R_2 = TBDPS
8-14 R_1 = H R_2 = H

Scheme 8-3. (a) TBAF/MeOH-MeOH, 0 °C
(b) *p*-TsOH·H_2O/MeOH, reflux.

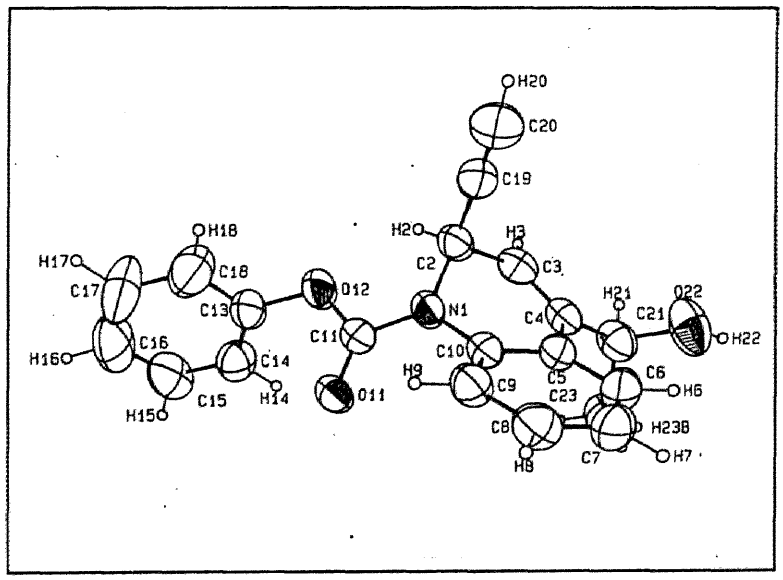
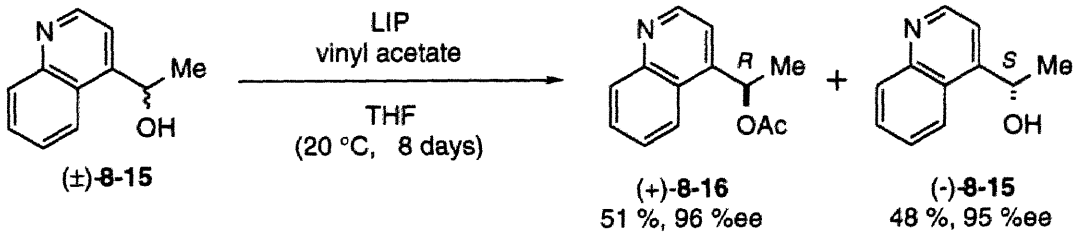


Figure 8-4. ORTEP drawing of 8-14

The remaining problem was to prepare the chiral alcohol **8-3** (R_1 = H) as starting material. After some consideration including chiral pool method using cinchona alkaloids, asymmetric alkylation (methylation)[7] of 4-quinolinecarboxaldehyde and asymmetric reduction[8] of the methylketone, we decided to use enzymatic resolution[9] of racemic alcohol **8-15**, because Heathcock reported preparative scale (ca. 60 g) resolution of 1-(1'-naphthyl)ethanol by lipase (PPL, Porcine Pancreatic Lipase).[10] After screening some commercial available lipases (Amano PS, AY, AK, *etc*), we found that LIP (immobilized lipase from TOYOBO) gave the acetate **8-16** and the alcohol **8-15** with high optical purities as well as high chemical yields. (This screening was performed by Miss Maki Yoshikai in our laboratory). Enantiomeric excess (ee %) were determined by ^{1}H NMR of its (*R*)-MTPA ester **8-17**.[11, 12, 13] The difficulty in the application of **8-15** to enzyme catalyzed resolution, was the extreme low solubility of alcohol **8-15** to less-polar organic solvents such as heptane, toluene *etc.* which were usually used in enzyme reactions. Although THF showed enough solubility to **8-15**, enzyme activity was lost during over night reaction. So that portionwise addition of the enzyme was required to complete the reaction. Absolute stereochemistry of the acetate **8-16** was determined by modified Mosher's method (**Figure 8-5**).[14]



Scheme 8-4

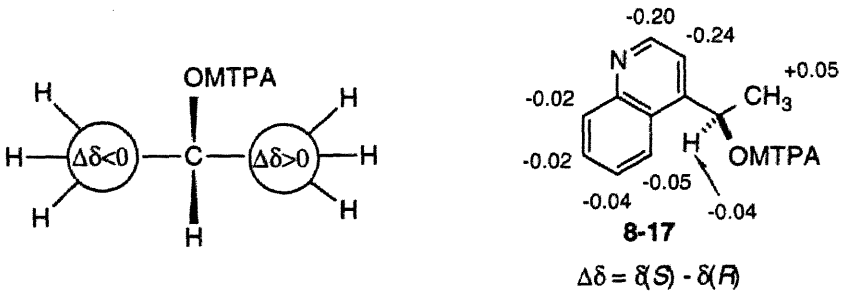
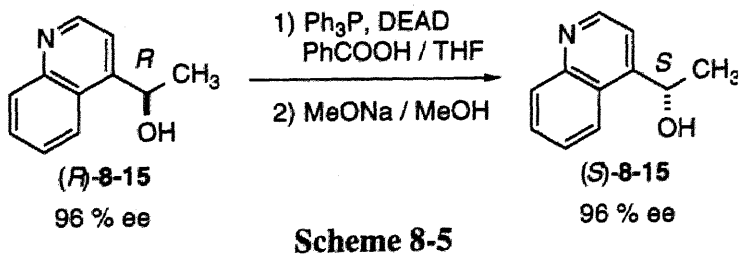


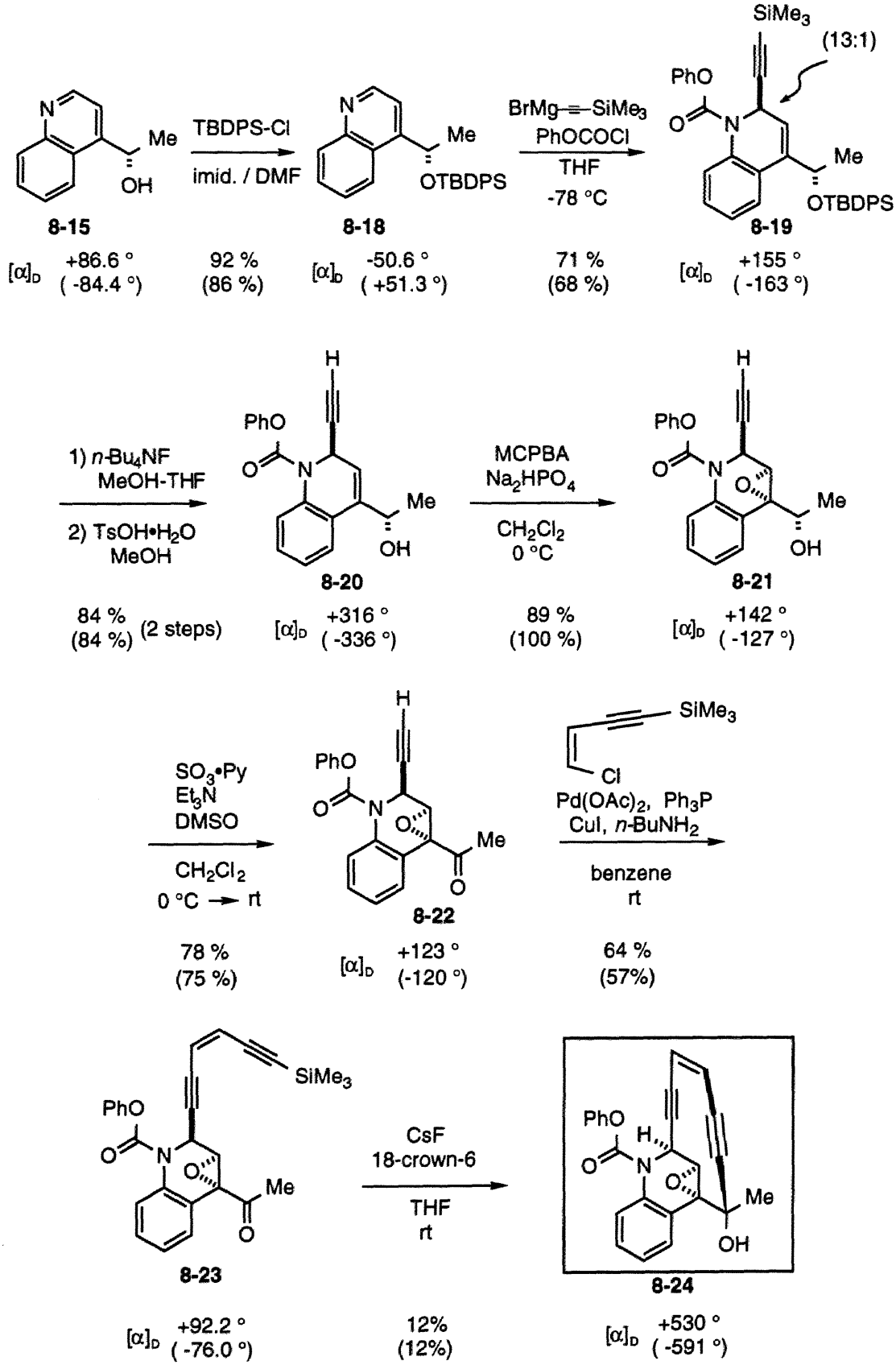
Figure 8-5. Determination of absolute configuration by modified Mosher's method

The chiral (*R*)-alcohol **8-15** could be inverted by Mitsunobu reaction and hydrolysis of the benzoate to the (*S*)-alcohol **8-15** with retaining the high optical purity (**Scheme 8-5**).[15] This experiment told that both enantiomer of **8-15** was used for the synthesis of **Model B** having the desired absolute configuration.



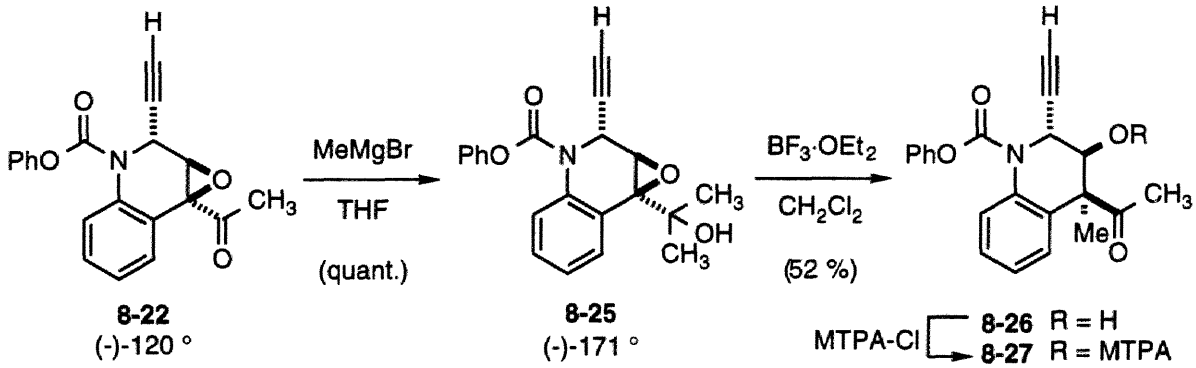
Scheme 8-5

The model compound (+)-**8-24** was synthesized from (+)-**8-15** as shown in **Scheme 8-6**. Synthetic route was quite similar to that of racemic one. Optical rotations of intermediates are shown below the structures in **Scheme 8-6**. The values of parentheses are the optical rotations of opposite enantiomers depicted in **Scheme 8-6**.



Scheme 8-6

The absolute stereochemistry of **8-24** was confirmed as follows. Addition of methylmagnesium bromide to (-)-ketone **8-22** gave *tert*-alcohol **8-25**. Semi-pinacol rearrangement of **8-25** induced by $BF_3 \cdot OEt_2$ gave **8-26**.[16, 17] The structure and conformation of **8-26** was confirmed by NMR analysis and molecular mechanics calculations (**Figure 8-6**). The stereostructure of rearranged product **8-26** indicated this rearrangement occurred through the concerted mechanism. The absolute stereochemistry of newly generated *sec*-alcohol in **8-26** was determined by modified Mosher's method (**Figure 8-7**).[15, 18] Since the *anti* relationship between acetylene and epoxide in **8-22** had been known, the absolute stereochemistry of (+)-**8-22** and (+)-**8-24** were determined as shown in **Scheme 8-6**.



Scheme 8-7

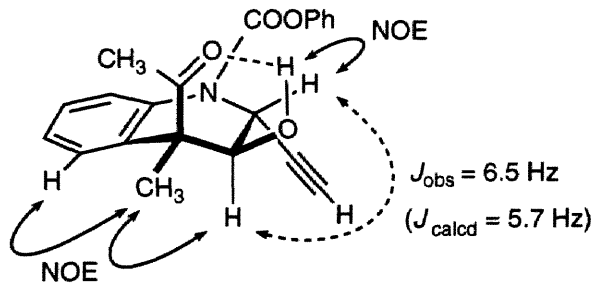


Figure 8-6

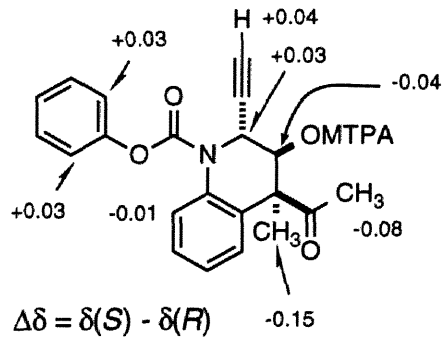


Figure 8-7

Argument of the absolute stereochemistry of (+)-**8-24** is of much interest in comparing proposed absolute stereostructure of dynemicin A and of (+)-model compound synthesized by K. C. Nicolaou's group.[2] DNA-cleaving activities of both synthesized enantiomers were indistinguishable by means of the assay using the topological change of ϕX174 DNA (**Figure 8-8**).

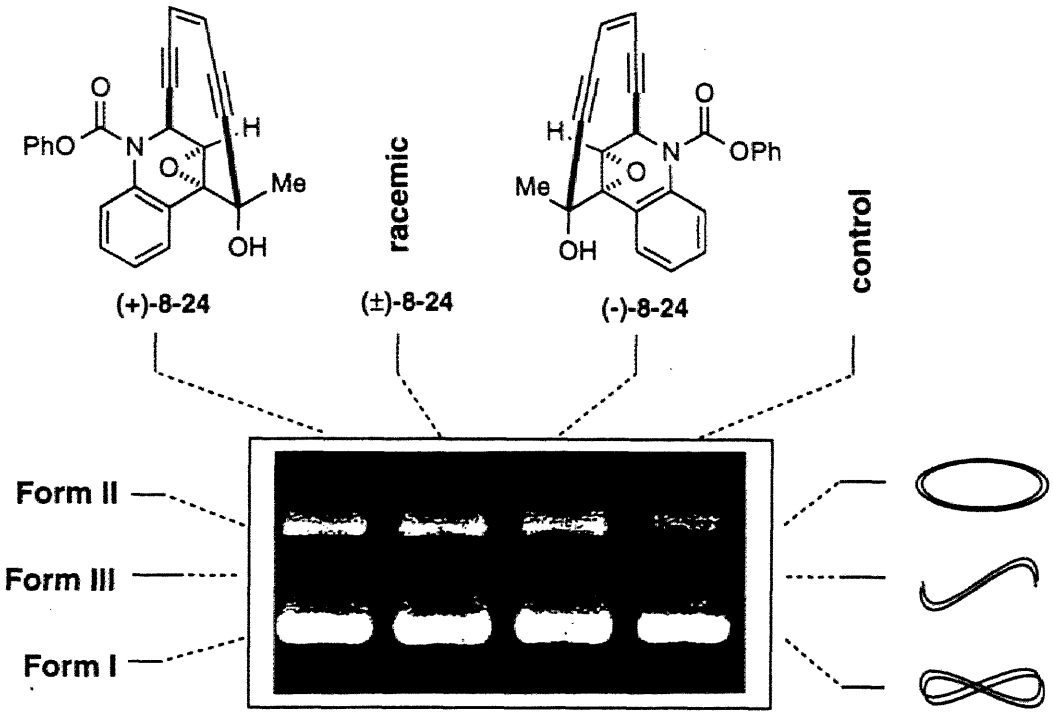


Figure 8-8. Agarose gel electrophoretic patterns of ethidium bromide stained ΦX174 DNA (90 % form I) after treatment with model compounds in phosphate buffer (pH 7.4) at 37 °C for 18 h.

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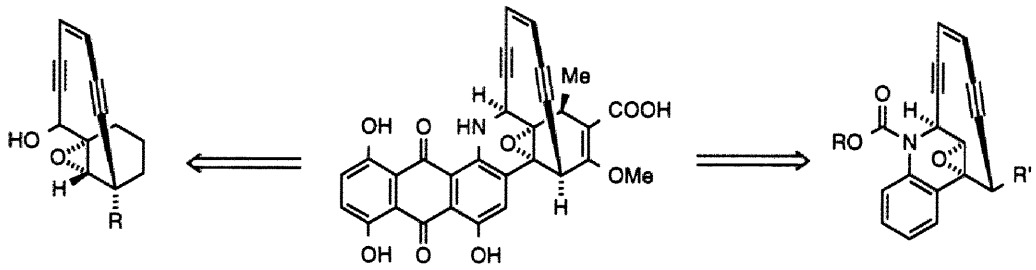
Summary and Trend of Enediyne Chemistry

Summary and Trend of Enediyne Chemistry

This thesis described about synthetic studies towards potent antitumor antibiotics, dynemicin A: molecular design, development of new reactions and the synthetic routes of mimics of dynemicin A. Outline of these results is as follows.

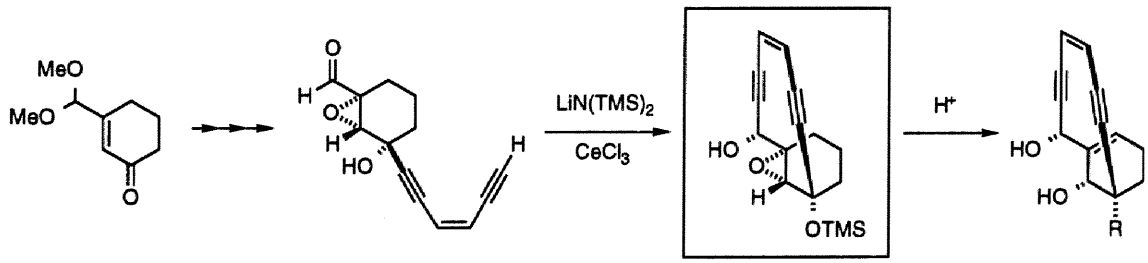
Extraordinary potent antitumor activities of cyclic enediyne antibiotics such as dynemicin A was attributed to double strand scission of DNA by carbon diradicals through Bergman reaction. The reactivity of Bergman reaction was correlated to the distance between acetylenic atoms in enediyne moiety. Based on molecular mechanics calculations, **Model A** and **B** were designed as candidates of active mimics. **Model A** included 10-membered enediyne ring and epoxide, on the other hand **Model B** included aniline, epoxide and 10-membered enediyne (**Scheme 9-1**).



Model A **dynemicin A** **Model B**

Scheme 9-1

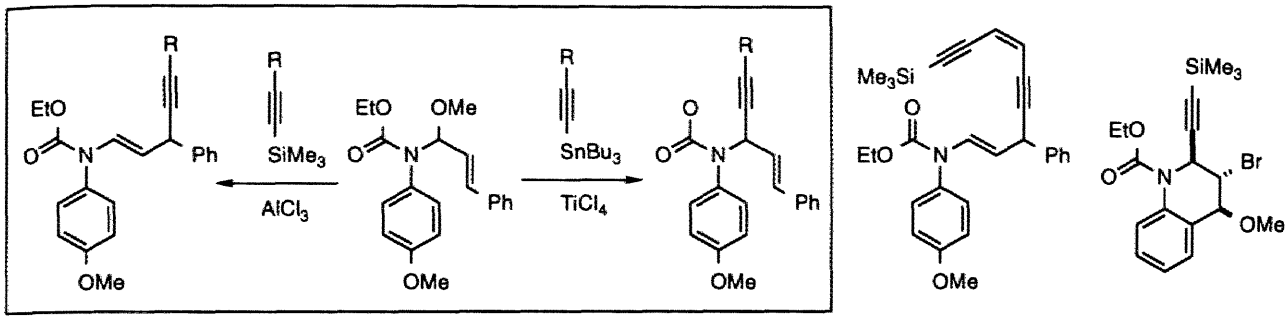
Compound **9-3** (an equivalent to **model A**) was synthesized from enone acetal **9-1** in 10 steps as shown in **Scheme 9-2**. However, treatment of epoxide **9-3** with acid did not give benzene derivative via Bergman reaction, but gave diol compound **9-4**, which was inert toward Bergman reaction.



9-1 **9-2** **9-3 (= Model A)** **9-4**

Scheme 9-2. Synthesis of Model A

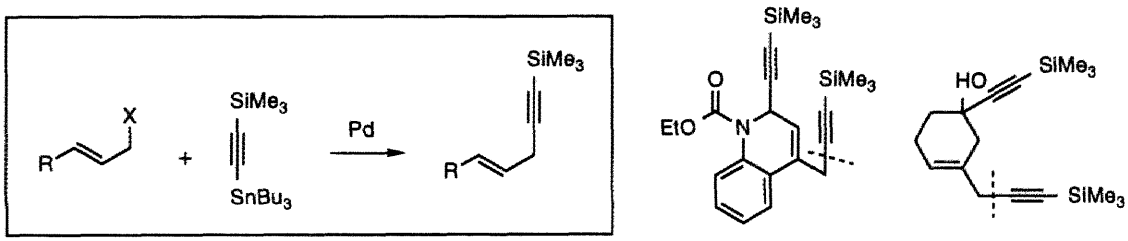
Addition of silyl- and tinacetylene toward acyliminium cation was developed. In the case of **9-5** as substrate, both 1,2- adduct **9-7** and 1,4-adduct **9-6** were selectively synthesized by using tinacetylene and silylacetylene, respectively. By using this reaction, compound **9-8** having enediyne and **9-9** were synthesized in one step from the corresponding α-ethoxycarbamates.



9-6 **9-5** **9-7** **9-8** **9-9**

Scheme 9-3

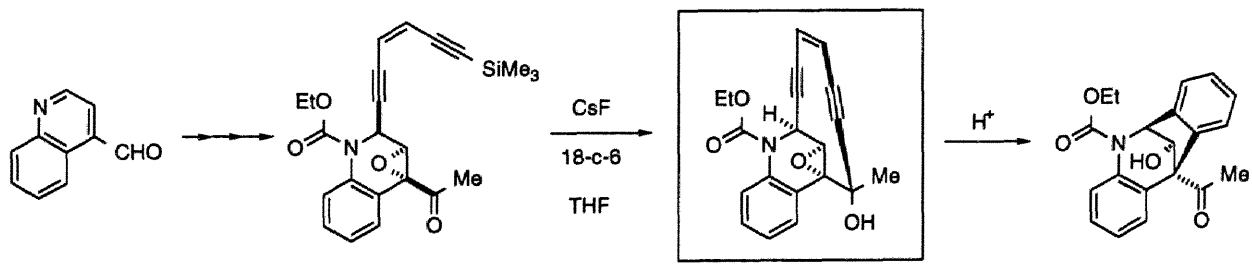
Palladium catalyzed coupling between allyl derivatives such as **9-10** and tinacetylene **9-11** was developed for the synthesis of precursor of enediyne compounds (**Scheme 9-4**). By using this reaction, compounds **9-13** and **9-14** were synthesized.



9-10 **9-11** **9-12** **9-13** **9-14**

Scheme 9-4

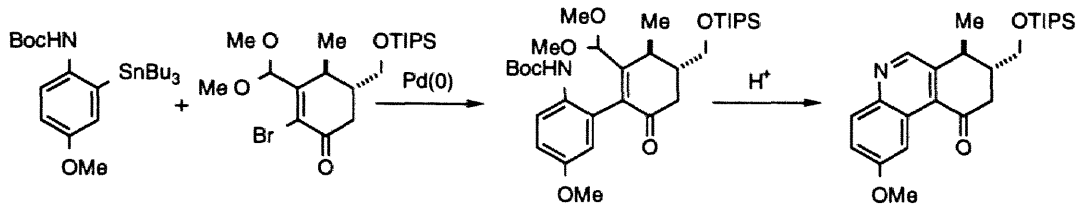
Compound **9-17** (an equivalent to **Model B**) was synthesized from 4-quinolinecarboxaldehyde **9-15** in 9 steps as shown in **Scheme 9-5**. The key step was ring closure of **9-16** which was achieved by intramolecular acetylide addition to carbonyl group with CsF in the presence of crown ether. Acid treatment of **9-17** gave the benzene derivative **9-18**, which indicated that **9-17** formed the radical species *via* Bergman reaction.



9-15 **9-16** **9-17 (Model B)** **9-18**

Scheme 9-5. Synthesis of Model B

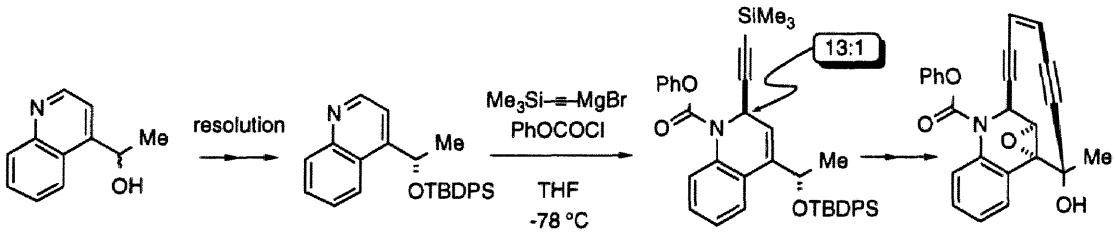
In order to synthesize the functionalized **Model B**, a new method for quinoline synthesis was developed. Palladium catalyzed coupling between aryltin **9-19** and vinylbromide **9-20** afforded **9-21**, which was converted into quinoline **9-22** under acidic condition. This results provided a promising method toward a variety of functionalized **Model B** of dynemicin A.



9-19 **9-20** **9-21** **9-22**

Scheme 9-6. New quinoline synthesis

Finally, in order to synthesize chiral **9-26** (**model B**), a new and highly selective 1,4-asymmetric induction in the addition of magnesium acetylide into quinoline nucleus was developed (**9-24** → **9-25** in **Scheme 9-7**). By using reaction, both enantiomers of **9-26** were synthesized from optically active alcohols **9-24** which were prepared by lipase catalyzed resolution of racemic alcohol **9-23**.



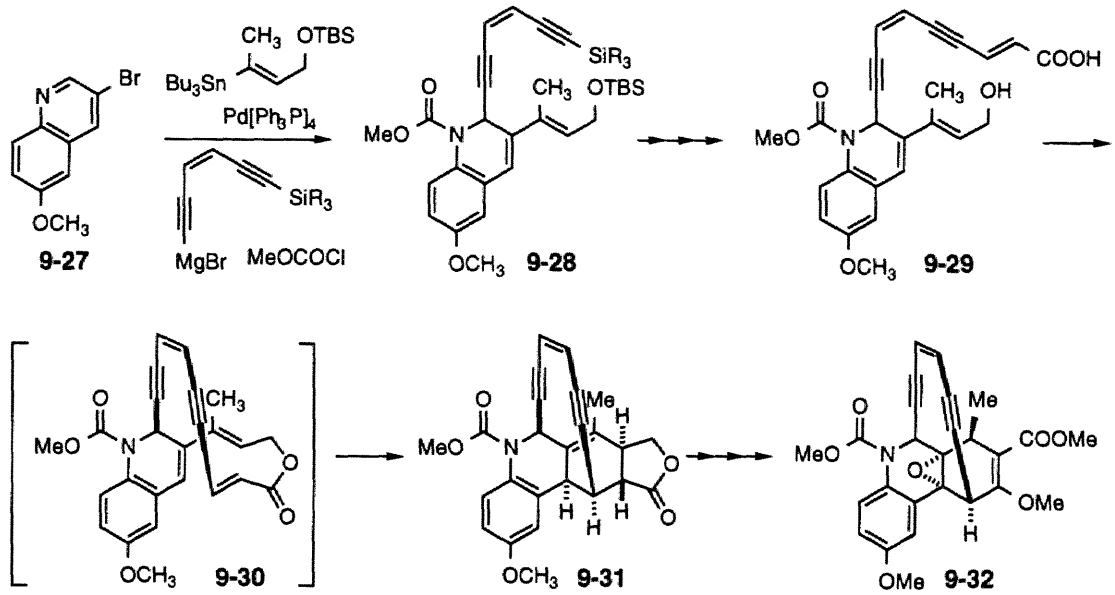
9-23 **9-24** **9-25** **9-26**

Scheme 9-7. Chiral synthesis of Model B

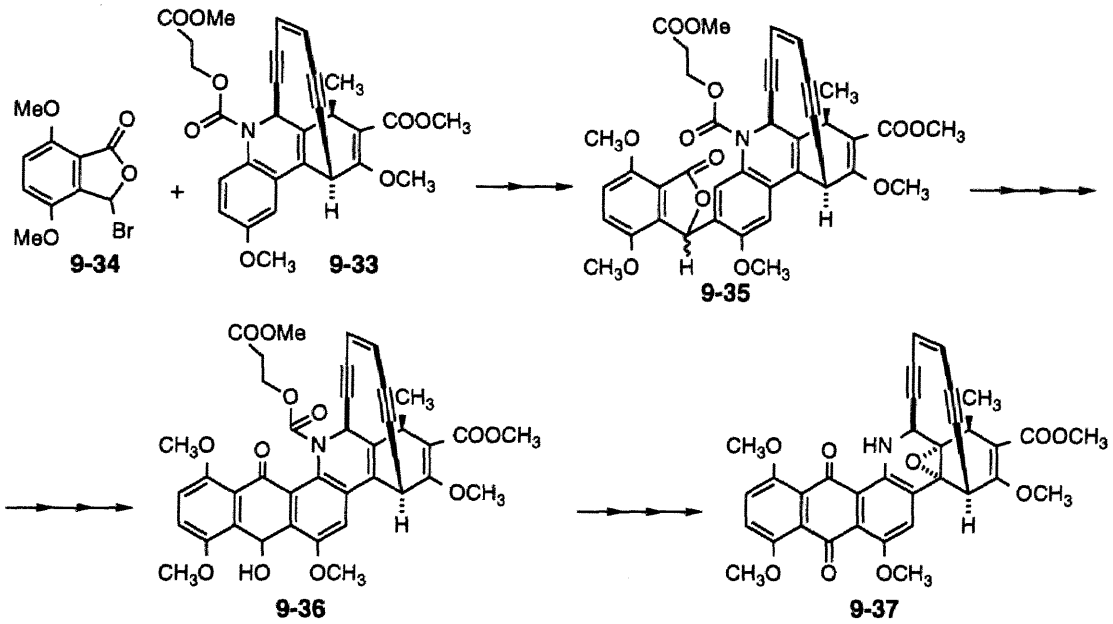
During our studies, a variety of synthetic approaches have been reported by some groups. The outlines of these synthetic studies were written below.

Schreiber's group at Harvard University have achieved the first total synthesis of *O*-methyl derivative of dynemicin A methyl ester **9-37**. At first, his group was developed an efficient method for 10-membered enediyne moiety using transannular Diels-Alder reaction (**Scheme 9-8**). The synthesis was started from 3-bromo-6-methoxyquinoline **9-27**, which was coupled with vinyltin compound and then alkynylated with magnesium acetylide in the presence of chloroformate, to give **9-28**. Lactonization of **9-29** gave **9-30**, which spontaneously underwent well-designed transannular Diels-Alder reaction at rt to furnish the pentacyclic compound **9-31**.[1] In **9-31** all the carbon atoms existed for the synthesis of enediyne core moiety of dynemicin A. In reality, **9-31** was converted into fully functionalized compound **9-32**.[2]

Based on above studies, Schreiber's group has achieved the first total synthesis of dynemicin A methylester as following manner. After conversion of **9-31** to **9-33**, dimethoxyphthalide **9-34** was introduced by Friedel-Crafts reaction.[3] Under careful conditions, **9-35** was transformed to methyl-dynemicin A **9-37**. The number of total steps was about 40.[4] Unfortunately, protective groups (methylether, ester) of **9-37** have not been removed under a variety of conditions.



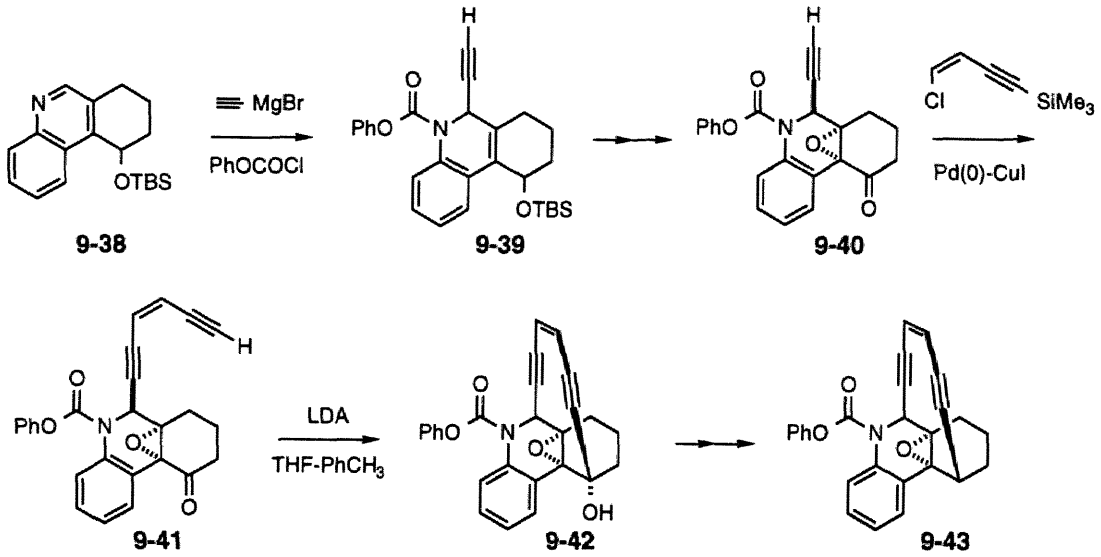
Scheme 9-8



Scheme 9-9

Nicolaou's group at Scripps Research Institute has reported many dynemicin A-related compounds such as **9-43**. Basic route for the synthesis of these compounds is as follows. Starting materials were quinoline derivative such as **38**, which were readily prepared from *p*-anisidine. Magnesium acetylide was introduced to **9-38** in the presence of chloroformate to give **9-39**, which was transformed to the epoxyketone **9-40**. After extension to acyclic enediyne, **9-41** was treated with LDA at -78 °C to give the cyclization product **9-42** in high yield. Finally hydroxy group was removed by Barton's method to afford **9-43**.[5] Nicolaou group applied this method to the syntheses of a variety of compounds (eg. **9-44**, [6] **9-45, 9-46,**[7] **9-47,** [8] **9-48** [9] in **Figure 9-1**). In particular, *N*-sulfonylethyl carbamate derivative **9-44** exhibited potent activity over dynemicin A itself toward a certain cell-lines. Protective group of **9-44** was readily cleaved under slightly basic conditions.[10] Recently his group reported that **9-44** induced apotosis (programmed cell death) which result proposed that the target of

9-44 was not DNA but also specific protein involved in the apotosis.[11] So that **9-44** may be useful as probe for searching the protein.



Scheme 9-10

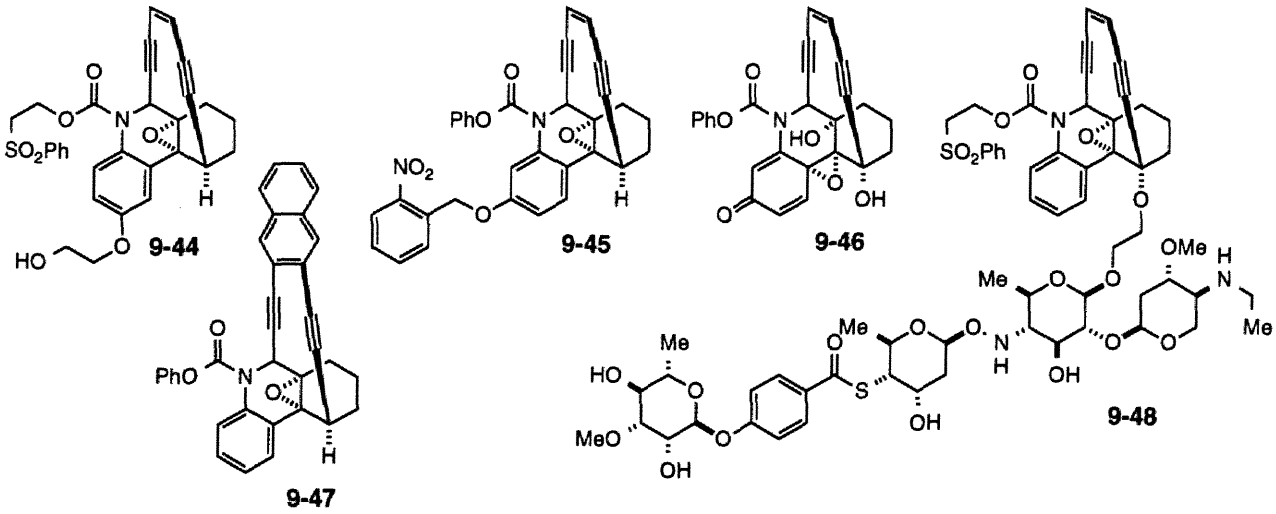
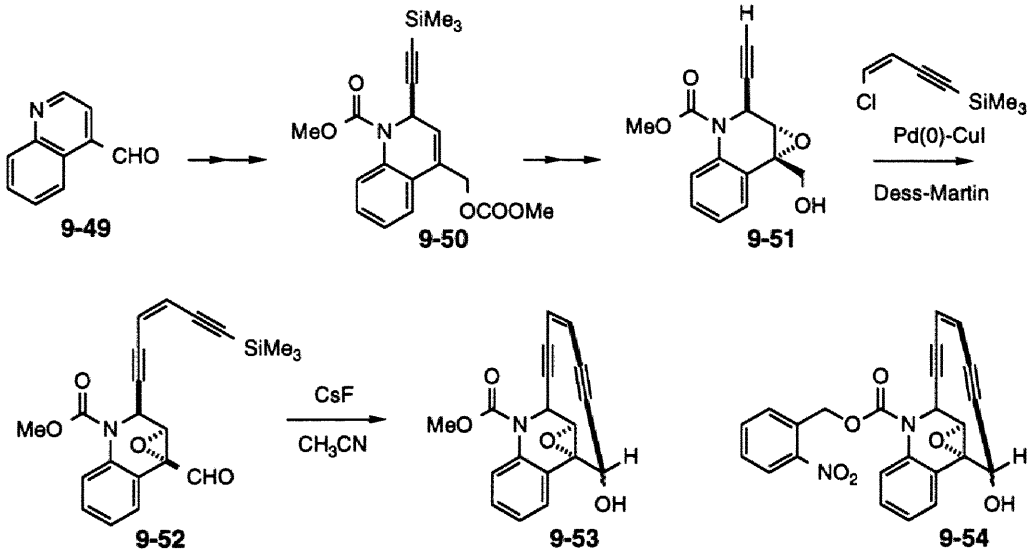


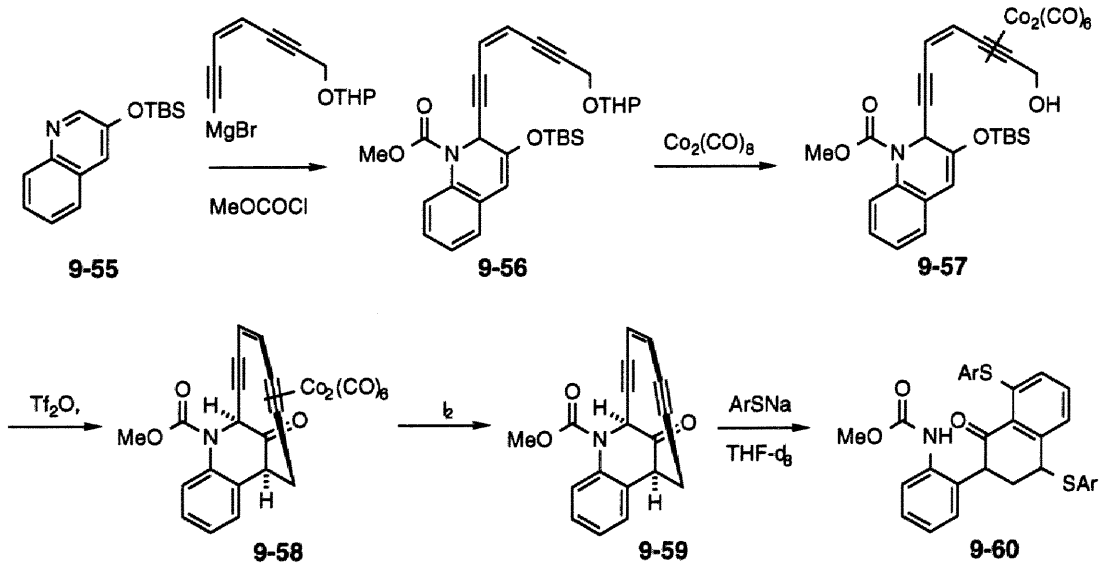
Figure 9-1

Wender at Stanford University synthesized similar compound **9-53** to ours (**Scheme 9-11**). They synthesized epoxy aldehyde **9-52** with Dess-Martin periodinate from the corresponding alcohol, and cyclized with CsF in acetonitril to give **9-53** in 21 %.[12] Recently, his group improved the condition of the cyclization to increase the yield (up to 69 %), to give the photochemically activatable analog **9-54**.[13]



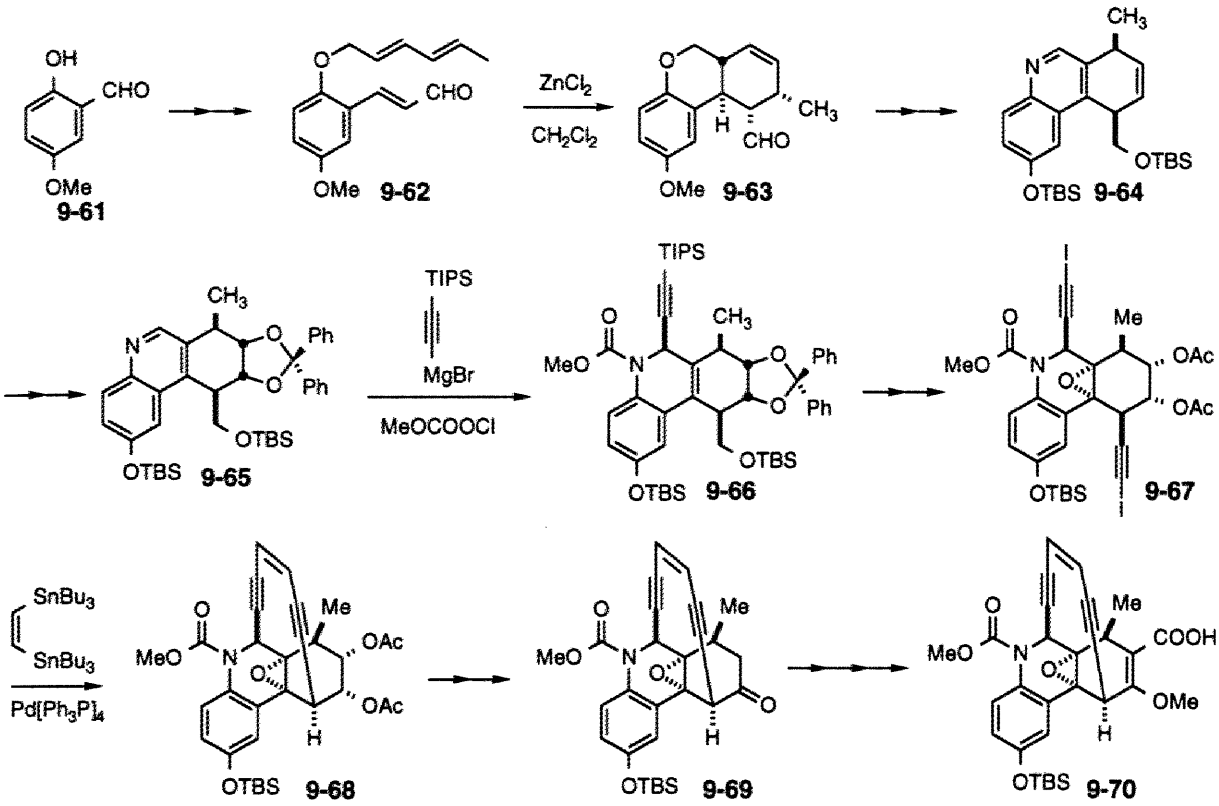
Scheme 9-11

Magnus at University of Texas reported an efficient synthesis of **9-59** in only 5 steps by using Nicholas reaction as a key step (**Scheme 9-12**).[14] The enediyne **9-59** underwent the non-radical (ionic) cycloaromatization in the presence of thiolate to afford **9-60** and exhibited the potent antitumor activities *in vitro* and *in vivo*.[15] These results indicated that unknown action mechanism to express the biological activities.



