





論文名(和文)

スルホニウム塩をアルキル化剤として用いた  
有機合成反応の開発

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**STUDIES ON THE ORGANIC SYNTHESIS USING SULFONIUM  
SALTS AS ALKYLATING REAGENTS**

**b y**

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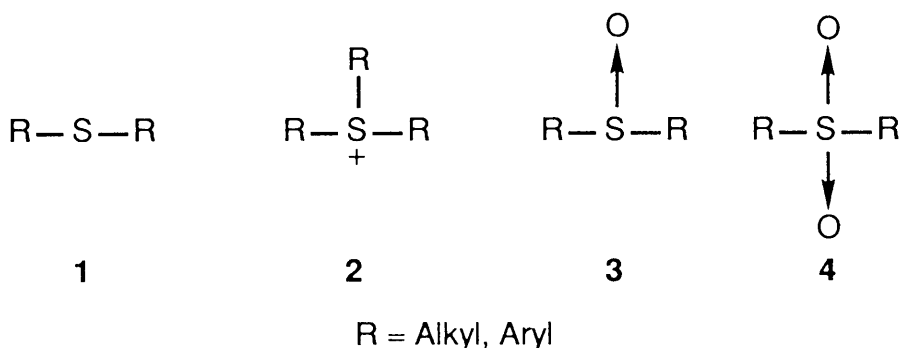
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## Introduction

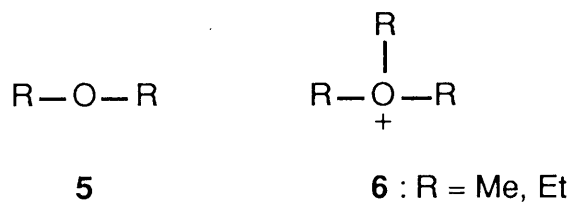
Sulfur atom can be in a variety of oxidation states, and there are many kinds of organic sulfur compounds, such as divalent sulfides **1**, trivalent sulfonium salts **2**, tetravalent sulfoxides **3**, and hexavalent sulfones **4**. These compounds **1-4** have frequently been



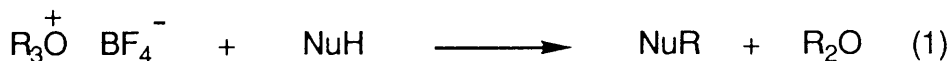
utilized in organic synthesis because of their unique reactivities.<sup>1</sup> For example, organic sulfides **1** are readily prepared from naturally occurring inorganic sulfur compounds such as  $\text{Na}_2\text{S}$  and are starting materials for the preparation of sulfonium salts **2**, sulfoxides **3**, and sulfones **4**. Sulfonium salts **2** play an important role as a starting material of sulfonium ylides in organic synthesis. As sulfoxides **3** possess a positive charge on sulfur atom and a negative charge on oxygen atom, sulfoxides **3** react with either electrophiles on oxygen atom or nucleophiles on sulfur atom. Sulfoxides **3** bearing two different substituents are dissymmetric and resolvable into optically active enantiomeric forms, and the optically active sulfoxides **3** are

extensively utilized in asymmetric synthesis. Thermolysis of sulfones **4** gave olefins *via* elimination of SO<sub>2</sub>.

On the other hand, although oxygen atom is homologous to sulfur one, organic oxygen compounds exist in only two kinds of oxydation states such as divalent ethers **5** and trivalent oxonium salts **6**. Meerwein reagent, namely oxonium salts **6**<sup>2</sup>, is very



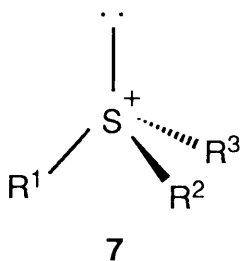
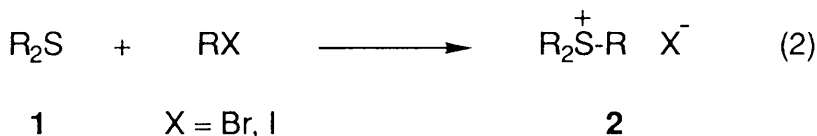
useful as a powerful alkylating reagent for such a variety of nucleophiles as alcohols, carboxylic acids, and amines (eq. 1).<sup>3</sup>



However, Meerwein reagent has a disadvantage that this reagent is difficult to handle because of its thermal lability and moisture-sensitivity, and that its alkyl groups R are limited as methyl and ethyl groups.

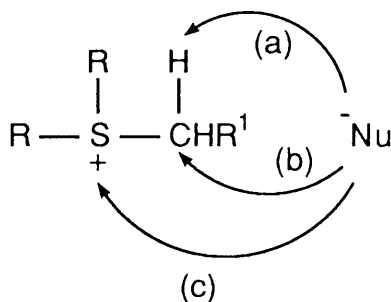
In contrast, sulfonium salts **2** are generally more stable than oxonium salts **6** and the compounds having a variety of alkyl and aryl groups can be easily obtained as isolable crystalline compounds by the reaction of sulfides **1** and alkyl halides (eq. 2).<sup>4</sup> Sulfonium



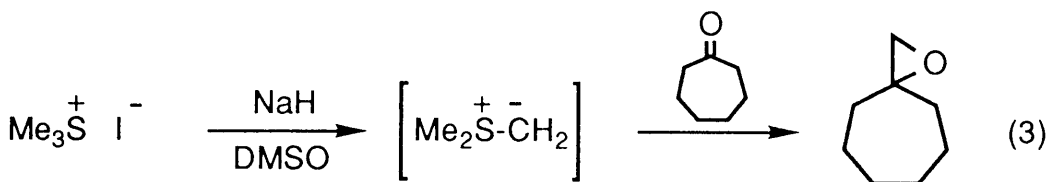


salts **2** are formally trivalent and bear a positive charge on sulfur atom, and the simplest way of describing this electronic arrangement is to consider the five valence electrons of  $\text{S}^+$  as being distributed in three bonds and one lone pair of electrons. The geometry of sulfonium compounds maintained stable pyramid structure **7**, since a number of optically pure sulfonium compounds are isolated.<sup>5</sup>

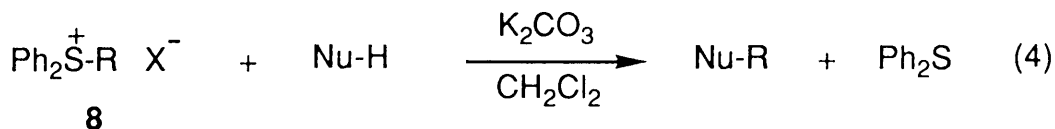
Reaction of sulfonium salts with nucleophiles are divided in three types (Figure 1). Route (a) is the formation of sulfonium ylides



from sulfonium salts. Since  $\alpha$ -hydrogen atom of sulfonium group is acidic, sulfonium salts under strongly basic conditions give sulfonium ylides which react with ketones to give epoxides as very important substances in organic syntheses (eq. 3).<sup>6</sup> As illustrated by route (b), sulfonium salts alkylate

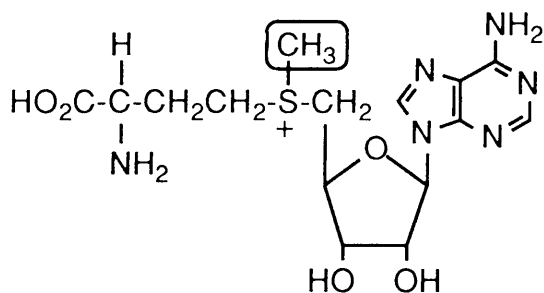


nucleophiles. For instance, it is well-known that diphenylsulfonium salts **8** act as good alkylating reagents toward nucleophiles such as carboxylate and phenolate ions, amines, and carbanions (eq. 4).<sup>7</sup> S-



NuH : PhCO<sub>2</sub>H, PhOH, PhNH<sub>2</sub>, etc.

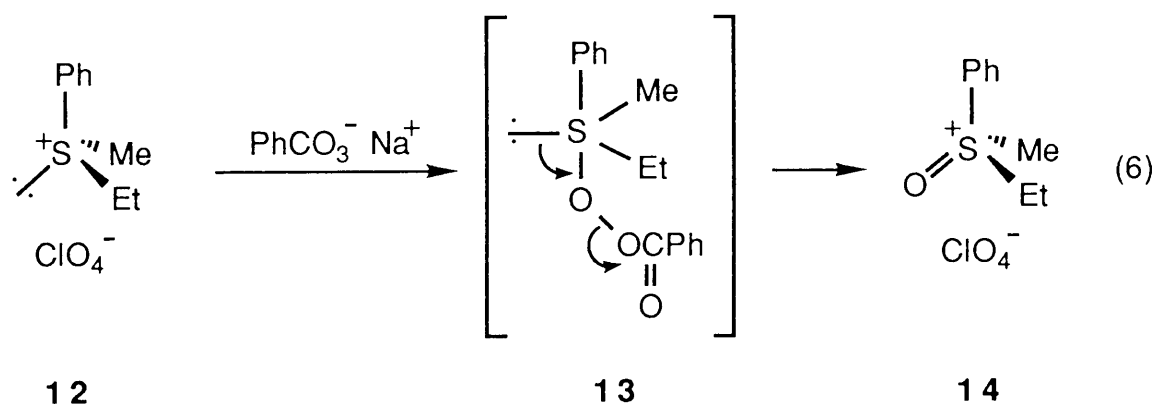
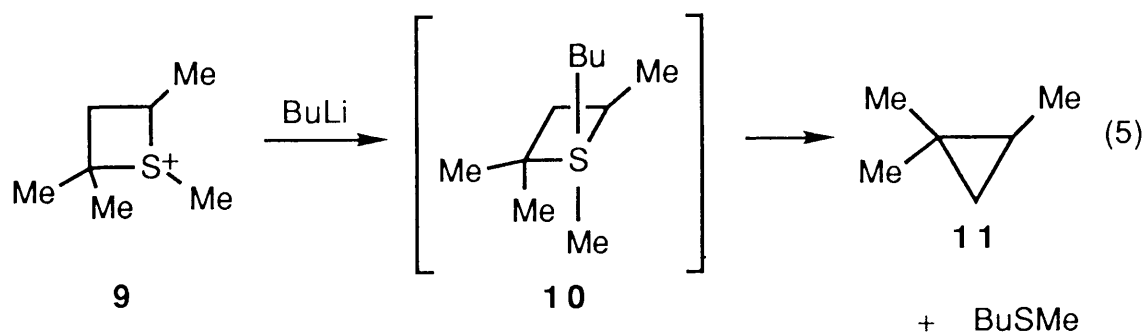
R : Me, Et, n-Bu, i-Pr, etc.



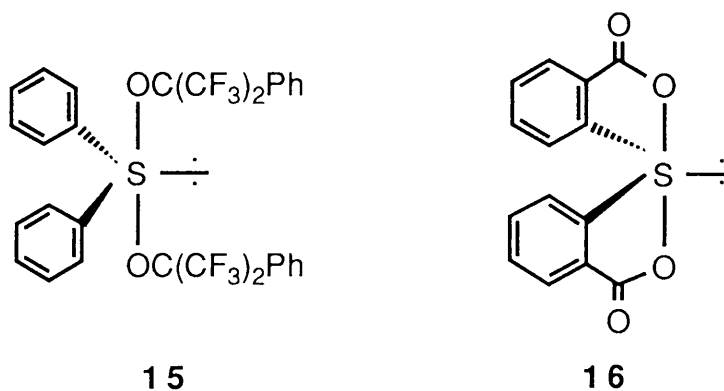
S-Adenosylmethionine

Adenosylmethionine has a sulfonium group and is known as a methylating reagent for many biological substances, such as DNA, RNA, proteins, and biological amines, *in vivo*.<sup>8</sup> Route (c) is the formation of  $\sigma$ -sulfurane. Since sulfonium salts

have positive charge on sulfur atom, nucleophiles attack a cationic sulfur atom to form  $\sigma$ -sulfuranes possessing a hypervalent sulfur atom. For example, the reaction of 1,2,2,4-tetramethylthietanium salt **9** with n-butyllithium gave 1,1,2-trimethylcyclopropane **11** *via*  $\sigma$ -sulfurane intermediate **10** (eq. 5).<sup>6,9</sup> Oxidation of (S)-ethylmethylphenylsulfonium perchlorate **12** with sodium perbenzoate afforded (R)-ethylmethylphenyloxosulfonium perchlorate **14** with retention of configuration on sulfur atom (eq. 6).<sup>10</sup> This result suggests that the



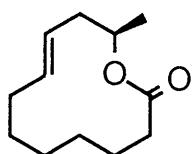
oxidation process proceeds via  $\sigma$ -sulfurane **13** formed by nucleophilic attack of perbenzoate toward sulfur atom of sulfonium salt **12**. In fact,  $\sigma$ -sulfurane compounds **15**<sup>11</sup> and **16**<sup>12</sup> with hypervalent sulfur atom stabilized by electronegative ligands are isolated.



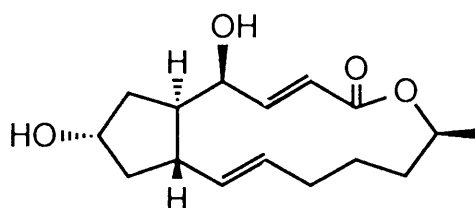


As mentioned above, sulfonium salts have been frequently used as a precursor of sulfonium ylides, and no effective synthetic methodology for alkylation with sulfonium salts has been appreciably developed in spite of the good and mild alkylating ability. So, the author investigated the utilization of sulfonium salts as alkylating reagents in organic synthesis.

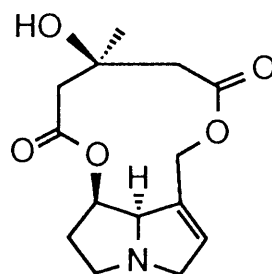
It is of great interest to synthesize lactones,<sup>13</sup> cyclic ester compounds, as naturally occurring products and biological active substances often contain a lactone skeleton. In particular, as macrocyclic lactones have attracted much interest due to their biological activities such as antitumor activities, much attention has been focused in recent years on the synthesis of macrolides. Known synthetic methods of macrocyclic lactones have a disadvantage that it is difficult to prepare medium-membered rings such as 9- to 13-membered lactones in good yields because of competing with the formation of diolides.



recifeiolide

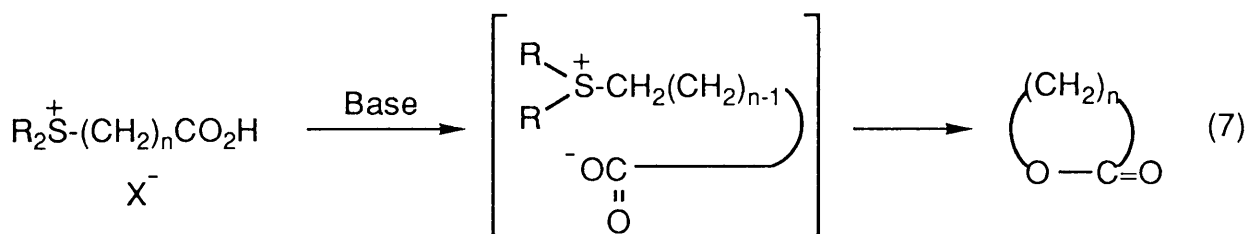


Brefeldin A



(+)-Dicrotaline

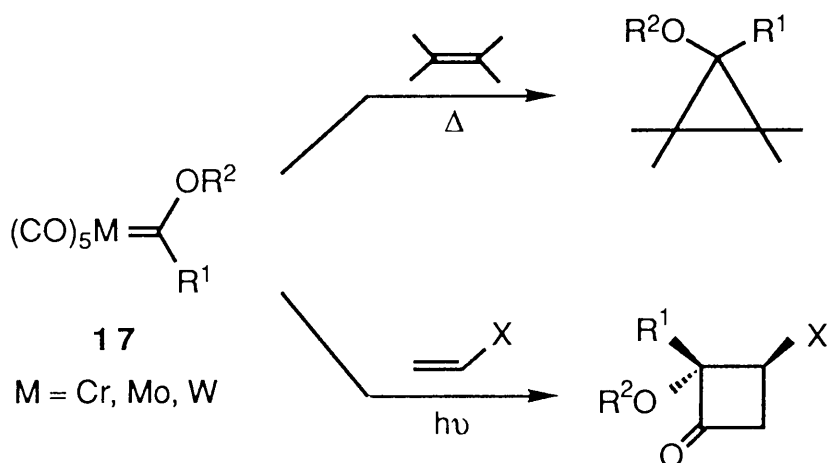
As shown in eq. 4, since the reaction of alkyldiphenylsulfonium salts with carboxylic acids under weakly basic conditions gives carboxylic esters,<sup>7</sup> the author made a plan for intramolecular alkylation using sulfonium salts to synthesize lactones. A new route to the synthesis of lactones was investigated by the reaction of ( $\omega$ -carboxyalkyl)sulfonium salts possessing a carboxyl group at  $\omega$ -position carbon atom under weakly basic conditions (eq. 7). As it is known that the reaction of sulfonium salts with hard nucleophiles such as perbenzoate affords  $\sigma$ -sulfurane intermediate by nucleophilic attack toward sulfonium cation (eq. 6),<sup>10,14</sup> it is also expected that intramolecular electrostatic interaction between the sulfonium cation and the carboxylate anion (hard nucleophile) of ( $\omega$ -carboxyalkyl)sulfonium salts stimulates this cyclization reaction.



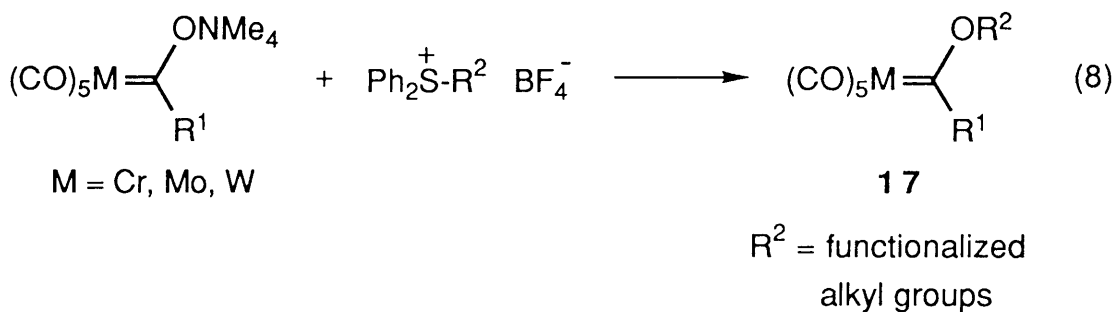
In recent years, organic synthetic methods mediated the attractive reaction of organometallic compounds have been developed extensively. In particular, metal-stabilized carbene complexes are not only suitable as carbene transfer agents but also unique agents not observed in the reaction of free-carbenes and carbenoids.<sup>15</sup> Thus, thermal reaction of Fischer-type (alkoxy)carbene complexes **17** with olefins produces cyclopropane derivatives, whereas photocyclo-

addition with olefins yields cyclobutanone derivatives (Scheme 1). A general synthetic method of (alkoxy)carbene complexes containing various functionalized alkoxy groups is required.

Scheme 1



The author studied a convenient method for the preparation of Fischer-type (alkoxy)carbene complexes **17** containing chromium, molybdenum, and tungsten as a metal, utilizing mild alkylation by diphenylsulfonium salts having a variety of functionalized alkyl groups (eq. 8).





In chapter 1, the intramolecular cyclization of ( $\omega$ -carboxy-alkyl)diphenylsulfonium salts under weakly basic and high-dilution conditions was described. This reaction was found to be an effective method for the preparation of 12- to 16-membered macrocyclic lactones.

A convenient synthetic method of macrocyclic thialactones containing a sulfur atom in the carbon chain was proposed in chapter 2. In the intramolecular reaction of ( $\omega$ -carboxyalkyl)thiolanium salts, the carboxylate anion attacked  $\alpha$ -carbon atom on five-membered ring of thiolanium salts to give sulfur-containing lactones *via* ring-expansion reaction.

In chapter 3, a new and effective route to the preparation of head-to-head type macrocyclic dilactones using ( $\omega$ -carboxyalkyl)-diphenylsulfonium salts containing an ester linkage was described. In addition, application to the synthesis of (+)-dicrotaline analog, naturally occurring macrocyclic dilactone, was investigated utilizing this lactonization method and the intramolecular reaction of sulfonium salts was found to be useful for the synthesis of compounds having complex structures such as natural products.

In chapter 4, the reaction mechanism of this cyclization *via* S-O sulfurane intermediate was proposed from the investigation of intramolecular reaction of sulfonium salt having an optically active carbon atom.

In chapter 5, the author studied alkylation of organometallic

compounds using sulfonium salts. The preparation of Fischer-type (alkoxy)carbene complexes by the mild alkylation of alkyldiphenyl-sulfonium salts gave excellent results.

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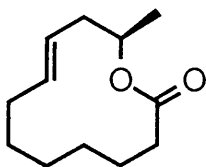
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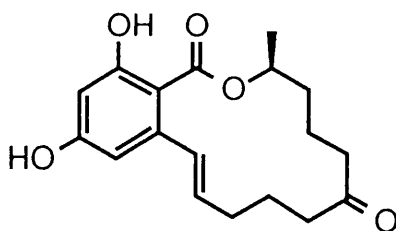
## Chapter 1

### Synthesis of Lactones from ( $\omega$ -Carboxyalkyl)- diphenylsulfonium Salts

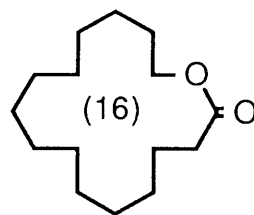
Lactones are attractive compounds, since naturally occurring products and biological active substances often contain a lactone skeleton. In particular, macrocyclic lactones have biological activities and are useful as perfumes. For example, pentadecanolide have a musk odor and is widely used as an artificial perfume. A variety of



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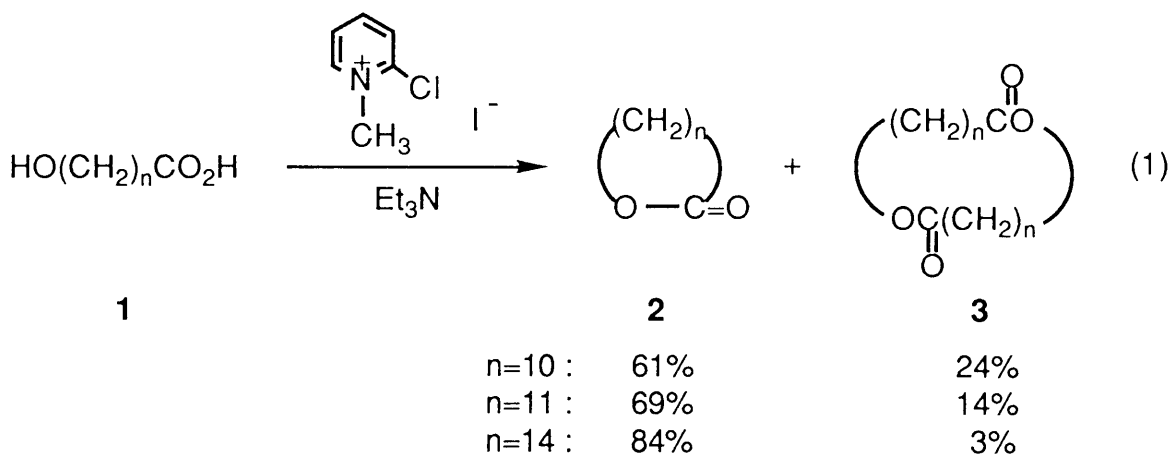
Zearalenone



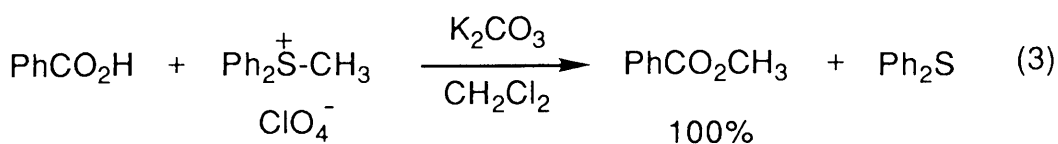
Pentadecanolide

synthetic approaches to macrocyclic lactones, involving mainly intramolecular esterification,<sup>1</sup> have been developed.<sup>2,3</sup> It is a problem that the cyclization is disadvantageous in entropy in the synthesis of medium- and large-sized cyclic compounds.<sup>4</sup> Consequently, although simple macrocyclic lactones have been prepared by many workers, it is difficult to prepare medium-membered rings such as 9- to 13-membered lactones in good yields because of competing with the formation of diolides.<sup>5</sup> Mukaiyama *et*

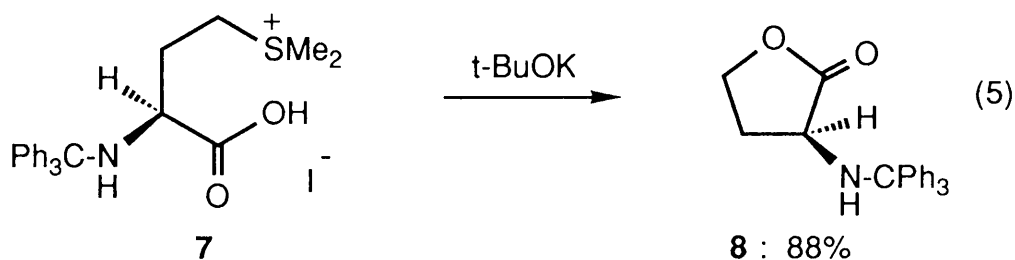
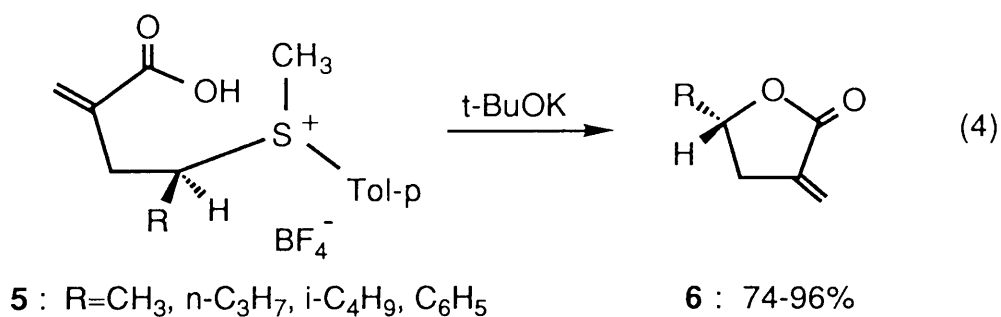
*al.* reported a general lactonization method which 2-chloro-1-methylpyridinium iodide activates  $\omega$ -hydroxycarboxylic acids **1** (eq. 1).<sup>1a</sup> As shown in eq. 2,  $\omega$ -iodocarboxylic acids **4** cyclized under weakly basic conditions to give lactones **2**.<sup>5e</sup> However, these two methods did not give good results in the synthesis of 12- and 13-membered lactones ( $n = 10, 11$ ).



It is well-known that alkylsulfonium salts act as good alkylating reagents for nucleophiles such as carboxylate anions. Badet *et al.* reported that methyldiphenylsulfonium perchlorate alkylated benzoic acid in the presence of  $\text{K}_2\text{CO}_3$  to give methyl benzoate quantitatively (eq. 3).<sup>6</sup> Bravo *et al.* performed the intramolecular

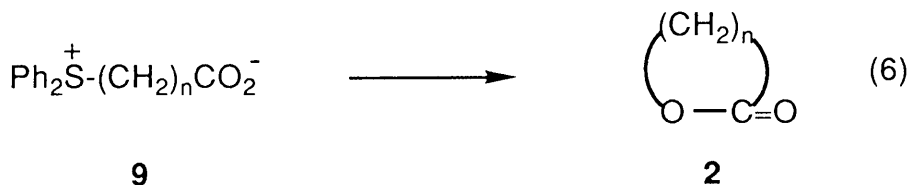


alkylation of methyl-p-tolylsulfonium tetrafluoroborates **5** under basic conditions to obtain optically active  $\gamma$ -lactones **6** in good yields (eq. 4).<sup>7</sup> Similarly, dimethylsulfonium iodide **7** also gave optically active  $\gamma$ -lactones **8** (eq. 5).<sup>8</sup> However, this cyclization method by the



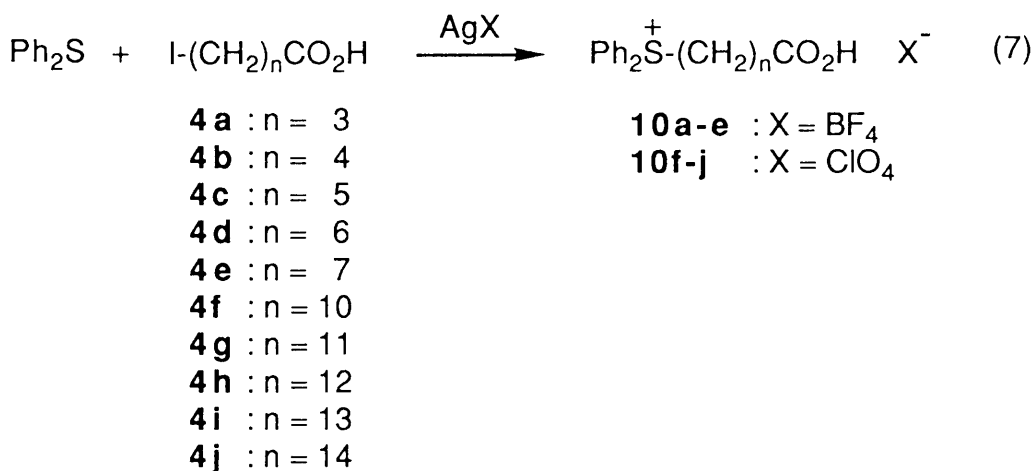
use of  $\omega$ -carboxyalkylsulfonium salts have not hitherto been applied to the synthesis of macrocyclic lactones. Therefore, the author investigated intramolecular cyclization of diphenylsulfonium salts **9** possessing a nucleophilic carboxyl group at the  $\omega$ -carbon atom (eq. 6). It is expected that intramolecularly electrostatic interaction between

the sulfonium cation and the carboxylic anion stimulates this cyclization reaction to give lactones **2** effectively.



## Results and Discussion

( $\omega$ -Carboxyalkyl)diphenylsulfonium salts **10** were prepared from diphenyl sulfide and  $\omega$ -iodocarboxylic acids **4** in the presence of  $\text{AgBF}_4$  or  $\text{AgClO}_4$  (eq. 7). Reactions of (10-carboxydecyl)diphenyl-



sulfonium perchlorate (**10f**) were carried out in the presence of base in refluxing solvent under several conditions (eq. 8), and the results are shown in Table 1. The reactions in the presence of  $\text{K}_2\text{CO}_3$  as a base under condition A gave undesired diolide **3f** as main product

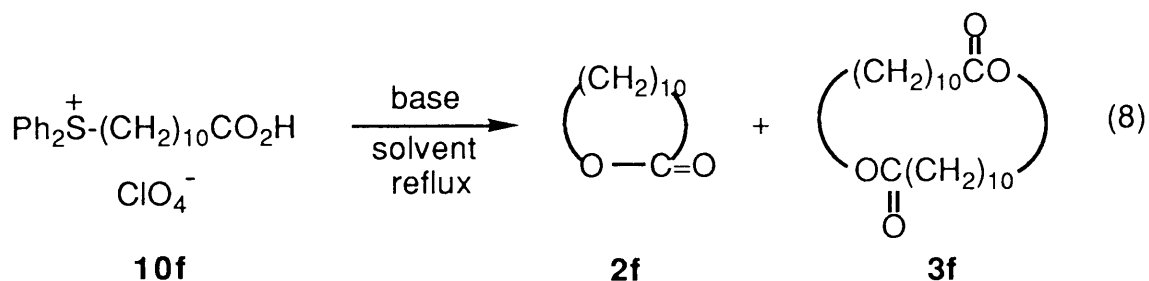


Table 1. Lactonization of Diphenylsulfonium Salt **10f**

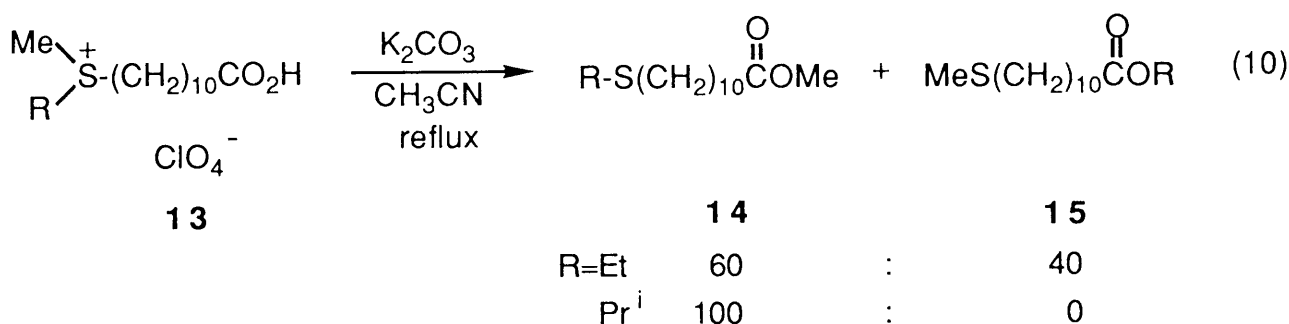
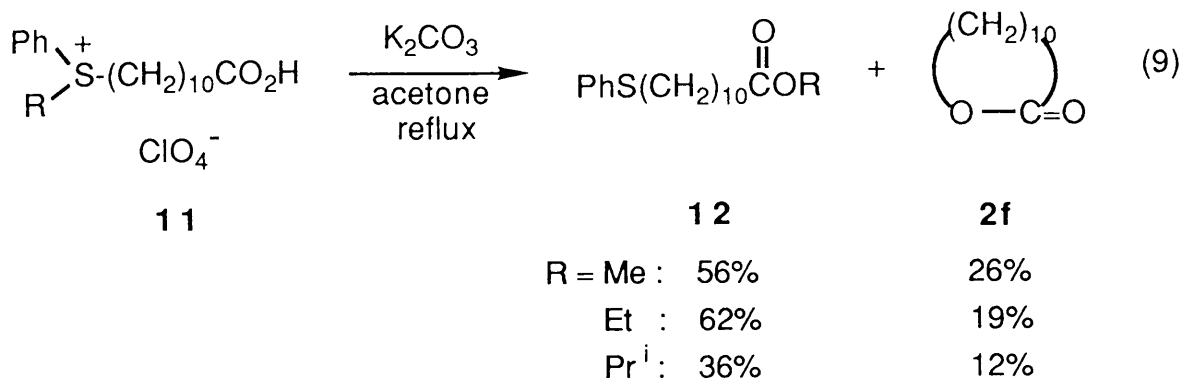
run	base <sup>a</sup>	solvent	condition <sup>b</sup>	Yield / % <sup>c</sup>	
				<b>2f</b>	<b>3f</b>
1	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>	A	6	46
2	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	A	13	87
3	K <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	A	7	70
4	t-BuOK <sup>e</sup>	CH <sub>3</sub> CN	A	4	2
5	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>	B	17	26
6	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	B	78	14
7	K <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	B	87	10

a) 3 equiv. b) A: **10f** (1 mmol), solvent (30 ml), 1 day. B: high-dilution conditions, **10f** (2 mmol), solvent (200 ml), 1.5 days. c) Isolated yield. d) Unreacted salt **10f** was recovered (40%). e) 18-crown-6 (0.4 mmol).

