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Lewis Acid-Promoted Rearrangement of 2,3-Epoxy Alcohol Derivatives: Stereochemical Control and Selective Formation of Two Types of Chiral Quaternary Carbon Centers from the Single Carbon Skeleton

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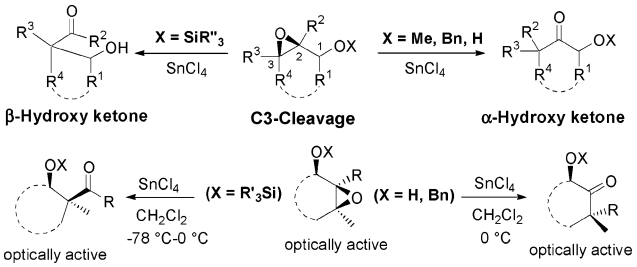


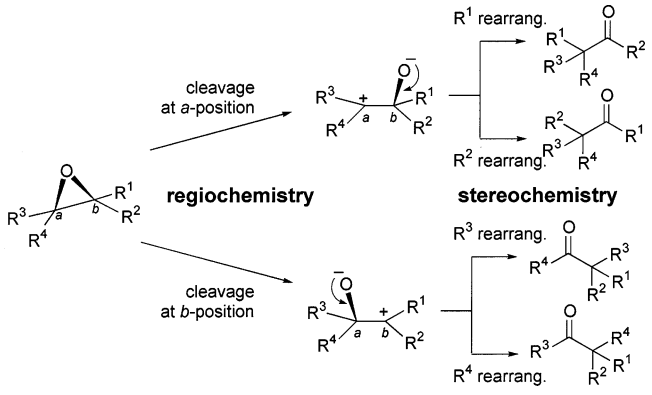
The Lewis acid-promoted rearrangement of 2,2,3,3-tetrasubstituted 2,3-epoxy alcohols with several kinds of protecting groups was investigated. When $SnCl_4$ is used as a Lewis acid, the reaction proceeds in a regio- and stereo-controlled manner to afford two types of carbonyl compounds selectively from a single 2,3-epoxy alcohol only by changing the protecting group of the alcohol. The method was then applied to the formation of two types of acyclic and cyclic quaternary carbon centers from the single compound in optically active forms.

Introduction

The rearrangement of epoxides and their derivatives with a Lewis acid (LA) is one of the most valuable tools for constructing carbonyl compounds.[1] In particular, much attention has been paid to the rearrangement of 2,3-epoxy alcohols and their derivatives.[2,3] This method is also useful for the asymmetric synthesis of natural products because of the easy availability of optically active 2,3-epoxy alcohols.[4,5] To make the reactions practical, it is necessary to solve two issues, that is, control of the regiochemistry and control of stereochemistry (Scheme 1).

As for the control of the regiochemistry, many studies have already been reported.[1−3] However, most of the studies reported to date are restricted to the 2,3-disubstituted, 2,2,3- or 2,3,3-trisubstituted epoxides, and the reaction occurs through the carbocations on the more substituted carbons if the epoxides do not have electron-stabilizing substituents such as a phenyl or vinyl group. On the other hand, to the best of our knowledge, the rearrangements of the 2,2,3,3-tetrasubstituted 2,3-epoxy

SCHEME 1. Considerable Pathways in the Rearrangement of Epoxide



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(1) For reviews of the Lewis acid-mediated rearrangement of epoxides, see: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737−799. (b) Rickborn, B. In *Comprehensive Organic Synthesis, Carbon−Carbon Bond Formation*; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.3, pp 733−775.

