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Synthesis of Medium-Membered Heterocyclic Allenes by [3,3]Sigmatropic Rearrangement and Its Synthetic Application to the Antifungal Constituent of *Sapium Japonicum* [1]

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Abstract: Medium-membered heterocyclic allenes were synthesized by the [3,3]sigmatropic rearrangement of cyclic thionocarbonates. Using this methodology and a novel application of a SmI_2-HMPA reduction, an antifungal constituent of *Sapium japonicum*, methyl 8-hydroxy-5,6-octadienoate, was synthesized.

We recently found that the [3,3]sigmatropic ring expansion of allylic cyclic thionocarbonates can be used in the highly stereoselective synthesis of either *Z* or *E* olefins in 10-membered thiolcarbonates (starting from 8-membered thionocarbonates).[2] The yield and stereoselectivity of this reaction encouraged us to see if it could be applied to alkynyl cyclic thionocarbonates, which (after ring expansion) would yield medium sized heterocyclic allenes,[3] a class of compounds otherwise difficult to synthesize.[4] We here report our successful conclusion to this study, and application to the synthesis of methyl 8-hydroxy-5,6-octadienoate which is an antifungal constituent of *Sapium japonicum*. The synthesis also features a novel application of a SmI_2-HMPA reduction to a cyclic thiolcarbonate.

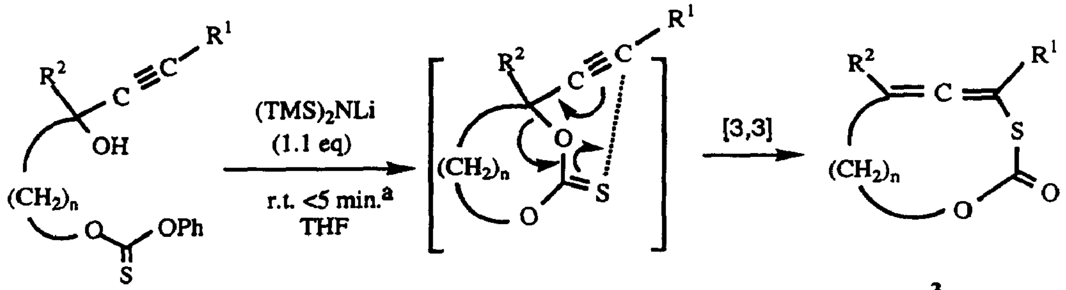
Treatment of an acetylene diol monothionocarbonates **1** with lithium bis(trimethylsilyl)amide [$(TMS)_2NLi$] gave the heterocyclic allenes **3** *via* spontaneous ring expansion of cyclic thionocarbonate intermediates **2**.[5] A general experimental procedure is as follows: A 1 M solution of $(TMS)_2NLi$ in THF (0.66 mmol) was injected to a solution of **1b** (0.6 mmol) in THF (60 ml) with stirring at room temperature. The reaction was quenched by the addition of H_2O within a 5 min. Usual workup and purification by flash chromatography gave the 10-membered allene **3b** (77% yield). The results are summarized in the Table. The ease of this reaction is noteworthy and it may be attributed to the favorable conformation of the intermediate **2b** during the rearrangement. The reaction gave 9-membered (run 6) as well as 11-membered (run 1) cyclic allenes, with recovery (40%) of the starting material in run 6.

For the application of the present method, we attempted the synthesis of a strong antifungal constituent **8**[6, 7] of *Sapium japonicum* (*Euphorbiaceae*), which is commonly found at the base of mountains in Japan (*Scheme*).

Addition of a lithium acetylide, prepared from *tert*-butyldimethylsilylpropargyl ether **4**, to the aldehyde **5**[8] afforded a diol monothionocarbonate **1g** in 94% yield. This was subjected to the present reaction. Reaction of **1g** with $(TMS)_2NLi$ afforded a 10-membered allene **3g**[9] in 56% yield. The yield is rather low, because of its tendency to dimerize during purification by silica gel column chromatography .

Next, we attempted reductive removal of SCO moiety in **3g**. The reaction of **3g** with lithium *p,p*'-di-*tert*-butylbiphenylide[10] gave only decomposed material at -70°C.

