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Synthesis of bicyclo[4.2.0]octan-2-ol, a substructure of solanoeclepin A

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ABSTRACT

A sesterterpenoid solanoeclepin A (**1**) has a unique structure including a bicyclo[4.2.0]octane substructure, for which a new synthetic methodology is explored particularly to cyclize functionalized cyclobutane rings. An optically active (*R*)-carvone and a racemic cyclohexenone were each converted into the respective epoxyvinylsulfones, and then subjected to the heteroatom-directed conjugate addition (HADCA) by a lithium acetylide nucleophile. The intermediate carbanions from HADCA were used for the following epoxide opening reaction yielding the four-membered carbocyclic products.

Synthesis of natural products allows us to confirm the stereo structure and the biological activity of these compounds particularly when they are only available in a trace amount from nature. In the case that a target compound would contain such a substructure as a functionalized cyclobutane ring, the methodologies are limited, so that a new methodology be explored. We became interested in the synthesis of solanoeclepin A (**1**), which was isolated in a small quantity (0.245 mg) from a large amount (ca. 1000) of potato plants cultivation, showing a hatching-stimulant activity toward the potato cyst nematodes, *Globodera rostochiensis* and *G. pallida*. Its structure contains 3, 4, 5, 6, and 7 membered rings with two bicyclic substructures as demonstrated by Shenk in 1999 from X-ray crystallographic analysis.[1] At the time, the absolute configuration of structure **1** was not determined and was only assumed to be the same as glycinoeclepin A **2**, having similar hatching-stimulant activity to soybean cyst nematodes.[2] Since then, it has been receiving the attention of the synthetic organic chemistry community.[3–12] Very recently Tanino and his colleagues have achieved the first total synthesis of **1**, confirming its absolute stereochemistry (Fig. 1).[13]

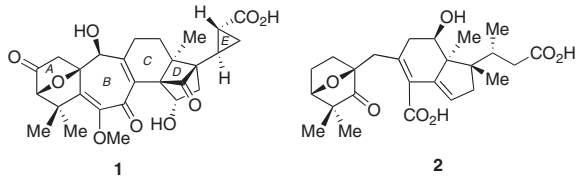
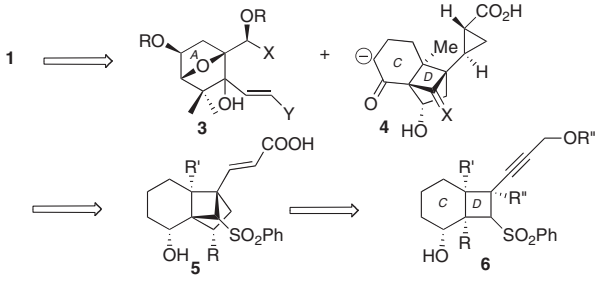


Figure 1. Solanoeclepin A and Glycinoeclepin A, nematode hatching-stimulant.

When we selected solanoeclepin A **1** as the synthetic target molecule, we first focused on developing a new methodology applicable for the synthesis of cyclobutane substructure having multiple functional groups. The retrosynthetic analysis can bisect **1** by disconnecting the seven-membered carbocyclic B-ring into two segments; **3** oxabicyclo[2.2.1]-heptanone[12] and **4** having a cyclobutane moiety (Scheme 1). In this retrosynthesis, segment **4** was further simplified into the tricyclic compound **5**, in which the bicyclo[2.1.1]hexane substructure could be constructed through a ring cyclization to form a cyclopentane starting from **6** having a bicyclo[4.2.0]octane substructure (Scheme 1). We have reported the synthesis of **3**,[12] and some results for the formation of cyclobutane by exploiting the heteroatom-directed conjugate addition (HADCA).[14,15] In this paper, we report the synthesis with a high stereochemical control of more advanced intermediates **6** having the bicyclo[4.2.0]octane moiety.



Scheme 1. Retrosynthesis of Solanoeclepin A **1** and simplified design of cyclobutane ring formation model study.

