Stereospecific Synthesis of (+)- and (−)-Cyclooctenone Derivatives Using a Ring Expansion Reaction with $Me_3SiSnBu_3$ and CsF

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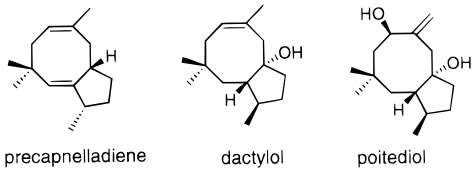
Abstract: Novel synthesis of an eight-membered compound by the ring expansion reaction of a two-carbon unit was developed using the stannyl anion generated from $Me_3SiSnBu_3$ and CsF in DMF. *cis*- and *trans*-cyclooctenone derivatives were synthesized from cyclohexanone derivatives having vinyl iodide in a tether by treatment with $Me_3SiSnBu_3$ and CsF in DMF in a stereospecific manner. The *trans*-cyclooctenone derivative was isomerized to the *cis*-isomer in the presence of $Me_3SiSnBu_3$ and CsF. It is known that the *trans*-eight-membered ring is an asymmetric compound. Using this procedure, (+)- and (−)-*trans*-cyclooctenone derivatives could be synthesized from the corresponding optically active cyclohexanone derivatives.

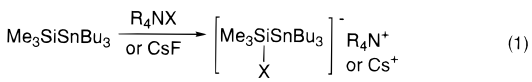
Among medium-sized cyclic compounds, the eight-membered ones are the most difficult to construct due to the high degree of ring strain and transannular interactions presented by these molecules. They occur widely in nature, particularly in higher plants and marine organisms, and many cyclooctanoid natural products have been found to exhibit interesting biological activities. Precapnelladiene,[1b] dactylol,[1c] and poitediol[1d] (Figure 1) are examples of sesquiterpenes isolated from marine sources that contain this ring size in their skeletons, and they have been the target of several synthetic works.[1]

Some examples of ring expansion from six- to eight-membered rings are described in the literature, most of which apply to the Claisen[2] or oxy-Cope rearrangement.[3] We planned the construction of an eight-membered ring by a ring expansion reaction using the stannyl anion generated from $Me_3SiSnBu_3$[4,5] (**1**) and CsF.[6] Reaction of $Me_3SiSnBu_3$ in the presence of R_4-NX or CsF produced a stannyl anion[7] via hypervalent silicate, which is a useful tool in synthetic organic chemistry (eq 1).[6]



precapnelladiene dactylol poitediol

Figure 1.



(1)

Ring Expansion to Cyclooctadiones from Cyclohexadiones Using $Me_3SiSnBu_3$ and F^-. Reaction of cyclohexadione derivative **Ia** with the stannyl anion should produce vinyl anion,[6] which reacts with the carbonyl group intramolecularly to produce the four-membered product **IIa** (Scheme 1). Then the ring opening of **IIa** would give the two-carbons-enlarged ring **IIIa**.[8]

(1) (a) Petasis, N.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757 and references therein. (b) Ayanogulo, E.; Gebreyesus, T.; Beechan, C.; Djerassi, C, *Tetrahedron* **1979**, *35*, 1035. (c) Schitz, F.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719. (d) Fenical, W.; Shulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978**, *43*, 3628.

(2) (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868. (b) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352.

(3) Paquette, L. A.; Liang, S.; Galatsis, P. *Synth. Lett.* **1990**, 663.

(4) (a) Tamborski, C.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237. (b) Schumann, H.; Ronecker, S. *Z. Naturforsch. B* **1967**, *B22*, 452. (c) Chenard, B. L.; Van Zyl, C. M. *J. Org. Chem.* **1986**, *51*, 3561.

(5) (a) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49. (b) Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3539. (c) Mitchell, T. N.; Killing, H.; Dicke, R.; Wickenkamp, R. *J. Chem. Soc., Chem. Commun.* **1985**, 354. (d) Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868. (e) Murakami, M.; Morita, Y.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 428. (f) Murakami, M.; Amii, H.; Takizawa, N.; Ito, Y. *Organometallics* **1993**, *12*, 4223. (g) Hada, M.; Tanaka, Y.; Ito, M.; Murakami, M.; Amii, H.; Ito, Y.; Nakatsuji, H. *J. Am. Chem. Soc.* **1994**, *116*, 8754. (h) Casson, S.; Kocienski, P.; Reid, G.; Smith, N.; Street, J. M.; Webster, M. *Synthesis* **1994**, 1301. (i) Murakami, M.; Yoshida, T.; Kawanami, S.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 6408. (j) Ito, Y.; Bando, T.; Matsuura, T.; Ishikawa, M. *J. Chem. Soc., Chem. Commun.* **1986**, 980. (k) Tsuji, Y.; Obora, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9368. (l) Lipshutz, B. H.; Reuter, D. C.; Ellsworth, E. L. *J. Org. Chem.* **1989**, *54*, 4975. (m) Chenard, B. L.; Laganis, E. D.; Davidson, F.; RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3666. (n) Obora, Y.; Tsuji, Y.; Asayama, M.; Kawamura, T. *Organometallics* **1993**, *12*, 4697.

(6) (a) Mori, M.; Kaneta, N.; Isono, N.; Shibasaki, M. *Tetrahedron Lett.* **1991**, *32*, 6139. (b) Mori, M.; Kaneta, N.; Isono, N.; Shibasaki, M. *J. Organomet. Chem.* **1993**, *455*, 255; (c) **1994**, *464*, 35. (d) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972. (e) Mori, M.; Hashimoto, A.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 6503. (f) Honda, T.; Mori, M. *Chem. Lett.* **1994**, 1013. (g) Sato, H.; Isono, N.; Okamura, K.; Date, T.; Mori, M. *Tetrahedron Lett.* **1994**, *35*, 2035. (h) Kinoshita, A.; Mori, M. *Chem. Lett.* **1994**, 1475. (i) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (j) Isono, N.; Mori, M. *Tetrahedron Lett.* **1995**, *36*, 9345. (k) Isono, N.; Mori, M. *Main Group Met. Chem.* **1996**, *19*, 277. (l) Sato, H.; Isono, N.; Miyoshi, I.; Mori, M. *Tetrahedron* **1996**, *52*, 8143. (m) Isono, N.; Mori, M. *J. Org. Chem.* **1996**, *61*, 7867.

(7) Stannyl anion prepared from organotin halides: (a) Kuivila, H. G.; Considine, J. L.; Kennedy, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 7206. (b) Kitching, W.; Olszowy, H.; Waugh, J.; Doddrel, D. *J. Org. Chem.* **1978**, *43*, 898. (c) Blake, D.; Coates, G. E.; Tate, J. M. *J. Chem. Soc.* **1961**, 618. (d) Tamborsky, C.; Ford, F. E.; Lehn, W. L.; Moore, G. J.; Soloski, E. J. *J. Org. Chem.* **1962**, *27*, 619. (e) Tamborsky, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 181. Stannyl anion prepared from hexaorganoditins: (f) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836. (g) *J. Am. Chem. Soc.* **1978**, *100*, 1481. (h) Quintard, J. P.; Hauvette-Frey, S.; Pereyre, M. *Bull. Soc. Chim. Belg.* **1978**, *87*, 505. Stannyl anion prepared from organotin hydrides: (i) Corriu, R. J. P.; Guerin, C. *J. Organomet. Chem.* **1980,** *197*, C19.

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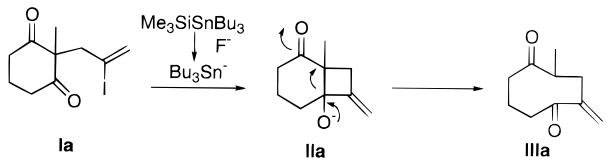
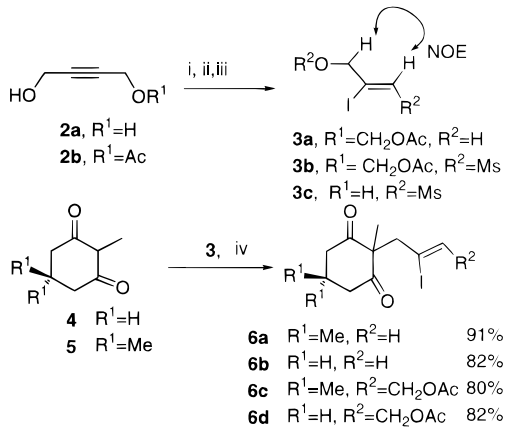
Scheme 1. Our Plan for the Ring Expansion Reaction Using $Me_3SiSnBu_3$

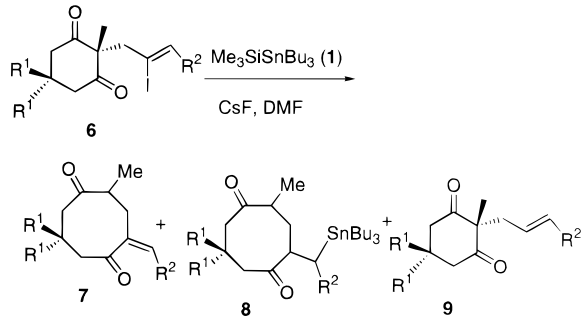


Scheme 2. Synthesis of the Starting Material[a]



[a] Conditions: (i) Ac_2O, Py, CH_2Cl_2, 45%. (ii) MaI, TMSCl, CH_3CN, 35%. (iii) MsCl, Et_3N, quant. (iv) Cs_2CO_3, NaI, DMF.