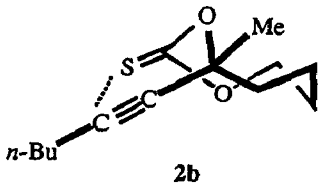
Table. Synthesis of Medium-membered Heterocyclic Allenes by the [3,3]Sigmatropic Ring Expansion of Cyclic Thionocarbonates



1 **2** **3**

Run	1; No	n	R^1	R^2	3; Ring Size	No	Yield (%)^b	^{13}C-NMR (ppm) [C=C=C]		
1	**1a**	5	n-C_4H_9	H	11	**3a**	28^c	207.4	97.1	93.4
2	**1b**	4	n-C_4H_9	CH_3	10	**3b**	77	202.4	102.9	96.0
3	**1c**	4	n-C_4H_9	H	10	**3c**	66	204.4	98.0	94.7
4	**1d**	4	$CH_3OCH_2OCH_2$	H	10	**3d**	47	205.9	95.6	95.5
5	**1e**	4	t-C_4H_9	H	10	**3e**	46de	203.7	108.8	94.5
6	**1f**	3	n-C_4H_9	H	9	**3f**	49^f	206.7	101.8	95.5

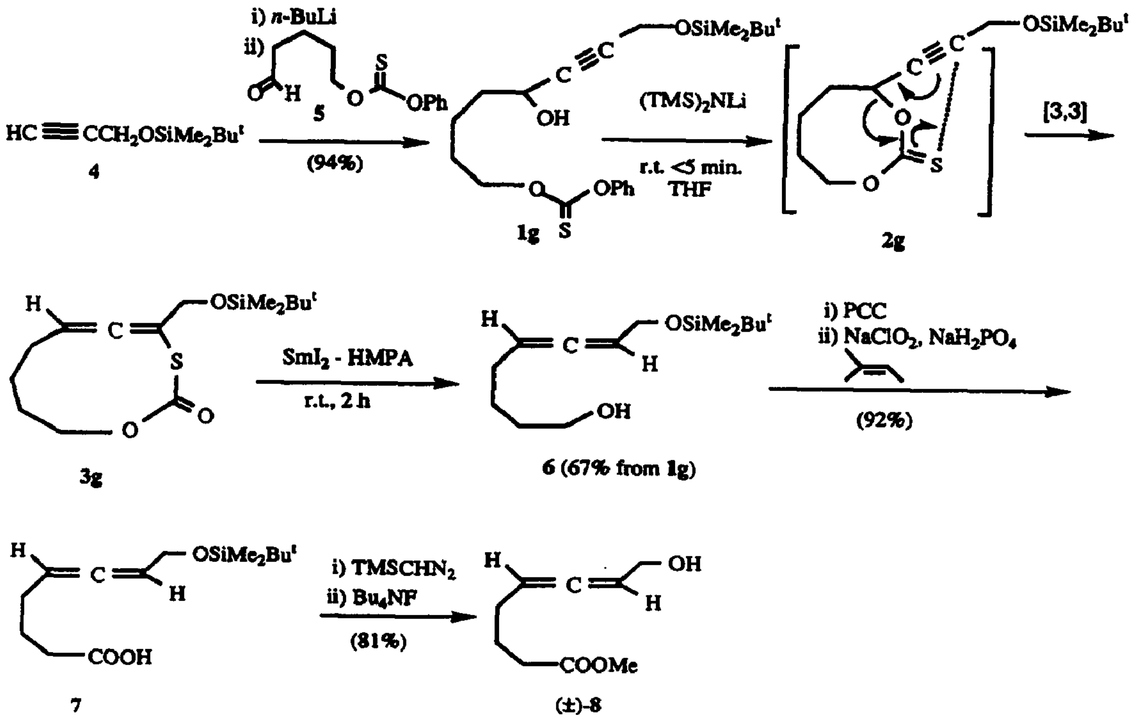
[a] Unless otherwise stated, the reactions were carried out according to general procedure (see text);
[b] Isolated yield; [c]Dimeric material was also obtained in 28% yield; [d]The reaction was carried out at room temperature for 0.5 h; [e]**1e** (36%) was recovered; [f]**1f** (40%) was recovered.