Our construction of the bicyclo[4.2.0]octane from heteroatom-directed conjugate addition (HADCA) showcases the synthesis of compounds having multifunctionalized cyclobutyl group using this strategy (Scheme 2). The plan is to add lithium acetylide nucleophile to epoxyvinylsulfone **7** by HADCA as shown in Scheme 2. The first step is chelation of the lithium acetylide nucleophile with α- and/or β-oxygen atom(s) which accelerates nucleophilic addition via α- or β-chelation effects.[16] The resulting intermediate

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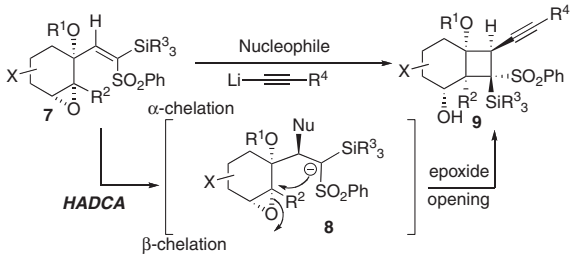
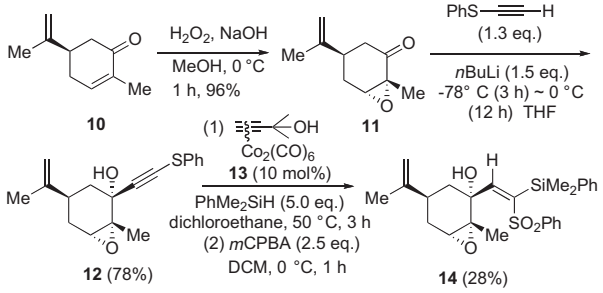


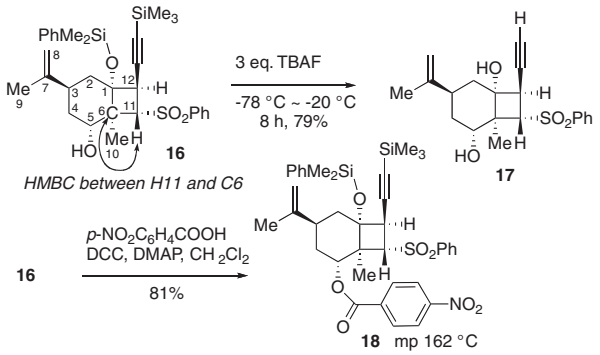
Scheme 2. HADCA leading to cyclobutane ring formation.



Scheme 3. Epoxyvinylsulfone **14** synthesis from (*R*)-Carvone **10**.

anion **8** is a second nucleophile for opening the epoxide ring to yield the cyclobutane compound as **9**. For this synthetic plan, we describe two examples in chiral and racemic cases.

A commercially available monoterpene (*R*)-carvone **10** was employed as a starting material for epoxyvinylsulfone **14**. Enone **10** was first treated with 35% hydrogen peroxide and 2 M sodium hydroxide as a basic catalyst in methanol to give the α-epoxy-ketone **11** selectively in 96% yield. Subsequently, lithium phenylthioacetylide was added to **11** at −78 °C then the temperature was raised to 0 °C to provide β-acetylenyl adduct **12** in 78% yield, two isomers (**12a** and **12b**, for details see in SI S4–5) in 6% and 5% yields, respectively. The hydrosilylation[17] of the acetylene moiety



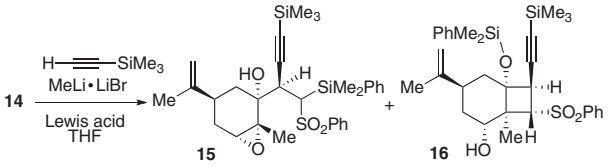
Scheme 4. Conversion of **16** to crystalline compound **18**.

of **12** was achieved in hot dichloroethane in the presence of dimethylphenylsilane and 10 mol % biscobalthexacarbonyl catalyst **13** to afford vinylsulfide in 69% yield. It was subsequently oxidized with 75% *m*CPBA at 0 °C to afford epoxyvinylsulfone **14** in 28% yield, together with a minor isomer **14a** (for details see in SI S5–7) in 13% yield in two steps, respectively (Scheme 3).

