Stereoselective Synthesis of δ-Lactones from 5-Oxoalkanals via One-Pot Sequential Acetalization, Tishchenko Reaction, and Lactonization by Cooperative Catalysis of Samarium Ion and Mercaptan

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By the synergistic catalysis of samarium ion and mercaptan, a series of 5-oxoalkanals was converted to (substituted) δ-lactones in efficient and stereoselective manners. This one-pot procedure comprises a sequence of acetalization, Tishchenko reaction and lactonization. The deliberative use of mercaptan, by comparison with alcohol, is advantageous to facilitate the catalytic cycle. The reaction mechanism and stereochemistry are proposed and supported by some experimental evidence. Such samarium ion/mercaptan cocatalyzed reactions show the feature of remote control, which is applicable to the asymmetric synthesis of optically active δ-lactones. This study also demonstrates the synthesis of two insect pheromones, (2*S*,5*R*)-2-methylhexanolide and (*R*)-hexadecanolide, as examples of a new protocol for asymmetric reduction of long-chain aliphatic ketones.

Introduction

Lanthanoid reagents have been widely utilized in organic synthesis.[1] SmI_2 can function as a one-electron reducing agent,[2] and both SmI_2 and SmI_3 can function as Lewis acids to promote a variety of reactions, such as aldol reactions,[3] Diels−Alder reactions,[4] Meerwein reductions,[5] oxirane rearrangements,[6] Tishchenko reactions,[3b,7] and sequential aldol-acetalization-Tishchenko reactions.[3c,7] Uenishi and co-workers[8] have demonstrated that 5-oxo-4-silyloxyhexanals can undergo the intramolecular Tishchenko oxidoreductions on treatment with stoichiometric amounts of (*t*-BuO)SmI_2 or aged SmI_2 solution (presumably containing Sm^{3+} ion), followed by in situ cyclizations, to give the corresponding δ-lactones. They also indicate that the silyloxy substituent is essential for such transformation. Otherwise, an unsubstituted substrate like 5-oxohexanal affords only a low yield (∼10%) of δ-methyl-δ-lactone on treatment with (*t*-BuO)SmI_2, or simply the pinacolic coupling product on treatment with freshly prepared SmI_2 solution. Iadonisi and co-workers[9] have employed (*t*-BuO)SmI_2 (2.5 equiv) to promote the Tishchenko reactions of hexos-5-uloses to give the *tert*-butyl esters of aldonic acids, which were subsequently converted into the corresponding sugar lactones. By using stoichiometric amounts of SmI_2 as the Lewis acid promoter, we have converted 5-trimethylsilyl-5-oxopentanal to δ-trimethylsilyl-δ-lactone in the presence of MeOH (Figure 1).[3b]

The above-mentioned reactions[3b,8,9] are presumably initiated by addition of ROH (or RO^-) to the aldehyde group to form a hemiacetal with the assistance of samarium ion as depicted in Figure 1. An intramolecular hydride transfer to the ketone group (Tishchenko reaction) occurs via a rigid chelate transition state.[3c,7] The δ-oxyester intermediate can proceed with an in situ cyclization in appropriate cases to give the observed δ-lactone product. Along this line, we considered that using mercaptan RSH to replace alcohol ROH would be advantageous. RSH would be a better nucleophile than ROH on addition to the aldehyde group of 5-oxopentanals, and the resulting thioester intermediates would also be more reactive than esters in the subsequent lactonizations. We thus set out a detailed study of such one-pot sequential acetalization, Tishchenko reaction, and lactonization by the promotion of samarium ions and mercaptans. The effects of substrates, nucleophiles,

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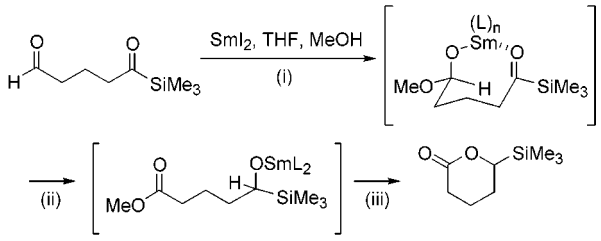
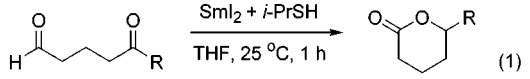


Figure 1. Samarium ion promoted formation of δ-lactone from 5-oxo-5-silylpentanal: (i) acetalization, (ii) Tishchenko reaction, and (iii) lactonization.

catalysts, and reaction conditions would be examined. In a preliminary report,[10] we have utilized SmI_2 and 2-propanethiol (*i*-PrSH) as the combined catalysts to convert 5-oxopentanals into their corresponding δ-lactones. (eq 1). Our ultimate goal is to devise a catalytic method for



(1)

the synthesis of optically active δ-lactones, which often occur in nature or as parts of natural products.[11]

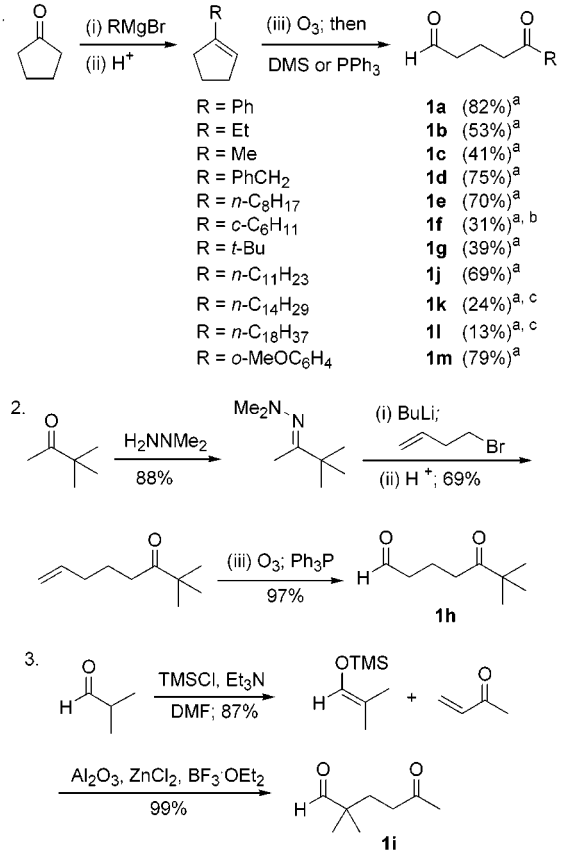
Results and Discussion

Preparations and Reactions of 5-Oxoalkanals. A series of 5-oxoalkanals **1a**−**g** and **1j**−**m** were prepared from cyclopentanone by a three-step sequence[12] (Scheme 1): (i) addition of Grignard reagents, (ii) dehydration, and (iii) ozonolysis. 6,6-Dimethyl-5-oxoheptanal (**1h**) was prepared by alkylation of the *N*,*N*-dimethylhydrazone of 3,3-dimethyl-2-butanone, followed by ozonolysis.[13] Alternatively, the silyl enol ether of isobutyraldehyde underwent a Michael addition with methyl vinyl ketone to give 2,2-dimethyl-5-oxohexanal (**1i**).[14] We found that this reaction was facilitated by using $BF_3.OEt_2$ as the promoter in addition to Al_2O_3−$ZnCl_2$.

Using 5-oxo-5-phenylpentanal (**1a**) as a model substrate, its reactions with SmI_2 in the presence of *i*-PrOH or *i*-PrSH were investigated (Table 1). In the presence of 50 mol % of SmI_2 and 50 mol % of *i*-PrOH, the tandem acetalization-Tishchenko reaction gave a 36% yield of isopropyl 5-hydroxy-5-phenylpentanoate. The subsequent lactonization did not occur under such reaction conditions (25 °C, 30 min). However, a dramatic increase of the δ-lactone product **2a** (53% yield) was obtained when *i*-PrSH was introduced to the reaction media (entry 2, Table 1). Moreover, a quantitative yield of lactone **2a** was procured when **1a** was stirred with SmI_2 (50 mol %) and *i*-PrSH (40 mol %) at room temperature for 30 min (entry 3, Table 1).

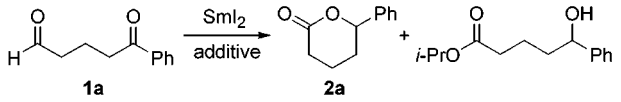
A quantitative yield of lactone **2a** was also obtained by using smaller amounts of promoters, 20 mol % of SmI_2, and 10 mol % of *i*-PrSH (entry 4, Table 1). The representative procedure is described in the Experimental Section (method D). No aldol or pinacol products were observed in such reaction conditions. However, using 10 mol % of SmI_2 only provided a low yield of the desired product (entries 5 and 6, Table 1). SmI_2 or *i*-PrSH alone did not promote the formation of lactone **2a**.

Scheme 1. Preparation of 5-Oxoalkanals 1a−m



(a) The overall yield of three steps. (b) The yield of **1f** was low because the dehydration step also gave a side product of benzylidenecyclopentane. (c) Because the alkene precursors were partially soluble in CH_2Cl_2 on ozonolysis, significant amounts of alkenes were also recovered.

Table 1. Reactions of 5-Oxo-5-phenylpentanal (1a) Promoted by SmI_2 in the Presence of *i*-PrSH or *i*-PrOH (THF, 25 °C, 30 min)



entry	mol % of SmI_2	additive (mol %)	yield (%) of **2a**
1	50	*i*-PrOH (50)	*a*
2	50	*i*-PrOH (50) + *i*-PrSH (50)	53[b,c]
3	50	*i*-PrSH (40)	99[b]
4	20	*i*-PrSH (10)	100[b]
5	10	*i*-PrSH (20)	27[b]
6	10	*i*-PrSH (5)	0

[a] This reaction gave 36% yield of isopropyl 5-hydroxy-5-phenylpentanoate. [b] The yield was estimated by ^1H NMR analysis of the crude product mixture. [c] This reaction also gave 3% yield of isopropyl 5-hydroxy-5-phenylpentanoate.

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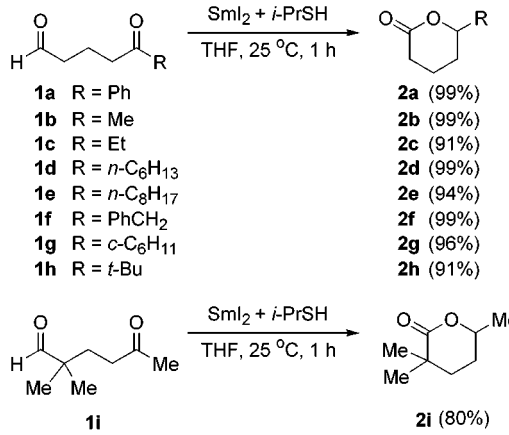
(13) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3. (b) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362. (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
(14) (a) Amice, P.; Blanco, L.; Conia, J. M. *Synthesis* **1976**, 197. (b) Ranu, B. C.; Saha, M.; Bhar, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2701. (c) Ranu, B. C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* **1993**, *34*, 1989.

Scheme 2. Conversion of 5-Alkyl- and 5-Phenyl-5-oxopentanals to δ-Lactones by Using the Premixing and Reinjection Procedure



To our surprise, only a small portion (<10%) of 5-alkyl-5-oxopentanals **1b**−**h** could be converted into their corresponding δ-substituted-δ-lactones **2b**−**h** by using the above-mentioned procedure with SmI_2 and *i*-PrSH as the promoters. This discrepancy might be attributable to the lower reactivity of aliphatic ketones (e.g., **1b**−**h**) by comparison with aromatic ketones (e.g., **1a**). Fortunately, we found that a slightly modified procedure, premixing and re-injection (method E in Experimental Section), could lead to efficient formations of lactones **2b**−**h** (Scheme 2). Thus, an aliquot of SmI_2/*i*-PrSH (1−5 mol % in 1 mL of THF) was premixed with the substrate (**1b**−**h**) in an oven-dried syringe. The resulting yellow solution, an indicator of trivalent samarium ion, was then added dropwise to the original SmI_2/*i*-PrSH (50/40 mol %) solution in THF (14 mL). Accordingly, the desired lactones **2b**−**h** were obtained in excellent yields (>90%). This modified procedure was also suitable for the transformation of aromatic ketone **1a** into lactone **2a**. Even the sterically demanding aldehyde **1i** was also successfully converted to lactone **2i** in 80% yield.

