Ring Enlargement of α-Ethylidenecycloalkanones to β-Alkylidenecycloalkanones Induced by Trimethylstannyllithium/Aldehyde Equivalents/Lewis Acids

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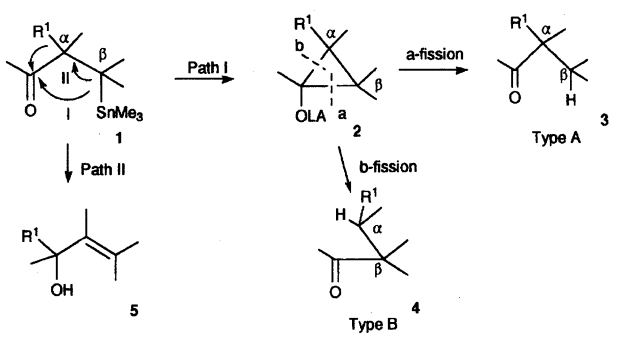
α-Ethylidenecycloalkanones underwent a ring enlargement to β-alkylidenecycloalkanones upon a treatment with trimethylstannyllithium/aldehyde equivalents/Lewis acids with high stereoselectivity.

We have reported that the Lewis acid-induced reaction of β-stannyl ketones **1** usually proceeds via cyclopropanol intermediates **2** (Path I), and affords saturated ketones **3** or **4**, according to the position of the bond cleavage of the cyclopropanol ring of **2**, a or b, in Scheme 1.[1,2] We call these reactions Type-A and Type-B, respectively. The general trend is that an increase in the number of substituents on the α-carbon favors the Type-A reaction, while an increase on the β-carbon favors the Type-B reaction. The Type-B reaction becomes the exclusive reaction pattern when the β-carbon is fully substituted. Only when an alkyl group of sufficient migratory aptitude occupies the antiperiplanar position against the stannyl group does the 1,2-alkyl migration compete with the cyclopropanation, affording products derived from **5** (Path II).[3,4] The Type-B reaction involves a carbon-skeleton rearrangement; we have utilized the reaction for the ring contraction of *endo*-type cyclic α,β-enones. It is expected that the Type-B reaction could be applied for a ring enlargement if it proceeds effectively with *exo*-type cyclic α,β-enones. Actually, the reaction proceeded as expected under specific conditions.

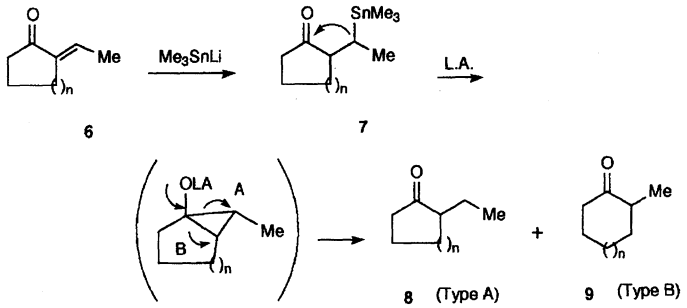
Results and Discussion

When β-stannyl ketones **7a**—**7d**, prepared by the conjugate addition of Me_3SnLi upon corresponding ethylidene cycloalkanones **6**, were treated with Lewis acids, the Type-A and Type-B reactions proceeded to afford the corresponding **8** and **9**, as shown in Scheme 2 and Table 1.[5] Evidently, the selectivity between the Type-A and Type-B reactions was not necessarily satisfactory, probably because both of the α and β-carbons of the cyclopropanol intermediate are tertiary. We have already found that one of the effective ways to increase the selectivity of the Type-B reaction is to introduce leaving groups into the 1′-position of the α-substituent, as shown in Scheme 3, thus facilitating an effective ring contraction to form **11** when applied to cyclic compounds, such as **10**.[6] Therefore, we intended to prepare **15**, which might proceed through the Type-B reaction, as shown in Scheme 4. The desired **15a**—**15g** were prepared by a conjugate addition of Me_3SnLi to **12**, followed by quenching the lithium enolates **13** either with appropriate electrophiles directly (Method A), or first with trimethylsilyl chloride to afford silyl enol ether **14**, and then with aldehydes or acetals (Method B). The results are shown in Table 2. Products **15a**—**15d** were obtained as single stereoisomers to which the *anti* structure was assigned in view of the generally accepted reaction pattern of trapping the enolates with electrophiles.[7] Products **15e**—**15g** were obtained as mixtures of two diastereomers. It would be reasonable to assume that, here again, the relative stereochemistry of the carbon–tin bond and the newly created carbon–carbon bond is fixed to the *anti* relation, and that diastereomeric scrambling arises from the configration of the aldol moiety. This was further confirmed by the following observations.



Scheme 1.

As shown in Runs 5 and 6, the diastereomer ratio of **15e** reversed according to the preparation methods, methods A and B. Each of the diastereomers was separable by column chromatography; their stereochemistries were unequivocally determined in the following way by utilizing our recent finding that the



Scheme 2.

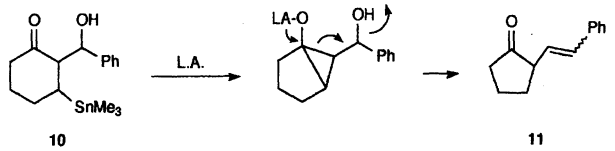
Table 1. Reaction of **7** with Lewis Acid

Run	Starting material	Lewis acid	Product ratio		Yield/%
			8	**9**	
1	**7a**	$TiCl_4$	0	100	44
2	**7b**	$TiCl_4$	89	11	69
3	**7c**	$TiCl_4$	74	26	86
4	**7c**	TMSOTf	11	89	78
5	**7d**	$TiCl_4$	51	49	82

Table 2. Reaction of **12** with Stannyl Anion and Electrophile

Run	Electrophile	Method	Product and yield/%		Diastereomer ratio
1	$ClCH_2I$	A	**15a**	47	—
2	$ClCH_2I$	A	**15b**	50	—
3	$Me_2N^+{=}CH_2I^-$/MeI	A	**15c**	78	—
4	CH_2O	B	**15d**	69[a)]	—
5	MeCHO	A	**15e**	76	75 : 25
6	MeCHO	B	**15e**	71[a)]	35 : 65
7	$MeCH(OMe)_2$	B	**15f**	40[a)]	17 : 83
8	$PhCH(OMe)_2$	B	**15g**	48[a)]	11 : 89

a) Yields from **14a**, which was prepared from **12a** in 97% yield.