Scheme 3



To examine the ring expansion reaction according to our plan, the starting cyclohexadione derivatives **6** were prepared as shown in Scheme 2. The vinyl iodide **3b** as the side chain was prepared from 2-butyne-1,4-diol (**2a**). The stereochemistry of **3b** was determined by an NOE experiment. Condensation of **4** or **5** with **3b** or **3c** proceeded smoothly to give **6a**−**d**, having a vinyl iodide in a tether.

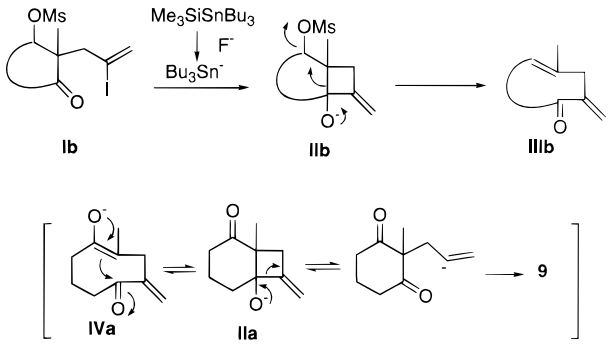
When a DMF solution of cyclohexadione **6a**, 2 equiv of $Me_3SiSnBu_3$, and 2 equiv of CsF was stirred at room temperature for 1.5 h, the expanded cyclooctadione **7a** was obtained in 24% yield along with the corresponding Michael adduct **8a** in 17% yield (Scheme 3). As a byproduct, dehalogenation product **9a** was formed in 25% yield. Similar results were obtained in the ring expansion of cyclohexanediones **6b**−**d**, as shown in Table 1. Compounds **6c** and **6d**, having a longer side chain, gave good results (runs 3 and 4).

These results indicate that the ring expansion reaction of a two-carbon unit was realized from cyclohexadione **6**, having vinyl iodide as a side chain, using $Me_3SiSnBu_3$ and CsF and that an eight-membered product was formed.

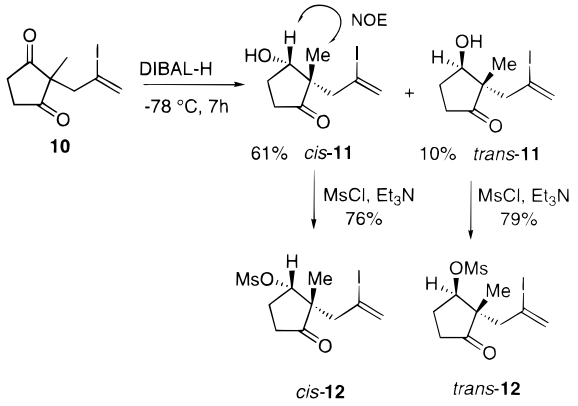
Table 1. Reaction of **2** with $Me_3SiSnBu_3$ and CsF

				yield (%)		
run	substrate	R^1	R^2	**7**	**8**	**9**
1	**6a**	Me	H	24	17	25
2	**6b**	H	H	39	3	33
3	**6c**	Me	CH_2OAc	38		16
4	**6d**	H	CH_2OAc	58		34

Scheme 4



Scheme 5. Synthesis of Vinyl Iodide



Ring Expansion to Cycloalkanones Using $Me_3SiSnBu_3$ and CsF. Our plan was slightly modified to increase the yield of the expanded product because the reaction of **Ia** with $Me_3SiSnBu_3$ and CsF is reversible and the yield of the dehalogenation product increases, as shown in Scheme 4. If the leaving group is placed at the 3-position of cyclohexanone **Ib**, having a vinyl group at the side chain, **Ib** would give cycloalkanone **IIIb** via **IIb** by treatment with $Me_3SiSnBu_3$ and CsF.

At first, we examined whether cyclopentanone derivative **12** could be expanded to cycloheptenone derivative **13** or **15**. For the synthesis of cyclopentanone derivatives, cyclopentadione **10** was reduced with DIBAL-H at −78 °C to give *cis*-**11** and *trans*-**11** in 61% and 10% yields, respectively (Scheme 5). In this report, *cis* and *trans* refer to the relative positions of the mesylate and the side chain containing the vinyl iodide. The stereochemistry of *cis*-**11** was determined by an NOE experiment. Mesylation of each isomer proceeded smoothly to provide *cis*-**12** and *trans*-**12** in 76% and 79% yields, respectively.

When the five-membered substrate *cis*-**12** was treated with 4 equiv of $Me_3SiSnBu_3$ and 4 equiv of CsF[9] in DMF at room temperature, the Michael adduct **13** was obtained in 25% yield along with dehalogenation product *trans*-**14**, which underwent further substitution of the mesyl group by the stannyl anion in

(8) (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Schreiber, S. *J. Am. Chem. Soc.* **1980**, *102*, 6163. (d) Mahajan, J. R.; de Araujo, H. C. *Synthesis* **1981**, 49.

(9) Because of the low molecular weight of the seven-membered α,β-unsaturated ketone **15** formed, an excess amount of $Me_3SiSnBu_3$ and CsF was used in order to convert it to the corresponding Michael addition product **13**.

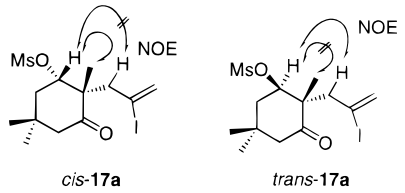
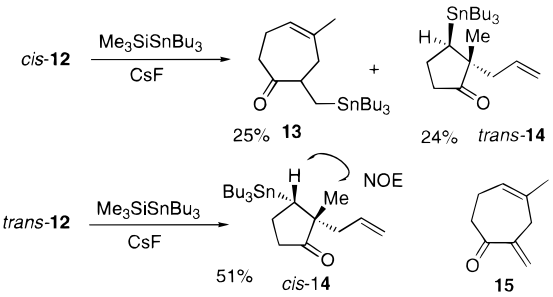
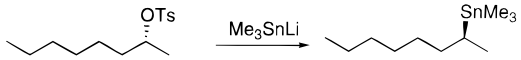


Figure 2.

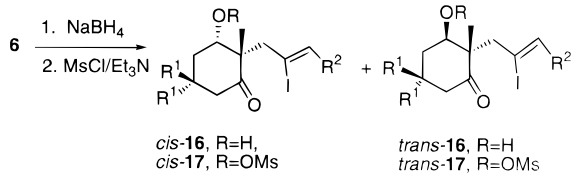
Scheme 6. Reaction of Cyclopentenes with $Me_3SiSnBu_3$ and CsF



Scheme 7



Scheme 8. Synthesis of the Starting Vinyl Iodide

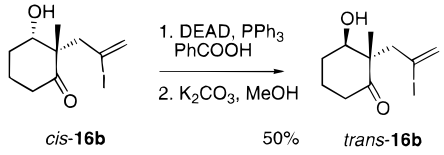


24% yield (Scheme 6). On the other hand, the reaction of *trans*-**12** did not give any expanded cycloheptenone, and only a substitution product, *cis*-**14**, was isolated in 51% yield. However, the result of an NOE experiment and the spectral data of *cis*-**14** revealed that these two products (*trans*- and *cis*-**14**) were epimers. This indicates that substitution of the mesyloxy group by the stannyl group occurred with inversion of configuration. This is in good agreement with the results obtained by San Filippo and Silberman[10a] and Ashby and DePriest,[10b] who verified that the substitution of optically active tosylate by trimethylstannylsodium or -lithium occurred with complete inversion of configuration by an S_N2 pattern, as shown in Scheme 7.

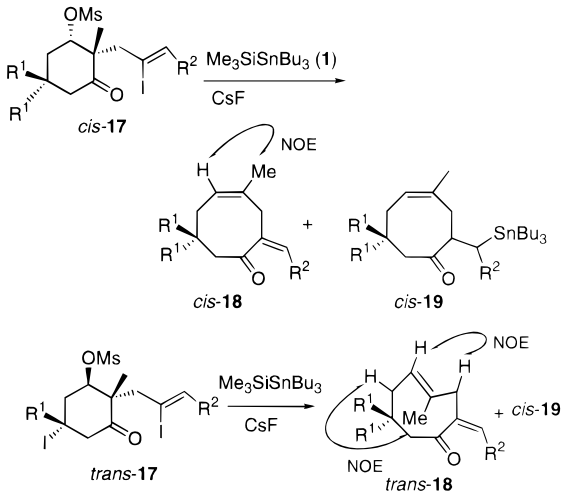
Next, we tried to synthesize an eight-membered compound by a ring expansion reaction. The starting cyclohexanones *cis*- and *trans*-**17** were prepared by reduction of cyclohexadione derivative **6** with $NaBH_4$ followed by mesylation (Scheme 8). The stereochemistry was determined by the NOE experiments on *cis*- and *trans*-**17a** (Figure 2), and we designated *cis* and *trans* as the relative positions of the mesylate and the side chain containing the vinyl iodide. In the case of the reduction of **6b** with $NaBH_4$, only a small amount of *trans*-**16b** was obtained (Table 2, run 2). Thus, *cis*-**16b** was converted into *trans*-**16b** using Mitsunobu's reaction (Scheme 9).[11]