Scheme 9-12

Quite recently, Danishefsky's group at Yale University reported the synthesis of the fully functionalized enediyne core **9-70**. This synthesis was characterized by interesting double Stille coupling of diiodide **9-67** for synthesis of 10-membered enediyne ring.[16] The synthesis started from intramolecular Diels-Alder reaction of **9-62**. The adduct **9-62** was converted into quinoline **9-64**. The diastereoselective addition of magnesium acetylide to **9-65** solved the stereochemical problem for the formation of 10-membered enediyne in dynemicin A.[17] The enediyne compound **9-68** was converted to **9-70** via carbonylation of the ketone **9-69**.



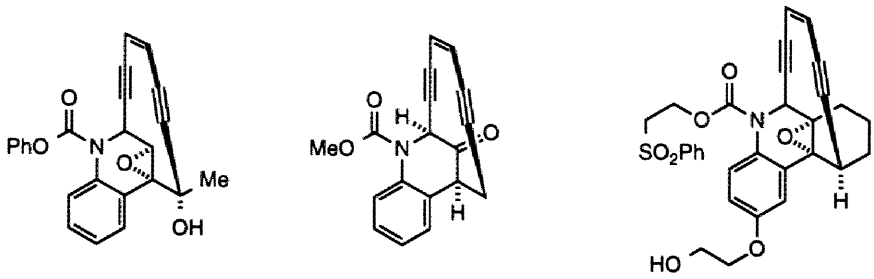
Scheme 9-13

The action mechanism of potent antitumor antibiotics dynemicin A has been believed that Bergman cycloaromatization of cyclic enediyne moiety generates carbon diradicals which abstracted hydrogen of DNA. Based on the results of our studies and others, however the other important possible mechanism may be involved in synthesized dynemicin A-related compounds in particular.

For examples, our **Model B 9-26** showed single strand cleavage of DNA and significant cytotoxicities (IC_{50} = 5.7 x 10^{-6} M to KB cell, IC_{50} = 8.4 x 10^{-6} M to L1210), but no radical formation through Bergman reaction occurred in the neutral buffer medium.[18]

Magnus reported radical formation of **9-59** was not required for biological activity. His model **9-59** exhibited considerable *in vitro* (IC_{50} = 0.21 μM to HCT116 human colon carcinoma cell) and *in vivo* antitumor activity (T/C (2 mg/Kg) = 175 % to P388). However, **9-59** was inert to Bergman reaction at ambient temperatures. For Bergman reaction, heating was required up to 97 °C. On the other hand, in the presence of thiolates, **9-59** gave several non-Bergman type products at 0 °C.

Nicolaou's model **9-44** was more toxic toward a certain tumor cell line (IC_{50} = 10^{-14} M to Molt-4 leukemia cell) than dynemicin A. In the neutral buffer at 37 °C, however **9-44** showed only slight DNA cleaving activities. They found that the strong cytotoxicities of **9-44** was due to induction of apotosis (program cell death) in Molt 4 cell.[11]



9-26 **9-59** **9-44**

Figure 9-2

Above results strongly suggested the different mechanism from previously proposed one (Bergman reaction & DNA scission by phenylene diradicals) might be involved with antitumor activities. Another mechanism such as DNA alkylation *etc* might be important (**Figure 9-3**). Induction of apotosis by Nicolaou's model **9-44** at low concentration (10^{-14} M) suggested that target of compound **9-44** might be specific protein involved in the expression of apotosis. In fact, protein damage by esperamicin/ calicheamicin type of synthetic enediyne was reported.

Further progress of the research including total synthesis, an efficient synthesis of more active compounds and clarification of the detail action mechanisms are expected.

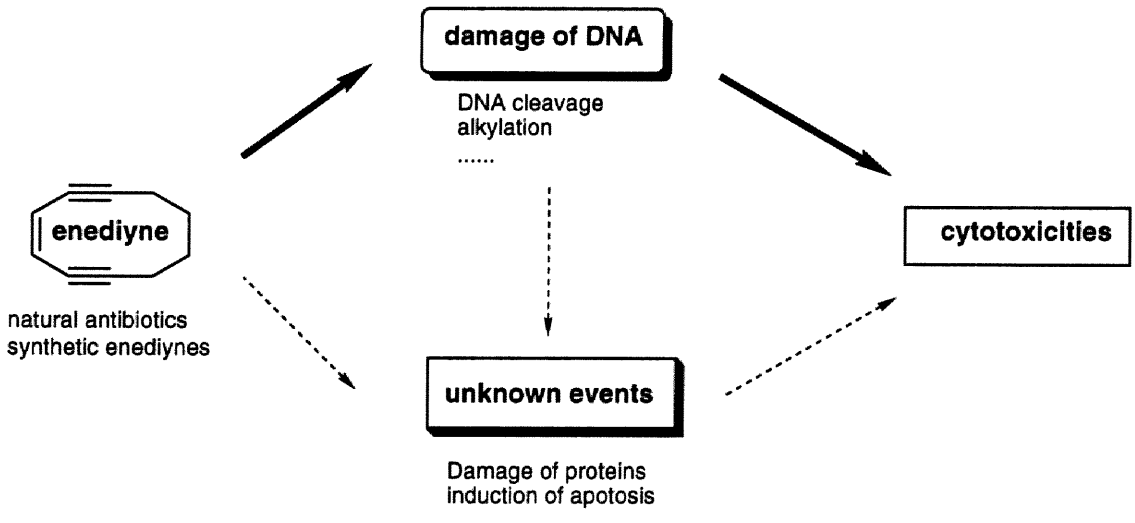


Figure 9-3

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Experimental Section

General:

Melting points (Mp) were measured with a Yanaco MP-S3 melting point apparatus and are not corrected.

Infrared (IR) spectra were recorded on a JASCO FT/IR spectrophotometer and are reported in wave number (cm^{-1}).

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on JEOL FX-200 (200 MHz), JEOL EX-270 (270 MHz) and Varian VXR 500 (500 MHz) spectrometers. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (0.00) or $CHCl_3$ (7.26) as an internal standard. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet).

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL FX-200 (50 MHz), JEOL EX-270 (67.9 MHz), Varian VXR 500 (125 MHz) spectrometers. Chemical shifts are reported as δ values in parts per million (ppm) relative to $CDCl_3$ (77.0) as an internal standard.

Low resolution mass spectra (EI) were recorded on JEOL JMS-D 100, DX-300 and DX-705L spectrometers and reported in *m/z*.

High-resolution mass spectra (HRMS) were recorded on a JEOL DX-705L spectrometer and reported in *m/z*.

Optical rotations were measured at room temperature with JASCO DIP-370.

Elemental analyses were performed by Analytical Laboratory at School of Agricultural Sciences, Nagoya University to which the author gratefully acknowledge.

Unless otherwise noted, non aqueous reactions were carried out under nitrogen or argon atmosphere. In particular, oxygen sensitive reactions were carried out under argon atmosphere by using vacuum line apparatus.

THF was distilled from potassium metal/benzophenone ketyl.

Benzene was dried over Na metal and used without distillation.

DMF and CH_2Cl_2 were dried over MS 4Å.

Pyridine was dried over KOH and used without distillation.

DMSO, *n*-$PrNH_2$ and *n*-$BuNH_2$ were distilled from CaH_2.

CCl_4 was distilled from P_2O_5.

Ethyl chloroformate was distilled under N_2 atmosphere.

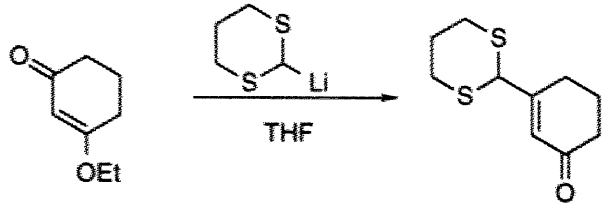
All other commercially obtained reagents were used as received.

Analytical thin-layer chromatography (TLC) was carried out by precoated silica gel plates (Art # 5715).

Preparative thin-layer chromatography (TLC) was carried out by precoated silica gel plates (Art # 5774), or prepared silica gel (Art # 7747).

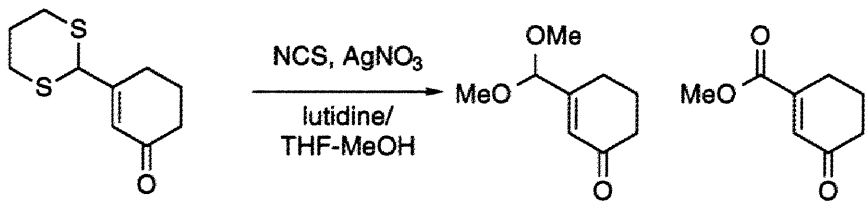
Silica gel for column chromatography were supplied from Fuji Devison (BW 820-MH).

Experimental for Chapter 3.



3-2 **3-4** [12043]

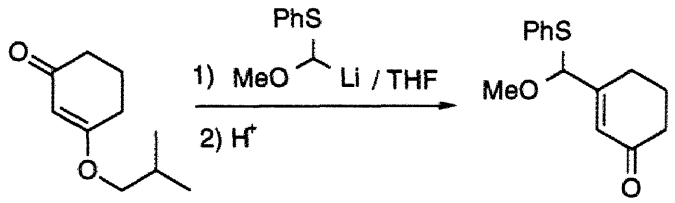
Compound 3-4. 1, 3-dithiane (14.5 g, 71.3 mmol) was dissolved in THF (200 mL) and cooled to -78 °C. To this solution was added *n*-BuLi (2.5 M in hexane, 45.6 mL, 114 mmol) dropwise. After stirring at -78 °C, the mixture was stirred at 0 °C for 45 min and cooled to -78 °C again. To this solution was added ethoxyclohexeneone **3-2** (10.0 g, 71.3 mmol) in THF (40 + 10 mL) over 10 min. After stirring for 3 h, the mixture was quenched with sat. NH_4Cl solution, extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 500 g, ether/hexane = 1:1) to give the ketodithiane **3-4** (14.7 g, 79 %). IR (KBr) ν_{max} 2939, 1668, 1624, 1419, 1256 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.83-2.21 (4H, m, CH_2 x2), 2.40 (2H, dd, J = 7, 6 Hz, CH_2), 2.52 (2H, td, J = 6, 1.5 Hz, CH_2), 2.93 (4H, m, S-CH_2 x2), 4.66 (1H, s, $CH(SCH_2)$), 6.22 (1H, br s, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.6, 25.1, 28.2, 30.5, 37.3, 51.8, 127.6, 160.4, 199.3. MS (EI) *m/z* 214 (M^+). Anal. Calcd for $C_{10}H_{14}OS_2$: C, 56.04; H, 6.58. Found C, 56.03; H, 6.59.



3-4 **3-6** **3-6'** [12089]

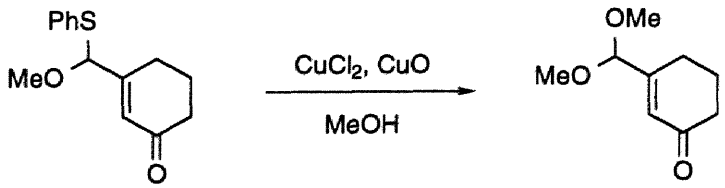
Ketoacetal 3-6. NCS (25.6g, 192.2 mmol), $AgNO_3$ (36.7 g, 216 mmol) and 2,6-lutidine (55.9 mL, 480 mmol) were dissolved in MeOH (500 mL). To this mixture was added the ketodithiane **3-4** (10.3 g, 48.0 mmol) in THF (100 mL). After stirring at rt for 40 min, sat. $NaHCO_3$ solution (150 mL), sat. Na_2SO_3 solution (100 mL) and brine (50 mL) were successively added. The mixture was filtrated through the pad of Super-Cel®. The filtrate was extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 1N HCl (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 400 g, AcOEt/hexane = 1:3) to give the ketoacetal **3-6** (5.54 g, 68 %) and ketoester **3-6'** (267 mg, 3.6 %). **ketoacetal 3-6:** IR (KBr) ν_{max} 2940, 1684, 1454, 1340, 1189, 1152 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.02 (2H, m, CH_2), 2.34 (2H, td, J = 6, 1.5 Hz, CH_2), 2.42 (2H,

t, J = 6 Hz, CH_2), 3.34 (6H, s, OCH_3 x2), 4.75 (1H, s, $CH(OMe)_2$), 6.13 (1H, q, J = 1 Hz, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.4, 24.6, 37.9, 53.5, 103.7, 126.8, 158.7, 199.9. MS (EI) *m/z* 170 (M^+), 139 (M-31). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found C, 63.51; H, 8.35. **ketoester 3-6'**: R (KBr) ν_{max} 2954, 1716, 1685, 1436, 1258, 1227, 1077 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.04 (2H, m, CH_2), 2.44 (2H, t, J = 7 Hz, CH_2), 2.58 (2H, td, J = 6, 2 Hz, CH_2), 3.82 (3H, s, $COOCH_3$), 6.72 (1H, br s, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.0, 24.7, 37.6, 52.5, 133.0, 148.7, 166.9, 200.0. MS (EI) *m/z* 154 (M^+). HRMS (EI) for $C_8H_{10}O_3$(M^+), calcd,154.0629, found 154.0632.



3-3 **3-5** [13046]

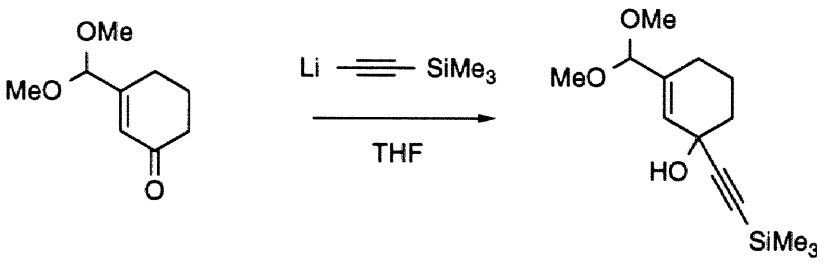
Monothioacetal 3-5. To a solution of methoxymethyl phenylsulfide (0.61 mL, 4.16 mmol) in THF (6 mL) cooled to -78 °C was added *n*-BuLi (1.55 M in hexane, 2.6 mL, 4.16 mmol) and stirred at -78°C for 1 h. A solution of **3-3** in THF (2 + 1 mL) was added over 5 min. After stirring at -78 °C for 1 h, the mixture was quenched with ice-cold sat. NH_4Cl solution, and extracted with ether (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 50 g, ether/hexane = 1:2 → 2:3) to give monothioacetal **3-5** (581 mg, 79 %). IR (KBr) ν_{max} 2946, 1671, 1629, 1439, 1186, 1083 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.87-2.00 (2H, m, CH_2), 2.16-2.40 (3H, m, CH_2, CH), 2.49-2.63 (1H, m, CH), 3.59 (3H, s, OCH_3), 5.01 (1H, d, J = 1 Hz, $CH(OMe)_2$), 5.74 (1H, q, J = 1 Hz, olefinic), 7.22-7.41 (5H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.4, 26.6, 37.7, 56.5, 91.4, 125.2, 128.6, 128.7, 129.0, 134.5, 158.9, 199.4. MS (EI) m/z 248 (M^+), 218. HRMS (EI) for $C_{14}H_{16}O_2S$ (M^+), calcd 248.0870, found 248.0857.



3-5 **3-6** [16035]

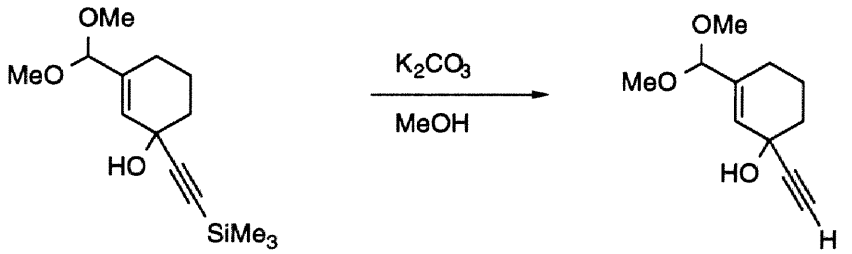
Dimethyl acetal 3-6. To a solution of the monothioacetal **3-5** (190 mg, 0.766 mmol) in MeOH (7.0 mL) were added $CuCl_2$ (153 mg, 1.14 mmol) and CuO (182 mg, 2.29 mmol). The mixture was heated at reflux temperature for 1.5 h. After cooling to rt, the mixture was filtrated through the pad of Super-Cel®. The filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2-H_2O, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to give **3-6** (95 mg, 73 %).



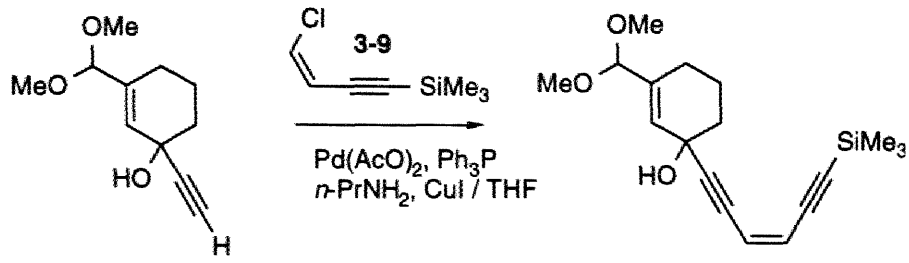
3-6 **3-7** [12090]

Compound 3-7. To a solution of trimethylsilylacetylene (8.27 mL, 58.5 mmol) in THF (180 mL) cooled to -78 °C was added *n*-BuLi (2.5 M in hexane, 19.5 mL, 48.8 mmol) over 10 min. This solution was stirred at 0 °C for 30 min, and cooled to -78 °C again. To this solution was added the ketoacetal **3-6** (5.54 g, 32.5 mmol) in THF (30 mL) over 15 min. After stirring for 2 h, the reaction was quenched with sat. NH_4Cl solution (150 mL) and water (100 mL). The mixture was extracted with ether-AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 300g, ether/hexane = 1:1) to give the propargyl alcohol **3-7** (7.83 g, 90 %). ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 1.70-2.07 (6H, m, $(CH_2)_3$), 2.25 (1H, br s, O*H*), 3.30 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 4.56 (1H, s, $CH(OMe)_2$), 5.87 (1H, br s, olefinic).



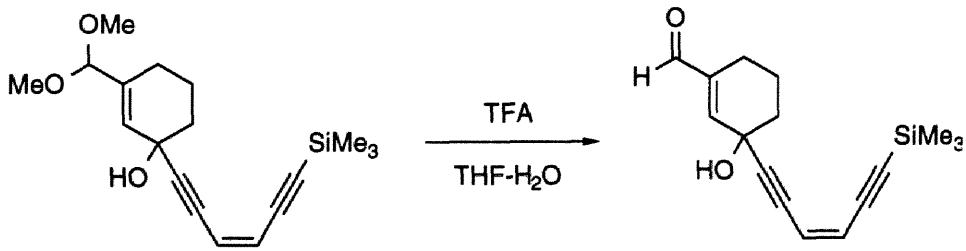
3-7 **3-8** [12115]

Compound 3-8. To a solution of **3-7** (7.83 g, 29.1 mmol) in MeOH (150 mL) was added K_2CO_3 (750 mg). After stirring at rt for 35 min, the mixture was quenched with sat. NH_4Cl solution (150 mL), extracted with CH_2Cl_2 (150 mL x3). The combined organic layer was washed with water (200 mL x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 200 g, ether/hexane = 1:1) to give **3-8** (4.98 g, 87 %). IR (KBr) ν_{max} 3413, 2956, 2146, 1685, 1250, 1059 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.72-2.15 (6H, m, $(CH_2)_2$), 1.53 (1H, s, C≡C-*H*), 3.30 (6H, s, OCH_3 x2), 4.56 (1H, s, $CH(OMe)_2$), 5.92 (1H, br s, olefinic). Anal. Calcd for $C_{11}H_{16}O_3SiCl$: C, 67.32; H, 8.21. Found C, 67.21; H, 8.05.



3-8 **3-10** [12150]

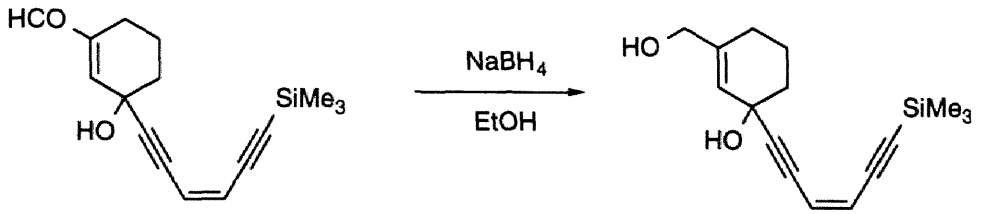
Enediyne 3-10. In a dried flask was placed $Pd(OAc)_2$ (215 mg, 0.95 mmol), Ph_3P (502 mg, 1.91 mmol), CuI (363 mg, 1.91 mmol) and benzene (100 mL). The mixture was degassed by two freeze-thaw cycles and covered with argon and stirred at rt for 15 min. To this solution were added acetylene **3-8** (3.76 g, 19.1 mmol) in benzene (15 mL), vinyl chloride **3-9** (5.82 mL, 32.5 mmol) in benzene (10 mL) and *n*-$PrNH_2$ (4.72 mL, 57.4 mmol) successively. The mixture was stirred at rt for 1 h 20 min. The reaction was quenched with sat. NH_4Cl solution (100 mL) and extracted with Et_2O (100 mL x3). The combined organic layer was washed with NH_4Cl solution (150 mL x2) and brine (150 mL x2), dried over anhydrous Na_2SO_4, an then concentrated under reduced pressure. The residue was purified by column chromatography (silica 350 g, ether/hexane = 2:3) to give **3-10** (4.64 g, 76 %). IR (KBr) ν_{max} 3400, 2938, 2832, 2145, 1250, 844 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, Si (CH_3)$_3$), 1.72-2.14 (6H, m, (CH_2)$_3$) 2.30 (1H, br s, O*H*), 3.28 (6H, s, OCH_3 x2), 4.55 (1H, s, C*H*(OMe)$_2$), 5.81 (1H, d, *J* = 11 Hz, C*H*=CH), 5.86 (1H, d, *J* = 11 Hz, CH=C*H*), 5.93 (1H, br s, C*H*=C-C-OH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 19.2, 23.4, 37.9, 53.2, 53.3, 65.9, 81.2, 100.3, 101.8, 102.9, 104.7, 119.8, 120.1, 128.4, 137.3. MS (EI) m/z 318 (M^+), 303 (M-15), 287. Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found C, 67.84; H, 8.30.



3-10 **3-11** [12160]

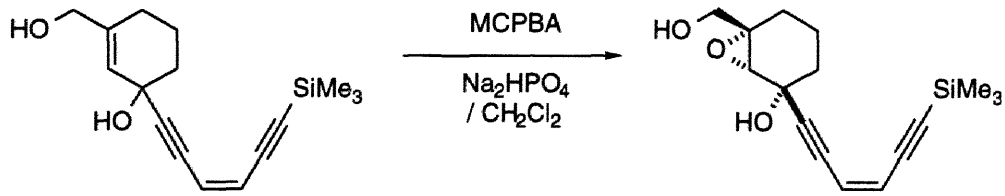
Enediyne 3-11. The acetal **3-10** (3.49 g, 10.9 mmol) was dissolved in THF (100 mL) and water (20 mL) and cooled to 0 °C. To this solution was added TFA (1.4 mL). After stirring at 0 °C for 30 min, the solution was warmed to rt and stirred for additional 15 min. The mixture was poured into ice-cold sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. This material was used to subsequent reaction without further purification. The analytical sample was prepared by preparative TLC (CH_2Cl_2). **3-11:** IR (KBr) ν_{max} 3449, 2957, 2148, 1684, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, Si(CH_3)$_3$), 1.80-2.28 (6H, m, (CH_2)$_3$), 2.54 (1H, br s, O*H*), 5.85 (1H, d, *J* = 11 Hz, C≡C-C*H*=CH), 5.91 (1H, d, *J* = 11 Hz, C≡C-C*H*=CH), 6.63 (1H, br s, C*H*=C-CHO, 9.52 (1H, s,

CHO). MS (EI) m/z 272 (M^+), 257 (M-15), 263 (M-29). Anal. Calcd for $C_{16}H_{20}O_2Si$: C, 70.54; H, 7.40. Found C, 69.73; H, 7..41.



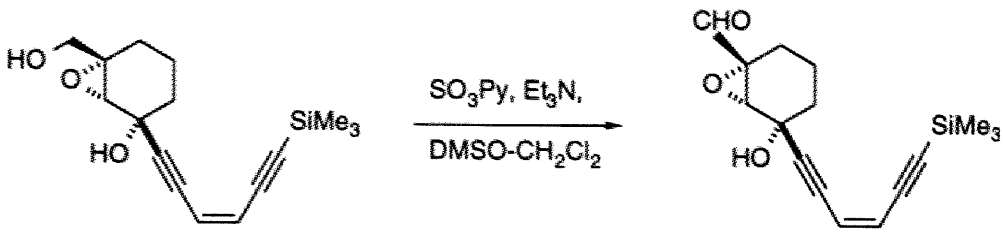
3-11 **3-12** [12160]

Enediyne 3-12. The crude aldehyde **3-11** (3.18 g) was dissolved in EtOH (80 mL) and cooled to 0 °C. To this solution was added $NaBH_4$ (165 mg, 4.38 mmol) portionwise. After stirring at 0 °C for 20 min, AcOH was added. After removal of solvent, the residue was dissolved with CH_2Cl_2 and water. The mixture was extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 100g, ether /hexane = 4:1) to give the alcohol **3-12** (2.30 g, 76 % in 2 steps). ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.77-2.18 (6H, m, $(CH_2)_3$), 4.04 (2H, br s, CH_2-OH), 5.79 (1H, br s, C=C*H*-C-OH), 5.82 (1H, d, J = 11 Hz, C*H*=CH), 5.88 (1H, d, J = 11 Hz, CH=C*H*). MS (EI) *m/z* 274 (M^+), 256 (M-18).



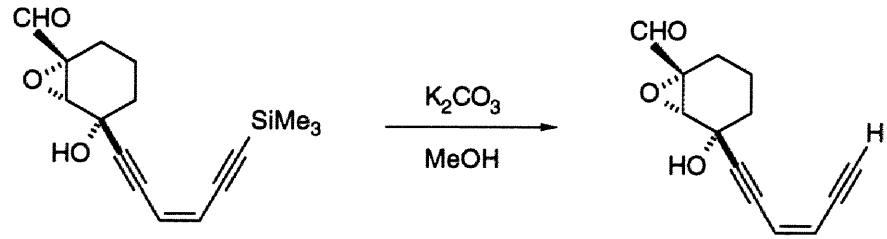
3-12 **3-13** [12162]

Epoxide 3-13. The allylic alcohol **3-12** (2.30 g, 8.38 mmol) and Na_2HPO_4 (3.57 g, 25.1 mmol) were dissolved in CH_2Cl_2 (90 mL) and cooled to 0 °C. To this solution was added MCPBA (80 %, 2.71 g, 12.5 mmol) portionwise. After stirring at 0 °C for 6 h, sat. Na_2SO_3 solution and sat. $NaHCO_3$ solution were added. The mixture was extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 100g, ether/hexane = 3:1) to give the epoxide **3-13** (2.07 g, 85 %). IR (KBr) ν_{max} 3355, 2955, 2147, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$,), 1.52-1.97 (6H, m, $(CH_2)_3$), 3.51 (1H, s, epoxide), 3.65 (1H, br d, J = 12 Hz, CH_AH_B-OH), 3.75 (1H, d, J = 12 Hz, CH_AH_B-OH), 5.90 (2H, s, C*H*=C*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ -0.1, 18.9, 23.4, 34.0, 61.0, 63.8, 64.8, 68.2, 82.8, 96.9, 101.6, 103.3, 119.4, 120.4. MS (EI) *m/z* 290 (M^+). Anal. Calcd for $C_{16}H_{22}O_3Si$: C, 66.16; H, 7.63. Found C, 65.42; H, 7.62.



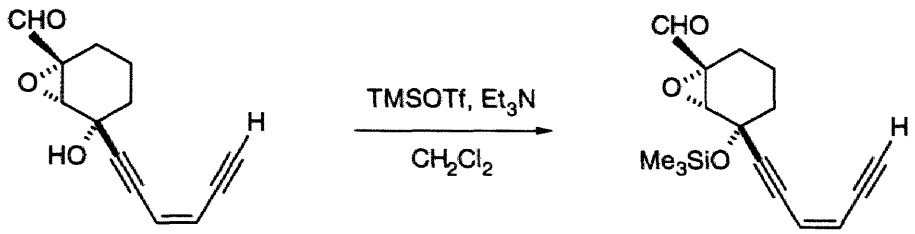
3-13 **3-14** [12173]

Epoxy aldehyde 3-14. The epoxide **3-13** (1.64 g, 5.65 mmol) was dissolved in CH_2Cl_2 (25 mL), DMSO (50 mL), and Et_3N (11.6 mL, 83.6 mmol), and the mixture was cooled to 0 °C. To this solution was added SO_3·Py (6.58 g, 41.3 mmol) portionwise over 2 h. After stirring at 0 °C for 3.5 h, ice-water was added and extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 90 g, ether/hexane = 1:1) to give the epoxyaldehyde **3-14** (1.37 g, 84 %). IR (KBr) ν_{max} 3409, 2957, 2146, 1731, 1250, 852 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 1.52-1.95 (5H, m, $(CH_2)_2$ + O*H*), 2.40-2.65 (2H, m, CH_2), 3.61 (1H, s, epoxide), 5.84 (1H, d, *J* = 11 Hz, olefinic), 5.93 (1H, d, *J* = 11 Hz, olefinic), 8.85 (1H, s, C*H*O). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 0.2, 18.2, 18.8, 33.6, 61.1, 65.3, 68.5, 83.7, 95.5, 101.4, 103.9, 118.8, 121.4, 197.0. HRMS (EI) for $C_{16}H_{20}O_3Si$ (M^+), calcd 288.1181, found 288.1179.



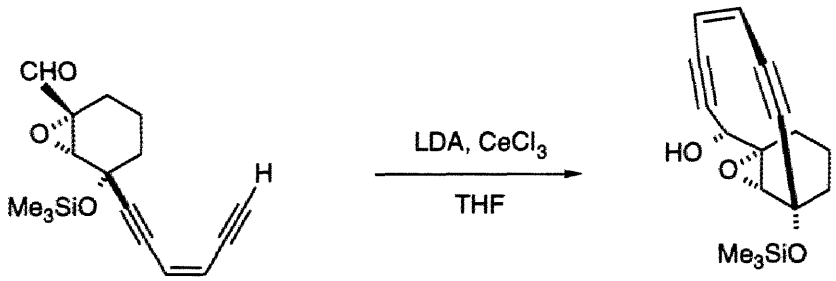
3-14 **3-15** [12178]

Epoxy aldehyde 3-15. A solution of epoxyaldehyde **3-14** (1.37g, 4.75 mmol) in MeOH (50 mL) was cooled to 0 °C. To this solution was added K_2CO_3 (500 mg) and stirred for 50 min. The reaction mixture was quenched with sat. NH_4Cl solution, extracted with CH_2Cl_2 (x5) and $CHCl_3$ (x2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 30 g, ether/hexane = 1:1 → 2:1) to give the epoxyaldehyde **3-15** (830 g, 81 %). IR (KBr) ν_{max} 3281, 2944, 2094, 1729 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (5H, m, CH_2 x2, O*H*), 2.40-2.67 (2H, m), 3.36 (1H, d, *J* = 2 Hz, C≡C-*H*), 3.63 (1H, s, epoxide), 5.48 (1H, dd, *J* = 12, 2 Hz, CH=C*H*-C≡C-H), 5.55 (1H, d, *J* = 12 Hz, C*H*=CH-C≡C-H), 8.85 (1H, s, -C*H*O). MS (EI) *m/z* 216 (M^+), 187 (M-29). HRMS (EI) for $C_{13}H_{12}O_3$ (M^+), calcd 216.0786, found 216.0772.



3-15 **3-16** [12178]

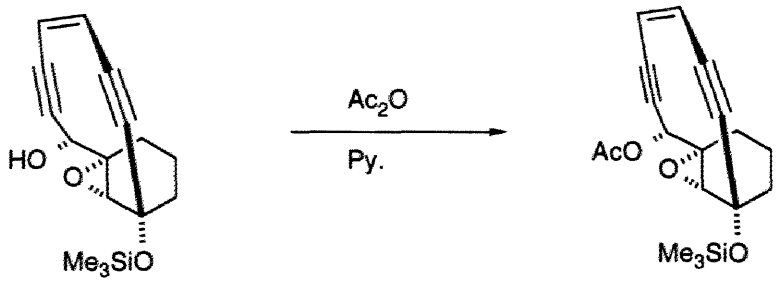
Epoxy aldehyde 3-16. To a solution of **3-15** (830 mg, 4.07 mmol) and Et_3N (2.27 mL, 16.2 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added TMSOTf (1.57 mL, 8.14 mmol). After stirring for 30 min, the mixture was quenched with brine, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 60 g, ether/hexane = 1:10) to give **3-16** (781 mg, 67 %). IR (KBr) ν_{max} 3294, 2957, 2095, 1731, 1251, 1108 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.27 (9H, s, $Si(CH_3)_3$,), 1.51-1.85 (5H, m), 2.47-2.59 (1H, m), 3.32 (1H, d, *J* = 2 Hz, C≡C-*H*), 3.54 (1H, s, epoxide), 5.86 (1H, dd, *J* = 11, 2 Hz, CH=C*H*-C≡C-H), 5.93 (1H, d, *J* = 11 Hz, C*H*=CH-C≡C-H), 8.81 (1H, s, -C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.02, 17.99, 18.82, 34.08, 61.95, 65.24, 70.25, 80.43, 84.81, 85.40, 96.36, 120.09, 120.13, 197.35. MS (EI) *m/z* 288 (M^+), 273 (M-15), 259 (M-29). HRMS (EI) for $C_{16}H_{20}O_3Si$ (M^+), calcd 288.1181, found 288.1168.



3-16 **3-17** [13011]

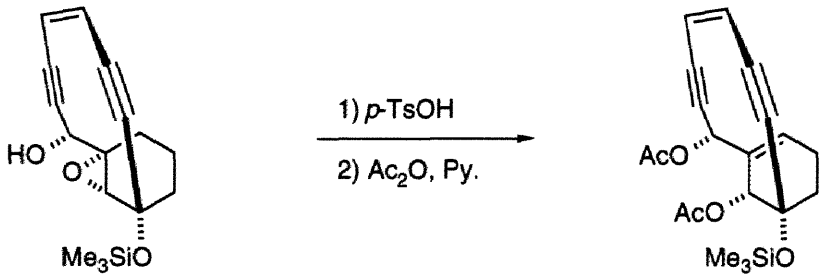
Cyclic Enediyne 3-17. Crystal of $CeCl_3 \cdot (H_2O)_7$ (387 mg, 1.04 mmol) was placed in two necked flask and heated at 150 °C *in vacuo* for 2 h. After cooling to rt, THF (30 mL) was added. To this suspension was added epoxyaldehyde **3-16** (98 mg, 0.34 mmol) and cooled to -78 °C. To this solution was added $LiN(TMS)_2$ (1.0 M, 8.6 mL, 8.67 mmol) over 2 h 20 min by syringe pump. After stirring at -78 °C for 3 h, the mixture was quenched with sat. NH_4Cl solution, extracted with ether-AcOEt (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane = 1:10 → 1:5 →1:2) followed by preparative TLC (ether/hexane = 1:2) to give **3-17** (6.4 mg, 6.5 %) and unreacted starting material **3-16** (80 mg, 81 %). IR (KBr) ν_{max} 3428, 2956, 2196, 1251, 1115 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.21 (9H, s, $Si(CH_3)_3$), 1.61 (5H, m), 2.08 (1H, d, *J* = 4 Hz, -O*H*), 2.17-2.32 (1H, m), 3.21 (1H, s, epoxide), 4.33 (1H, d, *J* = 4 Hz, C≡C-C*H*OH), 5.93 (1H, d, *J* = 10 Hz, C*H*=CH), 5.99 (1H, d, *J* = 10 Hz, CH=C*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.78, 19.56, 20.24, 32.67, 64.91, 67.92, 70.28, 72.20, 86.80, 92.11, 98.30, 100.12, 122.55,

122.83. MS (EI) *m/z* 288 (M^+), 259. HRMS (EI) for $C_{16}H_{20}O_3Si$ (M^+), calcd 288.1181, found 288.1163.



3-17 **3-18** [13012]

Cyclic Enediyne 3-18. A solution of alcohol **3-17** (9.2 mg, 0.032 mmol) in pyridine (1 mL) and Ac_2O (0.75 mL) was stirred at rt for 2 h. After toluene was added, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:2) to give acetate **3-18** (6.2 mg, 60 %). ^1H NMR (270 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 1.63-1.96 (5H, m), 2.13 (3H, s, O-$COCH_3$), 2.15-2.27 (1H, m), 3.32 (1H, s, epoxide), 5.05 (1H, s, AcO-C*H*), 5.95 (1H, d, J = 9.5 Hz, olefinic), 6.01 (1H, d, J = 9.5 Hz, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 1.78, 20.20, 20.39, 20.69, 32.39, 64.88, 65.69, 70.63, 72.08, 87.69, 92.08, 95.63, 100.11, 122.42, 123.33, 169.48. MS (EI) *m/z* 330 (M^+). HRMS (EI) for $C_{18}H_{22}O_4Si$ (M^+), calcd 330.1287, found 330.1276.

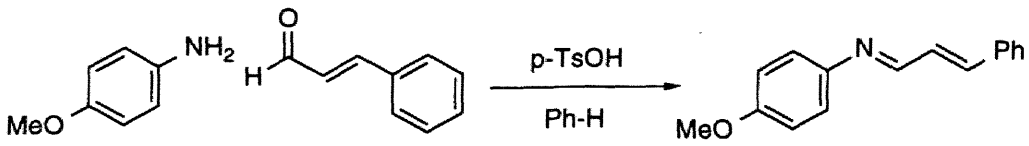


3-18 **3-19** [13013]

Cyclic Enediyne 3-19. The acetate **3-18** (5.0 mg, 0.015 mmol) was dissolved in benzene (0.4 mL)-cyclohexadiene (0.1 mL). To this solution was added AcOH (10 μL). After stirring for 3 h, TFA (11 μL) was added. The mixture was diluted with toluene and concentrated under reduced pressure. The residue was dissolved in benzene (0.8 mL) and cyclohexadiene (0.2 mL). To this solution was added *p*-TsOH·H_2O (trace) and the mixture was stirred overnight. After stirring at 40 °C for 2 h, the mixture was diluted with toluene and concentrated under reduced pressure. The residue was dissolved in Ac_2O (0.40 mL)-pyridine (0.48 mL). After stirring at rt for 2 h, the mixture was diluted with toluene, and then concentrated under reduced pressure. The residue was purified by preparative TLC (silica CH_2Cl_2/MeOH = 10:1) to give the allylic acetate **3-19** (1.8 mg, 40 %). IR (KBr) ν_{max} 3373, 2917, 2850, 2199, 1743, 1372, 1231 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.14 (3H, s, O-$COCH_3$), 2.15 (3H, s, O-$COCH_3$), 5.40 (1H, s, CH=C-C*H*(OAc)-C-OH), 5.75 (1H, s, C≡C-C*H*(OAc)-), 5.89

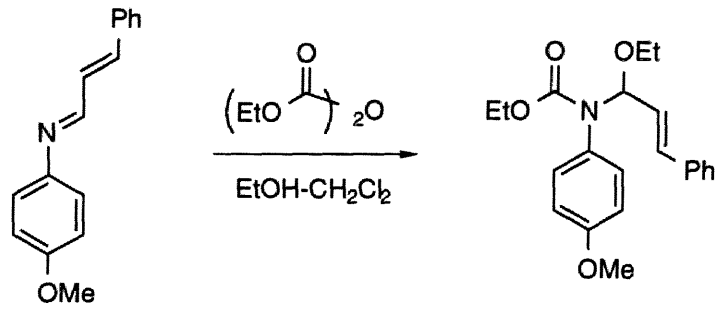
(1H, d, J = 10 Hz, C*H*=CH), 5.95 (1H, d, J = 10 Hz, CH=C*H*), 6.08 (1H, t, J = 3 Hz, C=C*H*-CH_2). MS (EI) *m/z* 300 (M^+), 258 (M-OAc), 198.

Experimental for Chapter 4



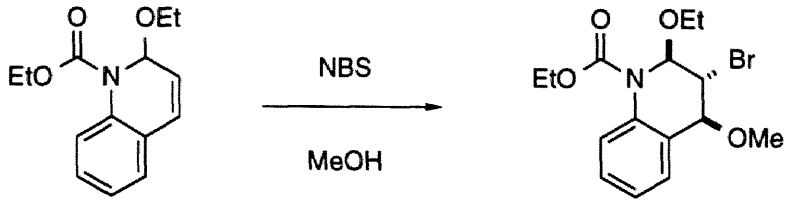
4-8 [11111]

Imine 4-8. In a 500 mL round-bottom flask, fitted with a benzene-filled Dean-Stark water separator, *p*-anisidine (5.00 g, 40.6 mmol), cinnamaldehyde (5.12 mL, 40.6 mmol), *p*-TsOH·H_2O (0.25 g, 1.31 mmol) and benzene (250 mL) were heated at reflux temperature. After 1 h, the mixture was concentrated under reduced pressure to give crude imine **4-8**. This material was used for next reaction without further purification. ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.83 (3H, s, Ar-OC*H*$_3$), 6.92 (2H, br d, *J* = 9 Hz, aromatic of ArOMe), 7.09-7.15 (2H, m), 7.21 (2H, br d, *J* = 9 Hz, aromatic of ArOMe), 7.30-7.46 (3H, m, aromatic), 7.50-7.57 (2H, m, aromatic), 8.30 (1H, m, N=C*H*).



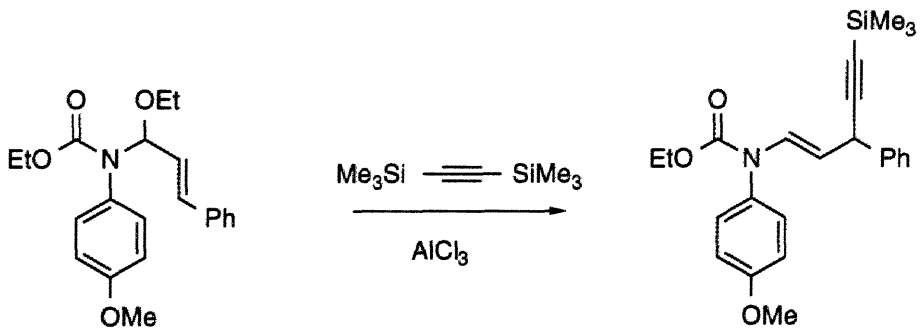
4-8 **4-9** [12065]

α-Ethoxy carbamate 4-9. The crude imine **4-8** (2.00 g, ca. 8.40 mmol) was dissolved in CH_2Cl_2 (10 mL) and EtOH (50 mL). To this solution was added diethyl pyrocarbonate (1.85 mL, 12.6 mmol). After stirring for 14 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica 150 g, ether/hexane = 1:3 → 1:2) to give α-ethoxycarbamate **4-9** (1.99 g, 67 %). IR (KBr) ν_{max} 2978, 1704, 1511, 1302, 1246 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, br t, *J* = 7 Hz), 1.31 (3H, t, *J* = 7 Hz), 3.63-3.95 (2H, m, -OC*H*$_2$-), 3.79 (3H, s, C*H*$_3$O-Ph), 4.16 (2H, m, COOC*H*$_2$), 5.86 (1H, dd, *J* = 16, 6 Hz, Ph-CH=C*H*), 6.23 (1H, br d, *J* = 6 Hz, N-C*H*-OEt), 6.65 (1H, d, *J* = 16 Hz, Ph-C*H*=CH), 6.84 (2H, d, *J* = 9 Hz, aromatic of Ar-OMe), 7.06 (2H, d, *J* = 9 Hz, aromatic of Ar-OMe), 7.24 (5H, m, aromatic). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.08; N, 3.94. Found C, 70.96; H, 7.19; N, 3.96.