Scheme 3.

treatment of β′-hydroxy-β-stannyl ketones with PCl_3 or $MeSO_2Cl$ (MsCl) induced a cyclopropanation,[8)] with an inversion of the configuration at both reaction centers.[9)]

When the major isomer in Run 5 was treated with MsCl, a spirocyclopropane **18** was obtained, while the major isomer in Run 6 gave an another spirocyclopropane **19** under the same conditions (Chart 1). In view of the ^1H NMR datum of **18**, which showed a single methyl signal and a single cyclopropane ring proton signal, we assigned the *cis*-dimethyl structure for this compound. On the other hand, the *trans*-dimethyl structure was assigned for **19**, because each of the signals of methyl and the cyclopropane ring proton appeared as a pair. These observations indicate that the major isomer in Run 5 has a stereostructure shown as *threo*-**15e**, while another isomer as *erythro*-**15e**. The assignment is consistent with the general scheme that the reaction from lithium enolate proceeds through a Zimmermann-type cyclic transition state **20**, while the F^--assisted aldol reaction with silyl enol ether proceeds through an open-chain transition state **21**. In view of the ^{13}C NMR spectra, **15f** and **15g** were found to be diastereomer mixtures, although the stereochemistries have not been assigned.

When **15a**—**15e** were treated with Lewis acids, they underwent the Type-B reaction, affording *exo*-type β,γ-enoles **17** with a ring enlargement as shown in Table 3. Only in the case of Run 5, did further isomerization of the double bond occur to give α,β-enone **22**. The reaction proceeded with high stereospecificity, affording only (*E*)-**17e** from *threo*-**15e**, while only (*Z*)-**17e** from *erythro*-**15e**. The geometry of the double bond in **17e** was assigned based on the ^{13}C NMR signals of C2 carbon, which appeared at a higher field (δ=48.64) for the (*Z*)-isomer than that for the (*E*)-isomer (δ=55.32),

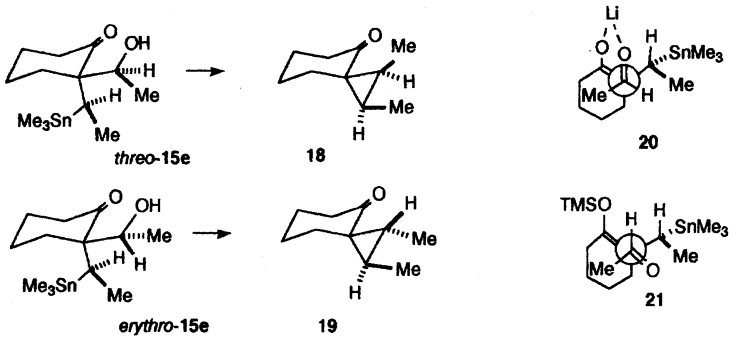
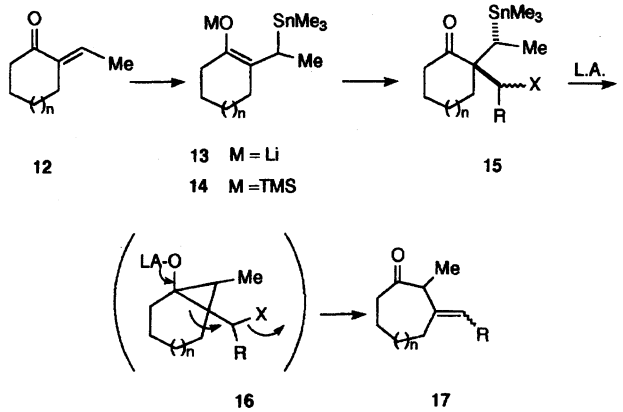


Chart 1.

Table 3. Reaction of **15** with Lewis Acid

Run	Starting material	Ratio	Lewis acid	Temp/°C	Time/min	Product	Yield/%	Ratio
1	**15a**	—	$TiCl_4$	0	30	**17a**	92	—
2	**15b**	—	$TiCl_4$	0	10	**17b**	82	—
3	**15c**	—	$TiCl_4$	R.T.	48(h)	**17a**	75	—
4	**15c**	—	$EtAlCl_2$	R.T.	48(h)	**17a**	65	—
5	**15c**	—	TMSOTf	R.T.	48(h)	**22**	75	—
6	**15d**	—	$TiCl_4$	0	5	**17a**	63	—
7	*t*-**15e**	100 : 0	$TiCl_4$	−78	5	(*E*)-**17e**	84	100 : 0
8	*e*-**15e**	100 : 0	$TiCl_4$	0	5	(*Z*)-**17e**	83	100 : 0
9	**15f**	90 : 10	$TiCl_4$	−78	30	(*E*)-**17e**	92	99 : 1
10	**15g**	89 : 11	$TiCl_4$	−78	10	(*E*)-**17g**[a]	40	99 : 1
11	*t*-**15e**	95 : 5	$EtAlCl_2$	R.T.	5	**25e**	79	80 : 20
12	*e*-**15e**	99 : 1	$EtAlCl_2$	R.T.	15	**25e**	54	90 : 10
13	**15f**	90 : 10	$EtAlCl_2$	R.T.	30	**25f**	59	93 : 7
14	**15g**	89 : 11	$EtAlCl_2$	0	10	**25g**	47	60 : 40

a) The starting enone **12a** (27%) was recovered.



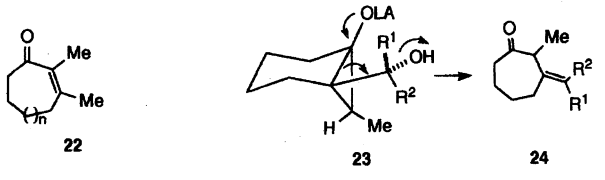
	n	R	X
a	1	H	Cl
b	7	H	Cl
c	1	H	Me_3N^+
d	1	H	OH
e	1	Me	OH
f	1	Me	OMe
g	1	Ph	OMe

Scheme 4.

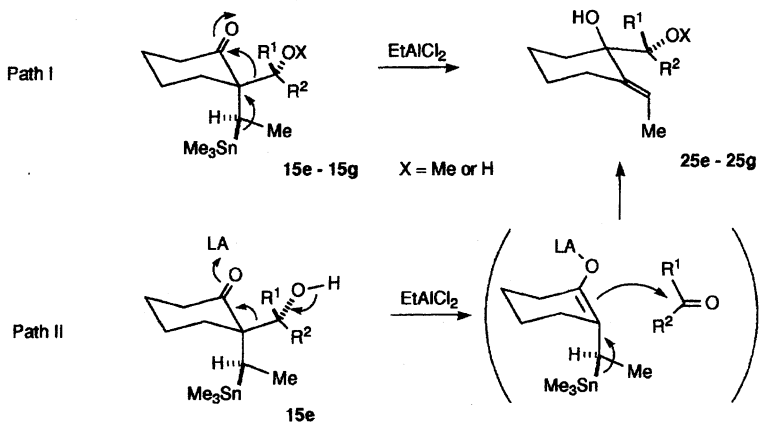
due to stereochemical compression. The observation of a 5% NOE enhancement between two methyl groups in the (*Z*)-isomer also supported the assignment.