When a DMF solution of *cis*-**17a** was stirred in the presence of $Me_3SiSnBu_3$ (3 equiv) and CsF (3 equiv) at room temperature for 2 h, *cis*-**19a** was obtained in 86% yield (Table 3, run 1;

Scheme 9



Scheme 10



Scheme 10). When the solvent was changed from DMF to THF, *cis*-**18a** was obtained in 70% yield (run 2). Since it was clear that *cis*-**19a** was obtained from *cis*-**18a** and the stannyl anion, *cis*-**17a** was treated with 1.5 equiv of $Me_3SiSnBu_3$ and CsF in DMF at room temperature to give *cis*-**18a** as a main product (run 3). On the other hand, when the *trans*-isomer **17a** was treated in a similar manner, *cis*-**19a** was obtained in 36% yield as a main product, and *trans*-isomer **18a** was obtained in 1% yield (run 4). A slight excess of $Me_3SiSnBu_3$ and CsF gave *trans*-**18a** in 33% yield from *trans*-**17a** (run 5). It is interesting that the *trans*-eight-membered ring, which is the smallest *trans*-cycloalkene isolable at room temperature,[12] was obtained under these reaction conditions. The stereochemistry of each isomer, *cis*-**18a** and *trans*-**18a**, was determined by NOE experiments. The ^1H NMR spectra of *cis*-**18a** at room temperature showed broad peaks, but those of *trans*-**18a** appeared as sharp signals. The result of a lower-temperature experiment (−50 °C) conducted on *cis*-**18** indicates that these peaks are clearly sharp (^1H NMR spectra are contained in Supporting Information).

The reactions of various cyclohexanone derivatives **17** with $Me_3SiSnBu_3$ and CsF were examined. When *cis*-**17b** was treated with $Me_3SiSnBu_3$ (3 equiv) and CsF (3 equiv) in DMF in a similar manner, *cis*-**18b** and *cis*-**19b** were obtained in 9% and 49% yields, respectively. In a similar treatment of *trans*-**17b** with $Me_3SiSnBu_3$ and CsF, *trans*-**18b** was obtained as a main product (run 7). Both *cis*-**17c** and *trans*-**17c** were reacted with $Me_3SiSnBu_3$ (2 equiv) and CsF (2 equiv) in DMF to give *cis*-**18c** and *trans*-**18c** in yields of 73% and 41%, respectively (runs 8 and 9). In all the reactions of *trans*-**17** with $Me_3SiSnBu_3$ and CsF, no *trans*-**19** was obtained, and *cis*-**19** and *trans*-**18** were isolated. Although it is not clear at this stage why *cis*-**19a** was obtained from *trans*-**17a** (run 4), the reaction is thought to proceed in a stereospecific manner (runs 3 and 5). When the leaving group and the cleaving carbon−carbon bond in the intermediary four-membered compound **V** generated from *cis*-

(10) (a) San Filippo, J., Jr.; Silberman, J. *J. Am. Chem. Soc.* **1982**, *104*, 2831. (b) Ashby, E. C.; DePriest, R. *J. Am. Chem. Soc.* **1982**, *104*, 6144.

(11) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(12) (a) Ziegler, K.; Wilms, H. *Justus Liebigs Ann. Chem.* **1950**, *567*, 1. (b) Cope, A. C.; Pike, R. I.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3212.

Table 2. Reduction of 6 with $NaBH_4$ Followed by Mesylation

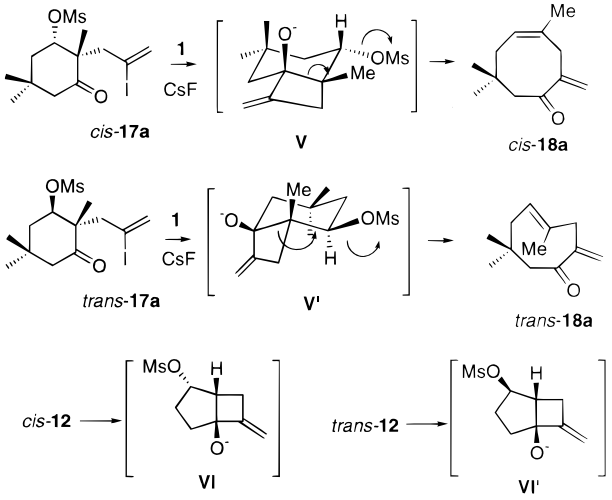
		cis-**16**				*trans*-**16**			
run	substrate	R^1	R^2	yield (%)	*cis*-**17** yield (%)	R^1	R^2	yield (%)	*trans*-**17** yield (%)
1	**6a**	Me	H	30	90	Me	H	67	87
2	**6b**	H	H	70	95	H	H	8	quant
3	**6c**	Me	CH_2OAc	36	90	Me	CH_2OAc	61	96

Table 3. Reaction of *cis*- and *trans*-**17** with $Me_3SiSnBu_3$ and CsF[a]

						yield (%)[b]		
run	substrate	R^1	R^2	amount of **1** (equiv)	solvent	*cis*-**18**	*cis*-**19**	*trans*-**18**
1	*cis*-**17a**	Me	H	3	DMF	0	86	0
2	*cis*-**17a**	Me	H	3	THF[c]	70	0	0
3	*cis*-**17a**	Me	H	1.5	DMF	42	4	0
4	*trans*-**17a**	Me	H	3	DMF	0	36	1
5	*trans*-**17a**	Me	H	1.5	DMF	0	0	33
6	*cis*-**17b**	H	H	3	DMF	9	49	0
7	*trans*-**17b**	H	H	3	DMF	0	4	32
8	*cis*-**17c**	Me	CH_2OAc	2	DMF	73	0	0
9	*trans*-**17c**	Me	CH_2OAc	2	DMF	0	0	41

[a] Reaction was carried out at room temperature in DMF. [b] Isolated yield. [c] Reaction was carried out at 0 °C.

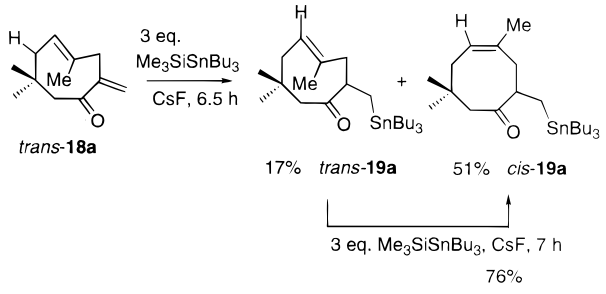
Scheme 11



17a are placed in antiperiplanar positions, the ring opening reaction is thought to proceed as shown in Scheme 11. On the other hand, *trans*-**17a** would proceed via **V′**, which satisfies the antiperiplanar positions required for synchronous fragmentation.[8] This mechanism can equally account for nonformation of a ring-expanded product from *trans*-**12**. The bicyclic intermediate **VI** formed from cyclopentanone derivative *cis*-**12** gave a ring expansion product, although the yield was low. However, *trans*-isomer **12** did not give the ring expansion product. The C−OMs bond of intermediate **VI′** is not placed at an antiperiplanar position in relation to the ring junction bond that will be cleaved if the bicyclic intermediate **VI′** is formed. *cis*-Eight-membered cyclic compounds occur widely in nature, and *cis*-**18c** is thought to be a key intermediate for the synthesis of precapnelladine, dactylol, or poitediol.

To investigate why *cis*-**19** was obtained from *trans*-**17** in the presence of an excess amount of $Me_3SiSnBu_3$ and CsF, *trans*-isomer **18a** was treated with 3 equiv of $Me_3SiSnBu_3$ and CsF (Scheme 12). As a result, *trans*-**19a** and *cis*-**19a** were obtained in 17% and 51% yields, respectively. The former product, *trans*-**19a**, was further treated in a similar manner to give *cis*-**19a** in high yield. These results show that isomerization of *trans* to *cis* occurs, although it is not clear whether the isomerization is caused by the stannyl anion or radical.[13]

Scheme 12



Synthesis of the Optically Active *trans*-Cyclooctenone Derivative. It is known that the *trans*-cyclooctene derivative is an asymmetric compound,[14] and it has attracted interest on account of its strained structure and conformation. There have been few reports on its synthesis,[15] and reports are even more scarce with respect to chiral forms.[16] Thus, we planned to prepare (+)- and (−)-*trans*-**18** from (+)- and (−)-*trans*-**17**, using this stannyl anion-promoted stereospecific ring expansion reaction (Scheme 13). For the synthesis of chiral *trans*-**18**, we chose (±)-*trans*-**17c** as the starting material, and the resolution of (±)-*trans*-**16c** was examined.

Various attempts were made to get the optically pure (+)- or (−)-*trans*-**16**, and we were able to separate *trans*-**20** and

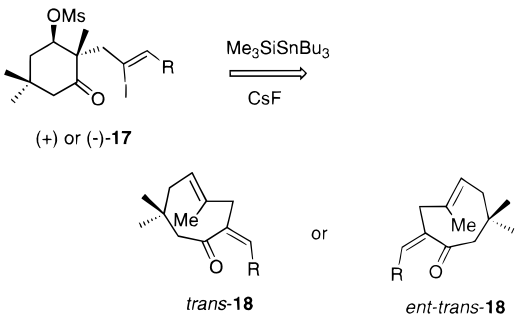
(13) Isomerization preferably occurs with *trans*-**18** rather than *trans*-**19**; because *trans*-**19a** was never obtained as a product from the reaction mixture, it was rationalized that, in the presence of an excess amount of stannyl anions, *trans*-**18a** first isomerizes to *cis*-**18a**, which then undergoes a conjugated addition, leading to *cis*-**19a**.

