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A NEW SYNTHESIS OF MEDIUM-MEMBERED LACTONES VIA INTRAMOLECULAR CONDENSATION OF α-CHLOROSULFIDES CONTAINING AN ESTER GROUP AND ALLYLSILANYL MOIETY

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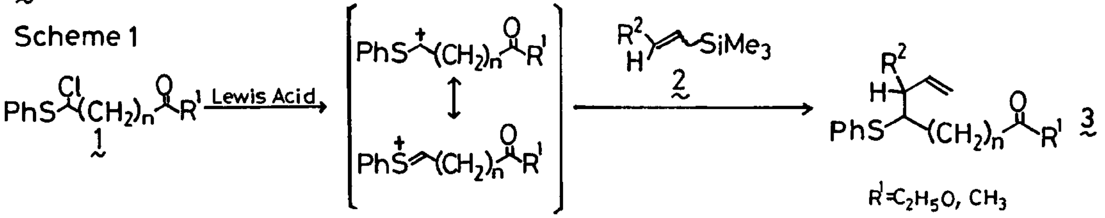
Abstract: Medium-membered lactones (8∼11 membered rings) were obtained in good yields by $EtAlCl_2$-promoted intramolecular condensation of α-chlorosulfides containing an ester group and allylsilanyl moiety without the need for high dilution conditions.

The construction of medium- and large-membered lactones has been recoginized as a current problem of intensive investigation in macrolide synthesis.[1] The most widely used method is intramolecular esterification of ω-hydroxy acids.[2∼8] Moreover, new approaches to synthesize medium- and large-membered lactones by intramolecular carbon-carbon bond formation are now known.[9∼13]

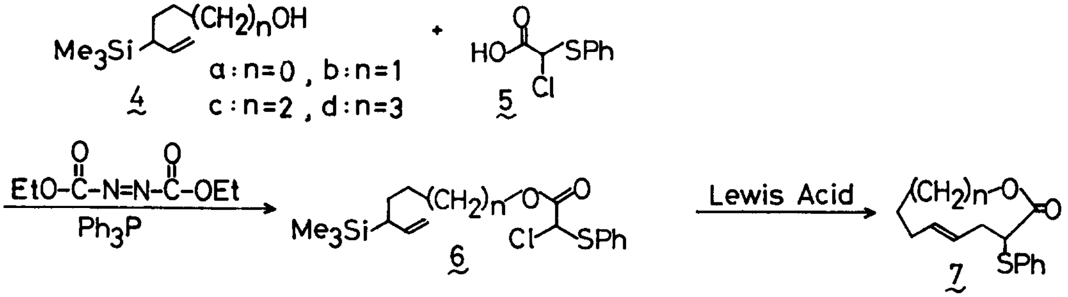
In a previous paper, we reported chemoselective reaction of α-chlorosulfides (1) containing a carbonyl group with allylsilanes (2) to substitute exclusively for the chlorine atom of 1, and the corresponding α-allylsulfides (3) were obtained in high yields.[14]

Scheme 1



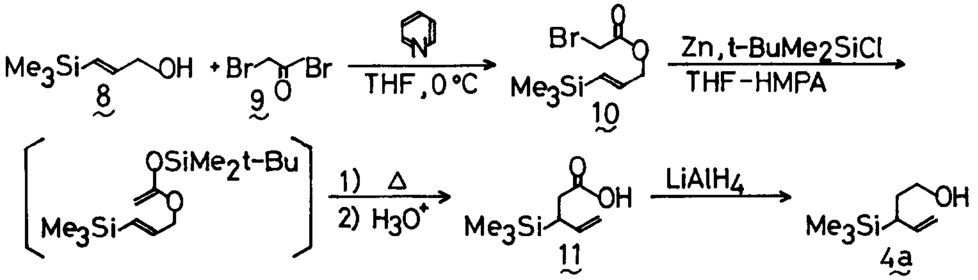
This reaction was successfully applied herein to a new synthesis of medium-membered lactones (7) via Lewis acid-promoted intramolecular carbon-carbon bond formation of α-chlorosulfides having an ester group and allylsilanyl moiety as shown in Scheme 2.

Scheme 2



3-Trimethylsilyl-4-pentene-1-ol (4a) was prepared by Reformatsky-Claisen rearrangement[15)] of 3-trimethylsilyl-2-propenyl α-bromoacetate (10) followed by reduction of the resulting carboxylic acid (11) with lithium aluminium hydride (over all yield: 68%). 10 was easily synthesized in 82% yield by the treatment of 3-trimethylsilyl-2-propen-1-ol (8)[17)] and bromoacetyl bromide (9).