In view of the high stereospecificity in the ring-enlargement reaction, we schemed the reaction as involving a concerted mechanism. With the structures of the aldols and the β,γ-enones now confirmed, it was concluded that the ring enlargement proceeded through a synperiplanar orientation of the hydroxyl group and a cleaving bond of the cyclopropanol, as shown in Scheme 5.[10] This is in sharp contrast to the stepwise fragmentation of 2-(1-hydroxyalkyl)-1-cyclopropanols, in which two hydroxyl groups can not occupy the same side of the cyclopropane ring.[11]

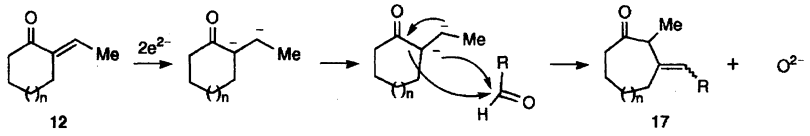
Diastereomer mixtures of **15f** and **15g** also underwent the ring enlargement with $TiCl_4$ to give **17f** and



Scheme 5.



Scheme 6.



Scheme 7.

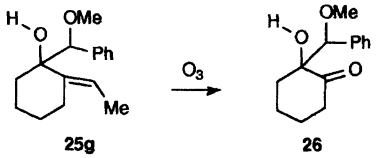


Chart 2.

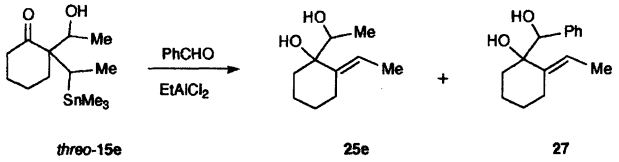


Chart 3.

17g, predominantly of *E*-geometry (Runs 9 and 10). Considering the *E*/*Z* stability of **17** under these conditions as revealed above, the high *E*-predominance could be rationalized by assuming a retro reaction of the minor diastereomer to the original enones. The retro reaction was actually observed in Run 10, where **12a** was recovered in 27% yield.

The nature of the Lewis acid is critical to induce the Type-B reaction. Although **15c** underwent the Type-B reaction with $EtAlCl_2$ as smoothly as with $TiCl_4$ (Run 4), **15e**—15g gave **25e**—**25g** by $EtAlCl_2$, without producing any amounts of the Type-B reaction products (Runs 11, 12, 13, and 14). In each case, the product was a mixture of two inseparable isomers, as revealed by the ^{13}C NMR spectrum. In order to assign the origin of the isomerism, the double bond in **25g** was cleaved by ozone, using a sample of a 60 : 40 diastereomer mixture. Since the product ketone **26** was also a 60 : 40 mixture of two isomers, it was concluded that the isomerism originated in the stereochemical scrambling at the 1,2-diol moiety, while the double bond in **25g** is fixed to a single geometry, probably the *E*-configuration (Chart 2). The reaction could be schemed either as involving 1,2-migration (Path I, Scheme 6) or, in the case of **15e**, a retroaldol reaction followed by coupling of the resulting γ-hydroxyallylstannane and aldehyde (Path II). As shown in Runs 11 and 12, both of the *threo* and *erythro*-**15e** gave a diastereomer mixture of **25e** with an identical stereochemical preference. While we have not assigned the stereochemistries of the diastereomers, the stereochemical scrambling favors a stepwise reaction mechanism through Path II. The stepwise intermolecular reaction scheme was further verified by the $EtAlCl_2$-induced reaction of **15e** in the presence of benzaldehyde, which afforded **27** in 76% yield as well as **25e** in 12% (Chart 3). In contrast, no such aldehyde scambling was observed with **15f** and **15g**, which favors the intramolecular reaction scheme (Path I).

Conclusion

In this study we found that although the stannyl compounds **7** underwent a ring enlargement to afford **9**, the reaction was not always selective, accompanied by the formation of **8**. In contrast, stannyl compounds **15** having leaving groups X underwent a ring enlargement stereoselectively to produce *E*, *Z*-defined **17**. In a previous paper[12] we proposed a synthon representation in order to characterize the reaction type typical of the tin-containing compounds, and represented Me_3SnLi as a reagent equivalent to a double electron. Thus, the present reaction can be represented essentially as shown in Scheme 7.

We have so far characterized the typical points of the reactions of the stannyl compounds as follows:[12] while the tin-bearing carbon exhibits a carbanionic nature, its low reactivity towards electrophilic centers allows us to prepare, as the first-stage reaction, stannyl compounds

having a variety of electrophilic centers within the same molecule, and we can activate the tin-carbon bond, as the second-stage reaction, in various ways by changing the nature of the elecrophilic centers, reaction conditions, and activation methods. The present reaction is another example which demonstrates the diversity in the reaction mode on tin-containing compounds involving the activation of the tin-carbon bond by cooperation of the carbonyl group, aldehyde equivalents, and Lewis acids.

Experimental

General Procedure and Instrumentation. GC experiments were carried out on a 2.5 m×3 mm stainless-steel column packed with Silicone SE 30 on silanized Chromosorb W and 25 m×0.25 mm capillary column (SE 30). Column chromatography was carried out on Kieselgel 60, Art. 7734 (70—230 mesh ASTM). ^{1}H NMR spectra (60 MHz) were recorded on a Hitachi R-24 or JEOL PMX 60 SI spectrometer. ^{1}H NMR (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were measured on a Hitachi JNM-PMX 60S R-90H spectrometer, and ^{1}H NMR (400 MHz) spectra on a JEOL GSX-400 spectrometer. GC-MS spectra were taken on a Shimadzu QP-1000 mass spectrometer, and high resolution mass spectra on a JEOL DX-300 mass spectrometer. IR spectra were recorded on a Perkin–Elmer 1640 type FT-IR. Unless otherwise stated, all of the spectroscopic data were determined on pure samples obtained by either distillation or column chromatography, checking the purity by TLC or GC analyses; the mass spectra were obtained by the EI method at 70 eV, the ^{1}H NMR on the 60 MHz machines with CCl_4 solutions, the ^{1}H NMR data on the 90 and 400 MHz machines and the ^{13}C NMR data with $CDCl_3$ solutions, and IR spectra with neat samples.