2b

On the other hand, when **3g** was added to a freshly prepared samarium (II) iodide (SmI_2) in THF-HMPA,[11] the allenic alcohol **6**[12] was obtained in 78% yield with the liberation of SCO. The allenic function itself was unaffected as determined by ^{1}H- and ^{13}C-NMR spectra. To our knowledge, no example of the reaction of thiolcarbonates with SmI_2 has been reported so far.[13] The overall yield (67%) of **6** from **1g** could be improved by using unpurified **3g** directly in the next reaction step.

The oxidation of the allenic alcohol **6** to the corresponding carboxylic acid **7** was not easy because of the instability of the allenic moiety. Thus, the oxidation was carried out first with PCC to the aldehyde followed by treatment with sodium chlorite[14a] in the presence of NaH_2PO_4 and 2-methyl-2-butene[14b] to give **7** in 92% overall yield. Esterification with trimethylsilyldiazomethane and deprotection with tetrabutyl-ammonium fluoride gave the target compound (±)-**8** in 81% yield. Spectroscopic data for the synthetic material was identical in all respects with those reported for the isolated natural product.[6, 7]



Scheme

Acknowledgments. We wish to thank Dr. T. Aoyama at Nagoya City University for his valuable suggestion at the oxidation step and Dr. K. Saiki at Kobe Women's College of Pharmacy for measurements of mass spectra.

References and Notes

1. This is Part 10 of the series entitled "[3,3]Sigmatropic Ring Expansion of Cyclic Thionocarbonates". Part 9, see S. Harusawa, S.; Takemura, S.; Osaki, H.; Yoneda, R.; Kurihara, T., *Tetrahedron*, **1993**, *49*, 7657.
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9. **3g**: IR (neat) 1950 (very weak, C=C=C), 1685 cm^{-1} (CO). ^{1}H-NMR (200 MHz, $CDCl_3$): 0.08 (6H, s), 0.90 (9H, s), 1.60-1.85 (4H, m), 2.13-2.44 (2H, m), 3.88 (1H, td, *J*=11.3, 2.7 Hz), 4.28 (2H, d, *J*=2.8 Hz), 4.94 (1H, ddd, *J*=11.3, 5.4, 2.5 Hz), 5.23-5.37 (1H, m). ^{13}C-NMR ($CDCl_3$): -5.1, 18.5, 26.0, 26.2, 28.4, 28.5, 64.5, 68.9, 96.0, 99.1, 169.4, 204.0.
10. a) Harusawa, S.; Takemura, S.; Osaki, H.; Yoneda, R.; Kurihara, T., *Tetrahedron*, **1993**, *49*, 7657. b) Harusawa, S.; Takemura, S.; Yoneda, R.; Kurihara, T., *ibid.*, in press.
11. Samarium metal (0.75 g, 5 mmol) and 1,2-diiodoethane (1.24 g, 4.4 mmol) in anhydrous THF (10 ml) were stirred at room temperature under an argon atmosphere for 2.5 h to give a deep blue solution. HMPA (1.2 ml) followed by *tert*-BuOH (0.1 ml) were added to the solution at 0 °C. After 0.5 h, a solution of **3g** (258 mg, 0.82 mmol) in THF (8 ml) was added and the mixture was stirred at 0 °C for 0.5 h followed by at room temperature for 2 h. Ice was added and the reaction mixture was exposed to air with stirring for 10 min, then filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (20% EtOAc in hexane) to give **6** (164 mg, 78%).
12. **6**: IR (neat) 1962 cm^{-1} (C=C=C). ^{1}H-NMR ($CDCl_3$): 0.10 (6H, s), 0.90 (9H, s), 1.40-1.68 (4H, m), 2.05 (2H, m), 3.65 (2H, t, *J*=7.5 Hz), 4.16 (2H, dd, *J*=7.5, 4.0 Hz), 5.20 (2H, m). ^{13}C-NMR ($CDCl_3$): -5.0, 18.5, 25.5, 26.1, 28.5, 32.3, 62.4, 62.8, 92.2, 92.5, 204.2.
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