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Methodology for stereochemical control in bioactive natural product synthesis—new methods toward enediyne antitumor antibiotics

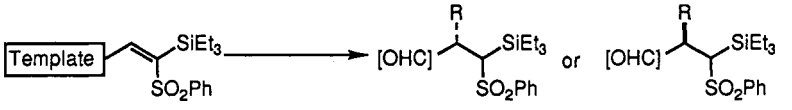
Minoru Isobe,* Toshio Nishikawa, Angkana Herunsalee, Takahiro Tsukiyama, Yumi Hirose, Ken-ichirou Shimokawa and Toshio Goto

Laboratory of Organic Chemistry, School of Agriculture, Nagoya University, Chikusa, Nagoya 464, Japan

ABSTRACT - Acetylenic compounds are of great interests in the development of the synthetic methodologies directed toward enediyne antitumor antibiotics. This paper discusses on the new asymmetric synthesis *via* heteroconjugate addition methodology by utilizing acetylide carbanions as the nucleophiles. On the other hand, silyl acetylenes can be nucleophiles under acidic condition and the products are quite useful as the precursor of heteroolefins. Most of the reactions undergo in highly stereoselective.

INTRODUCTION

Synthesis of stereochemically complex molecules from natural sources with biological activities has been the most challenging field even though so many methodologies have become available by now. This may be mainly because of the continuous efforts finding the biologically important natural products and new class of compounds which requests new synthetic methodologies. These examples are recent antitumor antibiotics with enediyne class containing medium size ring such as esperamicin, calicheamicin and dynemicin. We became interested in developing methodologies useful toward these molecules through asymmetric synthesis *via* heteroconjugate addition base. In our previous studies, some sugars (or a terpenoid) were employed as chiral templates in the electrophile **1**,[1] and several examples had been demonstrated in the total syntheses of a polyether, okadaic acid[2] and an ansa-macrolide, maytansine,[3] etc. Recently, we have reported a system exemplified by equation 1; where a sesquiterpene, camphor derivative, was employed as template in **1**.[4] Addition of alkyl carbanion to **1** could afford the adduct equivalent to **2** or **3** with high diastereoselectivity. Stereoselective C-C bond forming process giving products of type **2** (α) or type **3** (β) in eq. 1 are further awaited.

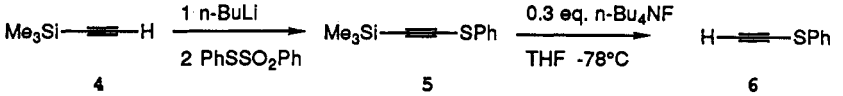


eq. 1

1 **2** **3**

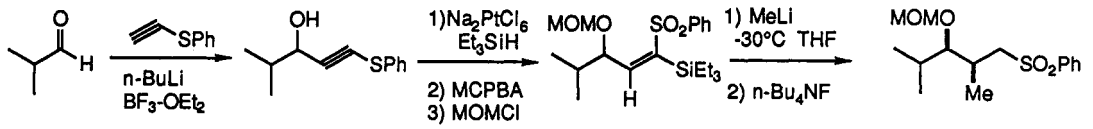
PREPARATION OF THE HETEROOLEFIN VIA HYDROSILATION AND ADDITION

The electrophilic olefins conjugated with two hetero atom groups, triethylsilyl and phenyl sulfonyl, had been prepared *via* Peterson olefination between an aldehyde and bistrimethylsilyl(thiophenyl)methyllithium which was followed by oxidation with MCPBA. An alternative route for the type **1** olefin (heteroatom group-conjugated olefin =hetero-olefin) generally involves hydrosilation to phenyl sulfinyl acetylenes followed by oxidation with oxone. It takes several steps if starting from an acetylenic compound such as **4**, which is sulfinylated *via* lithium acetylide intermediate to give **5**. Its de-silylated product **6**[5] was obtained in high yield by treatment at -78°C because it is unstable under basic condition. This can be a precursor of various kinds of heteroolefins.