All of the ^{1}H NMR signals of the methyl group on the tin atom at $\delta\approx0$ ppm accompanied splitting signals by ^{117}Sn (7.54% abundance, J=51 Hz) and ^{119}Sn (8.62% abundance, J=53 Hz). Mass spectral peaks of the tin-containing fragments showed isotope pattern typical to the tin atom, but only values corresponding to ^{120}Sn were shown.

Starting Materials and Reagents. The following compounds were prepared referring to the literature.[13] 2- Ethylidenecyclopentanone (**6a**),[14] 2- ethylidenecyclohexanone (**6b**=**12a**),[15] 2-ethylidenecycloheptanone (**6c**) [MS m/z 138 (M^+), 95, 81 (base), 68, 67. ^{1}H NMR, δ=1.70 (br.s, 6H), 1.78 (d, J=6.5 Hz, 3H), 2.45 (br.s, 4H), 6.52 (q, J=6.5 Hz, 1H)], 2-ethylidenecyclooctanone (**12b**) [MS m/z 152 (M^+), 110, 109, 96, 95, 81, 68, 67 (base). ^{1}H NMR δ=1.55 (br.s, 8H), 1.81 (d, J=6.3 Hz, 3H), 2.58 (br. s, 4H), 6.58 (q, J=6.3 Hz, 1H)], 2-ethylidenecyclododecanone [^{1}H NMR δ=1.26 (br.s, 14H), 1.5—2.0 (m, 2H). 1.85 (d, J=7.2 Hz, 3H), 2.23—2.72 (m, 4H), 6.52 (q, J=7.2 Hz, 1H)]. Trimethylsilyl trifuluoromethanesulfonate (TMSOTf) and $TiCl_4$ were obtained commercially, and purified by distillation. $EtAlCl_2$ was obtained commercially as hexane solution (0.93 M, 1 M=1 mol dm^{-3}), and used directly.

General Procedure for the Preparation of β-Stannyl Ketones 7. To a THF solution of Me_3SnLi (1.2—3.3 equiv) prepared as described in our previous report[6] was added a solution of the corresponding α,β-enones **6** (0.3—0.6, 1 equiv) in THF at 0 °C. After being stirred for the periods described below, the solution was quenched with water at room temperature. The ether extracts, after being dried over $MgSO_4$, were concentrated in vacuo. Column chromatography gave pure materials.

2- (1- Trimethylstannylethyl)- 1- cyclopentanone (7a). The product was obtained in 29% yield (0.040 g) from **6a** (0.056 g, 0.509 mmol) by stirring for 15 min. ^{1}H NMR δ=−0.05 (s, 9H), 1.10 (s, 3H), 1.4—2.4 (m, 8H).

2-(1-Trimethylstannylethyl)-1-cyclohexanone (7b). The product was obtained in 63% yield (0.636 g) from **6b** (0.433 g, 3.49 mmol) by stirring for 30 min. MS m/z 275 (M^+-15), 165, 135 (base). ^{1}H NMR δ=−0.13 (s, 9H), 0.90—2.00 (m, 10H), 2.0—2.5 (m, 3H).

2- (1- Trimethylstannylethyl)- 1- cycloheptanone (7c). The product was obtained in 86% yield (0.382 g) from **6c** (0.201 g, 1.46 mmol) by stirring for 15 min. ^{1}H NMR δ=−0.15 (s, 9H), 0.85—2.00 (m, 12H), 2.1—2.4 (m, 3H).

2-(1-Trimethylstannylethyl)-1-cyclooctanone (7d). The product was obtained in 77% yield (0.855 g) from **6d** (0.534 g, 3.51 mmol) upon stirring for 30 min. Two diastereomers were separated by column chromatography (69:31). For major fraction: MS, m/z 303 (M^+-15), 165, 135 (base). ^{1}H NMR δ=−0.10 (s, 9H), 1.00 (s, 3H), 1.15—2.00 (m, 11H), 2.10—2.30 (m, 2H), 2.60—2.90 (m, 1H). For minor fraction: MS m/z 303 (M^+-15), 165, 135 (base). ^{1}H NMR δ=−0.10 (s, 9H), 0.90—2.50 (m, 17H).

General Procedure for the Preparation of β-Stannyl Ketones 15 (Method A). To a THF solution of Me_3SnLi (1.2—3.3 equiv) prepared as described in our previous report[6] was added a solution of the corresponding α,β-enones (0.3—0.6 M, 1 equiv) in THF at 0 °C. After being stirred for 1 h, the solution was reacted with appropriate electrophiles at room temperature for periods as described below. The ether extracts, after being dried over $MgSO_4$, were concentrated in vacuo. Column chromatography gave pure materials.

2-Chloromethyl-2-(1-trimethylstannylethyl)-1-cyclohexane (15a). The product was obtained in 47% yield (0.643 g) from **12a** (0.500 g, 4.03 mmol) by a stepwise addition of a MeSnLi solution (10.0 mmol), and then chloroiodomethane (1.77 g, 10.0 mmol), by stirring for 8 h. The product was purified by column chromatography (hexane:ether=4:1). MS m/z 323 (M^+-15), 303, 287, 185 (base), 165, 138, 110, 95, 81, 67, 55. ^{1}H NMR δ=0.09 (s, 9H), 0.97 (d, J=8.4 Hz, 3H), 1.57—2.17 (m, 7H), 2.17—2.64 (m, 2H), 3.64 (s, 2H). HRMS. Found: m/z 323.0178. Calced for $C_{11}H_{20}OClSn$: (M−Me), 323.0225.

2-Chloromethyl-2-(1-trimethylstannylethyl)-1-cyclododecanone (15b). The product was obtained in 50% yield (2.11 g) from **12b** (2.08 g, 10.0 mmol), Me_3SnLi solution (12.0 mmol), and chloroiodomethane (2.66 g, 15.1 mmol) after stirring for 1 h. The product was purified by column chromatography (hexane:ether=19:1). Ms m/z 407 (M^+-15), 371, 222, 193, 185, 165 (base), 151, 135, 123, 109, 95, 81, 67. IR 2931, 2864, 1694, 1468, 1443, 1127, 1054, 766, 727 cm^{-1}. ^{1}H NMR δ=0.08 (s, 9H), 0.91 (d, J=7.0 Hz, 3H), 1.05—2.41 (m, 21H), 3.52 and 3.67 (ABq, J=14.0 Hz, 2H). HRMS (CI). Found: m/z 423.1463. Calcd for $C_{18}H_{36}OClSn$: (M+H), 423.1477.