Next, the addition of lithium trimethylsilylacetylide to **14** was examined under various conditions, and the results are summarized in Table 1. The lithium acetylide was first generated with Me-Li·LiBr complex at −40 °C. A THF solution of **14** was cooled down to −78 °C, and then acetylide was added and stirred for 1 h at this temperature. The temperature was then gradually raised to 0 °C over a few hours to give acetylene adduct **15** in 65% yield (entry 1). When the similarly prepared reaction mixture using 2 equiv of MeLi·LiBr at −78 °C and then at 25 °C was further heated to 60 °C, the cyclobutane compound was obtained in 20% yield (entry 2). Epoxide opening was found to take place slowly only at higher temperatures and not at room temperature.

To facilitate the epoxide opening, we tried adding 0.5 equiv $BF_3{\cdot}OEt_2$ as a Lewis acid to the lithium acetylide, but this resulted in many products (entry 3). However, a similar treatment with 0.7 equiv $BF_3{\cdot}THF$ yielded cyclobutane product **16** in 12% yield, together with the simple addition product **15** in 41% yield (entry 4).

Table 1
Lithium acetylide addition to **14** and/or epoxide opening



Entry	Nucleophile		Lewis acid[d] (equiv)	Temp. (°C)	Time (h)	Products yield (%)
	H—≡—SiMe$_3$	MeLi·LiBr				
1[a]	5 equiv	5 equiv	—	−78 °C to 0 °C	7	**15**[b]:65% (>95:5)
2[c]	5 equiv	2 equiv	—	−78 °C to −20 °C Then to 60 °C	1 5	**16**:20%
3[a]	5 equiv	5 equiv	$BF_3{\cdot}OEt_2$ (0.5)	−78 °C to 60 °C	32	Messy
4[a]	5 equiv	5 equiv	$BF_3{\cdot}THF$ (0.7)	−78 °C to rt	30	**15**:41% **16**:12%
5[a]	5 equiv	5 equiv	$BF_3{\cdot}THF$ (0.7)	−78 °C to 60 °C	30	**15**:30% **16**:10%
6[a]	5 equiv	5 equiv	$ZnCl_2$ (0.5)	−78 °C to 60 °C	30	**15**:86%
7[a]	10 equiv	10 equiv	$BF_3{\cdot}THF$ (1.4)	−78 °C to rt	24	**15**:50% **16**:8%

[a] The trimethylsilylacetylene was deprotonated with MeLi·LiBr at −40 °C for 1 h.
[b] Isolated yields after column chromatography; the ratios were determined by ^1H NMR.
[c] The trimethylsilylacetylene was deprotonated with MeLi·LiBr at −78 °C for 1 h.
[d] The Lewis acid was added to the mixture solution at 0 °C.

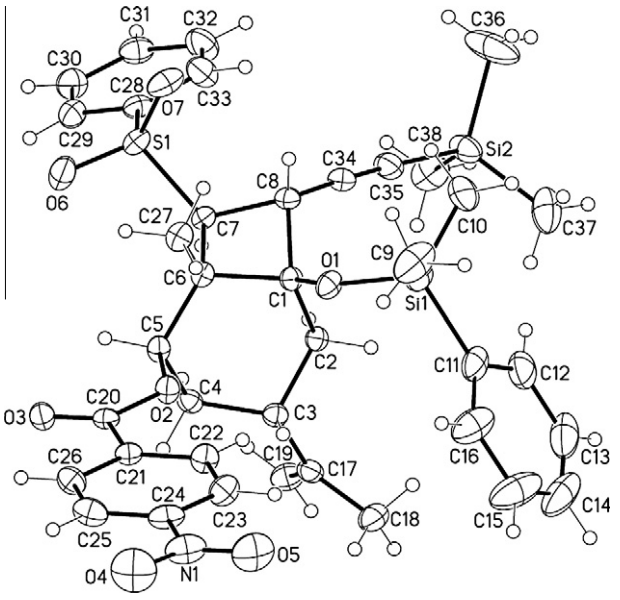
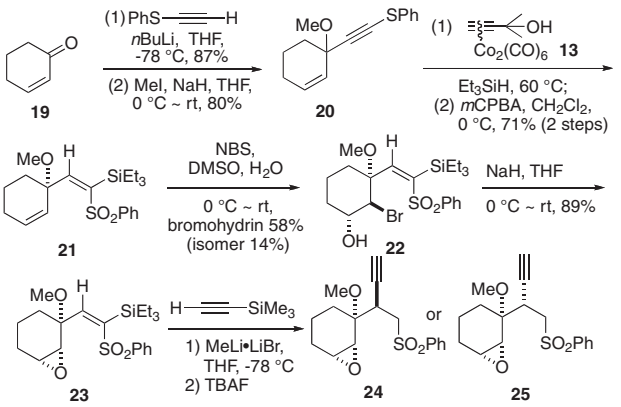