4 **5** **6**

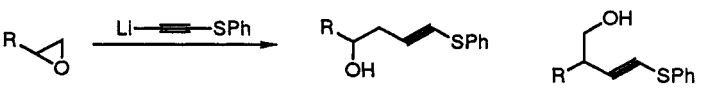
One simple example is the addition of its lithium acetylide of **6** to the aldehyde such as **7** and the product **8** was hydrosilated with triethylsilane in the presence of platinum catalyst and further oxidation and protection of the hydroxy group gave **9**. Conjugate addition of methyllithium and following desilylation gave *syn* product **10** as a single adduct.



7 **8** **9** **10**

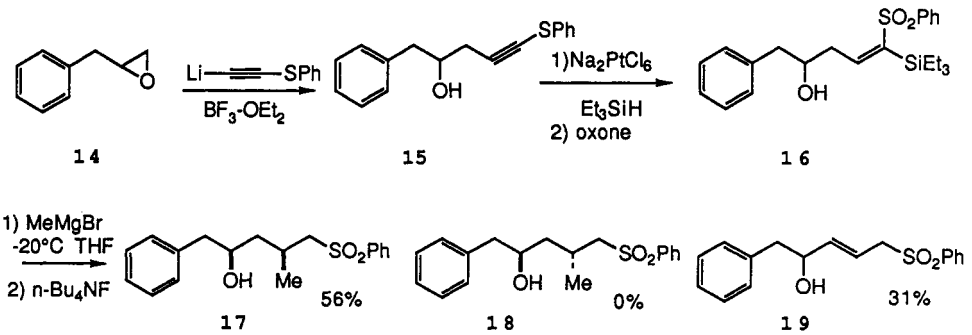
OPENING OF EPOXIDE AND 1,3-ASYMMETRIC INDUCTION

The second example includes opening of epoxide with the same lithium acetylide of **6** in the presence of BF_3-OEt_2 to the adduct. Alkyl epoxide gave **12** which reacted at the terminal position but the arylic (allylic) epoxide afforded the product **13** when 0.8 equiv. of the Lewis acid was used to the lithium acetylide.



11 **6** **12** **13**

The epoxide **14** gave **15**, which was subjected to the hydrosilation and then to an oxidation with a different reagent, oxone (K_2SO_4-$KHSO_4$-$2KHSO_5$) to give the heteroolefin **16**. Addition of the Grignard reagent and the following desilylation gave one single adduct **17** but no **18** and small amount of double bond migration product **19**. The selectivity in the heteroconjugate addition might become due to the chelation control of the nucleophile methylmagnesium bromide with alkoxide from the stable extended intermediate as shown in Fig. 1 but not as the more crowded intermediate in Fig. 2.



14 **15** **16**

17 **18** **19**

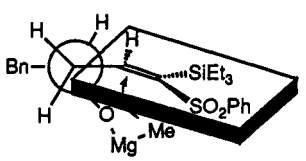


Fig. 1
Possible conformation of extended intermediate

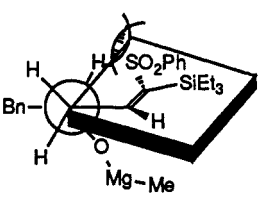


Fig. 2
Crowded conformation

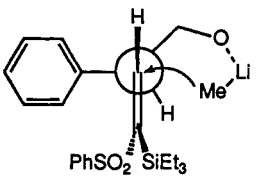
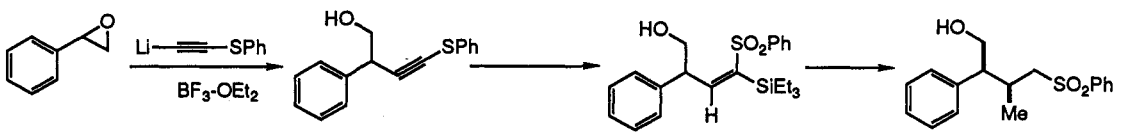