(14) (a) Cope, A. C.; Ganelin, C. R.; Johnson, H. W., Jr.; Van Auken, T. V.; Winkler, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 3276. (b) Cope, A. C.; Mehta, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 5626. (c) Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649. (d) Bach, R. D.; Mazur, U.; Hamama, I.; Lauderback, S. K. *Tetrahedron* **1963**, *28*, 1955. (e) Manor, P. C.; Shoemaker, D. P.; Parkes, P. S. *J. Am. Chem. Soc.* **1970**, *92*, 5260.

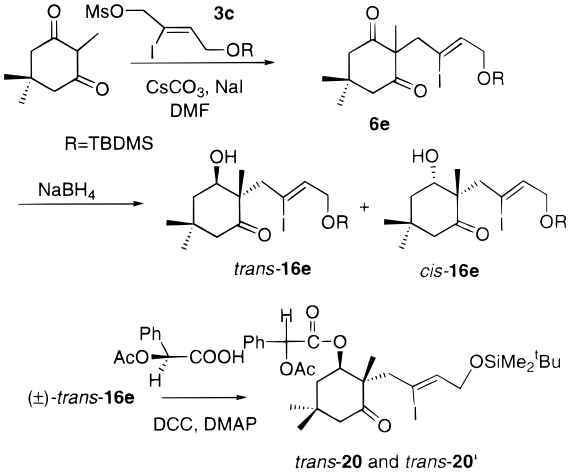
(15) (a) Coke, J. L.; Cooke, M. P., Jr.; Mourning, M. C. *Tetrahedron Lett.* **1968**, *18*, 2247. (b) Reese, C. B.; Shaw, A. *J. Am. Chem. Soc.* **1970**, *92*, 2566. (c) Whitham, G. H.; Wright, M. *J. Chem. Soc.* (*c*) **1971**, 886. (d) Prior, M. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 683. (e) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 3561. Synthesis by photoisomerization of *cis*-cyclooctene: (f) Swenton, J. S. *J. Org. Chem.* **1969**, *34*, 3217. (g) Deyrup, J. A.; Betkouski, M. *J. Org. Chem.* **1972**, *37*, 3561. (h) Inoue, Y.; Takamuku, S.; Sakurai, H. *Synthesis* **1977**, 111.

(16) (a) Corey, E. J.; Shulman, J. I. *Tetrahedron Lett.* **1968**, *33*, 3655. (b) Aratani, T.; Nakanishi, Y.; Nozaki, H. *Tetrahedron* **1970**, *26*, 4339. (c) Newton, P. F.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3072.

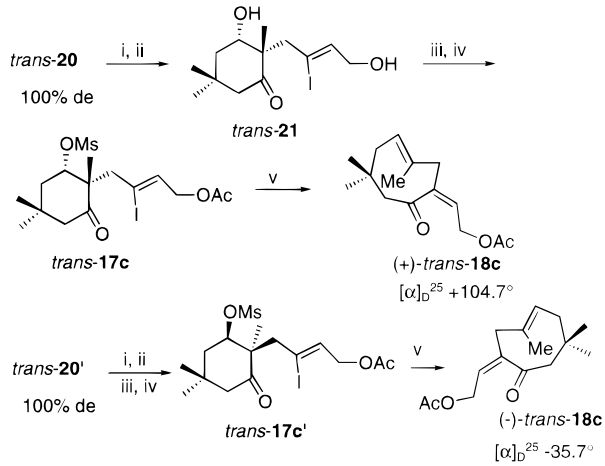
Scheme 13. Synthesis of Optically Active *trans*-Cyclooctenone



Scheme 14



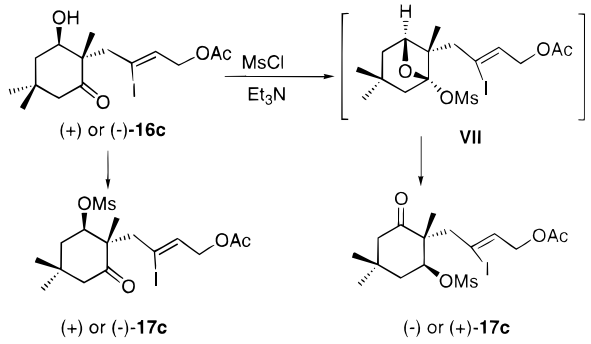
Scheme 15[a]



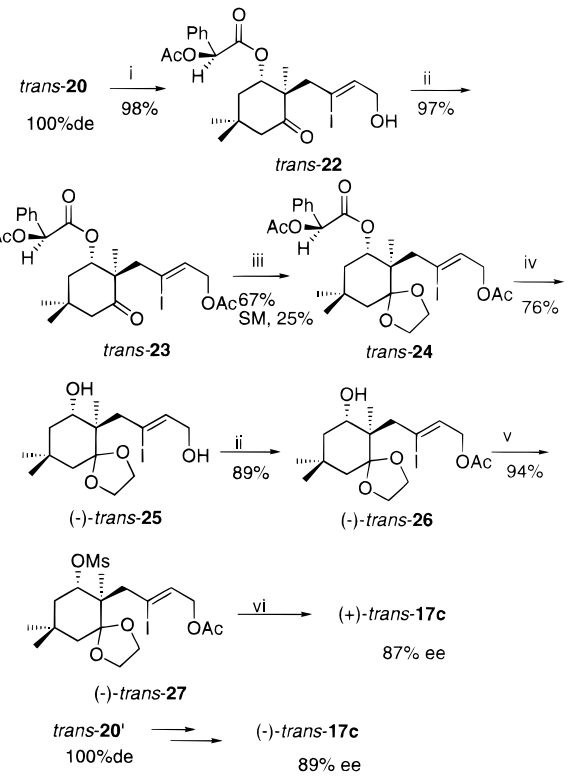
[a] Conditions: (i) K_2CO_3, MeOH. (ii) TBAF. (iii) Ac_2O/Py. (iv) MsCl, Et_3N. (v) $Me_3SiSnBu_3$, CsF.

trans-**20′**, obtained from (±)-*trans*-**16e** and (*R*)-*O*-acetylmandelic acid, respectively, by chromatography on silica gel, whose diastereomeric excesses are 100% (Scheme 14). Each isomer was converted into *trans*-**17c** and *trans*-**17c′**, respectively, which were treated with $Me_3SiSnBu_3$ and CsF (Scheme 15). Unfortunately, the $[\alpha]_D$ values of (+)-*trans*-**18c** and (−)-*trans*-**18c** were low and not the same. Back on the synthetic route, an examination by HPLC revealed that *trans*-**17c** and -**17c′** were almost racemized (37% and 7% ee, respectively), despite the separation of the diastereomeric pair *trans*-**20** and *trans*-**20′** in 100% de. During the conversion of *trans*-**16** or -**16′** to *trans*-**17** or -**17′**, oxetane **VII** would be partially formed, and this would

Scheme 16



Scheme 17[a]



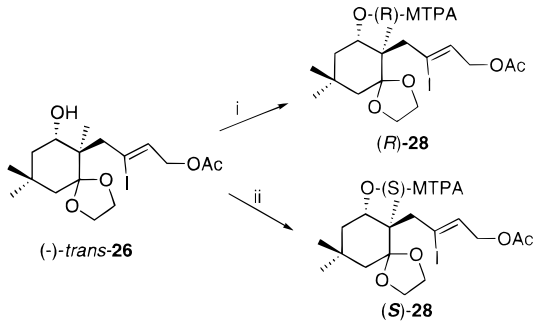
[a] Conditions: (i) AcOH−THF−H_2O, (3:1:1), rt, 5 h. (ii) Ac_2O, DMAP, py, CH_2Cl_2, rt, 1 h. (iii) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, rt. (iv) K_2CO_3, MeOH, rt, 2.5 h. (v) MsCl, Et_3N. (vi) $FeCl_3 \cdot H_2O$, CH_2Cl_2, rt.

be followed by a hydride shift to give *ent*-**17c**, as shown in Scheme 16.

Thus, we changed the synthetic route of *trans*-**17c** to avoid racemization. Namely, the carbonyl group should be protected until the hydroxy group is converted into the mesyloxy group. After the separation of the diastereomeric mixture of *trans*-**20** and -**20′**, we attempted ketalization of *trans*-**20**, but it proceeded in a low yield. However, replacement of the TBDMS group by an acetyl group gave a good result. That is, desilylation of *trans*-**20** afforded the primary alcohol *trans*-**22**, which was acetylated to give *trans*-**23** in 98% yield (Scheme 17). The ketalization of **23**[17] followed by hydrolysis gave (−)-*trans*-**25**, which was monoacetylated to give (−)-*trans*-**26**. Then secondary alcohol was mesylated to give the protecting starting material (−)-*trans*-**27**. The best condition for deketalization was the reaction with $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 at room temperature,[18] which resulted

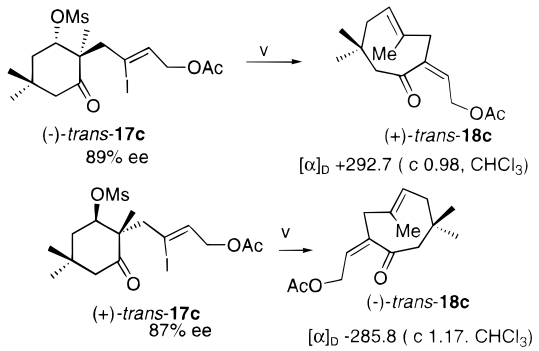
(17) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

Scheme 18[a]



[a] Conditions: (i) (+)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 3 days, 67%. (ii) (−)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 3 days, 48%.