Figure 2. ORTEP of the crystal structure of cyclobutane **18**.



Scheme 5. Synthesis of racemic epoxyvinylsulfone **23**.

After the reaction temperature was raised to 60 °C, the yields of **15** and **16** slightly decreased to 30% and 10%, respectively (entry 5). There was no clear enhancement of the cyclobutane yield by the use of Lewis acid, even when we employed double the amount of BF_3·THF (entry 7). When we utilized $ZnCl_2$ as a Lewis acid, this gave only the major addition product **15** in 86% yield without any formation of the cyclobutane product **16** (entry 6).

The cyclobutane compound **16** showed HMBC-correlation between H-11 and C-6 to indicate the cyclobutane ring formation (Scheme 4). The structure was further proven though desilylation to **17** and *p*-nitrobenzoylation, yielding a crystalline material **18** (mp 162 °C), which was analyzed by X-ray crystallography to the structure as shown in Figure 2.

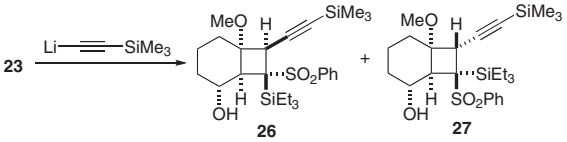
Judging from the structure **16** having the phenyldimethylsilyl group at the *tert*-hydroxy group, the intermediate after HADCA must be a dianion which underwent the Brook rearrangement.[18] This anion may be too reactive to undergo cyclobutane formation, causing side reactions such as deprotonation of the epoxide proton.

To prevent the formation of the dianion, it was decided that we would examine a substrate that had C1 alcohol protected as methyl ether. The desired epoxyvinylsulfone **23** was synthesized from cyclohexenone as shown in Scheme 5. The addition of the lithium phenylthioacetylide to **19** was followed by *O*-methylation with MeI to give **20**. Cobalt-catalyzed hydrosilylation with **13** and subsequent oxidation afforded the vinylsulfone **21**. Epoxidation of this vinylsulfone with *m*CPBA gave us a single epoxide, which was anti to OMe.[19] The alternative *syn* epoxide **23** was indirectly prepared via bromohydrin **22**. Thus, the treatment of **21** with *N*-bromosuccinimide (NBS) in dimethylsulfoxide (DMSO) containing 10% water[20] provided largely **22** in 58% yield together with its stereoisomer (see SI). Further the treatment of **22** with sodium hydride yielded epoxyvinylsulfone **23** possessing the epoxide *syn* to the OMe group.

HADCA by lithium trimethylsilylacetylide to **23** was first studied to determine the diastereoisomer ratio of the primary addition products (**24** and **25**) by quenching the reaction mixture at −78 °C. However, these products were not separable even after desilyltion by TBAF. So we further continued with cyclobutane formation under the conditions as summarized in Table 2. Acetylide was generated from ethynyltrimethylsilane by the treatment with MeLi·LiBr at −78 °C in THF. The addition of this nucleophile to **23** was implemented in THF at −78 °C for 1 h and then the reaction mixture was raised to 0 °C and further raised to room temperature to provide cyclobutane compound **26**. This cyclobutane product was obtained in 54% yield as a crystalline material (entry 1).