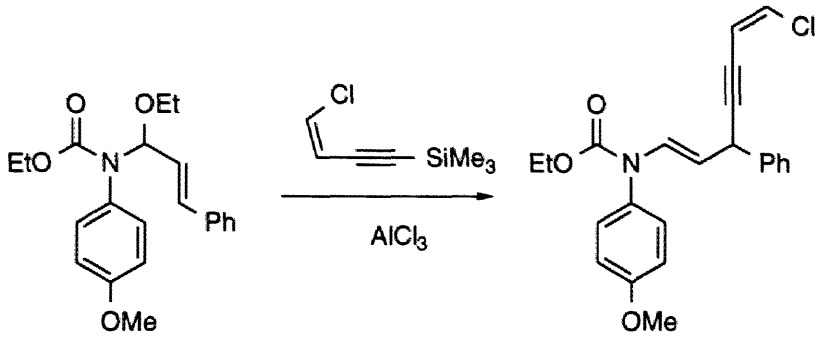
4-25 **4-26** [12084]

Compound 4-26. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, EEDQ **4-25** (1.00 g, 4.04 mmol) was dissolved in MeOH (30 mL) and cooled to -20 °C. To this solution was added NBS (1.00 g, 5.66 mmol) portionwise. After stirring at 0 °C for 1 h, the solution was warmed to 0 °C, and stirred for additional 2 h. After 5 h, the mixture was poured into sat. Na_2SO_3 solution, extracted with CH_2Cl_2 (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (45 g, ether/hexane = 1:4) to give **4-26** (1.37 g, 95 %). IR (KBr) ν_{max} 2981, 1716, 1489, 1311, 1077 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, t, J = 7 Hz, OCH_2CH_3), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 3.64 (2H, m, OCH_2CH_3), 3.69 (3H, s, OCH_3), 4.04 (1H, dd, J = 8, 2 Hz, Br-C*H*), 4.29 (2H, m, $COOCH_2CH_3$), 4.30 (1H, d, J = 8 Hz, CH_3OCH), 6.10 (1H, d, J = 4 Hz, N-C*H*-OEt), 7.22 (1H, td, J = 8, 2 Hz, aromatic), 7.32 (1H, td, J = 8, 2 Hz, aromatic), 7.43 (2H, br d, J = 8 Hz, aromatic). MS (EI) *m/z* 359 (M^+: ^{81}Br), 357 (M^+: ^{79}Br), 314, 312. Anal. Calcd for $C_{15}H_{20}NO_4Br$: C, 50.29; H, 5.62; N, 3.90. Found C, 50.16; H, 5.65; N, 3.87.



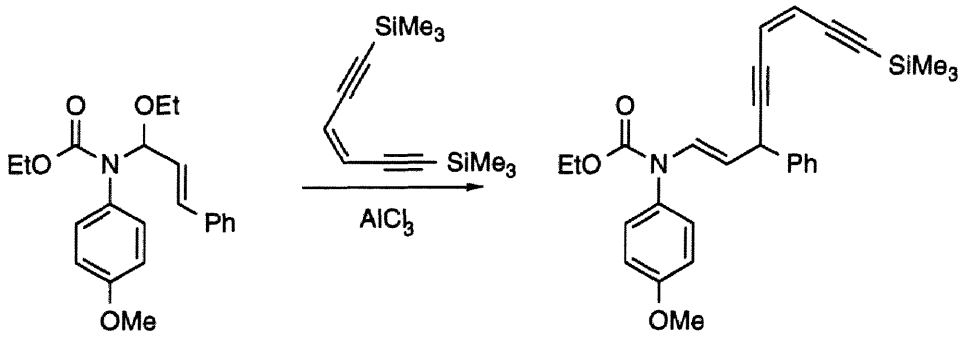
4-9 **4-12** [12076]

Compound 4-12. To a solution of **4-9** (100 mg, 0.281 mmol) and bis(trimethylsilyl)acetylene (0.12 mL, 0.56 mmol) in CH_2Cl_2 (4 mL) cooled to -20 °C was added $AlCl_3$ (grinded, 93 mg, 0.70 mmol). After stirring at -10 ~ -5 °C for 1 h, the mixture was poured into sat. potassium sodium tartrate solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2) to give **4-12** (46 mg, 40 %) and anisidine ethylcarbamate (17 mg, 32 %). ^1H NMR (270 MHz, $CDCl_3$) δ 0.19 (9H, s, $Si(CH_3)_3$), 1.23 (3H, t, J = 7 Hz, OCH_2CH_3), 3.80 (3H, s, Ar-OCH_3), 4.19 (2H, m, OCH_2CH_3), 4.34 (1H, d, J = 6 Hz, C≡C-C*H*), 4.50 (1H, dd, J = 13, 6 Hz, N-CH=C*H*), 6.89 (2H, br d, J = 9 Hz, aromatic of Ar-OMe), 7.06 (2H, br d, J = 9 Hz, aromatic of Ar-OMe), 7.25-7.32 (5H, m, aromatic), 7.52 (1H, d, J = 13 Hz, N-C*H*=CH). MS (EI) *m/z* 407 (M^+), 344 (M-73).



4-9 **14-5** [12080]

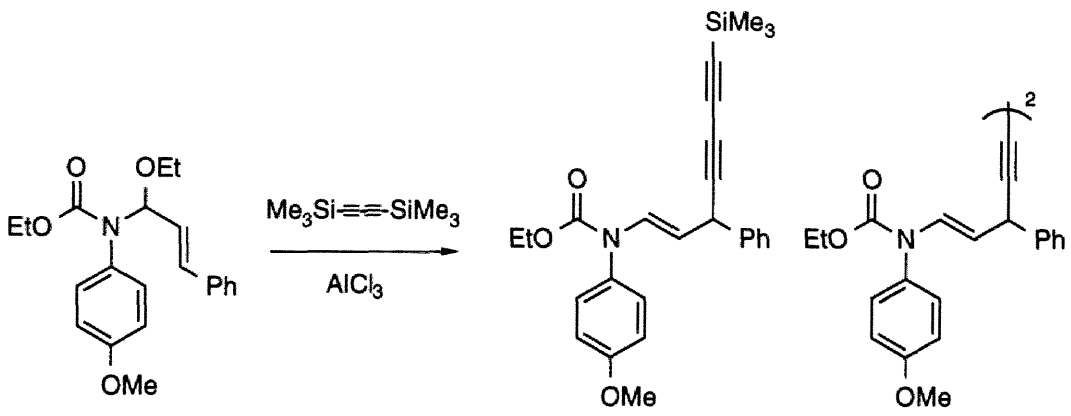
Compound 4-15. To a solution of **4-9** (95 mg, 0.26 mmol) and (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne (84 mg, 0.53 mmol) in CH_2Cl_2 (4 mL) cooled to -20 °C was added $AlCl_3$ (grinded 89 mg, 0.66 mmol). The mixture was stirred at -20 °C for 20 min and then at -10 °C for 2 h 20 min. The mixture was quenched with potassium sodium tartrate solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2) to give **4-15** (47 mg, 45 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (3H, m, C*H*$_3$-CH$_2$-O-), 3.80 (3H, s, Ar-OC*H*$_3$) , 4.19 (2H, q. *J* = 7 Hz, OC*H*$_2$CH$_3$), 4.46-4.62 (2H, m, N-CH=C*H*-C*H*), 5.91 (1H, dd, *J* = 8, 2 Hz, C≡C-C*H*=CHCl), 6.37 (1H, d, *J* = 8 Hz, C≡C-CH=C*H*Cl), 6.89 (2H, d, *J* = 9 Hz, aromatic of ArOMe), 7.06 (2H, d, *J* = 9 Hz, aromatic of ArOMe), 7.15-7.40 (5H, m, aromatic), 7.57 (1H, d, *J* = 13 Hz, N-C*H*=CH). MS (EI) *m/z* 397 (M^+: ^{37}Cl), 395 (M^+: ^{35}Cl).



4-9 **4-16** [12118]

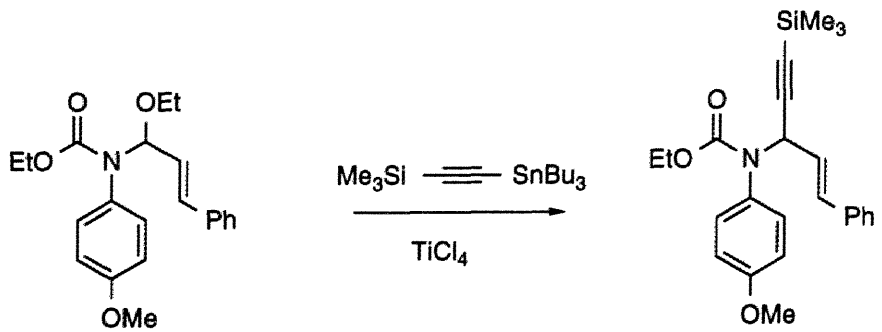
Compound 4-16. To a solution of **4-9** (102 mg, 0.286 mmol) and the (Z)-1,6-bis(trimethylsilyl)-hex-3-ene-1,5-diyne (94 mg, 0.43 mmol) in CH_2Cl_2 (4 mL) cooled to -20 °C was added $AlCl_3$ (grinded, 95 mg, 0.71 mmol). After stirring for 45 min, the mixture was poured into sat. potassium sodium tartrate solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:3) to give **4-16** (41 mg, 31 %). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, Si(C*H*$_3$)$_3$), 1.21 (3H, br t, *J* = 7 Hz, COOCH$_2$C*H*$_3$), 3.73 (3H, s, Ar-OC*H*$_3$), 4.18 (2H, q, *J* = 7 Hz, OC*H*$_2$CH$_3$), 4.49-4.62 (2H, m, N-CH=C*H*-C*H*), 5.79 (1H, d, *J* = 11 Hz, CH-C≡C-CH=C*H*), 5.90 (1H, dd, *J* = 11, 2 Hz, CH-C≡C-C*H*=CH), 6.88 (2H, d, *J* = 9 Hz, aromatic of Ar-OMe), 7.05 (2H,

d, J = 9 Hz, aromatic of Ar-OMe), 7.20-7.40 (5H, m, aromatic), 7.47 (1H, d, J = 13 Hz, N-C*H*=CH). MS (EI) *m/z* 427 (M^+), 398 (M-29), 354.



4-9 **4-13** **4-14** [12078]

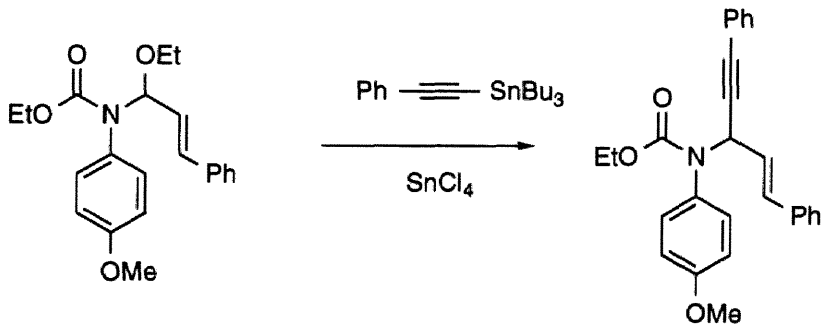
Compound 4-13, 4-14. To a solution of **4-9** (97 mg, 0.272 mmol) and 1,4-bis(trimethylsilyl)-1,3-butadiyne (105 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) cooled to -20 °C was added $AlCl_3$ (grinded, 90 mg, 0.68 mmol). After stirring at -10 ~ -5 °C for 1 h, the mixture was quenched with sat. potassium sodium tartrate and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:1) to give **4-13** (29 mg, 22 %) and dimer **4-14** (36 mg, 20 %). **4-13:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.18 (9H, s, Si(C*H*$_3$)$_3$), 1.23 (3H, br t, J = 7 Hz, OCH$_2$C*H*$_3$), 3.79 (3H, s, Ar-OC*H*$_3$), 4.18 (2H, br q, J = 7 Hz, OC*H*$_2$CH$_3$), 4.39 (1H, d, J = 8 Hz, N-CH=CH-C*H*), 4.47 (1H, dd, J = 14, 8 Hz, N-CH=C*H*-CH), 6.89 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.04 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.15-7.35 (5H, m, aromatic), 7.43 (1H, d, J = 14 Hz, N-C*H*=CH). MS (EI) *m/z* 415 (M^+), 386 (M-29), 342 (M-73). **Dimer 4-14:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, m, OCH$_2$C*H*$_3$), 3.80 (3H, s, Ar-OC*H*$_3$), 4.18 (2H, q, J = 7 Hz, OC*H*$_2$CH$_3$), 4.39 (1H, d, J = 8 Hz, N-CH=CH-C*H*), 4.48 (1H, dd, J = 14, 8 Hz, N-CH=C*H*), 6.90 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.05 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.15-7.35 (5H, m, aromatic), 7.42 (1H, d, J = 14 Hz, N-C*H*=CH).



4-9 **4-19** [12104]

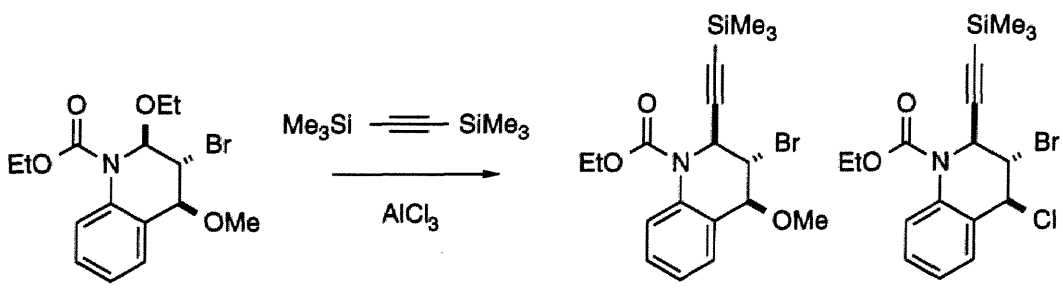
Compound 4-19. To a solution of **4-9** (85 mg, 0.239 mmol) and tributylstannyl (trimethylsilyl)ethyne (185 mg, 0.48 mmol) in CH_2Cl_2 (4 mL) cooled to -78 °C was added $TiCl_4$ [1.0

M in CH_2Cl_2, 0.35 mL, 0.35 mmol]. After 1 h, the mixture was stirred at -40 °C for 20 min and then at -10 °C overnight. The reaction was quenched with sat potassium sodium tartrate solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:1) to give **4-19** (73 mg, 75 %). IR (KBr) ν_{max} 2960, 2175, 1705, 1511, 1300, 1250, 1033 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 1.18 (3H, br , OCH_2CH_3), 3.79 (3H, s, CH_3-OAr), 4.15 (2H, br q, J = 7 Hz, CH_2-CH_3), 5.95-6.14 (1H, br, N-C*H*-C≡C), 6.15 (1H, dd, J = 16, 6 Hz, C*H*=CH-Ph), 6.66 (1H, d, J = 16 Hz, CH=C*H*-Ph), 6.82 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.12 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.20-7.35 (5H, m, aromatic). MS (EI) *m/z* 407 (M^+), 378 (M-29), 334 (M-73). Anal. Calcd for $C_{24}H_{29}NO_3Si$: C, 70.72; H, 7.17; N, 3.43. Found C, 70.83; H, 7.32; N, 3.43.



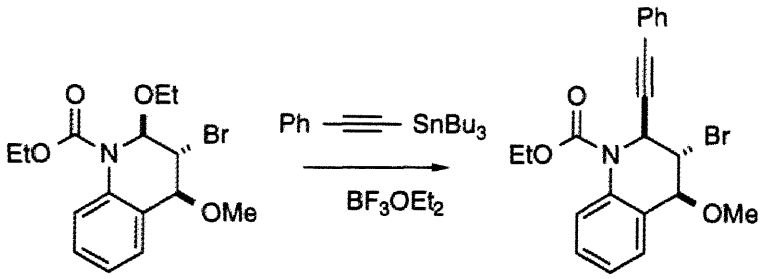
4-9 **4-20** [12107]

Compound 4-20. To a solution of **4-9** (79 mg, 0.22 mmol) and phenyl-2-(tributylstannyl) acetylene (0.173 mg, 0.44 mmol) in CH_2Cl_2 (4 mL) cooled to -78 °C was added $SnCl_4$ (39 μL, 0.33 mmol). After 1 h, the mixture was stirred at -40 °C for 30 min, and then at -20 °C for 1.5 h. The mixture was quenched with sat. potassium sodium tartrate solution and extracted with CH_2Cl_2 (x3) . The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2) to give **4-20** (46 mg, 51 %). IR (KBr) ν_{max} 2995, 1704, 1511, 1377, 1297, 1249, 1033 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, br, CH_3-CH_2O), 3.78 (3H, s, CH_3-OAr), 4.18 (2H, br t, J = 7 Hz, O-CH_2-CH_3) , 6.23 (1H, dd, J = 14, 6 Hz, C*H*=CH-Ph), 6.27 (1H, br, N-C*H*-C≡C), 6.74 (1H, d, J = 14 Hz, CH=C*H*-Ph), 6.85 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.20 (2H, d, J = 9 Hz, aromatic of Ar-OMe), 7.20-7.45 (10 H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.6, 52.1, 55.3, 62.0, 85.6, 87.3, 113.6, 122.7, 125.5, 126.7, 127.9, 128.2, 128.4, 128.5, 130.8, 131.6, 133.3, 136.3, 158.7. MS (EI) *m/z* 411 (M^+), 382 (M-29). Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.80; H, 6.12; N, 3.40. Found C, 78.90; H, 6.15; N, 3.20.



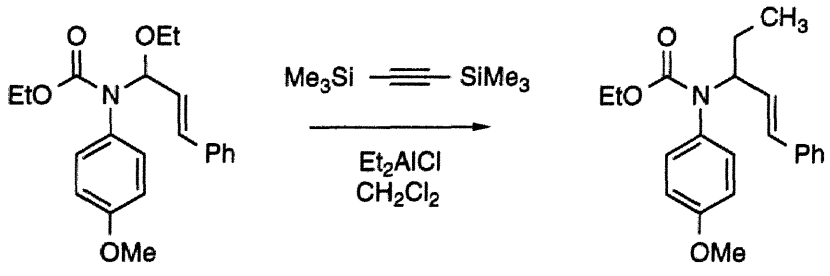
4-26 **4-27a** **4-27b** [11163]

Compound 4-27. To a solution of **4-26** (93 mg, 0.26 mmol) and bis(trimethylsilyl)acetylene (0.66 mg, 0.39 mmol) in CH_2Cl_2 (4.6 mL) cooled to -20 °C was added $AlCl_3$ (grinded, 86 mg, 0.64 mmol). After stirring for 10 min, the mixture was stirred at 0 °C for 30 min and then at -20 °C overnight. The mixture was quenched with sat. sodium potassium sodium tartrate solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:2) to give **4-27a** (17 mg, 16 %) and **4-27b** (24 mg, 23 %). **4-27b:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (9H, s, $Si(CH_3)_3$), 1.34 (3H, t, J = 7 Hz, OCH_2CH_3), 4.32 (2H, m, OCH_2CH_3), 4.87 (1H, dd, J = 3, 2 Hz, C*H*-Br), 5.39 (1H, br s), 5.72 (br s, J = 3 Hz), 7.19 (1H, td, J = 7, 1.5 Hz, aromatic), 7.34 (1H, td, J = 8, 2 Hz, aromatic), 7.51 (1H, dd, J = 8, 2 Hz, aromatic), 7.71 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.7, 14.4, 48.6, 52.6, 56.5, 62.9, 92.4, 99.2, 124.5,124.8, 128.7, 130.7, 134.2, 153.9. MS (EI) *m/z* 417, 415, 413, 334, 299 (M-BrCl).



4-26 **4-28a** [12095]

Compound 4-28a. To a solution of **4-26** (98 mg, 0.27 mmol) and phenyl-2-(tributylstannyl) acetylene (214 mg, 0.547 mmol) in CH_2Cl_2 (4 mL) cooled to -20 °C was added $BF_3{\cdot}OEt_2$ (46 μL, 0.64 mmol). After 20 min, the mixture was stirred at -5 °C for 30 min and then at rt for 1 h 15 min. The mixture was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/hexane = 1:1) to give **4-28a** (31 mg, 26 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7 Hz, OCH_2CH_3), 3.70 (3H, s, $ArOCH_3$), 4.33 (2H, m, OCH_2CH_3), 4.42 (1H, d, J = 5 Hz, C*H*-OMe), 4.48 (1H, dd, J = 5, 4 Hz, C*H*-Br), 5.83 (1H, d, J = 4 Hz, N-C*H*-C≡C), 7.15 (7H, m, aromatic), 7.46 (1H, br d, J = 8 Hz, aromatic), 7.66 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.5, 50.8, 51.6, 58.8, 62.7, 79.8, 84.5, 84.8, 122.1, 124.6, 125.0, 127.2, 127.9, 128.0, 128.2, 128.5, 131.8, 134.7, 153.9.

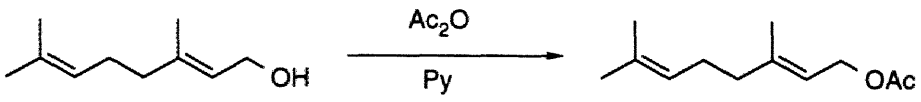


4-9 **4-18** [12112]

Compound 4-18. The carbamate **4-9** (88 mg, 0.24 mmol) and bis(trimethylsilyl)acetylene (0.11 mL, 0.49 mmol) were dissolved in CH_2Cl_2 (4 mL) and cooled to -20°C. To this solution was added Et_2AlCl (1M in hexane, 0.61 mL, 0.61 mmol). After 50 min, the mixture was quenched with sat. $NaHCO_3$ solution, and stirred with sat. potassium sodium tartrate solution. After extraction with CH_2Cl_2 (x3), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:1) to give 4-**18** (78 mg, 94 %). IR (KBr) ν_{max} 2961, 1697, 1511, 1290, 1247 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7 Hz, CH-CH_2CH_3), 1.16 (3H, br, OCH_2CH_3), 1.43-1.80 (2H, m, CH-CH_2CH_3), 3.80 (3H, s, CH_3-OAr), 4.12 (2H, q, *J* = 7 Hz, O-CH_2CH_3), 4.77 (1H, br q, *J* = 7 Hz, N-CH-CH=C), 6.05 (1H, dd, *J* = 19, 9 Hz, N-CH-CH=C), 6.56 (1H, d, *J* = 16 Hz, N-CH-CH=CH-Ph), 6.86 (2H, d, *J* = 9 Hz, aromatic), 7.05 (2H, d, *J* = 9 Hz, aromatic), 7.15-7.40 (5H, m, aromatic). MS (EI) *m/z* 339 (M^+), 310 (M-29). Anal. Calcd for $C_{21}H_{25}NO_3$: H, 7.42; C, 74.31; N, 4.13. Found H, 7.47; C, 74.30; N, 4.09.

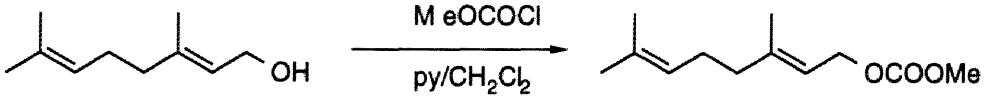
Experimental for Chapter 5

Synthesis of substrate



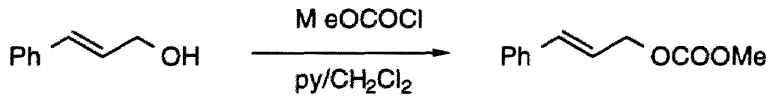
5-8a [13189]

Geranyl acetate 5-8a. A solution of geraniol (10.0 mL, 57.6 mmol) in pyridine (100 mL) and Ac_2O (50 mL) was stirred at rt for 1 h. The mixture was diluted with toluene, evaporated under reduced pressure. The residue was distilled by Kugelrohr apparatus to give geranyl acetate **5-8a** (10.56 g, 93 %, bp 120-125 °C/*in vacuo*).



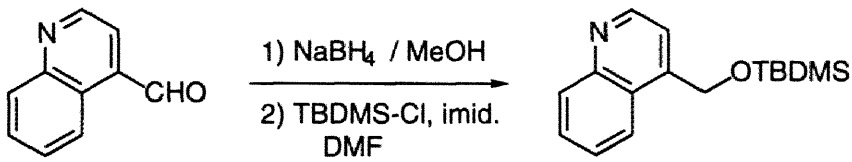
5-8b [13192]

Geranyl methylcarbonate 5-8b. To a solution of geraniol (10.0 mL, 57.6 mmol) in CH_2Cl_2 (150 mL) were added pyridine (13.9 mL, 172 mmol) and methyl chloroformate (6.67 mL, 86.4 mmol). After stirring at 0 °C for 3 h, the mixture was quenched with ice-cold water. The organic layer was washed with 1N HCl, dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. Distillation of crude product afforded **5-8b** (11.0 g, 90 %, bp 79-84 °C/in vacuo). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (3H, s, C=C-C*H*$_3$), 1.68 (3H, s, C=C-C*H*$_3$), 1.72 (3H, s, C=C-C*H*$_3$), 2.00-2.16 (4H, m, C=CH-C*H*$_2$C*H*$_2$-C=C), 3.77 (3H, s, OC*H*$_3$), 4.66 (2H, d, *J* = 7 Hz, C*H*$_2$-OCOOMe), 5.08 (1H, m, olefinic), 5.38 (1H, br t, *J* = 7 H, olefinic).



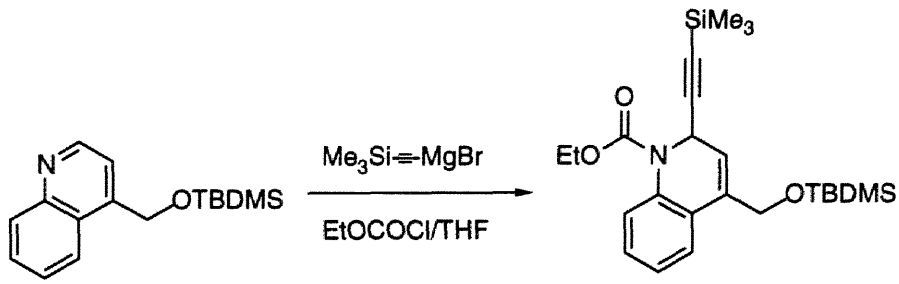
5-9b [13156]

Cinnamyl methylcarbonate 5-9b. Cinnamyl alcohol (24.8 g, 184 mmol) was dissolved in CH_2Cl_2 (300 mL)-pyridine (44 mL, 554 mmol) and cooled to 0 °C. To this solution was added methyl chloroformate (21.4 mL, 277 mmol) in CH_2Cl_2 (20 mL) over 40 min. After stirring for additional 15 min, the mixture was poured into ice-cold HCl solution and extracted with CH_2Cl_2 (x3). The combined organic layer was washed with aq. $CuSO_4$ solution, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was distilled by short-path distillation apparatus to give **5-9b** (34.4 g, 96.7 %, 92-98 °C/*in vacuo*). ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.78 (3H, s, C*H*$_3$), 4.77 (2H, dd, *J* = 6.5, 1.5 Hz, allylic), 6.28 (1H, dt, *J* = 10, 6.5 Hz, Ph-CH=C*H*), 6.67 (1H, br d, *J* = 16 Hz, Ph-C*H*=CH), 7.20-7.40 (5H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 54.6, 68.2, 122.3, 126.5, 128.0, 128.5, 134.6, 135.9, 155.5.



5-10 **5-11** [14039]

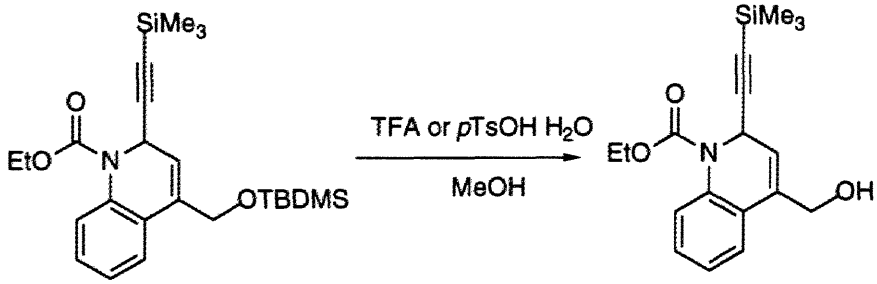
TBDMS ether 5-11. (1) To a solution of aldehyde **5-10** (14 g, 89.0 mmol) in MeOH (300 mL) cooled to 0 °C was added $NaBH_4$ (1.68 g, 44.5 mmol) portionwise. After stirring at 0 °C for 10 min, the reaction mixture was quenched with acetic acid (2 mL), concentrated under reduced pressure. The residue was dissolved with water, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product (14.8 g). This material was sufficiently pure for use in the next reaction. (2) To a solution of resulting alcohol in DMF (200 mL) cooled to 0°C was added successively imidazole (18.17 g, 267 mmol) and *tert*-butyldimethylchlorosilane (16.09 g, 106.8 mmol). The reaction mixture was stirred at rt for 1 h, poured into ice-water (300 mL). The mixture was extracted with AcOEt (200 mL x3). Combined organic layer was washed with water (300 mL x3), brine (300 mL x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 500 g = ether/hexane, 1:3) to give silylether **5-11** (22.6 g, 93%): IR (KBr) ν_{max} 2956, 2858, 1597, 1470, 1258, 1123 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (6H s, $Si(CH_3)_3$), 0.98 (9H s, $SiC(CH_3)_3$), 5.21 (2H, s, CH_2O), 7.47-7.61 (2H, m, aromatic), 7.69 (1H, t, J = 7.5 Hz, aromatic), 7.85 (1H, d, J = 8Hz, aromatic), 8.14 (1H, d, J = 7.5 Hz), 8.92 (1H, br s, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -5.4, 18.2, 25.7, 61.5, 117.4, 122.2, 125.3, 126.1, 128.7, 130.0, 146.3, 147.5, 150.3. Anal. Calcd for $C_{16}H_{23}NOSi$: C, 70.28; H, 8.48; N, 5.12. Found: C, 70.30; H, 8.50; N, 5.08.



5-11 **5-12** [14047]

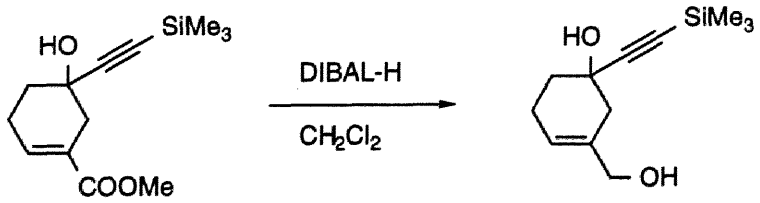
Ethylcarbamate 5-12. To a solution of trimethylsilylacetylene in dry THF (330 mL) cooled to 0 °C was added dropwise ethylmagnesium bromide (49 mL of a 3 M solution of THF, 148 mmol). The solution stirred at rt for 30 min and cooled to 0 °C again. To the resultant solution were added a solution of quinoline **5-11** (22.6 g, 82.6 mmol) in THF (80 mL) over 10 min, and then a solution of ethyl chloroformate (17.8 mL, 185 mmol) in THF (30 mL) at 0 °C. After stirring for 3 h, the mixture was quenched with sat. NH_4Cl solution, extracted with EtOAc (250 mL x3). Combined organic layer was washed with water (500 mL x2), brine (500 mL x2), dried over anhydrous Na_2SO_4, and then

concentrated under reduced pressure. Crystallization of the residue from hexane afford **5-12** (30.83 g, 89.8 %): IR (KBr) ν_{max}2953, 2856, 2165, 1705, 1495, 1324, 1287, 1257, 1103, 1039 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (H, s, C≡C-Si(CH_3)$_3$), 0.10 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3), 0.93 (9H, s, SiC(CH_3)$_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.48 (1H, dt, J = 14, 1.5 Hz, CH_AH_B-OH), 4.66 (1H, dd, J = 14, 1 Hz, CH_AH_B-OH), 5.90 (1H, br d, J = 7.5 Hz, NC*H*-C≡C), 6.08 (1H, td, J = 7.5 , 1.5 Hz, olefinic), 7.11 (1H, td, J = 7, 1 Hz, aromatic), 7.22 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -5.2, -5.1, -0.2, 14.4, 18.3, 25.9, 44.5, 62.3, 62.4, 88.1, 101.7, 120.8, 122.6, 124.1, 124.6, 126.1, 127.4, 134.0, 134.2, 153.6. Anal. Calcd for $C_{24}H_{37}O_3NSi$: C, 64.96; H, 8.40; N, 3.15. Found: C, 65.17; H, 8.51; N, 3.17.



5-12 **5-13** [14143]

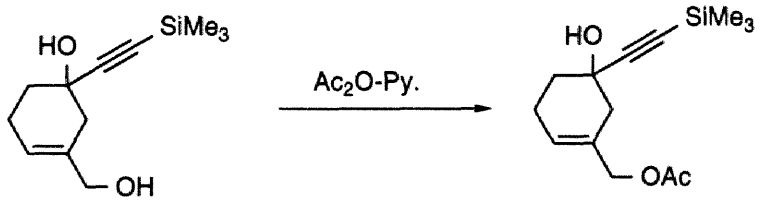
Allyl alcohol 5-13. To a solution of TBDMS ether **5-12** (20.0 g, 48.1 mmol) in MeOH (300 mL) was added p-TsOH·H_2O (4.57 g, 24 mmol). After stirring at rt for 2 h, the reaction mixture was diluted with AcOEt (400 mL). Sat. $NaHCO_3$ solution (400 mL) and water (200 mL) were successively added. The mixture was extracted with AcOEt (200 mL x2). Combined organic layer was washed with water (500 mL x2) and brine (400 mL x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Crystallization of the residue gave alcohol **5-13** (14.9 g, 94 %). IR (KBr) ν_{max} 3448, 2964, 2168, 1717, 1493, 1377, 1304, 1261, 1036 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, Si(CH_3)$_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.56 (2H, s, CH_2OH), 5.90 (1H, d, J = 6 Hz, olefinic or N-C*H*-C≡C), 6.10 (1H, d, J = 6 Hz, olefinic or N-C*H*-C≡C), 7.14 (1H, br t, J = 8 Hz, aromatic), 7.23-7.38 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.4, 44.3, 62.2, 62.5, 88.3, 101.4, 121.9, 122.9, 124.8, 125.7, 127.7, 134.3, 134.4, 153.5. MS (EI) *m/z* 329 (M^+), 300, 298. HRMS (EI) for $C_{18}H_{23}ONSi$ (M^+), calcd 329.1447, found 329.1459.



5-16 **5-17** [14189]

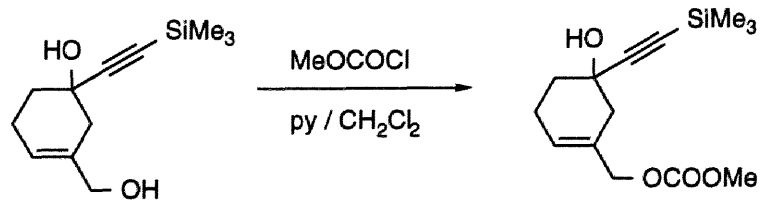
Alcohol 5-17. To a solution of DIBAL-H [1M in hexane, 114 mL, 114 mmol] cooled to -78 °C was added ester **5-16** (10.01 g, 39.6 mmol) in toluene (40 +10 mL) over 30 min. After stirring at

-78 °C for 1 h 15 min, DIBAL [1M in hexane, 10 mL, 10 mmol] was added. After 30 min, sat. NH_4Cl solution (30 mL) was added dropwise and warmed to rt gradually. After the mixture was diluted with ether, anhydrous Na_2SO_4 was added. The mixture was filtrated through the pad of Super-Cel®, concentrated under reduced pressure. The residue was purified by crystallization from CH_2Cl_2-ether-hexane to give **5-17** (7.77 g, 87.6 %). IR (KBr) ν_{max} 3354, 3241, 2958, 2165, 1250, 1041 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.14 (9H, s, $Si(CH_3)_3$), 1.84 (2H, m, $C{=}CH\text{-}CH_2CH_2$), 2.20 (2H, m, $C{=}CH\text{-}CH_2$), 2.33 (1H, br d, J = 17 Hz, $C{=}C\text{-}CH_AH_B\text{-}C\text{-}OH$), 2.45 (1H, br d, J = 17 Hz, $C{=}C\text{-}CH_AH_B\text{-}C\text{-}OH$), 3.96 (2H, br s, $CH_2\text{-}OH$), 5.67 (1H, m, $C{=}CH$). Anal. Calcd for $C_9H_{12}O_2$: C, 64.24; H, 8.98. Found C, 64.34; H, 8.92.



5-17 **5-18a** [16018]

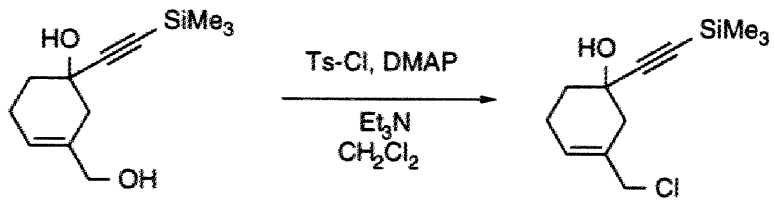
Acetate 5-18a. A solution of allylic alcohol **5-17** (575 mg, 2.56 mmol) in Ac_2O (5 mL)-pyridine (5 mL) was stirred at rt for 30 min. After dilution with toluene, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica 30 g, ether/hexane = 1:2) to give acetate **5-18a** (679 mg, 99.5 %). IR (KBr) ν_{max} 3420, 2961, 2166, 1741, 1251 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 1.86 (2H, t, J = 6.5 Hz, $C{=}CH\text{-}CH_2CH_2$), 2.07 (3H, s, $OCOCH_3$), 2.18-2.30 (2H, m, $C{=}C\text{-}CH_2\text{-}CH_2$), 2.31 (1H, br d, J = 17 Hz, $C{=}C\text{-}CH_AH_B\text{-}C\text{-}OH$), 2.47 (1H, br d, J = 1H, $C{=}C\text{-}CH_AH_B\text{-}C\text{-}OH$), 4.43 (1H, d, J = 12 Hz, $CH_AH_B\text{-}OAc$), 4.49 (1H, d, J = 12 Hz, $CH_AH_B\text{-}OAc$), 5.77 (1H, br s, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 20.8, 34.6, 40.2, 66.1, 68.1, 87.2, 108.9, 125.4, 129.3, 170.9. MS (EI) *m/z* 266 (M^+), 248 (M-18), 206, 191. Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found C, 63.10; H, 8.43.



5-17 **5-18b** [16020]

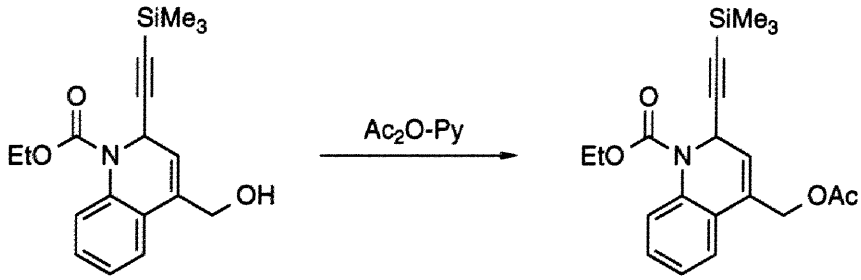
Methylcarbonate 5-18b. To a solution of allylic alcohol **5-17** (560 mg, 2.49 mmol) in CH_2Cl_2 were added pyridine (0.72 mL, 8.92 mmol) and methyl chloroformate (0.34 mL, 4.46 mmol). After stirring at rt for 30 min, the reaction was quenched with 1N HCl, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 35 g, ether hexane = 1:2) to give carbonate **5-18b** (705 mg, 100 %). IR (KBr) ν_{max} 3462, 2960, 2164, 1752, 1445, 1280 cm^{-1}. ^1H

NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 1.86 (2H, t, J = 6 Hz, C=CH-CH_2), 2.25 (3H, m, C=CH-CH_2-CH_2-CH-OH), 2.32 (1H, br d, J = 17 Hz, CH=C-CH_AH_B-CH-OH), 2.51 (1H, br d, J = 17 Hz, CH=C-CH_AH_B-CH-OH), 3.78 (3H, s, OCH_3), 4.50 (1H, br d, J = 12 Hz, CH_AH_B-OCOOMe), 4.55 (1H, br d, J = 12 Hz, CH_AH_B-OCOOMe), 5.81 (1H, br s, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 22.8, 24.6, 40.2, 54.7, 66.0, 71.6, 87.3, 108.8, 126.2, 128.8, 155.6. MS (EI) *m/z* 282 (M^+), 267 (M-15), 206, 191. Anal. Calcd for $C_{14}H_{22}O_4Si$: C, 59.54; H, 7.85. Found C, 59.61; H, 7.80.



5-17 **5-18c** [15011]

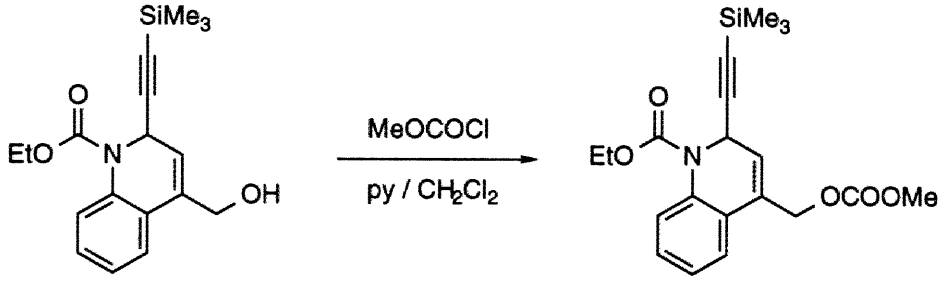
Chloride 5-18c. The allyl alcohol **5-17** (1.12 g, 50 mmol) was dissolved in CH_2Cl_2 (28 mL). To this solution were added DMAP (336 mg, 3.00 mmol), TsCl (1.14 g, 6.00 mmol) and Et_3N (0.69 mL, 5.00 mmol) successively. After stirring at rt for 6 h 20 min, the mixture was concentrated to about 5 mL, subjected to column chromatography (silica 80 g, CH_2Cl_2) to give allyl chloride **5-18c** (1.06 g, 85 %). IR (KBr) ν_{max} 3371, 2962, 2166, 1670, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (9H, s, $Si(CH_3)_3$), 1.86 (2H, t, J = 6 Hz, C=CH-CH_2-CH_2-), 2.26 (2H, m, C=CH-CH_2-), 2.39 (1H, br d, J = 17 Hz, C(OH)-CH_AH_B-C=C), 2.59 (1H, br d, J = 17 Hz, C(OH)-CH_AH_B-C=C), 4.01 (2H, br s, CH_2-Cl), 5.83 (1H, m, C=CH-). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 23.6, 34.6, 40.5, 49.6, 66.3, 67.7, 108.7, 126.3, 130.8. MS (EI) *m/z* 244 (M^+: ^{37}Cl), 242 (M^+: ^{35}Cl), 207 (M-Cl). Anal. Calcd for $C_{12}H_{19}OSiCl$: C, 59.36; H, 7.89. Found C, 59.28; H, 7.89.



5-13 **5-14a** [14018]

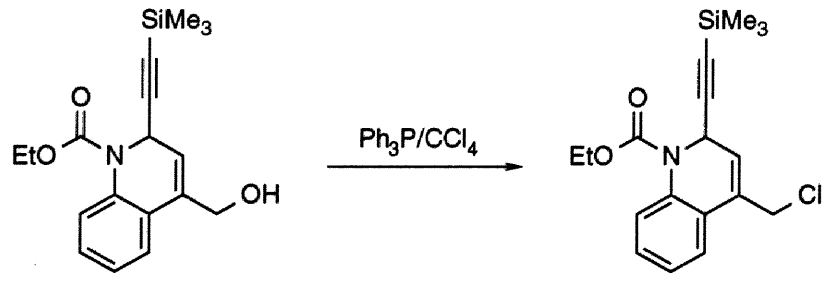
Allyl acetate 5-14a. A solution of alcohol **5-13** (1.93 g, 5.85 mmol) in Ac_2O (25 mL) and pyridine (25 mL) was stirred at rt for 12 h. The mixture was evaporated *in vacuo*. The residue was purified by column chromatography (silica 80 g, ether/hexane = 1:2) to give the acetate **5-14a** (2.18 g, 100 %). IR (KBr) ν_{max} 2962, 2172, 1742, 1716, 1495, 1378, 1324, 1033 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $Si(CH_3)_3$), 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 2.09 (3H, s, $OCOCH_3$), 4.28 (2H, m, OCH_2CH_3), 4.90 (1H, br d, J = 13 Hz, CH_ACH_B-OAc), 5.08 (1H, br d, J = 13 Hz, CH_ACH_B-OAc), 5.90 (1H, br d, J = 6.5 Hz, N-CH-C≡C or olefinic), 6.11 (1H, br d, J = 6.5 Hz, N-CH-C≡C or olefinic), 7.14 (1H, br t, J = 7.5 Hz, aromatic), 7.23-7.33 (2H, m, aromatic), 7.6 (1H, br d, J = 8 Hz, aromatic).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3, 14.4, 20.9, 44.3, 62.5, 63.0, 88.7, 101.1, 123.0, 124.4, 124.6, 124.8, 125.5, 128.0, 130.1, 134.5, 153.5, 170.6. Anal. Calcd for $C_{20}H_{25}O_4NSi$: C, 64.69; H, 64.70; N, 3.77. Found: C, 64.70; H, 6.82; N, 3.73.