Scheme 3



Other allylsilanes (4b, 4c, 4d) were obtained successively by carbon homologation of 5-chloro-3-trimethylsilyl-1-pentene prepared from 4a. Phenylthioacetic acid was treated with N-chlorosuccinimide in CCl_4 at 40 °C for 50 min to afford the corresponding α-chloro-α-phenylthioacetic acid in a quantitative yield. Precursors (6) for the synthesis of lactones (7) were conveniently prepared in high yields by the condensation of 4 and 5 under Mitsunobu conditions.[18)]

Therefore, we examined the cyclization of 6 in the presence of various Lewis acids. To a dichloromethane solution of 6 (∼0.1 M solution, 1 M=1 mol dm^{-3}) a Lewis acid was added at 0 °C and some of the results are summarized in Table 1. Tin tetrachloride, Titanium tetrachloride, and zinc chloride induced cyclization of 6a suffered from protodesilylation. Ethylaluminium dichloride[19)] should and did avoid this complication, which presumably arose from the adventitious presence of HCl contained in Lewis acids. Although no optimization of the yields was attempted, it was found that $EtAlCl_2$ was a superior Lewis acid to produce 7 from 6 as shown in Table 1.

Table 1 Synthesis of 7[a] from 6

6, n	Lewis Acid (eq)	Yield of 7 (%)[b]
a: 0	$SnCl_4$ (1.0)	18
	$TiCl_4$ (1.0)	22
	$ZnCl_2$ (1.0)	23
	Et_2AlCl (1.5)	33
	$EtAlCl_2$ (1.5)	34
b: 1	$EtAlCl_2$ (1.5)	48
c: 2	$EtAlCl_2$ (1.5)	48
d: 3	$EtAlCl_2$ (1.5)	55

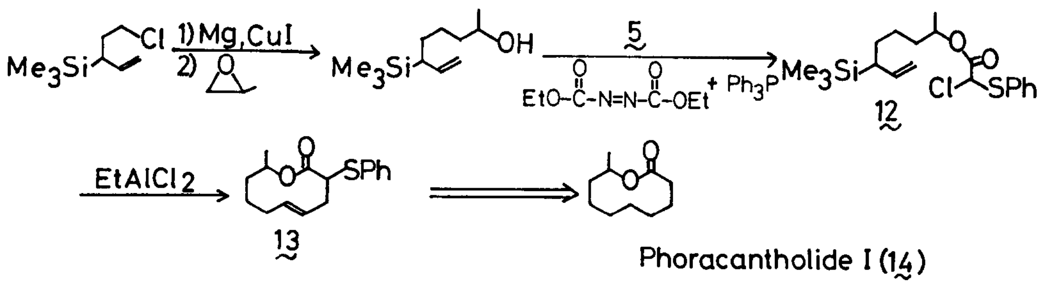
a) Satisfactory IR, ^1H NMR, MS, and elemental analyses data were obtained for these compounds. The IR spectrum of each 7 showed a distinct absorption band at 965 cm^{-1} due to E configuration of the double bond. However, ^1H NMR spectrum was so complicated that the ratio of E/Z isomers could not be determined nor the isomers were separable by HPLC or GLC under usual conditions.

b) Isolated yields by thin-layer chromatography (SiO_2, hexane:ethyl acetate=9:1).

Thus, it is noteworthy that medium-membered lactones (8~11 membered rings) were obtained in good yields without the need for high dilution conditions, although eight- and nine-membered rings are the most difficult to construct by any method of ring closure.[20)] We propose that the formation of medium-membered rings is attributable to a template effect[21)] resulting from steric constraints imposed on intermediates in which silicon of the allylsilane and the chlorine of the α-chlorosulfide are both co-ordinated to the Al catalyst.

In the next, we prepared the precursor (13)[22)] for the synthesis of Phoracantholide I (14) to demonstrate the application of this cyclization as follows. The precursor (13) was actually obtained in 42% yield from 12 and had been converted to 14 by Tsuji and co-workers.[10)]

Scheme 4



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16. Carboxylic acid (**11**) was also prepared in 44% yield by Ireland-Claisen rearrangement of 3-trimethylsilyl-2-propenyl acetate. Preparation of ethyl carboxylate of **11** has recently been recorded by orthoester-Claisen rearrangement of **8**. K. Mikami, T. Maeda, N. Kishi, and T. Nakai, *The 47th Annual Meeting of Chemical Society of Japan, Kyoto, April, 1983, Abstract II*, 1D15.
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22. The IR and ^{1}H NMR spectra of **13** were identical with those of an authentic sample kindly offered by Prof. J. Tsuji and Dr. T. Takahashi. Satisfactory MS and elemental analyses data were also obtained for **13**.

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