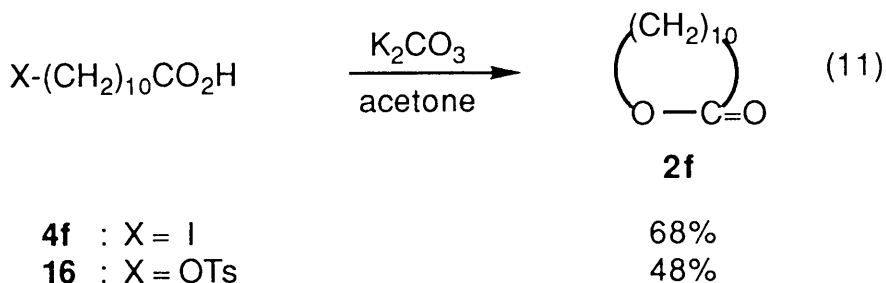


(run 1-3). The use of a strong base, *t*-BuOK, hardly afforded cyclization products **2f** and **3f** (run 4). On the other hand, under high-dilution conditions (condition B) in acetone, the desired lactone **2f** was obtained in high yield (87%) and the formation of diolide **3f** was prevented (run 7). Therefore, subsequent cyclizations of diphenylsulfonium salts **10** were carried out under K<sub>2</sub>CO<sub>3</sub> / acetone / high-dilution conditions.

In order to investigate the effect of some leaving groups in lactonization of ( $\omega$ -carboxyalkyl)sulfonium salts, the similar intramolecular reaction to diphenylsulfonium salt **10f** was performed using alkylphenylsulfonium perchlorates **11** and alkylmethylsulfonium perchlorates **13** having a variety of substituents on sulfur atom. Sulfonium salts **11** and **13** were readily prepared from the corresponding sulfide and 11-iodoundecanoic acid (**4f**) in the presence of AgClO<sub>4</sub> in acetonitrile. (10-Carboxydecyl)alkylphenylsulfonium perchlorates **11** gave both lactone **2f** and esters **12** (eq. 9). As shown in eq. 10, the reaction of (10-carboxydecyl)alkylmethylsulfonium perchlorates **13** was very slow and gave methyl esters **14** and alkyl esters **15** without lactone **2f**. These results show that the use of diphenylsulfonium salts **10** is suitable for the preparation of lactones **2** since the carboxylate anion can attack only the  $\alpha$ -carbon atom of the alkyl chain. The relative reactivity of alkyl groups on sulfur atom of **11** and **13**, which was estimated from the product ratio of esters, was following order: methyl > ethyl > isopropyl. This result means that attack of carboxylate anions toward a sterically hindered secondary carbon atom is not favorable.<sup>9</sup>



The intramolecular cyclization of  $\omega$ -iodoundecanoic acid (**4f**) and  $\omega$ -tosyloxyundecanoic acid (**16**) was carried out in a similar fashion, and the usefulness of leaving group Ph<sub>2</sub>S was confirmed (eq. 11). Although iodide and tosylate groups are good leaving ones, the



yields of lactone **2f** using **4f** or **16** were lower compared to that using diphenylsulfonium salt **10f** (87%). The acceleration of

intramolecular cyclization of **7f** can be accounted for by the electrostatic interaction between sulfur atom of the sulfonium ion and oxygen atom of carboxylate anion.

The intramolecular cyclizations of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts **10** ( $n = 3-14$ ) were performed under  $K_2CO_3$  / acetone reflux / high-dilution conditions (eq. 12) and the results are summarized in Table 2. In case of diphenylsulfonium tetrafluoroborates **10a-e**, the yields of five- to nine-membered lactones **2a-e** were moderate (run 1-5). Generally, it is difficult to synthesize medium-sized ring compounds including lactones, and seven- to nine-membered lactones **2c-e** were not obtained by the cyclization of appropriate  $\omega$ -halocarboxylic acids. For instance, Kellogg et al. reported that the cyclization of 6-iodohexanoic acid (**4c**) in the presence of  $Cs_2CO_3$  in DMF afforded only diolide **3c** without the formation of seven-membered lactone **2c**.<sup>5e</sup> Nine-membered lactone **2e** was not obtained by Hunsdiecker's method that was reaction of 8-bromooctanoic acid in the presence of  $K_2CO_3$ .<sup>10</sup> On the other hand, the present method has advantage for the synthesis of seven-membered **2c** and nine-membered lactone **2e** though the yields are moderate (run 3 and 5). For the reason that the total yields of lactones **2a-e** and diolides **3a-e** were lower than that of diphenyl sulfide produced as leaving group in this reaction system,  $\beta$ -elimination may be occurring as a side reaction,<sup>11</sup> although we failed to isolate the corresponding  $\beta$ -elimination product.

In the case of diphenylsulfonium perchlorates **10f-j** (run 6-

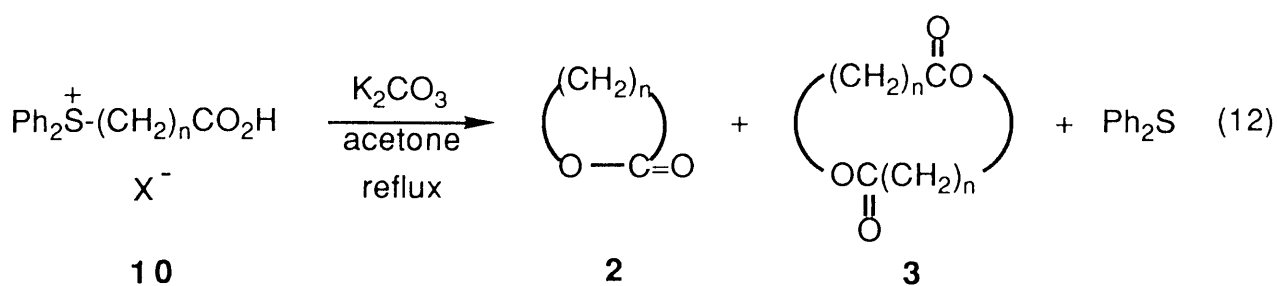


Table 2. Lactonization of Sulfonium Salts **10**

run	sulfonium salt	X	Ring size of <b>2</b>	Yield / % <sup>a</sup>		
				<b>2</b>	<b>3</b>	Ph <sub>2</sub> S
1	<b>10a</b>	BF <sub>4</sub>	5	28	2	65
2	<b>10b</b>	BF <sub>4</sub>	6	26	46	67
3	<b>10c</b>	BF <sub>4</sub>	7	30	6	82
4	<b>10d</b>	BF <sub>4</sub>	8	11	18	91
5	<b>10e</b>	BF <sub>4</sub>	9	33	12	84
6	<b>10f</b>	ClO <sub>4</sub>	12	83	10	87
7	<b>10g</b>	ClO <sub>4</sub>	13	86	8	97
8	<b>10h</b>	ClO <sub>4</sub>	14	87	0	86
9	<b>10i</b>	ClO <sub>4</sub>	15	85	11	91
10	<b>10j</b>	ClO <sub>4</sub>	16	92	trace	92

a) Isolated yields.

10), 12- to 16-membered macrocyclic lactones **2f-j** were obtained in high yields (83-92%). An important characteristic of this reaction is that 12- and 13-membered lactones **2f** and **2g**, which were not obtained in good yields by conventional methods,<sup>5</sup> are afforded in good yields (run 6 and 7). These results show that cyclization of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts has advantage for the synthesis of medium-sized lactones due to the electrostatic interaction between sulfur atom of the sulfonium ion and oxygen atom of the carboxylate anion.

## Experimental

$^1\text{H}$  NMR spectra were recorded on a JEOL PMX 60SI 60-MHz spectrometer. Infrared spectra were recorded on a Hitachi 260-10 spectrometer. Mass spectra were determined with a JEOL JMX-DX 300 mass spectrometer with JEOL JMA 5000 mass data system at an ionizing voltage of 70 eV. Melting points (uncorrected) were measured on a Yamato MP-21 apparatus in open capillary tubes. GLPC were recorded on a Hitachi G-3000 with 10% SE-30 1-m column. Column chromatography was performed with Wako gel C-200. Thin-layer chromatography was performed on 0.25-mm silica gel (Merck 60F254).

**Materials.** Dry solvents were obtained as follows: Acetone and  $\text{CH}_2\text{Cl}_2$  were dried over molecular sieves 4A;  $\text{CH}_3\text{CN}$  was distilled from  $\text{CaH}_2$ .

13-Bromotridecanoic acid and 14-bromotetradecanoic acid were prepared according to the literature.<sup>4</sup>

$\omega$ -Iodocarboxylic acids **4a-c** and **4e-i** were prepared quantitatively by treatment of the corresponding  $\omega$ -bromocarboxylic acids with KI (3 equiv.) in boiling acetone for 6 h. Recrystallization from ether-hexane yielded pure **4a-c** and **4e-i** as colorless crystals.

**4a:** mp 28-29 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.90-2.67 (m, 4H), 3.25 (t,  $J$  = 6.5 Hz, 2H), 11.0 (br s, 1H); IR (KBr) 3500-2500, 1720  $\text{cm}^{-1}$ .

**4b:** mp 53-54 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.68-2.20 (m, 4H), 2.43 (t,  $J$  = 6.5 Hz, 2H), 3.22 (t,  $J$  = 6.5 Hz, 2H), 9.40 (br s, 1H); IR (KBr) 3300-2300, 1680  $\text{cm}^{-1}$ .

**4c:** mp 40-41 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42-2.08 (m, 6H), 2.37 (t,  $J$  = 6.5 Hz, 2H), 3.14 (t,  $J$  = 6.5 Hz, 2H), 11.0 (br s, 1H); IR (KBr) 3300-2300, 1690  $\text{cm}^{-1}$ .

**4e:** mp 37 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-2.10 (m, 10H), 2.17-2.57 (m, 2H), 3.16 (t,  $J$  = 6.5 Hz, 2H), 11.0 (br s, 1H); IR (KBr) 3400-2400, 1687  $\text{cm}^{-1}$ ; MS  $m/z$  271 ( $\text{M}^++1$ ), 253, 169.

**4f:** mp 65 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.92 (m, 16H), 2.22-2.47 (m,

2H), 3.17 (t,  $J = 6.6$  Hz, 2H), 11.6 (br s, 1H); IR (KBr) 2770-3460, 1695  $\text{cm}^{-1}$ .

**4g**: mp 59-61 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.29 (m, 20H), 3.15 (t,  $J = 6.7$  Hz, 2H), 11.6 (br s, 1H); IR (KBr) 2770-3460, 1690  $\text{cm}^{-1}$ .

**4h**: mp 67-69 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.03 (m, 20H), 2.12-2.17 (m, 2H), 3.13 (t,  $J = 6.5$  Hz, 2H), 11.6 (br s, 1H); IR (KBr) 2770-3460, 1690  $\text{cm}^{-1}$ ; MS  $m/z$  341 ( $\text{M}^++1$ ), 323, 294.

**4i**: mp 65-67 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.07 (m, 22H), 2.21-2.44 (m, 2H), 3.14 (t,  $J = 6.9$  Hz, 2H), 11.6 (br s, 1H); IR (KBr) 2770-3460, 1690  $\text{cm}^{-1}$ ; MS  $m/z$  355 ( $\text{M}^++1$ ), 337, 308.

7-Iodoheptanoic acid (**4d**) was prepared by the reaction of 7-bromoheptanenitrile with 57% HI in AcOH under reflux conditions for 1 day.<sup>4</sup> After distillation of HI and AcOH, the residue was extracted with ether. The combined extracts were washed with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Recrystallization from ether-hexane gave **4d** as colorless crystals (91%): mp 42-45 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05-2.11 (m, 8H), 2.21-2.54 (m, 2H), 3.16 (t,  $J = 6.7$  Hz, 2H), 11.3 (br s, 1H); IR (KBr) 3300-2200, 1689  $\text{cm}^{-1}$ ; MS  $m/z$  257 ( $\text{M}^++1$ ), 239, 169.

15-Iodopentadecanoic acid (**4j**) was prepared by the reaction of 15-pentadecanolactone (4.81 g, 20 mmol) with 57% HI in AcOH (150 ml) under reflux conditions for 6 h. The work-up was carried out in a similar manner as above. Recrystallization from ether-hexane gave **4j** as colorless crystals (93%): mp 78 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-1.90 (m, 24H), 2.05-2.47 (m, 2H), 3.15 (t,  $J = 7.0$  Hz, 2H), 11.6 (br s, 1H); IR (KBr) 2770-3460, 1695  $\text{cm}^{-1}$ .

**( $\omega$ -Carboxyalkyl)diphenylsulfonium Salts 10.** In a round-bottomed flask were placed  $\omega$ -iodocarboxylic acids **4** (10 mmol) and  $\text{AgBF}_4$  or  $\text{AgClO}_4$  (11 mmol), and the mixture was cooled in an ice bath. Diphenyl sulfide (18.6 g, 0.1 mol) was added dropwise and then the ice bath was removed. The flask was covered with aluminum foil and then stirred for 3 days at room temperature. The reaction mixture was passed through a silica gel short column and eluted with

acetone. After removal of solvent, the residue was washed with ether to yield **7** (46-99%).

**10a**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.70-3.00 (m, 4H), 4.00-4.60 (m, 2H), 7.50-8.30 (m, 11H); IR (neat) 3600-2700, 1710, 1070  $\text{cm}^{-1}$ .

**10b**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.50-2.10 (m, 4H), 2.20-2.50 (m, 2H), 4.20-4.60 (m, 2H), 7.00 (br s, 1H), 7.50-8.20 (m, 10H); IR (neat) 3600-2500, 1720, 1060  $\text{cm}^{-1}$ .

**10c**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.50-2.10 (m, 6H), 2.27 (t,  $J = 6.0$  Hz, 2H), 4.33 (t,  $J = 6.0$  Hz, 2H), 7.70-8.30 (m, 11H); IR (neat) 3600-2700, 1710, 1070  $\text{cm}^{-1}$ .

**10d**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.27-1.99 (m, 8H), 2.13-2.50 (m, 2H), 4.17-4.60 (m, 2H), 7.56-7.88 (m, 6H), 7.98-8.39 (m, 4H), 9.60 (br s, 1H); IR (neat) 3675-2400, 1726, 1064  $\text{cm}^{-1}$ .

**10e**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.15-1.98 (m, 10H), 2.02-2.57 (m, 2H), 4.06-4.60 (m, 2H), 7.53-7.83 (m, 6H), 7.95-8.29 (m, 4H), 9.33 (br s, 1H); IR (neat) 3650-2400, 1704, 1066  $\text{cm}^{-1}$ .

**10f**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.27-3.20 (m, 18H), 4.38 (t,  $J = 7.0$  Hz, 2H), 7.25-7.80 (m, 6H), 7.98-8.20 (m, 4H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1710, 1080  $\text{cm}^{-1}$ .

**10g**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.27-1.90 (m, 18H), 1.95-2.38 (m, 2H), 4.22-4.48 (m, 2H), 7.53-7.80 (m, 6H), 7.95-8.15 (m, 4H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1707, 1092  $\text{cm}^{-1}$ .

**10h**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.25-1.90 (m, 20H), 2.14-2.43 (m, 2H), 4.13-4.50 (m, 2H), 7.48-7.81 (m, 6H), 7.90-8.17 (m, 4H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1707, 1095  $\text{cm}^{-1}$ .

**10i**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone) 1.25-1.90 (m, 22H), 2.13-2.43 (m, 2H), 4.25-4.53 (m, 2H), 7.53-7.83 (m, 6H), 7.97-8.20 (m, 4H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1705, 1095  $\text{cm}^{-1}$ .

**10j**: mp 69-72  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.27-2.40 (m, 26H), 4.25-4.49 (m, 2H), 7.55-7.80 (m, 6H), 8.00-8.17 (m, 4H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1730, 1095  $\text{cm}^{-1}$ .

( $\omega$ -Carboxyalkyl)sulfonium Salts **11** and **13**. In a round-bottomed flask, cooled in an ice bath, were placed 11-iodoundecanoic acid (**4f**) (10 mmol) and  $\text{AgClO}_4$  (2.29 g, 11 mmol). The appropriate



sulfide (11 mmol) in CH<sub>3</sub>CN (15 ml) was added dropwise and then the ice bath was removed. The flask was covered with aluminum foil and then stirred for 3 days at room temperature. The work-up was carried out in a similar manner as described for the preparation of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts **10**. The crude products obtained were recrystallized from acetone-ether to yield sulfonium salts **11** and **13** as colorless crystals.

**11 (R = Me)**: yield 88%; mp 62-64 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.26-2.53 (m, 18H), 3.41 (s, 3H), 3.63-4.07 (m, 2H), 7.65-7.93 (m, 3H), 7.97-8.27 (m, 2H), 9.73 (br s, 1H); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3000-3600, 1705, 1090 cm<sup>-1</sup>.

**11 (R = Et)**: yield 91%; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.26-2.47 (m, 21H), 3.67-4.13 (m, 4H), 7.67-7.95 (m, 3H), 7.95-8.27 (m, 2H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1705, 1085 cm<sup>-1</sup>.

**11 (R = Pr<sup>i</sup>)**: yield 59%; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.10-2.43 (m, 24H), 3.47-5.82 (m, 3H), 7.23-8.13 (m, 5H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1685, 1085 cm<sup>-1</sup>.

**13 (R = Et)**: yield 99%; mp 55-57 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.32-2.47 (m, 21H), 2.95 (s, 3H), 3.13-3.70 (m, 4H), 9.73 (br s, 1H); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3000-3600, 1707, 1097 cm<sup>-1</sup>.

**13 (R = Pr<sup>i</sup>)**: yield 34%; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.32-2.43 (m, 24H), 2.94 (s, 3H), 3.26-3.48 (m, 2H), 3.64-4.15 (m, 1H), 9.73 (br s, 1H); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3000-3600, 1726, 1090 cm<sup>-1</sup>.

(11-*p*-Tolylsulfonyloxy)undecanoic acid (**16**) was prepared by the reaction of 11-hydroxyundecanoic acid<sup>10</sup> with *p*-toluenesulfonyl chloride in pyridine at room temperature for 2 h (26%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.97-2.00 (m, 16H), 2.13-2.55 (m, 5H), 3.85-4.18 (m, 2H), 7.26 and 7.69 (ABq, *J* = 7.7 Hz, 4H), 9.97 (br s, 1H); IR (neat) 3500-2400, 1708, 1600, 1358, 1175 cm<sup>-1</sup>; MS *m/z* 338 (M<sup>+</sup>-18), 183, 173.

**General Procedure of Intramolecular Cyclization.** To a stirred suspension of K<sub>2</sub>CO<sub>3</sub> in refluxing acetone (100 ml) was added sulfonium salt (2 mmol) in acetone (100 ml) over 1.5 days. After the mixture was refluxed for an additional 12 h, the solution was cooled to room temperature, diluted with ether (100 ml), and passed

through a silica gel short column. The solvent was removed, and the residue was chromatographed on silica gel (hexane-ether) to give pure products.

**Intramolecular Reaction of 13.** A suspension of **13** (1 mmol) and  $K_2CO_3$  (838 mg, 6 mmol) in  $CH_3CN$  (20 ml) was refluxed for 6 h. The reaction mixture was diluted with ether (30 ml) and passed through a silica gel short column. After removal of solvent, the residue was extracted with ether to remove the esters from unreacted salt. The extract was analyzed by  $^1H$  NMR and gas chromatography. A mixture of esters **14** and **15** ( $R = Et$ ):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.62 (s, -OMe) / 2.08 (s, -SMe) = 6 : 4. **14** ( $R = Pri$ ):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.13-1.90 (m, 22H), 2.03-2.34 (m, 5H), 3.60 (s, 3H).

The lactones **2a-c** were identified by the comparison of  $^1H$  NMR, IR, mass spectral data, and retention time of GC with the authentic lactones from Aldrich Chemical Co., and diolides **3a-c** were determined by GC-MS measurement.

**3d:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.39-2.05 (m, 8H), 2.39-2.67 (m, 2H), 4.18-4.50 (m, 2H); IR (neat)  $1722\text{ cm}^{-1}$ ; MS  $m/z$  128 ( $M^+$ ), 100, 98.

**3e:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.17-2.00 (m, 10H), 2.10-2.47 (m, 2H), 4.13-4.43 (m, 2H); IR (neat)  $1735\text{ cm}^{-1}$ ; MS  $m/z$  142 ( $M^+$ ), 124, 112.

**3f:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.33-1.91 (m, 16H), 2.26-2.63 (m, 2H), 4.07-4.23 (m, 2H); IR (neat)  $1734\text{ cm}^{-1}$ ; MS  $m/z$  185 ( $M^++1$ ), 166, 148.

**3g:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.30-1.80 (m, 18H), 2.13-2.42 (m, 2H), 4.01-4.17 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ , MS  $m/z$  198 ( $M^+$ ), 180, 168.

**3h:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.32-2.00 (m, 20H), 2.23-2.50 (m, 2H), 3.97-4.23 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  212 ( $M^+$ ), 194, 176.

**3i:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.32-1.93 (m, 22H), 2.19-2.43 (m, 2H), 3.97-4.20 (m, 2H); IR (neat)  $1732\text{ cm}^{-1}$ ; MS  $m/z$  226 ( $M^+$ ), 208, 166.

**3j:** mp  $32-34\text{ }^\circ\text{C}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.30-1.87 (m, 24H), 2.20-2.43 (m, 2H), 4.01-4.18 (m, 2H); IR (neat)  $1735\text{ cm}^{-1}$ .

**4d:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.33-1.95 (m, 16H), 2.27-2.53 (m, 4H), 3.95-4.23 (m, 4H); IR (neat)  $1726\text{ cm}^{-1}$ ; MS  $m/z$  256 ( $M^+$ ), 197, 183.

**4e:** mp  $86-88\text{ }^\circ\text{C}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.12-1.98 (m, 20H), 2.07-2.63

(m, 4H), 3.99-4.29 (m, 4H); IR (KBr) 1727  $\text{cm}^{-1}$ ; MS  $m/z$  284 ( $\text{M}^+$ ), 265, 197.

**4f:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.92 (m, 32H), 2.21-2.43 (m, 4H), 3.98-4.17 (m, 4H); IR ( $\text{CCl}_4$ ) 1730  $\text{cm}^{-1}$ ; MS  $m/z$  368 ( $\text{M}^+$ ), 350, 332.

**4g:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28-1.81 (m, 36H), 2.14-2.41 (m, 4H), 3.97-4.13 (m, 4H); IR ( $\text{CCl}_4$ ) 1730  $\text{cm}^{-1}$ ; MS  $m/z$  396 ( $\text{M}^+$ ), 378, 360.

**4h:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.26-1.93 (m, 40H), 2.15-2.47 (m, 4H), 3.90-4.19 (m, 4H); IR ( $\text{CCl}_4$ ) 1733  $\text{cm}^{-1}$ ; MS  $m/z$  424 ( $\text{M}^+$ ), 406, 388.

**4i:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.02 (m, 44H), 2.13-2.47 (m, 4H), 3.92-4.20 (m, 4H); IR ( $\text{CCl}_4$ ) 1731  $\text{cm}^{-1}$ ; MS  $m/z$  452 ( $\text{M}^+$ ), 434, 269.

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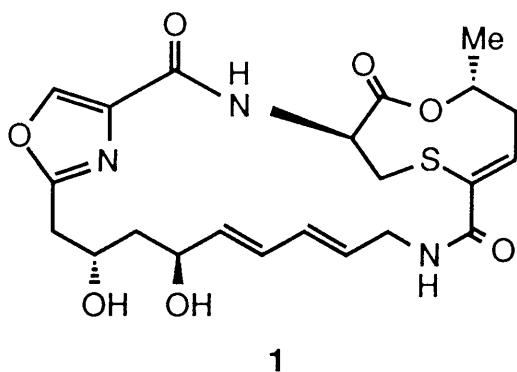
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## Chapter 2

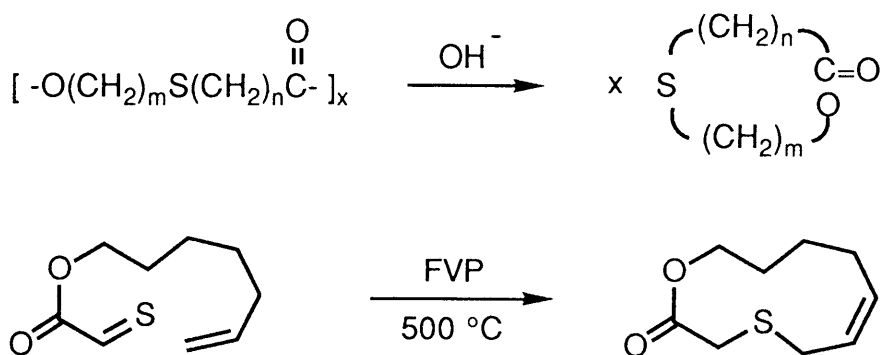
### Synthesis of Thialactones from S-( $\omega$ -Carboxyalkyl)-thiolanium Salts

Thialactones, which contain an atom of sulfur in the carbon chain, are building blocks of antibiotics (e.g., griseoviridin **1**) existing in nature,<sup>1</sup> and have been also studied as a perfume in order to

determine the effect on the odor caused by introduction of the sulfur atom in the carbon chain of the lactone.<sup>2</sup> However, as shown in scheme 1, known synthetic methods of thialactones required multisteps<sup>2</sup> and high temperature conditions.<sup>3</sup>

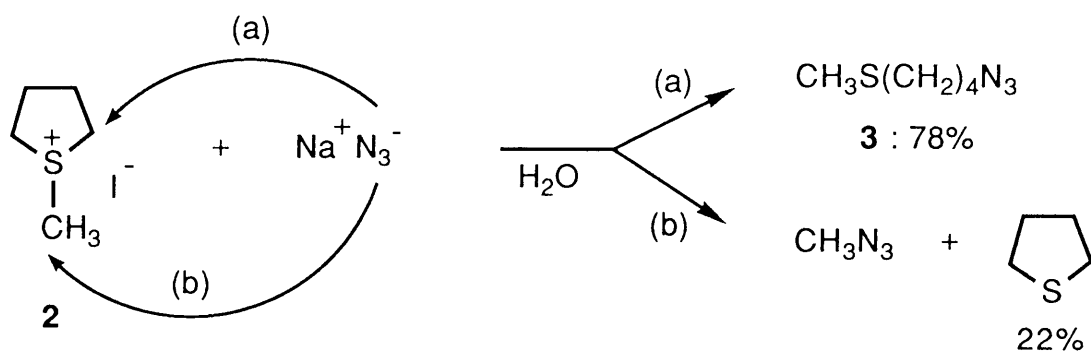


Scheme 1



Synthesis of lactones utilizing intramolecular alkylation of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts was described in chapter 1. Interestingly, as shown in Scheme 2, Eliel *et al.* reported that alkylation of sodium azide with S-methylthiolanium iodide **2** preferentially occurred on the  $\alpha$ -carbon atom of the five-membered ring to give 1-azido-4-methylthiobutane **3** as ring-opening product in good yield (path a).<sup>4</sup> Thus, it is expected that the intramolecular

Scheme 2

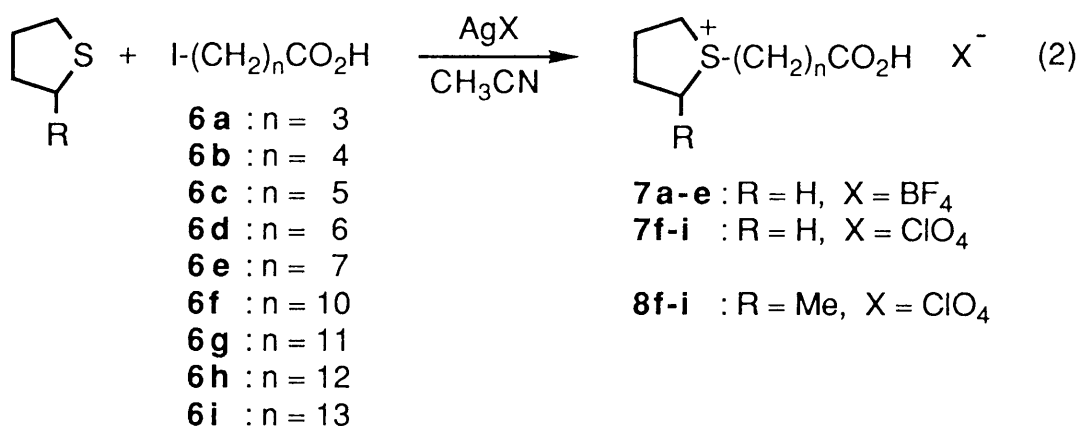


reaction of thiolanium salts **4** having a nucleophilic carboxyl group at the  $\omega$ -carbon atom takes place in a similar fashion to afford thialactones **5** *via* ring-expansion process (eq. 1). In this chapter, short-step synthesis of thialactones from S-( $\omega$ -carboxyalkyl)thiolanium salts under mild reaction conditions is described.



## Results and Discussion

S-( $\omega$ -Carboxyalkyl)thiolanium salts **7** and **8** were readily prepared from tetrahydrothiophene or 2-methyltetrahydrothiophene and  $\omega$ -iodocarboxylic acids **6** in the presence of AgClO<sub>4</sub> or AgBF<sub>4</sub> in acetonitrile (eq. 2). The reactions of S-(10-carboxydecyl)thiolanium



perchlorate (**7f**) were carried out in the presence of K<sub>2</sub>CO<sub>3</sub> as a base in refluxing solvent under several conditions (eq. 3), and the results are presented in Table 1. The reactions under condition A gave mixtures of desired 17-membered thialactone **5f** and undesired diolide **9f**, and selectivity of products was not observed (run 1-3). On the other hand, under high-dilution conditions (condition B) in acetone, the desired thialactone **5f** was obtained in good yield (86%) and the formation of diolide **9f** was prevented (run 6). Therefore, subsequent cyclizations of S-( $\omega$ -carboxyalkyl)thiolanium salts were carried out under K<sub>2</sub>CO<sub>3</sub> / acetone / high-dilution conditions.



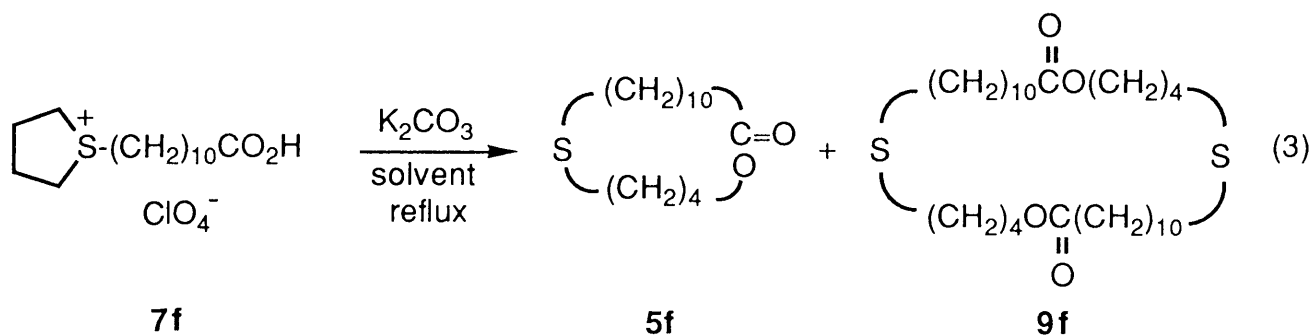


Table 1. Lactonization of Thiolanium Salt **7f**

run	solvent	condition <sup>a</sup>	Yield / % <sup>b</sup>	
			<b>5f</b>	<b>9f</b>
1	CH <sub>2</sub> Cl <sub>2</sub>	A	19	31
2	CH <sub>3</sub> CN	A	24	16
3	(CH <sub>3</sub> ) <sub>2</sub> C=O	A	33	
4	CH <sub>2</sub> Cl <sub>2</sub>	B	73	0
5	CH <sub>3</sub> CN	B	74	0
6	(CH <sub>3</sub> ) <sub>2</sub> C=O	B	86	8

a) A: **7f** (2 mmol), solvent (30 ml), 1 day. B: **7f** (2 mmol), solvent (200 ml), 1.5 days. b) Isolated yield.

