



Methylenecyclopentane Annulation via Formal [3 + 2] Cycloaddition Reaction

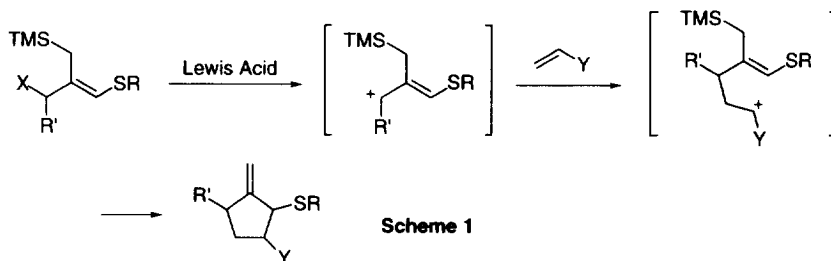
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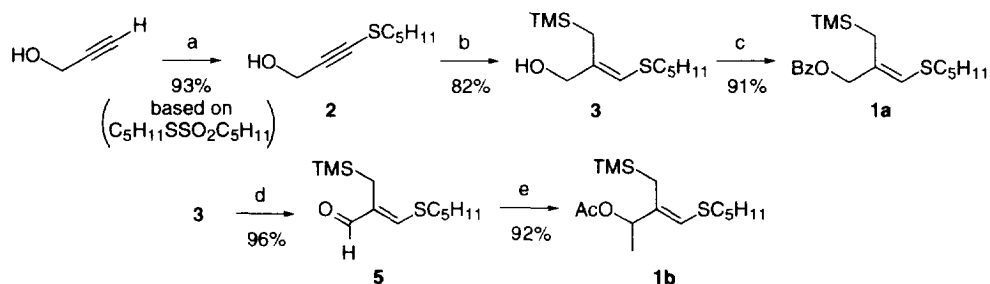
Abstract: A new method for methylenecyclopentane annulation via formal [3+2] cycloaddition reaction was developed. Under the influence of Lewis acids, enol ethers and vinylsulfides were treated with 1-(alkylthio)-2-(trimethylsilylmethyl)allyl esters **1a** or **1b** to afford methylenecyclopentanes in good yields. The reaction proceeds with almost complete regioselectivity as well as high stereoselectivity.
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Cyclopentanes are common structural units of many natural products.¹ Although intramolecular cyclization reaction of open-chain compounds are available for cyclopentane annulation,² [3+2] cycloaddition strategy seems to be more tactical and efficient.³ Recently we described cyclopentanone synthesis via formal [3+2] cycloaddition reaction of 1-(methylthio)-2-(siloxy)allyl cationic species and olefins.⁴ The methylthio group of the three-carbon unit plays important roles in stabilization of a 2-oxyallyl cation intermediate as well as control of the regiochemistry.

In the present paper, we report [3+2] type methylenecyclopentane annulation⁵ using 1-(alkylthio)-2-(trimethylsilylmethyl)allyl ester.



The starting materials **1a** and **1b** were prepared as shown in Scheme 2. The geometry of these vinylsulfides was strictly controlled as (*Z*) by hydroxy group directed carbolithiation of propargyl alcohol 2.



Scheme 2 a) BuLi (1.8 equiv) / THF then C₅H₁₁SSO₂C₅H₁₁ (0.75 equiv), 0 °C–rt; b) TMSCH₂Li (3.5 equiv) / toluene, rt; c) BzCl (1.1 equiv), Et₃N (1.5 equiv) / CH₂Cl₂, rt; d) MnO₂ / hexane, rt; e) MeLi (1.2 equiv) / ether, -45 °C then Ac₂O (1.4 equiv), -45 °C.

Initially, reactions of **1a** with electron-rich olefins were examined in the presence of several Lewis acids. While TiCl₄, SnCl₄, and AlCl₃ afforded desired products in moderate yields, use of BF₃·OEt₂, EtAlCl₂, or MeAl(OTf)₂ was found to give the most satisfactory results. The results are summarized in Table 1.

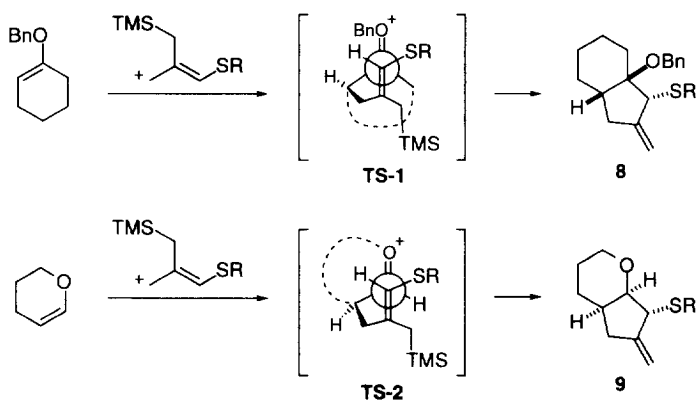
Table 1 methylenecyclopentane annulation with **1a**

entry	olefin	Lewis acid	conditions ^a	products ^b	%yield ^c
1		BF ₃ ·OEt ₂	-23 °C, 1.0 h 0 °C, 2.0 h		75
2		EtAlCl ₂	-23 °C, 0.5 h		81
3		MeAl(OTf) ₂	-23 °C, 0.5 h		78
4		BF ₃ ·OEt ₂	-23 °C, 16 h 0 °C, 2.5 h		50
5		EtAlCl ₂	-45 °C, 1.5 h -23 °C, 1.0 h 0 °C, 1.5 h		24
					18