Scheme 19[a]



[a] Conditions: (i) K_2CO_3, MeOH. (ii) TBAF. (iii) Ac_2O/Py. (iv) $Me_3SiSnBu_3$, CsF.

in 97% yield of (+)-*trans*-**17c** after 3 h. In a similar manner, *trans*-**20′** was converted into (−)-*trans*-**17c** in high yield. An HPLC analysis of the final substrate (+)- and (−)-*trans* **17c** (89% and 87% ee, respectively) indicated that the protection of the carbonyl group as the ketal before the mesylation step substantially, but not completely, prevented racemization. The mechanism for this process is unclear.

The absolute configuration of (−)-*trans*-**26**, and consequently of (+)-*trans*-**17c**, was determined as *S* by the improved Mosher's method developed by Kusumi et al.[19] utilizing the MTPA esters of (−)-*trans*-**26** (Scheme 18; Figure 3).

Treatment of (+)-*trans*-**17c** and (−)-*trans*-**17c** with $Me_3SiSnBu_3$ and CsF in DMF at room temperature for 3 h gave (−)-*trans*-**18c** and (+)-*trans*-**18c** in yields of 30% and 31%, respectively (Scheme 19). The $[\alpha]_D$ values for them are −285.8° (c 1.17, $CHCl_3$) and +292.7° (*c* 0.98, $CHCl_3$), respectively). Their CD spectra, shown in Figure 4, strongly suggest that they are enantiomeric isomers. Thus, we succeeded in the syntheses of (+)- and (−)-*trans*-cyclooctenone derivatives **17c** in optically active forms using a ring expansion reaction with $Me_3SiSnBu_3$ and CsF.

In conclusion, a novel synthesis of an eight-membered compound from cyclohexanone derivatives having vinyl iodide in a tether was developed by the ring expansion reaction of a two-carbon unit using the stannyl anion generated from $Me_3SiSnBu_3$ and CsF. The reaction proceeded in a stereospecific manner, and *cis*- and *trans*-cyclooctenone derivatives were obtained. It is interesting that the *trans*-eight-membered ring, which is the smallest *trans*-cycloalkene isolable at room temperature, was obtained under these reaction conditions, and

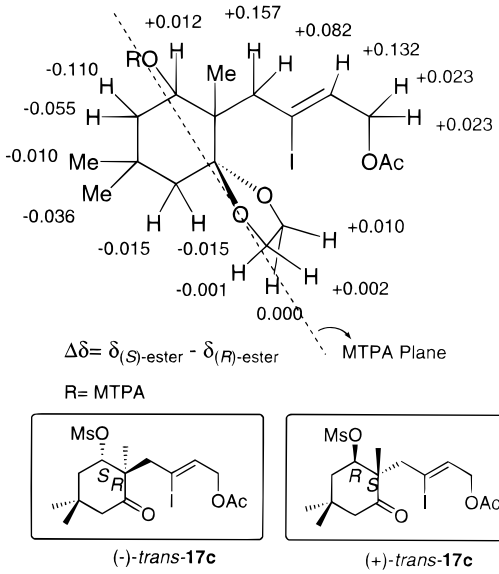


Figure 3.

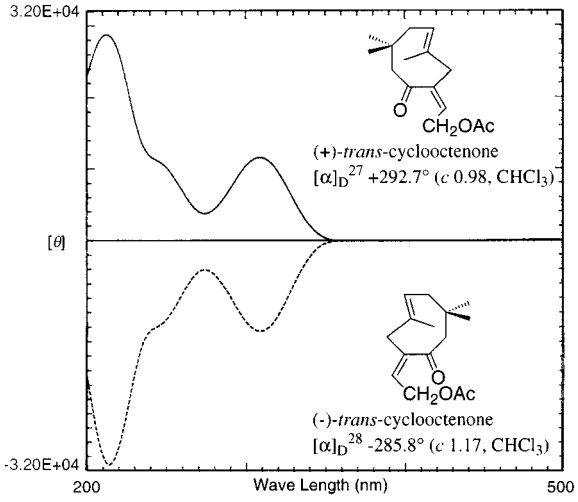


Figure 4.

that *trans*-cyclooctene was isomerized to *cis*-cyclooctene in the presence of $Me_3SiSnBu_3$ and CsF in DMF. It is known that the *trans*-cyclooctene derivative is an asymmteric compound. There have been few reports on its synthesis as a chiral form. We succeeded in the synthesis of (+)- and (−)-*trans*-cyclooctenone derivatives from the corresponding optically active (−)-and (+)-*trans*-cyclohexanone derivatives.

Experimental Section

General. All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70−230 mesh, 60 Å), and flash chromatography was performed on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvent. Melting points are uncorrected. Flash column chromatography was performed on silica gel 60 (Merck, 230−400 mesh) using the identical solvent.

General Procedure for Ring Expansion Reaction. To a solution of cyclohexanone derivative (1 equiv) and CsF (3 equiv) was added $Me_3SiSnBu_3$ (3 equiv) in DMF at 0 °C, and the solution was stirred at room temperature for several hours. The reaction was monitored by TLC. To this solution was added aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give the eight-membered product.

(18) Sen, S.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrat, J. *J. Org. Chem.* **1997**, *62*, 6684.

(19) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Ring Expansion to Cyclooctadione. 1,1,6-Trimethyl-4-methylidene-3,7-cyclooctanedione (7a), 1,1,6-Trimethyl-4-(tributylstannyl)methyl-3,7-cyclooctanedione (8a), and 2,5,5-Trimethyl-2-(2-propenyl)-1,3-cyclohexanedione (9a). Following the general procedure for the ring expansion, 165 mg (0.52 mmol) of the diketone **6a**, upon reaction with 0.36 mL (1.03 mmol) of $Me_3SiSnBu_3$ and 156.5 mg (1.03 mmol) of CsF in 3.5 mL of DMF, afforded, after 2 h of reaction at room temperature, 39.5 mg (17%) of the Michael adduct **8a**, 25 mg (25%) of the dehalogenated product **9a**, and 24 mg (24%) of the α,β-unsaturated cyclooctanedione **7a**. These products were purified by silica gel column chromatography (hexane/EtOAc 20:1, 10:1; 8:1 as gradient elution). **7a**: IR (neat) 2960, 2928, 2870, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.09 (s, 3 H), 1.13 (s, 3 H), 2.25 (d, J = 12.3 Hz, 1 H), 2.37 (d, J = 11.7 Hz, 1 H), 2.45 (dd, J = 9.4, 14.3 Hz, 1 H), 2.48 (d, J = 12.3 Hz, 1 H), 2.54 (d, J = 11.7 Hz, 1 H), 2.62−2.65 (m, 1 H), 2.86 (dd, J = 4.3, 14.3 Hz, 1 H), 5.37 (br s, 1 H), 6.12 (d, J = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.63, 29.32, 29.81, 34.92, 36.79, 50.48, 50.72, 50.87, 126.35, 145.19, 200.68, 212.40; MS *m*/*z* 194 (M^+), 179, 166, 110, 95, 83, 67; EI−HRMS *m*/*z* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1307. **8a**: IR (neat) 2956, 2924, 2870, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (dd, J = 9.4, 12.9 Hz, 1 H), 0.82−0.90 (m, 15 H), 0.97 (dd, J = 6.0, 12.9 Hz, 1 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.27−1.32 (m, 6 H), 1.43−1.48 (m, 6 H), 2.02 (ddd, J = 3.3, 6.8, 15.1 Hz, 1 H), 2.13 (d, J = 11.7 Hz, 1 H), 2.22 (d, J = 11.7 Hz, 1 H), 2.30 (ddd, J = 3.6, 10.1, 15.1 Hz, 1 H), 2.53 (d, J = 11.7 Hz, 1 H), 2.56−2.61 (m, 2 H), 2.62 (d, J = 11.7 Hz, 1 H);^{13}C NMR ($CDCl_3$) δ 9.52, 12.22, 13.62, 14.79, 27.33, 28.24, 29.01, 31.66, 35.80, 36.42, 46.48, 48.25, 49.33, 50.04, 211.73, 212.63; ^{119}Sn NMR ($CDCl_3$) δ −7.7; MS *m*/*z* 486 (M^+), 429, 251, 177; EI−HRMS *m*/*z* calcd for $C_{24}H_{46}O_2Sn$ 486.2520, found 486.2542. **9a**: IR (neat) 2956, 2928, 1726, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.05 (s, 3 H), 1.22 (s, 3 H), 2.47 (d, J = 6.2 Hz, 2 H), 2.49 (d, J = 14.6 Hz, 2 H), 2.63 (d, J = 14.6 Hz, 2 H), 5.05−5.09 (m, 2 H), 5.54−5.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.43, 27.94, 29.24, 30.62, 41.51, 51.66, 64.25, 119.29, 132.02, 209.45; MS *m*/*z* 194 (M^+), 149, 110, 83; EI−HRMS *m*/*z* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1300.