The intramolecular cyclization of S-( $\omega$ -carboxyalkyl)thiolanium salts **7** ( $n = 3-13$ ) was investigated under above-mentioned conditions (eq. 4). Carboxylate anion **10** formed from **7** under weakly basic conditions may attack on two kinds of carbon atoms; one is the  $\alpha$ -carbon atom of the five-membered ring (path a) and the other is the alkyl chain's  $\alpha$ -carbon atom (path b). The results are shown in Table 2. In the case of thiolanium tetrafluoroborates **7a-c**, path b process only occurred to give five- to seven-membered lactones **11a-c** in good yields (51-60%) without the formation of thialactones **5a-c** (run 1-3). Whereas, in the case of **7d-e** having a longer alkyl chain, thialactones **5d-e** were formed in low yields (5-15%) *via* path a, together with the moderate amounts of diolides (30-43%) (run 4 and 5). This difference in regioselectivity of intramolecular nucleophilic attack of carboxylate anions between **7a-c** and **7d-e** is of interest

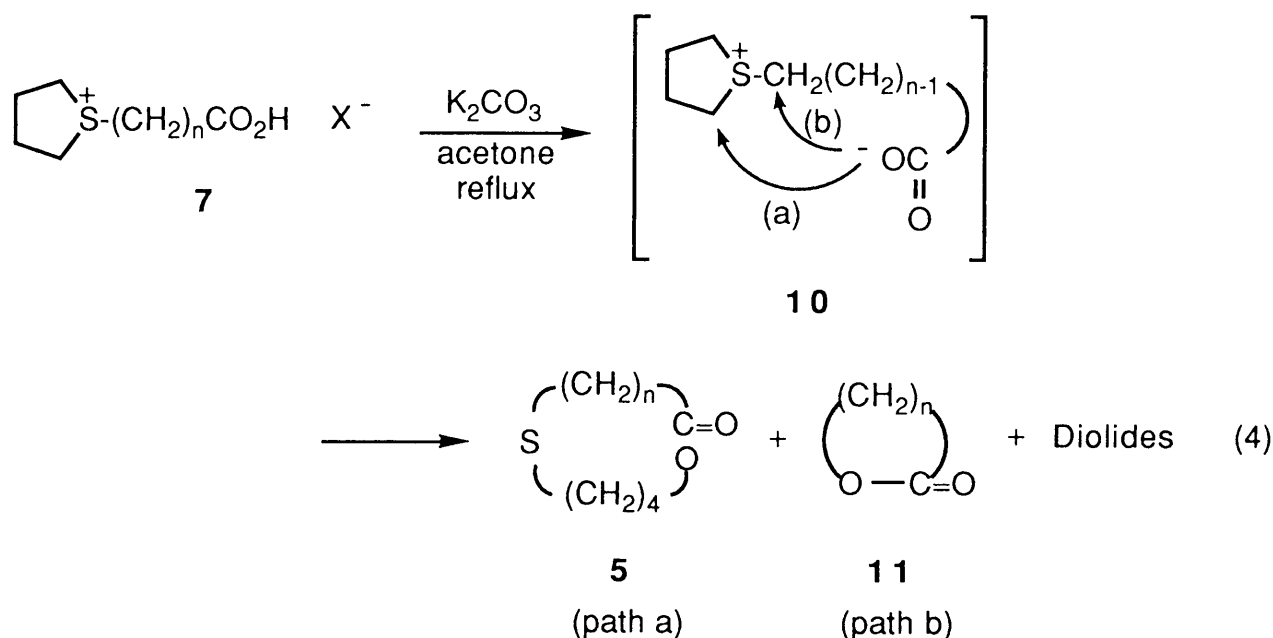
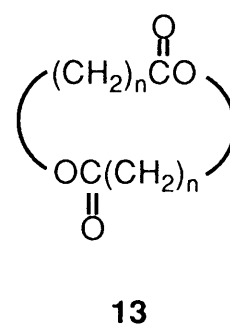
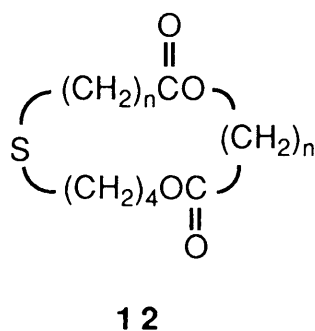
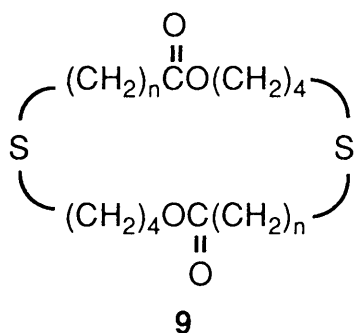


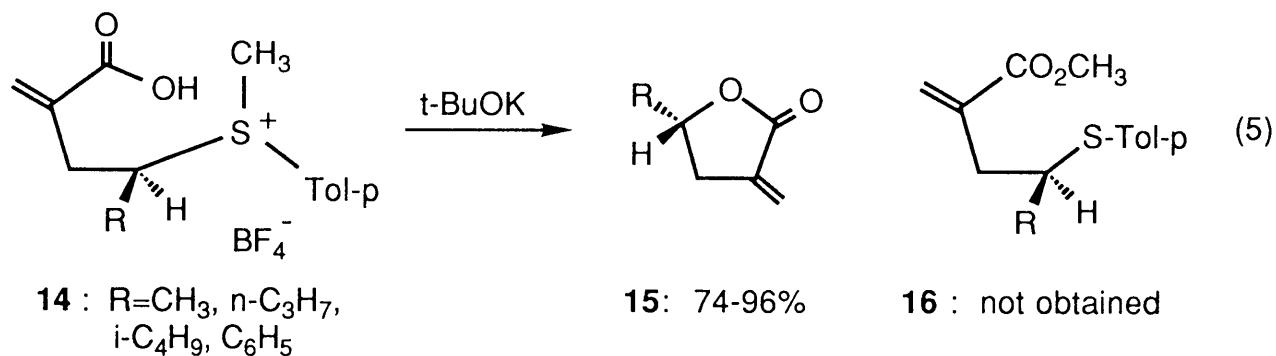
Table 2. Lactonization of Thiolanium Salts **7**

run	sulfonium		Ring size		Yield / % <sup>a</sup>	
	salt	X	of <b>5</b>	<b>5</b>	<b>11</b>	Diolides
1	<b>7a</b>	BF <sub>4</sub>	10	0	60	0
2	<b>7b</b>	BF <sub>4</sub>	11	0	60	0
3	<b>7c</b>	BF <sub>4</sub>	12	0	51	0
4	<b>7d</b>	BF <sub>4</sub>	13	5	0	30
5	<b>7e</b>	BF <sub>4</sub>	14	15	0	43
6	<b>7f</b>	ClO <sub>4</sub>	17	86	3	8
7	<b>7g</b>	ClO <sub>4</sub>	18	81	10	2
8	<b>7h</b>	ClO <sub>4</sub>	19	84	10	4
9	<b>7i</b>	ClO <sub>4</sub>	20	80	8	1

a) Isolated yield. b) Diolides are the following compounds **9**, **12**, and **13**.



and depends on the numbers of  $n$  in the carboxyalkyl group's alkyl chain of **7a-e**. It is speculated that if the carboxylate anions of **7a-c**, having a shorter alkyl chain, attack on the  $\alpha$ -carbon atom of the five-membered ring (path a), the intramolecular cyclization has to proceed *via* seven- to nine-membered transition states which is generally an unfavorable ring system.<sup>5</sup> Thus, the reaction of **7a-c** afforded lactones **11a-c** without the formation of thialactones **5a-c**. This speculation is supported from the results reported by Bravo *et al.* that intramolecular alkylation of (3-carboxyalkyl)methyl-*p*-tolyl-sulfonium tetrafluoroborates **14** gave only  $\gamma$ -lactones **15** without the formation of the corresponding methyl esters **16** *via* seven-membered transition state (eq. 5).<sup>6</sup> On the other hand, in the case of **7d-e**, thialactones **5d-e** were formed *via* path a due to unfavorable ring system of **11d-e** *via* path b.



In the case of thiolanium perchlorates **7f-i**, carboxylic anions formed under weakly basic conditions attacked regioselectively the  $\alpha$ -carbon atom of the five-membered ring (*via* path a) to form 17- to

20-membered thialactones **5f-i** in high yields *via* ring-expansion process (run 6-9), and the formation of lactone **11** (*via* path b) and diolides was prevented in low yields. Interestingly, in spite of the presence of a sulfur atom, 17-membered thialactone **5f** has a musk odor.<sup>2</sup> The sulfur atom in thialactones **5** may be possible to be converted into various functional groups; for example, double bond formation by elimination of SO<sub>2</sub> from oxydation product of **5**.

When intramolecular cyclization of S-( $\omega$ -carboxyalkyl)-2-methylthiolanium perchlorates **8** was carried out, carboxylate anions attacked regioselectively the unhindered  $\alpha$ -methylene carbon atom of the five-membered ring to afford macrocyclic thialactones **17** in good yields, together with minor amounts of **11** and diolides (eq. 6, Table 3). This result is consistent with the absence of nucleophilic attack of carboxylate anion on the secondary carbon atom as described in chapter 1.<sup>4</sup>

The reaction of S-( $\omega$ -carboxyalkyl)thianium perchlorates **20**, prepared from pentamethylene sulfide,  $\omega$ -iodocarboxylic acids **6f-i**, and AgClO<sub>4</sub>, was performed in a similar fashion (eq. 7). However, as shown in Table 4, regioselectivity of nucleophilic attack of carboxylate anions on the  $\alpha$ -carbon atom of the six-membered ring was not observed. The yields of **11** increased at the expense of thialactones **21**. The difference in regioselectivity between thiolanium salts **7** and thianium salts **20** depends on the ring size of sulfonium salts (five- or six-membered ring). The strain energy of five-membered ring, tetrahydrothiophene, is 2.24 kcal mol<sup>-1</sup> higher than that of six-membered ring, pentamethylene sulfide.<sup>7</sup> So, since

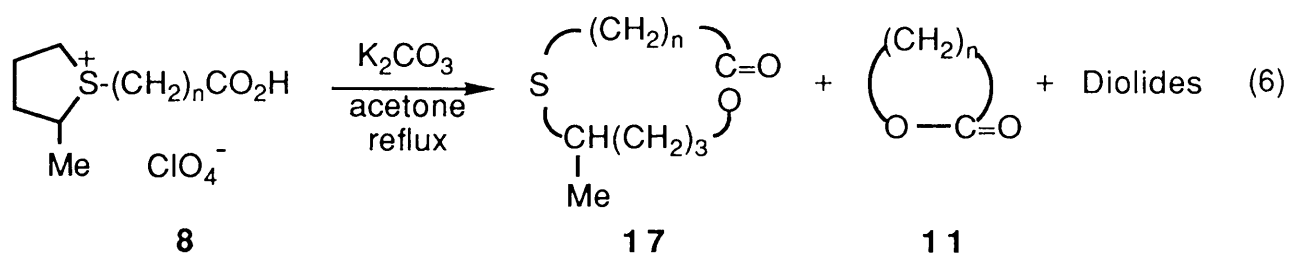
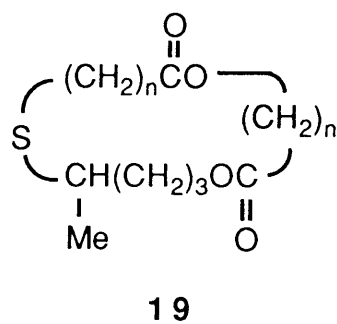
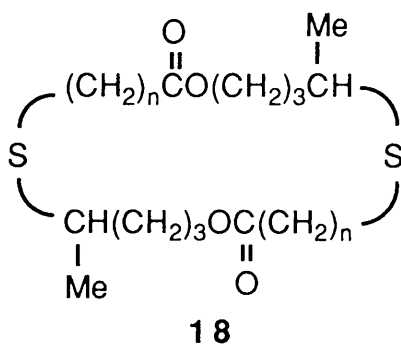


Table 3. Lactonization of 2-Methylthiolanium Salts **8**

sulfonium salt	Ring size of <b>17</b>	Yield / % <sup>a</sup>		
		<b>17</b>	<b>11</b>	Diolides <sup>b</sup>
<b>7f</b>	17	82	4	4
<b>7g</b>	18	72	7	4
<b>7h</b>	19	73	17	2
<b>7i</b>	20	77	14	5

a) Isolated yield. b) Diolides are the following compounds **13**, **18**, and **19**.



the five-membered ring of thiolanium salts **7** is easy to cleave by the ring strain, the carboxylate anions selectively attack on the  $\alpha$ -carbon atom of the five-membered ring to give thialactones **5**. In contrast, the six-membered ring of thianium salts **20** is so stable<sup>1</sup> that the carboxylate anion attacks the alkyl-chain's  $\alpha$ -carbon atom preferentially. These results are consistent with the reactivity of S-methylthianium iodide with nucleophiles such as azide anion reported by Eliel *et al.*<sup>4</sup>

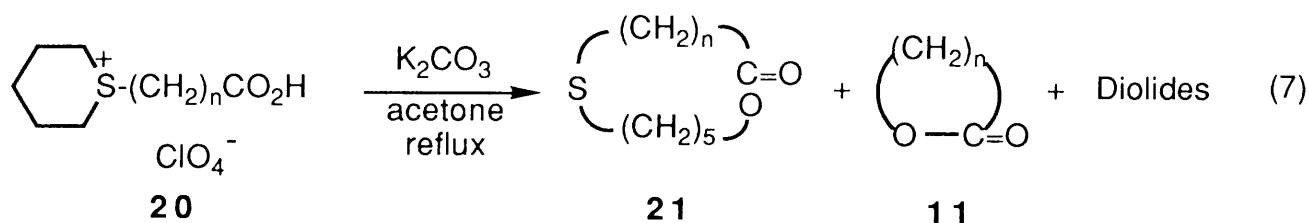
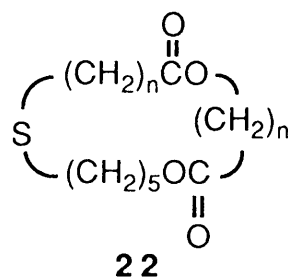


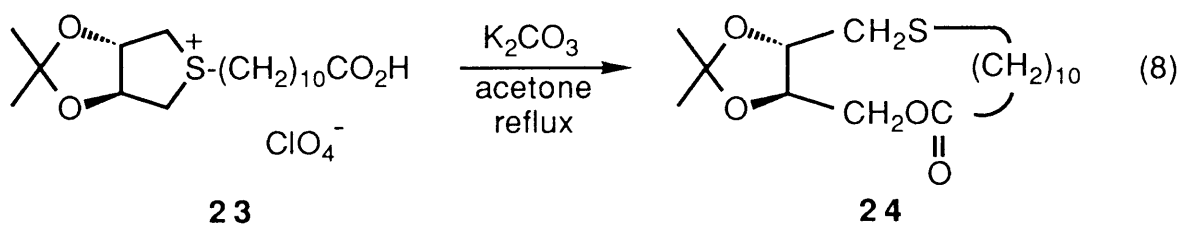
Table 4. Lactonization of Thianium Perchlorates **20**

sulfonium	Yield / % <sup>a</sup>		
salt	<b>21</b>	<b>11</b>	Diolides <sup>b</sup>
<b>20f</b>	27	18	18
<b>20g</b>	30	43	6
<b>20h</b>	15	36	3
<b>20i</b>	22	45	7



a) Isolated yield. b) Diolides are the following compounds **13** and **22**.

The introduction of chiral carbon atoms into a lactone ring utilizing ring-expansion process of ( $\omega$ -carboxyalkyl)thiolanium salts was attempted as shown in eq. 8. Intramolecular cyclization of thiolanium perchlorate **23**, which was prepared from 2,4-dioxa-3,3-dimethyl-7-thiabicyclo-[3.3.0]oactane,<sup>8</sup> 11-iodoundecanoic acid (**6f**), and AgClO<sub>4</sub>, afforded thialactone **24** (10%) having two chiral carbon atoms in the lactone ring *via* ring-expansion process.





## Experimental

Mass and high-resolution mass spectra were determined with a JEOL JMX-DX 300 mass spectrometer with JEOL JMA 5000 mass data system at an ionizing voltage of 70 eV. Optical rotations were measured in a 1.0- or 0.5-dm cell on a JASCO DIP-140 polarimeter.

**S-( $\omega$ -Carboxyalkyl)tholanium Salts 7, 8, and Thianium Salts 20.** In a round-bottomed flask, cooled in an ice bath, were placed  $\omega$ -carboxylic acids **6** (10 mmol) and AgClO<sub>4</sub> or AgBF<sub>4</sub> (11 mmol). The appropriate sulfide (11 mmol) in CH<sub>3</sub>CN (15 ml) was added dropwise and then the ice bath was removed. The flask was covered with aluminum foil and then stirred for 3 days at room temperature. The reaction mixture was passed through a silica gel short column and eluted with acetone. After removal of solvent, the residue was washed with ether. The crude products obtained were recrystallized from acetone-ether to yield thiolanium salts **7**, **8**, and thianium salts **20** as colorless crystals except for **7a-e** as oil (77-100%).

**7a:** <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.80-2.80 (m, 8H), 3.10-3.70 (m, 6H), 9.10 (br s, 1H); IR (CHCl<sub>3</sub>) 3700-2700, 1710, 1040 cm<sup>-1</sup>.

**7b:** <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.50-2.10 (m, 4H), 2.20-2.70 (m, 6H), 3.00-3.80 (m, 6H), 8.30 (br s, 1H); IR (CHCl<sub>3</sub>) 3600-2700, 1710, 1050 cm<sup>-1</sup>.

**7c:** <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.50-2.10 (m, 6H), 2.20-2.70 (m, 6H), 3.10-3.80 (m, 6H), 7.80 (br s, 1H); IR (CHCl<sub>3</sub>) 3600-2700, 1700, 1050 cm<sup>-1</sup>.

**7d:** <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.31-1.93 (m, 8H), 2.17-2.54 (m, 6H), 3.04-3.83 (m, 6H), 9.67 (br s, 1H); IR (neat) 3700-2400, 1728, 1047 cm<sup>-1</sup>.

**7e:** <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.00-1.93 (m, 10H), 2.17-2.53 (m, 6H), 3.06-3.78 (m, 6H), 9.21 (br s, 1H); IR (neat) 3700-2700, 1704, 1059 cm<sup>-1</sup>.

**7f:** mp 76-78 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  1.34-2.50 (m, 22H),

3.07-3.73 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1732, 1090  $\text{cm}^{-1}$ .

**7g**: mp 95-98 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.31-2.50 (m, 24H), 3.25-3.77 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1727, 1113  $\text{cm}^{-1}$ .

**7h**: mp 94-96 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.28-2.57 (m, 26H), 3.17-3.83 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1730, 1090  $\text{cm}^{-1}$ .

**7i**: mp 108-110 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.29-2.55 (m, 28H), 3.23-3.74 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1725, 1095  $\text{cm}^{-1}$ .

**8f**: mp 75 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone) 1.33-2.63 (m, 25H), 3.35-3.76 (m, 5H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1720, 1080  $\text{cm}^{-1}$ .

**8g**: mp 85-87 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.32-2.71 (m, 27H), 3.35-3.76 (m, 5H), 9.73 (br s, 1H), IR (KBr) 3000-3600, 1720, 1080  $\text{cm}^{-1}$ .

**8h**: mp 92-93 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.28-2.83 (m, 29H), 3.23-4.40 (m, 5H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1730, 1095  $\text{cm}^{-1}$ .

**8i**: mp 100-102 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.28-2.83 (m, 31H), 3.31-4.40 (m, 5H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1725, 1100  $\text{cm}^{-1}$ .

**20f**: mp 70-72 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.33-2.40 (m, 24H), 3.13-4.62 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1740, 1100  $\text{cm}^{-1}$ .

**20g**: mp 84-87 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.30-2.40 (m, 26H), 2.87-3.83 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1730, 1100  $\text{cm}^{-1}$ .

**20h**: mp 93-95 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.28-2.48 (m, 28H), 3.27-3.73 (m, 6H), 9.73 (br s, 1H); IR (KBr) 300-3600, 1740, 1100  $\text{cm}^{-1}$ .

**20i**: mp 104-106 °C;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.29-2.42 (m, 30H), 3.23-3.77 (m, 6H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1725, 1105  $\text{cm}^{-1}$ .

**General Procedure of Intramolecular Cyclization.** To a stirred suspension of  $\text{K}_2\text{CO}_3$  (831 mg, 6 mmol) in refluxing acetone (100 ml) was added sulfonium salt (2 mmol) in acetone (100 ml) over 1.5 days. After the mixture was refluxed for an additional 12 h, the solution was cooled to room temperature, diluted with ether (100 ml), and passed through a silica gel short column. The solvent was removed, and the residue was chromatographed on silica gel (hexane-ether) to give pure products.

**5d:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-2.07 (m, 12H), 2.26-2.72 (m, 6H), 3.94-4.30 (m, 2H); IR (neat)  $1725\text{ cm}^{-1}$ ; MS  $m/z$  216 ( $\text{M}^+$ ), 187, 157; HRMS calcd for  $\text{C}_{11}\text{H}_{20}\text{O}_2\text{S}$  216.1184, found 216.1148.

**5e:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.16-2.07 (m, 14H), 2.27-2.77 (m, 6H), 4.06-4.35 (m, 2H); IR (neat)  $1726\text{ cm}^{-1}$ ; MS  $m/z$  230 ( $\text{M}^+$ ), 171, 157; HRMS calcd for  $\text{C}_{12}\text{H}_{22}\text{O}_2\text{S}$  230.1340, found 230.1345.

**5f<sup>1</sup>:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.31-1.80 (m, 20H), 2.20-2.60 (m, 6H), 3.97-4.15 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  272 ( $\text{M}^+$ ), 231, 213; HRMS calcd for  $\text{C}_{15}\text{H}_{28}\text{O}_2\text{S}$  272.1810, found 272.1830.

**5g:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.77 (m, 22H), 2.13-2.58 (m, 6H), 3.93-4.13 (m, 2H); IR (neat)  $1733\text{ cm}^{-1}$ ; MS  $m/z$  286 ( $\text{M}^+$ ), 258, 245; HRMS calcd for  $\text{C}_{16}\text{H}_{30}\text{O}_2\text{S}$  286.1966, found 286.1962.

**5h:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28-1.93 (m, 24H), 2.08-2.65 (m, 6H), 3.90-4.17 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  300 ( $\text{M}^+$ ), 259, 241; HRMS calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_2\text{S}$  300.2123, found 300.2120.

**5i:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.29-2.03 (m, 26H), 2.10-2.35 (m, 6H), 3.93-4.23 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  314 ( $\text{M}^+$ ), 273, 255; HRMS calcd for  $\text{C}_{18}\text{H}_{34}\text{O}_2\text{S}$  314.2279, found 314.2298.

**9d:** mp 63-65 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.17-2.03 (m, 24H), 2.17-2.80 (m, 12H), 3.99-4.30 (m, 4H); IR (KBr)  $1727\text{ cm}^{-1}$ ; MS  $m/z$  432 ( $\text{M}^+$ ), 303, 217; HRMS calcd for  $\text{C}_{22}\text{H}_{40}\text{O}_4\text{S}_2$  432.2368, found 432.2426.

**9e:** mp 47-49 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05-2.03 (m, 28H), 2.16-2.71 (m, 12H), 3.90-4.30 (m, 4H); IR (KBr)  $1728\text{ cm}^{-1}$ ; MS  $m/z$  461 ( $\text{M}^++1$ ), 318, 231; HRMS calcd for  $\text{C}_{24}\text{H}_{44}\text{O}_4\text{S}_2$  460.2859, found 460.2898.

**9f:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-1.80 (m, 40H), 2.20-2.60 (m, 12H), 3.97-4.15 (m, 4H); IR ( $\text{CCl}_4$ )  $1734\text{ cm}^{-1}$ ; MS  $m/z$  456 ( $\text{M}^+$ ), 415, 397.

**9g:** MS  $m/z$  572 ( $M^+$ ), 517, 373.

**12d:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-2.03 (m, 20H), 2.15-2.71 (m, 8H), 3.97-4.26 (m, 4H); IR (neat)  $1727\text{ cm}^{-1}$ ; MS  $m/z$  344 ( $M^+$ ), 285, 217; HRMS calcd for  $\text{C}_{18}\text{H}_{32}\text{O}_4\text{S}$  344.2021, found 344.2006.

**12e:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-1.97 (m, 24H), 2.14-2.71 (m, 8H), 3.97-4.27 (m, 4H); IR (neat)  $1725\text{ cm}^{-1}$ ; MS  $m/z$  373 ( $M^++1$ ), 313, 231; HRMS calcd for  $\text{C}_{20}\text{H}_{36}\text{O}_4\text{S}$  372.2334, found 372.2288.

**12i:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.67-1.83 (m, 48H), 1.98-2.42 (m, 8H), 3.88-4.23 (m, 4H); IR ( $\text{CCl}_4$ )  $1732\text{ cm}^{-1}$ ; MS  $m/z$  540 ( $M^+$ ), 481, 435.

**17f:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.68 (m, 23H), 2.13-2.58 (m, 5H), 3.97-4.17 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  286 ( $M^+$ ), 271, 245; HRMS calcd for  $\text{C}_{16}\text{H}_{30}\text{O}_2\text{S}$  286.1967, found 286.1971.

**17g:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.32-1.88 (m, 25H), 2.15-2.87 (m, 5H), 3.98-4.18 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  300 ( $M^+$ ), 259, 241; HRMS calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_2\text{S}$  300.2123, found 300.2079.

**17h:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-1.90 (m, 27H), 2.07-2.67 (m, 5H), 3.93-4.17 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  314 ( $M^+$ ), 281, 259; HRMS calcd for  $\text{C}_{18}\text{H}_{34}\text{O}_2\text{S}$  314.2279, found 314.2266.

**17i:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.17-2.08 (m, 29H), 2.12-2.67 (m, 5H), 3.93-4.20 (m, 2H); IR (neat)  $1728\text{ cm}^{-1}$ ; MS  $m/z$  328 ( $M^+$ ), 273, 257; HRMS calcd for  $\text{C}_{19}\text{H}_{36}\text{O}_2\text{S}$  328.2436, found 328.2432.

**18f:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-1.68 (m, 46H), 2.17-2.77 (m, 10H), 3.93-4.13 (m, 4H); IR ( $\text{CCl}_4$ )  $1732\text{ cm}^{-1}$ ; MS  $m/z$  572 ( $M^+$ ), 558, 514.

**19h:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.00 (m, 47H), 2.12-2.45 (m, 7H), 3.87-4.17 (m, 4H); IR ( $\text{CCl}_4$ )  $1731\text{ cm}^{-1}$ ; MS  $m/z$  526 ( $M^+$ ), 467, 406.

**19i:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-1.93 (m, 51H), 2.12-2.60 (m, 7H), 3.93-4.27 (m, 4H); IR ( $\text{CCl}_4$ )  $1730\text{ cm}^{-1}$ ; MS  $m/z$  554 ( $M^+$ ), 495, 434.

**21f:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.32-1.87 (m, 22H), 2.17-2.60 (m, 6H), 3.98-4.17 (m, 2H); IR (neat)  $1730\text{ cm}^{-1}$ ; MS  $m/z$  286 ( $M^+$ ), 231, 213; HRMS calcd for  $\text{C}_{16}\text{H}_{30}\text{O}_2\text{S}$  286.1966, found 286.1981.

**21g:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28-1.87 (m, 24H), 2.12-2.60 (m, 6H), 4.00-4.17 (m, 2H); IR (neat)  $1732\text{ cm}^{-1}$ ; MS  $m/z$  300 ( $M^+$ ), 245, 227; HRMS calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_2\text{S}$  300.2123, found 300.2141.

**21h:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28-1.93 (m, 26H), 2.08-2.37 (m, 6H),

3.93-4.23 (m, 2H); IR (neat) 1733  $\text{cm}^{-1}$ ; MS  $m/z$  314 ( $\text{M}^+$ ), 259, 241; HRMS calcd for  $\text{C}_{18}\text{H}_{34}\text{O}_2\text{S}$  314.2280, found 314.2292.

**21i:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.27-2.00 (m, 28H), 2.15-2.67 (m, 6H), 3.90-4.22 (m, 2H); IR (neat) 1732  $\text{cm}^{-1}$ ; MS  $m/z$  328 ( $\text{M}^+$ ), 273, 255; HRMS calcd for  $\text{C}_{19}\text{H}_{36}\text{O}_2\text{S}$  328.2436, found 328.2416.

**22i:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25-1.99 (m, 50H), 2.12-2.67 (m, 8H), 3.87-4.21 (m, 4H); IR ( $\text{CCl}_4$ ) 1730  $\text{cm}^{-1}$ ; MS  $m/z$  554 ( $\text{M}^+$ ), 452, 434.

**Thiolanium Perchlorate 23.** (R,R)-(-)-1,4-Di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol<sup>8</sup> (4.71 g, 10 mmol) in DMF (20 ml) was added to a mixture of DMF (20 ml) and water (10 ml) dropwise. To the mixture was added aqueous sodium sulfide (15 mmol) dropwise.<sup>9</sup> After stirring for 12 days at room temperature, the reaction mixture was diluted with water (50 ml) and extracted with ether (2 x 100 ml). The organic layer was washed with water (5 x 30 ml) and dried over  $\text{Na}_2\text{SO}_4$ . After removal of solvent, the residue was purified by chromatography on silica gel (hexane-ether = 10 : 1). The solvent was removed under atmospheric pressure to give 2,4-dioxa-3,3-dimethyl-7-thiabicyclo[3.3.0]octane [940 mg (59%)] as a pale yellow oil:  $[\alpha]_{\text{D}} +144^\circ$  (c 1.52,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.33, 1.48 (s, 6H), 2.22-2.87 (m, 4H), 3.97-4.30 (m, 2H); MS  $m/z$  160 ( $\text{M}^+$ ), 145, 131. Following procedure described for **7**, the resulting sulfide (901 mg, 5.6 mmol), 11-iodoundecanoic acid (**6f**) (1.72 g, 5.5 mmol), and  $\text{AgClO}_4$  (1.24 g, 6 mmol) in  $\text{CH}_3\text{CN}$  (9 ml) afforded **23** [1.74g (71%)]: mp 104  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.33-1.88 (m, 22H), 2.17-2.41 (m, 2H), 3.43-4.09 (m, 8H), 9.73 (br s, 1H); IR (KBr) 3000-3600, 1725, 1085  $\text{cm}^{-1}$ .

**Intramolecular Cyclization of 23.** This reaction was carried out using thiolanium perchlorate **23** (897 mg, 2 mmol) and  $\text{K}_2\text{CO}_3$  (834 mg, 6 mmol) in acetone under high-dilution conditions as described above for general procedure of intramolecular cyclization. The reaction mixture was purified by chromatography on silica gel (hexane-ether = 30 : 1) to give **24** [72 mg (10%)]:  $[\alpha]_{\text{D}} -2.92^\circ$  (c 1.22,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.31-1.93 (m, 22H), 2.15-2.79 (m, 6H), 3.85-

4.17 (m, 4H); IR (neat) 1735  $\text{cm}^{-1}$ ; MS  $m/z$  344 ( $\text{M}^+$ ), 329, 301; HRMS calcd for  $\text{C}_{18}\text{H}_{32}\text{O}_4\text{S}$  344.2021, found 344.2006.

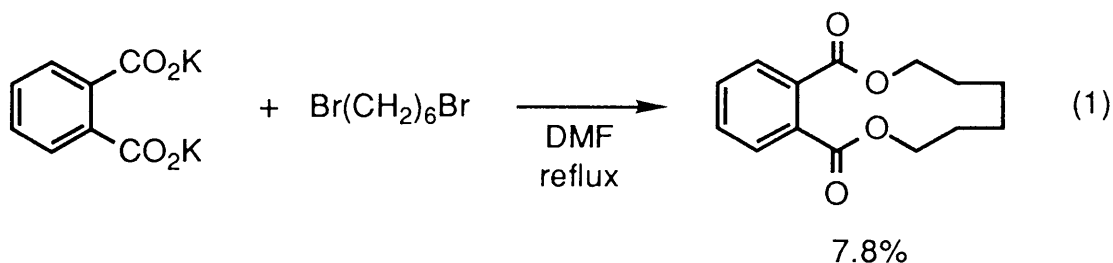
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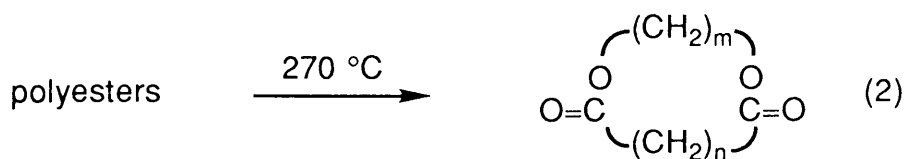
## Chapter 3

### Synthesis of Macrocyclic Dilactones by Cyclization of Sulfonium Salts

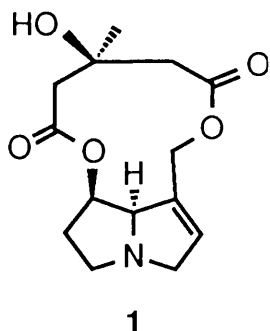
Much attention has been focused in recent years on the synthesis of macrolides, particularly dilactones, from the viewpoint of their bioactivities, ability to complex with metal cations, and usefulness as perfumes.<sup>1</sup> As described for the introduction in chapter 1, the growing need for macrocyclic compounds has stimulated research efforts for their efficient preparation,<sup>2</sup> and many preparative methods of macrocyclic lactones have been developed.<sup>3</sup> However, there is only a limited number of methods for the preparation of macrocyclic dilactones. Macrocyclic dilactones have been prepared by treatment of potassium dicarboxylates with alkyl dihalides (eq. 1),<sup>4</sup> by catalytic esterification of dicarboxylic acids with diols using lipase,<sup>5</sup> and by condensation or depolymerization (eq. 2).<sup>6</sup> These synthetic methods provided mixtures of dilactone and tetralactones and required harsh conditions such as high temperature and pressure.



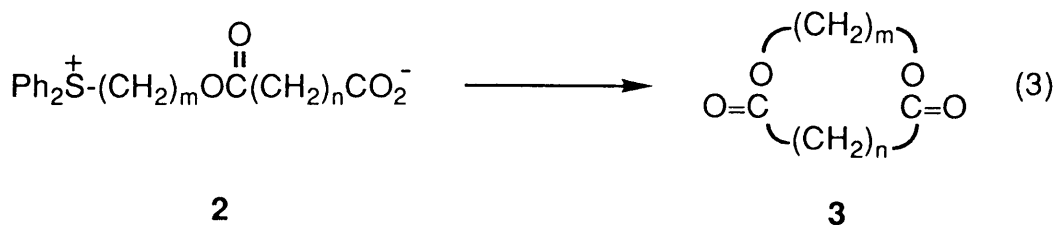




Macrocyclic dilactone pyrrolizidine alkaloids have attracted much interest due to their potent hepatotoxic and antitumor activities.<sup>7</sup> Successful syntheses of these macrocyclic pyrrolizidine alkaloids bearing 11-membered dilactonic skeleton such as (+)-dicrotaline (**1**) have been reported by Robins using Corey lactonization,<sup>8</sup> by Meinwald on crobarbatine acetate,<sup>9</sup> and by Vedejs utilizing fluoride-induced cyclization of mesylate.<sup>10</sup>



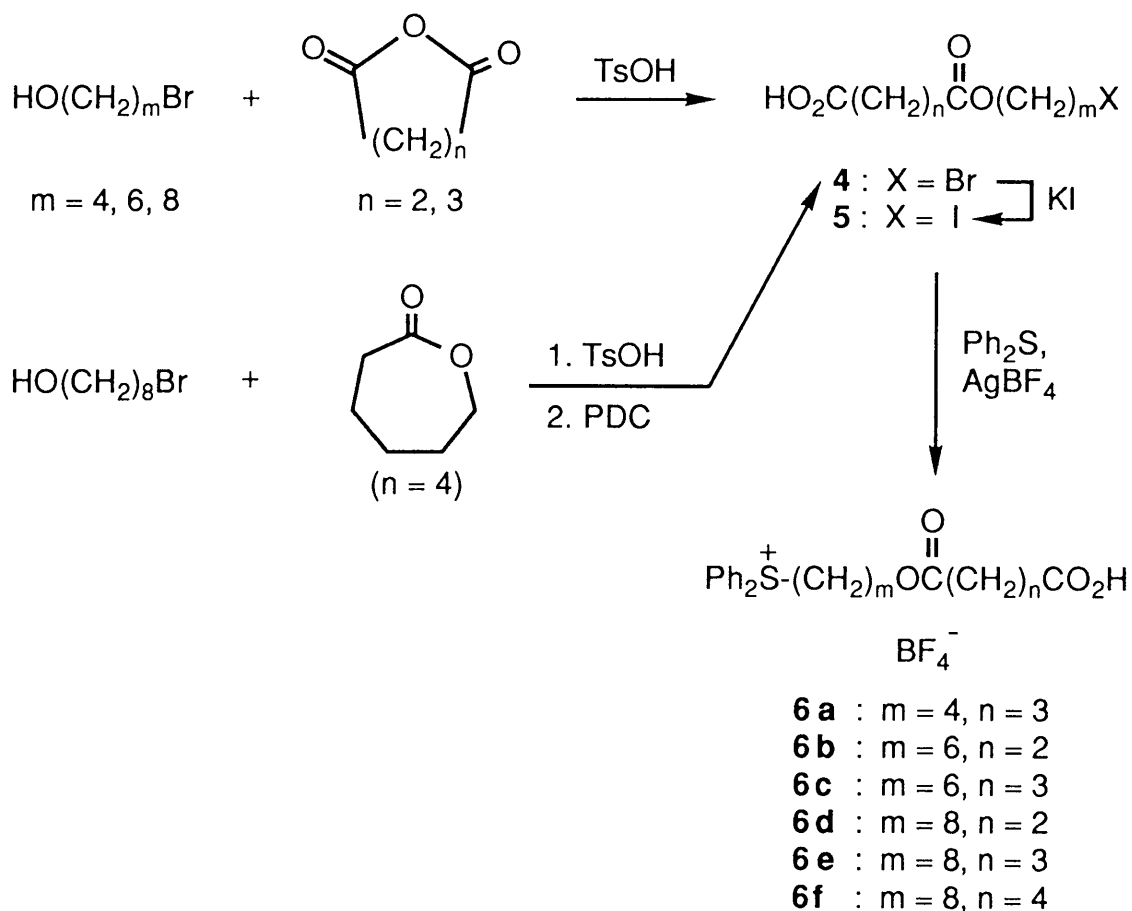
In chapter 1, cyclization of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts gave macrocyclic lactones in high yields under weakly basic conditions. It is expected that the reaction of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts **2** possessing an ester linkage gives macrocyclic dilactones **3** effectively (eq. 3). In this chapter, the author investigated synthesis of macrocyclic dilactones by cyclization of sulfonium salts and a further application of this methodology in the preparation of 13,13-dimethyl-1,2-didehydrocrotalanine, analogous to naturally occurring dilactone (+)-dicrotaline (**1**).