It was noted that lactone **2i** would not be prepared by Baeyer−Villiger oxidation of 2,2,5-trimethylcyclopentanone due to the incompatible regiochemistry.[15] When 5-oxotridecanal (**1e**) was treated with stoichiometric amounts of SmI_2 and *i*-PrOH, both Tishchenko oxidoreduction and intramolecular pinacolic coupling occurred to give a mixture of isopropyl 5-hydroxytridecanoate and 1-octyl-1,2-cyclopentanediol in a ratio of 1:1. No lactone **2e** was formed in the absence of mercaptan.

Reaction mechanism. On the basis of the above experimental results, one can propose a possible reaction mechanism for the formation of δ-lactones (Figure 2). A Lewis acid such as the presumed (*i*-PrS)SmI_2 or the related samarium species[16] can promote the addition of *i*-PrSH to the aldehyde group of a 5-oxopentanal substrate. The samarium-bound hemithioacetal intermediate (**A**) can undergo an intramolecular hydride shift to give the intermediate of δ-oxyacid thioester (**B**). The reaction would proceed further with an irreversible lactonization, and release the catalyst (*i*-PrS)SmI_2 (or the related samarium species) for the next cycle. *The deliberative use of mercaptan is proved to facilitate the catalytic cycle, due to its strong nucleophilicity toward aldehyde and the high aptitude of the thioester intermediate toward lactonization.*

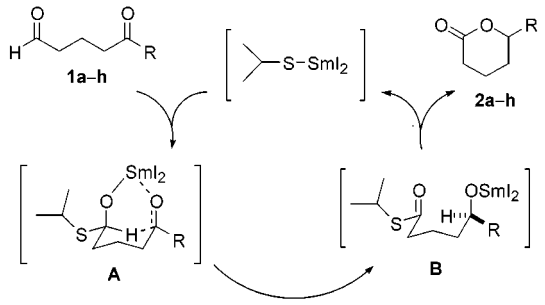


Figure 2. A proposed catalytic cycle for the formation of δ-lactones.

Table 2. Transformation of 5-Oxo-5-phenylpentanal (1a) and 5-Oxotridecanal (1e) into Lactones 2a and 2e by Using SmI_2 and Disulfide (THF, 25 °C, 1 h)

entry	substrate	mol % of SmI_2	disulfide (mol %)	product (yield, %)
1	**1a**	42	$(PhS)_2$ (20)	**2a** (100)
2	**1a**	12	$(PhS)_2$ (5)	**2a** (100)
3	**1a**	42	$(MeS)_2$ (20)	**2a** (67)
4	**1a**	42	$(i\text{-PrS})_2$ (20)	**2a** (68)
5	**1e**	42	$(PhS)_2$ (20)	**2e** (100)
6	**1e**	85	$(MeS)_2$ (40)	**2e** (87)
7	**1e**	42	$(i\text{-PrS})_2$ (20)	**2e** (56)

It is known that SmI_2 can cleave the S−S bond of diphenyl disulfide.[17] Indeed, by replacing SmI_2/*i*-PhSH with $SmI_2/(PhS)_2$, the reactions of oxoalkanals **1a** and **1e** also proceeded smoothly to give lactones **2a** and **2e** in quantitative yields (entries 1 and 5, Table 2). When $(MeS)_2$ or $(i\text{-PrS})_2$ were used instead of $(PhS)_2$, lactones **2a** and **2e** were obtained in modest yields (56−87%, entries 3, 4, 6, and 7, Table 2). This trend was consistent with the higher reactivity of diphenyl disulfide toward SmI_2 than dialkyl disulfides. The combination of SmI_3 (20 mol %) and PhSLi (20 mol %), instead of SmI_2 and mercaptan, was also utilized to promote the transformation of oxopentanal **1a** into lactone **2a** (99% yield) in an expedient manner. These experiments support that the in situ generated (RS)SmI_2 or the related species actually plays a role as a reactive catalyst to facilitate the sequence of acetalization, Tishchenko reaction and lactonization. The protocol using the solid reagent of $(PhS)_2$ to replace the odoriferous reagent *i*-PrSH also makes this method more attractive. A quantitative yield of lactone **2a** was also achieved by using even less amounts of promoters, SmI_2 (12 mol %), and $(PhS)_2$ (5 mol %) (entry 2, Table 2). By comparison, the conventional route to δ-lactones often requires excess amounts of oxidizing and reducing agents to convert 5-oxoalkanals into 5-hydroxyalkanoic acid for the subsequent lactonization. *From the point of atom economy, our method using catalytic amounts of samarium ion and mercaptan to effect the intramolecular oxidoreduction of 5-oxoalkanals appears to surpass the conventional methods of δ-lactone formation.*

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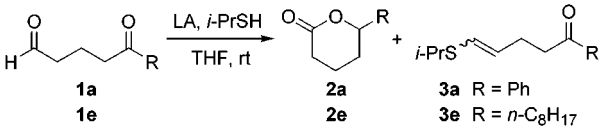
(16) It has been reported (ref 7a) that SmI_2 reacts with alcohol ROH to give (RO)SmI_2 in the presence of a metallic salt as the electron carrier.

(17) (a) Jia, X.; Zhang, Y.; Zhou, X. *Synth. Commun.* **1994**, *24*, 387. (b) Chen, R.; Zhang, Y. *Synth. Commun.* **1999**, *29*, 3699. It has been reported that disulfide RS-SR is reduced by Sm to give $(RS)_3Sm$ by the catalysis of Ph_2CO. See (c) Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett.* **1994**, *35*, 7789.

Table 3. Comparison of Different Lewis Acids in the Reactions of 5-Oxo-5-phenylpentanal (1a) and 5-Oxotridecanal (1e)



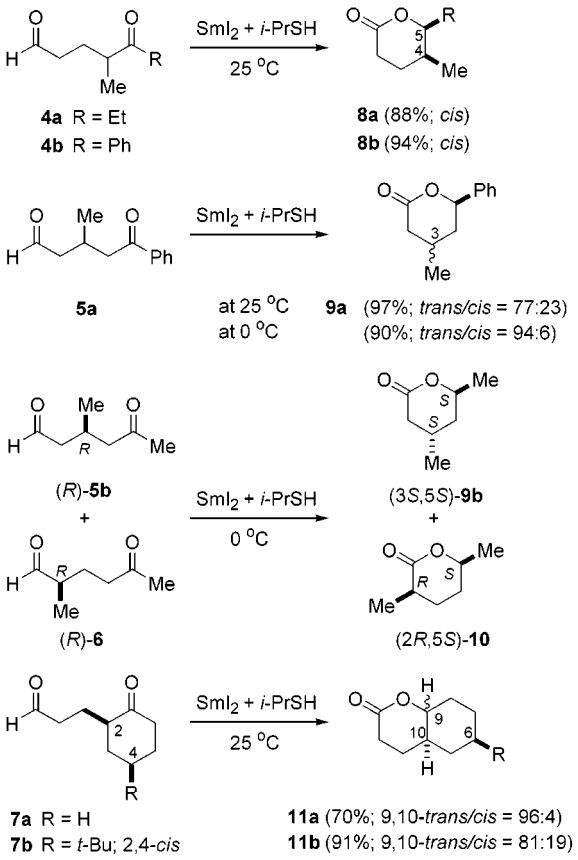
entry	substrate	Lewis acid (mol %)	mol % of *i*-PrSH	products (yield, %)
1	**1a**	SmI_2 (50)	40	**2a** (99)
2	**1a**	SmI_3 (110)	100	**3a** (85)[a]
3	**1a**	SmI_3 (10)	100	**3a** (75)[a]
4	**1a**	SmI_2 (25)/SmI_3 (25)	20	**2a** (67)
5	**1a**	SmI_2 (50)/SmI_3 (25)	20	**2a** (99)
6	**1a**	SmF_3 (20)	50	*b*
7	**1a**	$SmCl_3$ (20)	50	*b*
8	**1a**	$SmBr_3$ (20)	50	*b*
9	**1a**	$Sm(OAc)_3$ (20)	50	*b*
10	**1a**	$Sm(OTf)_3$ (20)	50	*b*
11	**1a**	Sm(*i*-PrO)$_3$ (20)	50	*b*
12	**1a**	Al(*i*-PrO)$_3$ (20)	50	*b*
13	**1a**	Ti(*i*-PrO)$_3$ (20)	50	*b*
14	**1e**	SmI_2 (50)	40	**2e** (94)
15	**1e**	SmI_3 (110)	100	**3e** (87)[a]
16	**1e**	SmI_3 (10)	100	**3e** (79)[a]

[a] The product **3a** (or **3e**) existed as a mixture of two geometric isomers (cis/trans = 1:1). [b] No compounds **2a** or **3a** were obtained.

Although evidence indicated that SmI_2 was actually a pre-catalyst to generate the corresponding trivalent samarium species as the real Lewis acid catalyst.[3−9] However, some studies (Table 3) also showed that the direct introduction of trivalent samarium species did not reach the same results as that using SmI_2 precatalyst. For example, treatment of **1a** with stoichiometric amounts of SmI_3 and *i*-PrSH gave thioenol ether **3a** (85% yield) but not lactone **2a** (entry 2, Table 3). When the amount of SmI_3 was decreased to 10 mol %, compound **3a** was still obtained in 75% yield in the presence of *i*-PrSH (entry 3, Table 3). The yields of **3a** changed as different amounts of *i*-PrSH were used. By using 20 and 40 mol % of *i*-PrSH along with SmI_3, oxopentanal **1a** was converted to thioenol ether **3a** in 18 and 38% yields, respectively. A variety of Lewis acids were also examined (entries 6−13, Table 3). However, neither SmF_3, $SmCl_3$, $SmBr_3$, $Sm(OAc)_3$, $Sm(OTf)_3$, Sm(*i*-PrO)$_3$, Al(*i*-PrO)$_3$, nor Ti(*i*-PrO)$_4$ could convert oxopentanal **1a** to lactone **2a** or thioenol ether **3a**. We speculated that SmI_3 underwent an ligand exchange with *i*-PrSH to produce the strong acid HI, which would promote the subsequent dehydration (a diverted elimination process of intermediate **A** in Figure 2).[18] Oxopentanal **1a** remained unchanged when an equimolar amount of Et_3N or 1,8-bis(dimethylamino)-naphthalene (Proton-Sponge) was added to the media of SmI_3/*i*-PrSH.

When the reaction of **1a** was conducted in the media containing both SmI_2 and SmI_3, the formation of lactone **2a** promoted by SmI_2 dominated over the formation of thioenol ether **3a** promoted by SmI_3 (entries 4 and 5, Table 3). The reactions of 5-oxotridecanal (**1e**) afforded lactone **2e** by the catalysis of SmI_2/*i*-PrSH (entry 14, Table 3) and produced thioenol ether **3e** in the presence of SmI_3/*i*-PrSH (entries 15 and 16, Table 3).