5-13 **5-14b** [14016]

Allyl methylcarbonate 5-14b. To a solution of alcohol **5-13** (1.64 g, 5.00 mmol) and pyridine (1.6 mL, 20 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added methyl chloroformate (0.77 mL, 10 mmol). After stirring at 0 °C for 30 min, the mixture was poured into ice-cold 1N HCl solution, extracted with CH_2Cl_2 (x2). The combined organic layer was washed with 1N HCl solution (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 60 g, ether/hexane, 1:2) to give the allyl carbonate **5-14b** (1.80 g, 93 %). IR (KBr) ν_{max} 2962, 2170, 1750, 1705, 1494, 1378, 1272 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 1.31 (3H, t, J = 7Hz, OCH_2CH_3), 3.79 (3H, s, $OCOOCH_3$), 4.27 (2H, m, OCH_2CH_3), 4.97 (1H, br d, J = 13 Hz, $MeOCOOCH_AH_B$), 5.11 (1H, br d, J = 13 Hz, $MeOCOOCH_AH_B$), 5.91 (1H, d, J = 8 Hz, N-CH-C≡C), 6.15 (1H, d, J = 8 Hz, olefinic), 7.14 (1H, td, J = 8, 1 Hz, aromatic), 7.24-7.32 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, 14.3, 44.2, 54.8, 62.4, 66.4, 88.6, 100.8, 122.9, 124.3, 124.7, 124.9, 125.1, 127.9, 129.5, 134.3, 153.3, 155.3. Anal. Calcd for $C_{20}H_{25}O_5NSi$: C, 62.02; H, 6.46; N, 3.62. Found: C, 61.97; H, 6.58; N, 3.51.

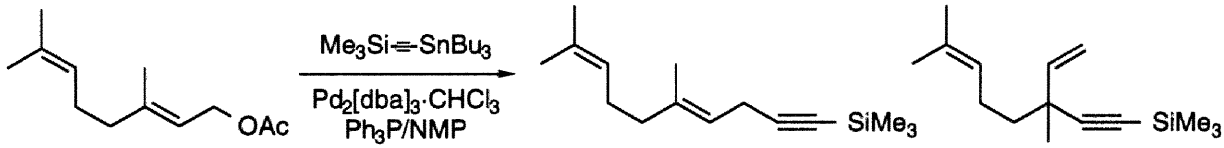


5-13 **5-14c** [14090]

Allyl chloride 5-14c. A solution of alcohol **5-13** (3.05 g, 9.25 mmol) and Ph_3P (3.39 g, 12.9 mmol) in dry CCl_4 (30 mL) was heated under reflux for 12 h. After cooling to rt, the mixture was diluted with hexane (20 mL), filtrated through the pad of Super-Cel®, washed with hexane. The combined filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica 150 g, ether/hexane = 1:10) to give chloride **5-14c** (3.02 g, 92 %): IR (KBr)

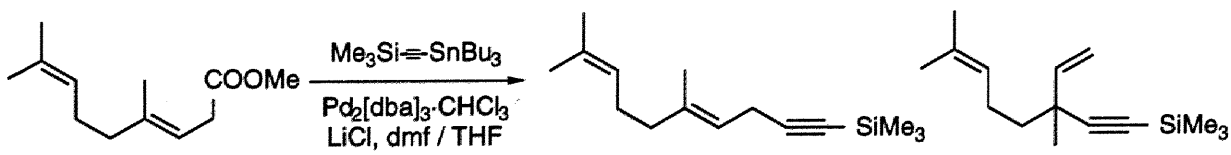
ν_{max} 2962, 2168, 1707, 1490, 1379, 1323, 1262, 1046 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (9H, s, $Si(CH_3)_3$), 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 4.29 (2H, m, OCH_2CH_3), 4.36 (1H, d, J = 12 Hz, CH_AH_BCl), 4.54 (1H, br d, J = 12 Hz, CH_AH_BCl), 5.91 (1H, br d, J = 6.5 Hz, N-C*H*-CH=C or N-CH-C*H*=C), 6.17 (1H, br d, J = 6.5 Hz, N-C*H*-CH=C or N-CH-C*H*=C), 7.18 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.31 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.39 (1H, dd, J = 7.5, 1.5 Hz, aromatic), 7.65 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.3, 14.4, 43.3, 44.4, 62.6, 88.9, 100.8, 123.3, 124.3, 124.9, 125.0, 125.5, 128.1, 131.6, 134.6, 153.4. MS (EI) *m/z* 349 (M^+: ^{37}Cl), 347 (M^+: ^{35}Cl), 320, 318, 298. Anal. Calcd for $C_{18}H_{22}NO_2SiCl$: C, 62.14; H, 6.37; N, 4.03. Found C, 62.37; H, 6.28; N, 3.95.

Coupling reaction between allyl derivative and tin acetylene.



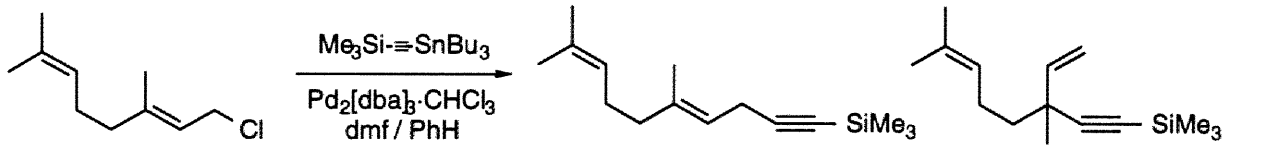
5-8a **5-19** **5-20** [13174]

Compound 5-19 and 5-20 (entry 1 in **Table 5-1**). In a two-necked flask, $Pd_2[dba]_3{\cdot}CHCl_3$ (31 mg, 0.03 mmol), Ph_3P (31 mg, 0.12 mmol) were dissolved in NMP (2 mL). The whole mixture was degassed three times and covered with argon. After stirring until the mixture became to be yellow, geranyl acetate **5-8a** (196 mg, 1.00 mmol) and tinacetylene **5-1** (425 mg, 1.10 mmol) in degassed NMP (3 mL) were added. The mixture was heated at 50-60 °C for 20 h. After cooling to rt, the mixture was poured into ice-cold $NaHCO_3$ solution, extracted with ether (x3). The combined organic layer was washed water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatographies (alumina 20 g, ether/hexane = 1:10 and then silica 10 g, hexane → ether/hexane = 1:40) to give **5-19** (102 mg, 44 %) and **5-20** (8.2 mg, 3.5 %). **5-19:** IR (KBr) ν_{max} 2962, 2175, 1459, 1376, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 1.60 (6H, br s, CH=C-C*H*$_3$ x2), 1.68 (3H, br s, CH=C-C*H*$_3$), 1.96-2.14 (4H, m, C=CH-C*H*$_2$C*H*$_2$-C=C), 2.94 (2H, d, J = 7 Hz, propargylic), 5.09 (1H, br t, J = 7 Hz, olefinic), 5.18 (1H, br t, J = 7 Hz, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 0.1, 16.1, 17.7, 19.0, 25.7, 26.4, 39.4, 83.7, 106.0, 118.6, 124.0, 131.5, 137.3. Anal. Calcd for $C_{15}H_{26}Si$: C, 76.84; H, 11.17. Found C, 76.81; H, 11.4. **5-20:** IR (KBr) ν_{max} 2960, 2111, 1458, 1376, 1249 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.17 (9H, s, $Si(CH_3)_3$), 1.26 (3H, s, C*H*$_3$-C-C≡C), 1.44 (2H, m, C*H*$_2$-C-CH$_3$), 1.55 (3H, s, C*H*$_3$-C=C), 1.68 (3H, s, C*H*$_3$-C=C), 2.04 (2H, m, C=CH-C*H*$_2$), 5.04 (1H, dd, J = 10, 2 Hz, CH=C*H*$_A$H$_B$), 5.12 (1H, m, Me$_2$C=C*H*), 5.35 (1H, dd, J = 17, 2 Hz, CH=CH$_A$*H*$_B$), 5.65 (1H, dd, J = 17, 10 Hz, C*H*=CH$_2$).



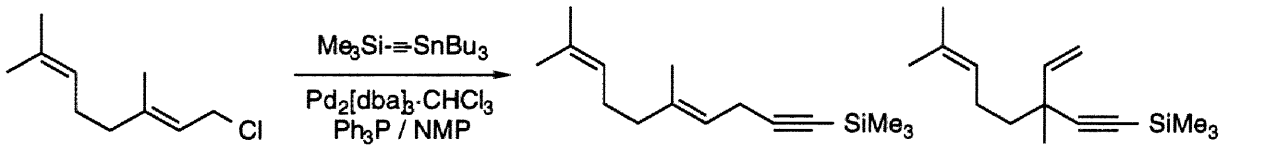
5-8b **5-19** **5-20** [14003]

Compound 5-19 and 5-20 (entry 1 in **Table 5-2**). The carbonate **5-8b** (212 mg, 1.00 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (31 mg, 0.030 mmol), dimethyl fumarate (21 mg, 0.15 mmol) LiCl (84 mg, 2.0 mmol) were dissolved in THF (5 mL) and the mixture was stirred at rt for 15 min under Ar. To this solution was added tinacetylene **5-1** (425 mg, 1.10 mmol). After stirring at 55 °C for 7 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (alumina 25 g, hexane; silica 12 g, hexane) to give **5-19** and **5-20** (155 mg, 66 %).



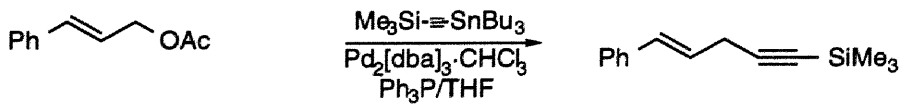
5-8c **5-19** **5-20** [13163]

Compound 5-19 and 5-20 (entry 1, **B** in **Table 5-3**). Geranyl chloride **5-8c** (172 mg, 1.00 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (31 mg, 0.030 mmol), dimethyl fumarate (21 mg, 0.15 mmol) were dissolved in benzene (5 mL) and the mixture was degassed by three freeze-thaw cycles and covered with Ar. To this solution was added tinacetylene **5-1** (425 mg, 1.10 mmol). After stirring at 55 °C for 11 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatographies (alumina 20 g, hexane; silica 15 g, hexane) to give **5-19** and **5-20** (155 mg, 66 %).



5-8c **5-19** **5-20** [14046]

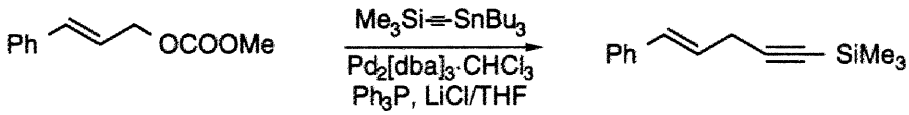
Compound 5-19 and 5-20 (entry 1, **A** in **Table 5-3**). Geranyl chloride **5-8c** (172 mg, 1.00 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (31 mg, 0.030 mmol), Ph_3P (31 mg, 0.12 mmol) were dissolved in NMP (5 mL) and the whole mixture was degassed three times and covered with Ar. After stirring at rt for 30 min, tinacetylene **5-1** (425 mg, 1.10 mmol) was added. This mixture was heated at 80 °C for 10 h. After cooling to 0 °C, the mixture was diluted with AcOEt. The mixture was washed with sat. $NaHCO_3$ solution, water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatographies (alumina 15 g, hexane and then silica 10 g, hexane) to give **5-19** and **5-20** (144 g, 61 %).



5-9a **5-21** [13184]

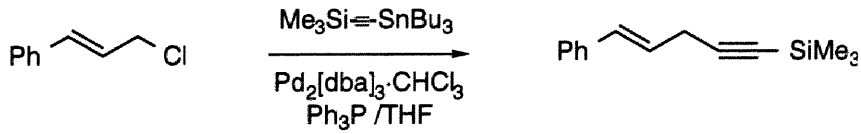
Compound 5-21 (entry 2 in **Table 5-1**). $Pd_2[dba]_3 \cdot CHCl_3$ (31 mg, 0.030 mmol), Ph_3P (31 mg, 0.12 mmol) were dissolved in THF (2 mL) and stirred at rt for 10 min. To this solution were added

cinnamyl acetate **5-9a** (152 mg, 1.00 mmol) and tinacetylene**5-1** (425 mg, 1.10 mmol) in THF (3 mL). The mixture was heated at 50 °C for 48 h, concentrated under reduced pressure. The residue was purified by column chromatographies (silica 30 g, hexane → ether/hexane = 1:20) to give **5-21** (161 mg, 87 %). IR (KBr) ν_{max} 2959, 2175, 1495, 1448, 1415, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.19 (9H, s, $Si(CH_3)_3$), 3.17 (2H, dd, *J* = 5.5, 1.5 Hz, allylic), 6.15 (1H, dt, *J* = 16, 5.5 Hz, Ph-CH=C*H*), 6.63 (1H, dt, *J* = 16, 1.5 Hz, Ph-C*H*=CH), 7.17-7.39 (5H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 0.1, 23.4, 87.1, 103.6, 124.0, 126.3, 127.3, 128.5, 131.4, 137.8. MS (EI) *m/z* 214 (M^+), 199 (M-15). HRMS (EI) for $C_{14}H_{18}Si$ (M^+), calcd 214.1177, found 214.1179.



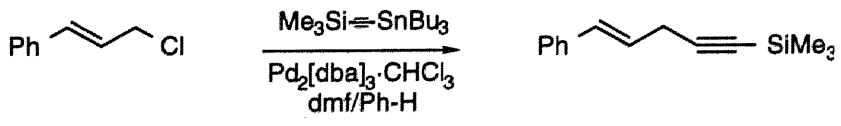
5-9b **5-21** [13177]

Compound 5-21 (entry 2 in **Table 5-2**). $Pd_2[dba]_3{\cdot}CHCl_3$ (31 mg, 0.030mmol), Ph_3P (31 mg, 0.12 mmol), LiCl (84 mg, 2.0 mmol) were dissolved in THF (2 mL). The whole mixture was degassed by three freeze-thaw cycles, covered with Ar. After stirring at rt for 15 min, a solution of cinnamyl carbonate **5-9b** (192 mg, 1.00 mmol) and tinacetylene **5-1** (425 mg, 1.10 mmol) in THF (3 mL) was added. The mixture was heated at 55 °C for 44 h under Ar. After cooling to rt, the mixture was quenched with sat. NH_4Cl solution, extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 35 g, hexane → ether/hexane = 1:20 → 1:10; alumina 10 g, hexane) to give **5-21** (92 mg, 43 %).



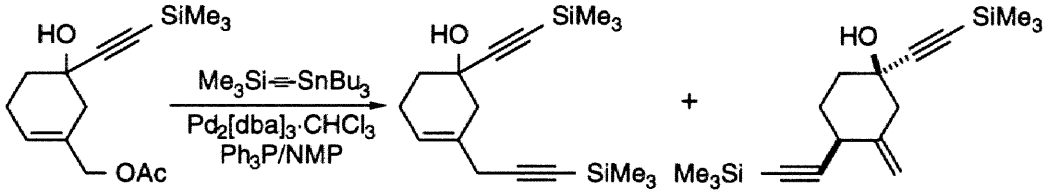
5-9c **5-21** [13186]

Compound 5-21 (entry 2 in **Table 5-3**). $Pd_2[dba]_3{\cdot}CHCl_3$ (31 mg, 0.030 mmol), Ph_3P (31 mg, 0.12 mmol) were dissolved in THF (2 mL). After stirring at rt for 10 min, a solution of cinnamyl chloride**5-9c** (152 mg, 1.00 mmol) and tinacetylene **5-1** (425 mg, 1.10 mmol) in THF (3 mL) were added. The mixture was heated at 55 °C for 44 h under argon. After removal of the solvent, the residue was purified by column chromatography (silica 30 g, hexane; alumina 10 g, hexane) to give **5-21** (119 mg, 55 %).



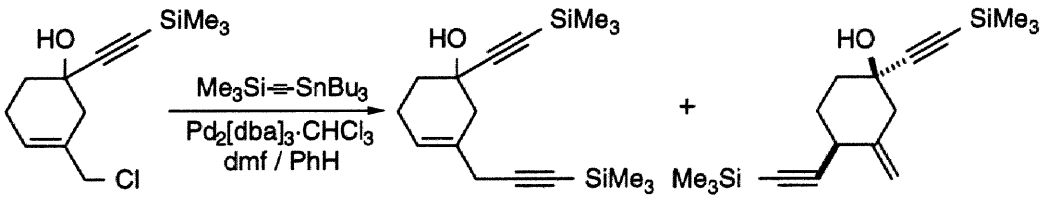
5-9c **5-21** [13162]

Compound 5-21 (entry 2 in **Table 5-3**). Cinnamyl chloride **5-9c** (152 mg, 1.00 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (31 mg, 0.030mmol), dimethyl fumarate (21 mg, 0.15 mmol) and benzene (5 mL) were placed in dry two-necked flask. The whole mixture was degassed by three freeze-thaw cycles, covered with Ar. After stirring at rt for 1 h, tinacetylene **5-1** (425 mg, 1.10 mmol) was added. The mixture was heated at 55 °C for 4.5 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (alumina 20 g, hexane; silica 13 g, hexane) to give **5-21** (129 mg, 60 %).



5-18a **5-24** **5-25** [16027]

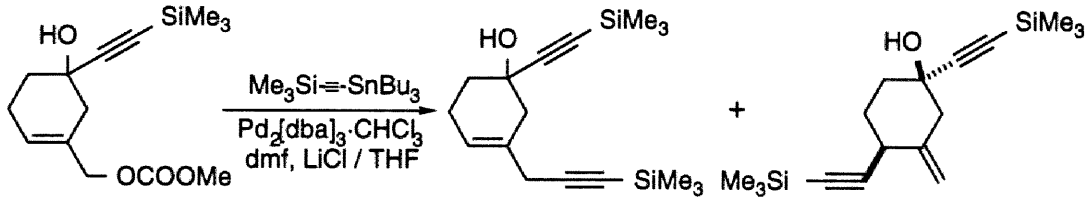
Compound 5-24 and 5-25 (entry 4 in **Table 5-1**). The allyl acetate **5-18a** (133 mg, 0.50 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (15 mg, 0.015 mmol), Ph_3P (15 mg, 0.060 mmol) were dissolved in NMP (2 mL) and the mixture was degassed three times and stirred at rt for 2.5 h. A solution of tinacetylene **5-1** (193 mg, 0.55 mmol) in NMP (0.5 mL) was added and the mixture was stirred at 80 °C for 40 h. After cooling to rt, sat. NH_4Cl solution was added. The mixture was extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:10) to give **5-24** and **5-25** (73 mg, 48 %).



5-18c **5-24** **5-25** [15012]

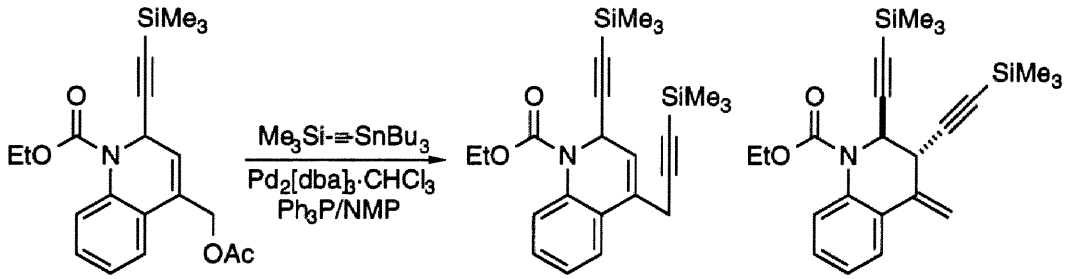
Compound 5-24 and 5-25 (entry 4 in **Table 5-3**). In a two-necked flask was placed the allyl chloride **5-18c** (1.06 g, 4.36 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (112 mg, 0.109 mmol), dimethyl fumarate (125 mg, 0.87 mmol) and benzene (20 mL). The whole mixture was degassed by three freeze-thaw cycles and covered with Ar. After stirring at rt for 1.5 h, tinacetylene **5-1** (1.85 g, 4.79 mmol) was added. The mixture was heated at 55 °C for 17 h, concentrated under reduced pressure. The residue was purified by column chromatography (silica 150 g, ether/hexane = 1:10) to give **5-24** (1.05 g, 80 %) and **5-25** (48 mg, 3.6 %). **5-24**: IR (KBr) ν_{max} 3422, 2956, 2176, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (9H, s, $Si(CH_3)_3$), 0.17 (9H, s, $Si(CH_3)_3$), 1.84 (2H, t, J = 6 Hz, $C(OH)\text{-}CH_2\text{-}CH_2$-), 2.18-2.32 (3H, m, $CH{=}C\text{-}CH_AH_B$), 2.47 (1H, br d, J = 16 Hz, $CH{=}C\text{-}CH_AH_B$), 2.90 (2H, br s, $C{\equiv}C\text{-}CH_2$-), 5.71 (1H, m, olefinic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 0.1, 23.0, 27.9, 35.0, 42.4, 66.7, 87.1, 87.2, 103.5, 109.0, 121.6, 128.8. MS (EI) *m/z* 304 (M^+), 289 (M-15). HRMS (EI) for

$C_{17}H_{18}OSi_2$ (M^+), calcd 304.1678, found 304.1670. **5-25**: IR (KBr) ν_{max} 3419, 2961, 2170, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (9H, s, $Si(CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$), 1.70-2.10 (4H, m, CH_2x2), 2.44 (1H, br d, J = 13.5 Hz, CH_AH_B), 2.67 (1H, br d, J = 13.5 Hz, CH_AH_B), 3.07 (1H, m, C≡C-C*H*), 4.91 (1H, br s, olefinic), 5.22 (1H, br s, olefinic). MS (EI) *m/z* 304 (M^+), 289 (M-15). HRMS (EI) for $C_{17}H_{28}OSi_2$ (M^+), calcd 304.1678, found 304.1672.



5-18c **5-24** **5-25** [16029]

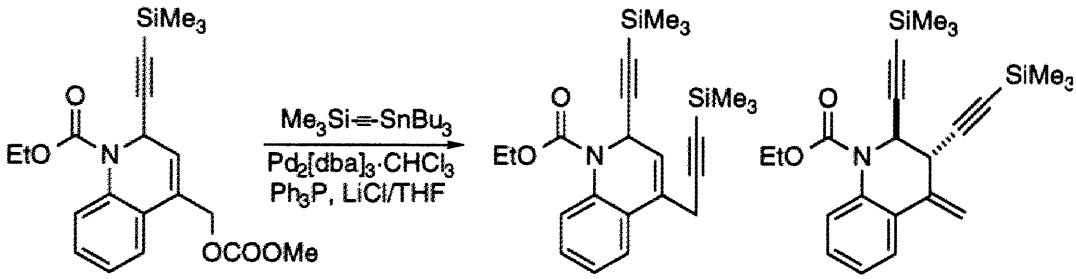
Compound 5-24, 5-25 (entry 4 in **Table 5-2**) The allyl carbonate **5-18c** (141 mg, 0.50 mmol), $Pd_2[dba]_3·CHCl_3$ (15 mg, 0.015 mmol), dimethyl fumarate (10 mg, 0.075 mmol) , LiCl (42 mg, 1.00 mmol) were dissolved in THF (3 mL). After stirring at rt for 2 h 40 min, tinacetylene **5-1** (212 mg, 0.55 mmol) was added. The mixture was heated at 65 °C for 18 h, concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:10) to give **5-24** and **5-25** (37 mg, 24 %).



5-14a **5-22** **5-23** [14020]

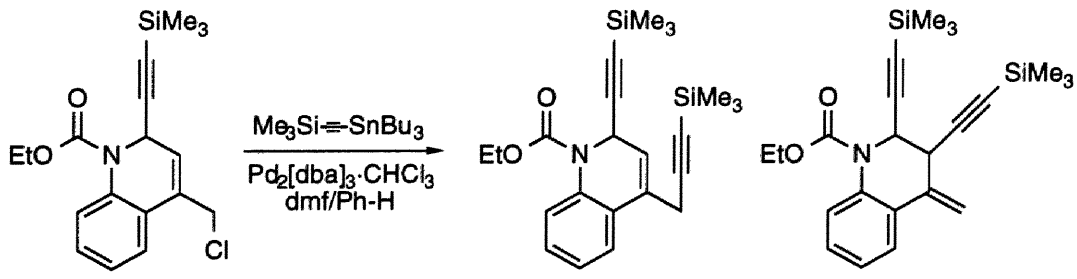
Compound 5-22 and **5-23** (entry 3 in **Table 5-1**). The allyl acetate **5-14a** (100 mg, 0.26 mmol), $Pd_2[dba]_3·CHCl_3$ (8.3 mg, 0.0081 mmol), Ph_3P (8.4 mg, 0.032 mmol) were dissolved in NMP (4 mL) , and the whole mixture was degassed three times and covered with argon. After stirring at rt for 25 min, tinacetylene **5-1** (115 mg, 0.295 mmol) was added. The mixture was heated at 80 °C for 44 h. After cooling to rt, ice-cold $NaHCO_3$ solution was added. The mixture was extracted with EtOAc (x2). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:2) to give **5-22** and **5-23** (28 mg, 28 %). **5-22:** IR (KBr) ν_{max} 2961, 2903, 2177, 1706, 1492, 1379, 1264, 1034 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (9H, s, $Si(CH_3)_3$), 0.20 (9H, s, $Si(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 3.31 (1H, dt, J = 20, 1 Hz, CH_AH_B-C≡C), 3.52 (1H, dd, J = 20, 2 Hz, CH_AH_B-C≡C), 4.28 (2H, m, CH_2CH_3), 5.91 (1H, d, J = 6.5 Hz, N-C*H*-CH=C), 6.22 (1H, dt, J = 6.5, 1 Hz, olefinic), 7.14 (1H, br t, J = 7 Hz, aromatic), 7.20-7.32 (2H, m, aromatic), 7.64 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 0.0, 14.4, 23.1, 44.7, 62.4,

88.1, 88.9, 101.7, 102.3, 122.6, 122.7, 124.3, 124.6, 126.9, 127.7, 129.8, 134.3, 153.5. MS (EI) *m/z* 409 (M^+), 394, 380. Anal. Calcd for $C_{23}H_{31}O_2NSi_2$: C, 67.43; H, 7.62; N, 3.41. Found: C, 67.40; H, 7.77; N, 3.29. **5-23:** IR (KBr) ν_{max} 2963, 2176, 1709, 1488, 1378, 1310, 1250, 1034 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ -0.06 (9H, s, $Si(CH_3)_3$), 0.06 (9H, s, $Si(CH_3)_3$), 1.35 (3H, t, *J* = 7 Hz, OCH_2CH_3), 3.64 (1H, d, *J* = 3Hz, N-CH-C*H*), 4.26 (2H, m, OCH_2CH_3), 5.16 (1H, d, *J* = 0.5 Hz, $C{=}CH_AH_B$), 5.61 (1H, d, *J* = 3 Hz, N-C*H*-CH), 5.76 (1H, s, $C{=}CH_AH_B$), 7.08 (1H, td, *J* = 7.5, 2 Hz, aromatic), 7.25 (1H, ddd, *J* = 9, 7, 2 Hz, aromatic), 7.63 (1H, dd, J = 8, 1.5 Hz, aromatic), 7.67 (1H, dd, *J* = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, -0.2, 14.5, 41.1, 49.6, 62.3, 101.8, 103.3, 112.6, 123.9, 124.0, 124.9, 125.0, 128.1, 134.6, 136.8. MS (EI) *m/z* 409 (M^+), 336. HRMS (EI) for $C_{23}H_{31}O_2NSi$ (M^+), calcd 409.1893, found 409.1891.



5-14b **5-22** **5-23** [14037]

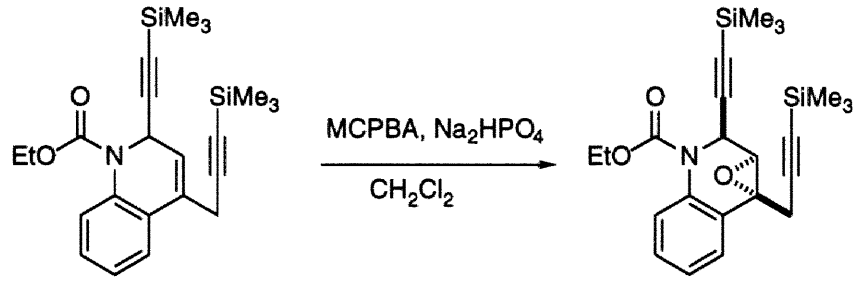
Compound 5-22 and **5-23** (entry 3 in **Table 5-2**). The carbonate **5-14b** (150 mg, 0.387 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (12 mg, 0.011 mmol), Ph_3P (12 mg, 0.046 mmol), LiCl (33 mg, 0.77 mmol) were dissolved in THF (5 mL) and stirred at rt for 40 min under Ar. To this yellow solution was added tinacetylene **5-1** (0.15 mL, 0.38 mmol). After stirring at 55 °C for 5 days, the mixture was quenched with ice-cold $NaHCO_3$ solution, extracted with AcOEt (x3). The combined organic layer was washed with brine (x3), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 13 g, ether/hexane = 1:10) to give **5-22** and **5-23** (36mg, 23 %).



5-14c **5-22** **5-23**

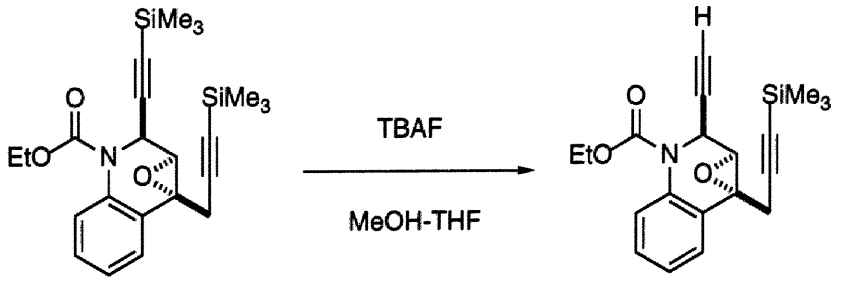
Bis acetylene 5-22 and **5-23** (entry 3 in **Table 5-3**). In a dry two necked flask was placed allyl chloride **5-14c** (1.43g, 4.12 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (106 mg, 0.10 mmol), dimethyl fumarate (119 mg, 0.82 mmol) and benzene (25 mL), and the whole mixture was degassed by two freeze-thaw cycles and covered with argon. After stirring until reaction mixture became yellow, tributylstannyl

(trimethylsilyl)ethyne **5-1** (1.75 g, 4.53 mmol) was added and was stirred at 60 °C for 5 days. Concentration of the mixture under reduced pressure provided an oil. The residue was purified by column chromatography (silica 150 g, ether/hexane, 1:10) to give **5-22** (1.07 g, 64 %) and **5-23** (67 mg, 4 %).



5-22 **5-26**

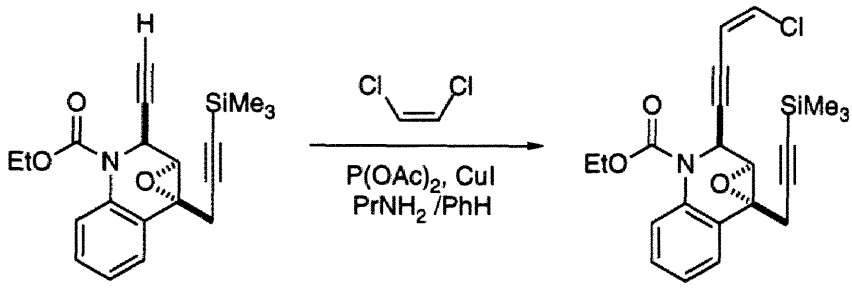
Epoxide 5-26. To a solution of enediyne **5-22** (1.00g, 2.44 mmol) and anhydrous Na_2HPO_4 (1.97 g, 13.8 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C was added MCPBA (70%, 1.10 g, 4.88 mmol) After stirring at 0 °C for 4h 20 min, sat. Na_2SO_3 solution was added until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2) and combined organic layer was washed with sat. $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 75 g, ether/hexane, 1:10 → 1:5) to give epoxide **5-26** (696 mg, 67 %). IR (KBr) ν_{max} 2963, 2181, 1715, 1496, 1250, 1044 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.00 (9H, s, $Si(CH_3)_3$), 0.14 (9H, s, $Si(CH_3)_3$), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 3.05 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.20 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.99 (1H, d, J = 3 Hz, epoxide), 4.20 (2H, m, OCH_2CH_3), 5.76 (1H, br s, N-CH-C≡C), 7.20 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.33 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.42 (1H, br, aromatic), 7.59 (1H, br d, J = 7.5 Hz, aromatic). ^{13}C NMR (78.9 MHz, $CDCl_3$) δ -0.4, -0.1, 14.3, 24.5, 44.1, 54.4, 62.6, 65.6, 88.6, 90.8, 99.1, 100.0, 124.9, 126.4, 126.9, 127.0, 128.3, 135.1. MS (EI) *m/z* 425 (M^+), 410 (M-15), 39 (M-29), 380, 352. HRMS (EI) for $C_{23}H_{31}O_3NSi_2$ (M^+), calcd 425.1842, found 425.1835.



5-26 **5-27** [14126]

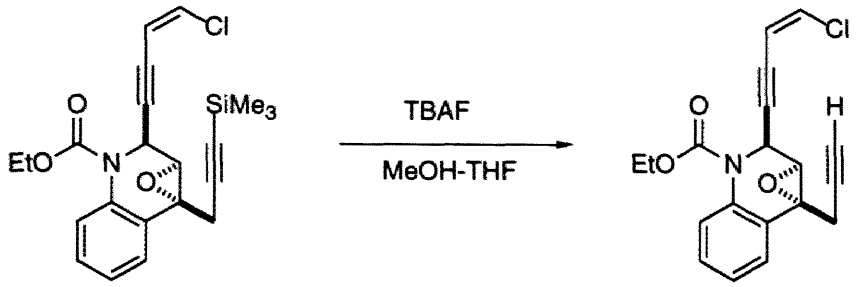
Mono TMS acetylene 5-27. To a solution of **5-26** (145 mg, 0.341 mmol) in THF (7 mL) and MeOH (0.13 mL, 3.4 mmol) cooled to -20 °C was added TBAF (1.0 M solution of THF, 0.13 mL, 0.13 mmol). After stirring at -20 °C for 1h, aq NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, and then concentrated under reduced

pressure. The residue was purified by column chromatography (silica 7 g, ether/hexane, 1:10) to give **5-27** (118 mg, 98 %). IR (KBr) ν_{max} 3283, 2963, 2182, 1712, 1496, 1321, 1251 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (9H, s, $Si(CH_3)_3$), 1.13 (3H, t, J = 7 Hz, OCH_2CH_3), 2.15 (1H, d, J = 2.5 Hz, C≡C-*H*), 3.00 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 3.24 (1H, d, J = 17 Hz, C≡C-CH_AH_B), 4.02 (1H, d, J = 3 Hz, epoxide), 4.26 (2H, m, OCH_2CH_3), 5.81 (1H, br s, N-C*H*-C≡C), 7.21 (1H, td, J = 7, 1.5 Hz, aromatic), 7.36 (1H, td, J = 8, 1.5 Hz, aromatic), 7.44 (1H, br d, J = 7 Hz, aromatic), 7.58 (1H, dd, J = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 24.33, 43.23, 54.43, 62.6, 65.2, 73.5, 77.69. 88.84, 99.9, 125.0, 126.1, 126.8, 127.0, 128.5, 134.9. MS (EI) *m/z* 353 (M^+), 324 (M-29). HRMS (EI) for $C_{20}H_{23}NO_3Si$ (M^+), calcd 353.1447, found 353.1429.



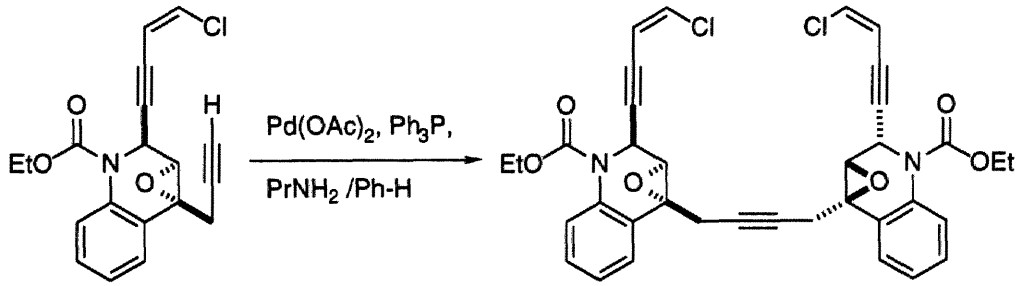
5-27 **5-28** [14137]

Enediyne 5-28. A suspension of acetylene **5-27** (360 mg, 1.02 mmol), $Pd(OAc)_2$ (11mg, 0.05 mmol), Ph_3P (26 mg, 0.10 mmol), CuI (19 mg, 0.101 mmol) in benzene (18 mL) was degassed by three freeze-thaw cycles and covered with argon. To this mixture were added successively (*Z*)-dichloroethylene (0.38 mL, 5.05 mmol), and *n*-propylamine (0.16 mL, 2.03 mmol). The solution was stirred at rt for 1 h 10 min, poured into ice-cold aq. NH_4Cl solution, and partitioned. The aqueous layer was extracted with AcOEt (x2). The combined organic layer was washed with NH_4Cl solution (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether:hexane, 1:10 → 1:5) to give the enediyne **5-28** (322 mg, 77 %). ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (9 H, s, $Si(CH_3)_3$), 0.20 (3H, t, J = 7 Hz, OCH_2CH_3), 1.97 (1H, d, J = 17 Hz, CH_AH_B-C≡C-Si), 2.16 (1H, d, J = 17 Hz, CH_AH_B-C≡C-Si), 2.99 (1H, d, J = 3Hz, epoxide), 3.16 (2H, m, OCH_2CH_3), 4.62 (1H, dd, J = 7.5, 2 Hz, C*H*=CHCl), 4.91 (1H, br s, N-C*H*-C≡C), 5.24 (1H, d, J = 7.5 Hz, CH=C*H*Cl), 6.12 (1H, td, J = 8, 1 Hz, aromatic), 6.24 (1H, td, J = 8, 1 Hz, aromatic), 6.37 (1H, br d, J = 8 Hz, aromatic), 6.51 (1H, dd, J = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 14,3, 24.3, 44.1, 54.4, 62.6, 65.3, 79.1, 88.7, 91.2, 99.8, 111.0, 125.0, 126.2, 127.0, 128.5, 130.0, 135.0. MS (EI) *m/z* 415 (M^+: ^{37}Cl), 413 (M^+: ^{35}Cl).



5-28 **5-29** [14138]

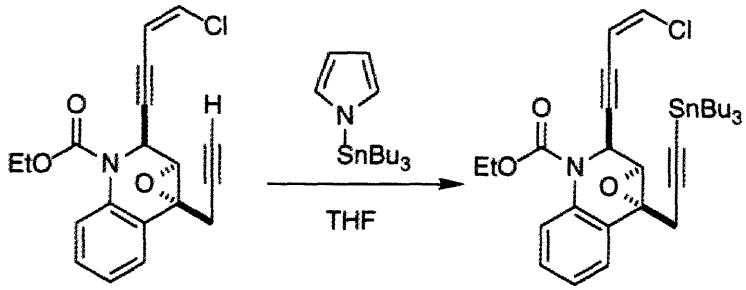
Enediyne 5-29. To a solution of silylacetylene **5-28** (322 mg, 0.777 mmol) in THF (10 mL) and MeOH (0.15 mL, 3.88 mL) cooled to 0 °C was added TBAF (1.0 M in THF solution , 0.38 mL, 0.38 mmol). After stirring at 0 °C for 2 h, the mixture was poured into ice-cold aq. NH_4Cl, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 15g, ether:hexane, 1:2) to give terminal acetylene **5-29** (265 mg, 100 %): IR (KBr) ν_{max} 3289, 3084, 2985, 2123, 1709, 1496, 1262 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7 Hz, OCH_2CH_3), 2.13 (1H, t, J = 3 Hz, C≡C-*H*), 3.04 (1H, dd, J = 17, 3 Hz, CH_AH_B-C≡C-H), 3.19 (1H, dd, J = 17, 3 Hz, CH_AH_B-C≡C-H), 4.09 (1H, d, J = 3 Hz, epoxide), 4.24 (2H, m, OCH_2CH_3), 5.70 (1H, dd, J = 7, 2 Hz, C*H*=CHCl), 5.98 (1H, br s, N-C*H*-C≡C), 6.32 (1H, d, J = 7 Hz, CH=C*H*Cl), 7.21 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.35 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.44 (1H, m, aromatic), 7.58 (1H, dd, J = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 23.1, 44.1, 54.5, 62.7, 65.5, 72.0, 77.8, 79.3, 91.0, 111.0, 125.1, 126.0, 126.9, 127.1, 128.6, 130.1, 135.1. MS (EI) *m/z* 341 (M^+: ^{37}Cl), 343 (M^+: ^{35}Cl). HRMS (EI) for $C_{19}H_{16}NO_3Cl$ (M^+), calcd 341.0818, found 341.0829.



5-29 **5-31** [14147]

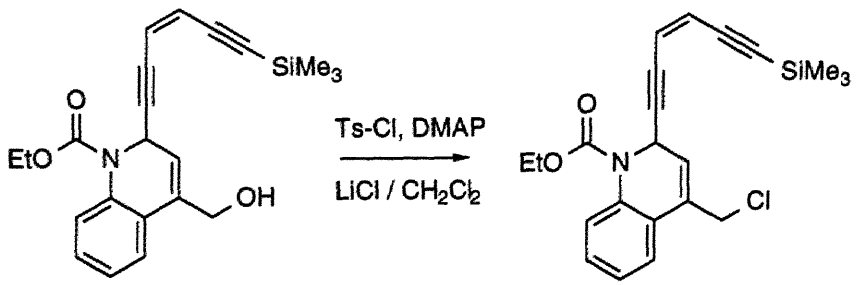
Dimer 5-31. A suspension of $Pd(OAc)_2$ (2.3 mg, 0.011 mmol), Ph_3P (5.6 mg, 0.021 mmol), CuI (4.0 mg, 0.021 mmol) in benzene (30 mL) was degassed by three freeze-thaw cycles and covered with argon. To this mixture were added successively acetylene **5-29** (73 mg, 0.21 mmol) in THF (5 mL), *n*-propylamine (35 μL, 0.42 mmol) in benzene (0.5 mL). The solution was stirred at rt for 2 h 10 min, poured into ice-cold aq. NH_4Cl solution, and extracted. The aqueous layer was extracted with AcOEt (x2). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 10 g, ether/hexane, 1:1) to give unreacted **5-29** (45 mg, 62 %) and the dimer **5-31** (11.4 mg, 7.8 %). **5-31**: IR (KBr) ν_{max} 2982, 1796, 1377, 1319, 1259 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7Hz, OCH_2CH_3), 1.27 (3H, t, J = 7Hz, OCH_2CH_3), 3.05 (1H, d, J = 17 Hz,

C≡C-CH_AH$_B$), 3.06 (1H, d, J = 17 Hz, C≡C-CH_AH$_B$), 3.22 (1H, d, J = 17 Hz, C≡C-CH$_A$$H_B$), 3.25 (1H, d, J = 17 Hz, C≡C-CH$_A$$H_B$), 4.01 (1H, d, J = 3 Hz, epoxide), 4.02 (1H, d, J = 3 Hz, epoxide), 4.08-4.34 (4H, m, OCH_2CH$_3$ x2), 5.64 (1H, dd, J = 7.5, 2Hz, CH=CHCl), 5.65 (1H, dd, J = 7.5, 2Hz, CH=CHCl), 5.95 (2H, br s, N-CH-C≡C x2), 6.24 (1H, d, J = 7.5 Hz, CH=CHCl), 6.26 (1H, d, J = 7.5 Hz, CH=CHCl), 7.21 (2H, td, J = 7.5, 1 Hz, aromatic), 7.35 (2H, td, J = 7.5, 1 Hz, aromatic), 7.44 (2H, br d, J = 7.5 Hz, aromatic), 7.52 (2H, br d, J = 7.5 Hz, aromatic). MS (FAB) *m/z* 681 (M+H).



5-29 **5-30** [14140]

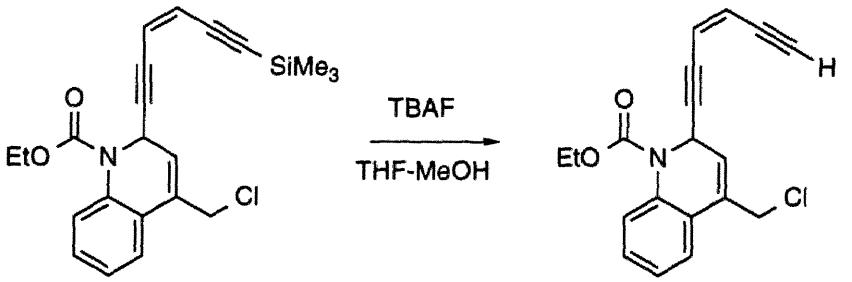
Tin Acetylene 5-30. To a solution of acetylene **5-29** (265 mg, 0.775 mmol) in THF (0.5 mL) was added *N*-tributyltin-pyrrole (0.49 mL, 1.55 mmol). After stirring at 80 °C for 96 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane, 1:10→1:5) to give tinacetylene **5-30** (214 mg, 44%) and starting material **5-29** (73 mg, 27%): IR (KBr) ν_{max} 2957, 2157, 1710, 1496, 1377, 1316, 1258 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84-0.98 (15H, m, SnCH_2(CH$_2$)$_2$CH_3 x 3), 1.22-1.38 (9H, Sn-CH$_2$-CH_2-CH$_2$-CH$_3$ x3, OCH$_2$CH_3), 1.52 (6H, m, Sn-CH$_2$-CH$_2$-CH_2-CH$_3$ x3), 3.10 (1H, d, J = 17 Hz, CH_AH$_B$-C≡C-Sn), 3.23 (1H, d, J = 17 Hz, CH$_A$$H_B$-C≡C-Sn), 4.09 (1H, d, J = 3 Hz, epoxide), 4.23 (2H, m, OCH_2CH$_3$), 5.68 (1H, dd, J = 7.5, 2 Hz, CH=CHCl), 5.97 (1H, br s, N-CH-C≡C), 6.31 (1H, d, J = 7.5 Hz, CH=CHCl), 7.17 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.32 (1H, td, J = 8, 1.5 Hz, aromatic), 7.43 (1H, br d, J = 8H, aromatic), 7.63 (1H, dd, J = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 10.9, 13.6, 14.3, 24.6, 26.9, 28.8, 44.2, 54.7, 62.6, 65.3, 79.0, 86.6, 91.4, 103.8, 111.1, 124.9, 126.5, 126.9, 127.2, 128.3, 129.9, 135.0. MS (FAB) *m/z* 632 (M+H).