## Results and Discussion

( $\omega$ -Carboxyalkyl)diphenylsulfonium tetrafluoroborates **6** containing an ester linkage were prepared as shown in Scheme 1. Succinic and glutaric anhydrides were treated with the corresponding  $\omega$ -bromo alcohols in the presence of a catalytic amount of p-toluenesulfonic acid to afford dicarboxylic acid mono( $\omega$ -bromoalkyl) esters **4a-e**. Bromide **4f** ( $n = 4$ ) was prepared by treatment of 6-hexanolide with 8-bromo-1-octanol, followed by PDC oxidation. After conversion of bromide **4** into iodide **5**, diphenylsulfonium tetra-

Scheme 1



fluoroborates **6** were obtained from an excess of diphenyl sulfide, iodide **5**, and AgBF<sub>4</sub>.

The cyclization using diphenylsulfonium tetrafluoroborate **6c** in refluxing solvents was carried out under condition A and B in the presence of alkali-metal carbonate as base (eq. 4), and the results are presented in Table 1. The use of Cs<sub>2</sub>CO<sub>3</sub> as a base in this reaction system gave desired dilactone **7c** in the best yield (run 1-3). Kellogg *et al.*<sup>11</sup> and other group<sup>12</sup> reported a beneficial property of cesium ion, so-called "cesium effect". It appears that cesium ion, relative to other alkali-metal cation, accelerates the reaction in esterification and macrocyclization of cesium carboxylate. Cesium cation is much larger than Na<sup>+</sup> and K<sup>+</sup>. Kellogg described that cesium carboxylate dissociated into solvated cations and "free" anions, which have the highest reactivity.<sup>11b</sup> Similarly, in the case of cyclization of diphenylsulfonium tetrafluoroborate **6c** using Cs<sub>2</sub>CO<sub>3</sub>, "free" carboxylate anion resulted in the best yield (run 3). On the other hand, condition B and acetonitrile as a solvent decreased the formation of dilactone **7c**. Thus, subsequent cyclization of diphenylsulfonium salts containing an ester linkage was carried out under Cs<sub>2</sub>CO<sub>3</sub> / acetone / high-dilution conditions.

The cyclization of diphenylsulfonium tetrafluoroborates **6a-f** was performed under above-mentioned conditions (eq. 5), and the results are summarized in Table 2. Eleven- to 16-membered dilactones **7** were obtained in moderate to good yields, together with a small amount of tetralactones **8**, without the formation of oligomers.

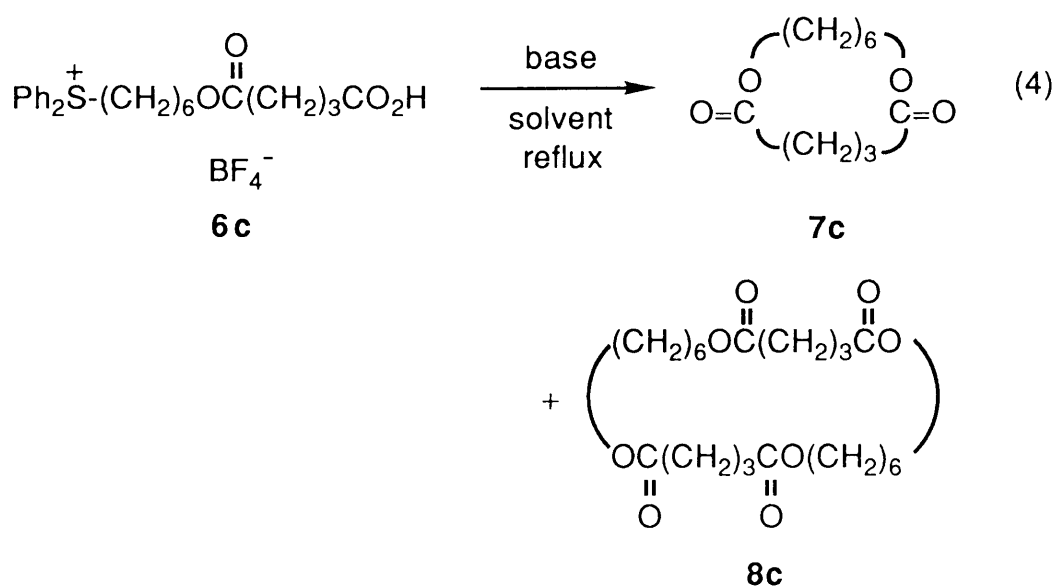


Table 1. Dilactonization of Diphenylsulfonium Tetrafluoroborate **6c**

run	Base	Solvent	Condition <sup>a</sup>	Yield / %	
				<b>7c</b>	<b>8c</b>
1	Na <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	A	64	1
2	K <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	A	71	1
3	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	A	75	1
4	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	A	51	8
5	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=O	B	22	1

a) A : high-dilution conditions, **6c** (2 mmol), solvent (200 ml), 1.5 days. B : **6c** (2 mmol), solvent (30 ml), 1 day.

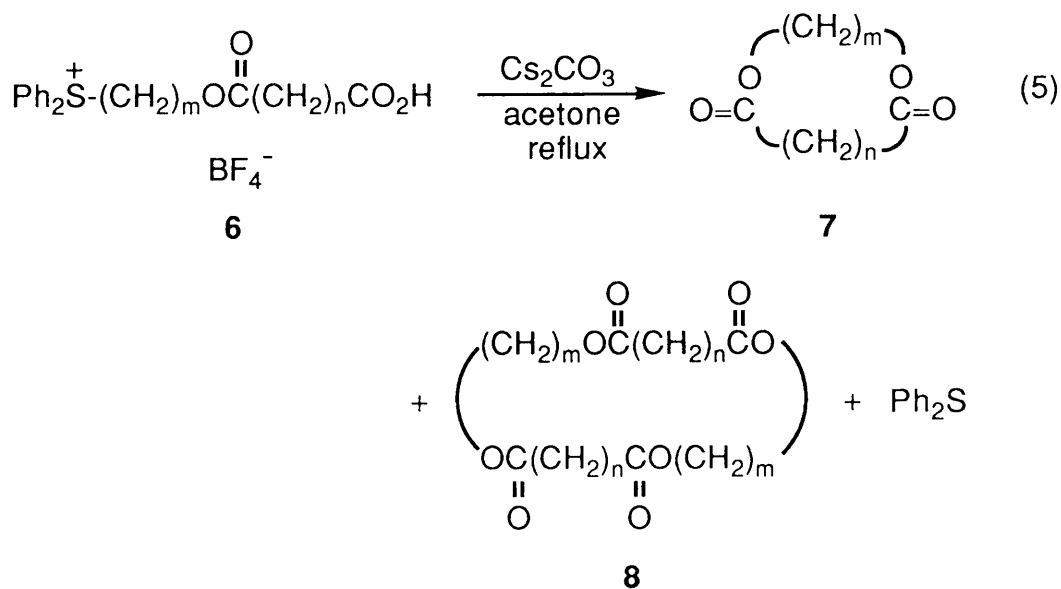
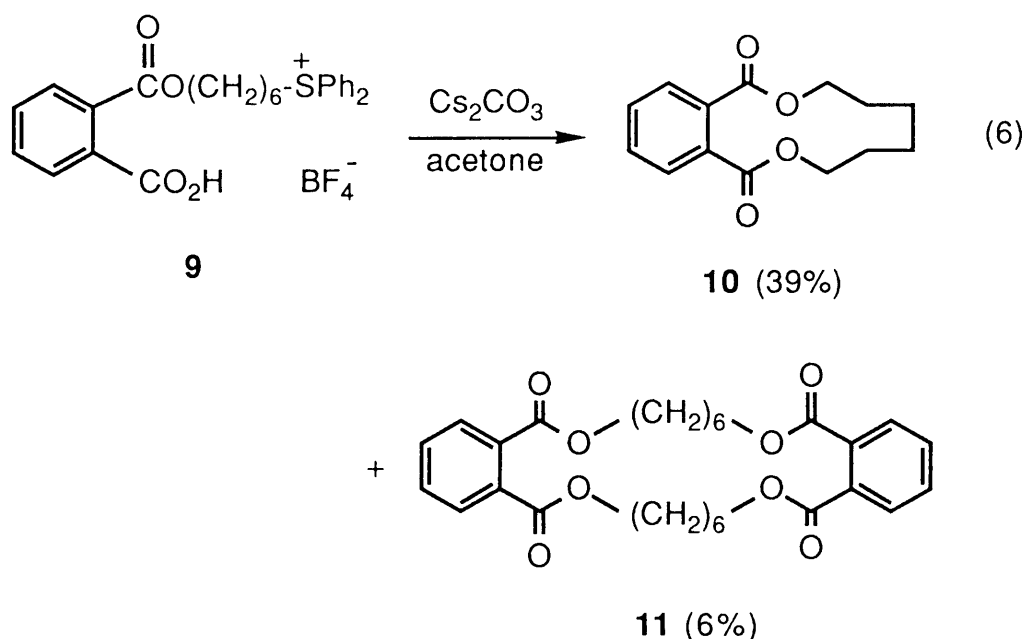


Table 2. Yields of Dilactones and Tetralactones from Diphenylsulfonium Tetrafluoroborates **6**

Sulfonium salt	Ring size of <b>7</b>	Yield / % <sup>a</sup>		
		<b>7</b>	<b>8</b>	Ph <sub>2</sub> S
<b>6 a</b>	11	42	trace	90
<b>6 b</b>	12	68	2	92
<b>6 c</b>	13	75	1	99
<b>6 d</b>	14	73	3	92
<b>6 e</b>	15	74	6	96
<b>6 f</b>	16	71	12	92

a) Isolated yield.

The inclusion of an aromatic ring moiety in macrocyclic dilactones greatly increases ability to complex with metal cations.<sup>4,13</sup> However, as shown in eq. 1, the yields of these compounds were low.<sup>4,6b</sup> The cyclization of diphenylsulfonium tetrafluoroborate **9**, prepared from phthalic anhydride as a starting material, gave 12-membered dilactone **10** containing a benzene moiety in moderate yield (eq. 6). These dilactonization reactions using diphenylsulfonium salts gave better results, in comparison with previous methods.<sup>4-6</sup>



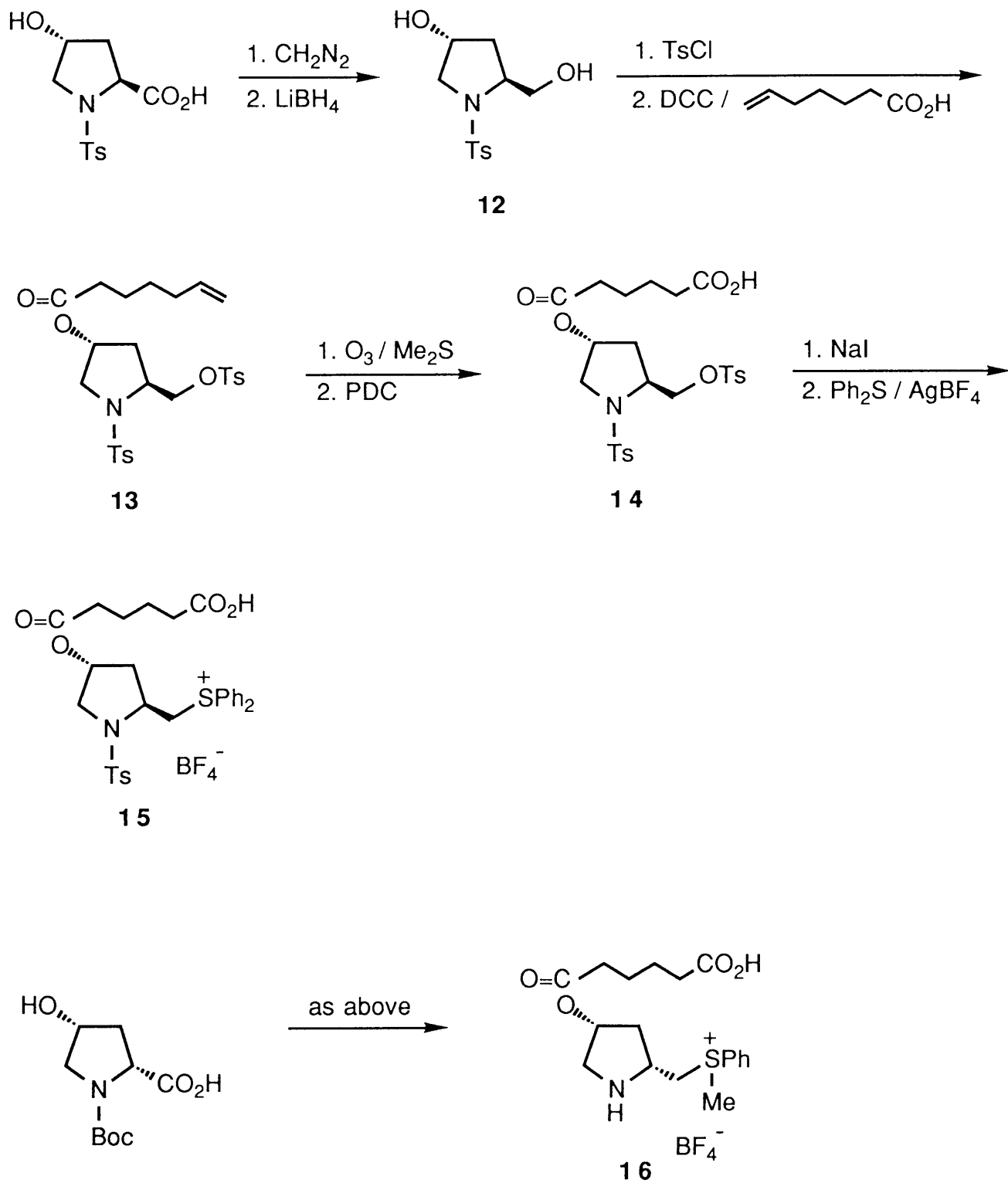
Although diphenyl sulfide was obtained quantitatively in this cyclization, the yields of dilactones and tetralactones were 42-83%.  $\beta$ -elimination reaction might occur as the side reaction of this cyclization.<sup>14</sup> However, we could not detect  $\beta$ -elimination products from the reaction mixture.

In order to investigate the relationship between the

configuration of sulfonium salts and their cyclization reaction, sulfonium salts trans-**15** and cis-**16** derived from 4-hydroxy-L- and -D-proline, respectively, were prepared (Scheme 2). The primary hydroxyl group of diol **12**, prepared from 4-hydroxy-L-proline according to the literature,<sup>15</sup> was selectively tosylated, and the tosylate was condensed with 6-heptenoic acid using DCC. The resulting ester **13** was treated with ozone, followed by PDC oxidation, to give carboxylic acid **14**, which was converted to the iodide. The resulting iodide was subjected to the reaction with diphenyl sulfide in the presence of AgBF<sub>4</sub> to give trans-sulfonium tetrafluoroborate **15**. The amino group of cis-4-hydroxy-D-proline was protected as an N-Boc group and then allowed similar reactions as above to afford cis-sulfonium tetrafluoroborate **16**.

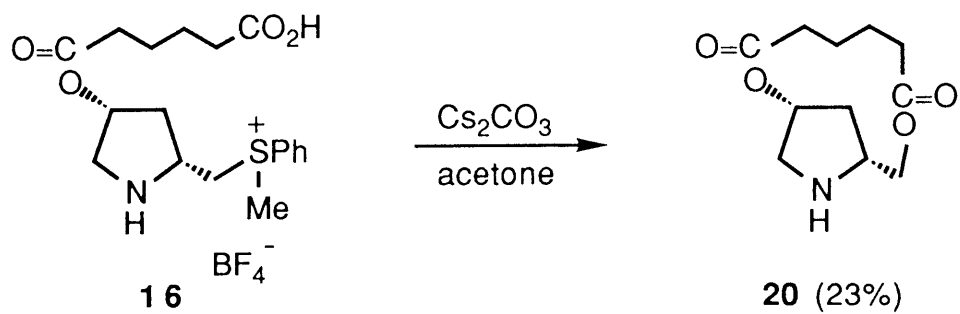
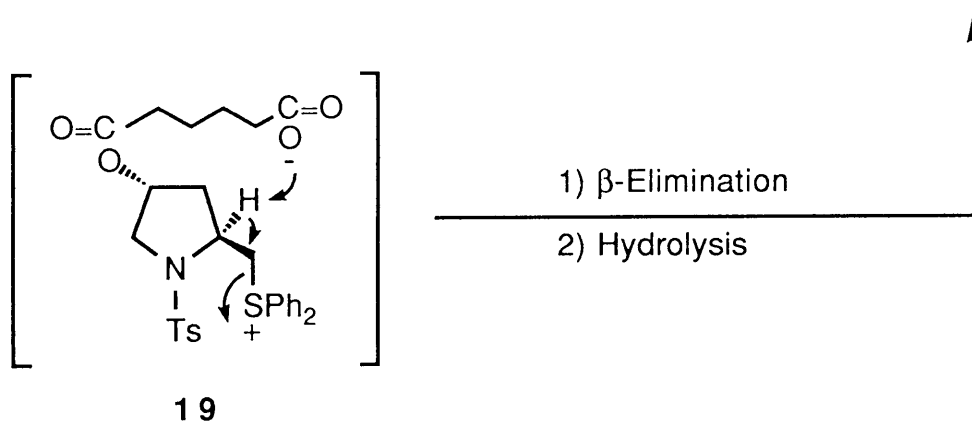
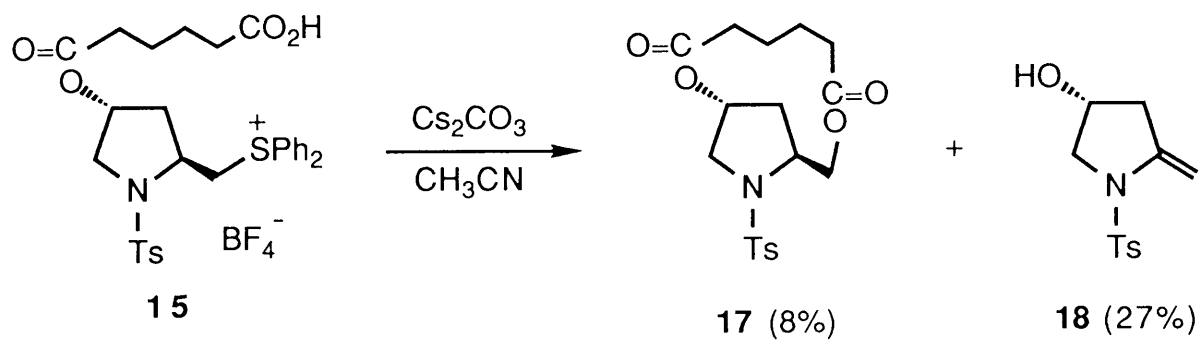
Inspection of molecular models of trans-**15** and cis-**16** suggested that trans-**15** would be more difficult to cyclize than cis-**16**. As shown in Scheme 3, trans-**15** cyclized to give a small amount of dilactone **17** (8%), and alcohol **18** was obtained in 27% yield by  $\beta$ -elimination reaction, followed by hydrolysis of the ester group. On the other hand, the reaction of cis-**16** gave dilactone **20** in 23% yield without formation of the corresponding  $\beta$ -elimination product. These findings suggest that carboxylate anion **19** attacks cis- $\beta$ -hydrogen intramolecularly, and  $\beta$ -elimination reaction takes place predominantly when the cyclization reaction of sulfonium salt is difficult. As mentioned above (Table 2),  $\beta$ -elimination reaction might occur

Scheme 2



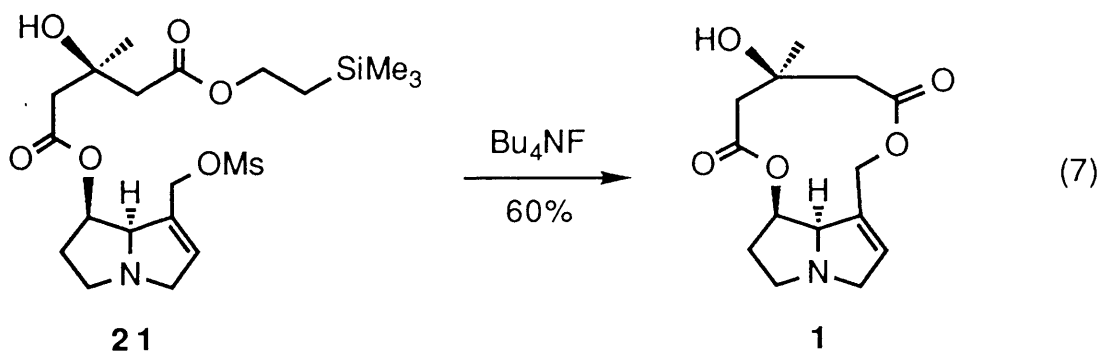


Scheme 3



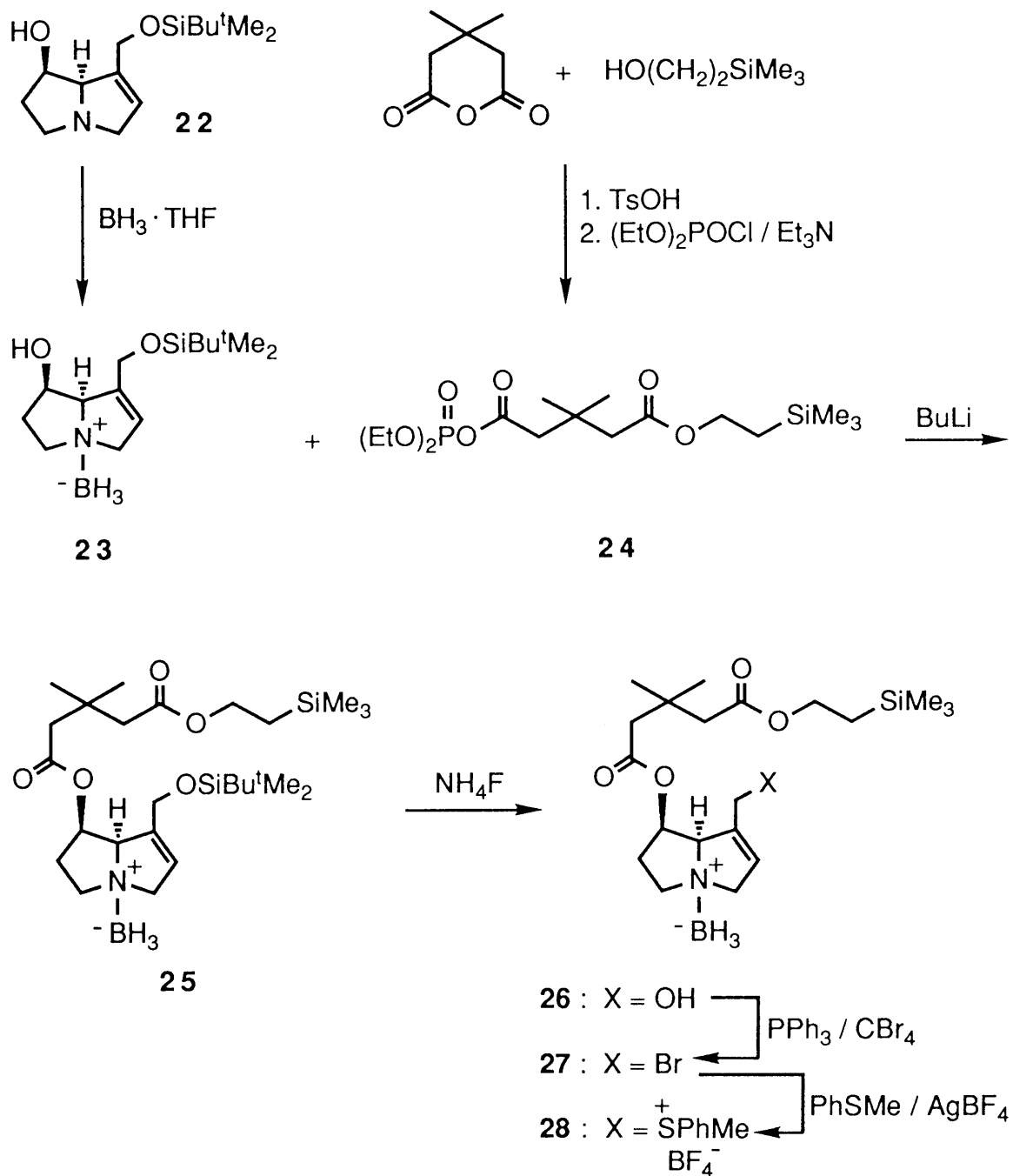
together with dilactonization, and diphenyl sulfide as leaving group was obtained quantitatively.

Vedejs *et al.* reported synthesis of (+)-dicrotaline (**1**), a naturally occurring dilactone, utilizing fluoride-induced cyclization of mesylate **21** (eq. 7).<sup>10a</sup> However, Vedejs's method has a



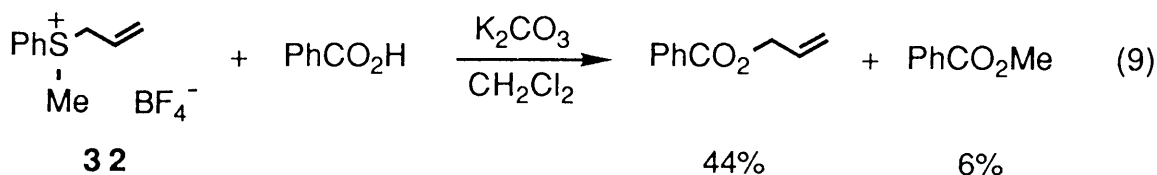
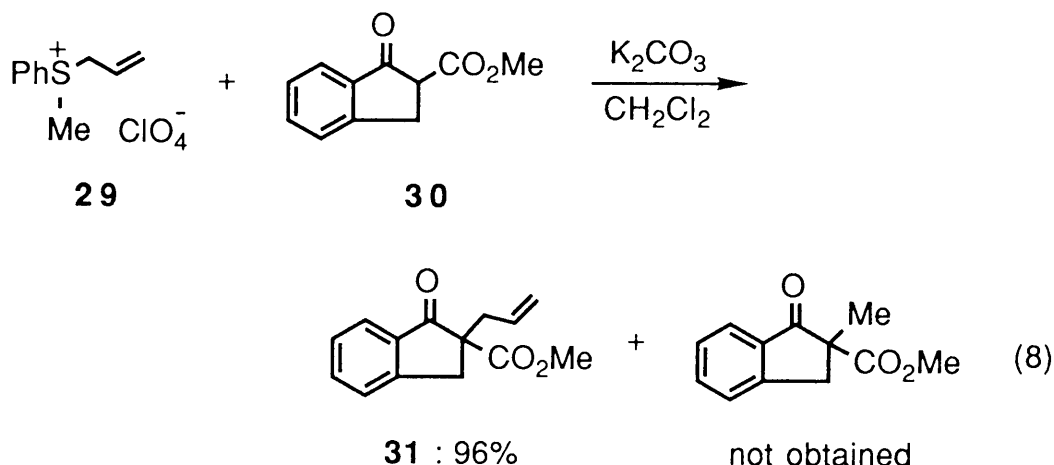
disadvantage that mesylate **21** is difficult to handle it because of its thermal lability. On the other hand, sulfonium salts containing an ester linkage have an advantage that they are thermally stable and that give macrocyclic dilactones in good yields (Table 2). Thus, the author applied cyclization of stable sulfonium salt to the synthesis of 13,13-dimethyl-1,2-didehydrocrotalanine **33**,<sup>8a</sup> analogous to (+)-dicrotaline (**1**). The corresponding sulfonium tetrafluoroborate **28** was prepared as illustrated in Scheme 4. According to the literature,<sup>10</sup> acyl phosphate **24** was obtained by the reaction of 3,3-dimethylglutaric anhydride with (2-trimethylsilyl)ethanol, followed by treatment with diethyl chlorophosphate. The resulting **24** was coupled<sup>10</sup> with retronecine-borane complex **23**<sup>16</sup>, which was prepared from retronecine tert-butyldimethylsilyl ether **22**<sup>17</sup> and

Scheme 4

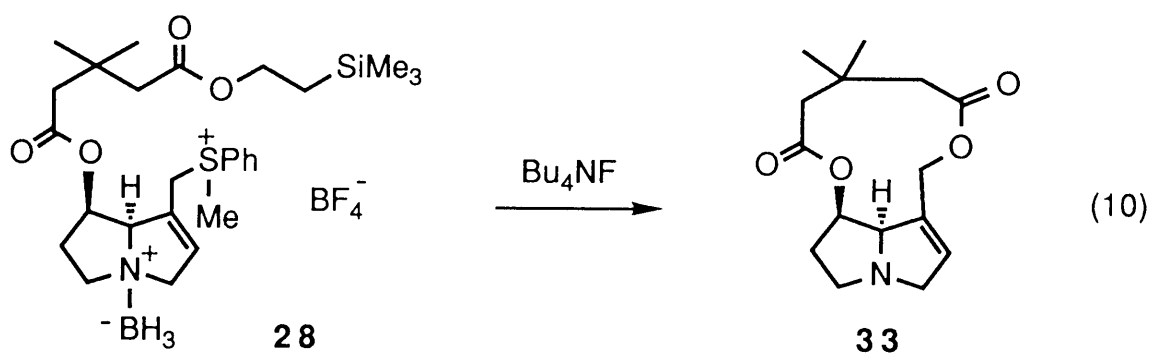


borane-THF. Diester **25** was deprotected with ammonium fluoride to give alcohol **26**,<sup>17b</sup> which was converted to bromide **27** by use of PPh<sub>3</sub> / CBr<sub>4</sub>.

Inspection of molecular models suggested that diphenylsulfonium salt (**28** : X = S<sup>+</sup>Ph<sub>2</sub> BF<sub>4</sub><sup>-</sup>) was difficult to cyclize because of steric repulsion between diphenylsulfonium group and the ester side chain. Previously, it was found that alkylation of 2-(methoxycarbonyl)-1-indanone (**30**) with allylmethylphenylsulfonium perchlorate (**29**) gave an allylated product **31** without competing methylation. (eq. 8).<sup>18</sup> As shown in eq. 9, alkylation of benzoic acid with allylmethylphenylsulfonium tetrafluoroborate (**32**) also gave allyl benzoate selectively. Therefore, it was expected that



the carboxylate ion of methylphenylsulfonium tetrafluoroborate **28** would selectively attack the allylic carbon atom. Sulfonium salt **28** was prepared from bromide **27** and thioanisole in the presence of  $\text{AgBF}_4$ . In the synthesis of **33**, the carboxylate anion was generated by fluoride-initiated deprotection of the trimethylsilyl ester in sulfonium salt **28**, rather than by  $\text{Cs}_2\text{CO}_3$  deprotonation of the free carboxylic acid in order to compare with previous reports.<sup>10</sup> When the reaction of **28** with tetrabutylammonium fluoride was carried out in  $\text{CH}_3\text{CN}$  at room temperature, the deprotected product, 13,13-dimethyl-1,2-didehydrocrotalanine **33** was obtained in good yield (70%) as the sole product (eq. 10). The spectral data of **33** obtained are identical with those of the literature.<sup>8a</sup> The yield of this cyclization was better than that of Robins's method<sup>8</sup> and was comparable to that reported by Vedejs.<sup>10a</sup>



## Experimental

$^1\text{H}$  NMR spectra were recorded at 60 or 400 MHz, and  $^{13}\text{C}$  NMR spectra were recorded at 22.5 or 100 MHz.

Dry solvents were purified as follows. Acetone was dried over molecular sieves (4A); acetonitrile, benzene,  $\text{CH}_2\text{Cl}_2$ , and DMF were distilled from  $\text{CaH}_2$ ; THF was freshly distilled from sodium benzophenone ketyl before use.

**$\omega$ -Iodocarboxylic Acids Containing an Ester Group 5.** A mixture of succinic or glutaric anhydride (10 mmol) and the corresponding  $\omega$ -bromo alcohols (11 mmol) in benzene (30 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was refluxed overnight. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography (hexane-ether = 1 : 1) to give **4** (70-74%). The resulting bromide **4** was treated with KI (3 equiv.) in refluxing acetone to give iodide **5** quantitatively.

**5a:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.50-2.20 (m, 6H), 2.27-2.67 (m, 4H), 3.07-3.39 (m, 2H), 3.97-4.32 (m, 2H), 10.7 (br s, 1H); IR (neat) 2400-3600, 1728, 1703  $\text{cm}^{-1}$ ; MS  $m/z$  314 ( $\text{M}^+$ ), 187, 169.

**5b:** mp 41-43  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.18-2.15 (m, 8H), 2.64 (s, 4H), 3.18 (t,  $J$  = 6.9 Hz, 2H), 3.96-4.27 (m, 2H), 11.0 (br s, 1H); IR (neat) 2700-3650, 1727, 1702  $\text{cm}^{-1}$ ; MS  $m/z$  329 ( $\text{M}^++1$ ), 311, 211; HRMS calcd for  $\text{C}_{10}\text{H}_{18}\text{O}_4\text{I}$  ( $\text{M}^++1$ ) 329.0250, found 329.0309.

**5c:** mp 29-31  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.13-2.21 (m, 10H), 2.27-2.67 (m, 4H), 3.18 (t,  $J$  = 6.6 Hz, 2H), 3.93-4.24 (m, 2H), 10.9 (br s, 1H); IR (neat) 2800-3650, 1710  $\text{cm}^{-1}$ ; MS  $m/z$  343 ( $\text{M}^++1$ ), 325, 211; HRMS calcd for  $\text{C}_{11}\text{H}_{19}\text{O}_4\text{I}$  342.0328, found 342.0404.

**5d:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05-2.13 (m, 12H), 2.63 (s, 4H), 3.17 (t,  $J$  = 6.7 Hz, 2H), 3.93-4.24 (m, 2H), 10.1 (br s, 1H); IR (neat) 2400-3700, 1732, 1713  $\text{cm}^{-1}$ ; MS  $m/z$  357 ( $\text{M}^++1$ ), 339, 239; HRMS calcd for  $\text{C}_{12}\text{H}_{21}\text{O}_4\text{I}$  356.0485, found 356.0504.