In order to facilitate the epoxide opening from the intermediate carbanion after the HADCA, BF_3·OEt_2 was further added to this reaction mixture at −40 °C and the temperature was gradually raised to room temperature (entry 2). It afforded two cyclobutane products, which were separated by silica gel column chromatography to give crystalline **26** in 71% and **27** in 14%. When the acetylide

Table 2
Acetylide addition to **23** to afford cyclobutane compounds



Entry	Nucleophile		Additive	Temp. (°C)	Time (h)	Products yield (%)
	H—≡—SiMe$_3$	Base				
1[a]	1.5 equiv	MeLi·LiBr (1.35 equiv)	—	−78 to 30	6	**26**:54%
2[a]	10 equiv	MeLi·LiBr (9.5 equiv)	BF_3·OEt_2[b]	−78 to 30	7	**26**:71% **27**:14%
3[c]	5.5 equiv	MeLi (5.0 equiv)	NaBr:LiBr (1:5)	−40 to 22	7	**26**:75%

[a] Solvent in THF and ether (from MeLi·LiBr).
[b] The BF_3·OEt_2 was added to the mixture solution at −40 °C.
[c] Solvent in *n*-hexane and ether (from MeLi). (see SI S16–S18).

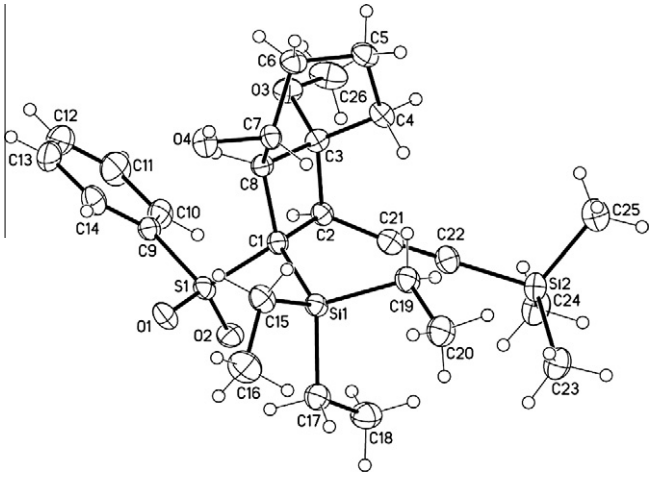


Figure 3. ORTEP of the crystal structure of cyclobutane **26**.

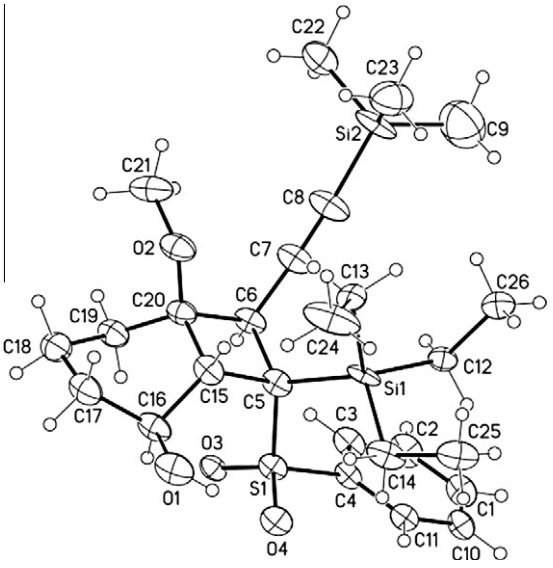


Figure 4. ORTEP of the crystal structure of cyclobutane **27**.

was generated in a mixed solvent of *n*-hexane–Et_2O at −20 °C, and reacted with **23** at −40 °C, the product was **26** (entry 3). The X-ray crystallographic analysis of **26** showed the structure in Figure 3 and the minor compound **27,** which was also crystalline, showed the isomeric structure (Fig 4). Thus the use of the methoxy group indeed facilitated cyclobutane formation.

We have reported that the epoxyvinylsulfones **14** and **23** underwent the conjugate addition of lithium acetylide to afford reactive carbanion intermediates, which further reacted intramolecularly to open the epoxide ring to produce cyclobutane products **16**, **26,** and **27**. Further synthetic studies toward solanoeclepin A are now under way along this line in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.152.

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