5-32 **5-33** [14086]

Compound 5-33. The alcohol **5-32** (1.64 g, 4.33 mmol) was dissolved in CH_2Cl_2 (40 mL). To this solution were added Ts-Cl (1.07g, 5.62 mmol) and DMAP (636 mg, 5.20 mmol). After stirring at rt for 12 h, LiCl (367 mg, 8.67 mmol) and Me_3NBnCl (160 mg, 0.867 mmol) were added.

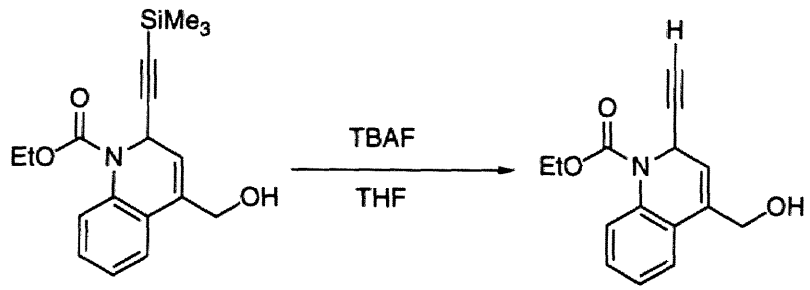
The mixture was stirred at rt for 3 h 15 min, filtrated through the pad of Super-Cel ®, washed with Et_2O. The filtrate was dried over anhydrous Na_2SO_4, evaporated under reduce pressure. The residue was purified by column chromatography (silica 80 g, ether/hexane = 1:10) to give **5-33** (1.55 g, 89 %). IR (KBr) ν_{max} 2962, 2145, 1709, 1492, 1377, 1323, 1263, 1045 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.34 (3H, t, J = 7 Hz, OCH_2CH_3), 4.28 (2H, m, OCH_2CH_3), 4.36 (1H, d, J = 12 Hz, CH_aH-Cl), 4.54 (1H, d, J =12 Hz, CHH_B-Cl), 5.70 (1H, dd, J = 11, 1 Hz, C*H*=CH-C≡C-TMS), 5.75 (1H, d, J = 11 Hz, CH=C*H*-C≡C-TMS), 6.18 (2H, m, N-C*H*-CH=C), 7.18 (1H, td, J = 7.5, 1 Hz, aromatic), 7.27-7.35 (2H, m, aromatic), 7.39 (1H, dd, J = 7.5, 1 Hz, aromatic), 7.67 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.4, 43.2, 44.4, 62.7, 80.9, 92.8, 101.6, 103.2, 119.9, 120.0, 123.4, 124.5, 124.8, 128.3, 128.5, 128.7., 131.8, 133.6, 133.8, 134.6, 153.4. MS (EI) *m/z* 399 (M^+: ^{37}Cl), 397 (M^+: ^{35}Cl), 370 (M-29), 368 (M-29), 348.



5-33 **5-34** [14116]

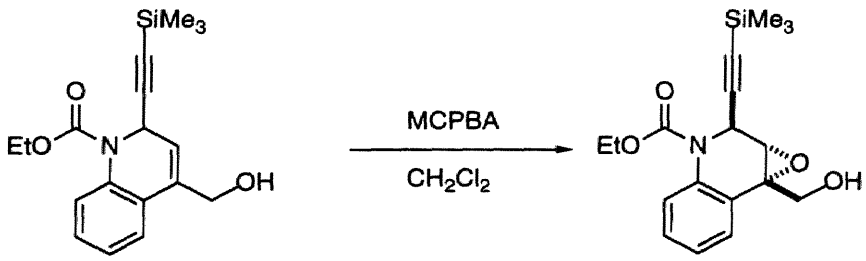
Compound 5-34. Compound **5-33** (1.06 g, 2.65 mmol) was dissolved in THF (30 mL) and MeOH (0.53 mL) and cooled to -78 °C. To this solution was added TBAF (1.32 mL). After stirring at -78 °C for 15 min, the mixture was stirred at 0 °C for 30 min. The mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with water (x2), brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane = 1:10 → 1:5) to give chloride **5-34** (802 mg, 92 %). IR (KBr) ν_{max} 3289, 2981, 2093, 1700, 1492, 1492, 1379 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 3.06 (1H, d, J = 2 Hz, C≡C-H), 4.30 (2H, m, OCH_2CH_3), 4.38 (1H, d, J = 12 Hz, CH_AH_B-Cl), 4.54 (1H, d, J = 12 Hz, CH_AH_B-Cl), 5.70 (1H, dd, J = 11, 2 Hz, CH=C*H*-C≡C-H), 5.78 (1H, dd, J = 11, 2 Hz, C*H*=CH-C≡C-H), 6.12 (1H, br d, J = 7 Hz, N-C*H*-CH=C), 6.22 (1H, d, J = 7 Hz, N-CH-C*H*=C), 7.18 (1H, br t, J = 7 Hz, aromatic), 7.32 (1H, br t, J = 8 Hz, aromatic), 7.40 (1H, dd, J = 7, 2 Hz, aromatic), 7.68 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.4, 43.2, 44.4, 62.7, 80.0, 80.9, 85.0, 92.9, 119.5, 121.0, 123.4, 124.4, 124.7, 124.9, 125.0, 128.2, 132.1, 134.7, 153.4. MS (EI) *m/z* 327 (M^+: ^{37}Cl), 325 (M^+: ^{35}Cl), 298 (M^+: ^{37}Cl -29), 296 (M^+: ^{35}Cl -29).

Experimental for Chapter 6



6-4 **6-5** [14070]

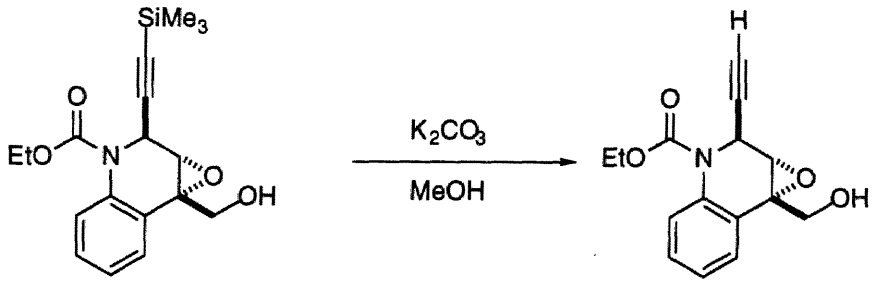
Alcohol 6-5. To a solution of **6-4** (4.15 g, 10.0 mmol) in THF (80 mL) and MeOH (4.0 mL, 100 mmol) cooled to -78 °C was added TBAF (1.0 M solution of THF, 10 mL, 10.0 mmol). After stirring at -78 °C for 15 min, the mixture was stirred at 0 °C for 2 h, poured into sat. NH_4Cl solution, extracted with AcOEt (x3). Combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 100 g, ether/hexane, 2:1) to give **6-5** (2.45 g, 95 %): IR (KBr) ν_{max} 3404, 3287, 2980, 2112, 1698, 1492 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7 Hz, OCH_2CH_3), 2.20 (1H, d, J = 2.5 Hz, C≡C-*H*), 4.29 (2H, m, OCH_2CH_3), 4.58 (2H, br s, CH_2-OH), 5.93 (1H, dd, J = 6, 2.5 Hz, N-C*H*-C≡C), 6.13 (1H, br d, J = 6 Hz, olefinic), 7.17 (1H, td, J = 8, 2 Hz, aromatic), 7.25-7.40 (2H, m, aromatic), 7.66 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 43.3, 61.7, 62.6, 71.5, 80.1, 121.0, 123.0, 124.4, 125.6, 127.8, 134.0, 134.8, 153.4. MS (EI) *m/z* 257 (M^+), 228, 184. HRMS (EI) for $C_{15}H_{15}O_3N$ (M^+), calcd 257.1051, found 257.1061.



6-4 **6-9a** [15131]

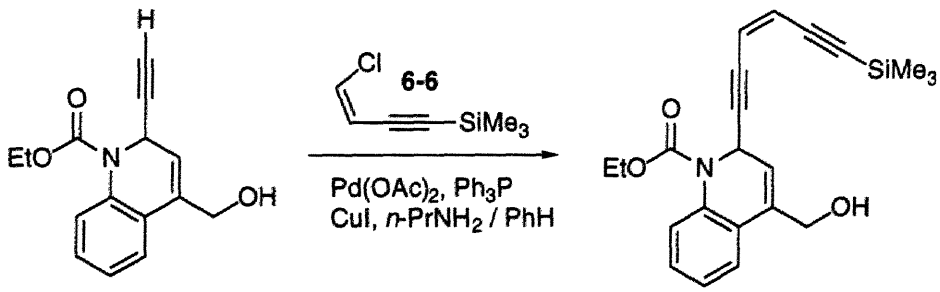
Epoxide 6-9a. To a solution of allyl alcohol **6-4** (1.00 g, 3.03 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added MCPBA (70 %, 1.48 g, 6.06 mmol). After stirring at 0 °C for 1.5 h, the solution was diluted with $CHCl_3$ (30 mL). The mixture was washed with aq. Na_2SO_3 solution (x2), aq. $NaHCO_3$ solution (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 50 g, ether/hexane, 1:1) to give epoxide **6-9a** (1.05 g, 100 %): IR (KBr) ν_{max} 3455, 2962, 2175, 1709, 1498, 1256, 1047 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ -0.01 (9H, s, $Si(CH_3)_3$), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3), 1.94

(1H, dd, J = 8.5, 5 Hz, CH_2-O*H*), 4.04 (1H, d, J = 3 Hz, epoxide), 4.10 (1H, dd, J = 12.5, 8.5 Hz, CH_AH_B-OH), 4.23 (2H, m, OCH_2CH_3), 4.46 (1H, dd, J = 12.5, 5 Hz, CH_AH_B-OH), 5.78 (1H, br s, N-C*H*-C≡C), 7.20 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.35 (1H, td, J = 8, 1.5 Hz, aromatic), 7.43 (1H, br d, J = 8 Hz, aromatic), 7.48 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.4, 14.3, 44.0, 56.5, 61.0, 62.6, 63.9, 91.1, 98.8, 125.2, 125.4, 126.5, 127.1, 128.5, 135.2. MS (EI) *m/z* 345 (M^+), 327, 314, 298. Anal. Calcd for $C_{18}H_{23}NO_4Si$; C; 62.57, H; 6.71, N; 4.05. Found C; 62.69, H; 6.89, N; 4.07



6-9a **6-9b** [15134]

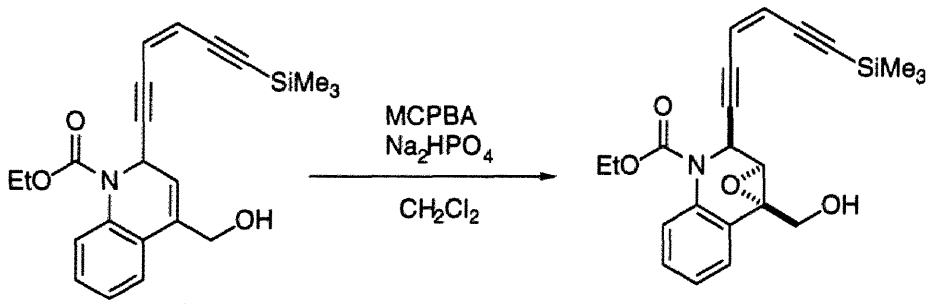
Epoxyalcohol 6-9b. To a solution of silylacetylene **6-9a** (280 mg, 0.81 mmol) in MeOH (8 mL) was added anhydrous K_2CO_3 (40 mg). The mixture was stirred at rt for 20 min, poured into aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane, 1:1) to give **6-9b** (216 mg, 100 %): IR (KBr) ν_{max} 3504, 3291, 2973, 2120, 1702, 1497 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7 Hz, OCH_2CH_3), 2.03 (1H, dd, J = 8.5 Hz, CH_2-O*H*), 2.16 (1H, d, J = 2.5 Hz, C≡C-*H*), 4.06 (1H, d, J = 3 Hz, epoxide), 4.12 (1H, dd, J = 12.5, 8 Hz, CH_AH_B-OH), 4.24 (2H, m, OCH_2CH_3), 4.44 (1H, dd, J = 12.5, 5 Hz, CH_AH_B-OH), 5.84 (1H, br s, N-C*H*-C≡C), 7.22 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.37 (1H, td, J = 7.5, 1.5 Hz, aromatic), 7.46 (1H, br d, J = 7.5 Hz, aromatic), 7.51 (1H, br d, J = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 43.1, 56.4, 60.9, 62.8, 63.8, 73.7, 77.5, 125.2, 125.3, 126.8, 127.0, 128.7, 135.0. MS (EI) *m/z* 273 (M^+), 242. HRMS (EI) for $C_{15}H_{15}O_4N$ (M^+), calcd 273.1000, found 273.1013.



6-5 **6-7** [14078] [15138]

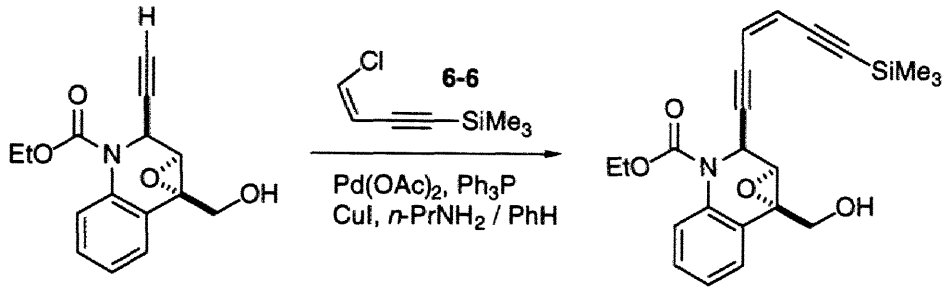
Enediyne 6-7. A suspension of $Pd(OAc)_2$ (106 mg, 0.476 mmol), Ph_3P (249 mg, 0.952 mmol), CuI (181 mg, 0.952 mmol) in benzene (50 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture were added successively acetylene **6-5** (2.45 g, 9.52 mmol) in benzene (8 mL)-THF (2 mL), vinyl chloride **6-6** (2.26 g, 14.2 mmol) in benzene (7 mL) and *n*-

propylamine (2.34 mL, 28.5 mmol). The solution was stirred at rt for 1.5 h, poured into ice-cold aq. NH_4Cl solution, and partitioned. The aqueous layer was extracted with ether (x2), the combined organic layer was washed with aq. NH_4Cl solution (x2), water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 120 g, ether/hexane, 2:1) to give the enediyne **6-7** (2.22 g, 61 %): IR (KBr) ν_{max} 3427, 2963, 2148, 1697, 1491, 1379, 1261 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.27 (2H, m, OCH_2CH_3), 4.54 (2H, br s, CH_2OH), 5.68 (1H, dd, J = 11, 1 Hz, CH-C≡C-CH=CH), 5.73 (1H, d, J = 11 Hz, C=CH-C≡C-Si), 6.08-6.17 (2H, m, C=CH-CH-N), 7.13 (1H, td, J = 8, 1 Hz, aromatic), 7.24-7.34 (2H, m, aromatic), 7.68(1H, br d, J = 8 Hz). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.4, 44.4, 62.1, 62.6, 80.5, 93.5, 101.6, 103.0, 119.7, 120.0, 121.4, 123.1, 124.5, 124.7, 125.6, 127.9, 134.3, 134.6, 153.5. MS (EI) *m/z* 379 (M^+), 350, 348, 306. HRMS (EI) for $C_{22}H_{25}O_3NSi$ (M^+), calcd 379.1603, found 379.1618.



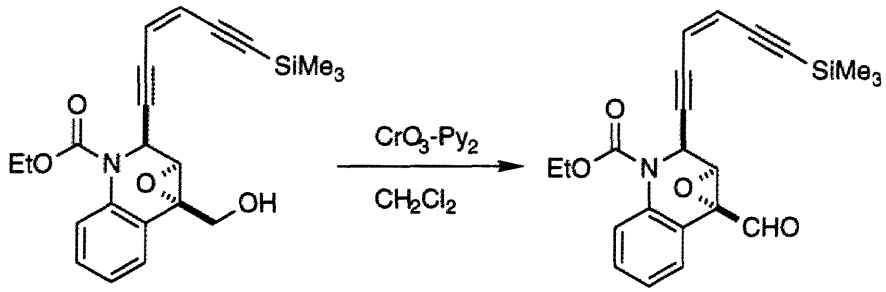
6-7 **6-8** [10063]

Compound 6-8 from 6-7. To a solution of allylic alcohol **6-7** (445 mg, 1.17 mmol) and Na_2HPO_4 (232 mg, 1.64 mmol) in CH_2Cl_2 cooled to 0 °C was added MCPBA (80 %, 354 mg, 1.64 mmol). After stirring at 0 °C for 4 h 50 min, additional Na_2HPO_4 (33 mg, 0.23 mmol) and MCPBA (80 %, 40 mg, 0.23 mmol) were added. After stirring at 0 °C for 2.5 h, the mixture was treated with aq. Na_2SO_3 solution, and extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane, 1:1) to give epoxide **6-8** (159 mg, 56 %). IR (KBr) ν_{max} 3508, 2959, 2144, 1701, 1498, 1140, 1028 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.23 (9H, s, $Si(CH_3)_3$), 1.29 (3H, t, J = 7 Hz, OCH_2CH_3), 1.89 (1H, m, OH), 4.08 (1H, d, J = 3H, epoxide), 4.04-4.36 (3H, m, OCH_2CH_3, CH_AH_B-OH), 4.46 (1H, dd, J = 13, 3 Hz, CH_AH_B-OH), 5.65 (1H, dd, J = 11, 2 Hz, CH=CH-C≡C-CH), 5.79 (1H, d, J = 11 Hz, Si-C≡C-CH=CH), 6.07 (1H, br s, N-CH-C≡C), 7.20 (1H, td, J = 8, 2 Hz, aromatic), 7.35 (1H, td, J = 8, 2 Hz, aromatic), 7.41-7.57 (2H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 14.3, 44.0, 56.5, 61.1, 62.7, 63.9, 82.3, 90.6, 101.4, 103.5, 119.2, 120.5, 125.1, 125.2, 126.8, 126.9, 128.6, 135.0. MS (EI) *m/z* 395 (M^+), 377, 364, 348. HRMS (EI) for $C_{22}H_{25}O_4NSi$ (M^+), calcd 395.1552, found 395.1539.



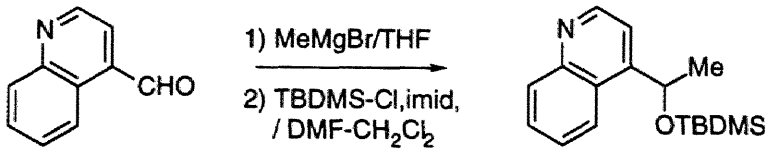
6-9b **6-8**

Enediyne epoxide 6-8 from 6-9. A suspension of $Pd_2[dba]_3 \cdot CHCl_3$ (9.5 mg, 0.0184 mmol), Ph_3P (9.6 mg, 0.036 mmol) and CuI (7.0 mg, 0.036 mmol) in benzene (5 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture were added successively acetylene **6-9b** (94 mg, 0.34 mmol) in THF (2 mL), vinyl chloride **6-6** (117 mg, 0.738 mmol) in benzene (1.5 mL) and *n*-propylamine (2.34 mL) in benzene (0.6 mL). The solution was stirred at rt for 1.5 h, poured into ice-cold aq. NH_4Cl solution and partitioned. The aqueous layer was extracted with AcOEt (x2), the combined organic layers were washed with aq. NH_4Cl solution (x2), water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane, 1:1 → 2:1) to give the enediyne **6-8** (101 mg, 74 %).



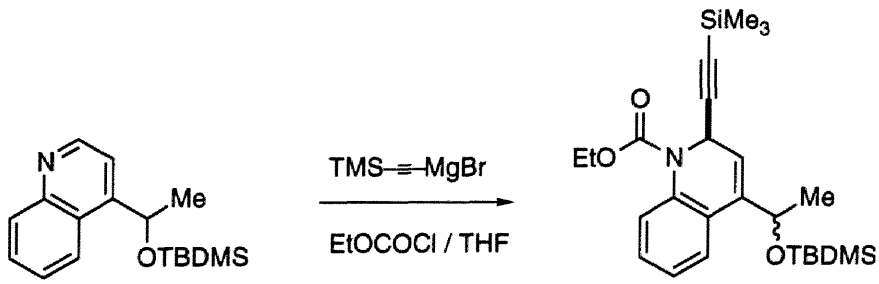
6-8 **6-10**

Epoxyaldehyde 6-10. To a solution of epoxyalcohol **6-8** (70 mg, 0.176 mmol) in CH_2Cl_2 cooled to 0 °C was added $CrO_3 \cdot Py_2$ (ca. 500 mg). After stirring at 0 °C for 30 min, the mixture was diluted with CH_2Cl_2 (2 mL), mixed with Super-Cel® and ether (5 mL). The mixture was filtrated through the pad of Hyflo Super-Cel ® and washed with AcOEt. The filtrate was concentrated under reduced pressure. The residue was purified by short column chromatography (silica, ether) to give epoxyaldehyde **6-10** (19 mg, 27 %). IR (KBr) ν_{max} 2962, 2144, 1733, 1709, 1495, 1258 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.21 (1H, s, $Si(CH_3)_3$), 1.28 (3H, t, J = 7 Hz, OCH_2CH_3), 4.16 (1H, d, J = 3 Hz, epoxide), 4.25 (2H, m, OCH_2CH_3), 5.64 (1H, dd, J = 11, 2 Hz, CH=CH-C≡C-Si), 5.80 (1H, d, J = 11 Hz, CH=CHC≡C-Si), 6.22 (1H, br s, N-CH-C≡C), 7.24 (1H, td, J = 7.5 Hz, 1.5 Hz, aromatic), 7.35-7.52 (2H, m, aromatic), 8.19 (1H, dd, J = 7.5, 1.5 Hz, aromatic), 9.25 (1H, s, CHO). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.3, 43.5, 56.9, 63.0, 64.8, 83.0, 89.1, 101.2, 103.9, 118.8, 120.7, 121.1, 125.4, 126.9, 128.3, 129.2, 134.8, 194.5. MS (EI) *m/z* 393 (M^+), 364. HRMS (EI) for $C_{22}H_{23}O_4NSi$ (M^+), calcd 393.1396, found 393.1380.



6-11 **6-16**

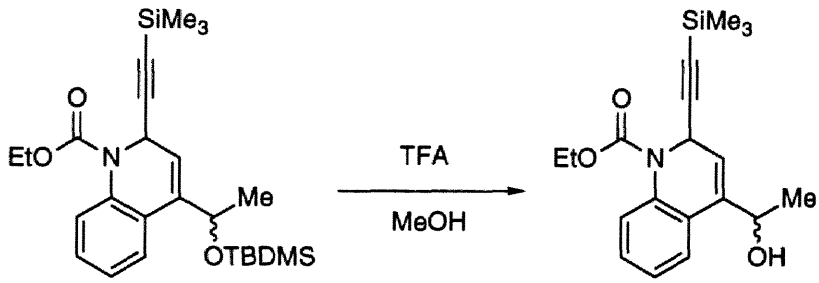
TBDMS-ether 6-16. To a solution of 4-quinolinecarboxaldehyde **6-11** (6.53 g, 41.5 mmol) in THF cooled to -40 °C was added MeMgBr (3.0 M in ether, 18.0 mL, 54.0 mmol). After stirring at -40 °C for 1.5 h, the solution was poured into sat. NH_4Cl solution, and extracted with AcOEt (x3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford crude product. This material was sufficiently pure for use in the next reaction. The resulting residue was dissolved with CH_2Cl_2 (120 mL) and DMF (24 mL). To this solution were added imidazole (8.44 g, 124 mmol) and TBDMS-Cl (9.33 g, 61.9 mmol). After stirring at rt for 16 h, the mixture was partitioned between water and CH_2Cl_2. The organic layer was washed with water (x2), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica 450 g, ether/hexane, 1:2) to give the silylether **6-16** (11.26 g, 94.5 % in 2 steps). IR (KBr) ν_{max} 2954, 2858, 1593, 1570, 1471 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.55 (3H, d, J = 6.5 Hz, CH_3CHOSi), 5.53 (1H, q, J = 6.5 Hz, CH_3CHOSi), 7.48 (1H, ddd, J = 8.2, 7.0, 1.5 Hz, aromatic), 7.55 (1H, d, J = 4.6 Hz, aromatic), 7.64 (1H, ddd, J = 8.2, 7.0, 1.5 Hz, aromatic), 7.95 (1H, br d, J = 8.2 Hz, aromatic), 8.09 (1H, br d, J = 8.2 Hz, aromatic), 8.83 (1H, d, J = 4.6 Hz, aromatic) ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.9, 18.3, 25.9, 26.4, 67.3, 117.3, 123.1, 125.2, 126.3, 128.9, 130.4, 148.2, 150.6, 152.3. MS (EI) *m/z* 287 (M^+), 272. HRMS (EI) for $C_{17}H_{25}NOSi$ (M^+), calcd 287.1705, found 287. 1709. Anal. Calcd for $C_{17}H_{25}NOSi$: C, 71.08; H, 8.71; N, 4.89. Found: C, 71.01; H, 8.76; N, 4.64.



6-16 **6-17**

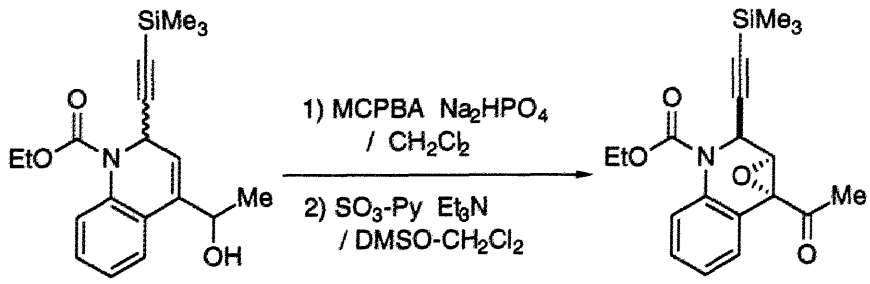
Compound 6-17. To an ice-cooled solution of trimethylsilyl acetylene (11.0 mL, 77.6 mmol) in THF (175 mL) was added EtMgBr (3M in ether, 24.6 mL, 73.7 mmol). The solution was stirred at rt for 30 min and cooled to 0 °C again. To this solution was added silylether **6-16** (11.4g, 38.8 mmol) in THF (45 mL) and ethyl chloroformate (9.27 mL, 97 mmol). The solution was stirred for 40 min without the cooling bath. After stirring at rt for 1 h, the solution was poured into sat. NH_4Cl solution and extracted with AcOEt (x3). The organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by column chromatography (silica 600 g, ether/hexane, 1:8) to give the acetylene adduct **6-17** (17.6 g, 99.5 %).

IR (KBr) ν_{max} 2958, 2169, 1710, 1569, 1490, 1379 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) * δ 0.05-0.25 (15H, m, $Si(CH_3)_3$, $Si(CH_3)_2$), 0.87-0.95 (9H, m, $SiC(CH_3)_3$), 1.25-1.45 (6H, m, CH_3CHOSi, OCH_2CH_3), 4.25 (2H, m, OCH_2CH_3), 4.64 [4.96] (1H, q [qd], J = 6.5 Hz [J = 6.5, 1.5 Hz], CH_3CHOSi), 5.80 [5.85] (1H, d, J = 6.5 Hz, propargylic), 5.93 [6.18] (1H, d [dd], J = 6.5 Hz [J = 6.5, 1.5 Hz], olefinic), 7.09 (1H, br t, J = 8.0 Hz, aromatic), 7.23 (1H, br t, J = 8.0 Hz, aromatic), 7.59 [7.65] (1H, br d, J = 8.0 Hz, aromatic), 7.85 (1H, dd, J = 8.0, 1.5 Hz, aromatic). * [ ] shows data of minor isomer, major : minor = 2 : 1 (by integration of ^1H NMR). EIMS *m/z* 457 (M^+), 442 (M^+-Me). HRMS(EI) for $C_{25}H_{39}NO_3Si$ (M^+), calcd 457.2468, found 457.2453.



6-17 **6-18**

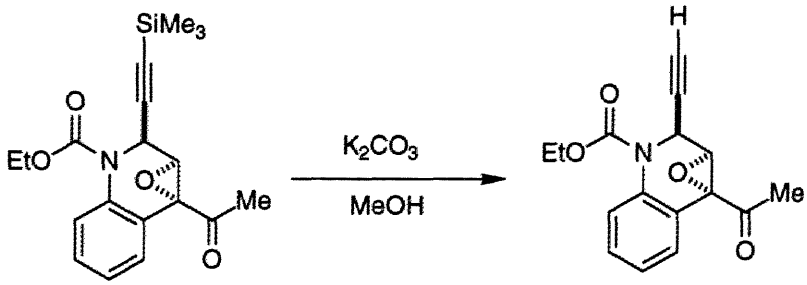
Compound 6-18. To a solution of silyl ether **6-17** (17.32 g, 37.9 mmol) in MeOH (250 mL) cooled to 0°C was added TFA (100 mL) over 1 h. After stirring at rt for 15 min, the mixture was diluted with toluene and evaporated *in vacuo* without heating. The residue was purified by column chromatography (silica 500 g, ether/hexane, 1:2) to give alcohol **6-18** (10.32 g, 79.4 %): IR (KBr) ν_{max} 3389, 2977, 2172, 1703, 1603, 1488, 1381 cm^{-1}. ^1H-NMR (270 MHz, $CDCl_3$),* δ 1.27 [1.29] (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.48 [1.33] (3H, d, J = 6.5 Hz, CH_3CHOH), 4.23 (2H, m, OCH_2CH_3), 4.82 [4.94] (1H, q [qd], J = 6.5 Hz [J = 6.5, 1.5 Hz], CH_3CHOH), 5.83 [5.85] (1H, d, J = 6.5 Hz, propargylic), 6.05 [6.14] (1H, d, J = 6.5 Hz [J = 6.5, 1.5 Hz], olefinic), 7.10 [7.08] (1H, br t, J = 8.0 Hz, aromatic), 7.23 (1H, br t, J = 8.0 Hz, aromatic), 7.50 (1H, dd, J = 8.0, 1.5 Hz, aromatic), 7.59 (1H, br d, J = 8.0 Hz, aromatic). * [ ] shows data of minor isomer, major : minor = 2 : 1 (by integration of ^1H NMR). MS (EI) *m/z* 343 (M^+). HRMS (EI) for $C_{19}H_{25}NO_3Si$ (M^+), calcd 343.1604, found 343.1598.



6-18 **6-20**

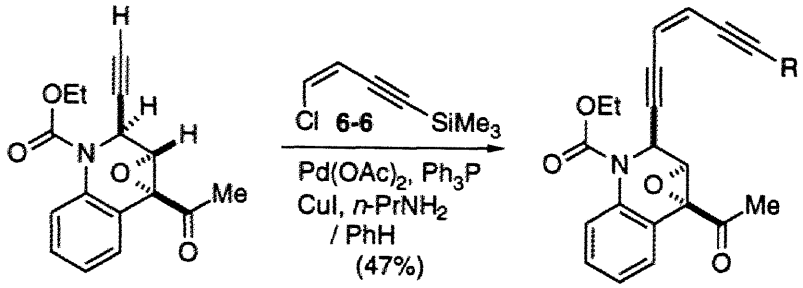
Epoxyketone 6-20. (1) To a solution of alcohol **6-18** (10.20 g, 29.7 mmol) and anhydrous Na_2HPO_4 (12.65 g, 89.1 mmol) in CH_2Cl_2 (200 mL) cooled to 0 °C was added MCPBA (80 %, 9.63 g, 44.6 mmol) portionwise over 25 min. After stirring at 0 °C for 3 h 20 min, sat. Na_2SO_3 solution

was added until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2). The combined organic layer was washed with sat. $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude epoxide **6-19**. (2) The resulting residue was dissolved with CH_2Cl_2 (80 mL), DMSO (160 mL), Et_3N (54.9 mL) and cooled to 0 °C. To this solution was added SO_3·Py (41.76 g, 262.0 mmol) portionwise over 40 min. After stirring at rt for 1 h 30 min, the mixture was cooled to 0 °C, poured into sat. NH_4Cl solution. The mixture was extracted with ether (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica 380 g, ether/hexane, 1:4) to give epoxy ketone **6-20** (8.02 g, 75. 8 % in 2 steps): IR (KBr) ν_{max} 2961, 2175, 1713, 1607, 1583, 1496 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.22 (9H, s, $Si(CH_3)_3$), 1.27 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 2.29 (3H, s, $C(O)CH_3$), 3.93 (1H, d, *J* = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.71 (1H, d, *J* = 2.9 Hz, propargylic), 7.13 (1H, br t, *J* = 7.8 Hz, aromatic), 7.30 (1H, td, *J* = 7.8, 1.5 Hz, aromatic), 7.38 (1H, br d, *J* = 7.8 Hz, aromatic), 7.56 (1H, br d, *J* = 7.8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.5, 14.3, 26.6, 43.6, 60.1, 62.8, 65.1, 92.2, 97.9, 122.1, 125.1, 127.2, 128.5, 128.8, 135.2, 154.7, 202.6. EIMS *m/z* 357 (M^+), 314. Anal. Calcd for $C_{19}H_{23}NO_4Si$: C, 63.87; H, 6.44; N, 3.92. Found: C, 63.95; H, 6.43; N, 3.74.



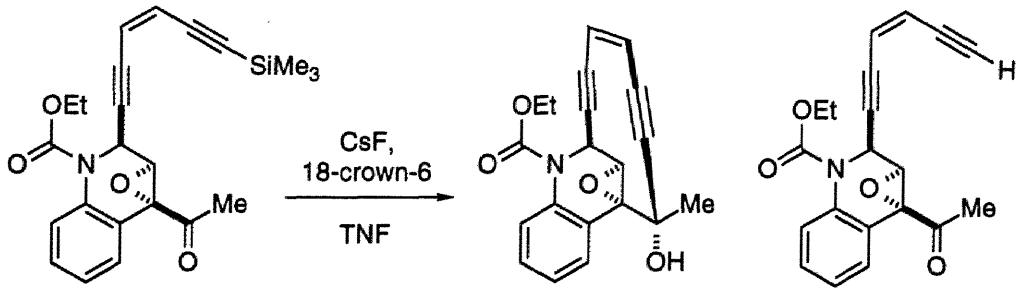
6-20 **6-21**

Compound 6-21. To a solution of epoxy ketone **6-20** (5.06 g, 14.2 mmol) in MeOH (150 mL) was added anhydrous K_2CO_3 (1.19 g). After stirring at rt for 1 h, ice-cold sat. NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (x3). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica 160 g, ether/hexane, 2:3) to give **6-21** (3.64 g, 85.2 %): Mp 114.5 - 116.0 °C. IR (KBr) ν_{max} 3278, 2987, 2126, 1704, 1581, 1497 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 2.20 (1H, d, *J* = 2.4 Hz, C≡C-*H*), 2.30 (3H, s, $C(O)CH_3$), 3.96 (1H, d, *J* = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.86 (1H, br t, *J* = 2.4 Hz, propargylic), 7.17 (1H, td, *J* = 8.0, 1.8 Hz, aromatic), 7.34 (1H, td, *J* = 8.0, 1.8 Hz, aromatic), 7.40 (1H, br d, *J* = 8.0 Hz, aromatic), 7.58 (1H, br d, *J* = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.3, 26.5, 42.7, 59.9, 62.9, 64.9, 74.5, 99.4, 121.8, 125.3, 127.1, 128.6, 129.0, 134.9, 154.6, 202.7. MS (EI) *m/z* 285 (M^+), 242. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.26; N, 4.91. Found: C, 67.50; H, 5.11; N, 4.73.



6-21 **6-22**

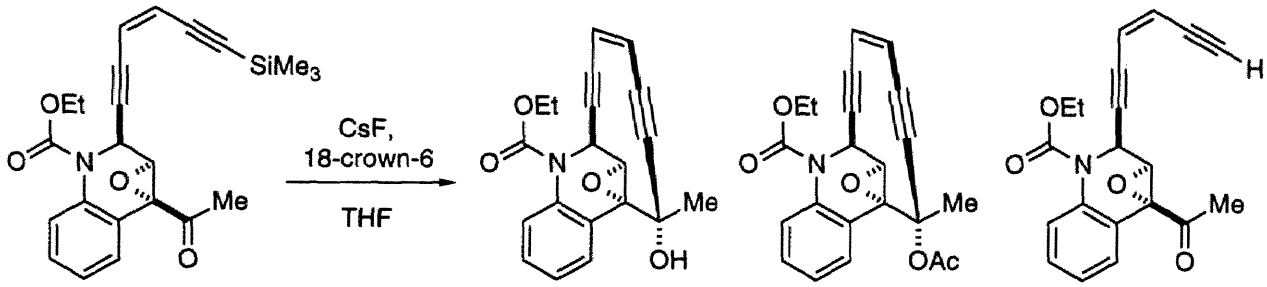
Enediyne 6-22. A mixture of acetylene **6-21** (1.05 g, 3.7 mmol), $Pd(OAc)_2$ (41.5 mg, 0.185 mmol), PPh_3 (96.9 mg, 0.370 mmol) and CuI (70.4 mg, 0.37 mmol) in dry benzene (30 mL) was degassed by two freeze-thaw cycles and covered under argon atmosphere. The (*Z*)-1-chloro-4-trimethylsilyl-1-buten-3-yne **6-6** (6.11 mL, 37.0 mmol) and *n*-$PrNH_2$ (0.76 mL, 9.25 mmol) were added. After stirring at rt for 1.5 h, the mixture was quenched with sat. NH_4Cl solution, extracted with ether (x3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 130 g, ether/hexane, 1:3) to give enediyne **6-22** (1.17 g, 77.6 %). IR (KBr) ν_{max} 2961, 2216, 2143, 1710, 1607, 1582, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.20 (9H, s, $Si(CH_3)_3$), 1.27 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.30 (3H, s, $C(O)CH_3$), 3.96 (1H, d, J = 2.9 Hz, epoxide), 4.22 (2H, m, OCH_2CH_3), 5.64 (1H, dd, J = 11.1, 1.8 Hz, CH=CHC≡CSi), 5.78 (1H, d, J = 11.1 Hz, CH=C*H*C≡CSi), 6.11 (1H, dd, J = 2.9, 1.8 Hz, propargylic), 7.16 (1H, br t, J = 8.0 Hz, aromatic), 7.25-7.48 (2H, m, aromatic), 7.61 (1H, br d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 14.3, 26.6, 43.6, 60.0, 62.9, 64.9, 82.9, 89.4, 101.4, 103.7, 119.1, 120.9, 121.7, 125.2, 127.1, 128.6, 129.0, 135.0, 154.7, 202.7. MS (EI) *m/z* 407 (M^+), 364. HRMS (EI) for $C_{23}H_{25}NO_4Si$ (M^+), calcd 407.1553, found 407.1539.



6-22 **6-24** **6-23**

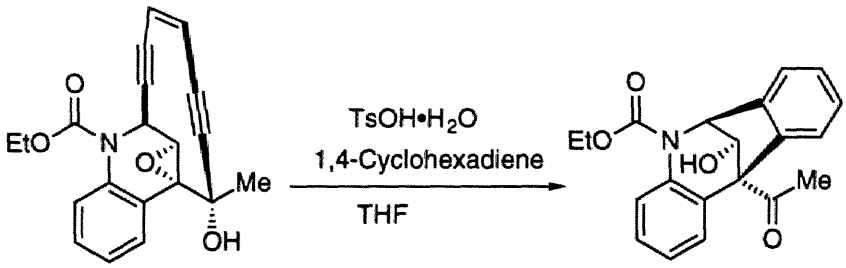
Cyclic Enediyne 6-24. In a dried two-necked flask was placed CsF (5.2 mg, 0.17 mmol), and heated at 100 °C for 1.5 h in *vacuo*. After cooling to rt, THF (2.5 mL) and enediyne **6-22** (69 mg, 0.17 mmol) in THF (1.5 mL) were added under argon. After stirring for 30 min, 18-crown-6 (76.1 mg, 0.288 mmol) in THF(1.0 mL) was added. The reaction mixture was stirred at rt for 21 h, poured into sat. NH_4Cl solution, and extracted with AcOEt (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane, 1:1) to give cyclic enediyne **6-24** (11 mg, 20 %)

and desilylated product **6-23** (12 mg, 21 %). **6-24**: IR (KBr) ν_{max} 3428, 2985, 2193, 2699, 1606, 1579, 1493 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.69 (3H, s, $CC{\equiv}C(OH)CH_3$), 4.02 (1H, d, *J* = 3.0 Hz, epoxide), 4.23 (2H, m, OCH_2CH_3), 5.64 (1H, dd, *J* = 10.0, 1.5 Hz, $CH{=}CHC{\equiv}CC(OH)CH_3$), 5.80 (1H, d, *J* = 10.0 Hz, $CH{=}CHC{\equiv}CC(OH)CH_3$), 5.82 (1H, m, propargylic), 7.19 (1H, br t, *J* = 8.0 Hz, aromatic), 7.31 (1H, td, *J* = 8.0, 1.5 Hz, aromatic), 7.37 (1H, br d, *J* = 8.0 Hz, aromatic), 8.75 (1H, br d, *J* = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.5, 25.4, 45.3, 61.9, 62.8, 66.2, 72.4, 89.0, 90.3, 93.0, 102.1, 122.3, 124.5, 125.1, 126.6, 126.8, 128.2, 131.7, 135.7. MS (EI) *m/z* 335 (M^+). HRMS(EI) for $C_{20}H_{17}NO_4$ (M^+), calcd 335.1157, found 335.1160. **6-23:** IR (KBr) ν_{max} 3287, 2980, 1711, 1494 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 2.30 (3H, s, $C(OH)CH_3$), 3.15 (1H, m, C≡C-*H*), 4.00 (1H, d, *J* = 2.9 Hz, epoxide), 4.24 (2H, m, OCH_2CH_3), 5.73 (2H, m, olefinic), 6.08 (1H, m, propargylic), 7.17 (1H, br t, *J* = 8.0 Hz, aromatic), 7.34 (1H, br t, *J* = 8.0, aromatic), 7.44 (1H, br d, *J* = 8.0 Hz, aromatic), 7.62 (1H, br d, *J* = 8.0 Hz, aromatic). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 26.6, 43.7, 60.1, 62.9, 65.0, 79.9, 82.7, 85.5, 89.4, 120.2, 120.6, 122.0, 125.0, 127.2, 128.2, 128.6, 135.2, 202.3 ppm. MS (EI) *m/z* 335 (M^+), 292. HRMS(EI) for $C_{20}H_{17}NO_4$ (M^+), 335.1157, found 335.1169.



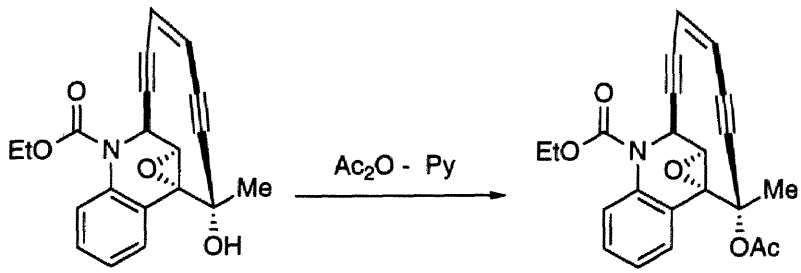
6-22 **6-24** **6-25** **6-23**

Cyclic enediyne 6-24 and *t*-acetate 6-25. In a dried two-necked flask was placed CsF (74.6 mg, 0.50 mmol), and heated at 100°C for 1.5 h *in vacuo*. After cooling to rt, THF (20 mL), enediyne **6-22** (100 mg, 0.245 mmol) in THF (2.5 mL) were added under Argon. After stirring for 30 min, 18-crown-6 (65 mg, 0.25 mmol) in THF (2.0 mL) was added. The reaction mixture was stirred at rt for 18 h and poured into sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane, 2:1) to give cyclic enediyne **6-24** (5.8 mg, 7.0 %), *t*-acetate **6-25** (9.5 mg, 10 %) and desilylated product **6-23** (6.5 mg, 7.9 %). **6-25:** IR (KBr) ν_{max} 2982, 2196, 1750, 1705, 1579, 1491 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.29 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.80 (3H, s, $C(OAc)\text{-}CH_3$), 2.21 (3H, s, $OC(O)CH_3$), 4.09 (1H, d, *J* = 3.0 Hz, epoxide), 4.23 (2H, m, OCH_2CH_3), 5.66 (1H, dd, *J* = 9.5, 1.5 Hz, $CH{=}CHC{\equiv}CC(CH_3)$), 5.83 (1H, d, *J* = 9.5 Hz, $CH{=}CHC{\equiv}CC(CH_3)$), 5.84 (1H, m, propargylic), 7.17 (1H, m, aromatic), 7.32 (1H, td, *J* = 8.0, 1.5 Hz, aromatic), 7.39 (1H, br d, *J* = 8.0, aromatic), 8.00 (1H, br d, *J* = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.5, 20.1, 22.0, 45.2, 61.0, 62.9, 65.4, 77.3, 90.5, 92.9, 99.3, 104.4, 122.9, 124.7, 125.0, 126.5, 127.2, 128.3, 130.0, 135.9, 169.1. MS (EI) *m/z* 377 (M^+). HRMS (EI) for $C_{22}H_{19}NO_5$ (M^+), calcd 377.1263, found 377.1251.