**5e:** mp 47-49  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.05-2.20 (m, 14H), 2.25-2.67

(m, 4H), 3.18 (t,  $J = 6.5$  Hz, 2H), 3.94-4.27 (m, 2H), 10.9 (br s, 1H); IR (KBr) 2500-3400, 1724, 1690  $\text{cm}^{-1}$ ; MS  $m/z$  370 ( $\text{M}^+$ ), 353, 324; HRMS calcd for  $\text{C}_{13}\text{H}_{23}\text{O}_4\text{I}$  370.0641, found 370.0726.

**5f:** oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.01-2.07 (m, 16H), 2.13-2.67 (m, 4H), 3.17 (t,  $J = 6.8$  Hz, 2H), 3.85-4.23 (m, 2H), 10.8 (br s, 1H); IR (neat) 2400-3600, 1730, 1705  $\text{cm}^{-1}$ ; MS  $m/z$  384 ( $\text{M}^+$ ), 367, 338; HRMS calcd for  $\text{C}_{14}\text{H}_{25}\text{O}_4\text{I}$  384.0798, found 384.0883.

**Diphenylsulfonium Salts 6.** To a mixture of **5** (3.4 mmol) and  $\text{AgBF}_4$  (0.87 g, 4.4 mmol), cooled in an ice bath, was added diphenyl sulfide (6.35 g, 34 mmol) dropwise. After being stirred for 3 days at room temperature, the reaction mixture was passed through a silica gel short column and eluted with acetone. After removal of solvent, the residue was washed with ether to give **6** (80-94%).

**6a:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.50-2.07 (m, 6H), 2.18-2.62 (m, 4H), 3.90-4.63 (m, 4H), 7.56-7.88 (m, 6H), 7.97-8.30 (m, 4H), 9.17 (br s, 1H); IR (neat) 2700-3600, 1726, 1061  $\text{cm}^{-1}$ .

**6b:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.18-1.93 (m, 8H), 2.58 (s, 4H), 3.77-4.57 (m, 4H), 7.46-7.89 (m, 6H), 7.98-8.35 (m, 4H), 9.17 (br s, 1H); IR (neat) 2700-3700, 1715, 1055  $\text{cm}^{-1}$ .

**6c:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.17-2.02 (m, 10H), 2.17-2.58 (m, 4H), 3.80-4.50 (m, 4H), 7.54-7.87 (m, 6H), 7.96-8.36 (m, 4H), 9.17 (br s, 1H); IR (neat) 2800-3660, 1719, 1056  $\text{cm}^{-1}$ .

**6d:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.16-1.98 (m, 12H), 2.59 (s, 4H), 3.87-4.67 (m, 4H), 7.47-7.87 (m, 6H), 7.97-8.33 (m, 4H), 9.17 (br s, 1H); IR (neat) 2700-3700, 1726, 1063  $\text{cm}^{-1}$ .

**6e:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.15-2.20 (m, 14H), 2.23-2.70 (m, 4H), 3.82-4.57 (m, 4H), 7.57-7.90 (m, 6H), 8.00-8.30 (m, 4H), 9.56 (br s, 1H); IR (neat) 2700-3700, 1724, 1056  $\text{cm}^{-1}$ .

**6f:** oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.17-1.97 (m, 16H), 2.15-2.57 (m, 4H), 3.73-4.57 (m, 4H), 7.57-7.88 (m, 6H), 7.97-8.33 (m, 4H), 8.92 (br s, 1H); IR (neat) 2700-3600, 1727, 1075  $\text{cm}^{-1}$ .

**Diphenylsulfonium Salt 9.** 6-Iodohexyl phthalic acid mono-ester was prepared from phthalic anhydride and 6-bromohexanol, followed by conversion of the bromide into the iodide with KI.

Reaction of the iodide and diphenyl sulfide in the presence of  $\text{AgBF}_4$  gave **9**: oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.27-2.01 (m, 8H), 4.03-4.53 (m, 4H), 7.42-7.87 (m, 10H), 7.95-8.22 (m, 4H), 9.56 (br s, 1H); IR (neat) 2700-3700, 1715, 1070  $\text{cm}^{-1}$ .

**General Procedure for Cyclization.** To a stirred suspension of  $\text{Cs}_2\text{CO}_3$  (1.97 g, 6 mmol) in refluxing acetone (100 ml) was added diphenylsulfonium salt (2 mmol) in acetone (100 ml) over 1.5 days. After refluxing for additional 12 h, the reaction mixture was passed through a silica gel short column. The solvent was removed, and the residue was chromatographed on silica gel (hexane-ether) to give pure product.

**7a**: oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.60-2.26 (m, 6H), 2.30-2.68 (m, 4H), 3.83-3.40 (m, 4H); IR (neat) 1731  $\text{cm}^{-1}$ ; MS  $m/z$  187 ( $\text{M}^++1$ ), 158, 128; HRMS calcd for  $\text{C}_9\text{H}_{15}\text{O}_4$  ( $\text{M}^++1$ ) 187.0970, found 187.0922.

**7b**: oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19-1.97 (m, 8H), 2.59 (s, 4H), 3.93-4.37 (m, 4H); IR (neat) 1732  $\text{cm}^{-1}$ ; MS  $m/z$  201 ( $\text{M}^++1$ ), 172, 154; HRMS calcd for  $\text{C}_{10}\text{H}_{17}\text{O}_4$  ( $\text{M}^++1$ ) 201.1127, found 201.1088.

**7c**: oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19-2.22 (m, 10H), 2.28-2.65 (m, 4H), 3.87-4.47 (m, 4H); IR (neat) 1733  $\text{cm}^{-1}$ ; MS  $m/z$  215 ( $\text{M}^++1$ ), 186, 156; HRMS calcd for  $\text{C}_{11}\text{H}_{19}\text{O}_4$  ( $\text{M}^++1$ ) 215.1284, found 215.1297.

**7d**: mp 67-68  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.23-2.00 (m, 12H), 2.63 (s, 4H), 3.97-4.40 (m, 4H); IR (KBr) 1725  $\text{cm}^{-1}$ ; MS  $m/z$  229 ( $\text{M}^++1$ ), 200, 157; HRMS calcd for  $\text{C}_{12}\text{H}_{21}\text{O}_4$  ( $\text{M}^++1$ ) 229.1440, found 229.1448.

**7e**: mp 27-28  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.19-2.23 (m, 14H), 2.30-2.67 (m, 4H), 3.97-4.37 (m, 4H); IR (neat) 1730  $\text{cm}^{-1}$ ; MS  $m/z$  243 ( $\text{M}^++1$ ), 214, 186; HRMS calcd for  $\text{C}_{13}\text{H}_{23}\text{O}_4$  ( $\text{M}^++1$ ) 243.1597, found 243.1503.

**7f**: oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.11-2.00 (m, 16H), 2.23-2.63 (m, 4H), 3.96-4.40 (m, 4H); IR (neat) 1731  $\text{cm}^{-1}$ ; MS  $m/z$  256 ( $\text{M}^+$ ), 228, 129; HRMS calcd for  $\text{C}_{14}\text{H}_{25}\text{O}_4$  ( $\text{M}^++1$ ) 257.1753, found 257.1737.

**10**: mp 63-64  $^\circ\text{C}$  (lit.<sup>4</sup> 63.7-64.5  $^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.33-2.10 (m, 8H), 4.10-4.63 (m, 4H), 7.33-7.87 (m, 4H); IR (neat) 1724  $\text{cm}^{-1}$ ; MS  $m/z$  248 ( $\text{M}^+$ ), 204, 149; HRMS calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_4$  248.1049, found 248.1064.



The following tetralactones **8b-f** and **11** were characterized by MS data.

**8b**: MS  $m/z$  401 ( $M^{+}+1$ ), 301, 201.

**8c**: MS  $m/z$  429 ( $M^{+}+1$ ), 400, 315.

**8d**: MS  $m/z$  456 ( $M^{+}$ ), 441, 429.

**8e**: MS  $m/z$  484 ( $M^{+}$ ), 440, 426.

**8f**: MS  $m/z$  514 ( $M^{+}+2$ ), 500, 480.

**11**: MS  $m/z$  497 ( $M^{+}+1$ ), 366, 352.

**Preparation of Ester 13.** To a solution of *p*-toluenesulfonyl chloride (5.35 g, 28 mmol) in pyridine (11 ml) at  $-20^{\circ}\text{C}$  was added **12**<sup>15</sup> (6.91 g, 25 mmol). After being stirred for 2 h, the mixture was quenched by additional of cooled 2 N HCl (120 ml) and extracted three times with AcOEt (300 ml). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure to yield the O-monotosylated product (9.80 g, 90%): oil;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  1.53-2.21 (m, 2H), 2.35 (s, 3H), 2.41 (s, 3H), 2.98-4.57 (m, 7H), 7.17-7.93 (m, 8H); IR (neat) 3520, 1360, 1340, 1168, 1150  $\text{cm}^{-1}$ ; MS  $m/z$  426 ( $M^{+}+1$ ), 407, 394;  $[\alpha]_{\text{D}}^{25}$   $-81.2^{\circ}$  (c 2.82, EtOH). To a  $\text{CH}_2\text{Cl}_2$  (6 ml) solution of the preceding tosylate (1.72 g, 4 mmol), 6-heptenoic acid (0.52 g, 4 mmol), and a catalytic amount of DMAP was added DCC (1.04 g, 5 mmol) at  $0^{\circ}\text{C}$ . The mixture was stirred for 5 min at  $0^{\circ}\text{C}$  and then overnight at room temperature. The resulting precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt = 3 : 1) to give ester **13** (1.39 g, 64%): oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.20-1.78 (m, 6H), 1.87-2.27 (m, 4H), 2.43 (s, 3H), 3.42-3.60 (m, 2H), 3.70-4.60 (m, 3H), 4.73-4.91 (m, 1H), 4.93-5.18 (m, 2H), 5.42-6.03 (m, 1H), 7.14-7.93 (m, 8H); IR (neat) 1732, 1641, 1346, 1160, 979, 913  $\text{cm}^{-1}$ ; MS  $m/z$  536 ( $M^{+}+1$ ), 467, 426; HRMS calcd for  $\text{C}_{26}\text{H}_{33}\text{O}_7\text{NS}_2$  535.1699, found 535.1681;  $[\alpha]_{\text{D}}^{25}$   $-70.1^{\circ}$  (c 2.93,  $\text{CHCl}_3$ ).

**Preparation of Carboxylic Acid 14.** A solution of **13** (0.54 g, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 ml) was treated with a stream of ozone at  $-78^{\circ}\text{C}$  until blue color persisted. The excess ozone was purged from the solution with a stream of nitrogen, and dimethyl sulfide (4.4 ml) was

added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred for 1 day. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 ml) and washed three times with brine (10 ml). The combined brine layers were extracted with  $\text{CH}_2\text{Cl}_2$  (50 ml), and the combined organics were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude product was chromatographed on silica gel (hexane-AcOEt = 1 : 1) to provide the aldehyde (0.39 g, 72%): oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10-1.90 (m, 6H), 1.95-2.22 (m, 2H), 2.26-2.57 (m, 8H), 3.35-3.63 (m, 2H), 3.66-4.57 (m, 3H), 4.83-5.15 (m, 1H), 7.10-7.92 (m, 8H), 9.63 (s, 1H); IR (neat) 2724, 1729, 1354, 1157  $\text{cm}^{-1}$ ; MS  $m/z$  538 ( $\text{M}^++1$ ), 509, 494; HRMS calcd for  $\text{C}_{25}\text{H}_{31}\text{O}_8\text{NS}_2$  537.1491, found 537.1554;  $[\alpha]_{\text{D}}^{25}$   $-63.6^\circ$  (c 3.21,  $\text{CHCl}_3$ ). A mixture of the preceding aldehyde (0.39 g, 0.7 mmol) and PDC (0.55 g, 1.4 mmol) in DMF (1.1 ml) under nitrogen was stirred for 6 h at room temperature. The reaction mixture was quenched with water (30 ml) and extracted 10 times with ether (50 ml). The combined extracts were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by chromatography on silica gel (hexane-AcOEt = 1 : 1) afforded carboxylic acid **14** (0.32 g, 77%): oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30-1.87 (m, 6H), 1.91-2.63 (m, 10H), 3.37-3.59 (m, 2H), 3.63-4.60 (m, 3H), 4.83-5.13 (m, 1H), 7.10-7.90 (m, 8H), 9.83 (br s, 1H); IR (neat) 2300-3700, 1733, 1707, 1348, 1159  $\text{cm}^{-1}$ ; MS  $m/z$  555 ( $\text{M}^++2$ ), 382, 368; HRMS calcd for  $\text{C}_{25}\text{H}_{32}\text{O}_9\text{NS}_2$  ( $\text{M}^++1$ ) 554.1519, found 554.1549;  $[\alpha]_{\text{D}}^{23}$   $-63.1^\circ$  (c 3.38,  $\text{CHCl}_3$ ).

**Preparation of Sulfonium Salt 15.** An acetone (8 ml) solution of **14** (1.12 g, 2 mmol) and NaI (0.92 g, 6 mmol) was refluxed for 3 h. The reaction mixture was diluted with ether, and the precipitate was removed by filtration. Concentration of the filtrate afforded the iodide (1.00 g, 97%) as a colorless solid: mp 76-78  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.17-1.83 (m, 6H), 1.88-2.60 (m, 7H), 3.39-4.57 (m, 5H), 4.87-5.17 (m, 1H), 7.13-7.45 (m, 2H), 7.52-7.90 (m, 2H), 10.4 (s, 1H); IR (KBr) 2500-3600, 1741, 1698, 1344, 1159  $\text{cm}^{-1}$ ; MS  $m/z$  511 ( $\text{M}^++2$ ), 492, 451; HRMS calcd for  $\text{C}_{18}\text{H}_{24}\text{O}_6\text{NSI}$  509.0369, found 509.0382;  $[\alpha]_{\text{D}}^{24}$   $-72.2^\circ$  (c 4.46,  $\text{CHCl}_3$ ). Sulfonium salt **15** (0.50 g, 41%) was prepared from the preceding iodide (0.96 g, 1.9 mmol),

diphenyl sulfide (7.06 g, 38 mmol), and AgBF<sub>4</sub> (0.44 g, 1.9 mmol): oil; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone) δ 1.32-1.78 (m, 6H), 2.14-2.57 (m, 7H), 2.76-3.97 (m, 3H), 4.85-5.50 (m, 3H), 7.20-7.90 (m, 10H), 8.02-8.37 (m, 5H); IR (CHCl<sub>3</sub>) 2800-3700, 1733, 1708, 1351, 1163 cm<sup>-1</sup>; [α]<sub>D</sub><sup>25</sup> -6.96° (c 2.34, CHCl<sub>3</sub>).

**Cyclization of Sulfonium Salt 15.** This reaction was carried out by use of **15** (0.24 g, 0.36 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.86 g, 2.7 mmol), and CH<sub>3</sub>CN (100 ml) in a similar manner as described in general procedure to give dilactone **17** (11 mg, 8%) and alcohol **18** (25 mg, 27%). **17**: oil; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.47-1.72 (m, 6H), 2.27-2.40 (m, 4H), 2.43 (s, 3H), 3.57 (t, *J* = 4.1 Hz, 2H), 3.81-4.13 (m, 1H), 4.32-4.50 (m, 2H), 4.87-5.14 (m, 1H), 7.32 and 7.72 (ABq, *J* = 8.2 Hz, 4H); IR (CHCl<sub>3</sub>) 1724, 1348, 1162 cm<sup>-1</sup>; MS *m/z* 381 (M<sup>+</sup>), 297, 253; HRMS calcd for C<sub>18</sub>H<sub>23</sub>O<sub>6</sub>SN 381.1246, found 381.1197; [α]<sub>D</sub><sup>23</sup> +6.03° (c 0.25, CHCl<sub>3</sub>). **18**: mp 111-113 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.07 (br s, 1H), 2.39 (s, 3H), 3.05-3.30 (m, 2H), 3.51 (d, *J* = 7.5 Hz, 2H), 3.97-4.05 (m, 1H), 5.76 (s, 2H), 7.25 and 7.62 (ABq, *J* = 8.2 Hz, 4H); IR (CHCl<sub>3</sub>) 3200-3600, 3015, 1656, 1350, 1165, 905 cm<sup>-1</sup>; MS *m/z* 253 (M<sup>+</sup>), 236, 184; HRMS calcd for C<sub>12</sub>H<sub>15</sub>O<sub>3</sub>SN 253.0773, found 253.0795; [α]<sub>D</sub><sup>27</sup> -99.3° (c 1.04, CHCl<sub>3</sub>).

**N-Boc-*cis*-4-hydroxy-D-proline.** To a mixture of *cis*-4-hydroxy-D-proline (0.92 g, 7 mmol), Et<sub>3</sub>N (1.46 ml), water (7 ml), MeOH (10.5 ml), and dioxane (3.5 ml) was added BOC-ON (1.73 g, 7 mmol), and the mixture was stirred for 3 h at room temperature. After removal of solvent, the residue was added to water (10 ml) and washed three times with benzene (14 ml). The solution was acidified with 5% citric acid and extracted three times with AcOEt (100 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Recrystallization from acetone-AcOEt afforded the pure product (1.39 g, 85%) as colorless crystals: mp 140-141 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone) δ 1.40 (s, 9H), 2.09-2.48 (m, 2H), 3.40-3.63 (m, 2H), 4.13-4.51 (m, 2H), 6.67 (br s, 2H); IR (KBr) 2300-3700, 1665-1736 cm<sup>-1</sup>; MS *m/z* 232 (M<sup>+</sup>+1), 186, 158; HRMS calcd for C<sub>10</sub>H<sub>18</sub>O<sub>5</sub>N (M<sup>+</sup>+1) 232.1185, found 232.1192; [α]<sub>D</sub><sup>22</sup> +47.1° (c 2.29, EtOH).

**N-Boc-*cis*-4-hydroxy-D-proline Methyl Ester.** To a MeOH (25 ml) solution of the preceding N-protected material (3.70 g, 16 mmol) was added an ether solution of CH<sub>2</sub>N<sub>2</sub> until yellow color persisted. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt = 1 : 2) to give the methyl ester (3.93 g, 70%) as colorless crystals: mp 78-79 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.42 (s, 9H), 2.07-2.64 (m, 2H), 3.37-3.67 (m, 3H), 3.73 (s, 3H), 4.13-4.53 (m, 2H); IR (KBr) 3475, 1727, 1675 cm<sup>-1</sup>; MS *m/z* 245 (M<sup>+</sup>), 172, 158; HRMS calcd for C<sub>11</sub>H<sub>19</sub>O<sub>5</sub>N 245.1263, found 245.1285; [α]<sub>D</sub><sup>25</sup> +63.8° (c 2.21, EtOH).

**N-Boc-*cis*-4-hydroxy-D-prolinol.** A suspension of the methyl ester (2.88 g, 12 mmol) and LiBH<sub>4</sub> (1.26 g, 58 mmol) in THF (45 ml) was stirred for 7 h at 0 °C and then overnight at room temperature. The reaction mixture, cooled in an ice bath, was quenched with water (30 ml) and neutralized with 0.5 N HCl. The solution was extracted three times with AcOEt (200 ml). The extracts were washed with 2 N NaOH, 0.5 N HCl, and water (30 ml), dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was recrystallized from ether-hexane to yield the pure product (1.88 g, 74%) as colorless crystals: mp 92-93 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.43 (s, 9H), 1.87-2.67 (m, 2H), 3.30-3.53 (m, 2H), 3.56-4.43 (m, 4H), 4.75 (br s, 2H); IR (KBr) 3443, 1683, 1653 cm<sup>-1</sup>; MS *m/z* 217 (M<sup>+</sup>), 186, 162; HRMS calcd for C<sub>10</sub>H<sub>19</sub>O<sub>4</sub>N 217.1314, found 217.1312; [α]<sub>D</sub><sup>23</sup> +42.6° (c 2.43, EtOH).

**N-Boc-3(*R*)-hydroxy-5(*R*)-[(tosyloxy)methyl]pyrrolidine:** mp 116-117 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.38 (s, 9H), 1.98-2.20 (m, 2H), 2.28 (br s, 1H), 2.42 (s, 3H), 3.30-3.53 (m, 2H), 3.84-4.53 (m, 4H), 7.28 and 7.72 (ABq, *J* = 8.0 Hz, 4H); IR (KBr) 3456, 1670, 1361, 1176 cm<sup>-1</sup>; MS *m/z* 371 (M<sup>+</sup>), 345, 327; HRMS calcd for C<sub>17</sub>H<sub>26</sub>O<sub>6</sub>NS (M<sup>+</sup>+1) 372.1481, found 372.1482; [α]<sub>D</sub><sup>25</sup> +17.7° (c 2.16, CHCl<sub>3</sub>).

**N-Boc-3(*R*)-(6-heptenoyloxy)-5(*R*)-[(tosyloxy)methyl]-pyrrolidine:** oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.17-1.77 (m, 13H), 1.90-2.34 (m, 6H), 2.43 (s, 3H), 3.37-3.65 (m, 2H), 3.90-4.32 (m, 3H), 4.80-4.90 (m, 1H), 4.93-5.37 (m, 2H), 5.45-6.07 (m, 1H), 7.29 and 7.73 (ABq, *J* = 8.5 Hz, 4H); IR (neat) 1734, 1692, 1639, 1364, 1175 cm<sup>-1</sup>; MS *m/z* 481

( $M^+$ ), 426, 381; HRMS calcd for  $C_{24}H_{35}O_7NS$  481.2134, found 481.2146;  $[\alpha]_D^{23} +11.9^\circ$  (c 2.60,  $CHCl_3$ ).

**N-Boc-3(R)-[(5-formylpentanoyl)oxy-5(R)-[(tosyloxy)-methyl]pyrrolidine:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.39 (s, 9H), 1.52-1.84 (m, 4H), 2.07-2.66 (m, 6H), 2.44 (s, 3H), 3.37-3.67 (m, 2H), 3.90-4.31 (m, 3H), 5.10-5.42 (m, 1H), 7.30 and 7.72 (ABq,  $J = 8.0$  Hz, 4H), 9.69 (s, 1H); IR (neat) 1731, 1691, 1366, 1176  $cm^{-1}$ ; MS (CI,  $i-C_4H_{10}$ )  $m/z$  526 ( $M^+ + C_3H_7^+$ ), 426, 441;  $[\alpha]_D^{26} +5.11^\circ$  (c 2.17,  $CHCl_3$ ).

**N-Boc-3(R)-[(5-carboxypentanoyl)oxy-5(R)-[(tosyloxy)-methyl]pyrrolidine:** oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.38 (s, 9H), 1.51-1.84 (m, 4H), 2.08-2.40 (m, 6H), 2.43 (s, 3H), 3.35-3.70 (m, 2H), 3.89-4.33 (m, 3H), 5.05-5.43 (m, 1H), 7.30 and 7.71 (ABq,  $J = 8.0$  Hz, 4H), 9.22 (br s, 1H); IR (neat) 2450-3700, 1733, 1694, 1368, 1175  $cm^{-1}$ ; MS (CI,  $i-C_4H_{10}$ )  $m/z$  542 ( $M^+ + C_3H_7^+$ ), 397, 310; HRMS calcd for  $C_{23}H_{34}O_9NS$  ( $M^+ + 1$ ) 500.1954, found 500.1952;  $[\alpha]_D^{25} +8.89^\circ$  (c 2.13,  $CHCl_3$ ).

**N-Boc-3(R)-[(5-carboxypentanoyl)oxy-5(R)-(iodomethyl)pyrrolidine:** mp 97-99  $^\circ C$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.45 (s, 9H), 1.57-1.88 (m, 4H), 2.15-2.65 (m, 6H), 3.17-3.70 (m, 4H), 3.83-4.33 (m, 1H), 5.08-5.39 (m, 1H), 9.38 (br s, 1H); IR (KBr) 3229, 1733, 1669  $cm^{-1}$ ; MS  $m/z$  456 ( $M^+ + 1$ ), 382, 354; HRMS calcd for  $C_{16}H_{27}O_6NI$  ( $M^+ + 1$ ) 456.0883, found 456.0821;  $[\alpha]_D^{26} +23.0^\circ$  (c 2.10,  $CHCl_3$ ).

**Sulfonium Salt 16.** Sulfonium salt **16** (0.20 g, 65%) was prepared from the preceding iodide (0.26 g, 0.6 mmol), thioanisole (0.15 g, 1.2 mmol), and  $AgBF_4$  (0.17 g, 0.8 mmol) in  $CH_3CN$  (2 ml): oil;  $^1H$  NMR ( $d_6$ -acetone)  $\delta$  1.47-1.78 (m, 4H), 2.17-2.59 (m, 7H), 2.77 (s, 3H), 3.20-3.73 (m, 4H), 3.93-4.47 (m, 1H), 5.00-5.77 (m, 1H), 7.13-7.88 (m, 5H), 8.07 (br s, 1H); IR (neat) 2700-3700, 1720, 1055  $cm^{-1}$ ;  $[\alpha]_D^{26} +14.3^\circ$  (c 14.5, acetone).

**Cyclization of Sulfonium Salt 16.** This reaction was carried out by use of **16** (0.19 g, 0.35 mmol),  $Cs_2CO_3$  (0.34 g, 1 mmol), and acetone (50 ml) as described in the general procedure to give the dilactone **20** (18 mg, 23%): oil;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.66-1.94 (m, 4H), 2.29-2.45 (m, 7H), 3.46-3.59 (m, 2H), 4.27 (br s, 2H), 4.69 (br

s, 1H), 5.35 (br s, 1H);  $^{13}\text{C}$  NMR (22.5 MHz,  $\text{CDCl}_3$ )  $\delta$  23.7, 29.7, 34.0, 34.2, 53.1, 57.3, 63.7, 75.2, 172.0, 173.3; IR ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$ ; MS  $m/z$  227 ( $\text{M}^++1$ ), 209, 169; HRMS calcd for  $\text{C}_{11}\text{H}_{17}\text{O}_4\text{N}$  ( $\text{M}^++1$ ) 227.1157, found 227.1137;  $[\alpha]_{\text{D}}^{28} -9.78^\circ$  (c 2.42,  $\text{CHCl}_3$ ).

**3,3-Dimethylglutaric Acid Mono[2-(trimethylsilyl)ethyl] Ester.** A mixture of 3,3-dimethylglutaric anhydride (1.42 g, 10 mmol), 2-(trimethylsilyl)ethanol (1.43 g, 13 mmol), and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 1 day. After concentration *in vacuo*, the residue was chromatographed on silica gel to give the desired product (2.31 g, 89%): oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.02 (s, 9H), 0.97 (t,  $J = 8.55\text{ Hz}$ , 2H), 0.99 (s, 6H), 2.39 (s, 2H), 2.45 (s, 2H), 4.14 (t,  $J = 8.55\text{ Hz}$ , 2H), 10.5 (br s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -1.57, 17.4, 27.7, 32.5, 45.0, 45.2, 62.5, 172.3, 177.7; IR (neat)  $2400\text{--}3600$ ,  $1724$ ,  $1704\text{ cm}^{-1}$ ; MS  $m/z$  262 ( $\text{M}^++2$ ), 245, 227.

**Esterification of 23 with 24<sup>10</sup>.** To a THF (11 ml) solution of the preceding carboxylic acid (0.62 g, 2.4 mmol) and  $\text{Et}_3\text{N}$  (0.33 ml) under nitrogen was added diethyl chlorophosphate (0.34 ml, 2.4 mmol) at  $0^\circ\text{C}$ , and the mixture was stirred for 1 h at room temperature. The resulting precipitate was removed by filtration and concentrated *in vacuo* to afford acyl phosphate **24**. To a THF (11 ml) solution of retronecine silyl ether **23** (0.33 g, 1.2 mmol), prepared from **22**<sup>17</sup> according to the literature,<sup>16</sup> and a catalytic amount of DMAP under nitrogen was added a hexane solution (1.1 ml) of *n*-BuLi (1.7 mmol) at  $0^\circ\text{C}$ . After the reaction mixture stirred for 10 min, a THF (6 ml) solution of **24** was added, and then the mixture was stirred for 1.5 h at room temperature. The solvent was removed *in vacuo*, and column chromatography of the residue on alumina (hexane-ether = 1 : 1) afforded retronesine monoester **25** (0.19 g, 31%): oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.01 (s, 15H), 0.87 (s, 9H), 0.92-0.96 (m, 2H), 1.05 (s, 3H), 1.06 (s, 3H), 1.97-2.02 (m, 1H), 2.31-2.44 (m, 5H), 3.02 (td,  $J = 5.70$  and  $11.4\text{ Hz}$ , 1H), 3.52-3.56 (m, 1H), 3.68-3.72 (m, 1H), 4.08-4.14 (m, 5H), 4.32 (br s, 1H), 5.40-5.42 (m, 1H), 5.53 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -5.53, -5.50, -1.58, 17.4, 18.2, 25.8, 27.6, 32.5, 33.3, 44.9, 45.1, 59.9, 62.2, 62.6, 71.9, 73.5,

84.2, 119.7, 137.1, 170.5, 171.7; IR (neat) 3500, 2362, 1727  $\text{cm}^{-1}$ ; MS  $m/z$  524 ( $\text{M}^+ - 1$ ), 496, 468,  $[\alpha]_{\text{D}}^{26} -14.7^\circ$  (c 1.48,  $\text{CHCl}_3$ ).

**Desilylation of 25.** This reaction was carried out according to the literature.<sup>17b</sup> Purification of column chromatography on silica gel (hexane-ether = 1 : 2) gave the desired alcohol **26** (34 mg, 34%): oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.02 (s, 9H), 0.95 (t,  $J = 8.55$  Hz, 2H), 1.04 (s, 3H), 1.08 (s, 3H), 2.02 (dd,  $J = 5.37$  and 13.7 Hz, 1H), 2.30-2.42 (m, 1H), 2.32 and 2.45 (ABq,  $J = 14.2$  Hz, 2H), 2.37, 2.43 (ABq,  $J = 15.6$  Hz, 2H), 3.02-3.08 (m, 1H), 3.58 (t,  $J = 9.03$  Hz, 1H), 3.70-3.74 (m, 1H), 4.09-4.19 (m, 6H), 4.35 (br s, 1H), 5.49 (br s, 1H), 5.60 (s, 1H); IR (neat) 3500, 2362, 1727  $\text{cm}^{-1}$ ; MS  $m/z$  410 ( $\text{M}^+ - 1$ ), 369, 309,  $[\alpha]_{\text{D}}^{22} +7.14^\circ$  (c 3.33,  $\text{CHCl}_3$ ).

**Bromination of Allylic Alcohol 26.** To a solution of alcohol **26** (30 mg, 0.07 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 ml) was added  $\text{PPh}_3$  (0.10 g, 0.38 mmol) and  $\text{CBr}_4$  (0.15 g, 0.45 mmol) rapidly at  $-15^\circ\text{C}$  under nitrogen. After being stirred for 1 h, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and washed with saturated  $\text{NaHCO}_3$  and brine (13 ml). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The oily residue was purified by chromatography on silica gel (hexane-ether = 1 : 1) to give bromide **27** (32 mg, 91%): oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 9H), 0.96 (t,  $J = 8.55$  Hz, 2H), 1.07 (s, 6H), 2.05 (dd,  $J = 5.38$  and 13.7 Hz, 1H), 2.36 (s, 2H), 2.41 (d,  $J = 3.91$  Hz, 2H), 2.44-2.49 (m, 1H), 3.08 (td,  $J = 5.70$  and 11.4 Hz, 1H), 3.60 (t,  $J = 9.04$  Hz, 1H), 3.70-3.77 (m, 1H), 3.89-4.21 (m, 3H), 4.17 (t,  $J = 13.9$  Hz, 2H), 4.46 (d, 21.5 Hz, 1H), 5.50 (br s, 1H), 5.78 (d,  $J = 9.28$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -1.57, 17.4, 27.8, 32.4, 33.3, 39.6, 44.6, 44.9, 62.4, 62.8, 71.7, 73.3, 84.3, 125.2, 133.0, 170.6, 171.8; IR (neat) 2354, 1734  $\text{cm}^{-1}$ ; MS  $m/z$  461 ( $\text{M}^+ - 14$ , Br = 81), 446, 415; HRMS calcd for  $\text{C}_{20}\text{H}_{37}\text{O}_4\text{NBSiBr}$  (Br = 81) 475.1748, found 475.1831;  $[\alpha]_{\text{D}}^{23} -14.4^\circ$  (c 1.37,  $\text{CHCl}_3$ ).

**Sulfonium Salt 28.** Sulfonium salt **28** (17 mg, 56%) was prepared from **27** (24 mg, 0.05 mmol), thioanisole (72 mg, 0.58 mmol), and  $\text{AgBF}_4$  (33 mg, 0.15 mmol) as described above: oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 9H), 0.94 (t,  $J = 8.06$  Hz, 2H), 1.02 (d,

$J = 5.37$  Hz, 3H), 1.08 (d,  $J = 2.44$  Hz, 3H), 2.20-2.26 (m, 1H), 2.37 (d,  $J = 6.35$  Hz, 2H), 2.43 (s, 2H), 2.77 (s, 1H), 3.30 (d,  $J = 32.7$  Hz, 3H), 3.40-3.42 (m, 1H), 3.74 (t,  $J = 8.79$  Hz, 1H), 4.01-4.21 (m, 3H), 4.12 (t,  $J = 8.55$  Hz, 2H), 4.35 (d,  $J = 17.1$  Hz, 1H), 4.47 (br s, 1H), 5.54 (br s, 1H), 5.95 (s, 1H), 7.63-7.76 (m, 3H), 7.97-8.05 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  -1.51, 17.4, 27.8, 32.6, 38.7, 39.3, 44.2, 44.8, 60.3, 62.5, 69.4, 72.1, 81.8, 118.9, 126.3, 131.1, 131.3, 132.6, 151.3, 171.2, 171.9; IR ( $\text{CH}_2\text{Cl}_2$ ) 2356, 1736, 1636, 1076  $\text{cm}^{-1}$ ;  $[\alpha]_{\text{D}}^{22} -147^\circ$  (c 0.87,  $\text{CHCl}_3$ ).

**Cyclization of Sulfonium Salt 28.**<sup>10</sup> To an  $\text{CH}_3\text{CN}$  (1 ml) solution of tetrabutylammonium fluoride (0.1 mmol) was added an  $\text{CH}_3\text{CN}$  (10 ml) solution of **28** (17 mg, 0.03 mmol) at room temperature over 4 h, and the mixture was stirred overnight. Concentration *in vacuo* and purification by silica gel column chromatography ( $\text{CHCl}_3$ -MeOH = 30 : 1) afforded **33**<sup>8a</sup> (5.3 mg, 70%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22 (s, 3H), 1.28 (s, 3H), 2.03-2.20 (m, 2H), 2.08 and 2.40 (ABq,  $J = 12.9$  Hz, 2H), 2.17 and 2.26 (ABq,  $J = 15.4$  Hz, 2H), 2.61-2.68 (m, 1H), 3.44-3.51 (m, 2H), 4.02 (d,  $J = 16.6$  Hz, 1H), 4.10 and 5.34 (ABq, 12.5 Hz, 2H), 4.47 (br s, 1H), 5.16 (br s, 1H), 5.91 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  29.7, 29.9, 34.1, 34.9, 43.7, 44.2, 53.7, 59.8, 61.6, 74.5, 77.2, 130.1, 132.8, 170.9, 171.2; IR ( $\text{CH}_2\text{Cl}_2$ ) 1733, 1675  $\text{cm}^{-1}$ ; MS  $m/z$  279 ( $\text{M}^+$ ), 234, 218; HRMS calcd for  $\text{C}_{15}\text{H}_{21}\text{O}_4\text{N}$  279.1471, found 279.1494;  $[\alpha]_{\text{D}}^{24} +42.4^\circ$  (c 0.17,  $\text{CHCl}_3$ ) (lit.<sup>8a</sup>  $[\alpha]_{\text{D}}^{22} +42.4^\circ$  ( $\text{CHCl}_3$ )).