Scheme 3. Stereoselective Sequential Acetalization, Tishchenko Reaction, and Lactonization



Stereochemistry. To know the stereochemistry in formation of substituted δ-lactones, we synthesized the 2-, 3-, and 4-methyl-5-oxoalkanals and examined their SmI_2/*i*-PrSH promoted reactions (Scheme 3). Compounds **4a**,**b**, **5a**, and **7a**,**b** were prepared via their hydrazone derivatives according to the procedure used for **1h** (Scheme 1).[13] Thus, the hydrazones of 3-pentanone and propiophenone were alkylated with 4-bromo-1-butene, followed by ozonolysis, to give the 4-methyl-5-oxoaldehydes **4a** and **4b**. The hydrazone of acetophenone was alkylated with 2-(2-iodopropyl)-1,3-dioxolane, followed by acid-catalyzed hydrolysis, to give 3-methyl-5-oxo-5-phenylpentanal (**5a**). The cyclic compounds **7a** and **7b** were similarly prepared from the hydrazone of cyclohexanone and 4-*tert*-butylcyclohexanone via alkylation with 2-(2-iodoethyl)-1,3-dioxolane and hydrolysis.

The SmI_2/*i*-PrSH-catalyzed reactions of substituted oxoalkanals occurred in a highly stereoselective manner. Lactones **8a**,**b**,[19,20] derived from 4-methyl-5-oxopentanals **4a**,**b**, had a cis configuration as indicated by a small coupling constant (3 Hz) between H-4 and H-5. Treatment of 3-methyl-5-oxo-5-phenylpentanal (**5a**) with SmI_2/*i*-PrSH at 25 °C in THF solution gave lactone **9a** as a mixture of trans and cis isomers (77:23).[21] The trans/cis isomeric ratio was increased to 94:6 by performing the

(18) Condensation of carbonyl compounds with mercaptans has been achieved by the promotion of $TiCl_4/Et_3N$ to give thioenol ethers. See (a) Mukaiyama, T.; Saigo, K. *Chem. Lett.* **1973**, 479. There is no previous report on the formation of thioenol ethers by using SmI_3 as the promoter. In our preliminary report (ref 10), we wrongly assigned the structures of **3a** and **3e** as isopropyl thioesters of 5-phenylpent-4-enoic acid and tridec-4-enoic acid.

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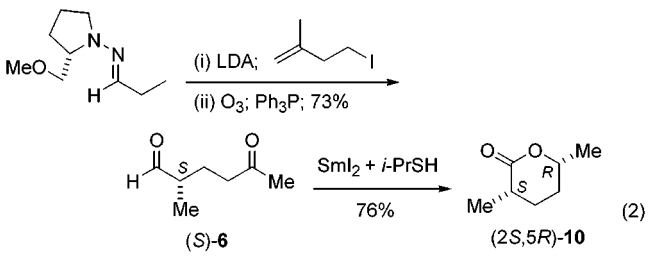
reaction at 0 °C. The trans lactone showed an NOE correlation between Me-3 and H-5, whereas the cis isomer was devoid of this effect. The SmI_2/*i*-PrSH-catalyzed reactions of 2-(3-oxopropyl)cyclohexanones **7a**,**b** at 25 °C afforded 1-oxa-2-decalones **11a**,**b** in preponderance of the 9,10-trans isomers.[22,23] The trans decalones had H-9 and H-10 on axial positions as characterized by the ddd splitting pattern (J = 10, 10, 4 Hz) of H-9 in the ^{1}H NMR spectra.

An inseparable mixture (1:1) of (*R*)-3-methyl-5-oxohexanal [(*R*)-**5b**] and (*R*)-2-methyl-5-oxohexanal [(*R*)-**6**] was prepared from (*R*)-3-methylcyclopentanone by a three-step sequence similar to that for **1b** (Scheme 1). Thus, the addition reaction with MeMgCl, followed by acid-catalyzed dehydration afforded a mixture of 1,3-dimethylcyclopentene and 1,4-dimethylcyclopentene, which was subjected to ozonolysis to give (*R*)-**5b** and (*R*)-**6**. Treatment of the mixture of (*R*)-**5b** and (*R*)-**6** (1:1) with SmI_2 (50 mol %) and *i*-PrSH (40 mol %) at 0 °C gave a mixture of lactones (3*S*,5*S*)-**9b** and (2*R*,5*S*)-**10** (1:1) according to the ^{1}H NMR analysis. The analytic samples of lactones (3*S*,5*S*)-**9b** and (2*R*,5*S*)-**10** were isolated by HPLC, and their optical rotations were in agreement with the reported values.[24,25] The enantiomer of lactone (2*R*,5*S*)-**10** is a pheromone of carpenter bee (*Xylocopa hirsutissima*).[25]

The stereochemical outcomes can be interpreted by comparisons of the transition states **C** versus **D** and **E** versus **F**. Transition state **C**, giving *cis*-**8a**,**b**, *trans*-**9a**,**b**, and *cis*-**10** is energetically favored due to the equatorial dispositions of substituents (R^2, R^3, and R^4), whereas the alternative transition state **D** exerts steric repulsions due to the axially oriented substituents. Transition state **E**, giving *trans*-**11a**,**b**, having hydride attack the cyclohexanone moiety from the axial direction is superior to an equatorial attack in the transition state **F**. Many previous studies support that axial H^- delivery to cyclohexanones is a kinetically favored process.[3d] Under such circumstances, product development control also favors formation of the more stable equatorial alcohol (as shown in **E**). The stereoselectivities are in agreement with the previous findings[3d,7c] of the related intermolecular Tishchenko reactions.

Synthesis of optically Active δ-Lactones. For the synthesis of optically active δ-lactones, many methods rely on obtaining chiral 5-hydroxyalkanoic acids or derivatives as the requisite starting materials. The asymmetric synthesis of δ-alkyl-δ-lactones, as those found in nature as sex pheromones, has extra difficulties in obtaining long-chain aliphatic precursors with chiral carbinyl centers. A general approach to δ-alkyl-δ-lactones utilizes the natural source of chiral alcohols, which are elaborated (often in a lengthy sequence) to reach the target molecules. For example,[25a] (*S*)-lactate and (*R*)-β-hydroxyisobutyrate have been used to synthesize a sex pheromone, (2*S*,5*R*)-2-hexanolide (**10**), in a ten-step sequence. Chemical resolution of alcohols, by derivatization and chromatographic separation, has provided an alternative source of optically active 5-hydroxy-6-hexadecynenitrile,[26] which is further elaborated to a pheromone of Oriental hornet (*Vespa orientalis*), (*R*)-5-hexadecanolide (**2j**). Although asymmetric reduction[27] of phenones and the ketones with adjuvant groups (e.g., α-methoxyketones and β-ketoesters) has advanced in this decade, the highly enantioselective reduction of unsubstituted long-chain aliphatic ketones remains a challenging task.[28] Microbial reduction (e.g., using bakers' yeast)[29] has shown some success in this aspect, but it is still limited by low yielding and substrate specificity.

As to the samarium ion catalyzed reactions, we synthesized many optically active δ-lactones via three routes: (i) using chiral 5-oxoalkanals such as (*S*)-**6**, (ii) using stoichiometric amount of chiral alcohols to react with 5-oxoalkanals, and (iii) using catalytic amount of chiral mercaptan to promote the conversion of 5-oxoalkanals. *All three methods showed a common feature of remote control to establish the chirality of carbinyl center at C-5*.



(2)

To prepare (*S*)-2-methyl-5-oxohexanal (**6**), propionaldehyde was condensed with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)[30] to give a chiral hydrazone (eq 2). Alkylation of such hydrazone with 4-iodo-2-methyl-1-butene, followed by ozonolysis, thus occurred in a highly stereoselective fashion to give (*S*)-**6**. Treatment of (*S*)-**6** with SmI_2 (50 mol %) and *i*-PrSH (40 mol %) afforded (2*S*,5*R*)-2-methylhexanolide (**10**) exclusively. The melting point (40−42 °C) and optical rotation ($[\alpha]_D$ +63.5) were in agreement with the values reported for the natural product.[25] The stereochemistry was consistent with the mirror image of transition state **C** (Figure 3), in which $R = R^2 = Me$ and $R^3 = R^4 = H$. The preferable equatorial

(21) Barbero, A.; Blakemore, D. C.; Fleming, I.; Wesley, R. N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1329.

(22) (a) Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **1999**, *10*, 1243. (b) Griffiths, D. V.; Wilcox, G. *J. Chem. Soc., Perkin Trans. 2* **1988**, 431. (c) Chandrasekhar, S.; Venkatesan, V. *J. Chem. Research (M)*, **1995**, 1137. It has been reported (ref 22c) that 2-(3-oxopropyl)cyclohexanone (**7a**) underwent an intramolecular Cannizzaro reaction in boiling NaOH solution (3 M) to give 3-(2-hydroxycyclohexyl)propionic acid, which was subjected to lactonization on treatment with concentrated HCl to give exclusively the trans isomer of **11a** (59%), based on an analysis of the ^{1}H NMR spectrum (90 MHz). In our hand, the two-step reaction afforded a *trans*/*cis* mixture of **11a** in a ratio of 91:9 based on an analysis of the ^{1}H NMR spectrum (300 MHz).

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(24) Carroll, F. J.; Meck, R. *Synth. Commun.* **1971**, 169. Carroll, F. J.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890.

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(30) (a) Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth.* **1987**, *65*, 183. (b) Enders, D.; Bockstiegel, B. *Synthesis* **1989**, *7*, 493.

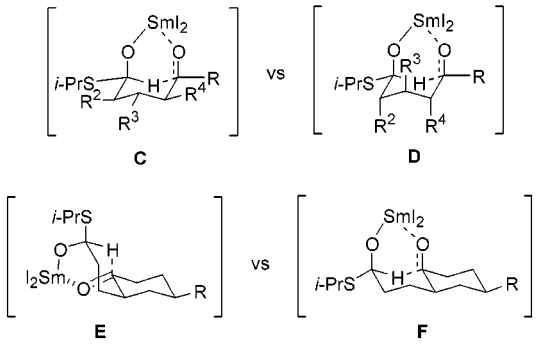
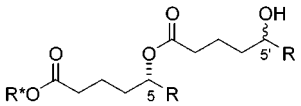


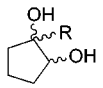
Figure 3. Transition states in the SmI_2/*i*-PrSH promoted reactions of substituted 5-oxoalkanals **4a**−**7b**. Transition state **C** having equatorial substituents is favored over transition state **D** having axial substituents. Transition state **E** with hydride transfer to the axial positions of cyclohexanones is favored over transition state **F** with hydride transfer to the equatorial positions of cyclohexanones.

orientation of R^2 group at C-2 determined the newly generated stereocenter at C-5 in a sense of remote control.