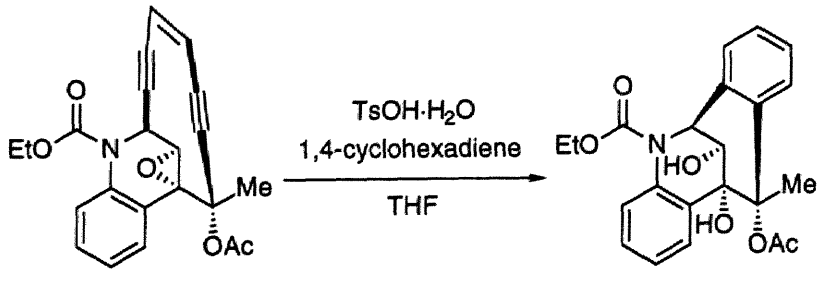
6-24 **6-31**

Bergman product 6-31. To s solution of enediyne **6-24** (5.0 mg, 0.15 mmol) and 1,4-cyclohexadiene (0.12 mL) was added $TsOH{\cdot}H_2O$ (2.9 mg, 0.15 mmol) in THF (0.25 mmol). After stirring at rt for 24 h, the mixture was subjected to short column (Na_2SO_4- SiO_2-Na_2SO_4), washed with AcOEt and concentrated. The residue was purified by preparative TLC (ether/hexane, 2:1) to give **6-31** (3.9 mg, 78 %). IR (KBr) ν_{max} 3415, 2992, 1700, 1484 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.45 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.51 (3H, s, $C(O)CH_3$), 2.61 (1H, d, J = 9.5 Hz, CHO*H*), 4.36 (2H, m, OCH_2CH_3), 4.52 (1H, dd, J = 9.5, 4.5 Hz, C*H*OH), 5.75 (1H, d, J = 4.5 Hz, benzylic), 6.96-7.10 (2H, m, aromatic), 7.18-7.31 (3H, m, aromatic), 7.40 (1H, br d, J = 7.0, aromatic), 7.58 (1H, br d, J = 7.0 Hz, aromatic), 8.23 (1H, d, J = 8.0 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.6, 29.4, 60.6, 62.7, 64.6, 72.1, 122.2, 123.9, 124.0, 124.9, 125.5, 126.6, 128.2, 128.5, 129.6, 134.8, 135.0, 145.1, 154.5, 207.4. MS (EI) *m/z* 337 (M^+), 294. HRMS (EI) for $C_{20}H_{19}NO_4$ (M^+), calcd 337.1314, found 337.1305.



6-24 **6-25**

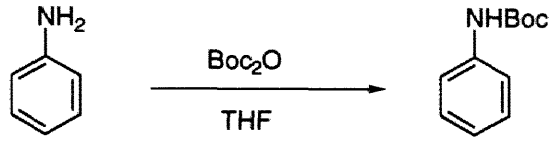
***t*-Acetate 6-25.** To a solution of **6-24** (17.1 mg, 0.051 mmol) in pyridine (0.8 mL) was added Ac_2O (0.8 mL). After stirring at rt for 34 h, the mixture was diluted with toluene and evaporated *in vacuo*. The residue was purified by preparative TLC to give acetate **6-25** (8.2 mg, 43 %) and unreacted **6-24** (4.8 mg, 28 %).



6-25 **6-32**

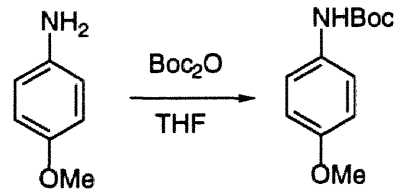
Bergman product 6-32. To a solution of **6-25** (8.2 mg, 0.022 mmol) and 1,4-cyclohexadiene in THF (0.85 mmol) was added $TsOH \cdot H_2O$ (4.6 mg, 0.024 mmol) in THF (0.25 mL). After stirring at rt for 21 h, the mixture was quenched with sat. $NaHCO_3$ solution and extracted with AcOEt (x3). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC to give **6-32** (6.5 mg, 75 %). IR (KBr) ν_{max} 3457, 3397, 2977, 1699, 1490 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.93 (3H, s, $C(OAc)CH_3$), 2.16 (3H, s, $OCOCH_3$), 3.04 (1H, br s, C-O*H*), 4.26 (1H, d, J = 4.5 Hz, C*H*OH), 4.36 (2H, q, J = 7.0 Hz, OCH_2CH_3), 6.03 (1H, d, J = 4.5 Hz, benzylic), 6.55 (1H, s, O*H*), 7.00 (1H, br t, J = 8.0 Hz, aromatic), 7.15 (1H, br t, J = 8.0 Hz, aromatic), 7.22-7.38 (4H, m, aromatic), 7.54 (1H, m, aromatic), 7.68 (1H, br d, J = 8.0 Hz, aromatic). MS (EI) *m/z* 397 (M^+), 337. HRMS(EI) for $C_{22}H_{23}NO_6$ (M^+), 397.1525, found 397.1535.

Experimental for Chapter 7



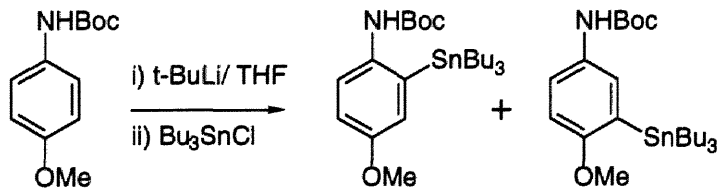
aniline **7-6** [13061]

***N*-Boc-aniline 7-6**. Aniline (5.11g, 54.8 mmol) and Boc_2O (14.4 mL, 63.0 mmol) were dissolved in THF (40 mL). After heating under reflux for 1.5 h, the mixture was concentrated under reduced pressure. The residue was crystallized from hot hexane to give *N*-Boc-aniline **7-6** (10.19 g, 96 %). IR (KBr) ν_{max} 3314, 2985, 1690, 1598, 1532, 1441, 1160, 1057 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.52 (9H, s, $OC(CH_3)_3$), 6.52 (1H, br, N*H*), 7.02 (1H, tt, J = 7, 1.5 Hz, aromatic), 7.23-7.40 (4H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 28.4, 80.5, 118.5, 123.0, 129.0, 138.3, 152.8.



7-8 **7-10** [13025]

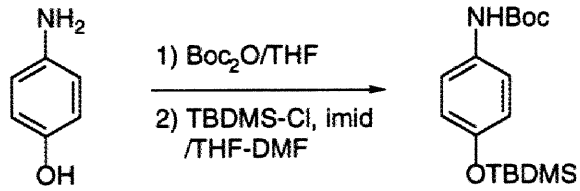
***N*-Boc-anisidine 7-10**. *p*-Anisidine **7-8** (5.00 g, 40.2 mmol) was dissolved in THF (40 mL). To this solution was added Boc_2O (9.74 g, 44.6 mmol) and heated at reflux temperature for 30 min. After cooling to rt, the mixture was evaporated under reduced pressure. The residue was dissolved with AcOEt, washed with 10 % tartaric acid solution (x2), water (x2) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was crystallized from hexane to give **7-10** (8.29 g, 92 %). Mp 93.5-95.0 °C. ^1H NMR (270 MHz, $CDCl_3$) δ 1.51 (9H, s, $C(CH_3)_3$), 3.77 (3H, s, OCH_3), 6.84 (2H, br d, J = 9 Hz, aromatic), 7.25 (2H, br d, J = 9 Hz, aromatic). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found C, 64.77; H, 7.77; N, 6.28.



7-10 **7-12a** **7-12b** [13026]

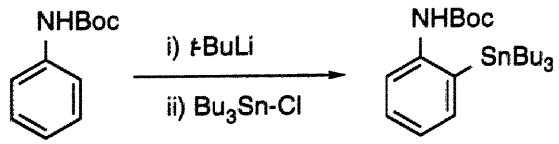
Tin compound 7-12. To a solution of **7-10** (100 mg, 0.447 mmol) in THF (4 mL) cooled to -78 °C was added *t*-BuLi (2.2 M in hexane, 0.50 mL, 1.1 mmol). After stirring at -78 °C for 2 min, the mixture was stirred at -20 °C for 1 h 40 min. To this solution was added *n*-Bu_3Sn-Cl (0.18 mL, 0.67 mmol) in THF (1 mL). The solution was stirred at -20° C for 1 h 30 min and for additional 45 min at 0

°C. The mixture was poured into ice-cold aq. $NaHCO_3$ solution and extracted with AcOEt (x3). The combined organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 17.5 g, ether/hexane = 1:10 → 1:5) to give **7-12a** (90.8 mg, 40 %) and **7-12b** (16.8 mg, 7.3 %). **7-12a:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (9H, t, *J* = 7 Hz, CH_3CH_2 x3), 1.03-1.14 (6H, m, CH_2 x2), 1.33 (6H, m, CH_2 x3), 1.49 (9H, s, $C(CH_3)_3$), 3.78 (3H, s, $ArOCH_3$,), 6.11 (1H, br, N*H*), 6.82 (1H, dd, *J* = 9, 3 Hz, aromatic), 6.91 (1H, d, *J* = 3 Hz, aromatic), 7.47 (1H, br d, *J* = 8.5 Hz, aromatic). **7-12b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (9H, t, *J* = 7 Hz, CH_3CH_2 x3), 0.96-1.06 (6H, m, CH_2 x3), 1.30 (6H, m, CH_2 x3), 3.73 (3H, s, $ArOCH_3$), 6.33 (1H, br, N*H*), 6.74 (1H, d, *J* = 4 Hz, aromatic), 7.05 (1H, d, *J* = 4 Hz, aromatic), 7.45 (1H, br, aromatic).



7-9 **7-11** [15081]

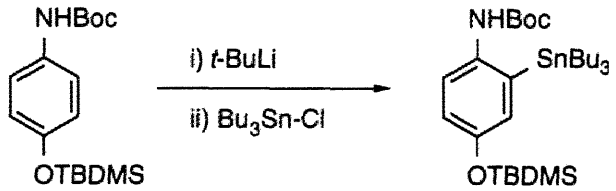
Compound 7-11. (1) To a suspension of *p*-aminophenol (5.00 g, 45.8 mmol) in THF (50 mL) was added Boc_2O (10.9 mL, 50.4 mmol). (This reaction was exo-thermic and the starting materials became gradually soluble during the reaction). After stirring at rt for 3 h, the mixture was concentrated under reduced pressure to afford a crude product. This material was sufficiently pure for use in the next reaction. (2) The resulting residue was dissolved in DMF (10 mL) and CH_2Cl_2 (50 mL). To this solution were added TBDMS-Cl (7.59 g, 50.4 mmol) and imidazole (6.85 g, 100 mmol). After stirring at rt for 3 h, the mixture was mixed with water and extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 350 g, ether/hexane = 1:10) to give **7-11** (14.4 g, 97 %). Mp 90-90.5 °C. IR (KBr) ν_{max} 3344, 2963, 2860, 1705, 1507, 1256, 1168 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.16 (6H, s, $Si(CH_3)_3$), 0.97 (9H, s, $Si(CH_3)_3$), 1.50 (9H, s, $OC(CH_3)_3$), 6.45 (1H, br s, N*H*), 6.76 (2H, br d, *J* = 9 Hz, aromatic), 7.20 (2H, br d, *J* = 9 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.5, 18.1, 25.7, 28.3, 80.1, 120.2, 131.9, 151.3, 153.0. Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found C, 63.24; H, 9.11; N, 4.35.



7-6 **7-7** [13069]

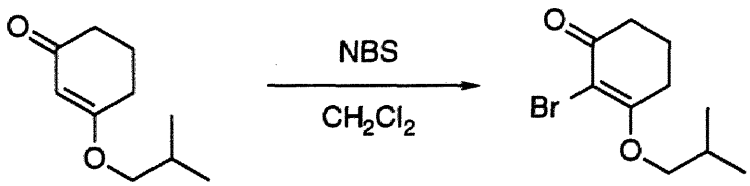
Tin compound 7-7. To a solution of *N*-Boc-aniline **7-6** (8.00 g, 41.4 mmol) in THF (200 mL) cooled to -78 °C was added *t*-BuLi (1.65 M in hexane, 62.7 mL, 103 mmol). After stirring 35

min, the reaction mixture was warmed to -20 °C. After stirring at -20 °C for 2 h 20 min, *n*-Bu_3Sn-Cl (16.8 mL, 62.1 mmol) in THF (30 mL) was added dropwise over 30 min. After stirring at -20 °C for 1 h 15 min, the reaction mixture was poured into aq. $NaHCO_3$ solution and extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 600 g, ether/hexane = 1:20) to give **7-7** (8.08 g, 51 %). IR (KBr) ν_{max} 3440, 3339, 2956, 1740, 1510, 1436, 1159 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (9H, t, *J* = 7 Hz, ($CH_3CH_2CH_2CH_2)_3Sn$), 1.06-1.14 (6H, m, CH_2 x3), 1.34 (6H, m, CH_2x3), 1.51 (9H, s, *t-Bu*), 1.45-1.60 (6H, m, CH_2 x3), 6.28 (1H, br s, N*H*), 7.06 (1H, td, *J* = 8, 1.5 Hz, aromatic), 7.24-7.36 (2H, m, aromatic), 7.69 (1H, br d, *J* = 8 Hz, aromatic). Anal. Calcd for $C_{23}H_{41}NO_2Sn$: C, 57.28; H, 8.57; N, 2.90. Found C, 57.28; H, 9.20; N, 2.87.



7-11 **7-13a** [13104]

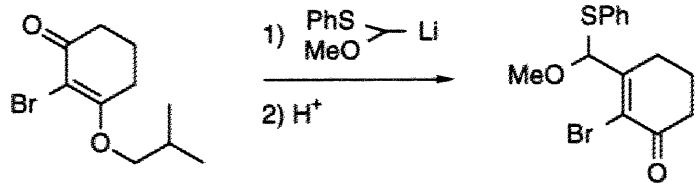
Tin Compound 7-13a. To a solution of **7-11** (10.0 g, 30.9 mmol) in THF (250 mL) cooled to -78 °C was added *t*-BuLi (1.65 M in hexane, 46.8 mL, 77.3 mmol) over 15 min. After stirring at -78 °C for 25 min, the mixture was stirred at -20 °C for 3 h. To this solution was added *n*-Bu_3Sn-Cl (12.5 mL, 46.3 mmol) in THF (30 mL) over 25 min. The solution was stirred at -20° C for 2 h 20 min. The mixture was poured into ice-cold aq. $NaHCO_3$ solution and extracted with ether (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 500 g, ether/hexane = 1:10) to give **7-13a** (13.0 g, 71 %). IR (KBr) ν_{max} 3442, 3344, 2930, 1736, 1585, 1497, 1250, 1156 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.18 (6H, s, $Si(CH_3)_3$), 0.90 (9H, t, *J* = 7 Hz, CH_3CH_2 x3), 0.98 (9H, s, $SiC(CH_3)_3$), 1.04-1.12 (6H, m, CH_2 x3), 1.34 (6H, m, CH_2 x3), 1.50 (9H, s, NCOO*tBu*), 1.46-1.60 (6H, m, CH_2 x3), 6.11 (1H, br, N*H*), 6.76 (1H, dd, *J* = 8.5, 3 Hz, aromatic), 6.83 (1H, d, *J* = 3 Hz, aromatic), 7.42 (1H, br d, *J* = 8.5 Hz, aromatic). Anal. Calcd for $C_{29}H_{55}NO_3SiSn$: C, 56.87; H, 9.05; N, 2.29. Found C, 56.64; H, 9.56; N, 2.19.



7-15 **7-16** [13021]

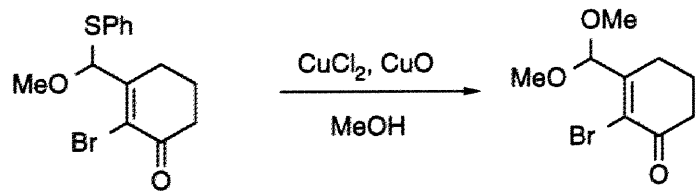
α-Bromo enone 7-16. To a solution of **7-15** (25.0 g, 0.148 mol) in CH_2Cl_2 (125 mL) cooled to 0 °C was added NBS (27.13 g, 0.152 mol) portionwise. After the mixture was stirred at 5-15 °C for 1

h 10 min, the mixture was filtrated, concentrated under reduced pressure. The residue was dissolved with AcOEt, washed with aq. $NaHCO_3$ (x3), water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. This crude product **7-16** was sufficient pure for use of next reaction. IR (KBr) ν_{max} 2964, 1656, 1580, 1267, 1015 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.04 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 1.99-2.14 (3H, m, CH_2, CH), 2.54 (2H, dd, J = 6 Hz, CH_2), 2.69 (2H, t, J= 6 Hz, CH_2), 3.90 (2H, d, J = 6.5 Hz, OCH_2). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 18.8, 20.5, 27.3, 28.6, 36.6, 75.3, 102.8, 172.9, 191.1. MS (EI) m/z 248 (M^+: ^{81}Br), 246 (M^+: ^{79}Br), 192 (M^+: ^{81}Br-56), 190 (M^+: ^{79}Br-56). Anal. Calcd for $C_9H_{13}O_3Br$: C, 43.40; H, 5.26. Found C, 43.38; H, 5.38.



7-16 **7-17** [13054]

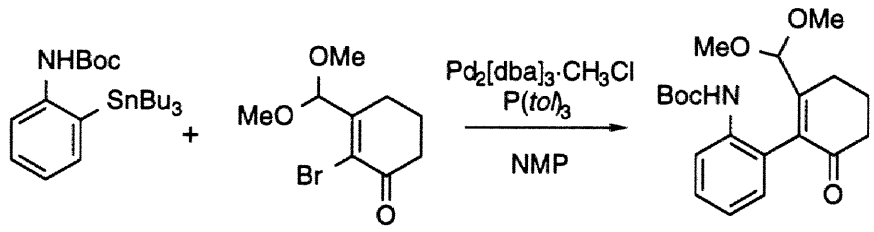
Monothioacetal 7-17. To a solution of methoxymethyl phenylsulfide (7.74 mL, 52.6 mmol) in THF (125 mL) cooled to -78 °C was added *n*-BuLi (2.0 M in hexane, 21.0 mL, 52.6 mmol) over 10 min. The mixture was stirred at -78 °C for 30 min and then at -50 °C for 20 min. After the mixture was cooled to -78 °C again, **7-16** (10.00 g, 40.4 mmol) in THF (37 mL) was added over 15 min. After stirring at -50 °C for 50 min, the mixture was poured into sat. NH_4Cl solution, extracted with ether-AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in ether-AcOEt (800 mL) and mixed with water (200 mL) and $HClO_4$ (6 mL). The mixture was stirred at rt for 10 min, and washed with water, sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 450 g, ether/hexane = 1:4) to give **7-17** (10.94 g, 83 %).



7-17 **7-18** [13092]

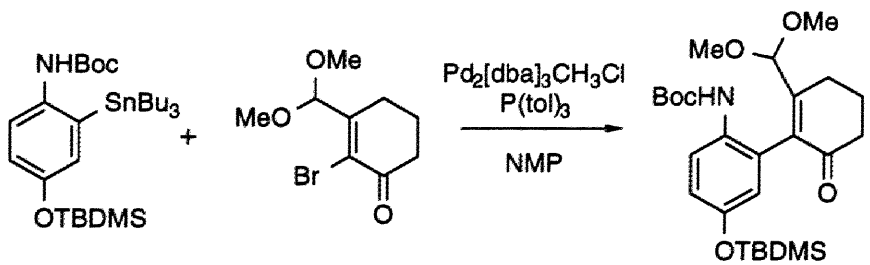
Acetal 7-18. The monothioacetal **7-17** (10.94 g, 33.43 mmol) was dissolved in MeOH (200 mL). To the solution were added $CuCl_2$ (5.39 g, 40.1 mmol) and CuO (6.37 g, 80.2 mmol). The mixture was heated at reflux temperature for 1.5 h. After cooling to rt, the solution was filtrated through the pad of Super-Cel®, concentrated under reduced pressure. The residue was dissolved with CH_2Cl_2 and water, extracted with CH_2Cl_2. The combined organic layer was filtrated through the pad of Super-Cel®, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 300 g, ether/hexane = 1:3 → 1:2) to give **7-18** (8.12 g,

97 %). IR (KBr) ν_{max} 2946, 2829, 1697, 1604, 1465, 1355, 1064 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.02 (2H, m, CH_2), 2.56 (2H, t, J = 6 Hz, CH_2), 2.64 (2H, t, J = 6.5 Hz, CH_2), 3.47 (6H, s, OCH_3 x2), 5.37 (1H, s, $CH(OMe)_2$). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.7, 26.1, 38.3, 55.6, 105.7, 123.1, 157.0, 191.4. MS (EI) *m/z* 219 (M: ^{81}Br-31), 217 (M: ^{79}Br -31). Anal. Calcd for $C_9H_{13}O_3Br$: C, 43.40; H, 5.26.; N, 0.00. Found C, 43.38; H, 5.38; N, 0.00.



7-8 **7-18** **7-19** [13097]

Compound 7-19. In a dried flask were placed **7-18** (200 mg, 0.80 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (16.5 mg, 0.016 mmol), P(*o*-tol)$_3$ (39.0 mg, 0.128 mmol) and NMP (2 mL), and the whole mixture was degassed, covered with argon, and stirred at rt for 20 min. To this solution was added a solution of aryltin **7-8** (460 mg, 0.95 mmol) in NMP (3 mL). The mixture was stirred at 70 °C for 2 h. After cooling to rt, the reaction was quenched with ice-cold aq. $NaHCO_3$ solution, and the mixture was extracted with Et_2O (x3). The combined organic layer was washed with water (x2) and brine (x2), then concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane = 1:2 → 1:1) to give **7-19** (225 mg, 78 %). Mp 106-107.5 °C. IR (KBr) ν_{max} 3333, 2937, 2831, 1727, 1671, 1518, 1448, 1367, 1160. ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (9H, s, *t-Bu*), 2.11 (2H, m, CH_2), 2.60 (4H, t, J = 6.5 Hz, CH_2 x2), 3.22 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 4.41 (1H, s, $CH(OMe)_2$), 6.26 (1H, br, N*H*), 6.94 (1H, dd, J = 7.5, 1.5 Hz, aromatic), 7.10 (1H, td, J = 7.5, 1 Hz, aromatic), 7.34 (1H, td, J = 8, 1.5 Hz, aromatic), 7.83 (1H, br d, J = 8 Hz, aromatic). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 23.3, 28.3, 38.5, 55.7, 80.2, 104.3, 122.6, 123.7, 126.0, 129.1, 130.6, 135.4, 136.4, 153.2, 157.5, 199.0. MS (EI) *m/z* 361 (M^+). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found C, 66.56; H, 7.37; N, 3.77.

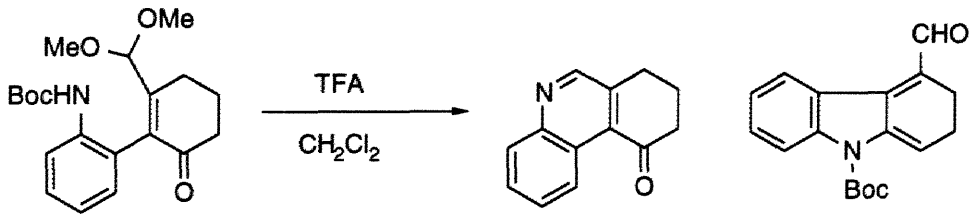


7-13a **7-18** **7-20** [16009][16031]

Compound 7-20. NMP as a solvent (entry 4 in **Table 7-1**): In a dried flask were placed bromide **7-18** (249 mg, 1.00 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (41 mg, 0.04 mmol), P(*o*-tol)$_3$ (97 mg, 0.32 mmol) and NMP (4 mL), and the whole mixture was degassed, covered with argon, and stirred at rt for 30 min. To this solution was added aryltin **7-13a** (918 mg, 1.50 mmol) in NMP (2.5 mL). The

mixture was stirred at 75 °C for 1.5 h. After cooled to rt, the reaction was quenched with ice-cold aq. $NaHCO_3$ solution, and the mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), and concentrated under reduced pressure. The residue was purified by column chromatography (silica 60 g, ether/hexane = 1:3 → 1:2) to give **7-20** (255 mg, 52 %). Mp 103.5-105 °C. IR (KBr) ν_{max} 3409, 2931, 2860, 1723, 1674, 1517, 1164 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.17 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.96 (9H, s, $SiC(CH_3)_3$), 1.43 (9H, s, *O-t-Bu*), 2.10 (2H, m, CH_2), 2.58 (4H, m, CH_2x2), 3.21 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 4.48 (1H, s, $CH(OMe)_2$), 6.08 (1H, br s, NH), 6.47 (1H, d, J = 3 Hz, aromatic), 6.82 (1H, dd, J = 9, 3 Hz, aromatic), 7.54 (1H, br d, J = 9 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.5, -4.4, 18.1, 22.1, 23.2, 25.6, 28.2, 38.4, 55.5, 55.6, 79.8, 104.2, 120.2, 121.9, 125.3, 128.7, 129.8, 135.5, 152.1, 153.7, 157.0, 198.8. Anal. Calcd for $C_{26}H_{41}NO_6Si$: C, 63.51; H, 8.40; N, 2.85. Found C, 63.49; H, 8.36; N, 2.66.

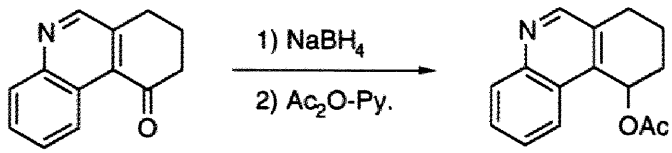
Toluene as a solvent (entry 6 in **Table 7-1**): In a dried flask were placed bromide **7-18** (249 mg, 1.00 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (41 mg, 0.04 mmol) P(*o*-tol)$_3$(41 mg, 0.04 mmol) and toluene (4 mL), and the whole mixture was degassed by two freeze-thaw cycles, covered with argon, and stirred at rt for 2 h 30 min. To this solution was added aryltin **7-13a** (918 mg, 1.50 mmol) in toluene (1.5 + 0.5 mL). The mixture was stirred at 80 °C for 2 h. After cooled to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica 60 g, ether/hexane = 1:5 → 1:3) to give **7-20** (341 mg, 69 %).



7-19 **7-22** **7-26** [15024]

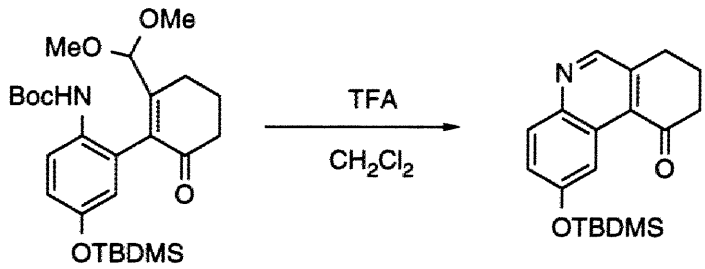
Quinoline 7-22. The acetal **7-19** (520 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. To this solution was added TFA (0.4 mL). After stirring at 0 °C for 1 h, the mixture was diluted with benzene (10 mL), and concentrated under reduced pressure. The residue was purified by column chromatography (silica 30 g, ether/hexane = 1:1 → 3:1) to give quinoline **7-22** (228 mg, 81 %) and **7-26** (37 mg, 9 %). **7-22:** IR (KBr) ν_{max} 2958, 1678, 1500, 1307, 1182, 1125 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.24 (2H, m, $CH_2CH_2CH_2C{=}O$), 2.79 (2H, dd, J = 7, 6 Hz, Ar-CH_2), 3.09 (2H, d, J = 6 Hz, CH_2-C=O), 7.60-7.72 (2H, m, aromatic), 8.08 (1H, dd, J = 7.5, 2 Hz, aromatic), 8.87 (1H, s, N=CH), 9.22 (1H, dd, J = 8, 2 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.7, 27.7, 40.6, 123.9, 126.0, 128.8, 129.1, 129.2, 132.0, 137.7, 147.4, 151.8, 200.1. HRMS (EI) for $C_{13}H_{11}NO$ (M^+), calcd 197.0840, found 197.0837. **7-26**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.91 (9H, s, *t-Bu*), 2.93 (2H, td, J = 9, 5 Hz, CH_2), 3.50 (2H, t, J = 9 Hz, CH_2), 7.08 (1H, t, J = 5 Hz, C=CH-CH_2), 7.47 (2H, m, aromatic), 8.10 (2H, m, aromatic), 9.66 (1H, s, -CHO). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.9, 25.0,

28.2, 76.9, 84.4, 115.0, 122.6, 123.0, 123.5, 126.1, 136.1, 137.3, 138.1, 146.9, 150.2, 191.3. MS (EI) *m/z* 297 (M^+), 241.



7-22 **7-25** [16034]

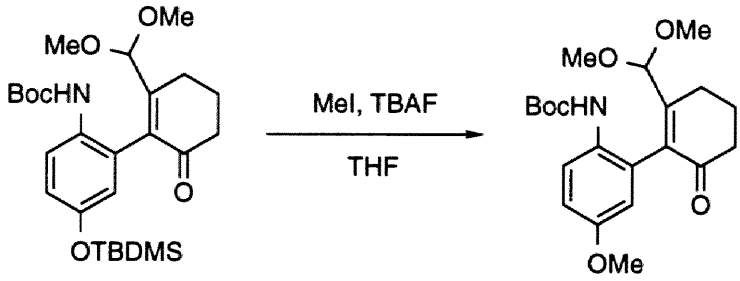
Acetate 7-25. The quinoline derivative **7-22** (26 mg, 0.13 mmol) was dissolved in MeOH (1.0 mL) and the methanolic solution was cooled to 0 °C. To this solution was added $NaBH_4$ (4 mg, 0.13 mmol). After stirring for 5 min, the reaction was quenched with 1 drop of AcOH, and the mixture was evaporated. The residue was dissolved with water, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was dissolved in Ac_2O (1 mL)-Py (1 mL) and stirred at rt for 2 h. The mixture was diluted with toluene and evaporated *in vacuo*. The residue was purified by preparative PLC (silica, ether/hexane = 2:1) to give the acetate **7-25** (31 mg, 100 %). IR (KBr) ν_{max} 2916, 2849, 1729, 1507, 1370, 1229 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.89-2.03 (3H, m, C*H*-CH_2), 2.05 (3H, s, OCOCH_3), 2.21-2.32 (1H, m, C*H*), 2.76-2.93 (1H, m, Ar-C$H_A$$H_B$), 3.03 (1H, dt, *J* = 17, 3 Hz, Ar-$CH_A$$H_B$), 6.57 (1H, m, C*H*-OAc), 7.53 (1H, ddd, *J* = 8, 7, 1 Hz, aromatic), 7.64 (1H, ddd, *J* = 8, 7, 1 Hz, aromatic), 7.76 (1H, dd, *J* = 8, 1 Hz, aromatic), 8.07 (1H, dd, *J* = 8, 1 Hz, aromatic), 8.70 (1H, s, C=N*H*). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.3, 21.2, 26.8, 28.8, 64.5, 122.4, 126.6, 127.3, 128.4, 130.1, 131.2, 136.8, 146.9, 152.5, 170.3. MS (EI) *m/z* 241 (M^+). HRMS (EI) for $C_{15}H_{15}NO_2$ (M^+), calcd 241.1102, found 241.1117.



7-20 **7-23** [16011]

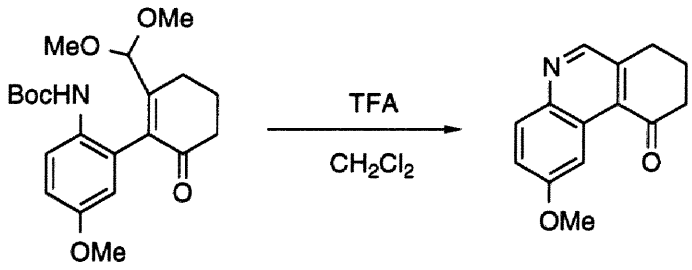
Quinoline 7-23. The acetal **7-20** (200 mg, 0.41 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C. To this solution was added TFA (0.10 mL). After stirring at 0 °C for 20 min, the reaction was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 10g, ether/hexane = 1:1) to give **7-23** (95 mg, 72 %). IR (KBr) ν_{max} 2955, 2856, 1685, 1612, 1500, 1427, 1263, 1238, 941, 858 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.33 (6H, s, Si(CH_3)$_2$), 1.03 (9H, s, Si-*t-Bu*), 2.25 (2H, quintet, *J* = 6.5 Hz, CH_2-CH_2-C=O), 2.81 (2H, t, *J* = 6.5 Hz, CH_2), 3.12 (2H, t, *J* = 6 Hz, CH_2), 7.28 (1H, dd, *J* = 9, 2.5 Hz, aromatic), 7.97 (1H, d, *J* = 9 Hz, aromatic), 8.74 (1H, s, N=C*H*), 8.81 (1H, d, *J* = 2.5 Hz, aromatic). ^{13}C NMR (67.9 MHz,

$CDCl_3$) δ -4.5, 18.2, 22.8, 25.6, 27.8, 40.8, 112.9, 124.4, 125.2, 130.3, 131.0, 138.0, 144.3, 149.4, 156.6, 200.3. MS (EI) *m/z* 327 (M^+), 270 (M-57). Anal. Calcd for $C_{19}H_{25}NO_2SiCl$: C, 69.68; H, 7.69; N, 4.28. Found C, 69.60; H, 7.61; N, 4.03.



7-20 **7-21** [15041]

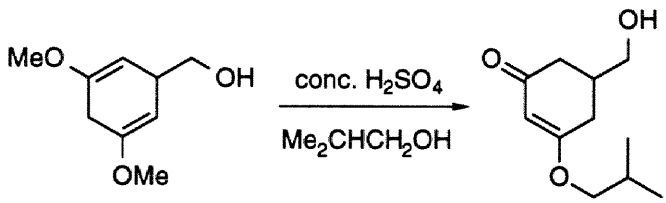
Compound 7-21. The TBDMS ether **7-20** was dissolved in THF (15 mL). To this solution was added MeI (0.17 mL, 2.73 mmol). TBAF (1.0 M in THF, 0.54 mL, 0.54 mmol) was added dropwise. After stirring for 25 min, the reaction was quenched with sat. NH_4Cl solution, and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:1 → 3:1) to give methyl ether **7-21** (165 mg, 77 %). IR (KBr) ν_{max} 3347, 2935, 2832, 1716, 1673, 1509, 1164, 1072 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.42 (9H, s, *t-BuO*), 2.10 (2H, m, C=C-CH_2-CH_2) 2.59 (4H, m, C=C-CH_2), 3.21 (3H, s, CH_3O-CH), 3.31 (3H, s, CH_3O-CH), 3.77 (3H, CH_3O-Ar), 4.48 (1H, br s, $CH(OMe)_2$), 6.06 (1H, br s, NH), 6.54 (1H, d, *J* = 3 Hz, aromatic), 6.90 (1H, dd, *J* = 9, 3 Hz, aromatic), 7.56 (1H, br d, *J* = 9 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.1, 23.3, 28.2, 38.4, 55.4, 55.6, 55.7, 79.8, 104.2, 114.5, 115.7, 126.0, 129.3, 135.7, 153.8, 156.4, 157.3, 198.9.



7-21 **7-24** [15046]

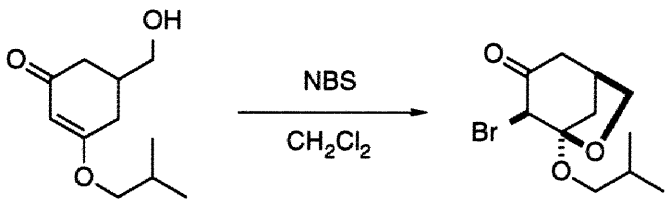
Compound 7-24. The acetal **7-21** (165 mg, 0.42 mmol) was dissolved with CH_2Cl_2 (8 mL) and cooled to 0 °C. To this solution was added TFA (0.16 mL). After stirring at 0 °C for 30 min, the solution was diluted with benzene (4 mL) and evaporated under reduced pressure. The residue was purified by column chromatography (silica 10 g, ether/hexane = 5:1) to give quinoline derivative **7-24** (71 mg, 74 %). IR (KBr) ν_{max} 2964, 1668, 1615, 1504, 1230 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.26 (2H, m, Ar-CH_2-CH_2), 2.82 (2H, dd, *J* = 7, 6 Hz, Ar-CH_2 or CH_2-C=O), 3.12 (2H, t, *J* = 6 Hz, Ar-CH_2 or CH_2-C=O), 3.98 (3H, s, OCH_3),7.35 (1H, dd, *J* = 9, 3 Hz, aromatic), 7.98 (1H, d, *J* = 9 Hz,

aromatic), 8.75 (1H, br s, N=C*H*), 8.77 (1H, d, *J* = 3 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.9, 28.0, 41.0, 55.6, 104.1, 121.5, 125.6, 130.6, 131.0, 138.2, 144.4, 149.1, 160.4, 200.7. HRMS (EI) for $C_{14}H_{13}NO_2$ (M^+), calcd 227.0946, found 227.0935.



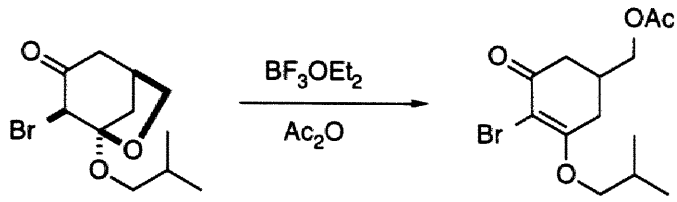
7-27 **7-28** [15080]

Compound 7-28. To a solution of **7-27** (2.04 g, 12 mmol) in 2-methyl-1-pronanol (60 mL) cooled to 0 °C was added conc. H_2SO_4 (1.2 mL) dropwise. After stirring at 0 °C for 20 min, the mixture was poured into ice-cold sat. $NaHCO_3$ solution (100 mL), and extracted with CH_2Cl_2 (x3). The combined organic layer was washed with water (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 80 g, AcOEt) to give **7-28** (1.67 g, 70 %). IR (KBr) ν_{max} 3424, 2962, 1636, 1601, 1386, 1214 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (6H, d, *J* = 7 Hz, $OCH_2C(CH_3)_2$), 2.03 (1H, m, $OCH_2CH(CH_3)_2$), 2.11-2.56 (5H, m, CH_2CHCH_2), 3.54-3.69 (4H, m, CH_2-OH, $OCH_2CH(CH_3)_2$), 5.34 (1H, s, olefinic). MS (EI) *m/z* 198 (M^+), 167, 143. HRMS (EI) for $C_{11}H_{18}O_3$ (M^+), calcd 198.1255, found 198.1251.



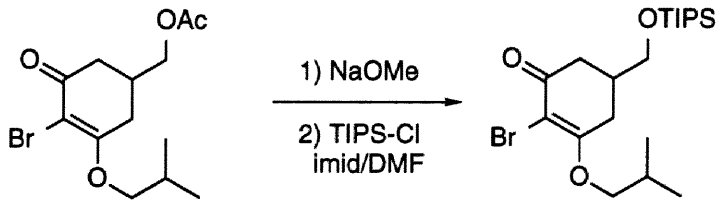
7-28 **7-29** [15162]

Compound 7-29. The alcohol **7-28** (2.69 g, 13.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and the CH_2Cl_2 solution was cooled to 0 °C. To this solution was added NBS (2.53 g, 14.2 mmol) portionwise. After stirring at 0 °C, the mixture was poured into ice-cold sat. $NaHCO_3$, and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 140 g, ether/hexane = 1:3) to give **7-29** (3.54 g, 94 %). IR (KBr) ν_{max} 2963, 2877, 1720, 1328, 1134, 1038 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (6H, d, *J* = 6.5 Hz, $OCH_2CH(CH_3)_2$), 1.88 (1H, m, $OCH_2CH(CH_3)_2$), 2.23 (1H, ddt, *J* = 12, 4, 2.5 Hz, CH-CH_AH_B-C-CBr), 2.47 (1H, br d, *J* = 17 Hz, O=C-CH_AH_B), 2.58-2.69 (2H, m, O=C-CH_AH_B-CH), 2.92 (1H, ddd, *J* = 16.5, 4, 2 Hz, CH-CH_AH_B-C-CBr), 3.36 (2H, d, *J* = 6.5 Hz, O-$CH_2CH(CH_3)_2$), 3.76 (1H, dd, *J* = 8, 1.5 Hz O-CH_AH_B-CH), 4.10 (1H, ddd, *J* = 8, 4, 2 Hz, O-CH_AH_B-CH), 4.32 (1H, t, *J* = 1.5 Hz, CH-Br). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.0, 28.2, 33.0, 34.1, 41.9, 51.4, 69.0, 73.6, 108.1, 200.9. MS (EI) m/z 278 (M^+: ^{81}Br), 276 (M^+: ^{79}Br), 222, 220. HRMS (EI) for $C_{11}H_{17}O_3Br$ (M^+), calcd 276.0361, found 276.0348.



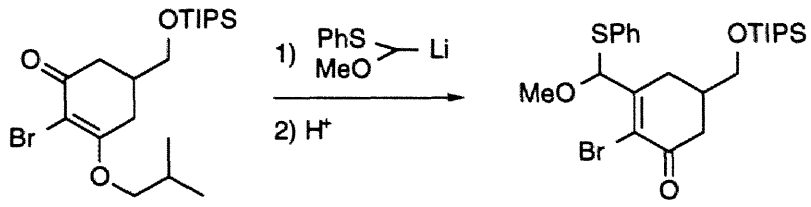
7-29 **7-30** [15169]

Compound 7-30. The acetal **7-29** (3.54 g, 12.7 mmol) was dissolved in Ac_2O (53 mL) and the solution was cooled to 0 °C. To this solution was added $BF_3 \cdot OEt_2$ (4.3 mL, 38 mmol). After stirring at 0 °C for 50 min, the mixture was poured into sat. $NaHCO_3$ solution, and extracted with AcOEt (x3). The combined organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 130g, ether/hexane = 5:1) to give acetate **7-30** (4.08 g, quant.). IR (KBr) ν_{max} 2966, 1739, 1667, 1586, 1245, 1048 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.04 (6H, d, J = 6.5 Hz, O-CH_2-CH(CH_3)$_2$), 2.09 (3H, s, O*Ac*), 2.30-2.60 (3H, m, CH_2-*CH*), 2.64-2.90 (2H, m, CH_2), 3.88 (1H, dd, J = 8.5, 6 Hz, O-CH_AH_B), 3.95 (1H, dd, J = 8.5, 6, O-CH_AH_B), 4.09 (2H, m, CH_2-OAc). MS (EI) m/z 320 (M^+: ^{81}Br), 318 (M^+: ^{79}Br), 260, 258. Anal. Calcd for $C_{13}H_{19}NO_4Br$: C, 48.92; H, 6.00. Found C, 48.89; H, 5.82.



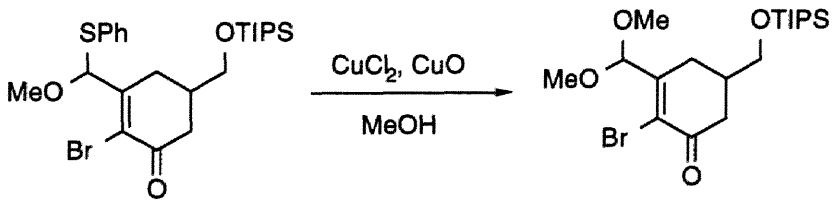
7-30 **7-31** [15170]

Compound 7-31. (1) The acetate **7-30** (4.10 g, 13.0 mmol) was dissolved in MeOH (62 mL) and the solution was cooled to 0 °C. To this solution was added NaOMe [2 M in MeOH, 1.3 mL, 2.6 mmol]. After stirring at 0 °C for 40 min, the mixture was poured into sat. NH_4Cl solution, and extracted with $CHCl_3$ (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product (3.83 g). (2) The crude product was dissolved in DMF (50 mL). To this solution were added TIPS-Cl (4.2 mL, 19.5 mmol) and imidazole (2.65 g, 39 mmol). After stirring at rt for 2 h, the reaction was quenched with ice-water, and the mixture was extracted with AcOEt (100 mL x3). The combined organic layer was washed with water (200 mL) and brine (150 mL x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 200 g, ether/hexane = 1:2) to give silyl ether **7-31** (3.82 g, 68 %). IR (KBr) ν_{max} 2949, 2865, 1667, 1585, 1464, 1235, 1115 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.00-1.16 (27H, m, Si(*CH*(CH_3)$_2$)$_3$ + $OCH_2CH(CH_3)_2$), 2.07 (1H, m, $OCH_2CH(CH_3)_2$), 2.26-2.48 (2H, m, CH_2), 2.53-2.67 (2H, m, CH_2), 2.79 (1H, dd, J = 17, 4.5 Hz, *CH*H), 3.70 (2H, m, Si-OCH_2), 3.90 (2H, m, $OCH_2CH(CH_3)_2$). MS (EI) *m/z* 434, (M^+: ^{81}Br), 432 (M^+: ^{79}Br), 391, 389. Anal. Calcd for $C_{20}H_{37}O_3SiBr$: C, 55.43; H, 8.55. Found C, 55.48; H, 8.54.