**Allylmethylphenylsulfonium Tetrafluoroborate (32).** To  $\text{AgBF}_4$  (1.97 g, 10 mmol), cooled in an ice bath, was added a mixture of allyl phenyl sulfide (1.51 g, 10 mmol) and methyl iodide (14.2 g, 0.1 mol) in  $\text{CH}_3\text{CN}$  (12 ml) dropwise. The mixture was stirred at room temperature for 3 days. The reaction mixture was passed through a silica gel short column and eluted with acetone. The eluate was concentrated *in vacuo* and washed with ether. The residue was recrystallized from acetone-ether to give impurity. The residue was concentrated *in vacuo* to afford **32** (1.43 g, 56%):  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  3.26 (s, 3H), 4.29 (dd,  $J = 12.7$  and 7.81 Hz, 1H), 4.38 (dd,  $J = 12.7$  and 7.33 Hz, 1H), 5.44-5.51 (m, 2H), 5.79 (td,  $J = 17.2$  and 7.65



Hz, dd,  $J = 15.9$  and  $4.79$  Hz, 1H), 7.71 (t,  $J = 7.57$  Hz, 2H), 7.77-7.82 (m, 1H), 7.95-8.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  24.8, 49.9, 124.8, 128.4, 131.5, 131.9, 135.3, 135.5; IR (neat) 1638, 1061  $\text{cm}^{-1}$ .

**Alkylation of Benzoic Acid with 32.** A suspension of **32** (0.26 g, 1 mmol), benzoic acid (0.13 g, 1 mmol), and  $\text{K}_2\text{CO}_3$  (0.18 g, 1.3 mmol) in  $\text{CH}_3\text{CN}$  (10 ml) was stirred at room temperature for 2 days. The reaction mixture was diluted with ether (10 ml) and passed through a silica gel short column. The eluate was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel (hexane : ether = 10 : 1) and by liquid chromatography. Allyl benzoate:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.72 (d,  $J = 8.0$  Hz, 2H), 5.00-5.45 (m, 2H), 5.60-6.20 (m, 1H), 7.03-7.45 (m, 3H), 7.73-8.02 (m, 2H). Methyl benzoate:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.81 (s, 3H), 7.03-7.45 (m, 3H), 7.73-8.02 (m, 2H).

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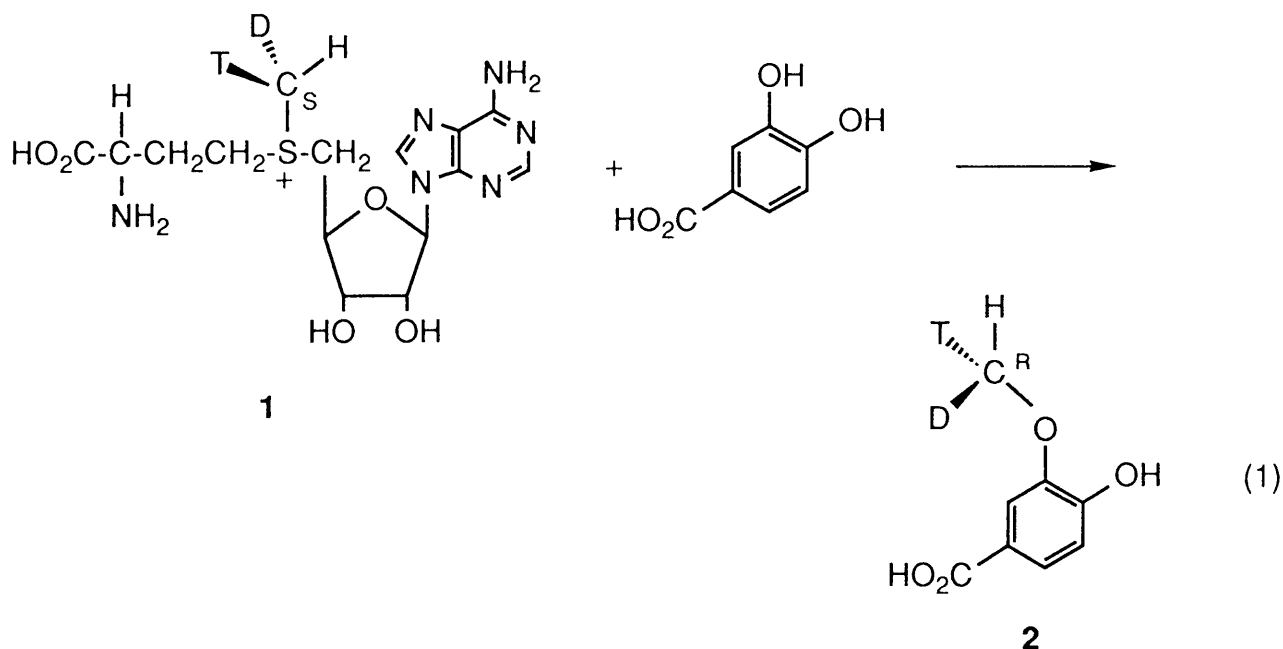
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## Chapter 4

### Reaction Mechanism of Cyclization of Sulfonium Salts

It is well-known that alkylsulfonium salts act as a good alkylating reagent toward various nucleophiles,<sup>1</sup> and the reaction mechanism of alkylation with sulfonium salts has been investigated. For example, S-adenosylmethionine is a methylating agent for biological substances *in vivo*.<sup>2</sup> Floss *et al.* reported that methylation of 3,4-dihydroxybenzoic acid with S-adenosylmethionine **1** having an optically active methyl group gave 3-methoxy-4-hydroxybenzoic acid **2** with an inversion of configuration at chiral methyl group (eq. 1).<sup>3</sup> In general, alkylation of nucleophiles with sulfonium salts has been



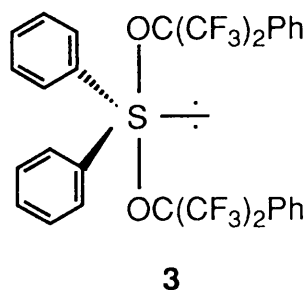
considered to proceed *via* S<sub>N</sub>2 reaction.<sup>4</sup>

Sulfur atom can be in a variety of oxydation states. In 1969, Musher proposed hypervalent compounds in which the bonding

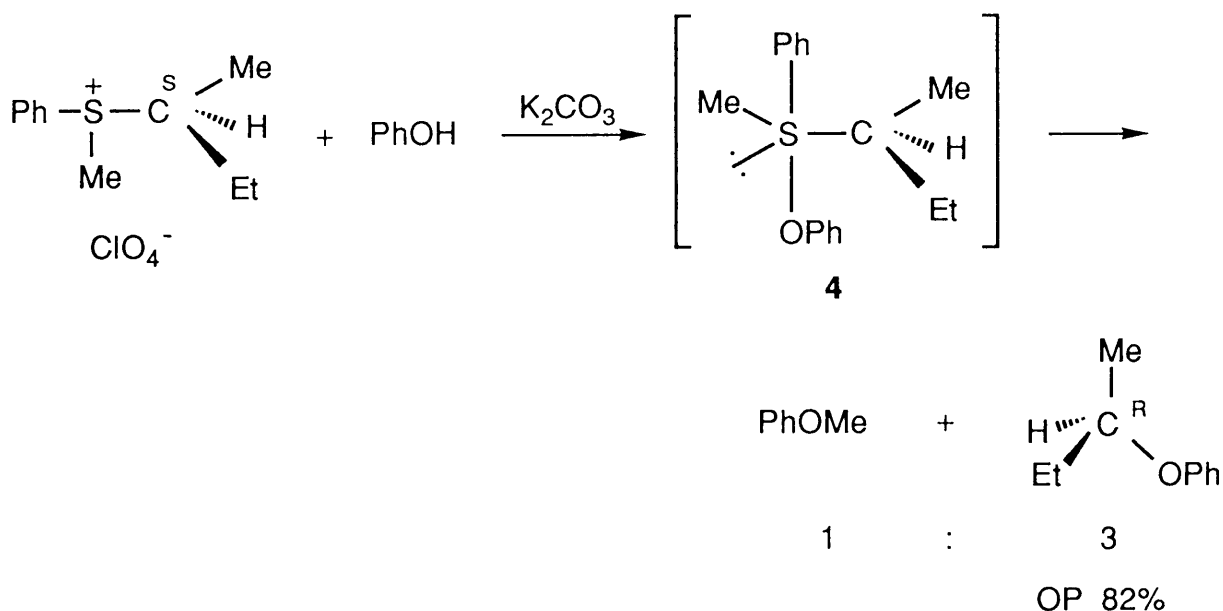
about the central atom involves expansion of the valence octet of electrons.<sup>5</sup> In recent

years, hypervalent sulfur compounds, namely  $\sigma$ -sulfurane **3** stabilized by electronegative ligands, were isolated by Martin *et al.*<sup>6</sup> As described for general introduction, reaction of sulfonium salts and nucleophiles *via*  $\sigma$ -sulfurane inter-

mediates was also reported.<sup>7</sup> For instance, Matsuyama *et al.* studied alkylation of several nucleophiles with alkylsulfonium salts and in



Scheme 1

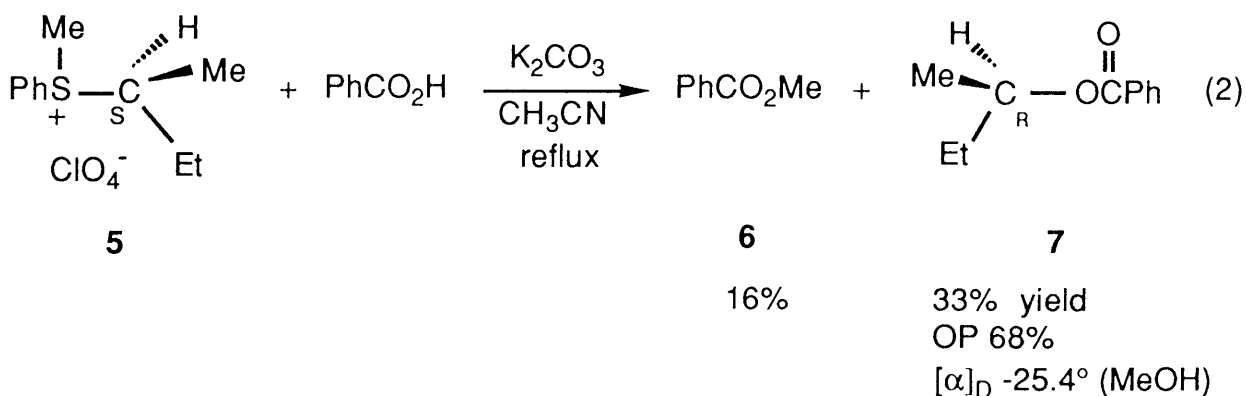


the case of hard nucleophiles, the reaction mechanism *via* S-O sulfurane intermediate **4**, not *via* S<sub>N</sub>2 reaction, was proposed on the basis of relative reactivities of the alkyl groups in sulfonium salts and stereochemistry of the resulting products (Scheme 1).<sup>8</sup>

In this chapter, the author investigated intramolecular cyclization of (ω-carboxyalkyl)sulfonium salt having an optically active carbon atom, and the reaction mechanism is discussed from stereochemistry of the resulting lactones.

## Results and Discussion

Firstly, intermolecular alkylation of benzoic acid with (*S*)-*sec*-butylmethylphenylsulfonium perchlorate (**5**)<sup>9</sup> was carried out in the presence of K<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN to give methyl benzoate (**6**, 16%) and (*R*)-*sec*-butyl benzoate (**7**, [α]<sub>D</sub> -25.4° (MeOH)) in 33% yield with an inversion of configuration at the chiral *sec*-butyl carbon atom (eq. 2). The optical purity (OP 68%) of (*R*)-*sec*-butyl benzoate (**7**) was

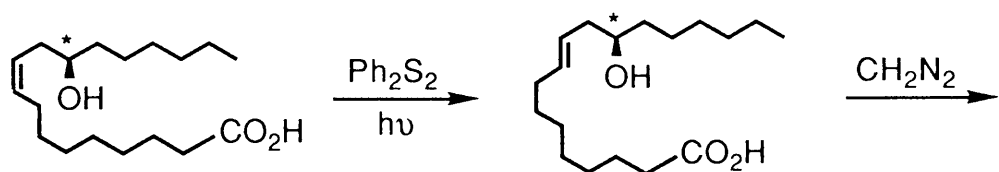


determined by comparison with (*S*)-*sec*-butyl benzoate ( $[\alpha]_D +37.1^\circ$  (MeOH)), which was prepared from benzoyl chloride and (*S*)-*sec*-butanol. The relative reactivity of methyl and *sec*-butyl groups of sulfonium salt **5** was  $\text{Me} : \text{Bu}^s = 1 : 2.06$  based on the yields of **6** and **7**. In general, the relative reactivity of alkyl groups in alkyl halides toward several nucleophiles *via*  $\text{S}_\text{N}2$  reaction is  $\text{Me} : \text{Et} : \text{Pr}^i = 1.0 : 0.05 : 0.001$ .<sup>10</sup> The present result is similar to that shown in Scheme 1<sup>8</sup> and suggests that the reaction mechanism of alkylation of carboxylate anion, which is a hard nucleophile, with alkylsulfonium salt is not  $\text{S}_\text{N}2$  reaction.

In order to investigate reaction mechanism of intramolecular cyclization of ( $\omega$ -carboxyalkyl)sulfonium salt, **14** having *S* configuration of secondary carbon atom was prepared as illustrated in Scheme 2. Ricinelaidic acid (**9**, OP 82%<sup>11</sup>), prepared by photoisomerization of ricinolic acid (**8**), was protected as methyl ester (*R*)-**10**. After tosylation of (*R*)-**10**, (*R*)-**11** was converted to sulfide (*S*)-**12** using sodium thiophenolate *via*  $\text{S}_\text{N}2$  reaction. Hydrolysis of the resulting (*S*)-**12** under basic conditions gave carboxylic acid (*S*)-**13**, which was alkylated with methyl iodide in the presence of  $\text{AgClO}_4$  to afford sulfonium salt (*S*)-**14**. The cyclization of (*S*)-**14** was performed in the presence of  $\text{K}_2\text{CO}_3$  under high-dilution conditions (eq. 4). Ricinelaidic acid lactone (**15**, 80%e.e.<sup>11</sup>) was obtained with an inversion of configuration at the chiral secondary carbon atom and methylated product (*S*)-**12** was also formed.



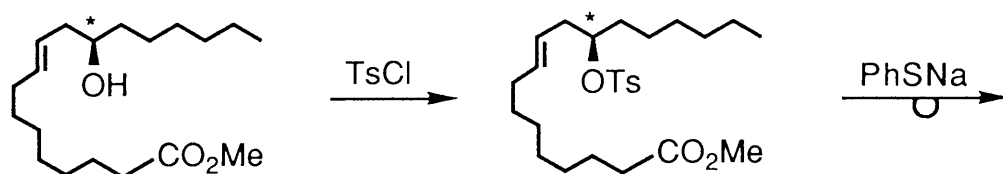
Scheme 2



(R)-8

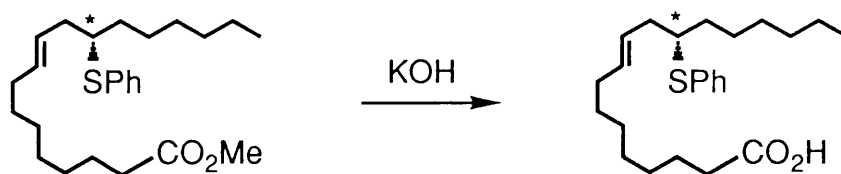
(R)-9

OP 82%



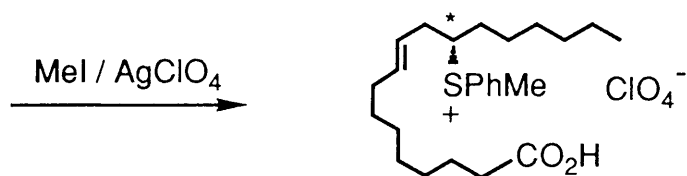
(R)-10

(R)-11

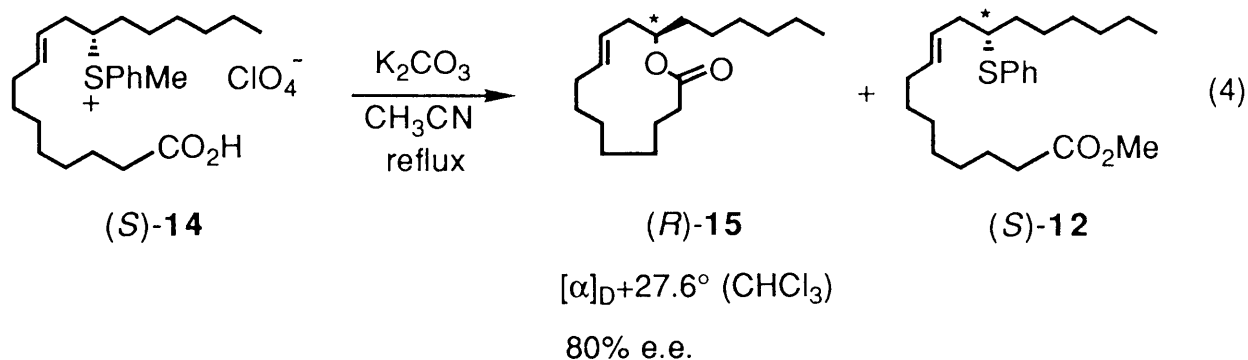


(S)-12

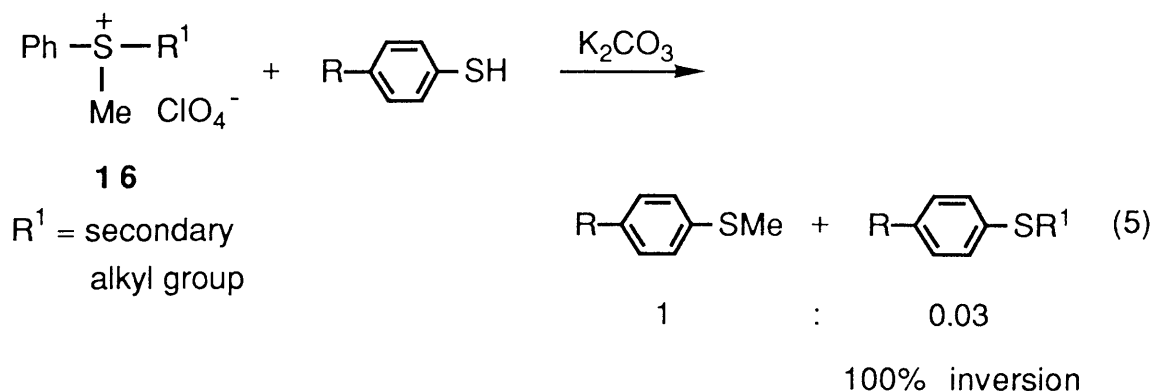
(S)-13



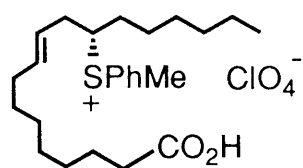
(S)-14



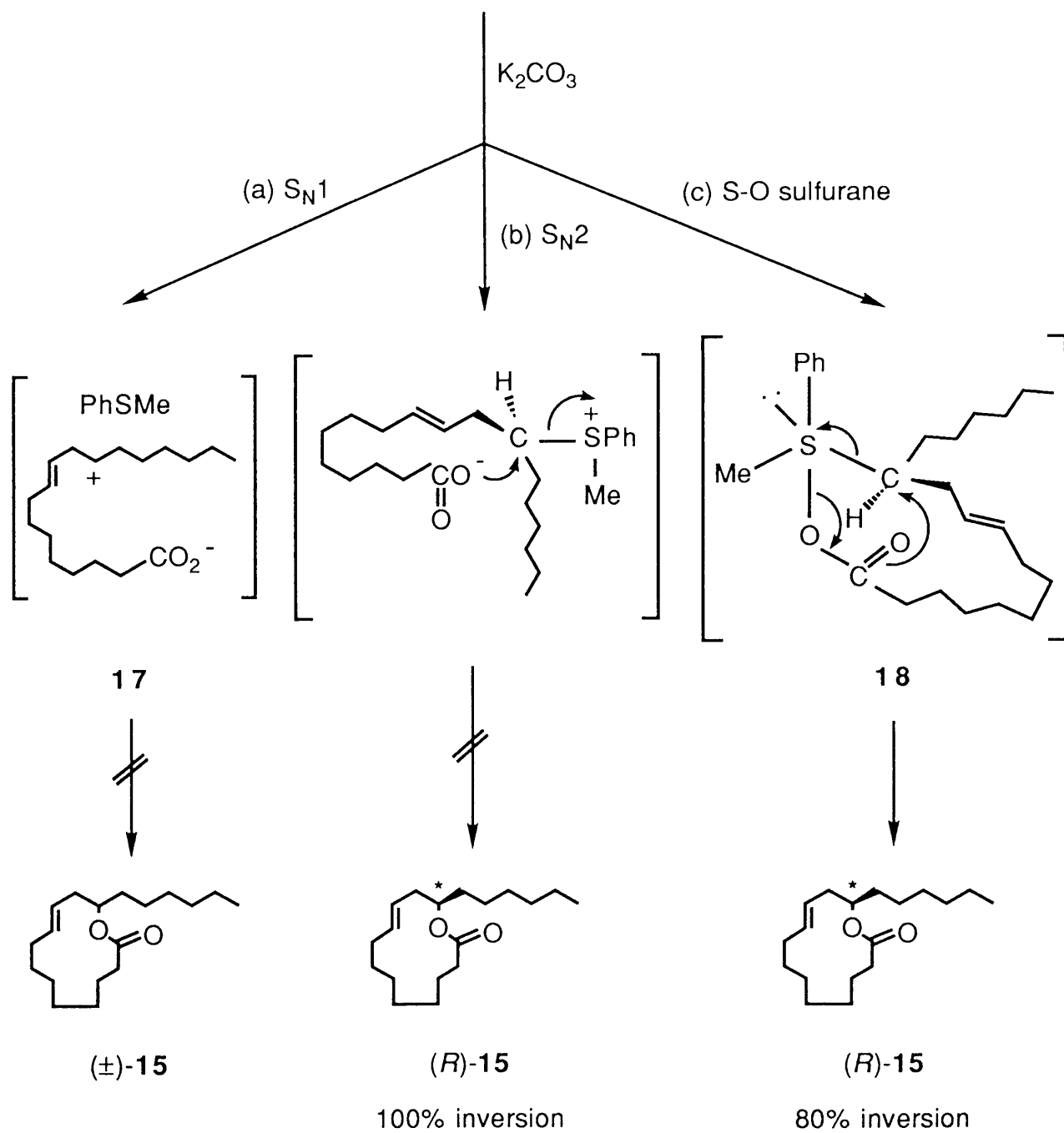
Three possible processes (a)-(c) about cyclization of ( $\omega$ -carboxyalkyl)sulfonium salt (**(S)-14**) are shown in Scheme 3. The first process (a) is  $\text{S}_{\text{N}}1$  reaction and methyl phenyl sulfide eliminates to form carbocation intermediate **17**,<sup>12</sup> which would give racemic lactone **15**. On the basis of the formation of (**(R)-15**) (80% e.e.), the process (a) is ruled out. The second process (b) is  $\text{S}_{\text{N}}2$  reaction. According to the report in  $\text{S}_{\text{N}}2$  reaction by Pearson *et al.*, it is important to stabilize transition state of pentavalent carbon atom by coordination either of soft leaving group and soft nucleophile or of hard leaving group and hard nucleophile.<sup>13</sup> In fact, Matsuyama *et al.* reported that alkylation of thiolate ion as a soft nucleophile with sulfonium salt **16** having a soft leaving group revealed reactivities of



Scheme 3



(S)-14



$S_N2$  reaction with 100% inversion (eq. 5).<sup>8</sup> In this study, since carboxylate anion is a hard nucleophile, it is presumed that  $S_N2$  reaction is unfavorable because of the absence of stabilization of transition state. Consequently, (*R*)-**15** with 80% inversion of configuration was obtained. The third process is formation of S-O sulfurane intermediate **18**,<sup>8,9</sup> by nucleophilic attack of carboxylate anion toward sulfonium cation. As described in chapter 1, intramolecular electrostatic interaction between the sulfonium cation and the carboxylate anion plays an important role in this cyclization of ( $\omega$ -carboxyalkyl)sulfonium salts. Thus, it is estimated that the reaction mechanism of this lactonization is the process (c) *via* S-O sulfurane intermediate **18**.

## Experimental

**(S)-*sec*-Butylmethylphenylsulfonium Perchlorate (5).** To AgClO<sub>4</sub> (314 mg, 1.5 mmol), cooled in an ice bath, was added a mixture of methyl iodide (1.92 g, 14 mmol) and (S)-*sec*-butyl phenyl sulfide (223 mg, 1.3 mmol, [ $\alpha$ ]<sub>D</sub> +16.2° (c 1.50, MeOH)), which was prepared from (R)-*sec*-butyl bromide ([ $\alpha$ ]<sub>D</sub> -22.9° (c 4.9, EtOH)) and sodium thiophenoxide in EtOH,<sup>9</sup> dropwise. After being stirred at room temperature for 3 days, the reaction mixture was passed through a silica gel short column and concentrated *in vacuo*. The residue was washed with ether to give **5** (100%): [ $\alpha$ ]<sub>D</sub> +3.91° (c 2.44, MeOH); <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  0.83-1.97 (m, 8H), 3.43 (s, 3H), 3.77-4.30 (m, 1H), 7.49-7.88 (m, 3H), 7.91-8.22 (m, 2H); IR (neat) 1090 cm<sup>-1</sup>.

**Alkylation of Benzoic Acid with 6.** A suspension of **5** (351 mg, 1.25 mmol), benzoic acid (159 mg, 1.3 mmol), and K<sub>2</sub>CO<sub>3</sub> (522 mg, 3.8 mmol) in CH<sub>3</sub>CN (10 ml) was refluxed for 40 h. The reaction mixture was diluted with ether (20 ml) and passed through a silica gel short column. After removal of solvent, the residue was chromatographed on silica gel (hexane-AcOEt = 50 : 1) to give (R)-*sec*-butyl benzoate **6** [73 mg (33%)] and methyl benzoate **7** [28 mg (16%)]. **6**: [ $\alpha$ ]<sub>D</sub> -25.4° (c 2.85, MeOH, OP 68%); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.95 (t, J = 7.0 Hz, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.43-1.97 (m, 2H), 4.73-5.33 (m, 1H), 7.07-7.58 (m, 3H), 7.77-8.13 (m, 2H); IR (neat) 1715 cm<sup>-1</sup>; MS *m/z* 178 (M<sup>+</sup>), 149, 123.

**Preparation of Authentic (S)-*sec*-Butyl Benzoate.** A mixture of (S)-2-butanol (234 mg, 3.2 mmol, [ $\alpha$ ]<sub>D</sub> +13.2° (c 7.97, MeOH)) and pyridine (2.38 g, 30 mmol) in benzene (10 ml) was cooled in an ice bath. To this mixture was added benzoyl chloride (488 mg, 3.5 mmol) in benzene (10 ml) dropwise, and then the ice bath was removed. After the mixture was stirred for 18 h at room temperature, the reaction mixture was diluted with water (50 ml) and extracted with ether (3 x 150 ml). The extracts were dried over MgSO<sub>4</sub> and purified by silica gel column chromatography (hexane-ether = 35 : 1) to give (S)-*sec*-butyl benzoate [527 mg (94%)]: [ $\alpha$ ]<sub>D</sub>

+37.1° (c 6.83, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.97 (t, J = 7.1 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 1.45-2.00 (m, 2H), 4.73-5.33 (m, 1H), 7.13-7.63 (m, 3H), 7.90-8.20 (m, 2H).

Ricinelaiddic acid (**9**) was prepared from ricinolic acid (**8**) according to the literature procedure<sup>11</sup> and purified by recrystallization from hexane as a colorless solid [12.2 g (34%)]: mp 45-47 °C [lit.<sup>11</sup> mp 51.0-51.5 °C]; [α]<sub>D</sub> +5.38° (c 8.37, EtOH) [lit.<sup>11</sup> [α]<sub>D</sub> +6.6° (c 10, EtOH) OP 82%]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.85-1.80 (m, 23H), 1.80-2.53 (m, 6H), 3.44-3.80 (m, 1H), 5.25-5.57 (m, 2H), 11.6 (br s, 1H); IR (CH<sub>2</sub>Cl<sub>2</sub>) 2770-3460, 1708 cm<sup>-1</sup>; MS *m/z* 299 (M<sup>+</sup>+1), 281, 263.

**Methyl [R-(E)]-12-Hydroxy-9-octadecenoate (10).** In a round-bottomed flask was placed ricinelaiddic acid (**9**) (10.4 g, 35 mmol) in ether (50 ml), and this was cooled in an ice bath. To the stirred mixture was added CH<sub>2</sub>N<sub>2</sub> (ether solution), until evolution of nitrogen was stopped. After removal of solvent, the residual oil was chromatographed on silica gel (hexane-AcOEt = 5 : 1) to give **11** [10.4 g (95%)]. Recrystallization from hexane gave a colorless solid: mp 27-28 °C; [α]<sub>D</sub> -0.20° (c 3.65, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.87-1.80 (m, 23H), 1.80-2.57 (m, 6H), 3.30-3.83 (m, 4H), 5.31-5.57 (m, 2H); IR (CCl<sub>4</sub>) 1740 cm<sup>-1</sup>; MS *m/z* 313 (M<sup>+</sup>+1), 294, 279; HRMS calcd for C<sub>19</sub>H<sub>36</sub>O<sub>3</sub> 312.2664, found 312.2709.

**Methyl [R-(E)]-12-[(*p*-Tolylsulfonyl)oxy]-9-octadecenoate(11).** To **10** (6.90 g, 22 mmol) in pyridine (35 ml) was added *p*-toluenesulfonyl chloride (5.10 g, 27 mmol) in pyridine (35 ml) dropwise. The mixture was stirred for 40 h at room temperature. After distillation of pyridine under reduced pressure, the residue was diluted with aqueous HCl (100 ml) and extracted with ether (2 x 200 ml). The organic layer was dried over MgSO<sub>4</sub> and purified by chromatography on silica gel (hexane-AcOEt = 10 : 1) to give **11** [5.95 g (58%)]: [α]<sub>D</sub> +12.6° (c 7.19, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.78-2.07 (m, 23H), 2.15-2.58 (m, 9H), 3.60 (s, 3H), 4.26-4.70 (m, 1H), 5.10-5.43 (m, 2H), 7.22 and 7.70 (ABq, J = 8.3 Hz, 2H); IR (neat) 1735, 1308, 1175 cm<sup>-1</sup>; MS *m/z* 466 (M<sup>+</sup>), 294, 263; HRMS calcd for C<sub>26</sub>H<sub>42</sub>O<sub>5</sub>S (M<sup>+</sup>+1) 467.2831, found 467.2753.

**Methyl [S-(E)]-12-(Phenylthio)-9-octadecenoate (12).**

Sodium (238 mg, 10 mmol) was added to stirred MeOH (10 ml), and then thiophenol (1.11 g, 10 mmol) in MeOH (10 ml) was added dropwise. After the mixture was stirred for 30 min at room temperature, **11** (4.67 g, 10 mmol) in MeOH (10 ml) was added dropwise. The mixture was refluxed for 3 h, and the solvent was removed. The product was diluted with water (80 ml) and extracted with ether (2 x 200 ml). The organic layers were dried over MgSO<sub>4</sub> and purified by chromatography on silica gel (hexane-AcOEt = 30 : 1) to give **12** [2.63 g (65%): [ $\alpha$ ]<sub>D</sub> -15.4° (c 4.03, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.86-1.80 (m, 23H), 1.80-2.50 (m, 6H), 2.82-3.33 (m, 1H), 3.60 (s, 3H), 5.30-5.53 (m, 2H), 7.03-8.87 (m, 5H); IR (neat) 1735 cm<sup>-1</sup>; MS *m/z* 404 (M<sup>+</sup>), 373, 327; HRMS calcd for C<sub>25</sub>H<sub>40</sub>O<sub>2</sub>S 404.2749, found 404.2732.

**[S-(E)]-12-(Phenylthio)-9-octadecenoic Acid (13).**

A mixture of **12** (2.34 g, 5.8 mmol) in MeOH (7 ml) and 1N NaOH (7.54 g, 7.5 mmol) was refluxed for 1.5 h. After removal of MeOH, the residue was acidified with aqueous HCl, and the product was extracted with ether (3 x 200 ml). The organic layers were dried over MgSO<sub>4</sub>. Removal of the solvent gave **13** [1.79 g (80%): [ $\alpha$ ]<sub>D</sub> -16.2° (c 2.78, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.85-1.77 (m, 23H), 1.79-2.53 (m, 6H), 2.80-3.31 (m, 1H), 5.17-5.53 (m, 2H), 6.96-7.47 (m, 5H), 11.6 (br s, 1H); IR (neat) 2770-3460, 1702 cm<sup>-1</sup>; MS *m/z* 390 (M<sup>+</sup>), 280, 207; HRMS calcd for C<sub>24</sub>H<sub>38</sub>O<sub>2</sub>S 390.2592, found 390.2550.

**Sulfonium Salt 14.** Sulfonium salt **14** [1.89 g (100%)] was prepared from **13** (1.47 g, 3.8 mmol), methyl iodide (5.53 g, 38 mmol), and AgClO<sub>4</sub> (936 mg, 4.5 mmol) in CH<sub>3</sub>CN (10 ml): [ $\alpha$ ]<sub>D</sub> +4.27° (c 6.14, acetone); <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  0.63-1.74 (m, 23H), 1.80-2.86 (m, 6H), 3.43 (s, 3H), 3.84-4.42 (m, 1H), 5.10-5.82 (m, 2H), 7.42-8.20 (m, 5H), 9.73 (br s, 1H); IR (neat) 3000-3600, 1702, 1093 cm<sup>-1</sup>.