4-Methyl-2-methylidene-1,5-cyclooctanedione (7b), 4-Methyl-2-(tributylstannyl)methyl-1,5-cyclooctanedione (8b), and 2-Methyl-2-(2-propenyl)-1,3-cyclohexanedione (9b). 7b: 39% yield; IR (neat) 2928, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 6.8 Hz, 3 H), 1.91−2.11 (m, 3 H), 2.42−2.77 (m, 5 H), 3.00 (ddd, J = 0.8, 4.3, 14.0 Hz, 1 H), 5.33 (br s, 1 H), 6.02 (d, J = 1.6 Hz, 1 H); MS *m*/*z* 166 (M^+), 127; EI−HRMS *m*/*z* calcd for $C_{10}H_{14}O_2$ 166.2188, found 166.2190. **8b**: 3% yield; IR (neat) 2956, 2926, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75−1.05 (m, 18 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.25−1.58 (m, 13 H), 1.90−2.10 (m, 2 H), 2.15−2.28 (m, 1 H), 2.32−2.50 (m, 2 H), 2.55−2.75 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 9.54, 11.71, 13.65, 14.97, 25.41, 27.57, 29.12, 36.97, 38.24, 39.14, 45.06, 47.89, 214.62, 215.56; MS *m*/*z* 458 (M^+), 401, 251, 235, 177; EI−HRMS *m*/*z* calcd for $C_{22}H_{42}O_2Sn$ 458.2187, found 458.2197. **9b**: 33% yield; IR (neat) 3734, 2964, 1726, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3 H), 1.79−2.08 (m, 2 H), 2.52 (br d, 2 H), 2.62−2.67 (m, 4 H), 5.06 (br d, 2 H), 5.49−5.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.44, 19.49, 38.12, 41.22, 65.12, 119.09, 132.20, 209.75; MS *m*/*z* 166 (M^+), 127; EI−HRMS *m*/*z* calcd for $C_{10}H_{14}O_2$ 166.2188, found 166.2180.

(*Z*)-1,1,6-Trimethyl-4-acetoxyethylidene-3,5-cyclooctanedione (7c): 38% yield; IR (neat) 2962, 2936, 1738, 1702, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.13 (s, 3 H), 2.07 (s, 3 H), 2.27 (d, J = 12.1 Hz, 1 H), 2.34 (d, J = 11.7 Hz, 1H), 2.41 (dd, J = 9.4, 14.4 Hz, 1 H), 2.52 (d, J = 11.7 Hz, 1 H), 2.55 (d, J = 12.1 Hz, 1 H), 2.61−2.67 (m, 1 H), 2.78 (dd, J = 4.2, 14.4 Hz, 1 H), 4.93 (dd, J = 4.6, 17.3 Hz, 1 H), 4.95 (dd, J = 5.6, 17.3 Hz, 1 H), 5.93 (br t, J = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.61, 20.93, 29.41, 29.92, 34.97, 37.83, 50.83, 50.86, 51.89, 63.94, 137.76, 141.29, 170.85, 202.11, 212.42; FAB-MS *m*/*z* 267 ($M^+ + 1$), 207, 154, 136; FAB−HRMS *m*/*z* calcd for $C_{15}H_{23}O_4$ ($M^+ + 1$) 267.1596, found 267.1567.

(*Z*)-4-Methyl-2-acetoxyethylidene-1,5-cyclooctanedione (7d) and (*E*)-2-Methyl-2-[(4-acetoxy)-2-butenyl]-1,3-cyclohexanedione (9d). 7d: 58% yield; IR (neat) 2968, 2934, 2872, 1740, 1704, 1680, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, J = 6.6 Hz, 3 H), 1.95−2.02 (m, 2 H), 2.05 (s, 3 H), 2.43−2.53 (m, 2 H), 2.55−2.63 (m, 3 H), 2.69−2.75 (m, 1 H), 2.94 (dd, J = 4.2, 14.5 Hz, 1 H), 4.87 (d, J = 5.3 Hz, 2 H), 5.83 (t, J = 5.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.32, 21.32, 25.13, 37.96, 39.90, 41.20, 49.32, 63.96, 138.32, 139.56, 171.27, 205.07, 214.98; MS *m*/*z* 238 (M^+), 107,178, 43; EI−HRMS *m*/*z* calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1230. **9d**: 34% yield; IR (neat) 2940, 2360, 2342, 1736, 1712, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.86−1.97 (m, 2 H), 2.01 (s, 3 H), 2.51 (d, J = 7.0 Hz, 2 H), 2.58−2.65 (m, 4 H), 4.44 (d, J = 5.7 Hz, 2 H), 5.51 (ddd, J = 7.0, 7.0, 15.5 Hz, 1 H), 5.57 (ddd, J = 5.7, 5.7, 15.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.36, 20.49, 20.85, 38.25, 39.01, 64.36, 64.84, 128.60, 129.09, 170.62, 209.70; MS *m*/*z* 238 (M^+), 178, 127, 43; EI−HRMS *m*/*z* calcd for $C_{11}H_{15}O_2$ (M^+ − OAc) 179.1072, found 179.1101.

4-Methyl-2-(tributylstannyl)methyl-4-cyclohepten-1-one (13) and (2*S,3*R**)-2-Methyl-2-(2-propenyl)-3-(tributylstannyl)methylcyclopentanone (*trans*-14).** Following the general procedure for the ring expansion, 84 mg (0.23 mmol) of the *cis*-substrate **13**, upon reaction with 0.33 mL (0.94 mmol) of $Me_3SiSnBu_3$ and 142 mg (0.94 mmol) of CsF in 1.7 mL of DMF, afforded, after 2 h of reaction at room temperature, 25 mg (25%) of the Michael adduct **13** and 24 mg (24%) of the product *trans*-**14**. These compounds were purified by preparative thin-layer chromatography (hexane/EtOAc 20:1). **13**: IR (neat) 2956, 2924, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68−0.83 (m, 7 H), 0.87−0.92 (m, 9 H), 1.00−1.05 (m, 1 H), 1.28−1.32 (m, 6 H), 1.43−1.50 (m, 6 H), 1.73 (s, 3 H), 2.15−2.17 (m, 3 H), 2.43−2.48 (m, 2 H), 2.67−2.68 (m, 1 H), 3.01−3.13 (m, 1 H), 5.53−5.54 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ 9.74, 12.04, 13.73, 23.77, 26.31, 27.46, 29.24, 41.08, 41.93, 48.03, 123.37, 136.86, 215.52; ^{119}Sn NMR ($CDCl_3$) δ −12.449; MS *m*/*z* 428 (M^+), 403, 387, 289; EI−HRMS *m*/*z* calcd for $C_{17}H_{31}OSn$ 371.1397, found 371.1412. *trans*-**14**: IR (neat) 2956, 2926, 1734, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89−0.94 (m, 15 H), 1.02 (s, 3 H), 1.30−1.37 (m, 6 H), 1.47−1.53 (m, 6 H), 1.66 (dd, J = 7.7, 12.1 Hz, 1 H), 1.85 (dd, J = 7.7, 13.8 Hz, 1 H), 1.91−2.07 (m, 2 H), 2.14−2.22 (m, 1 H), 2.30 (dd, J = 6.9, 14.0 Hz, 1 H), 2.35 (ddd, J = 2.8, 7.7, 19.1 Hz, 1 H), 4.96−5.05 (m, 2 H), 5.67−5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.43, 13.64, 21.43, 23.25, 27.51, 29.28, 37.71, 37.88, 41.97, 51.90, 117.60, 133.98, 221.76; ^{119}Sn NMR ($CDCl_3$) δ −21.204; MS *m*/*z* 371 (M^+ − Bu), 177, 84; EI−HRMS *m*/*z* calcd for $C_{18}H_{35}OSn$ (M^+− allyl) 387.1710, found 387.1708.

(2*S,3*S**)-2-Methyl-2-(2-propenyl)-3-(tributylstannyl)methylcyclopentanone (*cis*-14).** Following the general procedure for the ring expansion, 119 mg (0.33 mmol) of the *trans*-**12**, upon reaction with 0.46 mL (1.33 mmol) of $Me_3SiSnBu_3$ and 202 mg (1.33 mmol) of CsF in 2.4 mL of DMF, afforded, after 2 h of reaction at room temperature, 72.2 mg (51%) of *cis*-**14**. This compound was purified by flash column chromatography (hexane/EtOAc 30:1, 10:1, 3:1 as gradient elution): IR (neat) 2956, 2926, 1736, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87−0.92 (m, 15 H), 0.96 (s, 3 H), 1.29−1.37 (m, 6 H), 1.46−1.52 (m, 6 H), 1.86−1.95 (m, 2 H), 2.01 (dd, J = 8.7, 13.9 Hz, 1 H), 2.03−2.09 (m, 2 H), 2.35 (dd, J = 6.9, 13.8 Hz, 1 H), 2.45 (dd, J = 6.1, 13.7 Hz, 1 H), 4.98−5.04 (m, 2 H), 5.56−5.64 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.37, 13.62, 23.96, 24.08, 27.52, 29.29, 32.63, 39.48, 41.61, 51.95, 117.84, 134.73, 222.93; ^{119}Sn NMR ($CDCl_3$) δ −21.352; MS *m*/*z* 371 (M^+ − Bu), 291, 235, 177, 121; EI−HRMS *m*/*z* calcd for $C_{18}H_{35}OSn$ (M^+ − allyl) 387.1710, found 387.1682.