Fig. 3
Conformational preference due to acyclic A-strain effect

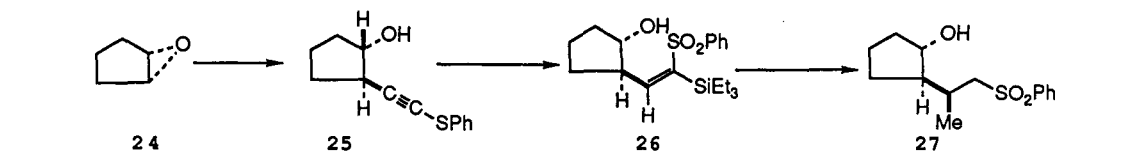
The epoxide, which is conjugated to olefin or aromatic system such as **20**, is cleaved at the benzylic (allylic) position under the same conditions to give hydroxymethyl product as **21**, which was hydrosilylated and oxidized to **22**. Addition of methyllithium afforded **23** as a single product. The mechanism is suggested as illustrated in Fig. 3, which indicates the predominant conformation at the transition state so that the nucleophile is guided through metal chelation.



20 **21** **22** **23**

OPENING OF EPOXIDE IN A RING AND ADDITION OF ACETYLENIC NUCLEOPHILES

Opening of an epoxide ring existing in a carbocyclic compound as **24** was employed because of the symmetry of the molecule. It is interesting to prepare the heteroolefin **26** under the same 3 step-reactions. Conjugate addition of MeLi to **26** afforded a single adduct **27** in 84% yield. In this case, the transition state is easy to estimate as shown in Fig. 4, which suggests the stereochemistry in **27a** with the asterisk to be that as shown. Addition of acetylenes as Li-C≡C-R (R= $SiMe_3$, C≡C-$SiMe_3$, C≡C-CH=CH-C≡C-$SiMe_3$) was also smooth to give the product (after desilylation with n-Bu_4NF) **28**, **29** and **30**.



24 **25** **26** **27**

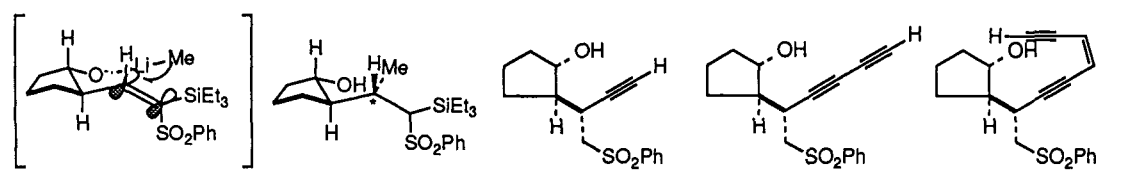
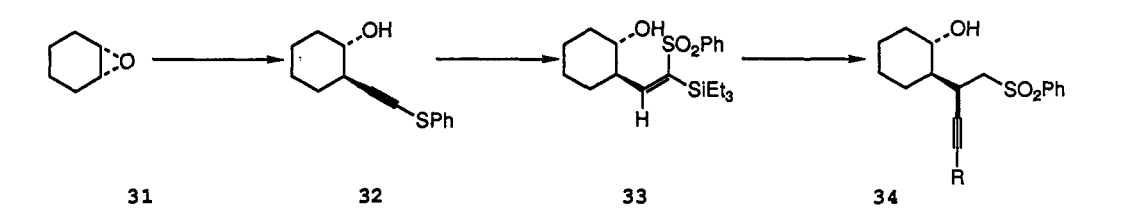


Fig. 4 **27a** **28** **29** **30**

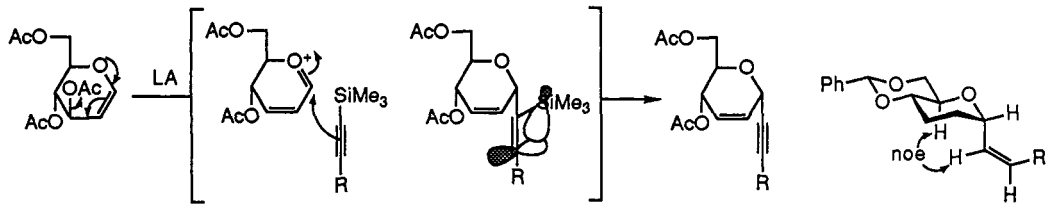
Another example such as **31** was demonstrated to undergo similar reactivity and selectivity for the preparation of **33** and for the heteroconjugate addition of nucleophiles (R= alkyl and alkynyl). The products **34** was again stereochemically pure with all three contiguous asymmetric centers.