2- (*N,N,N*- Trimethylammoniomethyl)- 2- (1- trimethylstannylethyl)-1-cyclohexanone Iodide (15c).

2-(*N*,*N*-Dimethylaminomethyl)-2-(1-trimethylstannylethyl)-1-cyclohexanone was obtained in 78% yield by treating the solution, prepared from **12a** (0.400 g, 3.23 mmol) and Me_3SnLi (4.00 mmol), with *N*,*N*-dimethyl(methylene)ammonium iodide (1.00 g, 5.40 mmol). MS (20 eV), *m/z* 332 (M^+-Me), 289, 165, 58 (base). IR 2938, 2864, 2819, 2768, 1696, 1458, 1040, 764 cm^{-1}. ^1H NMR $\delta=0.21$ (s, 9H), 1.06 (d, $J=7.6$ Hz, 3H), 1.50—2.50 (m, 9H), 2.27 (s, 6H), 2.60 (s, 1H), 2.67 (s, 1H). ^{13}C NMR $\delta=-7.56$, 12.86, 20.87, 26.64, 26.93, 36.35, 39.20, 48.32, 56.44, 63.13, 214.55. HRMS (20 eV). Found: *m/z* 332.0978. Calcd for $C_{13}H_{26}ONSn$: (M−Me), 332.1036. The ammonium iodide **15c** was obtained as a white solid after stirring the resulting 2-(*N*,*N*-dimethylaminomethyl)-2-(1-trimethylstannyl)-1-cyclohexanone (0.85 g, 2.46 mmol) with CH_3I (40 ml) in methanol (40 ml) for two days, and evaporating the solvent. IR (KBr) 2994, 2940, 2869, 1699, 1482, 1466, 1120, 925, 888, 769 cm^{-1}. ^1H NMR $\delta=0.32$ (s, 9H), 1.19 (d, $J=7.6$ Hz, 3H), 1.05—2.50 (m, 9H), 3.55 (s, 9H), 3.89, 4.06 (ABq, $J=14.0$ Hz, 2H). ^{13}C NMR $\delta=-7.56$, 12.73, 20.23, 26.25, 26.62, 37.08, 39.42, 55.94, 56.29, 68.02, 212.78.

***threo*- and *erythro*-2-(1-Hydroxyethyl)-2-(1-trimethylstannylethyl)-1-cyclohexanone (15e).** To a THF solution, prepared from **12a** (0.600 g, 4.84 mmol) and Me_3SnLi (5.57 mmol) was added a solution of acetaldehyde (0.639 g, 14.5 mmol) in THF (5 ml) at −78 °C, and stirred for 40 min at this temperature. The solution was worked-up in the same way as above to afford a mixture of *threo*- and *erythro*-**15e** (75 : 25) in 76% yield. Each of the products was purified on a silica-gel column (hexane : AcOEt = 5 : 1). For *threo*-**15e** (major component): IR 3462, 2938, 2867, 1690, 1458 cm^{-1}. ^1H NMR $\delta=0.19$ (s, 9H), 1.05 (dist.d $J=6.7$ Hz, 6H), 1.27—2.53 (m, 10H), 3.79 (q, $J=6.7$ Hz, 1H). ^{13}C NMR $\delta=-7.92$, 14.45, 18.35, 21.09, 25.80, 28.30, 32.55, 40.01, 58.98, 72.10, 217.06. For *erythro*-**15e** (minor component): IR 3498, 2938, 2867, 1682, 1455, 1108, 1054, 787, 764 cm^{-1}. ^1H NMR $\delta=0.14$ (s, 9H), 1.05 (d, $J=6.6$ Hz, 3H), 1.20 (d, $J=6.0$ Hz, 3H), 1.26—2.76 (m, 10H), 4.17 (q, $J=6.0$ Hz, 1H). ^{13}C NMR $\delta=-6.81$, 12.59, 19.36, 20.27, 25.92, 26.14, 30.31, 39.26, 58.45, 67.03, 213.95.

General Procedure for the Preparation of β-Stannyl Ketones 15 (Method B). 1-(Trimethylsilyloxy)-2-(1-trimethylstannylethyl)-1-cyclohexene (14a). To a THF solution of **13a**, prepared from **12a** (2.00 g, 16.2 mol) and Me_3SnLi (19.3 mmol), was added triethylamine (6.83 ml, 48.4 mmol) and then TMSCl (6.15 ml, 48.4 mmol) at room temperature. After being stirred for 10 min, the solution was quenched with sat. $NaHCO_3$ aq, and the product **14a** (5.70 g, 97%) was obtained. MS *m/z* 362 (M^+), 197 (base), 73. IR 2928, 2857, 2835, 1659, 1348, 1251, 1182, 920, 842 cm^{-1}. ^1H NMR $\delta=0.09$ (s, 9H), 0.24 (s, 9H), 1.27 (d, $J=7.6$ Hz, 3H), 1.47—2.90 (m, 9H). ^{13}C NMR $\delta=-9.86$, 1.08, 15.51, 22.08, 23.22, 23.89, 26.55, 30.42, 119.41, 139.42. HRMS (20 eV). Found: *m/z* 362.1128. Calcd for $C_{14}H_{30}OSiSn$: (M), 362.1088.

2-Hydroxymethyl-2-(1-trimethylstannylethyl)-1-cyclohexanone (15d). To a mixture of formalin (35%, 0.6 ml) and $Yb(OTf)_3$ (0.020 g) was added a solution of **14a** (0.072 g, 0.20 mmol) in THF (1 ml) at room temperature. The solution was stirred for 55 h, and extracted with ether. The product was purified by column chromatography to afford **15d** (0.044 g, 69%). IR 3445, 2936, 2866, 1694, 1454, 1119, 1043, 766 cm^{-1}. ^1H NMR $\delta=0.17$ (s, 9H), 1.05 (d, $J=7.8$ Hz, 3H), 1.22—2.75 (m, 9H), 3.20—3.91 (m, 3H). ^{13}C NMR $\delta=-8.19$, 13.16, 20.50, 24.79, 27.11, 34.73, 39.29, 57.24, 66.37, 217.34.

***threo*- and *erythro*-2-(1-Hydroxyethyl)-2-(1-trimethylstannylethyl)-1-cyclohexanone (15e).** A suspension of molecular sieve 4A (3 g) and TBAF (0.796 g, 3.04 mmol) in THF (7 ml) was stirred for 7 h at room temperature. To the mixture was added a solution of **14a** (0.330 g, 0.92 mmol) and acetaldehyde (0.405 g, 9.20 mmol) in THF (3 ml) at −78 °C. After being stirred for 1 h, it was quenched with sat. $NaHCO_3$ aq. The product was a mixture of *threo*- and *erythro*-**15e** (35 : 65) in 70% yield. Each of the products was purified on a silica-gel column (hexane : AcOEt = 5 : 1).