As shown in Table 4, the reaction of oxopentanal **1a** with (−)-menthol (110 mol %) was promoted by SmI_2 (100 mol %) to give the desired 5-hydroxy ester **12a** (61%), along with diester **13a** (31%) and pinacol **14a** (8%). The



13a R = Ph, R* = menthyl
13b R = Ph, R* = 8-Ph-menthyl
13c R = Ph, R* = neomenthyl
13e R = n-C_8H_{17}, R* = menthyl



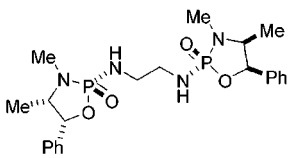
14a R = Ph
14e R = n-C_8H_{17}

hydroxyester **12a** was saponified and treated with acid to give lactone **2a** with predominance of the (*S*)-enantiomer (84% ee) as determined by HPLC analysis on a Chiralcel OB column.[31] The diastereomeric excess of hydroxyester **12a** was deduced to be 84% by analogy to that of lactone **2a**, although our primary examination of **12a** with 300 MHz NMR or HPLC analyses could not tell the difference of two diastereomers. Diester **13a** could be derived either by transesterification between two molecules of hydroxyester **12a**, or by the second acetalization-Tishcheko reaction of oxopentanal **1a** with hydroxyester **12a**. A clue was found by the following experiment. In the presence of SmI_2, oxopentanal **1a** (84% ee) was treated with an equimolar amount of hydroxyester **12a** in THF at room temperature for 30 min to give a mixture of **12a** (45%), **13a** (35%), and **2a** (20%). The mixture was then treated with trifluoroacetic acid in CH_2Cl_2 to give lactone **2a** (87% overall yield) with 72% ee in favor of the (*S*)-enantiomer. The ee value should keep unchanged if diester **13a** were formed by transesterification of two molecules of hydroxyester **12a**. As the ee values varied, oxopentanal **1a** and hydroxyester **12a** likely underwent the tandem acetalization-Tishchenko reaction to give **13a** with a predominance of the (5*S*,5′*R*) isomer. The subsequent lactonization would give both (*S*)- and (*R*)-enantiomers of **2a**, causing the ee value lower than 84%. It appeared that (−)-menthol with (*R*)-chirality at the carbinyl center directed the (*S*)-chirality in hydroxyester **12a**, whereas hydroxyester **12a** with (*S*)-chirality guided the (5′*R*)-chirality in diester **13a**.

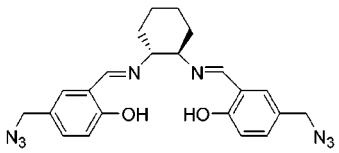
By the promotion of SmI_2, oxopentanal **1a** reacted with (−)-8-phenylmenthol to give hydroxyester **12b** (48% yield), which was subsequently converted to lactone **2a** with 72% ee in favor of the (*S*)-enantiomer. The reaction of **1a** with (+)-neomenthol gave a low yield (4%) of hydroxyester **12c** with decreasing stereoselectivity as deduced by its conversion to lactone **2a** of 21% ee (entry 3, Table 4). To avoid the complication of pinacolic coupling reactions, oxopentanal **1a** was treated with SmI_3 (20 mol %) and (−)-menthol (100 mol %) in refluxing THF for 1 h (entry 4, Table 4). The crude product mixture was subsequently treated with trifluoroacetic acid in CH_2Cl_2 to give lactone **2a** (65% overall yield) with 78% ee in favor of the (*S*)-enantiomer.

The SmI_2-promoted reaction of 5-oxotridecanal (**1e**) with (−)-menthol afforded hydroxyester **12e** (51%), diester **13e** (20%), pinacol **14e** (20%), and lactone **2e** (9%). The lactone **2e** obtained directly from this reaction had 32% ee in favor of the (*R*)-enantiomer, whereas hydroxyester **12e** was saponified and subjected to cyclization to give lactone **2e** with 72% ee in favor of the (*R*)-enantiomer.[32] When oxoalkanal **1e** was heated with (−)-menthol (100 mol %) and SmI_3 in refluxing THF, lactone **2e** (31% ee) was obtained after the subsequent treatment with CF_3CO_2H (entry 6, Table 4).

As we have demonstrated that oxoalkanals **1a**−**i** could be converted directly to δ-lactones **2a**−**i** by the synergistic catalysis of SmI_2 and mercaptan, we also wished to investigate whether the related asymmetric reactions could be achieved in the presence of chiral additives? Using the SmI_2/*i*-PrSH-promoted reaction of 5-oxotridecanal (**1e**) as a model, several additives were examined. The reaction of **1e** with SmI_2 (50 mol %), *i*-PrSH (40 mol %), and (*S*)-1,1-bi-2-naphthol (50 mol %) at room temperature gave lactone **2e** (42% yield) with 15% ee in favor of the (*R*)-enantiomer. No asymmetric induction was found with the chiral additives of (−)-sparteine, bisphosphoramide **15**[33], or salen **16**.[34] In the presence of (*R*)-



Bisphosphoramide **15**



Salen **16**

methyl *p*-tolylsulfoxide or (*S*)-proline, a reductive coupling reaction of **1e** was effected by SmI_2 to give pinacol **14e**, instead of the desired lactone **2e**.

As we have shown that chiral alcohols did induce the reactions of 5-oxoalkanals to give optically enriched 5-hydroxyesters and δ-lactones, we wished to devise the asymmetric catalytic reactions of 5-oxoalkanals by using chiral mercaptans to facilitate the formation of chiral δ-lactones. There are only a few chiral mercaptans available in nature; we thus prepared a series of chiral

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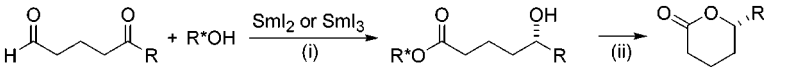
Table 4. Samarium Ion Promoted Reactions of 5-Oxoalkanals with Chiral Alcohols (Step i), and the Subsequent Lactonization (Step ii)



1a R = Ph
1e R = *n*-C_8H_{17}

12a R = Ph, R* = menthyl
12b R = Ph, R* = 8-Ph-menthyl
12c R = Ph, R* = neomenthyl
12e R = *n*-C_8H_{17}, R* = menthyl

2a R = Ph
2e R = *n*-C_8H_{17}

entry	substrate	R*OH	promoter (mol %)	step i (yield, %)	step ii (yield, %)	configuration[a] (% ee)
1	**1a**	(−)-menthol	SmI_2 (100)	**12a** (61)[b]	**2a** (65)	*S* (84)
2	**1a**	(−)-8-Ph-menthol	SmI_2 (100)	**12b** (48)[c]	**2a** (77)	*S* (72)
3	**1a**	(+)-neomenthol	SmI_2 (100)	**12c** (4)[d]	**2a** (70)	*R* (21)
4	**1a**	(−)-menthol	SmI_3 (20)	-[e]	**2a** (65)	*S* (78)
5	**1e**	(−)-menthol	SmI_2 (100)	**12e** (51)[f]	**2e** (69)	*R* (72)
6	**1e**	(−)-menthol	SmI_3 (20)	-[e]	**2e** (58)	*R* (31)

[a] The configuration of the major enantiomers of lactonic products. [b] This reaction also gave diester **13a** (31%) and pinacol **14a** (8%). [c] This reaction also gave lactone **2a** (21%), diester **13b** (25%) and pinacol **14a** (6%). [d] This reaction also gave lactone **2a** (14%), diester **13c** (52%), and pinacol **14a** (29%). [e] The reaction mixture was directly treated with CF_3CO_2H in CH_2Cl_2 to give lactone **2a** (or **2e**). [f] This reaction also gave lactone **2b** (9% yield, 32% ee), diester **13e** (20%) and pinacol **14e** (20%).

mercaptans **17**−**38** by derivatization of terpene alcohols, sterols, α-amino acids, and *β*-amino alcohols (Scheme 4). We also utilized the reaction of 5-oxotridecanal (**1e**) as a model to study the effects of chiral mercaptans on the enantioselective synthesis of *δ*-lactone **2e**.

The tosylate ester of (−)-menthol was treated with potassium thioacetate (AcSK), followed by reduction with DIBAL to give neomenthanethiol **17**,[35] a reminiscent of neomenthol. In the presence of SmI_2 (40 mol %) and mercaptan **17** (50 mol %), 5-oxotridecanal was converted to lactone **2e** (37% yield) in favor of the (*S*)-enantiomer (18% ee). The ee value was determined by HPLC analysis on a Chiracel OB column, and the absolute configuration of the preferable enantiomer was determined by comparison with the optical rotation of the authentic sample reported in the literature.[32] Since menthol exerted a higher asymmetric induction than neomenthol in the reaction with 5-oxoalkanal (compared entries 1 and 3 in Table 4), menthanethiol might be a better promoter for the enantioselective reaction of 5-oxoalkanal. However, attempts to prepare pure menthanethiol failed. The tosylate ester of (−)-menthol, having the tosyloxy group on the axial position, underwent elimination on treatment with AcSK, instead of the desired S_N2 reaction. Treatment of the dithiolane derivative of (−)-menthone with BuLi gave a mixture of menthanethiol and neomenthanethiol,[36] which could not be separated by chromatography. The reaction of **1e** with this mixture and SmI_2 gave 80% yield of **2e** with 33% ee in favor of the (*S*)-enantiomer. One might argue whether using enantiomerically pure menthanethiol as the promoter would enhance the enantioselective reaction?

When the pinane-type mercaptan **18**[37] and the cholesterol-type mercaptan **19**[38] were used together with SmI_2, the reactions of **1e** gave lactone **2e** in 20 and 14% ee, respectively, in favor of the (*R*)-enantiomer. We speculated that an annexed group at the neighboring position of the thiol might help in chelation with samarium ion, and thus improved the enantioselectivity in the reaction with **1e**. Indeed, the reaction occurred in higher enantioselectivities (38 and 44% ee) by using the camphor-type mercaptans[39] **20** and **21** annexed with hydroxyl groups. However, the reaction using the camphor-type mercaptans[39] **22**−**24** with neighboring alkoxy groups did not show any improved enantioselectivity (12−22% ee). It was noted that the isomeric mercaptans **22** and **24** showed the opposite enantiotopic preference in promoting lactone formation, a phenomenon also observed in the reactions promoted by menthol and neomenthol.

Derivatization of L-cysteine and (*S*)-proline gave the chiral mercaptans **25**[40] and **26**,[41] of which the *β*-carbons are chiral but the α-carbons are achiral. The enantioselectivities in the SmI_2 promoted reactions of **1e** with mercaptans **25** or **26** and SmI_2 turn out to be low, giving 24 and 10% ee of lactone **2e**. We found that the ephedrine-related mercaptans containing stereocenters at both α- and *β*-carbons showed higher enantioselectivities (up to 68% ee). The ephedrine-related mercaptans were generally prepared via the ring-opening reactions of aziridines with thio acids (Scheme 5).[42] For example, (1*R*,2*S*)-(−)-norephedrine underwent a Mitsunobu reaction (DIAD, Ph_3P, Et_3N) to give an aziridine, which was then treated with thioacetic acid to give mercaptan **30** after an in situ migration of the acetyl group. The chirality at C-1 was unchanged due to the double S_N2 reactions.[42] The structure of **30** was confirmed by an X-ray diffraction analysis. Mercaptan **33**[42] was similarly prepared form (1*R*,2*S*)-(−)-ephedrinium chloride, whereas mercaptan **36** was prepared from (1*R*,2*R*)-(−)-pseudoephedrine. Mercaptans **37** and **38** were prepared from (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol.