Ring Expansion to Cyclooctenone. (*Z*)-1,1,6-Trimethyl-4-methylidene-6-cyclooten-3-one (*cis*-18a): IR (neat) 2958, 2930, 2866, 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (−50 °C) δ 0.95 (s, 3 H), 1.04 (s, 3 H), 1.70 (s, 3 H), 1.79 (dd, J = 8.3, 13.7 Hz, 1 H), 2.34 (d, J = 11.2 Hz, 1 H), 2.43 (dd, J = 7.8, 13.7 Hz, 1 H), 2.68 (d, J = 12.7 Hz, 1 H), 3.58 (d, J = 14.7 Hz, 2 H), 5.16 (s, 1 H), 5.42 (t, J = 8.1 Hz, 1 H), 5.69 (d, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.78, 148.26, 136.43, 123.41, 120.17, 53.24, 39.80, 38.95, 37.35, 32.17, 25.07, 23.36; MS *m*/*z* 178 (M^+), 163, 122, 94, 79; EI−HRMS *m*/*z* calcd for $C_{12}H_{18}O$ 178.1358, found 178.1372.

(*Z*)-1,1,6-Trimethyl-4-(tributylstannyl)methyl-6-cyclooten-3-one (*cis*-19a). IR (neat) 2954, 2924, 2870, 2852, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.80−0.91 (m, 16 H), 0.94 (s, 3 H), 0.97 (dd, J = 5.9, 12.8 Hz, 1 H), 1.03 (s, 3 H), 1.27−1.32 (m, 6 H), 1.43−1.48 (m, 6 H), 1.74 (dd, J = 9.1, 13.1 Hz, 1 H), 1.74 (s, 3 H), 1.83 (br d, J = 12.1 Hz, 1 H), 1.92 (d, J = 13.4 Hz, 1 H), 2.13 (dd, J = 9.1, 13.1

Hz, 1 H), 2.54 (d, J = 12.1 Hz, 1 H), 2.58 (d, J = 13.4 Hz, 1 H), 2.65−2.71 (m, 1 H), 5.34 (br t, J = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.26, 9.49, 10.77, 12.62, 13.62, 24.00, 27.56, 28.99, 36.52, 37.05, 40.76, 49.68, 53.76, 123.56, 137.79, 214.42; ^{119}Sn NMR ($CDCl_3$, 100.55 MHz) δ −9.3; MS m/z 470 (M^+), 413, 251, 235, 177, 161; EI−HRMS m/z calcd for $C_{24}H_{46}OSn$ 470.2571, found 470.2562.

(*E*)-1,1,6-Trimethyl-4-methylidene-6-cyclooten-3-one (*trans*-18a): IR (neat) 2956, 2932, 2870, 1722, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 3 H), 1.11 (s, 3 H), 1.74 (d, J = 12.1 Hz, 1 H), 1.88 (s, 3 H), 1.86−1.89 (m, 1 H), 2.23 (dd, J = 12.6 Hz, 1 H), 2.30 (dd, J = 12.6, 12.6 Hz, 1 H), 2.81 (d, J = 12.7 Hz, 1 H), 3.48 (br d, J = 12.7 Hz, 1 H), 4.69 (d, J = 2.3 Hz, 1 H), 4.79 (d, J = 2.3 Hz, 1 H), 5.39 (ddd, J = 1.5, 1.5, 12.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.66, 156.91, 135.04, 128.02, 110.36, 53.50, 48.76, 43.83, 42.17, 33.21, 26.09, 17.49; MS m/z 178 (M^+), 163, 149, 122, 94, 79; EI−HRMS m/z calcd for $C_{12}H_{18}O$ 178.1358, found 178.1353.

(*Z*)-4-Methyl-2-methylidene-4-cycloocten-1-one (*cis*-18b): IR (neat) 2932, 2856, 1690, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.63 (br s, 3 H), 1.69−1.78 (m, 2 H), 2.21−2.25 (m, 2 H), 2.60−2.62 (m, 2 H), 3.12 (s, 2 H), 5.06 (d, J = 1.5 Hz, 1 H), 5.46 (ddd, J = 1.0, 8.0, 8.0 Hz, 1 H), 5.58 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.29, 149.42, 136.00, 125.79, 118.51, 42.44, 36.82, 28.63, 27.93, 22.47; MS m/z 150 (M^+), 135; EI−HRMS m/z calcd for $C_{10}H_{14}O$ 150.1044, found 150.1040.

(*Z*)-4-Methyl-2-(tributylstannyl)methyl-4-cycloocten-1-one (*cis*-19b): IR (neat) 2954, 2926, 2854, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84−0.92 (m, 16 H), 1.01 (dd, J = 5.7, 12.9 Hz, 1 H), 1.26−1.34 (m, 6 H), 1.44−1.55 (m, 7 H), 1.71 (s, 3 H), 1.72−1.78 (m, 1 H), 1.88 (dd, J = 3.9, 12.9 Hz, 1 H), 2.03−2.11 (m, 2 H), 2.17 (ddd, J = 2.9, 7.4, 11.6 Hz, 1 H), 2.56 (t, J = 12.9 Hz, 1 H), 2.68−2.74 (m, 1 H), 2.69 (ddd, J = 3.3, 11.6, 11.6 Hz, 1 H), 5.37 (t, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.86, 137.13, 125.32, 53.80, 37.60, 36.99, 29.14, 27.54, 27.37, 26.38, 23.73, 13.64, 11.76, 9.51; ^{119}Sn NMR ($CDCl_3$, 100.55 MHz) δ −9.3; MS m/z 413 (M^+ − Bu), 235, 177, 161; EI−HRMS m/z calcd for $C_{24}H_{46}OSn$ 470.2571, found 470.2562.

(*E*)-4-Methyl-2-methylidene-4-cycloocten-1-one (*trans*-18b): IR (neat) 2934, 1690, 1632, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (s, 3 H), 2.09−2.25 (m, 3 H), 2.27−2.36 (m, 2 H), 2.31 (ddd, J = 5.4, 12.2, 12.2 Hz, 1 H), 2.89 (d, J = 12.7 Hz, 1 H), 3.52 (br d, J = 12.7 Hz, 1 H), 4.73 (d, J = 2.4 Hz, 1 H), 4.85 (d, J = 2.4 Hz, 1 H), 5.18 (br d, J = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.67, 28.77, 31.42, 41.40, 48.94, 108.96, 129.08, 133.74, 156.59, 214.71; MS m/z 150 (M^+), 124, 109, 43; EI−HRMS m/z calcd for $C_{10}H_{14}O$ 150.1044, found 150.1030.

(4*Z*,6*Z*)-1,1,6-Trimethyl-4-acetoxyethylidene-6-cyclooctene-3-one (*cis*-18c): IR (neat) 2958, 2932, 1742, 1684, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (−50 °C) δ 0.94 (s, 3 H), 1.05 (s, 3 H), 1.68 (s, 3 H), 1.80 (dd, J = 8.3, 13.7 Hz, 1 H), 2.12 (s, 3 H), 2.30 (d, J = 11.2 Hz, 1 H), 2.42 (dd, J = 8.3, 13.7 Hz, 1 H), 2.56 (d, J = 14.3 Hz, 1 H), 2.65 (d, J = 11.2 Hz, 1 H), 3.60 (d, J = 14.3 Hz, 1 H), 4.80 (d, J = 5.4 Hz, 2 H), 5.42 (t, J = 8.3 Hz, 1 H), 5.66 (t, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (−50 °C) δ 205.78, 171.16, 142.26, 136.41, 131.55, 123.65, 62.69, 53.67, 39.85, 39.01, 37.88, 32.33, 25.02, 23.30, 21.16; MS m/z 235 (M^+ − Me), 208, 190, 43; HRMS (FAB) m/z calcd for $C_{15}H_{22}O_3$ (M^+ + 1) 251.1647, found 251.1666.

(4*Z*,6*E*)-1,1,6-Trimethyl-4-acetoxyethylidene-6-cyclooctene-3-one (*trans*-18c): IR (neat) 2956, 2934, 1742, 1684, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 3 H), 1.12 (s, 3 H), 1.78 (d, J = 12.3 Hz, 1 H), 1.86 (s, 3 H), 1.87 (dd, J = 3.5, 12.6 Hz, 1 H), 2.02 (s, 3 H), 2.21 (dd, J = 12.6 Hz, 1 H), 2.34 (d, J = 12.3 Hz, 1 H), 2.76 (d, J = 12.4 Hz, 1 H), 3.46 (br d, J = 12.4 Hz, 1 H), 4.31 (ddd, J = 2.1, 6.0, 13.1 Hz, 1 H), 4.37 (ddd, J = 0.9, 8.1, 13.1 Hz, 1 H), 5.28 (ddd, J = 2.1, 6.0, 8.0 Hz, 1 H), 5.36 (br d, J = 12.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.12, 170.55, 151.37, 134.39, 127.88, 118.49, 61.24, 53.74, 49.10, 43.25, 41.63, 32.92, 25.95, 20.80, 17.11; MS m/z 250 (M^+), 235, 208, 190, 152, 137, 107, 91, 43; EI−HRMS m/z calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1586.