2-(1-Methoxyethyl)-2-(1-trimethylstannylethyl)-1-cyclohexanone (15f). To a mixture of **14a** (0.200 g, 0.55 mmol) and acetaldehyde dimethyl acetal (0.294 ml, 2.77 mmol) in CH_2Cl_2 (7 ml) was added $TiCl_4$ (0.06 ml, 0.55 mmol) at −78 °C. After stirring for 30 min, the reaction mixture was treated with $NaHCO_3$ aq, and extracted with CH_2Cl_2. The product was **15f** (0.076 g, 40%). A GC-MS analysis revealed that the product was a mixture of two diastereomers (83 : 17). MS *m/z* 333 (M^+-15), 289, 275, 165, 135, 125, 59 (base). ^1H NMR (as mixture) $\delta=0.15$ (m, 9H), 1.15 (dist.d, $J=7.2$ Hz, 6H), 1.50—2.60 (m, 9H), 3.23 (s, 3H), 3.55 (q, $J=6.4$ Hz, 1H). HRMS. Found: *m/z* 333.0905. Calcd for $C_{13}H_{25}O_2Sn$: (M−Me), 333.0877.

2-(1-Methoxybenzyl)-2-(1-trimethylstannylethyl)-1-cyclohexanone (15g). To a mixture of benzaldehyde dimethyl acetal (0.304 g, 2.00 mmol) and BF_3–Et_2O (0.245 ml, 2.00 mmol) in CH_2Cl_2 (10 ml) was added **14a** (0.600 g, 1.66 mmol) at −78 °C. After strring for 4 h, the reaction mixture was treated with $NaHCO_3$ aq, and extracted with CH_2Cl_2. The product was **15g** (0.325 g, 48%). A GC-MS analysis revealed that the product was a mixture of two diastereomers (89 : 11). MS *m/z* 395 (M^+-15), 289, 165, 121 (base). IR 3062, 3029, 2934, 2867, 2822, 1691, 1452, 1249, 1133, 1094, 1075, 840, 759 cm^{-1}. ^1H NMR (as mixture) $\delta=0.11$ (s, 9H), 1.10 (br.s, 3H), 1.30—2.71 (m, 9H), 3.09 (s, 3H), 4.42 (s, 1H), 7.20 (br.s, 5H). HRMS. Found: *m/z* 395.0990. Calcd for $C_{18}H_{27}O_2Sn$: (M−Me), 395.1033.

General Procefure for the Lewis Acid-Induced Reactions of 7 or 15. A solution of stannyl ketones **7** or **15** and Lewis acid in CH_2Cl_2 was kept under the conditions specified below. The mixture was quenched with sat. $NaHCO_3$ aq, and the residue was purified by column chromatography. The results for **7** are given in Table 1, and for **15** in Table 3, respectively.

Reaction of 7a with $TiCl_4$. The reaction of **7a** (0.040 g, 0.145 mmol) and $TiCl_4$ (0.5 M, 0.291 ml) at 0°C for 15 min afforded **9a** (0.030 g, 44%) as a single product. **9a** was identical with the commercial sample.

Reaction of 7b with $TiCl_4$. The reaction of **7b** (0.100 g, 0.345 mmol) in CH_2Cl_2 (3.46 ml) and $TiCl_4$ (0.5 M, 0.692 ml) at 0 °C for 15 min afforded a mixture of **8b** and **9b** (0.030 g, 69%, 89 : 11 by GLC analysis). **9b** was identical with the sample prepared by the ring contraction of 2-cycloocten-1-one by Me_3SnLi/TMSOTf.[6]

For **8b**: MS *m/z* 126 (M^+), 111, 98 (base), 97, 84, 83, 82, 70, 69, 67.

For **9b**: MS *m/z* 126 (M^+), 111, 98 (base), 97, 84, 83, 82,

70, 69, 68, 67. ^{1}H NMR δ=1.00 (d, J=6.6 Hz, 3H), 1.20—2.10 (m, 8H), 2.10—2.80 (m, 3H).

Reaction of 7c with $TiCl_4$ The reaction of **7c** (0.050 g, 0.165 mmol) in CH_2Cl_2 (1.65 ml) and $TiCl_4$ (0.5 M, 0.330 ml) at 0 °C for 15 min afforded a mixture of **8c** and **9c** (0.020 g, 87%, 74 : 26 by GLC analysis).

For **8c**: MS m/z 140 (M^+), 125, 112, 111, 98, 97, 83, 69, 55 (base).

For **9c**: MS m/z 140 (M^+), 125, 112, 111, 98, 97 (base), 69.

Reaction of 7c with TMSOTf. The reaction of **7c** (0.050 g, 0.165 mmol) in CH_2Cl_2 (1.65 ml) and TMSOTf (0.5 M, 0.330 ml) at 0 °C for 15 min afforded a mixture of **8c** and **9c** (0.018 g, 78%, 11 : 89 by GLC analysis).

Reaction of 7d with $TiCl_4$. The reaction of **7d** (0.100 g, 0.315 mmol) in CH_2Cl_2 (3.15 ml) and $TiCl_4$ (0.5 M, 0.631 ml) at 0 °C for 15 min afforded a mixture of **8d** and **9d** (0.040 g, 82%, 51 : 49 by GLC analysis).

For **8d**: MS m/z 154 (M^+), 139, 126, 98, 83, 69, 55 (base).

For **9d**: MS m/z 154 (M^+), 139, 97 (base), 69, 55.

Reaction of 15a with $TiCl_4$. The reaction of **15a** (0.098 g, 0.30 mmol) and $TiCl_4$ (0.057 g, 0.30 mmol) in CH_2Cl_2 (5 ml) at 0 °C for 30 min afforded **17a** (0.384 g, 92%). MS m/z 138 (M^+), 123, 110, 95, 81, 67 (base), 55. IR 3395, 3092, 2933, 2860, 1709, 1641, 1448, 1256, 1154, 897 cm^{-1}. ^{1}H NMR δ=1.14 (d, J=6.6 Hz, 3H), 1.51—1.98 (m, 4H), 1.98—2.59 (m, 4H), 3.08 (q, J=6.6 Hz, 1H), 4.94 (br.s, 1H), 4.90 (br.s, 1H). HRMS. Found: m/z 138.1052. Calcd for $C_9H_{14}O$: (M), 138.1045.