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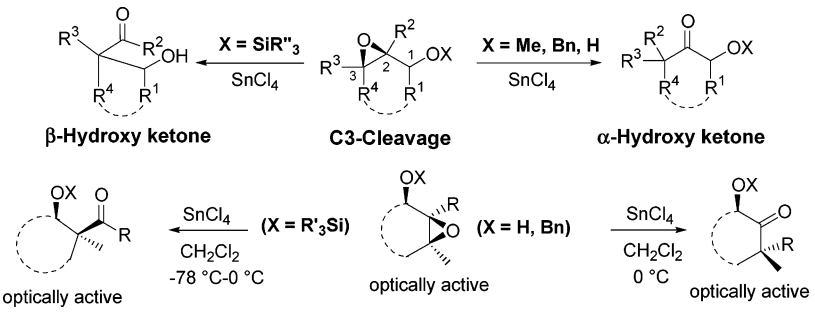
SCHEME 2



alcohol derivatives are comparatively few.[6] We have been interested in the rearrangements of the 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives in which the C2- and C3-carbocations have a similar stability. Recently, we succeeded in controlling the regiochemistry of the rearrangements of 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives using acyl and sulfonyl groups,[4] which are known as strong electron-withdrawing groups, as the protecting group of the alcohol. By using this method, several desirable chiral quaternary carbon centers and chiral spiro centers have been synthesized in optically active forms, and the asymmetric syntheses of several biologically active natural products have been achieved.[4]

We next planned to solve the problem of controlling the stereochemistry of the rearrangements of the 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives, in other words, controlling the migrating groups of the rearrangements. Reports on the control of the stereochemistry during the rearrangements of the epoxy alcohol derivatives are few, and to the best of our knowledge, only two groups have reported their studies on this issue. Maruoka and Yamamoto used silylated epoxy alcohol derivatives, and the stereocontrol of the reaction was achieved by changing the type of LA.[2f] Recently, Suda and Takanami reported controlling the stereochemistry of the rearrangement by changing the metal in the porphyrin complex.[2a] They succeeded in controlling the stereochemistry by changing the type of the LAs. On the other hand, we communicated the control of the stereochemistry by the combination of the protecting group of the alcohol and the LA. The most interesting result was the control of the stereochemistry using the single LA, $SnCl_4$.[7] The method was then applied to the formation of two types of quaternary carbon centers from the single compound in optically active forms (Scheme 2). We now report the full details of a new method for the control of the rearrangements of the 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives and its application by a combination of a LA and the protecting group of the alcohol (Scheme 2).

Results and Discussion

As shown in Scheme 1, once the regiochemistry is controlled, the remaining problem is the control of the stereochemistry. We then chose the 2,3-epoxy-1-alcohol derivatives because the control of their regiochemistry had already been solved.[4] To control the stereochemistry of the rearrangement reactions, we paid attention to the two lone pairs of the oxygen atom on the oxiran ring, which occupy the opposite sides of the oxygen atom. When the reaction proceeds in a stereoselective manner, the migrating groups of the rearrangements depend on the attacking course of the LA (Scheme 3). If the protecting group has a nucleophilic ability, that is, the protecting group prefers to chelate to the LA, the LA approaches the lone pair of the oxygen from the same side of the alcohol, and the alkyl group would preferably migrate (route a). On the contrary, when the protecting group repels the LA, the LA approaches the lone pair of the oxygen from the opposite side of the alcohol, and the hydroxy alkyl group would preferably migrate (route b).

Rearrangement of Cyclic 2,3-Epoxy Alcohols. First of all, we selected the six-membered ring 2,3-epoxy alcohol derivatives as the substrates and examined the influence of the type of LA and the protecting group of the alcohol. These results are

(2) For examples, see: (a) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554−9555. (b) Jeon, S.; Walsh, P. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545. (c) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D. *J. Org. Chem.* **1993**, *58*, 5944−5951. (d) Marson, C. M.; Khan, A.; Porter, R. A.; Cobb, A. J. A. *Tetrahedron Lett.* **2002**, *43*, 6637−6640. (e) Marson, C. M.; Oare, C. A.; McGregor, J.; Walsgrove, T.; Grinter, T. J.; Adams, H. *Tetrahedron Lett.* **2003**, *44*, 141−143. (f) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663−3672. (g) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307−310. (h) Jung, M. E.; Heuvel, A. V. D. *Tetrahedron Lett.* **2002**, *43*, 8169−8172. (i) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J. M. *Org. Lett.* **2003**, *5*, 3159−3161. (j) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818−1826. (k) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212−8216. (l) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129−8132. (m) Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791−3794.