Isomerization of *trans*-Cyclooctenone to *cis*-Cyclooctenone. The *trans*-cyclooctenone **18a** (14.5 mg, 0.08 mmol) reacted with 80 mL (0.24 mmol) of silylstannane and 36.5 mg (0.24 mmol) of CsF in 0.5 mL of DMF at room temperature for 6.5 h. After workup of the reaction mixture and purification by preparative thin-layer chromatography (hexane/Et2O 50:1), 6.2 mg (17%) of the *trans*-**19a** was isolated, together with 19.0 mg (51%) of the isomerized *cis*-**19a**. *trans*-**19a**: IR (neat) 2932, 1738, 1684, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (t, J = 8.2 Hz, 6 H), 0.82 (dd, J = 6.8, 13.1 Hz, 1 H), 0.89 (t, J = 7.3 Hz, 9 H), 0.99 (s, 3 H), 1.02 (dd, J = 8.0, 13.1 Hz, 1 H), 1.13 (s, 3 H), 1.25−1.33 (m, 6 H), 1.42−1.47 (m, 6 H), 1.60 (d, J = 12.6 Hz, 1 H), 1.85 (dd, J = 3.4, 12.5 Hz, 1 H), 1.97 (d, J = 1.0 Hz, 3 H), 2.18 (dd, J = 12.5, 12.5 Hz, 1 H), 2.23 (d, J = 12.6 Hz, 1 H), 2.33 (dd, J = 5.0, 11.8 Hz, 1 H), 2.48 (dd, J = 11.8 Hz, 1 H), 3.14−3.21 (m, 1 H), 5.19 (br d, J = 11.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.02, 9.41, 10.97, 13.74, 18.11, 26.37, 27.43, 29.20, 33.35, 40.78, 41.81, 51.91, 54.29, 125.85, 137.18, 217.34; ^{119}Sn NMR ($CDCl_3$, 100.55 MHz) δ −12.0; MS m/z 413 (M^+ − Bu), 235, 177, 161; EI−HRMS m/z calcd for $C_{20}H_{37}OSn$ (M^+ − Bu) 413.1867, found 413.1888.

The isolated Michael adduct *trans*-**19a** (100 mg, 0.21 mmol) reacted further with 0.22 mL (0.64 mmol) of $Me_3SiSnBu_3$ and 97 mg of CsF (0.64 mmol) in 1.9 mL of DMF. After 7 h of reaction time at room temperature, 95 mg of a mixture of *trans*-**19a** and *cis*-**19a** was obtained, in the ratio of 1:3.16, determined by ^{1}H NMR, which corresponds to 76% of isomerization.

Ring Expansion of Chiral (+)-*trans*-17c. The chiral substrate (+)-*trans*-**17c** (200 mg, 0.42 mmol) reacted with 0.30 mL (0.85 mmol) of $Me_3SiSnBu_3$ and 129 mg (0.85 mmol) of CsF in 3.0 mL of DMF at room temperature for 2 h and 50 min, resulting in 24.5 mg (31%) of the cyclooctenone (+)-*trans*-**18c** ($[\alpha]^{27}_D$ +292.7 (*c* 0.980, $CHCl_3$), other spectral data consistent with the racemic cyclooctenone).

Ring Expansion of Chiral (−)-*trans*-17c. The chiral substrate (−)-*trans*-**17c** (252 mg, 0.53 mmol) reacted with 0.37 mL (1.07 mmol) of $Me_3SiSnBu_3$ and 162 mg (1.07 mmol) of CsF in 3.8 mL of DMF at room temperature for 2 h and 50 min, resulting in 40 mg (30%) of the cyclooctenone (−)-*trans*-**18c** ($[\alpha]^{28}_D$ −285.8 (*c* 1.170, $CHCl_3$), other spectral data consistent with the racemic cyclooctenone).

(*R*)-MTPA Ester 28. To a solution of 31.5 mg (71.87 mmol) of the secondary alcohol **26** in 1 mL of dichloromethane were added 4.4 mg (35.93 mmol) of DMAP and 24.4 mg (118.58 mmol) of DCC. The solution was cooled to 0 °C, and 25.2 mg (107.80 mmol) of (+)-MTPA was added. The mixture was stirred at room temperature for 3 days, quenched with ammonium chloride, and extracted with ethyl acetate. The crude product was purified by silica gel column chromatography (hexane/EtOAc 5:1), and 31 mg (67%) of the (*R*)-MTPA ester was isolated: IR (neat) 2988, 1742, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3 H), 1.12 (s, 3 H), 1.25 (s, 3 H), 1.45 (s, 2 H), 1.60 (dd, J = 11.6, 12.9 Hz, 1 H), 1.75 (dd, J = 4.6, 12.9 Hz, 1 H), 2.06 (s, 3 H), 2.38 (d, J = 14.8 Hz, 1 H), 2.97 (d, J = 14.8 Hz, 1 H), 3.58 (s, 3 H), 3.79 (ddd, J = 7.9, 7.9 Hz, 1 H), 3.83 (ddd, J = 5.4, 7.9, 7.9 Hz, 1 H), 3.92 (ddd, J = 7.9, 7.9 Hz, 1 H), 4.02 (ddd, J = 5.4, 7.9, 7.9 Hz, 1 H), 4.54 (dd, J = 5.8, 13.8 Hz, 1 H), 4.56 (dd, J = 5.8, 13.8 Hz, 1 H), 5.26 (dd, J = 4.6, 11.6 Hz, 1 H), 5.53 (t, J = 5.8 Hz, 1 H), 7.39−7.41 (m, 3 H), 7.54−7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.71, 20.90, 26.79, 30.20, 33.30, 38.51, 40.69, 46.82, 48.02, 55.56, 62.50, 63.92, 69.27, 78.57, 83.94 (q, J = 28 Hz), 104.97, 111.95, 123.32 (q, J = 288 Hz), 127.07, 128.33, 129.52, 132.28, 132.40, 165.56, 170.56; MS m/z 654 (M^+), 527, 421, 189; EI−HRMS m/z calcd for $C_{27}H_{34}IO_7F_3$ 654.1302, found 654.1304.

(*S*)-MTPA 28. To a solution of 35.3 mg (80.5 mmol) of the secondary alcohol **26** in 1.2 mL of dichloromethane was added 13.0 mL (35.93 mmol) of pyridine. The solution was cooled to 0 °C, and 22.6 mL (120.80 mmol) of (−)-MTPA-Cl was added. The mixture was stirred at room temperature for 3 days, quenched with brine, washed with 10% HCl solution, and extracted with ethyl acetate. The crude product was purified by silica gel column chromatography (hexane/EtOAc 5:1), and 25 mg (48%) of the (*S*)-MTPA ester was isolated: IR (neat) 2954, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 1.11 (s, 3 H), 1.25 (s, 3 H), 1.44 (s, 2 H), 1.49 (dd, J = 11.5, 13.0 Hz, 1 H), 1.69 (dd, J = 4.5, 13.0 Hz, 1 H), 2.04 (s, 3 H), 2.54 (dd, J = 0.6, 14.8 Hz, 1 H), 3.06 (d, J = 14.8 Hz, 1 H), 3.50 (s, 3 H), 3.80 (ddd, J = 7.9 Hz, 1 H), 3.84 (ddd, J = 5.4, 7.9, 7.9 Hz, 1 H), 3.92 (ddd, J = 7.9 Hz, 1 H), 4.02 (ddd, J = 5.4, 7.9, 7.9 Hz, 1 H), 4.57 (dd, J = 5.8, 13.7 Hz, 1 H), 4.59 (dd, J = 5.8, 13.7 Hz, 1 H), 5.27 (dd, J = 4.5, 11.5 Hz, 1 H), 5.66 (t, J = 5.8 Hz, 1 H), 7.42−7.43 (m, 3 H), 7.52−7.54 (m, 2

H); ^{13}C NMR ($CDCl_3$) δ 15.87, 20.89, 26.93, 30.13, 33.19, 38.15, 40.69, 46.75, 48.40, 55.31, 62.57, 63.91, 69.28, 78.82, 84.75 (q, J = 27 Hz), 104.92, 112.04, 120.43 (q, J = 288 Hz), 127.56, 128.44, 129.57, 131.65, 132.54, 165.78, 170.59; MS *m*/*z* 654 (M^+), 527, 421, 189; EI−HRMS *m*/*z* calcd for $C_{27}H_{34}IO_7F_3$ 654.1302, found 654.1282.

Supporting Information Available: Experimental procedures for the synthesis of **6a**−**d**, **10**, *cis*- and *trans*-**11** and -**12**, *cis*- and *trans*-**16a**−**e**, **17a**−**c**, (2*R*,3*S*)- and (2*S*,3*R*)-**20**−**27** and (+)- and (−)-**17c**; ^{1}H NMR spectra for *cis*-**18a** and *trans*-**18a**, and *cis*-**18a** at −50 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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