By comparison of the reactions of **1e** promoted by SmI_2 and mercaptans **27**−**38**, it appeared that the chirality of the lactonic product **2e** was dictated by the chirality at

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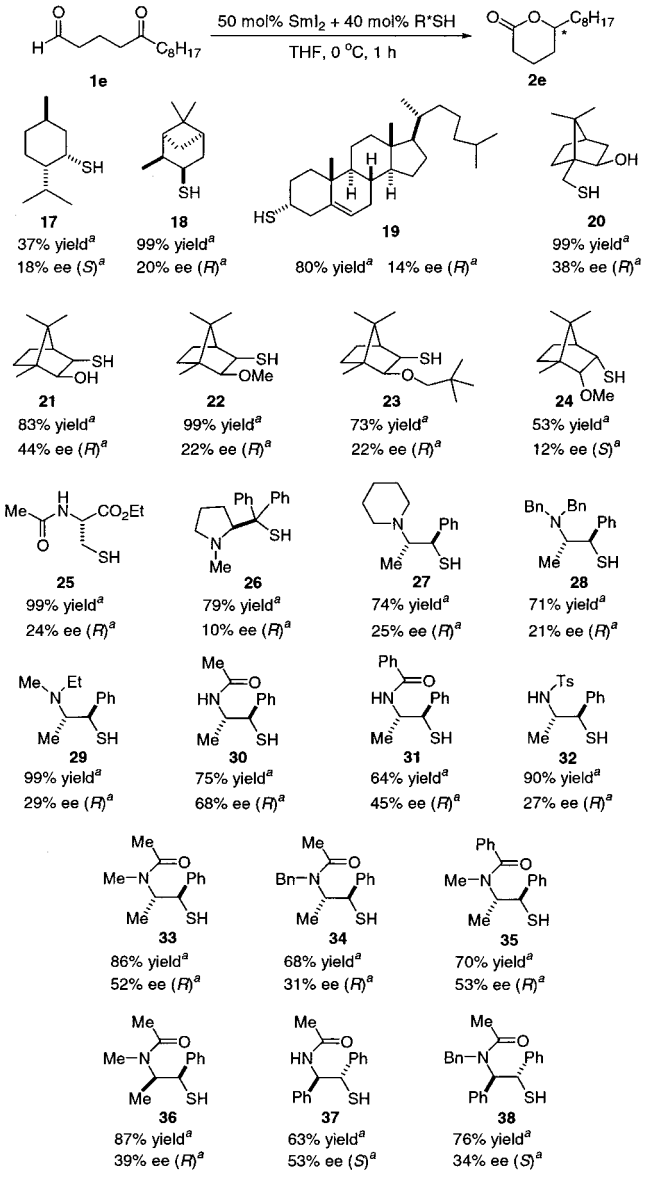
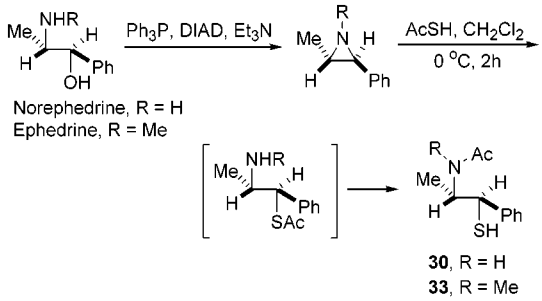
Scheme 4 Enantioselective Formation of δ-Lactone 2e by Treatment of 1e with SmI_2 and Chiral Mercaptans in THF at 0 °C



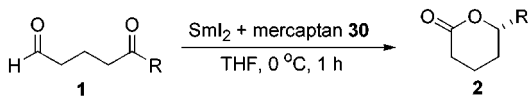
[a] Referring to the yield and ee value of the lactonic product **2e** obtained by using the individual mercaptan promoter.

Scheme 5. Preparation of Ephedrine-Related Mercaptans via the Aziridine Intermediates



the α-carbons of mercaptans. For example, the mercaptans **30**, **33**, and **36** with (*R*)-chirality at the α-carbons induced the (*R*)-enriched lactone **2a**, whereas the mercaptans **37** and **38** with (*S*)-chirality at the α-carbons promoted the formation of (*S*)-enriched **2e**. The chirality at the *β*-carbons of mercaptans hardly had influence on the enanatiomeric preference of lactone **2e**. The reactions using mercaptans with the neighboring acetamido group appeared to give lactone **2a** in a higher ee value (compared mercaptan **30** with **29** and **33**). Among the examined examples, we obtained a 75% yield of (*R*)-enriched lactone **2e** (68% ee) by treatment of 5-oxotridecanal with SmI_2 (50 mol %) and mercaptan **30** (40 mol %) in THF at 0 °C for 1 h.

Table 5. Reactions of 5-Oxoalkanals Promoted by SmI_2 (50 mol %) and Mercaptan 30 (40 mol %) at 0 °C in THF Solution



entry	substrate	R	product (yield, %)	% ee (configuration)[a]	$[\alpha]_D$
1	**1a**	Ph	**2a** (83)	49 (*S*)	−19.1
2	**1b**	Me	**2b** (84)	47 (*R*)	+14.8
3	**1d**	*n*-hexyl	**2d** (80)	40 (*R*)	+18.6
4	**1e**	*n*-octyl	**2e** (75)	68 (*R*)	+22.0
5	**1f**	benzyl	**2f** (73)	48[b]	+7.7
6	**1g**	*c*-hexyl	**2g** (74)	43[b]	−11.3
7	**1h**	*t*-Bu	**2h** (73)	44[b]	−12.0
8	**1j**	*n*-undecyl	**2j** (75)	74 (*R*)	+27.9
9	**1k**	*n*-tetradecyl	**2k** (76)	63[b]	+16.0
10	**1l**	*n*-octadecyl	**2l** (84)	65[b]	+10.2
11	**1m**	*o*-$MeOC_6H_4$	**2m** (74)	49[b]	−9.4

[a] The absolute configuration of major enantiomer. The ee value was determined by HPLC analysis on chiral columns. The absolute configuration of major enantiomer was determined by comparison of optical rotation with that reported in the literature. [b] The absolute configuration of major enantiomer was not determined.

Mercaptan **30** was also applied to the enantioselective synthesis of other *δ*-lactones (Table 5). A series of optically enriched *δ*-lactones **2a**−**m** was obtained by treatments of 5-oxoalkanals **1a**−**m** with SmI_2 (50 mol %) and mercaptan **30** (40 mol %). All the reactions occurred in a consistent enantiotopic preference. The observed enantioselectivity was accounted on the intramolecular hydride transfer to the 5-keto group, similar to the intermediate **A** depicted in Figure 2. Thus, the major 5-phenyl lactones **1a** and **1m** have the (*S*)-configuration via the *si*-face hydride transfer, whereas the major lactones **1b**, **1d**, **1e**, and **1j** with primary alkyl substituents have the (*R*)-configuration via the *re*-face hydride transfer. Accordingly, a hornet pheromone (*R*)-5-hexadecanolide[43] (74% ee) was synthesized in 75% yield from 5-oxohexadecanal (entry 8, Table 5). The major enantiomers of **2a**, **2f**, and **2m** having phenyl substituents tended to be less retained in Chiralcel OB and OB-H columns than their corresponding minor enantiomers. On the other hand, the major enantiomers of **2b**, **2d**, **2e**, and **2g**−**l** with alkyl substituents had longer retetion times on the chiral columns. It was noted that lactones **2a** and **2m** were formed in the same enantioselectivity (entries 1 and 11, Table 5), even though the *ortho* methoxy group of **1m** might involve in the coordination with samarium ion.

Conclusion. We have demonstrated a general method for conversion of various 5-oxoalkanals to substituted *δ*-lactones and 1-oxa-2-decalones by the synergistic ca-

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talysis of samarium ion and mercaptan. This transformation involves a sequential acetalization, Tishchenko reaction, and lactonization in a one-pot procedure. The deliberative use of mercaptan is advantageous to facilitate the catalytic cycle (Figure 2). For example, 5-oxo-5-pentanal (**1a**) was converted to 5-phenylpentanolide (**2a**) in a quantitative yield by using 20 mol % of SmI_2 and 10 mol % of *i*-PrSH as the promoters (entry 4, Table 1). The active catalyst may be considered as RS-SmI_2. Thus, SmI_2/RSSR and SmI_3/PhSLi can replace SmI_2/*i*-PrSH to promote the transformation of 5-oxoalkanals to their corresponding δ-lactones (Table 2). This approach to δ-lactones adapts the atom economy of intramolecular redox process, unlike the conventional methods requiring excess amounts of oxidizing and reducing agents to convert 5-oxoalkanals into 5-hydroxyalkanoic acid for the subsequent lactonization.

The SmI_2/*i*-PrSH-promoted reactions of 2-methyl-, 3-methyl-, and 4-methyl-5-oxoalkanals occurred in a high stereoselective manner. The stereochemistry can be explained by the favorable transition states **C** and **E** (Figure 3). We have also utilized the remote control of such samarium-ion-catalyzed reactions to synthesize optically active δ-lactones via three routes, by using chiral substituted-5-oxoaldehydes (eq 2), stoichiometric amount of chiral alcohols (Table 4), and catalytic amount of chiral mercaptan (Scheme 4). Thus, enantiomerically pure (2*S*,5*R*)-2-methylhexanolide (**10**), (*S*)-enriched 5-phenylpentanolide (**2a**, 78% ee), and (*R*)-enriched hexadecanolide (**2j**, 74% ee) were synthesized from their corresponding 5-oxoalkanals practically in one-pot procedures. *The synthesis of insect pheromones **2j** and **10** also demonstrates a new protocol for asymmetric reduction of long-chain aliphatic ketones.*

Experimental Section

General. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon or nitrogen. Syringes and needles for the transfer of reagents were dried at 100 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, and amines from CaH_2. Reactions were monitored by TLC precoated with a 0.25 mm layer of silica gel containing a fluorescent indicator (Merck Art. 5544). Column chromatography was carried out on Kieselgel 60 (40−63 μm). HPLC was performed on Lichrosorb Si 60 and Nucleosil 100 columns (25 cm × 1 cm i.d.) with particle size of 7 μm. Chiracel OB, OB-H, and OD columns (25 cm × 0.46 cm i.d.) were used for analysis of enantiomeric excesses. Refractive index or UV detectors were used. Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a cuvette of 10 cm length. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line of t) 77.0]. Coupling constants (*J*) are given in hertz (Hz). Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals. The X-ray diffraction data were collected on a CAD-4 diffractometer. The analyses were carried out on a microVAX III computer using NRC VAX software.

Representative Procedure for the Preparation of 5-Oxoalkanals (Scheme 1).

Method A.[12] Under an atmosphere of N_2, an ethereal solution (20 mL) of Grignard reagent was prepared from bromobenzene (6.0 g, 38 mmol) and Mg (960 mg, 40 mmol) by the activation of I_2 (small amount). A solution of cyclopentanone (2.5 g, 30 mmol) in Et_2O (10 mL) was added dropwise at room temperature (25 °C). The mixture was stirred for 2 h and then poured into an ice-cold 1 N HCl solution (60 mL). The mixture was extracted with Et_2O (3 ×). The ethereal phase was combined, washed with brine (3×), dried (Na_2SO_4), and concentrated to give a crude addition product.

The crude product was dissolved into benzene (30 mL), and *p*-TsOH (20 mg) was added. The mixture was heated at reflux for 8 h while the generated water was removed azeotropically via Dean−Stark equipment. The mixture was concentrated and purified on a silica gel column by elution with hexane to give alkene (4.0 g, 93%).

The alkene was dissolved into CH_2Cl_2 (40 mL), and a stream of ozone passed through the solution at −78 °C until the light blue color of ozone persisted. The solution was purged with N_2, and stirred at room temperature for 10 min. The mixture was stirred with Me_2S (5 mL) for 5 h, followed by addition of Ph_3P in portions (4 × 1 g). The mixture was stirred for 5 h, concentrated, and purified on a silica gel column by elution with EtOAc/hexane (1:4) to give 5-oxo-5-phenylpentanal (**1a**, 4.3 g, 88%).

Method B.[13] A mixture of pinacolone (3.0 g, 30 mmol) and 1,1-dimethylhydrazine (3.6 g, 60 mmol) was heated at reflux for 10 h. Distillation using Kugelrohr apparatus gave hydrazone product (3.80 g, 89%).