31 **32** **33** **34**

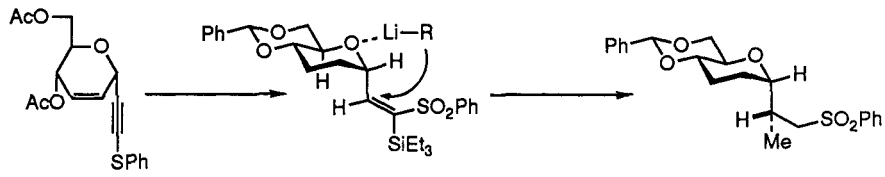
C-GLYCOSIDATION METHOD AND FURTHER FUNCTIONALIZATION

A glucose derivative, **35** D-glucal triacetate, was utilized for C-glycosidation[6] with silyl acetylene as nucleophile indicated in the intermediate **36** under acidic condition with Lewis Acid. The intermediate **37** indicates stabilization due to possible σ-π conjugation from which the trimethylsilyl group eliminates to give **38**. The stereochemistry in the glycosidation was proved to be alpha through the noe studies in the NMR of the dihydro derivative **39**, in which the acetylene was partially hydrogenated.



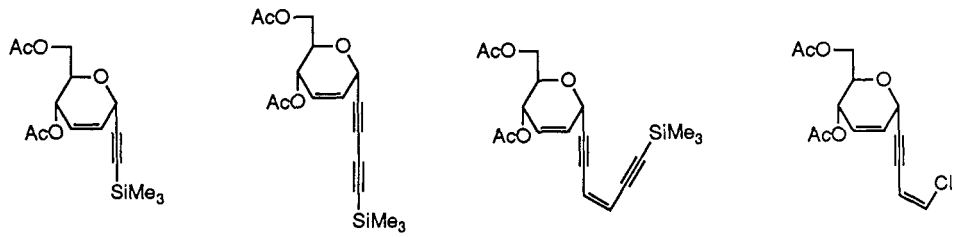
35 36 37 38 39

This is a convenient method for introduction of functionalized acetylenic groups into pyranosyl skeleton in alpha selective manner. One example is **40**, having thiophenyl end, which was hydrosilated and oxidized and further several steps into the heteroolefin **41**. Addition of methyllithium gave **42** as a single product.



40 41 42

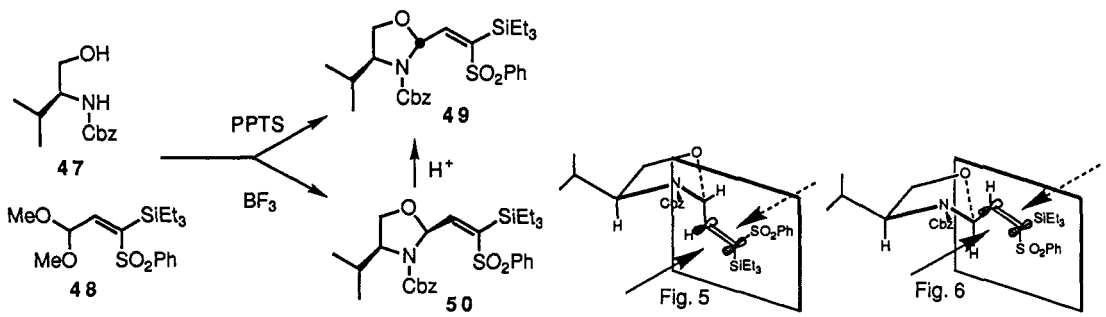
Further examples **43-46** prepared from **35** are listed below, some of them are clearly related to enediyne class compound. Functionalization or conversion of the acetylenic chain are under investigation.