^a Typical procedure: To a solution of phenyl vinyl sulfide (13.1 μL, 0.10 mmol) and **1a** (35.4 μL, 0.10 mmol) in CH₂Cl₂ (0.3 mL) was added BF₃·OEt₂ (12.3 μL, 0.10 mmol) at -23 °C. After stirring for 1 h at -23 °C and then for 2 h at 0 °C, triethylamine (42 μL, 0.30 mmol) was added. Usual aqueous workup followed by purification by silica gel column chromatography afforded 22 mg (75%) of **6**. ^b Stereochemistry of the products was determined by NOE experiments. ^c Isolated yield of analytically pure product. ^d Containing a small amount of *cis* isomer (*trans* : *cis* = 94 : 6).

Several characteristic features of the reaction have also been clarified: (1) Although the reaction with the enol silyl ether leads to a mixture of annulation product **10** and an acyclic by-product **11** (entry 5), enol alkyl ethers and vinylsulfides afforded corresponding cycloadducts in good yields. (2) The cycloadducts were obtained as a single regioisomer containing vicinal two hetero atoms. Thus, the initial C-C bond formation reaction between the olefins and the 1-(pentylthio)-2-(trimethylsilylmethyl)allyl cation intermediate selectively occurs at the γ -position of sulfur.⁴ (3) Complete diastereoselection was usually achieved to form *trans* isomers exclusively: a small amount of *cis* isomer was formed only in the reaction of phenyl vinyl sulfide (entry 1). The stereochemistry of **6**, **7**, and **8** was assigned by observation of NOE between the allylic methyne proton and SPh, SMe, and OCH₂Ph groups, respectively. The *cis* configuration of pentylthio group and the angular methyne proton of **9** was also determined by NOE experiment.

The configuration of **8** and **9** provides information concerning the origin of the stereochemistry. Despite both of the cycloadducts have analogous bicyclo[4,3,0]nonane skeleton, pentylthio group of **8** and **9** have different orientations, *endo* and *exo*. The annulation reaction proceeds through stepwise mechanism involving an initial C-C bond formation to yield oxonium ion intermediate followed by intramolecular addition of allylsilane moiety, and these stereochemical outcomes are consistent with antiperiplanar transition states TS-1 and TS-2 of the second step (Scheme 3).



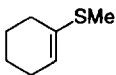
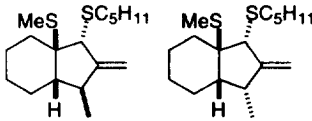
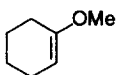
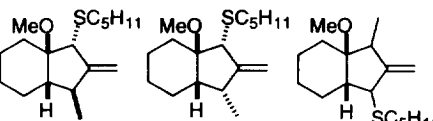
Scheme 3

Next, use of *sec*-allyl acetate **1b** for similar annulation was also briefly examined (Table 2). High regioselectivity as well as good diastereoselectivity was again observed in these cases. Thus, corresponding cycloadduct was obtained from 1-(methylthio)cyclohexene as a 10:1 mixture of epimers at methyl group, while the reaction of 1-methoxycyclohexene afforded analogous products along with a slight amount of regioisomer.

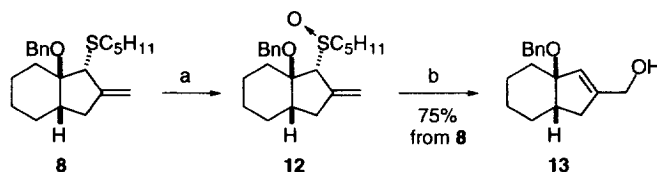
The present method provides a new entry to methylenecyclopentane annulation using electron-rich olefins. Furthermore, pentylthio group of the products is quite useful for introduction of other functional groups. For example, cycloadduct **8** was easily converted into allyl alcohol **13** through [2,3]-sigmatropic rearrangement⁷ of corresponding sulfoxide **12** (Scheme 4).

The present transformation seems to be very useful for synthesis of triquinane sesquiterpenes having consecutive five-membered ring and we are currently investigating their total synthesis.

Table 2 methylenecyclopentane annulation with **1b**

entry	olefin	solvent	conditions ^a	products ^b	%yield ^c (ratio ^d)
1		toluene	-45 °C, 1 h -23 °C, 1 h		81 (91 : 9)
2		CH ₂ Cl ₂	-78 °C, 0.5 h -45 °C, 0.5 h -23 °C, 0.5 h		64 (83 : 13 : 4)

^a For a typical procedure, see Table 1. ^b Stereochemistry of the products was determined by NOE experiments. ^c Isolated yield of analytically pure product. ^d Determined by ¹H NMR.



Scheme 4 a) *m*CPBA (1.5 equiv) / CH₂Cl₂, -78 °C; b) piperidine (5.0 equiv) / MeOH, reflux

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