7-31 **7-33** [15179]

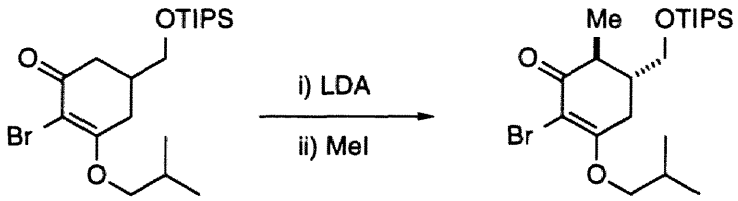
Compound 7-33. To a solution of methoxymethyl phenylsulfide (0.64 mL, 4.38 mmol) in THF (15 mL) cooled to -78 °C was added *n*-BuLi (1.6 M in hexane, 2.44 mL, 3.91 mmol), and the mixture was stirred at -78 °C for 30 min and at -50 °C for 20 min. After the mixture was cooled to -78 °C again, **7-31** (1.00 g, 2.25 mmol) in THF (8 mL) was added over 10 min. After stirring at -78 °C for 1 h, the mixture was poured into sat. NH_4Cl solution, and extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was dissolved in ether (15 mL)-AcOEt (15 mL) and mixed with water (15 mL) and $HClO_4$ (0.15 mL). The whole mixture was stirred at rt for 5 min. The mixture was washed with water (x3), and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 50 g, ether/hexane = 1:20) to give **7-33** (820 mg, 71 %). IR (KBr) ν_{max} 2945, 2866, 1688, 1596, 1466, 1114 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.97-1.10 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.80-1.96 (1H, m, C*H*-CH_2O), 2.01 (1H, br d, J = 18.5 Hz, CH_AH$_B$), 2.23 (1H, dd, J = 18.5, 11 Hz, CH$_A$$H_B$), 2.39 (1H, dd, J = 16.5, 13 Hz, CH_CH$_D$), 2.70 (1H, ddd, J = 16.5, 4, 1.5 Hz, CH$_C$$H_D$), 3.40-3.59 (2H, m, C$H_2$-O-Si), 3.54 (3H, s, OC$H_3$), 5.67 (1H, s, PhS-C*H*(OMe)), 7.26-7.38 (3H, m, aromatic), 7.50-7.58 (2H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 11.7, 17.9, 31.0, 36.9, 40.8, 56.5, 65.8, 92.7, 120.6, 128.9, 130.9, 134.5, 135.5, 158.4, 191.3. MS (EI) *m/z* 436 (M^+: ^{79}Br), 434 (M^+: ^{81}Br), 406, 404. Anal. Calcd for $C_{24}H_{37}O_3SiBrS$: C, 56.13; H, 7.26. Found C, 56.19; H, 7.19.



7-33 **7-35** [15191]

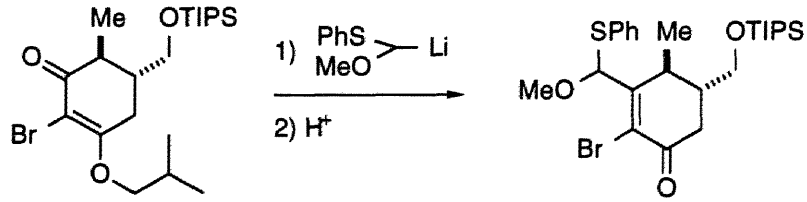
Compound 7-35. A solution of **7-33** (820 mg, 1.60 mmol), $CuCl_2$ (430 mg, 3.20 mmol) and CuO (509 mg, 6.40 mmol) in MeOH (20 mL) was heated at reflux temperature for 2 h. After cooling to rt, the mixture was filtered through a pad of Super-Cel®, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane = 1:10) to give acetal **7-35** (599 mg, 86 %). IR (KBr) ν_{max} 2946, 2867, 1693, 1463, 1108, 1070 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.98-1.14 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 2.18-2.36 (1H, m, CH_2-C*H*), 2.39 (1H, dd, J = 17.5, 10 Hz, CH_AH$_B$), 2.53 (1H, dd, J = 16, 12 Hz, CH_CH$_D$), 2.69 (1H, ddd, J = 17.5, 4,

1.5 Hz, CH_AH_B), 2.78 (1H, ddd, J = 16, 4, 1.5 Hz, CH_CH_D), 3.46 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.69 (2H, dd, J = 5, 1 Hz, CH_2-OSi), 5.38 (1H, s, $CH(OMe)_2$). MS (EI) m/z 405 (M-30: ^{81}Br), 403 (M-30: ^{79}Br), 393, 391. Anal. Calcd for $C_{19}H_{35}O_4SiBr$: C, 52.40; H, 8.10. Found C, 52.40; H, 8.19.



7-31 **7-32** [15187]

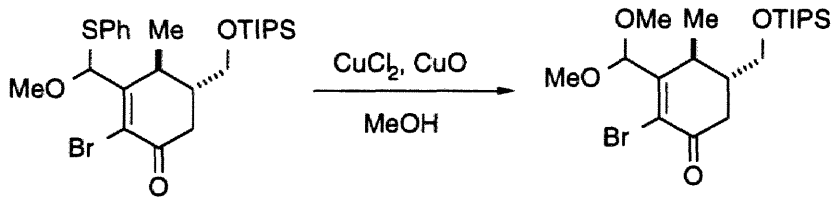
Compound 7-32. To a solution of diisopropylamine (0.25 mL, 1.84 mmol) in THF (8 mL) cooled to -78 °C was added *n*-BuLi [1.6 M in hexane, 1.00 mL, 1.61 mmol], and the solution was stirred at -78 °C for 30 min. To this solution was added **7-31** (500 mg, 1.15 mmol) in THF (4 mL) over 10 min. After stirring at -78 °C for 1 h, MeI (0.14 mL, 2.3 mmol) was added. After stirring at -20 °C for 1 h, the mixture was quenched with sat. NH_4Cl solution, and the mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 30 g, ether/hexane = 1:4) followed by crystallization (from hexane) to give **7-32** (409 mg, 80 %). Mp 68-69 °C. IR (KBr) ν_{max} 2941, 2866, 1663, 1594, 1465, 1367, 1245 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.00-1.16 (27H, m, $Si(CH(CH_3)_2)_3$, $CH(CH_3)_2$), 1.23 (3H, d, J = 7 Hz, CH_3-CH), 1.93-2.15 (2H, m, OCH_2CHMe_2, CH-CH_2-OSi), 2.45 (1H, dq, J = 10, 7 Hz, CH_3-CH-C=O), 2.74 (1H, dd, J = 17, 7.5 Hz, C=C-CH_AH_B), 2.81 (1H, dd, J = 17, 6 Hz, C=C-CH_AH_B), 3.74 (1H, dd, J = 10, 6 Hz, O-CH_AH_B), 3.79 (1H, dd, J = 10, 4 Hz, O-CH_AH_B), 3.90 (2H, m, OCH_2). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 11.8, 13.5, 17.9, 18.8, 28.7, 29.2, 41.5, 42.2, 64.0, 75.0, 101.7, 170.8, 193.3. Anal. Calcd for $C_{21}H_{39}O_3SiBr$: C, 56.36; H, 8.78. Found C, 56.31; H, 8.63.



7-32 **7-34** [16002]

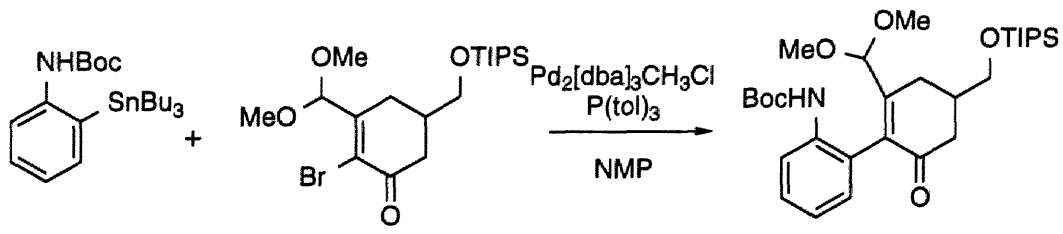
Compound 7-34. To a solution of methoxymethyl phenylsulfide (0.75 mL, 5.14 mmol) in THF (15 mL) cooled to -78 °C was added *n*-BuLi (1.6 M in hexane, 2.8 mL, 4.6 mmol), and the solution was stirred at -78 °C for 1 h 15 min. To this solution was added **7-32** (1.15 g, 2.57 mmol) in THF (6 mL) over 5 min. After stirring at -78 °C for 1 h, the mixture was poured into sat. NH_4Cl solution, and extracted with ether-AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was dissolved in ether (10 mL)-AcOEt (10 mL) and mixed with water (10 mL) and $HClO_4$

(0.2 mL). After stirring at rt for 20 min, the organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 85 g, ether/hexane = 1:20) to give **7-34** (873 mg, 65 %) as a diastereomeric mixture. IR (KBr) ν_{max} 2942, 2865, 1690, 1584, 1464, 1108 cm^{-1}. MS (EI) *m/z* 485 (M-43: ^{81}Br), 483 (M-43: ^{79}Br), 419, 417.



7-34 **7-36** [16003]

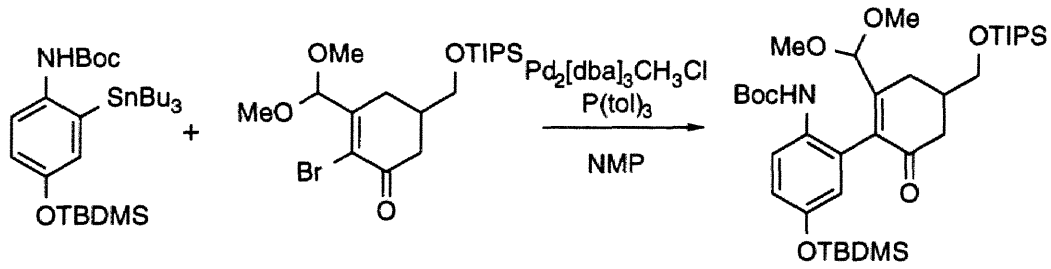
Dimethylacetal 7-36. A MeOH (25 mL) solution of **7-34** (873 mg, 1.65 mmol), $CuCl_2$ (443 mg) and CuO (524 mg, 6.6 mmol) was heated at reflux temperature for 2 h. After cooling to rt, the mixture was filtrated through the pad of Super-Cel®, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2-H_2O, extracted with CH_2Cl_2 (x3), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane = 1:10) to give **7-36** (626 mg, 85 %). IR (KBr) ν_{max} 2941, 2866, 1694, 1465, 1108, 1073 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.98-1.10 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.35 (3H, d, *J* = 7 Hz, CH-C*H*$_3$), 2.13 (1H, m, C*H*-CH_2-OTIPS), 2.71 (1H, br dd, *J* = 17.5, 3 Hz, C*H*$_A$H$_B$-C=O), 2.88 (1H, dd, *J* = 17.5, 5 Hz, CH$_A$*H*$_B$-C=O), 3.05 (1H, qd, *J* = 7, 2 Hz, C*H*-CH_3), 3.44 (3H, s, CH-OC*H*$_3$), 3.53 (3H, s, CH-OC*H*$_3$), 3.56-3.63 (2H, m, C*H*$_2$-OTIPS), 5.34 (1H, s, C*H*(OMe)$_2$). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 11.8, 17.9, 19.8, 32.9, 36.1, 43.0, 55.7, 56.6, 64.8, 106.9, 123.3, 159.0, 190.4. MS (EI) m/z 449 (M^+: ^{81}Br), 447 (M^+: ^{79}Br), 407 (M-43), 405 (M-43). Anal. Calcd for $C_{20}H_{37}O_4BrSi$: C, 53.55; H, 8.32. Found C, 53.56; H, 8.46.



7-8 **7-35** **7-37** [15193]

Compound 7-37 (entry 1 in **Table 7-2**). In a dried flask were placed bromide **7-35** (200 mg, 0.46 mmol), $Pd_2[dba]_3$·$CHCl_3$ (9.5 mg, 0.0092 mmol), P(*o*-tol)$_3$ (22.4 mg, 0.0736 mmol) and NMP (4 mL) and the whole mixture was degassed and covered with argon and stirred at rt for 30 min. To this solution was added tin **7-8** (288 mg, 0.598 mmol) in NMP (2.5 mL). The mixture was stirred at 85 °C for 1 h. After cooling to rt, the reaction was poured into ice-cold sat. $NaHCO_3$ solution, and extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), concentrated under reduced pressure. The residue was purified by column chromatography (silica 20

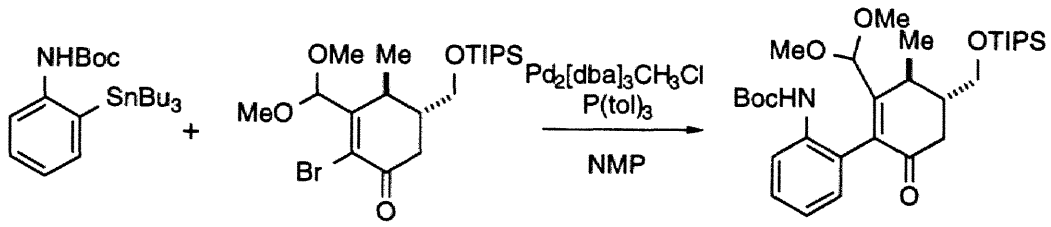
g, ether/hexane = 1:10 → 1:3) to give **7-37** (200 mg, 80 %). IR (KBr) ν_{max} 2941, 2866, 1732, 1684, 1518, 1449 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.03-1.17 (21H, m, $Si(CH(CH_3)_2)_3$), 1.44 (9/2H, s, $C(CH_3)_3$), 1.46 (9/2 H, s, $C(CH_3)_3$), 2.30-2.80 (5H, m, CH_2-CH-CH_2), 3.21 (3/2H, s, OCH_3), 3.22 (3/2H, s, OCH_3), 3.25 (3/2H, s, OCH_3), 3.26 (3/2H, s, OCH_3), 3.66-3.83 (2H, m, CH_2-OTIPS), 4.42 (1/2H, s, $CH(OMe)_2$), 4.46 (1/2H, s, $CH(OMe)_2$), 6.21 (1/2H, br s, N*H*), 6.31 (1/2H, br s, N*H*), 6.91-6.99 (1H, m, aromatic), 7.05-7.15 (1H, m, aromatic), 7.31-7.40 (1H, m, aromatic), 7.79 (1/2H, br d, *J* = 8 Hz, aromatic), 7.87 (1/2H, *J* = 8 Hz, aromatic). MS (EI) *m/z* 547 (M^+). HRMS (EI) for $C_{30}H_{49}NO_6Si$ (M^+), calcd 547.3328, found 547.3313.



7-13a **7-35** **7-38** [15197][16032]

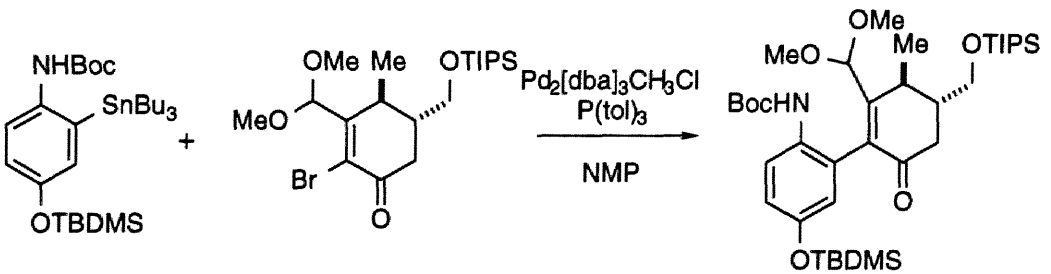
Compound 7-38. NMP as a solvent (entry 2 in Table 7-2): In a dried flask were placed bromide **7-35** (100 mg, 0.23 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (4.7 mg, 0.0046 mmol), P(*o*-tol)$_3$ (12.2 mg, 0.036 mmol) and NMP (2 mL) and the whole mixture was degassed and covered with argon and stirred at rt for 30 min. To this solution was added tin **7-13a** (211 mg, 0.345 mmol) in NMP (2.0 mL). The mixture was stirred at 85 °C for 1 h 15 min. After cooling to rt, the reaction was poured into ice-cold sat. $NaHCO_3$ solution and extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), concentrated under reduced pressure. The residue was purified by column chromatography (silica 15 g, ether/hexane = 1:10 → 1:5) to give **7-38** (75 mg, 48 %). IR (KBr) ν_{max} 2941, 2867, 1731, 1680, 1510, 1465, 1169 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.16-0.20 (6H, m, $Si(CH_3)_2$), 0.96 (9H, s, $SiC(CH_3)_3$), 1.02-1.12 (21H, m, $Si(CH(CH_3)_2)_3$), 1.42 (9/2H, s, O-$C(CH_3)_3$), 1.43 (9/2H, s, O-$C(CH_3)_3$), 2.26-2.79 (5H, m, CH_2-CH-CH_2), 3.21 (3/2H, s, OCH_3), 3.22 (3/2H, s, OCH_3), 3.29 (3/2H, s, OCH_3), 3.31 (3/2H, s, OCH_3), 3.67-3.83 (2H, m, CH_2-OSi), 4.49 (1/2H, s, $CH(OMe)_2$), 4.56 (1/2H, s, $CH(OMe)_2$), 6.02 (1/2H, br s, N*H*), 6.13 (1/2H, br s, N*H*), 6.46 (1/2H, d, *J* = 3 Hz, aromatic), 6.49 (1/2H, d, *J* = 3 Hz, aromatic), 6.82 (1H, dd, *J* = 8.5, 3 Hz, aromatic), 7.48 (1/2H, br d, *J* = 8.5 Hz, aromatic), 7.59 (1/2H, br d, *J* = 8.5 Hz, aromatic). HRMS (EI) for $C_{36}H_{63}NO_7Si_2$ (M^+), calcd 677.4142, found 677.4121.

Toluene solvent (entry 3 in **Table 7-2**): In a dried flask were placed bromide **7-35** (107 mg, 0.24 mmol), $Pd_2[dba]_3 \cdot CHCl_3$ (10 mg, 0.0098 mmol), P(*o*-tol)$_3$ (23.9 mg, 0.078 mmol) and toluene (2 mL) and the whole mixture was degassed and covered with argon and stirred at rt for 2h. To this solution was added tin **7-13a** (225 mg, 0.369 mmol) in toluene (1.5 + 0.5 mL). The mixture was stirred at 80 °C for 40 min. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:10 → 1:5) to give **7-38** (117 mg, 70 %).



7-8 **7-36** **7-39** [16013]

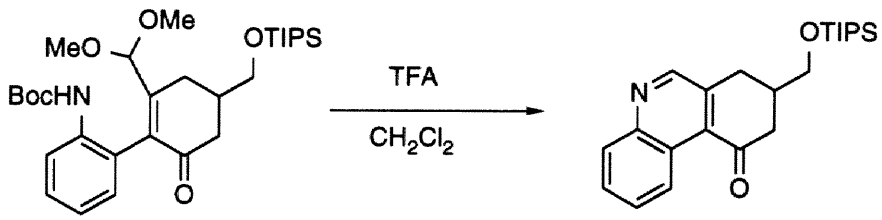
Compound 7-39. In a dried flask was placed bromide **7-36** (200 mg, 0.446 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (13 mg, 0.013 mmol), P(*o*-tol)$_3$ (32 mg, 0.107 mmol) and NMP (4 mL) and the whole mixture was degassed and covered with argon and stirred at rt for 30 min. To this solution was added tin **7-8** (279 mg, 0.579 mmol) in NMP (2.0 mL). The mixture was stirred at 70 °C for 1 h 10 min. After cooling to rt, the reaction was quenched with ice-cold sat. $NaHCO_3$ solution and extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:4) to give **7-39** (205 mg, 82 %). IR (KBr) ν_{max} 2942, 2866, 1734, 1670, 1507, 1457, 1160, 1070 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.00-1.16 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.42-1.49 (12H, m, OC(C*H*$_3$)$_3$ + C*H*$_3$-CH), 2.24 (1H, m, C*H*-CH$_2$-OTIPS), 2.41-3.12 (3H, m, C*H*$_2$-C=O + C*H*-CH$_3$), 3.18 (3/2H, s, OC*H*$_3$), 3.21 (3H, br s, OC*H*$_3$), 3.22 (3/2H, s, OC*H*$_3$), 3.60-3.80 (2H, m, C*H*$_2$-OTIPS), 4.36 (1/2H, s, C*H*(OMe)$_2$), 4.42 (1/2H, s, C*H*(OMe)$_2$), 6.19 (1/2H, br s, N*H*), 6.39 (1/2H, br s, N*H*), 6.85 (1/2H, dd, *J* = 7.5, 1.5 Hz, aromatic), 6.97 (1/2H, dd, *J* = 7.5, 1.5 Hz, aromatic), 7.03-7.15 (1H, m, aromatic), 7.28-7.40 (2H, m, aromatic), 7.79 (1/2H, br d, *J* = 8 Hz, aromatic), 7.86 (1/2H, br d, *J* = 8 Hz, aromatic). MS (EI) *m/z* 561(M$^+$). HRMS (EI) for $C_{31}H_{51}NO_6Si$ (M$^+$), calcd 561.3485, found 561.3497.



7-13a **7-36** **7-40** [16033]

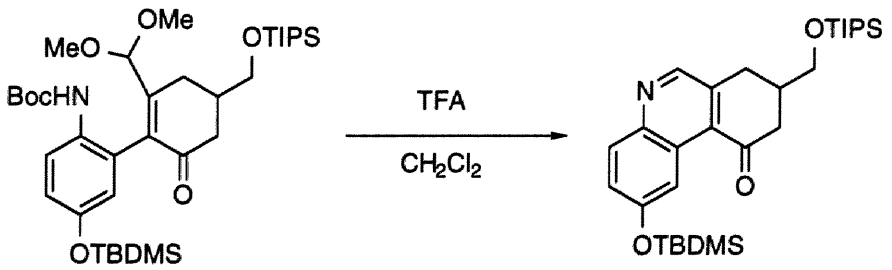
Compound 7-40. In a dried flask were placed bromide **7-36** (102 mg, 0.23 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (9.4 mg, 0.0091 mmol), P(*o*-tol)$_3$ (22 mg, 0.073 mmol) and toluene (2 mL), and the whole mixture was degasses by three freeze-thaw cycles, covered with argon, and stirred at rt for 30 min. To this solution was added tin **7-13a** (208 mg, 0.34 mmol) in toluene (1.5 mL). The mixture was stirred at 80 °C for 2 h 30 min. After cooling to rt, the reaction was concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 1:10 → 1:5) to give **7-40** (75 mg, 48 %). IR (KBr) ν_{max} 3330, 2933, 2867, 1728, 1669, 1510, 1162 cm^{-1}. ^{1}H

NMR (270 MHz, $CDCl_3$) δ 0.15 (3H, s, Si-CH_3), 0.16 (3H, s, Si-CH_3), 0.17 (3H, s, Si-CH_3), 0.18 (3H, s, Si-CH_3), 0.96 (9H, s, $SiC(CH_3)_3$), 1.01-1.11 (21H, m, Si-($CH(CH_3)_2)_3$), 1.40-1.48 (12H, m, CH-CH_3, $OC(CH_3)_3$), 3.18 (3/2H, s, OCH_3), 3.20 (3/2H, s, OCH_3), 3.25 (3H, s, OCH_3), 3.61-3.78 (2H, m, CH_2-OTIPS), 4.43 (1/2H, s, $CH(OMe)_2$), 4.48 (1/2H, s, $CH(OMe)_2$), 6.01 (1/2H, br s, N*H*), 6.22 (1/2H, br s, N*H*), 6.35 (1/2H, d, *J* = 3 Hz, aromatic), 6.48 (1/2H, d, *J* = 3 Hz, aromatic), 6.81 (1H, dd, *J* = 9, 3 Hz, aromatic), 7.49 (1/2H, br d, *J* = 8.5 Hz, aromatic), 7.58 (1/2H, br d, *J* = 8.5 Hz, aromatic). MS (EI) *m/z* 691 (M^+). HRMS (EI) for $C_{37}H_{65}NO_7Si_2$ (M^+), calcd 691.4299, found 691.4274.



7-37 **7-42** [15202]

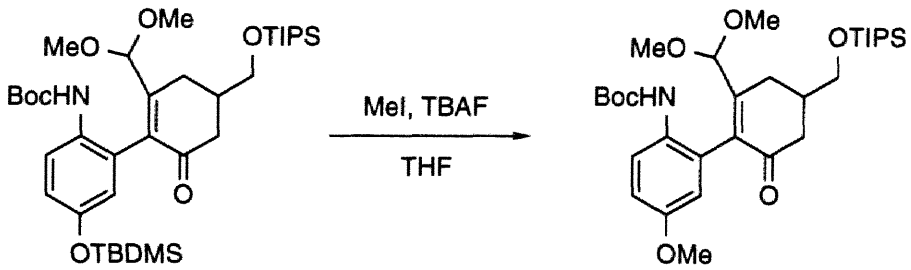
Quinoline 7-42. To a solution of acetal **7-37** (200 mg, 0.365 mmol) in THF (10 mL) cooled to 0 °C was added TFA (0.20 mL). After stirring at 0 °C for 15 min, the reaction was quenched with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:2) to give **7-42** (124 mg, 89 %). IR (KBr) ν_{max} 2941, 2866, 1685, 1460, 1104 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.03-1.15 (21H, m, $Si(CH(CH_3)_2)_3$), 2.56 (1H, m, C*H*-CH_2-OSi), 2.75 (1H, dd, *J* = 16, 12 Hz, CH_AH_B-C=O), 2.89 (1H, ddd, *J* = 16, 4, 1.5 Hz, CH_AH_B-C=O), 3.11 (1H, dd, *J* = 17, 10 Hz, Ar-CH_AH_B), 3.20 (1H, br dd, *J* = 17, 5 Hz, Ar-CH_AH_B), 3.79 (1H, dd, *J* = 10, 5 Hz, CH_AH_B-OTIPS), 3.85 (1H, dd, *J* = 10, 4.5 Hz, CH_AH_B-OTIPS), 7.62-7.75 (2H, m, aromatic), 8.11 (1H, br d, *J* = 7.5 Hz, aromatic), 8.94 (1H, br s, N=C*H*), 9.29 (1H, br d, *J* = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 11.8, 17.9, 30.6, 38.0, 43.6, 66.3, 123.9, 126.0, 128.7, 129.1, 129.7, 131.7, 137.1, 148.0, 152.4, 200.6. MS (EI) *m/z* 383 (M^+), 340 (M-43), 310. Anal. Calcd for $C_{23}H_{33}NO_2Si$: C, 72.02; H, 8.68; N, 3.65. Found C, 72.01; H, 8.90; N, 3.42.



7-38 **7-43** [15204]

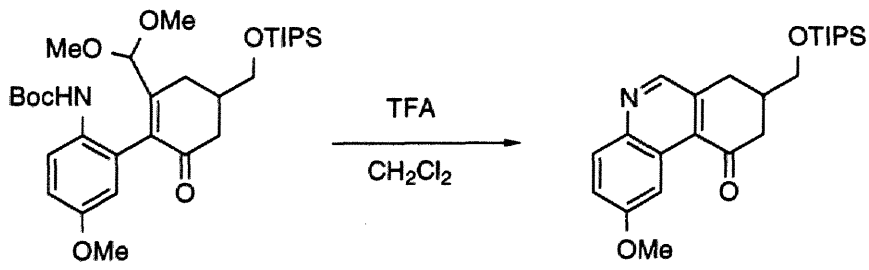
Quinoline 7-43. The acetal **7-38** (30 mg, 0.044 mol) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. To this solution was added TFA (30 μL) and stirred for 10 min. The reaction was quenched with sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4,, concentrated under reduced pressure. The residue was purified by

preparative TLC (ether/hexane = 1:2) to give **7-43** (20 mg, 88 %). IR (KBr) ν_{max} 2943, 2864, 1685, 1611, 1499, 1264, 1237 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.33 (6H, s, $Si(CH_3)_2$), 1.03 (9H, s, $SiC(CH_3)_3$), 1.01-1.12 (21H, m, $Si(CH(CH_3)_2)_3$), 2.54 (1H, m, CH-CH_2-OTIPS), 2.72 (1H, dd, J = 16, 12 Hz, CH_AH_B-C=O), 2.87 (1H, dd, J = 16, 4, 1.5 Hz, CH_AH_B-C=O), 3.07 (1H, dd, J = 17, 9.5 Hz, Ar-CH_AH_B), 3.16 (1H, br dd, J = 17, 5 Hz, Ar-CH_AH_B), 3.78 (1H, dd, J = 10, 5 Hz, CH_AH_B-OTIPS), 3.84 (1H, dd, J = 10, 4.5 Hz, CH_AH_B-OTIPS), 7.28 (1H, dd, J = 9, 3 Hz, aromatic), 7.97 (1H, d, J = 9 Hz, aromatic), 8.76 (1H, s, N=CH), 8.82 (1H, d, J = 3 Hz, aromatic). MS (EI) *m/z* 513 (M^+), 470 (M-43). HRMS (EI) for $C_{29}H_{47}NO_3Si_2$ (M^+), calcd 513.3094, found 513.3081.



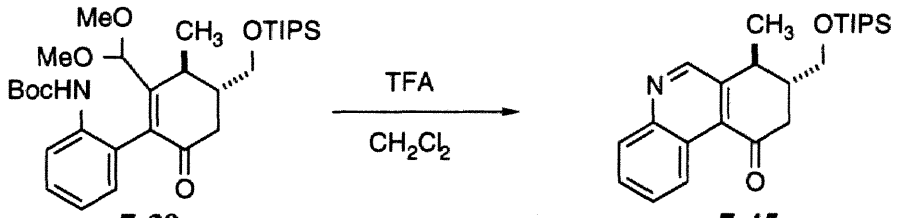
7-38 **7-41** [15184]

Compound 7-41. The TBDMS-ether **7-38** (59 mg, 0.087 mmol) was dissolved in THF (2.0 mL). To this solution were added MeI (22 μL, 0.35 mmol) and TBAF (1.0 M in THF, 95 mL). After stirring at rt for 1 h 10 min, the mixture was quenched with sat. NH_4Cl solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:1) to give methylether **7-41** (34 mg, 70 %) and phenol (7 mg, 14 %). IR (KBr) ν_{max} 2946, 2866, 1724, 1683, 1508, 1457, 1163 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.03-1.17 (21H, m, $Si(CH(CH_3)_2)_3$), 1.42 (9/2H, s, $C(CH_3)_3$), 1.43 (9/2H, s, $C(CH_3)_3$), 2.22-2.80 (5H, m, CH_2-CH-CH_2), 3.21 (3/2H, s, CH-OCH_3), 3.22 (3/2H, s, CH-OCH_3), 3.31 (3/2H, s, CH-OCH_3), 3.33 (3/2H, s, CH-OCH_3), 3.68-3.80 (2H, m, CH_2OTIPS), 3.77 (3H, s, Ar-OCH_3), 4.49 (1/2H, s, $CH(OMe)_2$), 4.53 (1/2H, s, $CH(OMe)_2$), 6.00 (1/2H, br s, NH), 6.10 (1/2H, br s, NH), 6.53 (1/2H, d, J = 3 Hz, aromatic), 6.56 (1/2H, d, J = 3 Hz, aromatic), 6.86-6.94 (1H, m, aromatic), 7.50 (1/2H, br d, J = 8.5 Hz, aromatic), 7.60 (1/2H, br d, J = 8.5 Hz, aromatic). MS (EI) *m/z* 577 (M^+). HRMS (EI) for $C_{31}H_{51}NO_7Si$ (M^+), calcd 577.3434, found 577.3452.



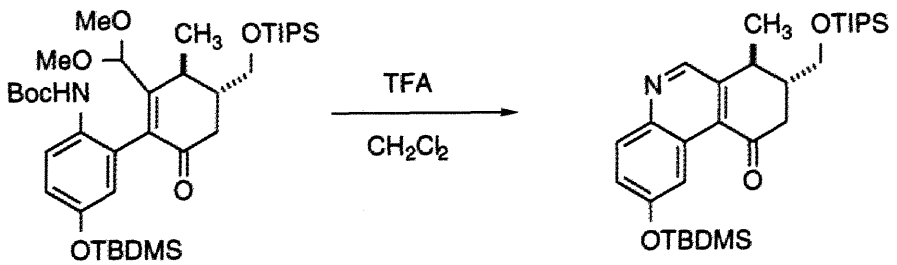
7-41 **7-44** [15185]

Compound 7-44. The acetal **7-41** (32 mg, 0.055 mol) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. To this solution was added TFA (30 μL) and stirred for 25 min. The reaction was quenched with sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 1:1) to give **7-44** (19 mg, 84 %). IR (KBr) ν_{max} 2942, 2865, 1676, 1617, 1506, 1227 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.02-1.18 (21H, m, Si(C*H*(CH_3)$_3$), 2.46-2.62 (1H, m, C*H*-CH_2-OTIPS), 2.74 (1H, dd, *J* = 16, 12 Hz, C$H_A$$H_B$-C=O), 2.88 (1H, ddd, *J* = 16, 4.5, 1.5 Hz, $CH_A$$H_B$-C=O), 3.02-3.23 (2H, m, CH_2-Ar), 3.81 (2H, m, CH_2-OTIPS), 3.98 (3H, s, Ar-OCH_3), 7.34 (1H, dd, *J* = 9, 3 Hz, aromatic), 7.98 (1H, d, *J* = 9 Hz, aromatic), 8.76 (1H, s, N=C*H*), 8.78 (1H, d, *J* = 3 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 11.8, 17.9, 30.7, 38.0, 43.8, 55.6, 66.4, 103.9, 121.4, 125.4, 130.2, 131.0, 137.5, 144.4, 149.4, 160.3, 201.0. MS (EI) m/z 413 (M^+), 370 (M-43), 340. HRMS (EI) for $C_{24}H_{35}NO_3Si$ (M^+), calcd 413.2386, found 413.2373.



7-39 **7-45** [16014]

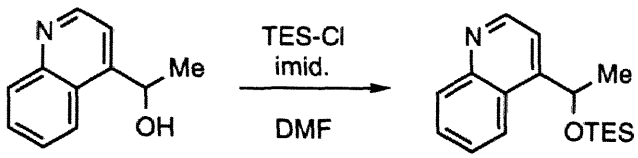
Quinoline 7-45. The acetal **7-39** (40 mg, 0.071 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. To this solution was added TFA (40 μL). After stirring for 20 min, the mixture was diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative PLC (ether/hexane = 1:2) to give **7-45** (26 mg, 92 %). R (KBr) ν_{max} 2944, 2866, 1689, 1499, 1462, 1112 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.90-1.06 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.55 (3H, d, *J* = 7 Hz, CH-CH_3), 2.35 (1H, m, C*H*-CH_2-OTIPS), 2.80 (1H, dd, *J* = 17, 5.5 Hz, C$H_A$$H_B$-C=O), 3.05 (1H, dd, *J* = 17, 5 Hz, $CH_A$$H_B$-C=O), 3.44 (1H, qd, *J* = 7, 3.5 Hz, C*H*-CH_3), 3.70 (1H, dd, *J* = 10, 6.5 Hz, C$H_A$$H_B$-OTIPS), 3.82 (1H, dd, *J* = 10, 5.5 Hz, $CH_A$$H_B$-OTIPS), 7.60-7.76 (2H, m, aromatic), 8.10 (1H, br d, *J* = 7.5 Hz, aromatic), 8.96 (1H, s, N=C*H*), 9.22 (1H, br d, *J* = 7.5 Hz, aromatic). MS (EI) m/z 354 (M-43). HRMS (EI) for $C_{21}H_{28}NO_2Si$ (M-C_3H_7), calcd 354.1889, found 354.1868.



7-40 **7-46** [16040]

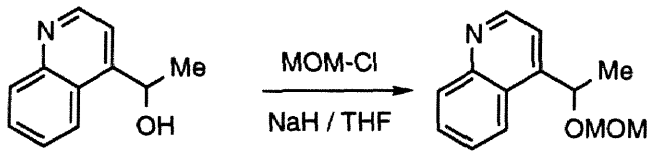
Quinoline 7-46. To a solution of **7-40** (39 mg, 0.057 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added TFA (40 μL). After stirring at 0 °C for 15 min, the reaction was quenched with $NaHCO_3$ solution, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative PLC (ether/hexane = 1:2) to give **7-46** (23 mg, 76 %). IR (KBr) ν_{max} 2946, 2866, 1683, 1612, 1500, 1264, 1239, 1105 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.33 (6H, s, $Si(CH_3)_2$), 0.91-1.02 (21H, m, $Si(CH(CH_3)_3)$), 1.03 (9H, s, $Si(CH_3)_3$), 1.53 (3H, d, J = 7 Hz, $CH\text{-}CH_3$), 2.32 (1H, m, $CH\text{-}CH_2\text{-OTIPS}$), 2.77 (1H, dd, J = 17, 5 Hz, $CH_AH_B\text{-C=O}$), 3.03 (1H, dd, J = 17, 5.5 Hz, $CH_AH_B\text{-C=O}$), 3.39 (1H, qd, J = 7, 3.5 Hz, $CH\text{-}CH_3$), 3.69 (1H, dd, J = 10, 6.5 Hz, $CH_AH_B\text{-OTIPS}$), 3.80 (1H, dd, J = 10, 5 Hz, $CH_AH_B\text{-OTIPS}$), 7.28 (1H, dd, J = 9, 2.5 Hz, aromatic), 7.96 (1H, d, J = 9 Hz, aromatic), 8.76 (1H, d, J = 2.5 Hz, aromatic), 8.78 (1H, s, $N{=}CH$). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -4.4, 11.8, 17.9, 21.9, 25.7, 33.0, 39.8, 42.9, 65.4, 113.0, 124.6, 124.9, 129.7, 130.9, 141.1, 144.0, 149.7, 156.7, 200.0. MS (EI) *m/z* 527 (M^+), 484 (M-43). HRMS (EI) for $C_{30}H_{49}NO_3Si_2$ (M^+), calcd 527.3250, found 527.3267.

Experimental for Chapter 8



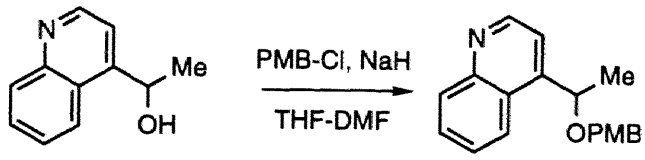
8-20 **8-7** [1055]

TES ether 8-7. The alcohol **8-20** (420 mg, 2.43 mmol), imidazole (500 mg, 7.35 mmol), were dissolved in DMF (12.6 mL). To this solution was added TES-Cl (0.61 mL, 3.63 mmol), and the mixture was stirred at rt for 15 h. The mixture was quenched with water (12 mL), extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica, 18 g, ether/hexane = 1:2) to give **8-7** (440 mg, 63 %). IR (KBr) ν_{max} 2956, 2875, 1593, 1507 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.55-0.66 (6H, m, $OSi(CH_2CH_3)_3$), 0.93 (9H, d, J = 8.0 Hz, $OSi(CH_2CH_3)_3$), 1.58 (3H, d, J = 6.5 Hz, $CH\text{-}CH_3$), 5.58 (1H, q, J = 6.5 Hz, CH-OTES), 7.55 (1H, ddd, J = 8.5, 7.0, 1.0 Hz, aromatic), 7.63 (1H, d, J = 4.5 Hz, aromatic), 7.70 (1H, ddd, J = 8.5, 7.0, 1.0 Hz, aromatic), 8.02 (1H, dd, J = 8.5, 1.0 Hz, aromatic), 8.15 (1H, dd, J = 8.5, 1.0 Hz, aromatic), 8.90 (1H, J = 4.5 Hz, N=CH).



8-20 **8-5** [1097]

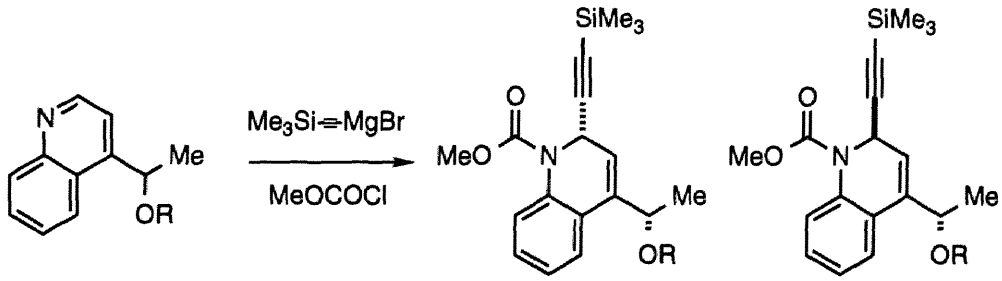
MOM ether 8-5. NaH (60 % oil suspension, 160 mg, 4.00 mmol) was placed in dry flask, and the oil was removed by washing with hexane (x2) After addition of THF (4.0 mL) and DMF (4.0 mL), a solution of alcohol **8-20** (346 mg, 2.00 mmol) in DMF (2.0 mL) was added. To this solution was added MOM-Cl (0.23 mL, 3.0 mmol) dropwise. After stirring at rt for 1 h, the mixture was quenched with ice-cold sat. NH_4Cl solution (8 mL) and extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 20 g, ether/hexane = 3:1) to give **8-5** (276 mg, 65 %). ^1H NMR (270 MHz, $CDCl_3$) δ 1.62 (3H, d, J = 7.0 Hz, $CHCH_3$), 3.40 (3H, s, OCH_3), 4.61 (1H, d, J = 7.0 Hz, $O\text{-}CH_AH_B\text{-}OMe$), 4.72 (1H, d, J = 7.0 Hz, CH-OMOM), 5.51 (1H, d, J = 7.0 Hz, $O\text{-}CH_AH_B\text{-}OMe$), 7.54 (1H, d, J = 4.5 Hz, aromatic), 7.56 (1H, ddd, J = 8.5, 7.0, 1.0 Hz, aromatic), 7.71 (1H, ddd, J = 8.5, 7.0, 1.0 Hz, aromatic), 8.08 (1H, dd, J = 8.0, 1.0 Hz, aromatic), 8.15 (1H, dd, J = 8.0, 1.0 Hz, aromatic), 8.91 (1H, d, J = 4.5 Hz, N=CH).



8-20 **8-6** [1093]

MPM ether 8-6. NaH (60 % oil suspension, 160 mg, 4.00 mmol) was placed in dry flask, and the oil was removed by washing with hexane (x2). After addition of THF (4.0 mL) and DMF (4.0 mL), a solution of alcohol **8-20** (330 mg, 2.00 mmol) in DMF (1.0 mL) was added. To this solution was added PMB-Cl (0.41 mL, 3.00 mmol) dropwise. After stirring at rt for 1 h, the mixture was quenched with ice-cold NH_4Cl solution (8 mL) and extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was dissolved in pyridine(15 mL) and Ac_2O (7.5 mL). After stirring at rt for 1 h, the mixture was diluted with toluene, concentrated under reduced pressure. The residue was purified by column chromatography (silica 35 g, ether) to give **8-6** (474 mg, 85 %). ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (3H, d, J = 7.0 Hz, CH_3-CH-), 3.80 (3H, s, Ar-OCH_3), 4.32 (1H, d, J = 11 Hz, O-CH_AH_B-Ph), 4.48 (1H, d, J = 11 Hz, O-CH_AH_B-Ph), 5.22 (1H, q, J = 7.0 Hz, CH_3-C*H*), 6.88 (2H, d, J = 8.5 Hz, aromatic of MPM), 7.24 (2H, d, J = 8.5 Hz, aromatic of MPM), 7.57 (1H, d, J = 4.0 Hz, aromatic), 7.55 (1H, ddd, J = 8.0, 6.5, 1.0 Hz, aromatic), 7.72 (1H, ddd, J = 8.0, 6.5, 1.0 Hz, aromatic), 8.10 (1H, d, J = 8.5 Hz, aromatic), 8.17 (1H, d, J = 8.5 Hz, aromatic), 8.90 (1H, d, J = 4.0 Hz, N=C*H*).

General procedure for Table 1.