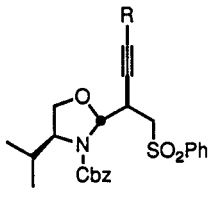
43 44 45 46

HETEROCONJUGATE ADDITION WITH OXAZOLIDINE AS CHIRAL TEMPLATE

The *trans* oxazolidine **49** and *cis* one **50** were selectively prepared by the coupling between the L-valine derivative **47** and heteroolefin acetal **48** depending upon the acidic catalyst. What was expected were the addition of the nucleophile from the front faces in Fig. 5 and Fig. 6.[7]



Heteroconjugate addition of lithium (or magnesium) acetylides gave the adduct as **51** and **52** from the corresponding *trans* and *cis* oxazolidine heteroolefin, respectively; the stereochemistry at the newly generated center being identical. Enediyne derivatives **53** and **54** were introduced from **49**.



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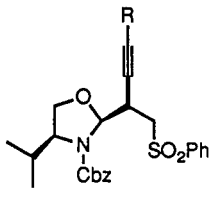

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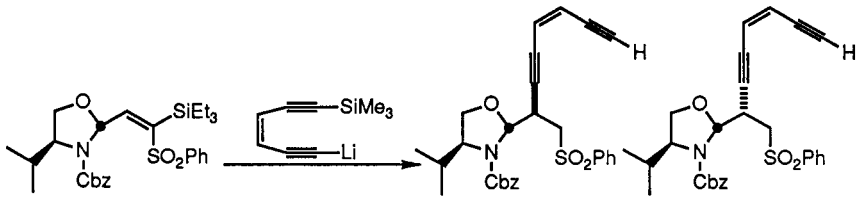
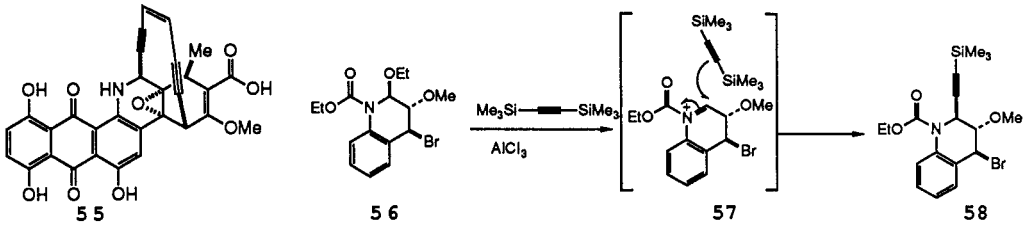


49 53 54

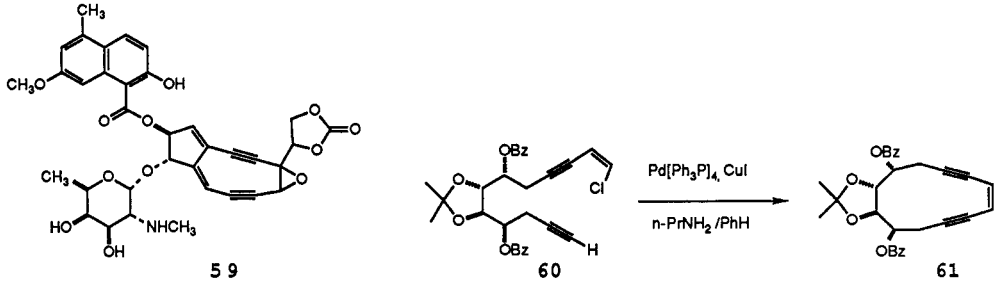
C–C BOND FORMATION WITH SILYL ACETYLENES TO ACYLIMINIUM SALT

The recently reported enediyne antitumor antibiotic, dynemicin **55** with bicyclo[7,3,1]-tridecane, has a propargylic aniline moiety with crucial epoxide ring. One of the key reactions for its synthesis might be the similar silyl acetylene as indicated in a model compound **56**, for example, to form the intermediate acyliminium cation[8] **57** and the similar bond as shown in **58**.



55 56 57 58

Another similar enediyne system as NCS chromophore (**59**) with bicyclo[7,3,0]dodecane ring system. A possible precursor to this might be derived from 12-membered enediyne as **61** cyclized from **60**.



59 60 61

CONCLUSION

The above silyl or sulfinyl acetylenes are demonstrated to be quite useful for the synthesis of natural and unnatural acetylenic derivatives containing enediyne moiety. The methodologies are to be applied in the syntheses of that class compounds in the near future.

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