To a solution of the hydrazone product (1.0 g, 7.2 mmol) in THF (10 mL) was added dropwise BuLi (6.0 mL of 1 M solution in hexane) at 0 °C. The mixture was stirred for 30 min, and 4-bromo-1-butene (1.29 g, 9.6 mmol) was added dropwise. The mixture was stirred at room temperature for 10 h, quenched by addition of water (5 mL), and extracted with EtOAc (2×). The organic phase was concentrated, after which acetone (20 mL) and acidic resin (Amberlyte IR 120, ca. 2 g) were added. The mixture was stirred for 9 h, concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (5:95) to give alkene product (762 mg, 69%). Ozonation by a procedure similar to that for **1a** gave 6,6-dimethyl-5-oxoheptanal (**1h**, 241 mg, 97%).

Method C.[14] Isobutyraldehyde (2.37 g, 32.9 mmol) was added to a mixture of Me_3SiCl (5.23 g, 49.3 mmol) and Et_3N (6.6 g, 65.8 mmol) in DMF (20 mL). The mixture was heated at reflux for 4 h, cooled, diluted with hexane (40 mL), and washed with cold aqueous $NaHCO_3$ solution (3 ×). The organic phase was dried (Na_2SO_4) and distilled at 70 °C to give the corresponding silyl enol ether (4.10 g, 87%).

A mixture of the silyl enol ether (1.02 g, 7.1 mmol) and methyl vinyl ketone (840 mg, 12 mmol) was added to a suspension of Al_2O_3 (5.00 g) and $ZnCl_2$ (1.35 g) in Et_2O (30 mL) at 0 °C. The mixture was stirred for 30 min, after which BF_3·OEt_2 (1.5 mL) was added. The mixture was stirred at 0 °C for 4 h, and quenched by addition of water (1 mL). Chromatography on a short silica gel column by elution with EtOAc/hexane (1:4) gave 2,2-dimethyl-5-oxohexanal (**1i**, 992 mg, 99%).

Representative Procedure for Transformation of 5-Oxoalkanals to δ-Lactones (Schemes 2, 3 and 4). Method D. Under an atmosphere of argon, *i*-PrSH (30 mg, 0.04 mL, 0.4 mmol) was added to a deep blue SmI_2 (0.5 mmol) solution freshly prepared from samarium (80 mg) and 1,2-diiodoethane (140 mg) in THF (15 mL). The mixture was stirred for 5 min at room temperature, and a THF solution (5 mL) of 5-oxo-5-phenylpentanal (**1a**, 176 mg, 1.0 mmol) was added dropwise. The mixture was stirred for 1 h, and then filtered through a short silica gel column by elution with EtOAc/hexane (1:1). The filtrate was concentrated by rotary evaporation to give a practically pure lactone **2a** (174 mg, 99%).

Method E. A slightly modified procedure was conducted by premixing an aliquot of SmI_2/*i*-PrSH (ca. 3 mol % in 1 mL of THF) with the THF solution (5 mL) of 5-oxohexanal (**1b**, 114 mg, 1.0 mmol) in an oven-dried syringe. The resulting yellow solution, an indicator of trivalent samarium ion, was then added dropwise to the original SmI_2/*i*-PrSH (50/40 mol %) solution in THF (14 mL). Accordingly, the desired product 5-hexanolide (**2b**, 133 mg) was also obtained in an excellent yield (99%).

By a similar procedure, chiral mercaptans were used to replace *i*-PrSH in the enantioselective reactions (Scheme 4 and Table 5).

Representative Procedure for the Reactions of 5-Oxoalkanals with Chiral Alcohols Promoted by SmI_2 or SmI_3 (Table 4). Method F. A solution of 5-oxo-5-phenylpentanal (88 mg, 0.5 mmol) and (−)-menthol (79 mg, 0.5 mmol) in THF (10 mL) was added to the freshly prepared SmI_2 (5 mL of 0.1 M solution in THF). The mixture was stirred for 1 h at room temperature, and filtered through a short silica gel column by elution with EtOAc/hexane (1:1). The filtrate was concentrated to give a mixture of lactone **2a**, hydroxyester **12a**, and diester **13a** in a ratio of 61:31:8 as indicated by the ^{1}H NMR analysis. Hydroxyester **12a** was further separated by chromatography with elution of EtOAc/hexane (1:9). Saponification of **12a**, followed by acidification, gave lactone **2a** with 84% ee in favor of the (*S*)-enantiomer as determined by HPLC analysis on a Chiralcel OB column.

Method G. A solution of SmI_3 was prepared from Sm (150 mg, 1 mmol) and I_2 (390 mg, 1.5 mmol) in THF (1.5 mL). An aliquot of SmI_3 solution (0.15 mL, 0.15 mmol) was taken, and the reaction of 5-oxo-5-phenylpentanal (100 mg, 0.57 mmol) and (−)-menthol (95 mg, 0.61 mmol) was conducted in refluxing THF (10 mL) for 1 h. The crude product was treated with trifluoroacetic acid (0.5 mL) in CH_2Cl_2 (10 mL) at 0 °C for 3 h to give lactone **2a** (65 mg, 65% yield) with 78% ee in favor of the (*S*)-enantiomer.

5-Phenyl-5-pentanolide (2a).[31] Solid, mp 91−93 °C; HPLC (Chiralcel OB column) $t_R(S)/t_R(R) = 13.4$ min/15.9 min, eluent 10% *i*-PrOH in hexane, flow rate 2 mL/min (UV 254 nm). $[\alpha]^{26}_D = -19.1$ ($c = 0.9$, $CHCl_3$, 49% ee in favor of the *S*-enantiomer).

5-Hexanolide (2b).[44] HPLC (Chiralcel OB column) $t_R(S)/t_R(R) = 11.0$ min/14.3 min, eluent 10% *i*-PrOH in hexane, flow rate 2 mL/min (UV 225 nm). $[\alpha]^{29}_D = +14.8$ ($c = 0.3$, $CHCl_3$, 47% ee in favor of the *R*-enantiomer)

5-Heptanolide (2c).[45] By a procedure similar to that for **2b** (Method E), 5-oxoheptanal (**1c**, 170 mg, 1.3 mmol) was treated with SmI_2/*i*-PrSH (0.5 mmol/0.4 mmol) at room temperature to give the title compound **2c** (155 mg, 91%).

5-Undecanolide (2d).[29b] By a procedure similar to that for **2b** (Method E), 5-oxoundecanal (**1d**, 184 mg, 1.0 mmol) was treated with SmI_2/*i*-PrSH (0.5 mmol/0.4 mmol) at room temperature to give the title compound **2d** (182 mg, 99%). HPLC (Chiralcel OB-H column) $t_R(S)/t_R(R) = 15.5$ min/16.9 min, eluent 5% *i*-PrOH in hexane, flow rate 1 mL/min (RI detector). $[\alpha]^{24}_D = +18.6$ ($c = 0.9$, $CHCl_3$, 40% ee in favor of the *R*-enantiomer).

5-Tridecanolide (2e).[32] By a procedure similar to that for **2b** (Method E), 5-oxotridecanal (**1e**, 220 mg, 1.0 mmol) was treated with SmI_2/*i*-PrSH (0.5 mmol/0.4 mmol) at room temperature to give the title compound **2e** (207 mg, 94%). Solid, mp 42−43 °C; HPLC (Chiralcel OB-H column) $t_R(S)/t_R(R) = 8.7$ min/11.2 min, eluent 5% *i*-PrOH in hexane, flow rate 1.0 mL/min (UV 225 nm or RI detector). $[\alpha]^{27}_D = +22.0$ ($c = 0.7$, $CHCl_3$, 68% ee in favor of the *R*-enantiomer).

5-Phenyl-5-hexanolide (2f).[46] By a procedure similar to that for **2b** (Method E), 5-oxo-6-phenylhexanal (**1f**, 97 mg, 0.5 mmol) was treated with SmI_2/*i*-PrSH (0.25 mmol/0.23 mmol) at room temperature to give the title compound **2f** (96 mg, 99%). HPLC (Chiralcel OB column) t_R(minor isomer)/t_R(major isomer) = 12.0 min/13.3 min, eluent 10% *i*-PrOH in hexane, flow rate 1 mL/min (UV 254 nm). $[\alpha]^{30}_D = +7.7$ ($c = 0.5$, $CHCl_3$, 48% ee in favor of the less retained enantiomer).

5-Cyclohexyl-5-pentanolide (2g).[47] By a procedure similar to that for **2b** (Method E), 5-oxo-5-cyclohexylpentanal (**1g**, 49 mg, 0.27 mmol) was treated with SmI_2/*i*-PrSH (0.25 mmol/0.23 mmol) at room temperature to give the title compound **2g** (47 mg, 96%). Solid, mp 47−49 °C; HPLC (Chiralcel OD column) t_R(minor isomer)/t_R(major isomer) = 9.1 min/10.3 min, eluent 5% *i*-PrOH in hexane, flow rate 1.3 mL/min (UV 225 nm). $[\alpha]^{29}_D = -11.3$ ($c = 1.0$, $CHCl_3$, 43% ee in favor of the more retained enantiomer).

6,6-Dimethyl-5-heptanolide (2h).[48] By a procedure similar to that for **2b** (Method E), 6,6-dimethyl-5-oxoheptanal (**1h**, 181 mg, 1.2 mmol) was treated with SmI_2/*i*-PrSH (0.50 mmol/0.34 mmol) at room temperature to give the title compound **2h** (165 mg, 91%). HPLC (Chiralcel OB column) t_R(minor isomer)/t_R(major isomer) = 9.9 min/11.0 min, eluent 5% *i*-PrOH in hexane, flow rate 1.5 mL/min (UV 225 nm). $[\alpha]^{30}_D = -12.0$ ($c = 0.3$, $CHCl_3$, 44% ee in favor of the more retained enantiomer).

2,2-Dimethyl-5-hexanolide (2i).[49] By a procedure similar to that for **2b** (Method E), 2,2-dimethyl-5-oxohexanal (**1i**, 58 mg, 0.41 mmol) was treated with SmI_2/*i*-PrSH (0.17 mmol/0.15 mmol) at room temperature to give the title compound **2i** (46 mg, 80%).

5-Hexadecanolide (2j).[43] By a procedure similar to that for **2b** (Method E), 5-oxo-hexadecanal (**1j**, 51 mg, 0.20 mmol) was treated with SmI_2/*i*-PrSH (0.15 mmol/0.13 mmol) at room temperature to give the title compound **2j** (43 mg, 85%). Solid, mp 39−40 °C; HPLC (Chiralcel OB-H column) $t_R(S)/t_R(R) = 21.9$ min/23.3 min, eluent 1.25% *i*-PrOH in hexane, flow rate 0.5 mL/min (RI detector). $[\alpha]^{26}_D = +27.9$ ($c = 0.5$, THF, 74% ee in favor of the *R*-enantiomer).

5-Nonadecanolide (2k). By a procedure similar to that for **2b** (Method E), 5-oxononadecanal (**1k**, 110 mg, 0.37 mmol) was treated with SmI_2/*i*-PrSH (0.40 mmol/0.30 mmol) at room temperature to give the title compound **2k** (84 mg, 76%). Solid, mp 49−51 °C; TLC [EtOAc/hexane (20:80)] $R_f = 0.40$; IR (neat) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (3 H, br t, J = 6.1 Hz), 1.23 (20 H, br s), 1.51−1.71 (4 H, m), 1.75−1.93(2 H, m), 2.41−2.56 (2 H, m), 4.18−4.28 (1 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0 (CH_3), 18.5 (CH_2), 22.6 (CH_2), 24.9 (CH_2), 27.8 (CH_2), 29.3 (CH_2), 29.37 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 35.8 (CH_2), 80.6 (CH), 171.9 (C). HR-FAB-MS calcd for $C_{19}H_{37}O_2$ ($M^+ + 1$): 297.2794. Found: 297.2793. HPLC (Chiralcel OB-H column) t_R(minor isomer)/t_R(major isomer) = 18.6 min/20.1 min, eluent 1.25% *i*-PrOH in hexane, flow rate 0.8 mL/min (RI detector). $[\alpha]^{25}_D = +16.0$ ($c = 1.5$, $CHCl_3$, 63% ee in favor of the more retained enantiomer).