Reaction of 15b with $TiCl_4$. The reaction of **15b** (0.160 g, 0.37 mmol) and $TiCl_4$ (0.37 mmol) in CH_2Cl_2 (5 ml) at 0°C for 10 min afforded **17b** (0.069 g, 82%). MS m/z 222 (M^+), 207, 193, 175, 123, 109, 95 (base), 82, 81. IR 3082, 2931, 2860, 1712, 1639, 1458, 1369, 1120, 898 cm^{-1}. ^{1}H NMR δ=1.12 (d, J=7.0 Hz, 3H), 1.06—1.85 (m, 16 H), 1.85—2.75 (m, 4H), 3.12 (q, J=7.0 Hz, 1H), 4.91 (br.s, 1H), 4.95 (br.s, 1H). ^{13}C NMR δ=15.61, 22.15, 24.79, 24.90, 25.08, 25.23, 25.34, 32.69, 39.57, 53.77, 112.45, 147.58, 210.95. HRMS. Found: m/z 222.1965. Calcd for $C_{15}H_{26}O$: (M), 222.1984.

Reaction of 15c with $TiCl_4$ or $EtAlCl_2$. A mixture of **15c** (0.140 g, 0.29 mmol) and $TiCl_4$ (0.06 ml, 0.57 ml) in CH_2Cl_2 (5 ml) was kept at room temperature for 48 h. The work-up gave **17a** (0.030 g, 75%). The reaction with $EtAlCl_2$ gave identical results.

Reaction of 15c with TMSOTf. The reaction of **15c** (0.170 g, 0.349 mmol) with TMSOTf (0.155 g, 0.697 mmol) in CH_2Cl_2 (4 ml) at 0 °C for 2 h and then at room temperature for 46 h gave the product **22**[16] in 75% yield.

Reaction of 15d with $TiCl_4$. The reaction of **15d** (0.100 g, 0.13 mmol) with $TiCl_4$ (0.07 ml, 0.63 mmol) at 0 °C for 5 min gave **17a** (0.029 g, 63%).

Reaction of *threo*-15e with $TiCl_4$. The reaction of *threo*-**15e** (0.090 g, 0.27 mmol) and $TiCl_4$ (0.059 g, 0.54 mmol) in CH_2Cl_2 (6 ml) at −78 °C for 5 min afforded (*E*)-**17e** (0.035 g, 84%). MS m/z 152 (M^+), 109, 95 (base), 81, 67. IR 2939, 2860, 1708, 1446, 1151, 788 cm^{-1}. ^{1}H NMR δ=1.15 (d, J=7.2 Hz, 3H), 1.68 (d, J=6.8 Hz, 3H), 1.40—2.62 (m, 8H), 3.05 (q, J=6.9 Hz, 1H), 5.48 (q, J=6.9 Hz, 1H). ^{13}C NMR δ=13.11, 15.26, 26.86, 28.78, 29.30, 42.12, 55.32, 122.83, 139.50, 214.86. HRMS. Found: m/z 152.1162. Calcd for $C_{10}H_{16}O$: (M), 152.1201.

Reaction of *erythro*-15e with $TiCl_4$. The reaction of *erythro*-**15e** (0.042 g, 0.126 mmol) and $TiCl_4$ (0.046 g, 0.252 mmol) in CH_2Cl_2 (5 ml) at 0 °C for 5 min afforded (*Z*)-**17e** (0.016 g, 83 %). MS m/z 152 (M^+), 109, 95 (base), 81, 67. IR 2930, 2860, 1711, 1660, 1446, 1158 cm^{-1}. ^{1}H NMR (400 MHz) δ=1.09 (d, J=7.0 Hz, 3H), 1.67 (d, J=7.0 Hz, 3H), 1.35—1.65 (m, 2H), 1.59—1.73 (m, 2H), 1.75—1.98 (m, 2H), 2.21—2.37 (m, 2H), 3.42 (q, J=6.8 Hz, 1H), 5.51 (q, J=6.8 Hz, 1H). ^{13}C NMR δ=13.36, 13.93, 26.69, 32.26, 34.55, 42.66, 48.64, 123.49, 139.61, 214.43. HRMS. Found: m/z 152.1184. Calcd for $C_{10}H_{16}O$: (M), 152.1201.

Reaction of 15f with $TiCl_4$. The reaction of **15f** (90 : 10 diastereomer mixture, 0.104 g, 0.30 mmol) and $TiCl_4$ (0.080 ml, 0.69 mmol) in CH_2Cl_2 (5 ml) at −78 °C for 30 min afforded (*E*)-**17e** (0.042 g, 92%).

Reaction of 15g with $TiCl_4$. The reaction of **15g** (89 : 11 diastereomer mixture, 0.300 g, 0.73 mmol) and $TiCl_4$ (0.16 ml, 1.47 mmol) in CH_2Cl_2 (6 ml) at −78 °C for 10 min afforded (*E*)-**17g** (0.063 g, 40 %). MS m/z 214 (M^+, base), 199, 171, 157, 143, 129, 118, 115, 95, 91. IR 2932, 2861, 1704, 1644, 1446, 699 cm^{-1}. ^{1}H NMR δ=0.61—2.72 (m, 8H), 1.24 (d, J=6.6 Hz, 3H), 3.19 (q, J=6.6 Hz, 1H), 6.42 (br.s, 1H), 7.27 (br.s, 1H). ^{13}C NMR δ=15.53, 26.14, 29.97, 30.20, 42.59, 55.69, 126.49, 128.13, 128.22, 128.26, 128.37, 128.59, 137.33, 141.82, 212.98. HRMS. Found: m/z 214.1335. Calcd for $C_{15}H_{18}O$: (M), 214.1357.

Reaction of *erythro*- and *threo*-15e with $EtAlCl_2$. The reaction of *threo*-**15e** (containing 5% of *erythro*-isomer, 0.200 g, 0.60 mmol) and $EtAlCl_2$ (0.93 M–hexane, 1.94 ml, 1.80 mmol) at room temperature for 5 min gave **25e** (0.080 g, 79%). MS m/z 170 (M^+), 152, 137, 125 (base), 79, 67, 55. IR 3416, 2931, 2859, 1449, 1375, 1094, 1055, 1005, 982, 904, 787 cm^{-1}. ^{1}H NMR δ=0.93 (d, J=6.2 Hz, 3H), 1.10—2.90 (m, 10H), 1.57 (d, J=6.4 Hz, 3H), 3.91 (q, J=6.2 Hz, 1H), 5.52 (q, J=6.4 Hz, 1H). ^{13}C NMR[17] δ=[12.40*, 12.75], [15.22, 17.03*], [22.67, 23.36*], [25.65, 26.00*], [26.84, 27.02*], [36.33, 37.63*], [67.14*, 67.71], [76.58, 77.00*], [114.90*, 117.06], [141.32, 140.86*], (90 : 10). HRMS. Found: m/z 152.1190. Calcd for $C_{10}H_{16}O$: (M−H_2O), 152.1201. The reaction of *erythro*-**15e** gave almost identical results.