**Intramolecular Cyclization of 14.** Sulfonium salt **14** (865 mg, 1.7 mmol) in CH<sub>3</sub>CN (100 ml) was added to a suspension of K<sub>2</sub>CO<sub>3</sub> (720 mg, 5.2 mmol) in refluxing CH<sub>3</sub>CN (100 ml) over 1.5 days. The reaction mixture was worked up in a procedure similar to that

described for alkylation of benzoic acid with **5** to give ricinelaidic acid lactone [**15**, 16 mg (3%):  $[\alpha]_D +27.6^\circ$  (c 0.82,  $\text{CHCl}_3$ , OP 66%) [lit.<sup>1</sup>  $[\alpha]_D +42^\circ$  (c 1,  $\text{CHCl}_3$ )];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.72-1.83 (m, 23H), 1.83-2.48 (m, 6H), 4.76-5.17 (m, 1H), 5.27-5.57 (m, 2H); IR ( $\text{CCl}_4$ )  $1721\text{ cm}^{-1}$ ; MS  $m/z$  280 ( $\text{M}^+$ ), 207, 166, 137, 68; HRMS calcd for  $\text{C}_{18}\text{H}_{32}\text{O}_2$  280.2403, found 280.2391. Methyl ester **12** [113 mg (16%)] was also obtained. **12**:  $[\alpha]_D -13.5^\circ$  (c 5.33,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.83-1.76 (m, 23H), 1.78-2.42 (m, 6H), 2.82-3.27 (m, 1H), 3.58 (s, 3H), 5.23-5.49 (m, 2H), 6.95-7.40 (m, 5H); IR (neat)  $1740\text{ cm}^{-1}$ ; MS  $m/z$  404 ( $\text{M}^+$ ), 373, 327.



## References

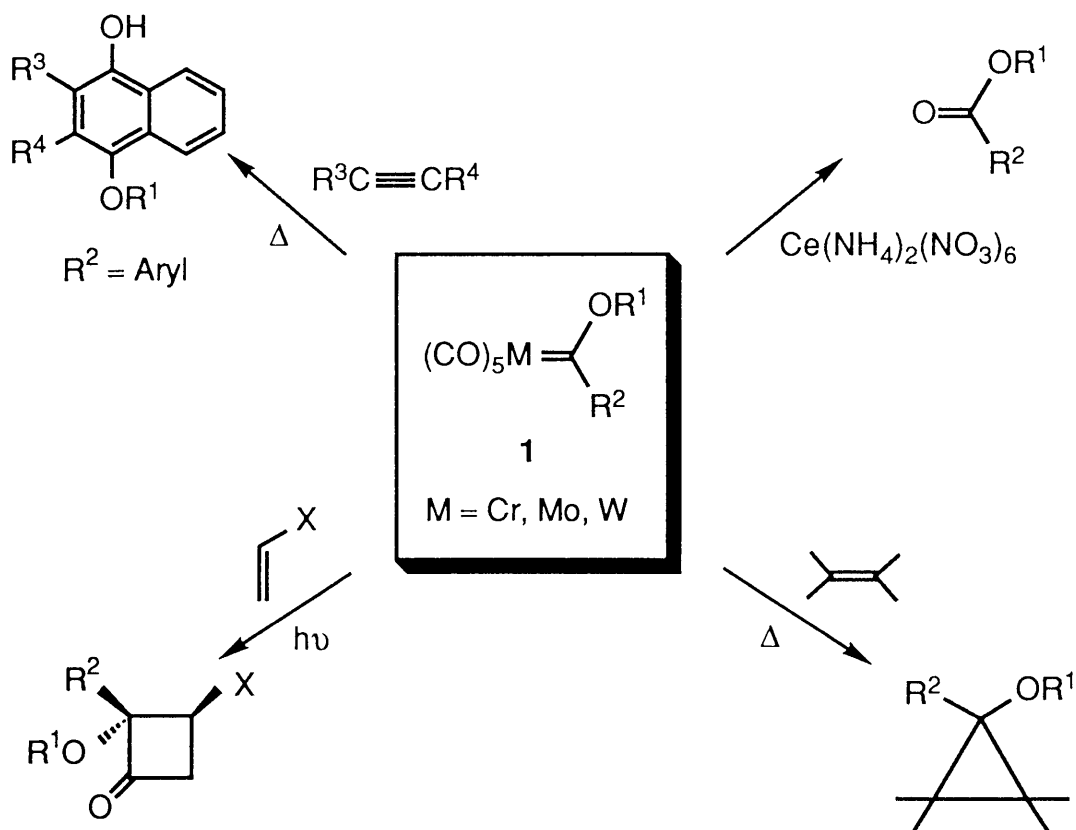
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## Chapter 5

### Synthesis of Fischer-type (Alkoxy)carbene Complexes with Diphenylsulfonium Salts

One of the most outstanding properties of transition metal is their ability to stabilize short-lived molecules, such as carbenes, as coordination ligands. Metal-stabilized carbene complexes, in particular Fischer-type (alkoxy)carbene complexes **1**, have attracted much

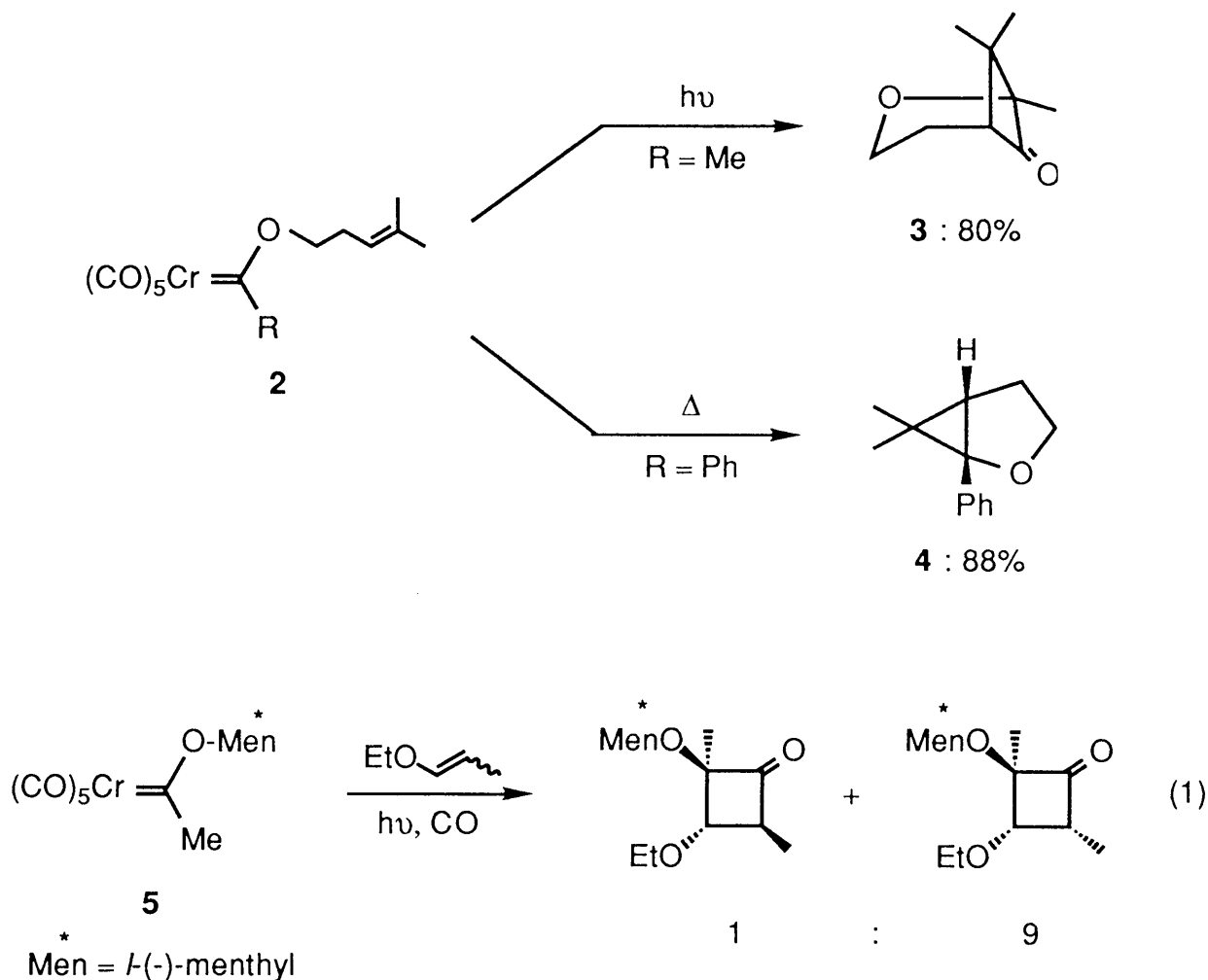
Scheme 1



attention as synthetically useful reagents since the first studies of Fischer *et al.*<sup>1</sup> Typical reactions of (alkoxy)carbene complexes **1** are shown in Scheme 1. Complexes **1** can be regarded as ester equivalent, and the oxidation of **1** with ceric ammonium nitrate (CAN) gives corresponding esters in high yields.<sup>2</sup> Metal-coordinated carbenes **1** could also be used as cyclopropane building blocks.<sup>3</sup> Photolytic reaction of **1** generates ketene species, which react with olefins to afford cyclopropanes as [2+2] cycloaddition products.<sup>4</sup> The addition of alkyne to complexes **1**, which contain an aryl carbene ligand, leads to naphthol compounds.<sup>5</sup> These reactions can also be used for the synthesis of natural products such as vitamins<sup>7</sup> or antibiotics.<sup>8</sup>

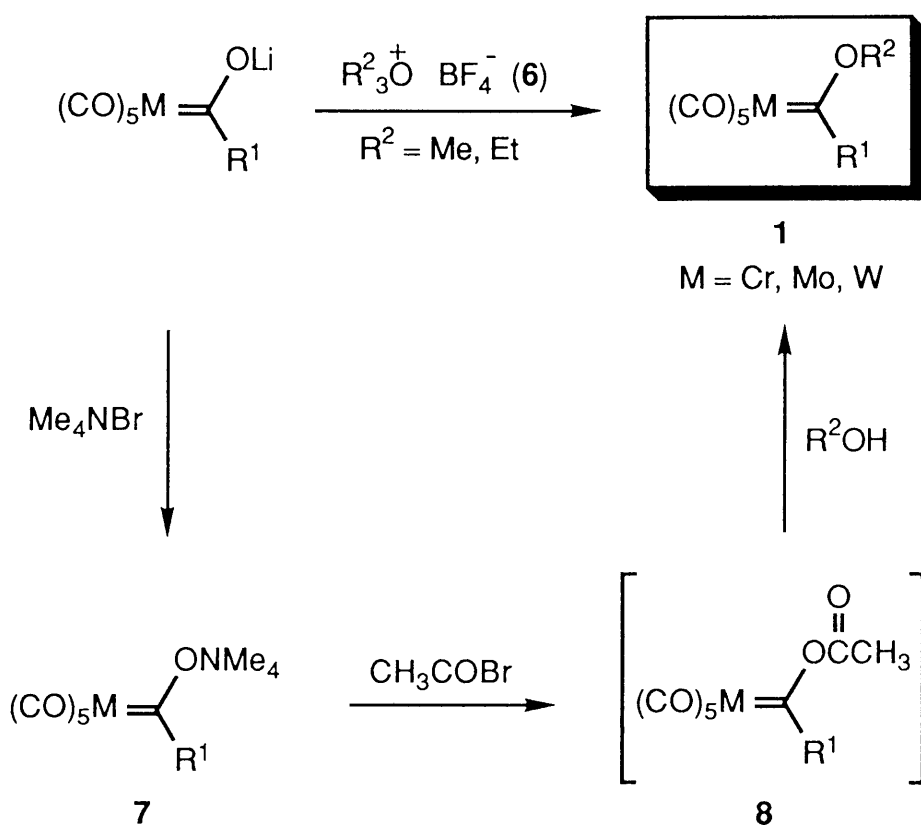
The intra- and intermolecular reaction of (alkoxy)carbene complexes possessing functionalized alkyl groups is also useful for the preparation of important intermediates in organic syntheses. As shown in Scheme 2, photolysis of (alkenyloxy)(methyl)carbene complex **2** produced the bicyclic cyclobutanone **3** in good yield,<sup>4</sup> and thermal intramolecular cyclopropanation of (alkenyloxy)(phenyl)-carbene complex **2** easily undergoes to give the bicyclic cyclopropane **4**.<sup>6</sup> Photoreaction of (menthyloxy)carbene complex **5** with olefin affords cyclobutanone derivatives diastereoselectively (eq. 1).<sup>6</sup> A general synthetic method of these (alkoxy)carbene complexes possessing various functionalized alkoxy groups is required.

Scheme 2

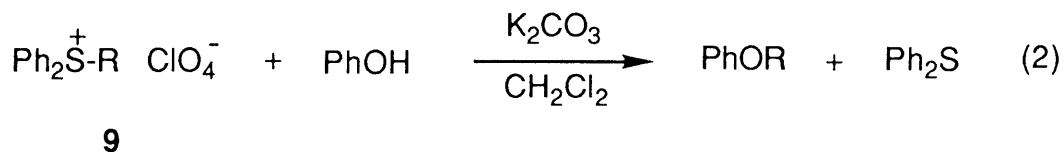


As illustrated in Scheme 3, (alkoxy)carbene complexes **1** have been prepared utilizing alkylation with oxonium salts **6** (Meerwein reagent)<sup>9</sup> and by treatment of (acyloxy)carbene complexes **8** with alcohols.<sup>6</sup> However, the former method only limits to the formation of (methoxy)- or (ethoxy)carbene complexes **1** ( $\text{R}^2 = \text{Me}, \text{Et}$ ), and the latter method has the disadvantage that the intermediary acyloxy complexes **8** are thermally labile<sup>11</sup> and difficult to handle them.

Scheme 3

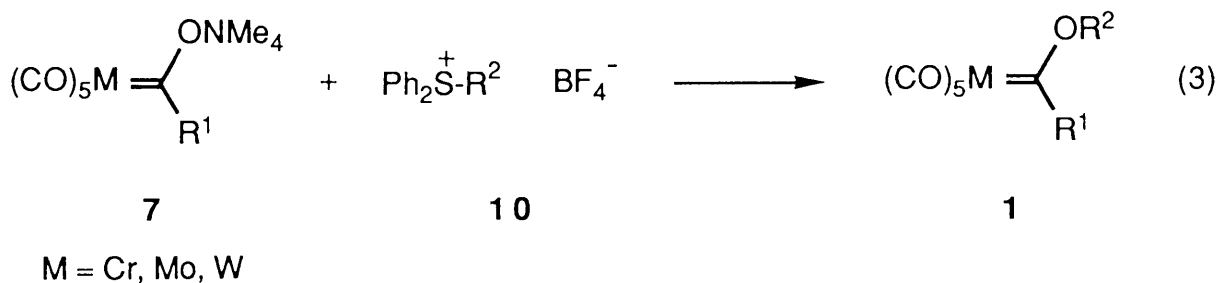


In contrast to oxonium salts **6**, sulfonium salts have the advantage that compounds bearing a variety of functionalized alkyl groups are stable and easily available<sup>11</sup> and that they have ability to alkylate nucleophiles. Diphenylsulfonium salts **9** having a good leaving group  $\text{Ph}_2\text{S}$  react with nucleophiles, such as phenol, under mild conditions to give alkylated products in good yields (eq. 2).<sup>12</sup>



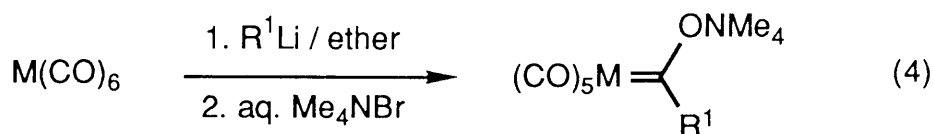
R : Me, Et, n-Bu,  
i-Pr, etc.

In this chapter, the author describes a new and general method for preparing Fischer-type (alkoxy)carbene complexes **1** utilizing alkylation of tetramethylammonium acylate complexes **7** with alkyldiphenylsulfonium salts **10** (eq. 3).



## Results and Discussion

The tetramethylammonium acylate complexes **7** were prepared by treating  $\text{M}(\text{CO})_6$  ( $\text{M} = \text{Cr, Mo, W}$ ) with organolithium reagents, followed by addition of  $\text{Me}_4\text{N}^+\text{Br}^-$  according to the literature<sup>13</sup> (eq. 4). Alkyldiphenylsulfonium tetrafluoroborates **10** were readily obtained by the reaction of a large excess of  $\text{Ph}_2\text{S}$  with the corresponding alkyl halides in the presence of  $\text{AgBF}_4$  (eq. 5). Reaction of pentacarbonyl[tetramethylammonium (methyl)carbenyl oxide]chromium (**7a**) with methyldiphenylsulfonium tetrafluoro-



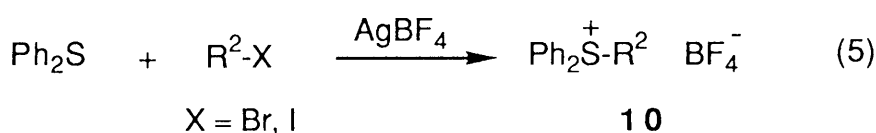
**7a** : M = Cr, R<sup>1</sup> = Me

**7b** : M = Cr, R<sup>1</sup> = Bu<sup>n</sup>

**7c** : M = Cr, R<sup>1</sup> = Ph

**7d** : M = Mo, R<sup>1</sup> = Me

**7e** : M = W, R<sup>1</sup> = Me



borate (**11**) in CH<sub>2</sub>Cl<sub>2</sub> was performed under Ar at room temperature for 12 h (eq. 6), and the results are summarized in Table 1. Alkylation with **11** took place easily to give pentacarbonyl-[(methoxy)(methyl)carbene]chromium (**12a**) in high yield (run 1). (Alkoxy)carbene complexes are unstable under acidic conditions. As oxonium salts **6** are acidic compounds, care must be taken in controlling pH of the reaction solution in the case of the known method using oxonium salts **6**. Generally, sulfonium salts are also acidic compounds. Since carbene complex **12a** may decompose under these reaction conditions, alkylation of **7a** with **11** was carried out in

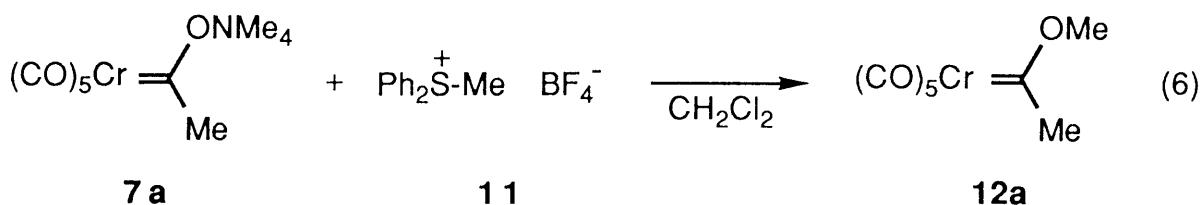


Table 1. Preparation of Carbene Complex **12a** from Ammonium Salt **7a** with Sulfonium Salt **11**<sup>a</sup>

run	additive (mmol)	Yield of <b>12a</b> / %
1	none	84
2	K <sub>2</sub> CO <sub>3</sub> (1.0)	73
3	pyridine (1.2)	0 <sup>b</sup>
4	2,6-lutidine (1.2)	52

a) **7a** (1 mmol), **11** (1 mmol), CH<sub>2</sub>Cl<sub>2</sub> (5 ml). b) (CO)<sub>5</sub>Cr·pyridine was obtained (15%).<sup>14</sup>

the presence of bases (run 2-4). However, the use of bases decreased the yields of complex **12a**. These results show that sulfonium salts are mild and useful alkylating reagent for the preparation of (alkoxy)carbene complex **12a**. Thus, subsequent alkylation with sulfonium salts was performed under conditions of run 1.

Alkylation of ammonium chromium (acylate)complexes **7a-c** was investigated with diphenylsulfonium salts **10** possessing various alkyl groups (eq. 7). As shown in Table 2, chromium (alkoxy)carbene complexes **12-23** were obtained in moderate to high yields. In contrast to known methods,<sup>6,9</sup> the present method using sulfonium

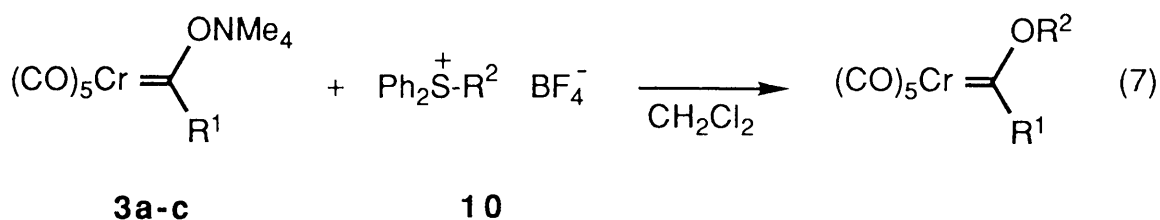




Table 2. Preparation of Chromium (Alkoxy)carbene Complexes

Product (%) <sup>a</sup>		
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{OMe} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	<b>12</b>	$\text{R}^1 = \text{Me}$ (84) $\text{Bu}^n$ (82) $\text{Ph}$ (85)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{OPr}^i \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	<b>13</b>	$\text{R}^1 = \text{Me}$ (92) $\text{Bu}^n$ (94) $\text{Ph}$ (90)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_7\text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>14</b>	(91)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_2\text{OEt} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	<b>15</b>	$\text{R}^1 = \text{Me}$ (68) $\text{Bu}^n$ (71) $\text{Ph}$ (66)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{CN} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	<b>16</b>	$\text{R}^1 = \text{Me}$ (84) $\text{Bu}^n$ (79) $\text{Ph}$ (67)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{Cl} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	<b>17</b>	$\text{R}^1 = \text{Me}$ (88) $\text{Bu}^n$ (83) $\text{Ph}$ (83)

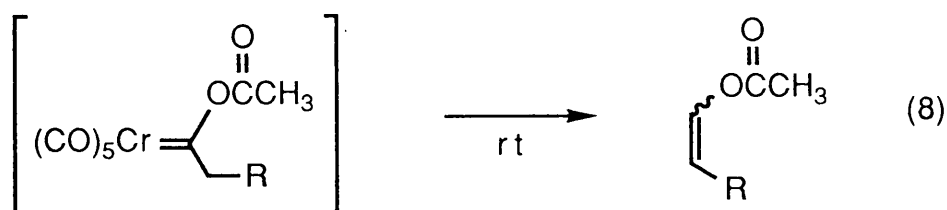
a) Isolated yield.

Table 2. Preparation of Chromium (Alkoxy)carbene Complexes (continued)

Product (%) <sup>a</sup>		
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{OH} \\ \diagup \\ \text{R}^1 \end{array}$	<b>18</b>	$\text{R}^1 = \text{Me}$ (41) $\text{Bu}^n$ (31)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{OCH}_2\text{CO}_2\text{Me} \\ \diagup \\ \text{R}^1 \end{array}$	<b>19</b>	$\text{R}^1 = \text{Me}$ (90) $\text{Bu}^n$ (93) $\text{Ph}$ (57)
$\left[ (\text{CO})_5\text{Cr}=\begin{array}{c} \text{O} \text{---} \text{CH}_2\text{CH}_2\text{---} \\ \diagup \\ \text{R}^1 \end{array} \right]_2$	<b>20</b>	$\text{R}^1 = \text{Me}$ (60) $\text{Bu}^n$ (61) $\text{Ph}$ (26)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O} \text{---} \text{CH}_2\text{CH}_2\text{CH}=\text{CHMe} \\ \diagup \\ \text{Me} \end{array}$	<b>21</b>	(55)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O} \text{---} \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \\ \diagup \\ \text{R}^1 \end{array}$	<b>22</b>	$\text{R}^1 = \text{Me}$ (87) $\text{Ph}$ (92)
$(\text{CO})_5\text{Cr}=\begin{array}{c} \text{O}(\text{CH}_2)_5\text{CO}_2\text{Me} \\ \diagup \\ \text{R}^1 \end{array}$	<b>23</b>	$\text{R}^1 = \text{Me}$ (66) $\text{Bu}^n$ (86) $\text{Ph}$ (93)

a) Isolated yield.

salts has advantages as follows: 1) This reaction requires longer reaction time (12 h) than known method<sup>9</sup> using oxonium salts **6**, but a variety of functionalized alkyl groups such as secondary carbon, ether, nitrile, ester, halide, alcohol, and unsaturated linkages, could be effectively introduced: 2) This reaction can be carried out at room temperature, although known method using acyloxy intermediate **8** affords enol esters at room temperature in the case of the presence of  $\alpha$ -hydrogen to the carbene carbon atom (eq. 8):<sup>16</sup> 3) The present



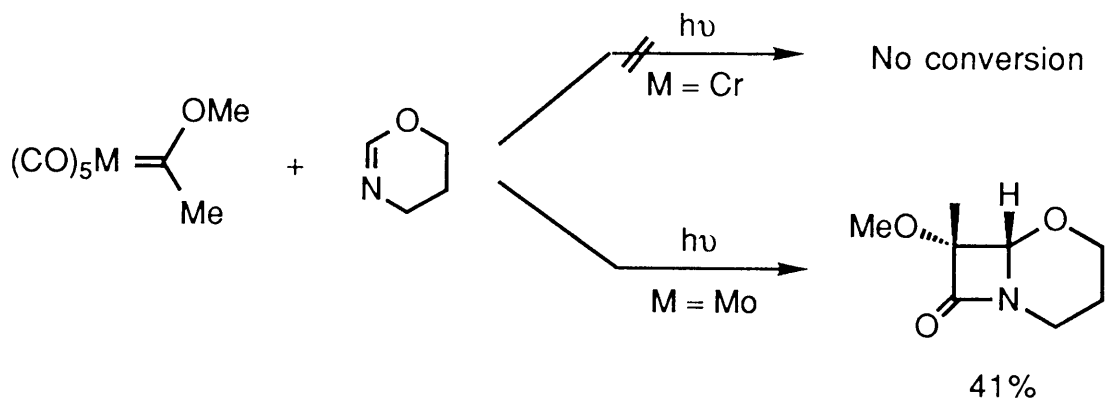
method is useful for the preparation of carbene complexes **18** having a hydroxyl group, because known method<sup>6</sup> using acyloxy intermediate **8** should give mixtures of **18** and biscarbene complexes such as **20**: 4) The use of diphenylsulfonium salt as an alkylating reagent affords novel biscarbene complexes **20**.

Chromium (alkoxy)carbene complexes **12-23** were identified by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and MS spectra. In particular, <sup>13</sup>C NMR spectra of complexes **12-23** are characteristic because of carbene carbon signals in a low-field position between  $\delta = 350$  and  $370$  ppm. Most of chromium complexes were stable, if stored in a freezer ( $-20$  °C). However, complexes **15a-c** containing an ether group, and **17c**, **19a-b** and **23a** containing an ester group slowly decomposed in a

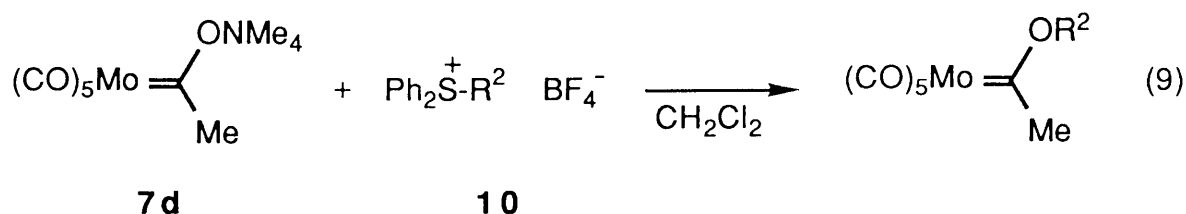
freezer. Complexes **19a-c** were decomposed under purification by column chromatography on silica gel.

Generally, molybdenum carbene complexes are more unstable than the corresponding chromium and tungsten complexes. There are less reports of the preparation and application of molybdenum carbene complexes to organic syntheses.<sup>3b,17</sup> However, as shown in Scheme 4, although photoreactions of chromium complex with imine do not occur, the use of the corresponding molybdenum complex gives bicyclic lactam compound because of high reactivities of the molybdenum complex.<sup>15</sup> A general and mild method of introduction of various functionalized alkyl groups is required in the preparation of molybdenum (alkoxy)carbene complexes.

Scheme 4



Alkylation of tetramethylammonium molybdenum (acylate) complex **7d** with sulfonium salts **10** was investigated in a similar manner as the synthesis of chromium complexes (eq. 9). This method afforded molybdenum (alkoxy)carbene complexes **24-31** containing



various functionalized alkoxy groups in moderate to good yields (Table 3). Although the yields of molybdenum complexes **24-31** decreased compared with those of chromium compounds **12-23**, it was found that molybdenum (alkoxy)carbene complexes containing various functional groups were easily available using this method.

Molybdenum (alkoxy)carbene complexes **24-31** also have characteristic  $^{13}\text{C}$  NMR signals of carbene carbon in a low-field position between  $\delta = 340$  and  $360$  ppm. Complexes **29** and **31** were stable in non-polar solvent, but decomposed rapidly at room temperature without solvent. Complexes **26-28** slowly decomposed in a freezer.

Similarly, preparation of tungsten complexes **32-39** from acylate complex **7e** and diphenylsulfonium salts **10** also gave good results (eq. 10, Table 4). Most of tungsten (alkoxy)carbene complexes **32-39** were stable similarly to chromium complexes. Compounds **38** containing a hydroxy group was very unstable without solvent.

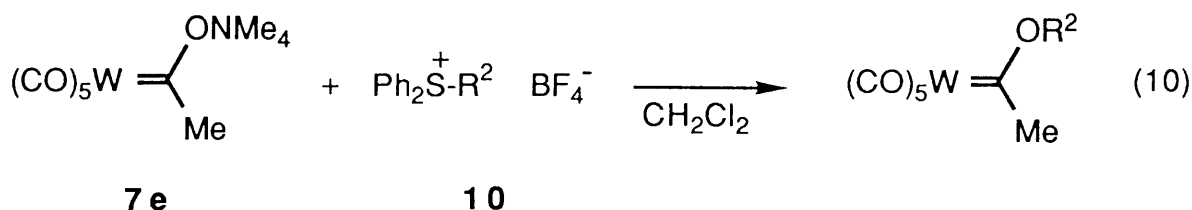


Table 3. Preparation of Molybdenum  
(Alkoxy)carbene Complexes

Product (%) <sup>a</sup>		
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{OMe} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>24</b>	(67)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{OPr}^i \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>25</b>	(74)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}(\text{CH}_2)_7\text{CH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>26</b>	(66)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}(\text{CH}_2)_2\text{OEt} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>27</b>	(57)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{CN} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>28</b>	(42)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{Cl} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>29</b>	(67)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>30</b>	(67)
$(\text{CO})_5\text{Mo}=\begin{array}{c} \text{O}(\text{CH}_2)_5\text{CO}_2\text{Me} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>31</b>	(65)

a) Isolated yield.

Table 4. Preparation of Tungsten (Alkoxy)-carbene Complexes

Product (%) <sup>a</sup>		
$(\text{CO})_5\text{W}=\begin{array}{c} \text{OMe} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 2</b>	(93)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{OPr}^i \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 3</b>	(95)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}(\text{CH}_2)_2\text{OEt} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 4</b>	(85)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{CN} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 5</b>	(69)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{Cl} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 6</b>	(90)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 7</b>	(91)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}(\text{CH}_2)_3\text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 8</b>	(48)
$(\text{CO})_5\text{W}=\begin{array}{c} \text{O}(\text{CH}_2)_5\text{CO}_2\text{Me} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Me} \end{array}$	<b>3 9</b>	(85)

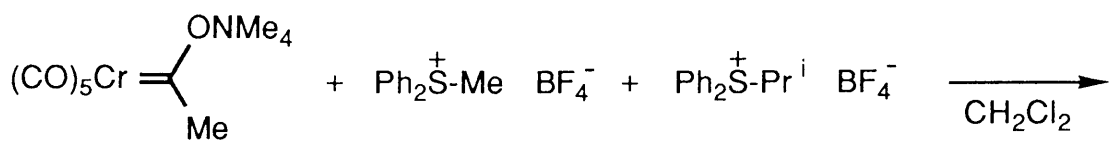
a) Isolated yield.

Complexes **36** and **39** slowly decomposed in a freezer. All tungsten (alkoxy)carbene complexes **32-39** have characteristic carbene carbon signals of  $^{13}\text{C}$  NMR between  $\delta = 320$  and  $340$  ppm.

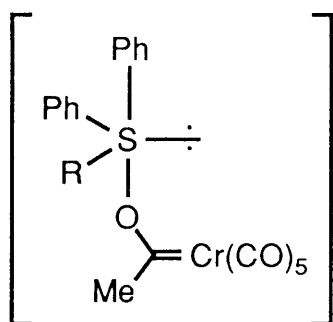
Alkylation with diphenylsulfonium salts was found to be a simple and general synthetic method of Fischer-type chromium, molybdenum, and tungsten (alkoxy)carbene complexes with various functionalized alkoxy groups. It is expected that novel intra- and intermolecular reactions of the resulting carbene complexes can be developed utilizing the functional groups in these complexes.

As described in chapter 4, alkylation of carboxylate anion with alkylsulfonium salts was stimulated to proceed *via* sulfurane intermediates on the basis of the relative reactivity of alkyl groups in sulfonium salts. The competitive alkylation of **7a** (1 mmol) with methyldiphenylsulfonium tetrafluoroborate (5 mmol) and isopropyl-diphenylsulfonium tetrafluoroborate (5 mmol) was investigated in a similar manner (eq. 11). In this reaction system, the relative reactivity of methyl and isopropyl groups was  $\text{Me} : \text{Pr}^i = 1 : 9$  based on the yields of **12a** and **13a**. This result reveals that reactivity of secondary alkyl group increased compared to that shown in chapter 4 ( $\text{Me} : \text{Bu}^s = 1 : 2.06$ ).<sup>18</sup> Thus, the reaction mechanism of the present alkylation is not  $\text{S}_{\text{N}}2$  reaction but is estimated to proceed *via* S-O sulfurane intermediate **40**.

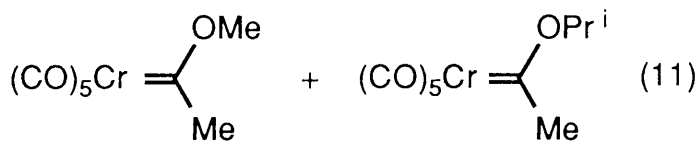




**7 a**



**40**



**12 a**

8%

1

**13 a**

72%

9

:

## Experimental

$^1\text{H}$  NMR spectra were recorded at 400 MHz on a JEOL EX 400 spectrometer, and  $^{13}\text{C}$  NMR spectra were recorded at 100 MHz. Mass and high-resolution mass spectra were determined with a JEOL JMS-AX 500 mass spectrometer with JEOL JMA-DA 5000/DA 6000 mass data system at an ionizing voltage of 70 eV. Melting points (uncorrected) were measured on a Yanaco MP-500D apparatus. Column chromatography was performed with Daisogel 1001w containing 10% water. Gel-permeation chromatography was performed using a JAI LC-908 liquid chromatography with two JAIGEL-1H columns (20 mm x 600 mm) with chloroform as eluent.

Dry solvents were purified as follows. Dichloromethane was distilled from  $\text{CaH}_2$ ; Ether was freshly distilled from sodium benzophenone ketyl before use.