5-Tricosanolide (2l).[50] By a procedure similar to that for **2b** (Method E), 5-oxotricosanal (**1l**, 170 mg, 0.48 mmol) was treated with SmI_2/*i*-PrSH (0.30 mmol/0.25 mmol) at room temperature to give the title compound **2l** (146 mg, 86%). Solid, mp 56−57 °C; HPLC (Chiralcel OB-H column) t_R(minor isomer)/t_R(major isomer) = 19.9 min/22.1 min, eluent 1.25% *i*-PrOH in hexane, flow rate 0.8 mL/min (RI detector). $[\alpha]^{25}_D = +10.2$ ($c = 3.0$, $CHCl_3$, 65% ee in favor of the more retained enantiomer).

5-(2-Methoxyphenyl)-5-pentanolide (2m). By a procedure similar to that for **2b** (Method E), 5-(2-methoxyphenyl)-5-oxopentanal (**1m**, 206 mg, 1.0 mmol) was treated with SmI_2/*i*-PrSH (0.50 mmol/0.40 mmol) at room temperature to give the title compound **2m** (176 mg, 85%). Solid, mp 79−81 °C; TLC [EtOAc/hexane (50:50)] $R_f = 0.33$; IR (neat) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70−1.86 (1 H, m), 1.89−1.98 (2 H, m), 2.14−2.20 (1 H, m), 2.49−2.74 (2 H, m), 3.87 (3 H, s), 5.67 (1 H, dd, J = 10.1 Hz, J = 3.5 Hz), 6.83−7.00 (3 H, m), 7.22−7.38 (2 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.5 (CH_3), 28.9 (CH_2), 29.7 (CH_2), 55.3 (CH_3), 76.9 (CH), 110.3 (CH), 120.7 (CH), 126.4 (CH), 128.1 (C), 128.9 (CH), 155.6 (C), 171.8 (C). HR-FAB-MS calcd for $C_{12}H_{15}O_3$ ($M^+ + 1$): 207.1021. Found: 207.1017. HPLC (Chiralcel OB column) t_R(major isomer)/t_R(minor isomer) = 10.9 min/13.5 min, eluent 20% *i*-PrOH in hexane, flow rate 2 mL/min (254 nm). $[\alpha]^{24}_D = -9.4$ ($c = 1.5$, $CHCl_3$, 49% ee in favor of the less retained enantiomer).

4-Methyl-5-heptanolide (8a).[19] By a procedure similar to that for **2b** (Method E), 4-methyl-5-oxoheptanal (**4a**, 160 mg, 1.23 mmol) was treated with SmI_2/*i*-PrSH (0.50 mmol/0.43 mmol) at room temperature to give the title compound **8a** (cis

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isomer, 155 mg, 91%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (3 H, t, J = 6.7 Hz), δ 0.96 (3 H, d, J = 7.4 Hz), 1.44−1.72 (3 H, m), 1.90−2.05 (2 H, m), 2.47 (2 H, t, J = 7.6 Hz), 4.14 (1 H, ddd, J = 11.5 Hz, J = 5.5 Hz, J = 2.8 Hz).

4-Methyl-5-phenyl-5-pentanolide (8b).[20] By a procedure similar to that for **2b** (Method E), 4-methyl-5-oxo-5-phenylpentanal (**4b**, 61 mg, 0.32 mmol) was treated with SmI_2/*i*-PrSH (0.25 mmol/0.17 mmol) at room temperature to give the title compound **8b** (cis isomer, 57 mg, 94%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (3 H, d, J = 6.1 Hz), 1.68−1.81 (1 H, m), 2.10−2.31 (2 H, m), 2.67 (2 H, dd, J = 7.2 Hz, J = 6.7 Hz), 5.48 (1 H, d, J = 3.0 Hz), 7.13−7.36 (5 H, m).

3-Methyl-5-phenyl-5-pentanolide (9a).[21] By a procedure similar to that for **2b** (Method E), 3-methyl-5-oxo-5-phenylpentanal (**5a**, 94 mg, 0.48 mmol) was treated with SmI_2/*i*-PrSH (0.50 mmol/0.43 mmol) at room temperature to give the title compound **9a** (91 mg, 97%) as a mixture of trans and cis isomers (77:23). The isomeric ratio changed to trans/cis = 94:6 when the reaction was conducted at 0 °C. *trans*-**9a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (3 H, d, J = 6.2 Hz), 1.82−1.88 (1 H, m), 2.02−2.31 (3 H, m), 2.68 (1 H, dd, J = 16.3 Hz, J = 5.3 Hz), 5.50 (1 H, dd, J = 7.3 Hz, J = 4.6 Hz), 7.27−7.36 (5 H, m). *cis*-**9a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (3 H, d, J = 6.4 Hz), 1.49−1.56 (1 H, m), 2.12−2.19 (3 H, m), 2.79 (1 H, dd, J = 11.9, 1.9 Hz), 5.29 (1 H, dd, J = 12.0, 3.1 Hz), 7.30−7.38 (5 H, m).

(3*S*,5*S*)-3-Methyl-5-hexanolide (9b)[24] **and (2*R*,5*S*)-2-Methyl-5-hexanolide (10)**[25]**.** By a procedure similar to that for **2b** (Method E), a mixture of 3-methyl-5-oxohexanal (**5b**) and 2-methyl-5-oxohexanal (**6**) (1:1, 128 mg, 1.0 mmol) was treated with SmI_2/*i*-PrSH (0.5 mmol/0.4 mmol) at 0 °C to give a mixture of (3*S*,5*S*)-**9b** and (2*R*,5*S*)-**10** (1:1). The analytic samples were isolated by HPLC with elution of EtOAc/hexane (3:7). (3*S*,5*S*)-**9b**: $[\alpha]^{25}_D$ = −57.7 (c = 0.1, MeOH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 21.4, 23.7, 36.6, 37.3, 73.6, 172.4. (2*R*,5*S*)-**10**: $[\alpha]^{25}_D$ = −82.5 (c = 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (3 H, d, J = 6.8 Hz), 1.34 (3 H, d, J = 6.2 Hz), 1.49−1.64 (2 H, m), 1.87−1.93 (1 H, m), 2.02−2.10 (1 H, m), 2.52−2.60 (1 H, m), 4.42−4.47 (1 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 21.1, 25.6, 28.4, 33.0, 74.4, 176.3.

(2*S*,5*R*)-2-Methyl-5-hexanolide (10).[25] By a procedure similar to that for **1h** (Method B), propanal was condensed with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine to give the corresponding hydrazone. The hydrazone was alkylated with 4-iodo-2-methyl-1-butene, followed by ozonolysis, to give (*S*)-2-methyl-5-oxohexanal, $[\alpha]^{26}_D$ = −6.7 (c = 0.6, $CHCl_3$). By a procedure similar to that for **2b** (Method E), (*S*)-2-methyl-5-oxohexanal (71 mg, 0.6 mmol) was treated with SmI_2/*i*-PrSH (0.3 mmol/0.25 mmol) at room temperature to give (2*S*,5*R*)-**10** (54 mg, 76%). Solid, mp 40−42 °C; $[\alpha]^{21}_D$ = +63.5 (c = 0.2, $CHCl_3$).

1-Oxa-2-decalone (11a).[22] By a procedure similar to that for **2b** (Method E), 3-(2-oxocyclohexyl)propanal (**7a**, 79 mg, 0.51 mmol) was treated with SmI_2/*i*-PrSH (0.25 mmol/0.17 mmol) at room temperature to give the title compound **11a** (trans/cis = 96:4, 55 mg, 70%). *trans*-**11a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95−2.03 (11 H, m), 2.47−2.61 (2 H, m), 3.82 (1 H, ddd, J = 10.2 Hz, J = 10.2 Hz, J = 4.2 Hz)/4.44 (br dd, J = 6.7, 3.3 Hz for cis isomer).

1-Oxa-6-*tert*-butyl-2-decalone (11b).[23] By a procedure similar to that for **2b** (Method E), 3-(2-oxo-5-*tert*-butylcyclohexyl)propanal (**7b**, 160 mg, 1.2 mmol) was treated with SmI_2/*i*-PrSH (0.50 mmol/0.43 mmol) at room temperature to give the title compound **11b** (141 mg, 88%) as a mixture of trans and cis isomers (81:19). *trans*-**11b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (9 H, s), 0.82−1.17 (3 H, m), 1.40−1.60 (3 H, m), 1.80−1.87 (3 H, m), 2.09−2.16 (1 H, m), 2.51−2.69 (2 H, m), 3.80 (1 H, ddd, J = 10.5 Hz, J = 10.4 Hz, J = 4.5 Hz). *cis*-**11b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (9 H, s), 1.06−1.33 (3 H, m), 1.46−1.61 (4 H, m), 1.81−1.87 (1 H, m), 2.07−2.14 (2 H, m), 2.48 (2 H, t, J = 7.4 Hz), 4.42 (1 H, d, J = 2.6 Hz).

(1′*R*,2′*S*,5′*R*,5*SR*)-5-Hydroxy-5-phenylpentanoic acid 2-isopropyl-5-methylcyclohexyl ester (12a). TLC [EtOAc/hexane (20:80)] R_f = 0.26; IR (neat) 3443, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (3 H, d, J = 6.9 Hz), 0.86 (3 H, d, J = 6.9 Hz), 0.87 (3 H, d, J = 6.6 Hz), 0.93−1.10 (1 H, m), 1.25−1.52 (2 H, m), 1.60−1.81 (8 H, m), 1.89−2.01 (2 H, m), 2.27−2.31 (2 H, m), 4.60−4.69 (2 H, m), 7.20−7.45 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.1, 20.6, 21.1, 21.9, 23.3, 26.1, 31.1, 34.1, 34.2, 38.2, 40.8, 46.9, 73.8, 73.9, 125.7 (2×), 127.3, 128.3 (2×), 144.5, 173.1; HRMS calcd for $C_{21}H_{32}O_3$: 332.2351. Found: 332.2341.

(1′*R*,2′*S*,5′*R*,5*SR*)-5-Hydroxy-5-tridecanoic acid 2-isopropyl-5-methylcyclohexyl ester (12e). TLC [EtOAc/hexane (20:80)] R_f = 0.55; IR (neat) 3449, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.73 (3 H, d, J = 6.9 Hz), 0.83−1.11 (12 H, m), 1.24−2.11 (25 H, m), 2.29 (2 H, dt, J = 7.4, 1.9 Hz), 3.52−3.59 (1 H, m), 4.66 (1 H, ddd, J = 10.8, 10.8, 4.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (CH_3), 16.3 (CH_3), 20.7 (CH_3), 21.1 (CH_2), 22.0 (CH_3), 22.6 (CH_2), 23.4 (CH_2), 25.6 (CH_2), 26.3 (CH), 29.3 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.7 (CH), 31.9 (CH_2), 34.3 (CH_2), 34.5 (CH_2), 36.7 (CH_2), 37.5 (CH_2), 40.9 (CH_2), 47.0 (CH_2), 71.4 (CH), 74.1 (CH), 173.3 (C); HR-FAB-MS calcd for $C_{23}H_{45}O_3$ ($M^+ + 1$): 369.3369. Found: 369.3362.

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)-ethane-1,2-diamine (15).[33] According to the known procedure, the chiral phosphorus(V) reagent **15** was prepared from (1*R*,2*S*)-(−)-ephedrine hydrochloric salt by subsequent treatments with $POCl_3$/Et_3N and ethylenediamine.