Reaction of 15f with $EtAlCl_2$. The reaction of **15f** (90 : 10 diastereomer mixture, 0.255 g, 0.74 mmol) and $EtAlCl_2$ (0.93 M–hexane, 2.66 ml, 2.48 mmol) at room temperature for 30 min gave **25f** (0.067 g, 54 %). MS m/z 184 (M^+), 152, 137, 125 (base), 79, 67. IR 3479, 2932, 2860, 1447, 1373, 1316, 1134, 1097, 1087, 985, 788 cm^{-1}. ^{1}H NMR δ=1.10—2.82 (m, 8H), 1.18 (d, J=6.2 Hz, 3H), 1.69 (d, J=7.0 Hz, 3H), 2.45 (br.s, 1H), 3.29 (s, 3H), 3.59 (q, J=6.2 Hz, 1H), 5.43 (q, J=7.0 Hz, 1H). ^{13}C NMR δ=12.84, 13.03, 22.54, 25.81, 27.09, 36.26, 57.77, 76.18, 78.10, 115.23, 141.74. HRMS. Found: m/z 184.1507. Calcd for $C_{11}H_{20}O_2$: (M), 184.1463.

Reaction of 15g with $EtAlCl_2$. The reaction of **15g** (89 : 11 diastereomer mixture, 0.170 g, 0.42 mmol) and $EtAlCl_2$ (0.93 M–hexane, 0.89 ml, 0.83 mmol) at 0 °C for 10 min gave **25g** (0.049 g, 47%) as a mixture of 60 : 40 diastereomer mixture. The minor component was isolated in pure state. The data for major component was deduced from those of the mixture. For minor component: MS (20 eV) m/z 246 (M^+), 228, 214, 213, 125 (base), 121. IR 3023, 2952, 2928, 2858, 1448, 1334, 1089, 1068, 990, 695 cm^{-1}.

^{1}H NMR δ=1.20—2.87 (m, 9H), 1.31 (d, J=6.6 Hz, 3H), 3.15 (s, 3H), 4.23 (s, 1H), 5.05 (q, J=6.6 Hz, 1H), 7.00 (br.s, 5H). ^{13}C NMR δ=12.29, 23.53, 26.27, 26.87, 37.10, 57.44, 77.00, 83.64, 117.32, 127.18, 127.29, 128.02, 137.24, 138.49. For major component: ^{1}H NMR δ=1.20—2.87 (m, 9H), 1.68 (d, J=6.6 Hz, 3H), 3.05 (s, 3H), 4.18 (s, 1H), 5.35 (q, J=6.6 Hz, 1H), 7.00 (br.s, 5H).

***cis*-1,2-Dimethylspiro[4.2]octan-4-one (18).** To a solution of *threo*-**15e** (0.070 g, 0.21 mmol) in hexane (6 ml) were added triethylamine (0.12 ml, 0.54 mmol) and mesyl chloride (0.08 ml, 0.54 mmol) at 0 °C. After being stirred for 10 min, the solution was stirred at room temperature for another 20 min. It was quenched with sat. $NaHCO_3$ aq, and the product was purified on a silica-gel column (hexane : AcOEt=15 : 1) to afford product (0.012 g, 36%). MS m/z 152 (M^+), 137 (base), 123, 109, 95, 81, 79, 67. IR 2932, 2866, 1686, 1456, 1292, 1182, 1141, 1081, 787 cm^{-1}. ^{1}H NMR (400 MHz) δ=0.93 (m, 6H), 1.47—1.89 (m, 8H), 2.34 (t, J=6.9 Hz, 2H). ^{13}C NMR δ=7.21, 22.45, 23.57, 25.64, 34.56, 39.73, 212.37. HRMS. Found: m/z 152.1208. Calcd for $C_{10}H_{16}O$: (M), 152.1201.

***trans*-1,2-Dimethylspiro[4.2]octan-4-one (19).** To a solution of *erythro*-**15e** (0.260 g, 0.78 mmol) in hexane (16 ml) were added triethylamine (0.44 ml, 3.13 mmol) and mesyl chloride (0.31 ml, 3.13 mmol) at 0 °C. After being stirred for 10 min, the solution was stirred at room temperature for another 20 min, and quenched with sat. $NaHCO_3$ aq. The product was purified on a silica-gel column (hexane : AcOEt=15 : 1) to afford product (0.043 g, 37%). MS m/z 152 (M^+), 137 (base), 123, 109, 95, 81, 79, 67. IR 2931, 2868, 1690, 1448, 1287, 1130, 1076, 962 cm^{-1}. ^{1}H NMR (400 MHz) δ=0.71 (quint, J=5.9 Hz, 1H), 0.89 (d, J=5.9 Hz, 3H), 0.98 (d, J=6.2 Hz, 3H), 1.36—2.07 (m, 8H), 2.46 (m, 1H). ^{13}C NMR δ=12.34, 12.39, 23.14, 24.11, 24.84, 30.46, 34.08, 38.24, 42.15, 209.54. HRMS. Found: m/z 152.1161. Calcd for $C_{10}H_{16}O$: (M), 152.1201.

Reaction of *threo*-15e with $EtAlCl_2$ in the Presence of Benzaldehyde. The $EtAlCl_2$-induced reaction of *threo*-**15e** (0.21 mmol) was carried out in the presence of benzaldehyde (0.63 mmol) under otherwise the same conditions as described above. The crossed product **27** was isolated in 76% yield, as well as 12% of **25e**. For **27**: MS (20 eV) m/z 214 (M^+-18), 199, 196, 185, 181, 125 (base), 105. IR 3427, 3352, 3019, 2923, 2858, 1451, 1216, 1042, 756 cm^{-1}. ^{1}H NMR δ=1.39 (d, J=6.6 Hz, 3H), 1.06—2.73 (m, 10H), 4.60—5.13 (m, 2H), 7.07 (br.s, 5H). ^{13}C NMR δ=12.37, 23.36, 26.47, 26.89, 37.36, 74.20, 77.53, 116.99, 127.11, 127.42, 127.86, 127.91, 128.04, 139.47, 140.24. HRMS. Found: m/z 214.1342. Calcd for $C_{15}H_{18}O$: ($M-H_2O$), 214.1358.

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