Pentacarbonyl[tetramethylammonium (methyl)carbenyl oxide]chromium (**7a**), pentacarbonyl[tetramethylammonium (*n*-butyl)carbenyl oxide]chromium (**7b**), pentacarbonyl[tetramethylammonium (phenyl)carbenyl oxide]chromium (**7c**), pentacarbonyl-tetramethylammonium (methyl)carbenyl oxide]molybdenum (**7d**), and pentacarbonyl[tetramethylammonium (methyl)carbenyl oxide]-tungsten (**7e**), were prepared according to the literature.<sup>13,16</sup>

Alkyl iodides, which were used for the preparation of diphenylsulfonium salts **10**, were prepared from commercially available alkyl bromides and KI (3 equiv.) in refluxing acetone. The reaction mixture was diluted with ether and passed through a silica gel short column. The eluate was concentrated *in vacuo*, diluted with ether, washed with aqueous  $\text{Na}_2\text{SO}_3$ , and dried over  $\text{MgSO}_4$ . After removal of solvent, the residue was distilled or recrystallized from ether-hexane to give pure products (74-95%).

**2-Iodoethyl Ether:** bp 61 °C (32 mmHg);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.23 (t,  $J$  = 7.08 Hz, 3H), 3.25 (t,  $J$  = 7.08 Hz, 2H), 3.55 (q,  $J$  = 7.00 Hz, 2H), 3.70 (t,  $J$  = 6.84 Hz, 2H); MS  $m/z$  200 ( $\text{M}^+$ ), 171, 155.

**3-Iodo-1-propanol:** bp 78 °C (7 mmHg);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$

2.04 (quintet,  $J = 6.23$  Hz, 2H), 2.66 (s, 1H), 3.30 (t,  $J = 6.84$  Hz, 2H), 3.72 (t,  $J = 5.86$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.13, 25.6, 62.1; IR (neat)  $3338\text{ cm}^{-1}$ ; MS  $m/z$  186 ( $\text{M}^+$ ), 168, 155.

**4-Iodobutanonitrile:** bp  $75\text{ }^\circ\text{C}$  (3 mmHg);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.15 (quintet,  $J = 6.71$  Hz, 2H), 2.54 (t,  $J = 6.84$  Hz, 2H), 3.30 (t,  $J = 6.59$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.13, 18.4, 28.7, 118.3; IR (neat)  $2247\text{ cm}^{-1}$ ; MS  $m/z$  195 ( $\text{M}^+$ ), 155, 141.

Methyl 6-iodohexanoate was prepared by treatment of 6-iodohexanoic acid (see chapter 1) with  $\text{CH}_2\text{N}_2$  in ether at  $0^\circ\text{C}$  (99%): oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44 (quintet,  $J = 7.57$  Hz, 2H), 1.66 (quintet,  $J = 7.57$  Hz, 2H), 1.84 (quintet,  $J = 7.20$  Hz, 2H), 2.33 (t,  $J = 7.32$  Hz, 2H), 3.19 (t,  $J = 7.08$  Hz, 2H), 3.67 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.46, 23.7, 29.8, 33.0, 33.7, 51.4, 173.8; IR (neat)  $1737\text{ cm}^{-1}$ ; MS  $m/z$  256 ( $\text{M}^+$ ), 225, 197.

**Diphenylsulfonium Tetrafluoroborate 10.** To  $\text{AgBF}_4$  (9.74 g, 50 mmol), cooled in an ice bath, was added a mixture of diphenyl sulfide (93.2 g, 0.5 mol) and alkyl halides (55 mmol) dropwise. The mixture was covered with an aluminium foil and stirred at room temperature for 3 days. The reaction mixture was passed through a silica gel short column and eluted with acetone. The eluate was concentrated *in vacuo*. After being washed with ether, the residue was dried under reduced pressure or recrystallized from  $\text{CH}_2\text{Cl}_2$ -ether.

**Methyldiphenylsulfonium Tetrafluoroborate:** mp  $51.0\text{--}53.0\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  3.70 (s, 3H), 7.63-7.77 (m, 6H), 7.90-7.96 (m, 4H); IR (KBr)  $1584, 1067\text{ cm}^{-1}$ .

**Isopropyldiphenylsulfonium Tetrafluoroborate:** mp  $126.0\text{--}127.0\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.50 (d,  $J = 6.35$  Hz, 6H), 4.91 (m, 1H), 7.72-7.84 (m, 6H), 8.11-8.13 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  19.3, 52.4, 125.9, 133.0, 133.3, 136.7; IR (KBr)  $1683, 1061\text{ cm}^{-1}$ .

***n*-Octyldiphenylsulfonium Tetrafluoroborate:** oil;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  0.85 (t,  $J = 6.84$  Hz, 3H), 1.16-1.30 (m, 8H), 1.55 (quintet,  $J = 7.45$  Hz, 2H), 1.74 (quintet,  $J = 7.57$  Hz, 2H), 4.21 (t,  $J = 7.57$  Hz, 2H), 7.69-7.80 (m, 6H), 8.03-8.05 (m, 4H);  $^{13}\text{C}$  NMR

(CD<sub>3</sub>OD)  $\delta$  15.1, 24.2, 26.2, 29.6, 30.5, 33.2, 45.8, 127.0, 132.2, 133.1, 136.2; IR (neat) 1585, 1066, 749, 687 cm<sup>-1</sup>.

**(2-Ethoxyethyl)diphenylsulfonium Tetrafluoroborate:** mp 68.3-69.6 °C; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.04 (t, J = 7.08 Hz, 3H), 3.40 (t, J = 7.00 Hz, 2H), 3.83 (t, J = 5.37 Hz, 2H), 4.46 (t, J = 5.37 Hz, 2H), 7.68-7.79 (m, 6H), 8.01-8.03 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  15.7, 47.2, 65.1, 68.3, 126.8, 132.2, 132.9, 136.0; IR (KBr) 1063 cm<sup>-1</sup>.

**(5-Methoxycarbonylpentyl)diphenylsulfonium Tetrafluoroborate:** oil; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.58-1.62 (m, 4H), 1.73-1.78 (m, 2H), 2.30 (t, J = 6.84 Hz, 2H), 3.62 (s, 3H), 4.20 (t, J = 7.57 Hz, 2H), 7.70-7.79 (m, 6H), 8.02-8.04 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  24.7, 24.9, 27.9, 44.7, 51.9, 125.8, 131.3, 132.2, 135.4, 175.0; IR (neat) 1733, 1164 cm<sup>-1</sup>.

**(3-Hydroxypropyl)diphenylsulfonium Tetrafluoroborate:** mp 78.1-79.6 °C; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.98 (quintet, J = 6.47 Hz, 2H), 3.77 (t, J = 5.86 Hz, 2H), 4.26 (t, J = 7.33 Hz, 2H), 4.72 (s, 1H), 7.68-7.79 (m, 6H), 8.00-8.02 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  27.9, 42.7, 59.9, 125.8, 130.9, 132.0, 135.1; IR (KBr) 3100-3700, 1051 cm<sup>-1</sup>.

**(3-Chloropropyl)diphenylsulfonium Tetrafluoroborate:** mp 107.3-108.5 °C; <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone)  $\delta$  2.33 (quintet, J = 6.96 Hz, 2H), 3.87 (t, J = 6.59 Hz, 2H), 4.50 (t, J = 7.57 Hz, 2H), 7.74-7.86 (m, 6H), 8.17-8.19 (m, 4H); <sup>13</sup>C NMR (*d*<sub>6</sub>-acetone)  $\delta$  28.8, 42.7, 43.2, 126.0, 131.8, 132.5, 135.8; IR (KBr) 1065 cm<sup>-1</sup>.

**(4-Methyl-3-pentenyl)diphenylsulfonium Tetrafluoroborate:** oil; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.39 (s, 3H), 1.65 (s, 3H), 2.49-2.52 (m, 2H), 4.24 (t, J = 7.08 Hz, 2H), 5.18 (m, 1H), 7.66-7.76 (m, 6H), 7.99-8.02 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  24.1, 27.6, 34.8, 45.7, 119.1, 125.8, 130.1, 131.3, 135.3, 136.5; IR (neat) 1666, 1054 cm<sup>-1</sup>.

**Bistetrafluoroborate Salt of 1,4-Bis-(diphenylsulfonio)butane:** oil; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.03 (br s, 4H), 4.20 (br s, 4H), 7.61-7.75 (m, 12H), 7.90-7.96 (m, 8H); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  23.7, 43.7, 125.4, 131.2, 132.2, 135.5; IR (neat) 1080 cm<sup>-1</sup>.

**(3-Cyanopropyl)diphenylsulfonium Tetrafluoroborate:**

oil;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  2.14 (quintet,  $J = 7.45$  Hz, 2H), 2.80 (t,  $J = 7.33$  Hz, 2H), 4.27 (t,  $J = 7.57$  Hz, 2H), 7.68-7.80 (m, 6H), 8.01-8.03 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  16.7, 22.4, 44.1, 120.5, 125.8, 132.0, 133.0, 136.3; IR (neat) 2249, 1067  $\text{cm}^{-1}$ .

**(Methoxycarbonylmethyl)diphenylsulfonium Tetrafluoroborate:** mp 94.0-94.8  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $d_6$ -acetone)  $\delta$  3.73 (s, 3H), 5.53 (s, 2H), 7.71 (t,  $J = 7.57$  Hz, 4H), 7.79 (t,  $J = 7.57$  Hz, 2H), 8.16 (t,  $J = 7.81$  Hz, 4H);  $^{13}\text{C}$  NMR ( $d_6$ -acetone)  $\delta$  47.7, 54.7, 125.8, 131.6, 132.4, 135.7, 165.0; IR (KBr) 1733, 1064  $\text{cm}^{-1}$ .

**General Procedure for Preparation of (Alkoxy)carbene Complexes.** A mixture of ammonium acrylate complexes **7** and diphenylsulfonium tetrafluoroborate **10** in  $\text{CH}_2\text{Cl}_2$  (30 ml) under Ar was stirred at room temperature for 12 h. The solvent was removed under reduced pressure at 0  $^\circ\text{C}$ , and the residue was diluted with ether. The ether solution was passed through a silica gel short column and concentrated *in vacuo*. The crude products were separated by gel-permeation chromatography or by column chromatography on silica gel (hexane-ether).

**12a:** yellow needles; mp 33.4-34.0  $^\circ\text{C}$  [lit.<sup>13</sup> mp 34  $^\circ\text{C}$ ];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.94 (s, 3H), 4.70 (s, 3H).

**12b:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (s, 3H), 1.34 (s, 2H), 1.46 (s, 2H), 3.30 (s, 2H), 4.76 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.5, 28.4, 62.9, 67.6, 216.5, 223.2, 363.9; IR (neat) 2056, 1925, 1254, 1032  $\text{cm}^{-1}$ ; MS  $m/z$  292 ( $\text{M}^+$ ), 279, 264; HRMS  $\text{C}_{11}\text{H}_{12}\text{O}_6\text{Cr}$  calcd for 292.0039, found 291.9992.

**12c:** red needles; mp 47.0-48.3  $^\circ\text{C}$  [lit.<sup>13</sup> mp 46  $^\circ\text{C}$ ];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.65 (s, 3H), 7.28 (s, 3H), 7.38 (s, 2H).

**13a:** yellow needles; mp 54.0-55.1  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.55 (d,  $J = 5.37$  Hz, 6H), 2.90 (s, 3H), 5.82 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.5, 50.3, 87.2, 216.6, 223.5, 352.2; IR (KBr) 2058, 1957, 1915  $\text{cm}^{-1}$ ; MS  $m/z$  279 ( $\text{M}^++1$ ), 251, 223; HRMS  $\text{C}_{10}\text{H}_{10}\text{O}_6\text{Cr}$  calcd for 277.9882, found 277.9882.

**13b:** yellow needles; mp 37.9-38.3  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91

(s, 3H), 1.54 (br s, 10H), 3.23 (s, 2H), 5.82 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.4, 28.3, 63.0, 87.1, 216.6, 223.5, 355.3; IR (KBr) 2062, 1984, 1935, 1908  $\text{cm}^{-1}$ ; MS  $m/z$  320 ( $\text{M}^+$ ), 292, 264; HRMS  $\text{C}_{13}\text{H}_{16}\text{O}_6\text{Cr}$  calcd for 320.0352, found 320.0430.

**13c:** red needles; mp 39.2-39.7  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.55 (s, 6H), 5.63 (s, 1H), 7.35 (s, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.6, 85.8, 122.5, 128.2, 129.8, 153.8, 216.3, 224.5, 345.6; IR (KBr) 2058, 1985, 1940, 1912  $\text{cm}^{-1}$ ; MS  $m/z$  340 ( $\text{M}^+$ ), 312, 284; HRMS  $\text{C}_{15}\text{H}_{12}\text{O}_6\text{Cr}$  calcd for 340.0040, found 340.0078.

**14:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.90 (s, 3H), 1.31 (s, 10H), 1.50 (s, 2H), 1.98 (s, 2H), 2.93 (s, 3H), 4.93 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 25.9, 29.2, 29.3, 31.7, 49.9, 82.0, 216.6, 223.5, 357.4; IR (neat) 2061, 1926  $\text{cm}^{-1}$ ; MS  $m/z$  348 ( $\text{M}^+$ ), 320, 292; HRMS  $\text{C}_{15}\text{H}_{20}\text{O}_6\text{Cr}$  calcd for 348.0665, found 348.0637.

**15a:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (s, 3H), 2.99 (s, 3H), 3.62 (s, 2H), 3.95 (s, 2H), 5.02 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.1, 49.6, 67.2, 68.4, 80.1, 216.5, 223.5, 359.5; IR (neat) 2060, 1920  $\text{cm}^{-1}$ ; MS  $m/z$  308 ( $\text{M}^+$ ), 252, 224; HRMS  $\text{C}_{11}\text{H}_{12}\text{O}_7\text{Cr}$  calcd for 307.9988, found 308.0046.

**15b:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (s, 3H), 1.24 (s, 3H), 1.34 (s, 2H), 1.48 (s, 2H), 3.32 (s, 2H), 3.60 (s, 2H), 3.94 (s, 2H), 5.09 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 15.1, 22.4, 28.5, 62.9, 67.0, 68.4, 80.6, 216.4, 223.3, 362.4; IR (neat) 2162, 1923  $\text{cm}^{-1}$ ; MS  $m/z$  350 ( $\text{M}^+$ ), 294, 266; HRMS  $\text{C}_{14}\text{H}_{18}\text{O}_7\text{Cr}$  calcd for 350.0457, found 350.0417.

**15c:** dark red oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.24 (s, 3H), 3.60 (s, 2H), 3.95 (s, 2H), 4.92 (s, 2H), 7.26-7.39 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.1, 67.0, 68.4, 79.8, 122.9, 128.2, 130.1, 153.5, 216.2, 224.4, 350.2; IR (neat) 2068, 1930  $\text{cm}^{-1}$ ; MS  $m/z$  370 ( $\text{M}^+$ ), 314, 286; HRMS  $\text{C}_{16}\text{H}_{14}\text{O}_7\text{Cr}$  calcd for 370.0145, found 370.0088.

**16a:** yellow crystals; mp 40.8-42.0  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.37 (s, 2H), 2.64 (s, 2H), 2.99 (s, 3H), 4.96 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.4, 25.5, 49.2, 76.0, 118.5, 216.3, 223.4, 360.6; IR (KBr) 2256,

2061, 1921  $\text{cm}^{-1}$ ; MS  $m/z$  303 ( $\text{M}^+$ ), 275, 247; HRMS  $\text{C}_{11}\text{H}_9\text{O}_6\text{N}\text{Cr}$  calcd for 302.9835, found 302.9753.

**16b**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.92 (s, 3H), 1.36 (s, 2H), 1.47 (s, 2H), 2.61 (s, 2H), 3.33 (s, 2H), 5.07 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.8, 14.4, 22.4, 25.6, 28.6, 62.9, 78.3, 118.3, 216.2, 223.0, 363.9; IR (neat) 2247, 2057, 1926  $\text{cm}^{-1}$ ; MS  $m/z$  345 ( $\text{M}^+$ ), 317, 289; HRMS  $\text{C}_{14}\text{H}_{15}\text{O}_6\text{N}\text{Cr}$  calcd for 345.0304, found 345.0271.

**16c**: dark red oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.35 (s, 2H), 2.66 (s, 2H), 4.80 (s, 2H), 7.18 (s, 2H), 7.42 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.3, 25.6, 62.7, 118.3, 122.1, 128.4, 130.2, 153.4, 215.9, 224.1, 351.8; IR (neat) 2250, 2061, 1924  $\text{cm}^{-1}$ ; MS  $m/z$  365 ( $\text{M}^+$ ), 309, 281; HRMS  $\text{C}_{16}\text{H}_{11}\text{O}_6\text{N}\text{Cr}$  calcd for 364.9992, found 365.0084.

**17a**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.45 (s, 2H), 2.97 (s, 3H), 3.77 (s, 2H), 5.03 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.0, 40.7, 49.3, 76.1, 126.4, 223.4, 359.5; IR (neat) 2059, 1922  $\text{cm}^{-1}$ ; MS  $m/z$  312 ( $\text{M}^+$ , Cl = 35), 283, 255; HRMS  $\text{C}_{10}\text{H}_9\text{O}_6\text{Cl}\text{Cr}$  calcd for 311.9492, found 311.9425.

**17b**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (s, 3H), 1.35 (s, 2H), 1.46 (s, 2H), 2.45 (s, 2H), 3.32 (s, 2H), 3.74 (s, 2H), 5.12 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.5, 28.5, 32.2, 40.7, 62.9, 77.6, 216.3, 223.2, 362.8; IR (neat) 2059, 1915  $\text{cm}^{-1}$ ; MS  $m/z$  354 ( $\text{M}^+$ , Cl = 35), 326, 298; HRMS  $\text{C}_{13}\text{H}_{15}\text{O}_6\text{Cl}\text{Cr}$  calcd for 353.9962, found 353.9962.

**17c**: dark red oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.42-2.45 (m, 2H), 3.78 (t,  $J$  = 6.10 Hz, 2H), 4.89 (s, 2H), 7.20 (br s, 2H), 7.40-7.41 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.1, 40.7, 76.7, 122.2, 128.3, 130.1, 153.6, 216.1, 224.3, 351.0; IR (neat) 2063, 1929  $\text{cm}^{-1}$ ; MS  $m/z$  374 ( $\text{M}^+$ , Cl = 35), 346, 290; HRMS  $\text{C}_{15}\text{H}_{11}\text{O}_6\text{Cl}\text{Cr}$  calcd for 373.9649, found 373.9726.

**18a**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.24 (s, 2H), 2.96 (s, 3H), 3.68 (s, 1H), 3.89 (s, 2H), 5.01 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.0, 49.7, 58.7, 77.7, 216.5, 223.4, 358.4; IR (neat) 3361, 2060, 1933  $\text{cm}^{-1}$ ; MS  $m/z$  295 ( $\text{M}^+ + 1$ ), 239, 221; HRMS  $\text{C}_{10}\text{H}_{10}\text{O}_7\text{Cr}$  calcd for 293.9832, found 293.9783.

**18b**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (s, 3H), 1.36 (s, 4H),

2.22 (s, 2H), 3.30 (s, 3H), 3.86 (s, 2H), 5.10 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.8, 22.3, 28.3, 32.2, 58.8, 62.8, 78.5, 216.4, 223.2, 361.3; IR (neat) 3354, 2052, 1915  $\text{cm}^{-1}$ ; MS  $m/z$  336 ( $\text{M}^+$ ), 294, 280; HRMS  $\text{C}_{13}\text{H}_{16}\text{O}_7\text{Cr}$  calcd for 336.0301, found 336.0241.

**19a:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.06 (s, 3H), 3.86 (s, 3H), 5.59 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  49.3, 52.9, 74.7, 166.8, 215.8, 223.1, 363.4; IR (neat) 2067, 1928, 1768  $\text{cm}^{-1}$ ; MS  $m/z$  308 ( $\text{M}^+$ ), 280, 252; HRMS  $\text{C}_{10}\text{H}_8\text{O}_8\text{Cr}$  calcd for 307.9624, found 307.9583.

**19b:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.92 (s, 3H), 1.38 (s, 2H), 1.56 (s, 2H), 3.40 (s, 2H), 3.86 (s, 3H), 5.65 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.5, 28.8, 52.8, 63.4, 75.4, 166.9, 215.8, 222.9, 367.2; IR (neat) 2061, 1929, 1765  $\text{cm}^{-1}$ ; MS  $m/z$  350 ( $\text{M}^+$ ), 322, 294; HRMS  $\text{C}_{13}\text{H}_{14}\text{O}_8\text{Cr}$  calcd for 350.0094, found 350.0014.

**19c:** dark red crystals; mp 38.8-39.3  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.82 (s, 3H), 5.41 (s, 2H), 7.29-7.40 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  52.8, 73.9, 122.9, 128.3, 130.5, 152.9, 166.9, 215.7, 224.3, 353.0; IR (KBr) 2060, 1972, 1932, 1765  $\text{cm}^{-1}$ ; MS  $m/z$  370 ( $\text{M}^+$ ), 342, 314; HRMS  $\text{C}_{15}\text{H}_{10}\text{O}_8\text{Cr}$  calcd for 369.9781, found 369.9704.

**20a:** yellow needles; mp 77.5-80.4  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.26 (s, 4H), 2.98 (s, 6H), 5.01 (s, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.2, 49.8, 80.2, 216.5, 223.3, 359.0; IR (KBr) 2063, 1991, 1981, 1939, 1900  $\text{cm}^{-1}$ ; MS  $m/z$  526 ( $\text{M}^+$ ), 469, 414; HRMS  $\text{C}_{18}\text{H}_{14}\text{O}_{12}\text{Cr}_2$  calcd for 525.9296, found 525.9358.

**20b:** yellow needles; mp 67.5-69.0  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.92 (s, 6H), 1.36 (s, 4H), 1.48 (s, 4H), 2.23 (s, 4H), 3.32 (s, 4H), 5.08 (s, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.5, 26.3, 28.6, 63.0, 80.6, 216.5, 223.2, 362.2; IR (KBr) 2057, 1966, 1933, 1902  $\text{cm}^{-1}$ ; MS  $m/z$  610 ( $\text{M}^+$ ), 418, 414; HRMS  $\text{C}_{24}\text{H}_{26}\text{O}_{12}\text{Cr}_2$  calcd for 610.0234, found 610.0204.

**20c:** red needles; mp 90.5-92.5  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.28 (s, 4H), 4.89 (s, 4H), 7.21-7.40 (m, 10H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.4, 79.7, 122.5, 128.3, 130.2, 153.5, 216.1, 224.1, 350.2; IR (KBr) 2060, 1989, 1937, 1903  $\text{cm}^{-1}$ ; MS  $m/z$  650 ( $\text{M}^+$ ), 454, 398; HRMS  $\text{C}_{28}\text{H}_{18}\text{O}_{12}\text{Cr}_2$  calcd for 649.9609, found 649.9522.



**21**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.74 (s, 6H), 2.68 (s, 2H), 2.94 (s, 3H), 4.89 (s, 2H), 5.21 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.9, 25.8, 28.3, 49.7, 81.2, 118.1, 136.0, 216.6, 223.4, 357.6; IR (neat) 2064, 1929, 1739  $\text{cm}^{-1}$ ; MS  $m/z$  317 ( $\text{M}^+ - 1$ ), 287, 271; HRMS  $\text{C}_{13}\text{H}_{14}\text{O}_6\text{Cr}$  calcd for 318.0196, found 318.0145.

**22a**<sup>4</sup>: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.10 (s, 2H), 2.31 (s, 2H), 2.94 (s, 3H), 4.94-5.12 (m, 4H), 5.86 (s, 1H).

**22c**<sup>6</sup>: red oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.10 (s, 2H), 2.31 (s, 2H), 4.80 (s, 2H), 5.05-5.13 (m, 2H), 5.82 (s, 1H), 7.22 (s, 2H), 7.39 (s, 3H).

**23a**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.57 (s, 2H), 1.75 (s, 2H), 2.02 (s, 2H), 2.38 (s, 2H), 2.94 (s, 3H), 3.68 (s, 3H), 4.92 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.5, 25.5, 29.1, 33.8, 49.9, 51.6, 81.7, 173.9, 216.6, 223.4, 357.9; IR (neat) 2063, 1917, 1739  $\text{cm}^{-1}$ ; MS  $m/z$  364 ( $\text{M}^+$ ), 332, 308; HRMS  $\text{C}_{14}\text{H}_{16}\text{O}_8\text{Cr}$  calcd for 364.0250, found 364.0205.

**23b**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.91 (s, 3H), 1.34 (s, 2H), 1.45 (s, 2H), 1.55 (s, 2H), 1.75 (s, 2H), 2.01 (s, 2H), 2.37 (s, 2H), 3.29 (s, 2H), 3.68 (s, 3H), 4.98 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9, 22.4, 24.5, 25.5, 28.4, 29.2, 33.8, 51.6, 63.0, 81.6, 173.8, 216.5, 223.3, 360.9; IR (neat) 2054, 1919, 1737  $\text{cm}^{-1}$ ; MS  $m/z$  406 ( $\text{M}^+$ ), 350, 322.

**23c**: dark red oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.58 (s, 2H), 1.73 (s, 2H), 2.03 (s, 2H), 2.36 (s, 2H), 3.66 (s, 3H), 4.81 (s, 2H), 7.23 (s, 2H), 7.39 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.5, 25.5, 29.3, 33.8, 51.6, 80.8, 122.6, 128.2, 130.1, 153.7, 173.8, 216.2, 224.3, 349.4; IR (neat) 2058, 1928, 1738  $\text{cm}^{-1}$ ; MS  $m/z$  426 ( $\text{M}^+$ ), 370, 342.

**24**<sup>9</sup>: yellow solids; mp 40.5-41.0  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.90 (s, 3H), 4.68 (s, 3H); IR (KBr) 2072, 2002, 1928  $\text{cm}^{-1}$ ; MS  $m/z$  294 ( $\text{M}^+$ ), 266, 238.

**25**: yellow solids; mp 57.8-58.5  $^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.53 (d, J = 6.34 Hz, 6H), 2.85 (s, 3H), 5.67 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.2, 50.5, 89.2, 205.7, 213.5, 343.6; IR (KBr) 2066, 1957, 1916  $\text{cm}^{-1}$ ; MS  $m/z$  322 ( $\text{M}^+$ ), 294, 266.

**26**: orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.90 (t, J = 6.60 Hz, 3H), 1.30-1.38 (m, 8H), 1.46-1.52 (m, 2H), 1.97 (quintet, J = 7.08 Hz, 2H), 2.89 (s, 3H), 4.89 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.1, 22.7, 25.9, 29.3,

31.8, 50.2, 205.8, 213.4, 348.9; IR (neat) 2073, 1926  $\text{cm}^{-1}$ ; MS  $m/z$  392 ( $\text{M}^+$ ), 336, 308.

**27:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J = 6.84$  Hz, 3H), 2.94 (s, 3H), 3.61 (q,  $J = 7.00$  Hz, 2H), 3.95 (t,  $J = 4.40$  Hz, 2H), 5.00 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.1, 50.4, 67.0, 68.3, 82.8, 205.7, 213.3, 350.9; IR (neat) 2064, 1919  $\text{cm}^{-1}$ ; MS  $m/z$  352 ( $\text{M}^+$ ), 324, 296.

**28:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.37 (quintet,  $J = 6.47$  Hz, 2H), 2.63 (t,  $J = 7.08$  Hz, 2H), 2.94 (s, 3H), 4.99 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.5, 25.5, 50.4, 80.5, 118.4, 205.5, 213.1, 351.9; IR (neat) 2249, 2067, 1944  $\text{cm}^{-1}$ ; MS  $m/z$  347 ( $\text{M}^+$ ), 319, 291.

**29:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.44 (quintet,  $J = 6.11$  Hz, 2H), 2.91 (s, 3H), 3.74 (t,  $J = 6.35$  Hz, 2H), 5.03 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.0, 40.7, 50.3, 79.8, 205.6, 213.3, 351.9; IR ( $\text{CH}_2\text{Cl}_2$ ) 2070, 1981, 1947  $\text{cm}^{-1}$ ; MS  $m/z$  356 ( $\text{M}^+$ ,  $\text{Cl} = 35$ ), 328, 300.

**30:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.08 (quintet,  $J = 6.84$  Hz, 2H), 2.28 (q,  $J = 7.16$  Hz, 2H), 2.89 (s, 3H), 4.90 (br s, 2H), 5.06 (d,  $J = 9.28$  Hz, 1H), 5.10 (d,  $J = 16.1$  Hz, 1H), 5.85 (ddt,  $J = 17.1, 10.3, 6.78$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.4, 30.0, 50.2, 83.3, 116.1, 136.7, 205.8, 213.4, 349.4; IR (neat) 2066, 1923, 1643  $\text{cm}^{-1}$ ; MS  $m/z$  348 ( $\text{M}^+$ ), 292, 264.

**31:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.55 (quintet,  $J = 7.81$  Hz, 2H), 1.74 (quintet,  $J = 7.57$  Hz, 2H), 2.00 (quintet,  $J = 7.08$  Hz, 2H), 2.38 (t,  $J = 7.33$  Hz, 2H), 2.89 (s, 3H), 3.68 (s, 3H), 4.89 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.5, 25.5, 29.0, 33.8, 50.3, 51.6, 83.8, 173.8, 205.7, 213.3, 349.3; IR (neat) 2071, 1931, 1737  $\text{cm}^{-1}$ ; MS  $m/z$  410 ( $\text{M}^+$ ), 354, 326.

**32:** yellow needles; mp 52.3-53.0  $^{\circ}\text{C}$  [lit.<sup>13</sup> mp 52  $^{\circ}\text{C}$ ];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.89 (s, 3H), 4.59 (s, 3H).

**33:** yellow needles; mp 67.1-67.8  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.52 (d,  $J = 6.34$  Hz, 6H), 2.86 (s, 3H), 5.60-5.67 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.2, 52.6, 89.9, 197.1, 203.5, 325.5; IR (KBr) 2064, 1908  $\text{cm}^{-1}$ ; MS  $m/z$  410 ( $\text{M}^+$ ), 365, 337.

**34:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J = 6.84$  Hz, 3H), 2.92

(s, 3H), 3.61 (q,  $J = 7.00$  Hz, 2H), 3.94 (t,  $J = 4.64$  Hz, 2H), 4.90 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.1, 52.5, 67.0, 68.2, 83.5, 197.3, 203.5, 332.0; IR (neat) 2063, 1911  $\text{cm}^{-1}$ ; MS  $m/z$  440 ( $\text{M}^+$ ), 412, 384.

**35:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.35 (quintet,  $J = 6.47$  Hz, 2H), 2.62 (t,  $J = 6.84$  Hz, 2H), 2.90 (s, 3H), 4.88 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.5, 25.3, 52.3, 81.3, 118.4, 197.0, 203.4, 332.5; IR (neat) 2251, 2071, 1921  $\text{cm}^{-1}$ ; MS  $m/z$  435 ( $\text{M}^+$ ), 407, 379.

**36:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.44 (quintet,  $J = 6.11$  Hz, 2H), 2.89 (s, 3H), 3.75 (t,  $J = 6.11$  Hz, 2H), 4.93 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.9, 40.7, 52.3, 80.5, 197.1, 203.5, 331.8; IR (neat) 2069, 1912  $\text{cm}^{-1}$ ; MS  $m/z$  444 ( $\text{M}^+$ ,  $\text{Cl} = 35$ ), 416, 388.

**37:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.08 (quintet,  $J = 6.84$  Hz, 2H), 2.28 (q,  $J = 7.00$  Hz, 2H), 2.88 (s, 3H), 4.80 (br s, 2H), 5.05-5.12 (m, 2H), 5.84 (ddt,  $J = 17.1, 10.3, 6.65$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.2, 30.0, 52.3, 84.0, 116.1, 136.7, 197.3, 203.5, 330.7; IR (neat) 2058, 1906, 1638  $\text{cm}^{-1}$ ; MS  $m/z$  436 ( $\text{M}^+$ ), 380, 352.

**38:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.13 (br s, 1H), 2.23 (quintet,  $J = 6.11$  Hz, 2H), 2.89 (s, 3H), 3.88 (t,  $J = 6.10$  Hz, 2H), 4.93 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.9, 52.3, 58.9, 81.4, 197.3, 203.6, 331.0; IR (neat) 3100-3500, 2071, 1909  $\text{cm}^{-1}$ ; MS  $m/z$  426 ( $\text{M}^+$ ), 398, 370.

**39:** orange oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.52-1.58 (m, 2H), 1.74 (quintet,  $J = 7.57$  Hz, 2H), 1.99 (quintet,  $J = 7.08$  Hz, 2H), 2.37 (t,  $J = 7.32$  Hz, 2H), 2.88 (s, 3H), 3.68 (s, 3H), 4.80 (br s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.5, 25.5, 28.9, 33.8, 51.6, 52.3, 84.5, 173.8, 197.3, 203.5, 330.6; IR (neat) 2065, 1912, 1739  $\text{cm}^{-1}$ ; MS  $m/z$  496 ( $\text{M}^+$ ), 440, 412.

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## Summary

The author studied the utilization of alkylsulfonium salts as alkylating reagents in organic synthesis and developed useful synthetic methods of macrocyclic lactones and Fischer-type (alkoxy)carbene complexes using sulfonium salts.

(1) The intramolecular cyclization of ( $\omega$ -carboxyalkyl)diphenylsulfonium salts under weakly basic and high-dilution conditions gave macrocyclic lactones in high yields. An important characteristic of this reaction is that 9-, 12-, and 13-membered lactones, which were not obtained effectively by conventional methods, were afforded in better yields.

(2) A convenient synthetic method of macrocyclic thialactones was developed. ( $\omega$ -Carboxyalkyl)thiolanium salts reacted intramolecularly to afford macrocyclic thialactones in good yields *via* ring-expansion process. It was found that the ring strain of five-membered ring in ( $\omega$ -carboxyalkyl)thiolanium salts resulted in the selective formation of thialactones.

(3) ( $\omega$ -Carboxyalkyl)diphenylsulfonium salts containing an ester linkage cyclized readily to produce head-to-head type macrocyclic dilactones in good yields. This cyclization methodology is applicable to the synthesis of 13,13-dimethyl-1,2-didehydrocrotalanine, naturally

occurring (+)-dicrotaline analog containing an 11-membered dilactonic skeleton.

(4) In this lactonization reaction, it is presumed that intramolecularly electrostatic interaction between the carboxylate ion and the sulfonium cation of ( $\omega$ -carboxyalkyl)sulfonium salts plays an important role. The reaction mechanism was estimated to proceed *via* S-O sulfurane intermediate on the basis of stereochemistry of the resulting lactone with 80% inversion of configuration from ( $\omega$ -carboxyalkyl)sulfonium salts having an optically active secondary carbon atom.

(5) A new and general method for preparing Fischer-type chromium, molybdenum, and tungsten (alkoxy)carbene complexes utilizing alkyl diphenylsulfonium salts was developed. The use of sulfonium salts as an alkylating reagent made it possible to introduce functionalized alkyl groups such as secondary carbon, ether, nitrile, ester, halide, alcohol, and unsaturated linkages to (alkoxy)carbene complexes.

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