8-5 ~ 8-8 **8-9 ~ 8-13** (syn : anti)

General procedure exemplified the synthesis of 8-9 the for Table 1. To a solution of trimethylsilylacetylene (0.14 mL, 0.98 mmol) in THF (3.0 mL) cooled to 0 °C was added EtMgBr (3 M in ether, 0.33 mL, 0.98 mmol). After stirring at rt for 30 min, the solution was cooled to 0 °C. To this solution were added MOM-ether **8-5** (102 mg, 0.47 mmol, dried by azeotropic removal of water with benzene) in THF (1.0 mL) and then methyl chloroformate (0.09 mL, 1.20 mmol). After stirring at 0 °C for 1 h, the mixture was quenched with sat. NH_4Cl solution and extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 9 g, ether/hexane = 1:4) to give the **8-9** as diastereomixture (136 mg, 77 %).

8-9 (R_1 = MOM, R_2 = Me): Prepared in 77 % from **8-5** in a similar manner. ^{1}H NMR (270 MHz, $CDCl_3$) δ major [1.36 (d, J = 7 Hz, CHCH_3)] : minor [1.47 (d, J = 7 Hz, CHCH_3)] = 1:1.1 (by integration). IR (KBr) ν_{max} 2958, 2170, 1712, 1601, 1488 m^{-1}.. MS (EI) *m/z* 373 (M^+), 358 (M-15), 311, 284.

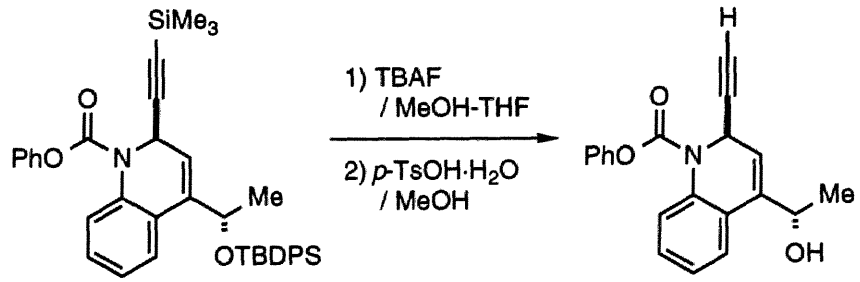
8-10 (R_1 = PMB, R_2 = Me): Prepared in 93 % from **8-6** in a similar manner. ^{1}H NMR (270 MHz, $CDCl_3$) δ major [1.46 (d, J = 6.5 Hz, CHCH_3), 6.04 (d, J = 6.5 Hz, olefinic or propargylic)] : minor [1.37 (d, J = 6.5 Hz, CHCH_3), 6.19 (dd, J = 6.5, 1.0 Hz, olefinic or propargylic)] = 1:1.3 (by integration). MS (EI) *m/z* 449 (M^+).

8-11 (R_1 = TES, R_2 = Me): Prepared in 80 % from **8-7** in a similar manner. ^{1}H NMR (270 MHz, $CDCl_3$) δ major [4.65 (q, J = 6 Hz, C*H*CH$_3$)] : minor [4.96 (qd, J = 6, 1.5 Hz)] = 1:1.5 (by integration). IR (KBr) ν_{max} 2957, 2876, 2170, 1710, 1488 cm^{-1}. MS (EI) *m/z* 443 (M^+), 428 (M-Me), 414 (M-29), 384 (M-59).

8-12 (R_1 = TBDPS, R_2 = Me): Prepared in 78 % from **8-8** in a similar manner. ^{1}H NMR (270 MHz, $CDCl_3$) δ major [4.58 (q, J = 6 Hz, C*H*CH$_3$)] : minor [4.94 (qd, J = 6, 1 Hz, C*H*CH$_3$)] = 1:2.3 (by integration). MS (EI) *m/z* 567 (M^+).

8-13 (R_1 = TBDPS, R_2 = Ph, at 0 °C): Prepared in 100 % from **8-8** in a similar manner. ^{1}H NMR (270 MHz, $CDCl_3$) δ major [1.07 (s, SiC(CH_3)$_3$), 5.78 (d, J = 6.5 Hz, propargylic or olefinic), 5.86 (d, J = 6.5 Hz, propargylic or olefinic)] : minor [1.12 (s, SiC(CH_3)$_3$), 6.04 (d, J = 6.5 Hz, propargylic or olefinic), 6.48 (dd, J = 6.5, 1.0 Hz, propargylic or olefinic)] = 1:4.9 (by integration).

8-13 (R_1 = TBDPS, R_2 = Ph, at -78 °C): prepared in 87 % from **8-8** in a similar manner to that described for chiral **8-24**.

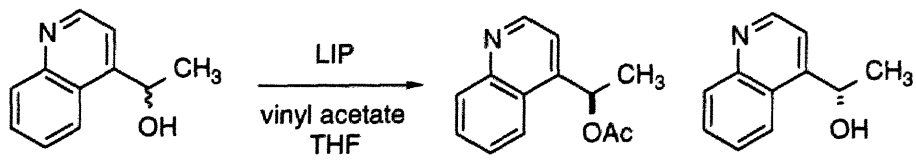


8-13 **8-14**

Alcohol **8-14.** Prepared from **8-13** in a similar manner to that described for chiral **8-20**. Crystallization from ethanol gave prisms.

Crystallographic Data for 8-14.

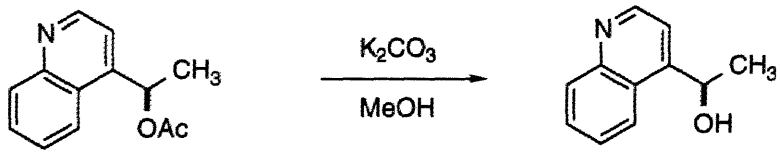
Formula	$C_{20}H_{17}NO_3$
Mr	319.36
F(000)	672
Crystal dimensions (mm)	0.53 x 0.45 x 0.18
Crystal system	monoclinic
Space group	$P2_1/C$ (No. 14)
Cell dimensions	
a (Å)	8.021 (1)
b (Å)	19.131 (9)
c (Å)	11.593 (2)
β (°)	107.46 (1)
V (Å^3)	1696.9 (8)
Z	4
Dx (g/cm^3)	1.25
μ (cm^{-1})	6.5
X-ray source	graphite monochromated Cu Kα (λ = 1.54184 Å)
Lattice-parameter measurement	
Θ range (°), number of reflections	18.22 ≤ Θ ≤ 21.39, 16
Scan method	ω - 2Θ
Range h	-7 to 7
k	-17 to 0
l	0 to 10
2 Θ max (°)	120.0
Number of unique reflections	2505
Number of observed reflections	2092
Criterion for observed reflections	Fo ≥ 3 σ(Fo)
R, wR	0.043, 0.066
Weighting scheme	1 / σ^2(Fo)
Number of parameters refined	268
Method of locating and refining H atoms	from D-Fourier map with Beq of bonded atom
Max height in final difference Fourier map (eÅ^3)	0.23 (3) (minimum -0.21(0))
Computer programs	MOLEN/VAX
Computer	VAX-11/750
Diffractometer	Enraf-Nonius CAD4



(±)-**8-15** (+)-**8-16** (-)-**8-15** [1187]

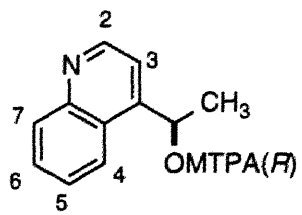
Resolution of racemic alcohol 8-15. The (±)-alcohol **8-15** (10.0 g, 57.7 mmol) was dissolved in dry THF (80 mL) and vinyl acetate (freshly distilled, 27 mL, 290 mmol). To this mixture was

added lipase **LIP** (2.00 g) and the mixture was stirred at rt overnight. The lipase (2.0 g) was added each day until a total of 10 g had been added to the reaction mixture. After stirring additional overnight, the mixture was filtered through the pad of Super-Cel®, washed with AcOEt. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica 350g, ether/hexane = 4:1) to give the acetate (+)-**8-16** (6.28 g, 51 %) and the alcohol (-)-**8-15** (4.78 g, 48 %). (+)-**Acetate 8-16:** $[\alpha]_D$ +39.0 ° (*c* 1.00, $CHCl_3$). IR (KBr) ν_{max} 2992, 1742, 1236 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, d, *J* = 8 Hz, CH_3-CH), 2.17 (3H, s, CH_3CO), 6.60 (1H, q, *J* = 8 Hz, CH_3-CH), 7.47 (1H, d, *J* = 5.5 Hz, aromatic), 7.60 (1H, dd, *J* = 11, 8.5, 1.5 Hz, aromatic), 8.05 (1H, br d, *J* = 11 Hz, aromatic), 8.15 (1H, dd, *J* = 11, 1 Hz, aromatic), 8.91 (1H, br d, *J* = 5.5 Hz, N=CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.1, 21.7, 68.2, 117.1, 122.8, 125.0, 126.8, 129.2, 130.4, 147.1, 148.3, 150.2, 169.9. MS (EI) *m/z* 215 (M^+). HRMS (EI) for $C_{13}H_{13}NO_2$ (M^+), calcd 215.0946, found 215.0938. (-)-**Alcohol 8-15:** $[\alpha]_D$ -86.6 ° (*c* 1.00, $CHCl_3$). IR (KBr) ν_{max} 3215, 2975, 1592, 1511, 1121, 1070 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.64 (3H, d, *J* = 6.5 Hz, CH_3-CH), 3.32 (1H, br s, CH-OH), 5.65 (1H, q, *J* = 6.5 Hz, CH-CH_3), 7.53 (1H, ddd, *J* = 8.5, 7, 1.5 Hz, aromatic), 7.57 (1H, d, J = 4.5 Hz, aromatic), 7.67 (1H, ddd, *J* = 8.5, 7, 1.5 Hz, aromatic), 8.01 (1H, dd, *J* = 8, 1.5 Hz, aromatic), 8.08 (1H, dd, *J* = 8, 1.5 Hz, aromatic), 8.76 (1H, d, *J* = 4.5 Hz, N=CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 24.6, 65.9, 116.7, 123.0, 125.3, 126.5, 129.1, 129.9, 147.9, 150.3, 151.7. MS (EI) m/z 173 (M^+). HRMS (EI) for $C_{11}H_{11}NO$ (M^+), calcd 173.0840, found 173.0834. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.26; H, 6.40; N, 8.09. Found C, 76.49; H, 6.28; N, 7.80.



(+)-**8-16** (+)-**8-15** [2091]

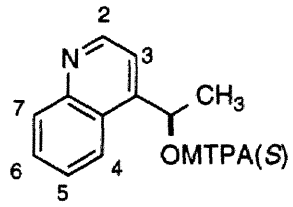
(+)-**Alcohol 8-15.** The acetate (+)-**8-16** (4.27 g, 19.9 mmol) was dissolved in MeOH (130 mL). To this solution was added K_2CO_3 (2.6 g). After stirring at rt for 30 min, the mixture was evaporated. The residue was dissolved in CH_2Cl_2-water, extracted with CH_2Cl_2 (x2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica, CH_2Cl_2/MeOH = 20:1) to give alcohol (+)-**8-15**. $[\alpha]_D$ +84.4 ° (*c* 1.19, $CHCl_3$).



[1030]

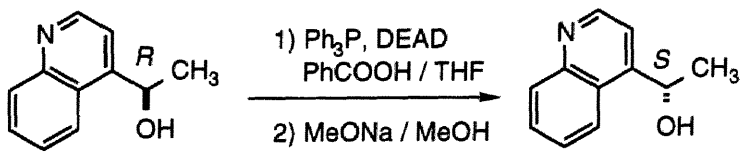
(*R*)-**MTPA ester 8-17.** The (+)-alcohol **8-15** (15.4 mg, 0.089 mmol) and DMAP (10.9 mg, 0.089 mmol) were dissolved in CH_2Cl_2 (0.3 mL). To this solution were added Et_3N (61 μL, 0.43 mmol) and (*S*)-MTPA-Cl (20 μL, 0.11 mmol). After stirring at rt for 30 min, additional (*S*)-MTPA-Cl

(10μL, 0.053 mmol) and Et_3N (25 μL, 0.18 mmol) were added. After stirring at rt for 30 min, 3-(dimethylamino)propylamine (30 μL) was added. The mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane = 1:1 x3) to give **8-17** (24.6 mg, 70 %). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.72 (3H, d, J = 6 Hz, CH_3-CH), 3.49 (3H, br q, J = 1 Hz, CH_3O), 6.84 (3H, br q, J = 6 Hz, C*H*-OMTPA), 7.32-7.53 (5H, m, aromatic of MTPA), 7.42 (1H, d, J = 4.5 Hz, 3-H), 7.60 (1H, ddd, J = 8, 7, 1 Hz, H-6), 7.75 (1H, m, J = 8, 7, 1 Hz, H-7), 8.02 (1H, br d, J = 8 Hz, H-5), 8.17 (1H, br d, J = 8 Hz, H-8), 8.89 (1H, d, J = 4.5 Hz, H-2).



[1031]

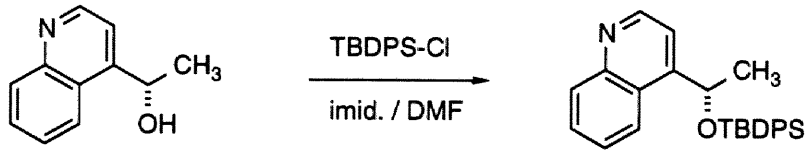
(*S*)-MTPA ester 8-17. The (+)-alcohol **8-15** (10.4 mg, 0.060 mmol) and DMAP (7.3 mg, 0.060 mmol) were dissolved in CH_2Cl_2 (0.2 mL). To this solution were added Et_3N (40 μL, 0.29 mmol) and (*R*)-MTPA-Cl (13 μL, 0.072 mmol). After stirring at rt for 30 min, additional (*R*)-MTPA-Cl (5 μL, 0.027 mmol) and Et_3N (10 μL, 0.072 mmol) were added. After stirring at rt for 10 min, 3-(dimethylamino)propylamine (20 μL) was added. The mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (silica, ether/hexane = 1:1 x4) to give **8-17** (12.4 mg, 53 %). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.78 (3H, d, J = 6.5 Hz, CH_3-CH), 3.62 (3H, br q, J = 1 Hz, CH_3 of MTPA), 6.80 (1H, q, J = 7 Hz, C*H*-OMTPA), 7.18 (1H, d, J = 5 Hz, H-3), 7.31-7.50 (5H, aromatic of MTPA), 7.56 (ddd, J = 8, 7, 1 Hz, H-6), 7.73 (1H, ddd, J = 8, 7, 1 Hz, H-7), 7.97 (1H, br d, J = 8 Hz, H-5), 8.15 (1H, br d, J = 8 Hz, H-8), 8.79 (1H, d, J = 5 Hz, H-1).



(+)-**8-15** (-)-**8-15**

Mitsunobu Inversion: (1) The alcohol **(+)-8-15** (100 mg, 0.58 mmol) was dissolved in THF (2.5 mL). To this solution were added Ph_3P (302 mg, 1.20 mmol) and benzoic acid (140 mg, 1.20 mmol) and the mixture was cooled to 0 °C. DEAD (0.2 mL, 1.2 mmol) was added, the mixture was allowed to warm to rt. After stirring at rt for 1 h, the mixture was evaporated. The residue was dissolved in ether, the solution was washed with sat. $NaHCO_3$ solution (x3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25g, ether/hexane = 3:1) and then preparative TLC (silica, AcOEt/hexane = 3:1) to give the benzoate (124 mg, 77 %). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.83 (3H, d, J = 6.5 Hz, CH_3), 6.84 (1H, q, J = 6.5 Hz, C*H*-OBz), 7.44-7.78 (6H, m, aromatic), 8.10-8.20 (4H, m, aromatic), 8.92 (1H, d, J = 4H, aromatic). (2) The benzoate (23 mg, 0.083 mmol) was dissolved in MeOH (1.2

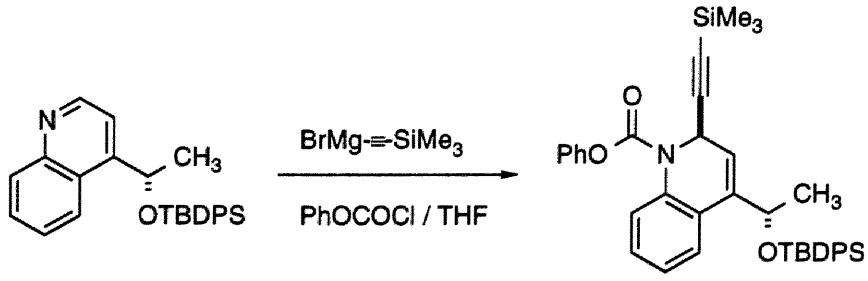
mL). After cooling to 0 °C, MeONa (2M solution in MeOH, 0.04 mL, 0.083 mmol) was added. After stirring at 0 °C for 1 h 10 min, the solution was stirred at rt for 25 min. The mixture was mixed with water, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by preparative TLC to give alcohol **(-)-8-15** (13 mg, 90 %, 96 % ee, ^1H NMR analysis of its (*R*)-MTPA ester).



(+)-8-15 **(-)-8-18** [2005]

(-)-8-18. A solution of alcohol (+)-**8-15** (4.61 g, 26.6 mmol), imidazole (5.50g, 80.8 mmol) and TBDPS-Cl (8.40 mL, 32.3 mmol) was stirred at 70 °C for 19 h. After cooling to 0 °C, the mixture was quenched with sat. $NaHCO_3$ solution, extracted with ether (x4). The combined organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 300 g, ether/hexane = 1:3) to give the **(-)-8-18** (10.2 g, 92 %). $[\alpha]_D$ -50.6 ° (*c* 0.810, $CHCl_3$). IR (KBr) ν_{max} 3072, 2933, 2858, 1592, 1510, 1472, 1428 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (9H, s, $SiC(CH_3)_3$), 1.48 (3H, d, *J* = 6 Hz, $CH\text{-}CH_3$), 5.55 (1H, q, *J* = 6 Hz, $CH_3\text{-}CH$), 7.18 (2H, tt, *J* = 7, 1.5 Hz, aromatic), 7.30 (1H, tt, *J* = 7, 1.5 Hz, aromatic), 7.36-7.50 (6H, m, aromatic), 7.61-7.67 (1H, m, aromatic), 7.67 (1H, d, *J* = 5 Hz, aromatic), 7.73-7.78 (2H, m, aromatic), 7.80 (1H, br d, *J* = 8 Hz, aromatic), 8.11 (1H, br d, *J* = 8 Hz, aromatic), 8.90 (1H, d, *J* = 5 Hz, *CH*=N). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.2, 26.0, 26.8, 68.2, 117.4, 123.0, 124.9, 126.0, 127.4, 127.6, 128.7, 129.6, 129.7, 130.1, 132.9, 133.7, 135.5, 135.7, 148.1, 150.4, 151.6. MS (EI) *m/z* 354 ($M\text{-}C_6H_5$). Anal. Calcd for $C_{27}H_{31}ONSi$: C, 78.79; H, 7.10; N, 3.40. Found C, 78.82; H, 7.00; N, 3.38.

(+)-8-18. Prepared in 86 % from **(-)-8-15** in a similar manner to **(-)-18**. $[\alpha]_D$ +51.3 ° (c 1.07, $CHCl_3$).

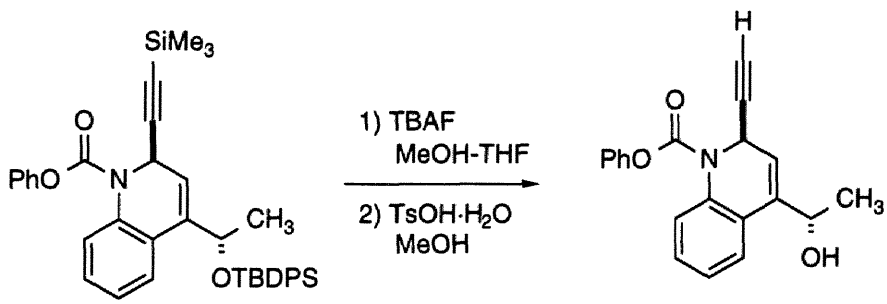


(-)-8-18 **(+)-8-19** [2063]

(+)-8-19. To a solution of trimethylsilylacetylene (3.6 mL, 26 mmol) in dry THF (56 mL) cooled to 0 °C was added dropwise EtMgBr (3M in Et_2O, 8.6 mL, 26 mmol). The solution was stirred at rt for 30 min, and cooled to -78 °C again. To the resultant solution was added a solution of (-)-**8-18** (7.05 g, 17 mmol) in THF (28 mL) *via* cannula tube. After stirring at -78 °C for 2 h 10 min, a solution

of phenyl chloroformate (4.3 mL, 34 mmol) in THF (21 mL) cooled to -78 °C was added *via* cannula tube. After stirring at -78 °C for 2 h 35 min, the reaction mixture was quenched with sat. NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 400 g, ether/hexane = 1:15) to give **(+)-8-19** (7.68 g, 71 %). $[\alpha]_D$ +155 ° (*c* 1.08, $CHCl_3$). IR (KBr) ν_{max} 3072, 2962, 2856, 2171, 1783, 1720, 1593, 1488 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.06 (9H, s, $Si(CH_3)_3$), 1.06 (9H, s, $SiC(CH_3)_3$), 1.43 (3H, d, *J* = 6.5 Hz, CH_3-CH), 4.63 (1H, q, *J* = 6.5 Hz, C*H*-OTBDOS), 5.78 (1H, d, *J* = 7 Hz, olefinic, or propargylic), 5.85 (1H, d, *J* = 7 Hz, olefinic, or propargylic), 7.12-7.46 (14H, m, aromatic), 7.63-7.78 (2H, m, aromatic), 7.72-7.77 (2H, m, aromatic), 7.86 (1H, dd, *J* = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 19.3, 23.8, 27.0, 44.8, 71.6, 88.7, 101.0, 121.6, 124.6, 125.0, 125.7, 127.4, 127.6, 129.3, 129.6, 129.7, 133.2, 134.2, 135.8, 136.2, 138.4, 151.0. MS (EI) *m/z* 629 (M^+). Anal. Calcd for $C_{39}H_{43}O_3NSi_2$: C, 74.36; H, 6.89; N, 2.22. Found C, 74.41; H, 6.80; N, 2.23.

(-)-8-19. Prepared in 68 % from **(+)-8-18** in a similar manner to **(+)-8-19**. $[\alpha]_D$ -163 ° (c 1.02, $CHCl_3$).

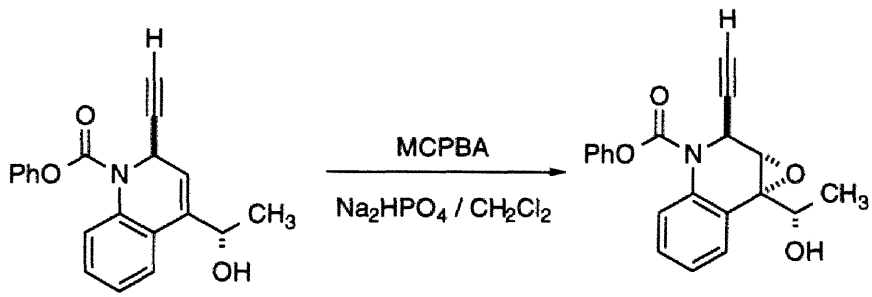


(+)-8-19 **(+)-8-20** [2067] [2069]

(+)-8-20. The acetylene **(+)-8-19** (1.99 g, 3.15 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. To this solution were added MeOH (0.26 mL, 6.30 mmol) and *n*-Bu_4NF (1 M in THF, 1.6 mL, 1.6 mmol). After stirring at -78 °C for 25 min, the reaction mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was dissolved in MeOH (40 mL) and mixed with $TsOH{\cdot}H_2O$ (1.27 g, 6.68 mmol). The mixture was heated at reflux temperature for 11.5 h. After cooling to rt, pyridine (1.1 mL, 13.4 mmol) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in AcOEt and organic layer was washed with water (x2), sat. NH_4Cl solution (x1) and brine (x2), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by column chromatography (silica 80 g, ether/hexane = 3:2) to give **(+)-alcohol 8-20** (850 mg, 84 % 2 steps). $[\alpha]_D$ +316 ° (*c* 0.434, $CHCl_3$). IR (KBr) ν_{max} 3442, 3290, 2974, 2112, 1713, 1592, 1489 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ . 1.56 (3H, d, *J* = 6 Hz, CH_3-CH), 1.87 (1H, d, *J* = 4 Hz, O*H*), 2.23 (1H, d, *J* = 3 Hz, C≡C-*H*), 4.91 (1H, m, CH_3-C*H*), 6.00 (1H, dd, *J* = 6, 3 Hz, propargylic), 6.18 (1H, dd, *J* = 6, 1 Hz, olefinic), 7.15-7.42 (7H, m, aromatic), 7.60 (1H, dd, *J* = 8, 2 Hz, aromatic), 7.76 (1H, d, *J* = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.9, 43.9, 66.8, 72.1, 79.6, 121.5, 124.0,

124.9, 125.1, 125.8, 128.1, 129.4, 139.2, 150.8. MS (EI) *m/z* 319 (M^+), 275, 242. HRMS (EI) for $C_{20}H_{17}NO_3$ (M^+), calcd 319.1208, found 319.1218.

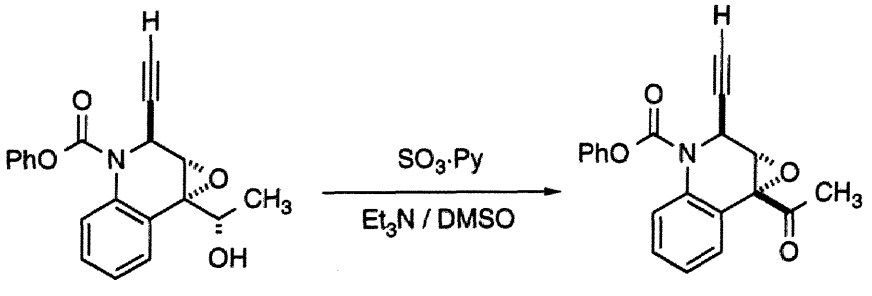
(-)-8-20. Prepared in 84 % from **(-)-8-19** in a similar manner to **(+)-8-20**. $[\alpha]_D$ -336 ° (c 0.957, $CHCl_3$).



(+)-8-20 **(+)-8-21** [2075]

(+)-Epoxy alcohol 8-21. (+)-Allylic alcohol **8-20** (829 mg, 2.60 mmol) and Na_2HPO_4 (1.55 g, 8.82 mmol) were dissolved in CH_2Cl_2 (25 mL) and the mixture was cooled to 0 °C. To this solution was added MCPBA (ca. 80 % purity, 952 mg, 4.41 mmol) portionwise. After stirring at 0 °C for 2 h 10 min, additional MCPBA (80 % purity, 112 mg, 0.52 mmol) was added. The mixture was stirred at 0 °C for 1 h and quenched with Na_2SO_3 until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 45 g, ether/hexane = 3:1) to give (+)-epoxide **8-21** (776 mg, 89 %). $[\alpha]_D$ +142 ° (*c* 1.01, $CHCl_3$). IR (KBr) ν_{max} 3514, 3284, 2981, 2121, 1721, 1593, 1495 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 6 Hz, CH_3-CH), 1.58 (1H, s, *OH*), 2.23 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 4.09 (1H, d, *J* = 3 Hz, epoxide), 4.84 (1H, br q, *J* = 6 Hz, *CH*-OH), 5.94 (1H, t, *J* = 2 Hz, *CH*-C≡C), 7.13 (2H, d, *J* = 7 Hz, aromatic), 7.18-7.30 (2H, m, aromatic), 7.32-7.43 (3H, m, aromatic), 7.54 (1H, dd, *J* = 8 Hz, aromatic), 7.60 (1H, br d, *J* = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.3, 43.4, 58.8, 61.5, 62.2, 74.2, 77.1, 121.4, 124.9, 125.6, 125.7, 126.7, 127.2, 128.7, 129.3, 135.0, 150.8. MS (EI) *m/z* 335 (M^+). HRMS (EI) for $C_{20}H_{17}NO_4$ (M^+), calcd 335.1157, found 335.1142.

(-)-8-21. Prepared in 99 % from **(-)-8-20** in a similar manner to **(+)-8-21**. $[\alpha]_D$ -127 ° (*c* 1.18, $CHCl_3$).

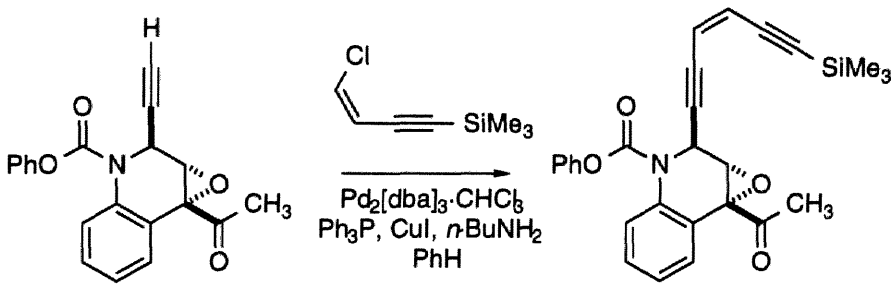


(+)-8-21 **(+)-8-22** [2077]

(+)-Epoxyketone 8-22. (+)-epoxyalcohol **8-21** (768 mg, 2.29 mmol) was dissolved in CH_2Cl_2 (6 mL) and DMSO (12 mL) and Et_3N (4.8 mL, 34 mmol) and the mixture was cooled to 0 °C. To this

solution was added SO_3·Py (3.64 g, 22.9 mmol) portionwise. After stirring at rt for 1.5 h, the mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with brine (x3), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane = 1:1) to give (+)-epoxyketone **8-22** (593 mg, 78 %). $[\alpha]_D$ +123 ° (*c* 0.957, $CHCl_3$). IR (KBr) ν_{max} 3289, 3073, 2123, 1720, 1493 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.27 (1H, d, *J* = 2 Hz, C≡C-*H*), 2.37 (3H, s, CH_3CO), 4.04 (1H, d, *J* = 3 Hz, epoxide), 5.99 (1H, dd, *J* = 3 Hz, C≡C-C*H*), 7.13 (2H, br d, *J* = 8 Hz, aromatic), 7.26 (2H, tt, *J* = 8, 1 Hz, aromatic), 7.32-7.45 (3H, m, aromatic), 7.58 (1H, br d, *J* = 8 Hz, aromatic), 7.69 (1H, dd, *J* = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 26.5, 43.2, 59.9, 64.5, 75.0, 76.0, 121.3, 122.1, 125.8, 127.2, 128.7, 129.2, 129.3, 134.6, 150.8. MS (EI) *m/z* 333 (M^+). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found C, 72.02; H, 4.49; N, 4.17.

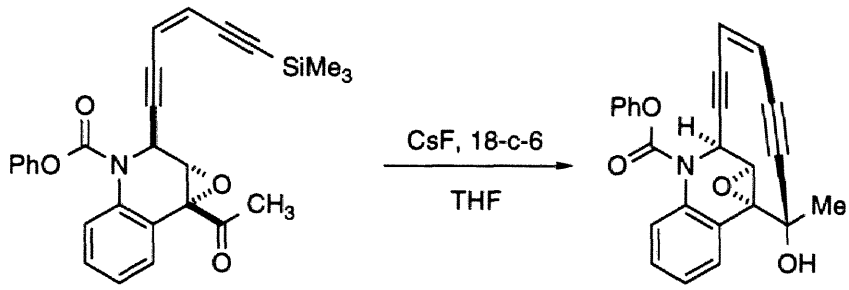
(-)-8-22. Prepared in 75 % from **(-)-8-21** in a similar manner to **(-)-8-22.** $[\alpha]_D$ -120 ° (*c* 1.08, $CHCl_3$).



(+)-8-22 **(+)-8-23** [2079]

(+)-Enediyne 8-23. A suspension of (+)-acetylene **8-22** (203 mg, 0.609 mmol), $Pd_2[dba]_3$·$CHCl_3$ (15.5 mg, 0.152 mmol), Ph_3P (16 mg, 0.061 mmol) and CuI (11.6 mg, 0.061 mmol) in benzene (7.5 mL) was degassed by three freeze-thaw cycles and covered in argon. To this mixture were added the (Z)-chloro-4-trimethylsilyl-1-buten-3-yne (80 % purity, 456 mg, 2.44 mmol) in benzene (1.5 mL) and *n*-$BuNH_2$ (0.12 mL, 1.22 mmol). After stirring at rt for 2 h under argon, the mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with brine, died over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane = 1:3) to give (+)-enediyne **8-23** (176 mg, 64 %). $[\alpha]_D$ +92.2 ° (*c* 0.434, $CHCl_3$). IR (KBr) ν_{max} 3049, 2967, 2142, 1716, 1582, 1492 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.23 (9H, s, $Si(CH_3)_3$), 2.37 (3H, s, CH_3CO), 4.07 (1H, d, *J* = 2.5 Hz, epoxide), 5.69 (1H, dd, *J* = 11, 2 Hz, C*H*=CH-C≡C-TMS), 5.84 (1H, d, *J* = 11 Hz, CH=C*H*-C≡C-TMS), 6.24 (1H, t, *J* = 2.5 Hz, C*H*-C≡C), 7.14 (2H, d, *J* = 8 Hz, aromatic), 7.19-7.29 (2H, m, aromatic), 7.33-7.44 (3H, m, aromatic), 7.59 (1H, br d, *J* = 8 Hz, aromatic), 7.71 (1H, dd, *J* = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 26.5, 44.1, 59.9, 64.5, 83.3, 88.7, 101.3, 103.8, 118.9, 121.1, 121.3, 122.1, 125.8, 127.2, 128.7, 129.1, 129.3, 134.6, 150.6, 202.5. MS (EI) *m/z* 456 (M^+). Anal. Calcd for $C_{27}H_{25}O_4NSi$: C, 71.18; H, 5.53; N, 3.07. Found C, 71.21; H, 5.49; N, 3.07.

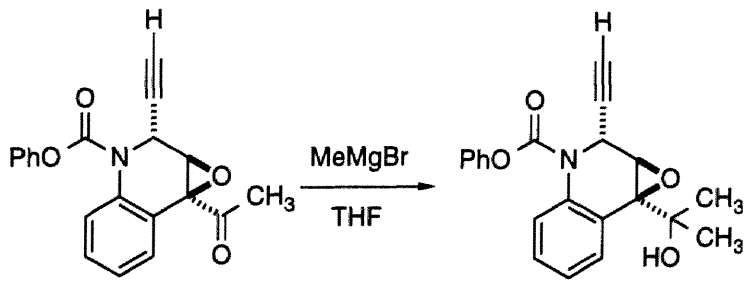
(-)-8-23. Prepared in 57 % from **(-)-8-22** in a similar manner to **(+)-8-23**. $[\alpha]_D$ -76.0 ° (*c* 0.570, benzene).



(+)-8-23 **(+)-8-24** [2081]

(+)-Cyclic enediyne 8-24. Powder of CsF (67 mg, 0.44 mmol) was placed in a dry two necked flask and heated at 100 °C *in vacuo* for 1 h 50 min. After cooling to rt, dry THF (20 mL) was added. To this suspension were added **(+)-8-23** (115 mg, 0.253 mmol) in THF (2.5 mL) and 18-crown-6 (100 mg, 0.379 mmol) in THF (1.0 mL). After stirring at rt for 4 h, the reaction was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with water (x2), brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2) to give the cyclic enediyne **8-24** (10.8 mg, 12 %). $[\alpha]_D$ +530 ° (*c* 0.54, benzene). IR (KBr) ν_{max} 3469, 3060, 1720, 1492, 1381, 1324, 1204 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.73 (3H, s, C(OH)C*H*$_3$), 4.07 (1H, d, *J* = 3 Hz, epoxide), 5.67 (1H, dd, *J* = 10, 2 Hz, N-CH-C≡C-C*H*=CH), 5.82 (1H, d, *J* = 10 Hz, N-CH-C≡C-CH=C*H*), 5.89 (1H, dd, *J* = 3, 2 Hz, propargylic), 7.14 (2H, br d, J = 8 Hz, aromatic), 7.20-7.28 (2H, m, aromatic), 7.31-7.41 (3H, m, aromatic), 7.51 (1H, br d, *J* = 8 Hz, aromatic), 8.80 (1H, dd, *J* = 8, 1.5 Hz, aromatic). MS (EI) *m/z* 383 (M^+). HRMS (EI) for $C_{24}H_{17}O_4N$ (M^+), 383.1157, found 383.1156.

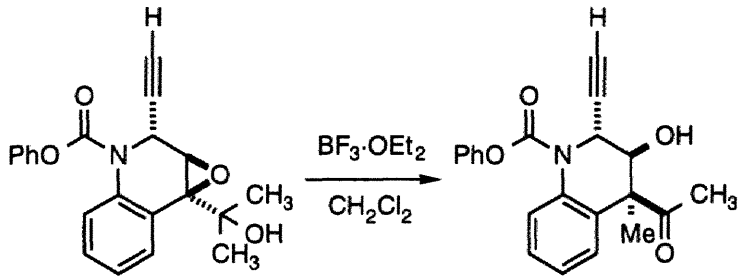
(-)-8-24. Prepared in 12 % from **(-)-8-23** in a similar manner to **(+)-8-24.** $[\alpha]_D$ -591 ° (*c* 0.50, benzene).



(-)-8-22 **(-)-8-25** [16175]

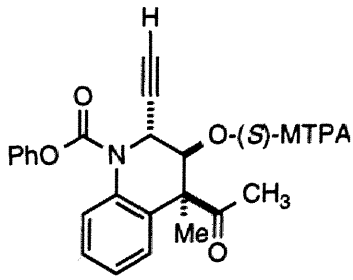
Compound 8-25. The epoxyketone **(-)-8-22** (166 mg) was dissolved in THF (5 mL) and cooled to 0 °C. To this solution was added MeMgBr (0.9 M in THF, 0.83 mL, 0.75 mmol). After stirring at 0 °C for 20 min, the mixture was quenched with sat. NH_4Cl solution, and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 10 g, ether/hexane =

1:1) to give **8-25** (175 mg, quant). $[\alpha]_D$ -171 ° (*c* 1.39, $CHCl_3$). IR (KBr) ν_{max} 3468, 3290, 2979, 2121, 1717, 1492, 1378, 1327, 1205 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 (3H, s, CH_3-C-OH), 1.70 (3H, s, CH_3-C-OH), 2.20 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 4.21 (1H, d, *J* = 3 Hz, epoxide), 5.86 (1H, t, *J* = 3 Hz, C≡C-C*H*), 7.09-7.41 (7H, m, aromatic), 7.56 (1H, br d, *J* = 8 Hz, aromatic), 8.05 (1H, br d, *J* = 8 HZ, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 25.9, 27.5, 43.5, 61.6, 63.8, 70.6, 74.1, 77.2, 121.4, 125.3, 125.5, 125.6, 127.8, 129.2, 129.6, 135.7, 150.9. MS (EI) *m/z* 349 (M^+). HRMS (EI) for $C_{21}H_{19}NO_4$ (M^+), calcd 349.1313, found 349.1300.



8-25 **8-26** [16171]

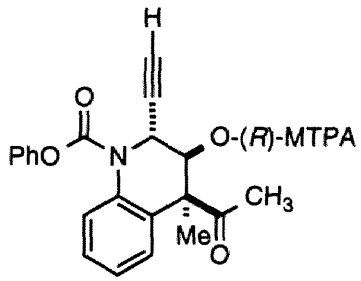
Compound 8-26. The alcohol **8-25** (32 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to -78 °C. To this solution was added $BF_3{\cdot}OEt_2$ (0.45 M in CH_2Cl_2, 0.10 mL, 0.046 mmol). After stirring for 35 min, the reaction mixture was allowed to warm to -20 °C and stirred for 1 h. The mixture was quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 2:1, CH_2Cl_2) to give **8-26** (16.8 mg, 52 %). $[\alpha]_D$ -222 ° (*c* 0.28, $CHCl_3$). IR (KBr) ν_{max} 3490, 3289, 2929, 2121, 1728, 1489, 1375, 1321, 1201 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.75 (3H, s, Ar-C-CH_3), 1.83 (3H, s, CH_3-CO), 2.33 (1H, d, *J* = 2Hz, C≡C-*H*), 3.61 (1H, dd, *J* = 12, 7 Hz, C*H*-OH), 4.24 (1H, d, *J* = 12 Hz, O*H*), 5.10 (1H, br d, *J* = 7 Hz, C≡C-C*H*), 7.15 (2H, br d, *J* = 8 Hz, aromatic of PhO), 7.23 (1H, br t, *J* = 7.5 Hz, aromatic), 7.32-7.48 (5H, m, aromatic), 7.62 (1H, br d, *J* = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.6, 26.7, 53.0, 54.2, 71.6, 82.3, 83.2, 121.4, 124.8, 125.8, 126.3, 126.9, 128.7, 129.3, 133.9, 135.5, 150.8, 152.0, 214.9. MS (EI) *m/z* 306 (M-C_2H_3O), 289 (306-OH). MS (FAB) *m/z* 350 (M+H). HRMS (FAB) for $C_{21}H_{20}NO_4$ (M+H), calcd 350.1392, found 350.1379.



[16167]

(*S*)-MTPA ester 8-27. ^1H NMR (270 MHz, $CDCl_3$) δ 1.53 (3H, s, CH_3-C-Ar), 1.79 (3H, s, CH_3-CO), 2.37 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 3.61 (3H, br s, CH_3O), 5.31 (1H, d, *J* = 7 Hz, C*H*-

OMTPA), 5.58 (1H, br d, J = 7 Hz, C≡C-C*H*), 7.16 (2H, J = 18 Hz, aromatic of PhO), 7.23 (1H, br t, J = 8 Hz, aromatic), 7.30-7.47 (8H, m, aromatic), 7.63 (2H, m, aromatic of MTPA), 7.66 (1H, br d, J = 7.5 Hz, aromatic).



[16169]

(*R*)-MTPA ester 8-27. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, s, CH_3-C-Ar), 1.87 (3H, s, CH_3CO), 2.33 (1H, d, J = 2.5 Hz, C≡C-*H*), 3.56 (3H, br s, CH_3O), 5.35 (1H, d, J = 7 Hz, C*H*-OMTPA), 5.55 (1H, dd, J = 7, 2.5 Hz, C≡C-C*H*), 7.13 (2H, J = 8 Hz, aromatic of PhO), 7.22 (1H, br t, J = 7.5 Hz, aromatic), 7.31-7.47 (8H, m, aromatic), 7.8 (2H, m, aromatic of MTPA), 7.67 (1H, br d, J = 8 Hz, aromatic).

List of Publications:

1. Nishikawa, T.; Isobe, M.; late Goto, T. (Trimethylsilyl)- and (Tributylstannyl) acetylenes as Nucleophiles Toward Acyliminium Cation: A Plausible Key Reaction for Dynemicin, an Enediyne Antitumor Antibiotic. *Synlett*, **1991**, 99-101.

2. Nishikawa, T.; Ino, A.; Isobe; M. and Goto, T. Synthesis of a Simple Model Compound of Dynemicin and Cycloaromatization with Pinacol-Pinacolone Rearrangement in the Strained Enediyne Medium Ring. *Chemistry Letters*, **1991**, 1271-1274.

3. Nishikawa, T.; Isobe, M.; Goto, T. Synthetic Studies on the Bicyclo[7.3.1]-tridecendiyne System in an Antitumor Antibiotic, Dynemicin A. *Synlett*, **1991**, 393-395.

4. Nishikawa, T.; Ino, A.; Isobe, M. Synthetic Studies on Antibiotic Dynemicin A. Synthesis of Cyclic Enediyne Model Compound of Dynemicin A. *Tetrahedron* **1994** , *50*, 1449-1468.

5. Nishikawa, T.; Isobe, M. Synthetic Studies on Dynemicin A. New Quinoline Synthesis for C, D and E Rings. *Tetrahedron* **1994**, *50*, 5621-5632.

6. Nishikawa, T.; Yoshikai, M.; Obi, K.; Isobe, M. Synthesis of Both Enantiomers of Dynemicin A Model Compound. New Remote Asymmetric Induction in Acetylide Addition into Quinoline Nucleus. *Tetrahedron Letters* in press.

List of additional Publications:

1. Isobe, M.; Fukami, N.; Nishikawa, T.; Goto, T. Synthesis of Chiral Cyclohexanes from Levoglucosenone and its Application to an Indole Alkaloid Reserpine. *Heterocycles,* **1987**, *25*, 521-532.

2. Isobe, M.; Nishikawa, T.; Fukami, N.; Goto, T. Synthetic Studies on a Stereochemically Complex Natural Product: Designs for the Total Synthesis of (-)-Tetrodotoxin. *Pure & Applied Chemistry,* **1987**, *59* , 399-406.

3. Isobe, M.; Nishikawa, T.; Pikul, S.; Goto, T. Synthetic Studies on Tetrodotoxin (1). Stereocontrolled Synthesis of the Cyclohexane Moiety: *Tetrahedron Letters*, **1987**, *28* , 6485-6488.

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論　文　目　録

報告番号	※　第　　号	氏名	西川　俊夫
主論文	題目 Synthetic Studies on Cyclic Enediyne Antibiotic, Dynemicin A （環状エンジイン抗生物質ダイネミシンAの化学合成研究） 主論文（要約）の印刷公表の方法および時期は別紙のとおり		
参考論文	(有)・無 参考論文の印刷公表の方法および時期は別紙のとおり		
備考			

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