Salen 16. By a procedure similar to that for the related salen compounds,[34] the chiral salen reagent **16** was prepared by condensation of (1*R*,2*R*)-(−)-1,2-cyclohexanediamine with 4-azidomethyl-2-hydroxybenzaldehyde.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexanethiol (17).[35] Treatment of (−)-menthol (3.12 g, 20 mmol) with *p*-toluenesulfonyl chloride (7.70 g, 40 mmol) in pyridine (30 mL) at room temperature for 16 h gave the corresponding tosylate (6.05 g, 97%). The tosylate (2.60 g, 8.4 mmol) was heated (50−60 °C) with potassium thioacetate (AcSK, 2.80 g, 25 mmol) in Me_2SO (17 mL) for 36 h. The mixture was cooled and extracted with $CHCl_3$ (5 × 15 mL). The organic phase was dried (Na_2SO_4), concentrated, and distilled (80 °C, 0.05 mmHg) to give (1*S*)-neomenthyl acetate (1.31 g, 73%). Diisobutylaluminum hydride (DIBAL, 6 mmol, 1 M solution in CH_2Cl_2) was added dropwise to a CH_2Cl_2 solution (20 mL) of (1*S*)-neomenthyl acetate (420 mg, 1.96 mmol) at 0 °C. The mixture was stirred for 5 h and quenched by addition of saturated NH_4Cl. Water (40 mL) and 1 M HCl (20 mL) were added, and the mixture was extracted with Et_2O (4 × 30 mL). The organic phase was washed with brine, dried (Na_2SO_4), concentrated, and distilled (90 °C, 9 mmHg) to give the title compound **17** (330 mg, 98%). $[\alpha]^{25}_D$ +53.6 (c = 3.1, $CHCl_3$).

(1*S*,2*S*,3*R*,5*R*)-3-Pinanethiol (18).[37] By a procedure similar to that for **17**, (+)-isopinocampheol was activated as the mesylate, which was subsequently treated with AcSK and DIBAL to give the title compound **18**. $[\alpha]^{25}_D$ = −5.7 (c = 3.7, $CHCl_3$).

(3*R*)-Cholestanethiol (19).[38] A THF solution (5 mL) of 3β-chloesterol (772 mg, 2.0 mmol) was treated with a mixture of Ph_3P (630 mmol, 2.4 mmol) and diisopropyl diazocarbodiimide (DIAD, 485 mg, 2.4 mmol) in THF (15 mL) at 0 °C for 2 h to give the corresponding thioacetate (590 mg, 78%). Reduction of the thioacetate (138 mg, 0.3 mmol) with $LiAlH_4$ (120 mg, 3.0 mmol) in Et_2O (10 mL) for 30 min gave the title compound **19** (122 mg, 99%). Solid, 80−82 °C.

(1*S*,2*R*,4*R*)-(−)-10-Mercaptoisoboneol (20).[39] Treatment of (1*S*)-(+)-camphorsulfonic acid (1.16 g, 5 mmol) with $SOCl_2$ gave the corresponding sulfonyl chloride, which was reduced with $LiAlH_4$ to give the title compound **20** (37% overall yield) and its *endo* isomer (7%). **20**: Solid, mp 70−72 °C; $[\alpha]^{27}_D$ = −56.1 (c = 1.1, $CHCl_3$).

(*S*)-(+)-2-(α-Mercapto-α-phenylbenzyl)-1-methylpyrrolidine (26).[41] According to the known procedure,[41] (*S*)-proline-*N*-benzyl carbamate was subjected to a sequence of esterification, addition with PhMgBr, reduction with $LiAlH_4$ and substitution with Lawesson reagent to give the title compound **26** in 32% overall yield. $[\alpha]^{25}_D$ = +249.5 (c = 1.0, $CHCl_3$).

(1*R*,2*S*)-(−)-1-Phenyl-2-piperidyl-1-propanethiol (27).[42b] (1*R*,2*S*)-(−)-Norephedrine (2.3 g, 10 mmol) was alkylated with 1,5-dibromopentane, followed by activation to the corresponding mesylate. The mesylate was treated with AcSK, followed by reduction with DIBAL, to give the title compound **27** in 42% overall yield. $[\alpha]^{27}_D$ −64.2 (c = 1.2, $CHCl_3$).

(1*R*,2*S*)-2-Dibenzylamino-1-phenyl-1-propanethiol (28). (1*R*,2*S*)-(−)-Norephedrine (2.3 g, 10 mmol) was subjected to reductive alkylation with PhCHO/$NaBH_3CN$ (two repeated processes) to give (1*R*,2*S*)-*N*,*N*-dibenzylamino-1-phenylpropanol, which was activated as a mesylate. The mesylate was treated with AcSK, followed by saponification (KOH in aqueous MeOH), to give the title compound **28** in 39% overall yield. $[\alpha]^{28}_D$ −101.1 (c = 1.4, $CHCl_3$).

(1*R*,2*S*)-1-Phenyl-2-(*N*-methylethylamino)-1-propanethiol (29) and (1*R*,2*S*)-1-Phenyl-2-(*N*-methylacetamido)-1-propanethiol (33).[42a] (1*R*,2*S*)-(−)-Ephedrine (4.02 g, 20 mmol) was treated with Ph_3P (1.1 g, 4 mmol), Et_3N (8 mL) and diethyl azodicarbodiimide (DEAD, 6.9 g, 40 mmol) in THF (60 mL) at room temperature for 10 h. After the solids were filtered, the filtrate was concentrated and distilled (70 °C, 0.5 mmHg) to give (2*S*,3*S*)-1,2-dimethyl-3-phenylaziridine (2.53 g, 89%). The aziridine (1.41 g, 9.9 mmol) was treated with AcSK (1.51 g, 19.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C for 2 h to give compound **33** (2.09, 95%), via the ring opening reaction and transesterification. Reduction of **33** (299 mg, 1.3 mmol) with $LiAlH_4$ (120 mg, 3.0 mmol) in refluxing THF (20 mL) for 5 h gave compound **29** (178 mg, 64%). **29**: $[\alpha]^{29}_D$ = −224.7 (c = 2.5, $CHCl_3$). **33**: $[\alpha]^{25}_D$ −93.4 (c = 1.96, CH_2Cl_2).

(1*R*,2*S*)-2-Acetamido-1-phenyl-1-propanethiol (30). (1*R*,-2*S*)-(−)-Norephedrine (1.51 g, 10 mmol) was treated with Ph_3P (3.2 g, 12 mmol) and DIAD (2.2 g, 11 mmol), by procedure similar to that for **33**, to give (2*S*,3*S*)-2-methyl-3-phenylaziridine (1.15 g, 86%). The aziridine (259 mg, 1.9 mmol) was treated with thioacetic acid (500 mg, 6.5 mmol) in CH_2Cl_2 at 0 °C for 2 h to give the title compound **30** (350 mg, 86%). Solid, mp 78−80 °C; TLC [EtOAc/hexane (1:1)] R_f = 0.26; $[\alpha]^{29}_D$ = −67.3 (c = 0.9, $CHCl_3$); IR (neat) 3285, 1650, 1554 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (3 H, d, J = 6.6 Hz), 1.85 (1 H, d, J = 7.3 Hz, SH), 1.92 (3 H, s), 4.29 (1 H, dd, J = 7.3, 5.0 Hz), 4.34−4.45 (1 H, m), 5.71 (1 H, br s), 7.20−7.39 (5 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9 (CH_3), 23.4 (CH_3), 49.1 (CH), 50.2 (CH), 127.4 (CH), 127.8 (CH × 2), 128.4 (CH × 2), 140.5 (C), 169.3 (C=O). HR-FAB-MS calcd for $C_{11}H_{16}NOS$ (M^+ + 1): 210.0953. Found: 210.0960.

(1*R*,2*S*)-2-Benzamido-1-phenyl-1-propanethiol (31). By a procedure similar to that for **30**, the aziridine derived from (1*R*,2*S*)-(−)-norephedrine (164 mg, 1.2 mmol) was treated with thiobenzoic acid (255 mg, 6.5 mmol) to give the title compound **31** (331 mg, 99%). Solid, mp 145−146 °C; $[\alpha]^{29}_D$ −51.1 (c = 1.90, $CHCl_3$).

(1*R*,2*S*)-1-Phenyl-2-(4-toluenesulfonamido)-1-propanethiol (32). (1*R*,2*S*)-(−)-Norephedrine was treated with *p*-toluenesulfonyl chloride to give the corresponding sulfonamide. By a procedure similar to that for **28**, the sulfonamide was converted to the title compounds **32** in 69% yield, via substitution of the mesylate with AcSK and saponification. Solid, mp 89−90 °C; $[\alpha]^{24}_D$ −35.0 (c = 1.0, $CHCl_3$).

(1*R*,2*S*)-2-(*N*-Benzylacetamido)-1-phenyl-1-propanethiol (34). (1*R*,2*S*)-(−)-Norephedrine was subjected to reductive alkylation with PhCHO/$NaBH_3CN$ to give (1*R*,2*S*)-2-benzylamino-1-phenylpropanol (70% yield), which was converted to the corresponding aziridine (64% yield) by treatment with Ph_3P/CCl_4 in CH_3CN solution at room temperature for 18 h. The aziridine (228 mg, 1.0 mmol) was treated with thioacetic acid, by a procedure similar to that for **30**, to give the title compound **34** (262 mg, 88%). Solid, mp 92−94 °C; $[\alpha]^{25}_D$ −25.3 (c = 2.1, $CHCl_3$).

(1*R*,2*S*)-2-(*N*-Methylbenzamido)-1-phenyl-1-propanethiol (35). By a procedure similar to that for **31**, (2*S*,3*S*)-1,2-dimethyl-3-phenylaziridine (626 mg, 4.2 mmol) was treated with thiobenzoic acid acid (740 mg, 5.3 mmol) to give the title compound **35** (1.19 g, 99%). $[\alpha]^{25}_D$ −22.5 (c = 1.25, CH_2Cl_2).

(1*R*,2*R*)-2-(*N*-Methylacetamido)-1-phenyl-1-propanethiol (36). By a procedure similar to that for **30**, (1*R*,2*R*)-(−)-pseudoephedrine (1.65 g, 10 mmol) was treated with Ph_3P and DIAD to give the corresponding aziridine (1.24 g, 84%). The aziridine (139 mg, 0.94 mmol) was treated with thioacetic acid to give the title compound **36** (169 mg, 80%). Solid, mp 95−97 °C; $[\alpha]^{27}_D$ −195.0 (c = 1.0, $CHCl_3$).

(1*S*,2*R*)-2-Acetamido-1,2-diphenyl-1-ethanethiol (37). By a procedure similar to that for **30**, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (587 mg, 2.8 mmol) was treated with Ph_3P and DIAD to give the corresponding aziridine (496 mg, 93%). The aziridine (333 mg, 1.7 mmol) was treated with thioacetic acid to give the title compound **37** (519 mg, 66%). Solid, mp 189−190 °C; $[\alpha]^{27}_D$ = −70.2 (c = 1.0, DMSO-d_6).

(1*S*,2*R*)-2-(*N*-Benzylacetamido)-1,2-diphenyl-1-ethanethiol (38). By a procedure similar to that for **34**, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol was sequentially treated with PhCHO/$NaBH_3CN$, Ph_3P/DIAD, and thioacetic acid to give the title compound **38** in 48% overall yield. $[\alpha]^{27}_D$ = −82.3 (c = 1.2, $CHCl_3$).

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Supporting Information Available: Additional experimental procedures, spectral data, and ^1H and ^{13}C spectra of some selected compounds, as well as the crystal data, bond distances, bond angles, and ORTEP drawing of compound **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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