(3) (a) Maruoka, K.; Hasegawa, H.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem.* Soc. **1986**, *108*, 3827−3829. (b) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431−6432. (c) Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5449−5450. (d) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515−3518. (e) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891−5894. (f) Nakagawa, T.; Taya, M.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949−8950. (g) Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749−3762.

(4) For recent examples, see: (a) Fujioka, H.; Kitagaki, S.; Imai, R.; Kondo, M..; Okamoto, S.; Yoshida, Y.; Akai, S.; Kita, Y. *Tetrahedron Lett.* **1995**, *36*, 3219−3222. (b) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Fujioka, H. *Tetrahedron Lett.* **1997**, *38*, 1061−1064. (c) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem.* **1997**, *62*, 4991−4997. (d) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka H. *J. Org. Chem.* **2003**, *68*, 5917−5924. (e) Fujioka, H.; Yoshida, Y.; Kita, Y. *J. Synth. Org. Chem., Jpn.* **2003**, *61*, 133−143. (f) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2003**, *44*, 411−413.

(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (c) Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934−935.

(6) There is only one example for practical use, except for our work (ref 4), see: Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Zaragozá, R. J. *Synlett* **1993**, 895−896.

(7) Part of this study was published as a preliminary communication: Kita, Y.; Matsuda, S.; Inoguchi, R.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2005**, *46*, 89−91.

SCHEME 3. Concept for the Control of Stereochemistry

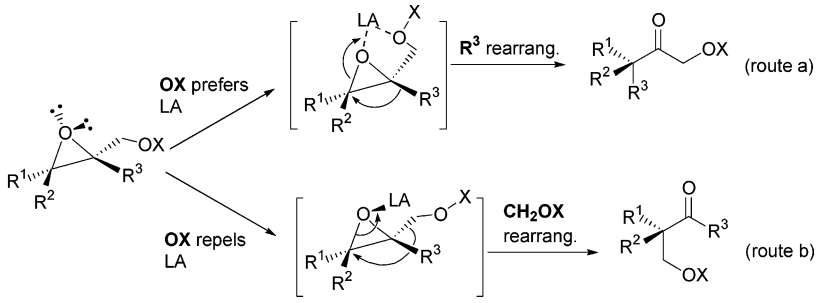
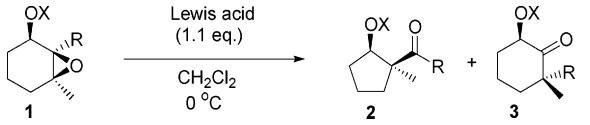


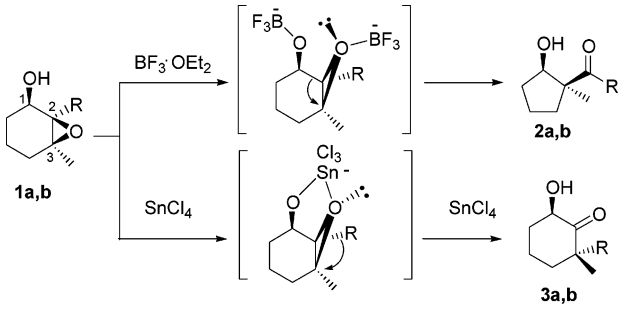
TABLE 1. Rearrangement of Cyclic 2,3-Epoxy Alcohol Derivatives



					product (yield, %)[a]		
entry	R	**1**	X	Lewis acid	**2**	**3**	ratio[b] (**2**:**3**)
1	Et	**1a**	H	$SnCl_4$		**3a**; X = H (69)	**3** only
2	Bu	**1b**	H	$SnCl_4$		**3b**; X = H (98)	**3** only
3	Bu	**1c**	Bn	$SnCl_4$	**2c**; X = Bn (20)	**3c**; X = Bn (44)	1:2.2
4	Bu	**1d**	Me	$SnCl_4$	**2d**; X = Me (8)	**3d**; X = Me (59)	1:7.3
5	Bu	**1e**	Me_3Si	$SnCl_4$	**2b**; X = H (39)		**2** only
6	Bu	**1f**	Et_3Si	$SnCl_4$	**2b**; X = H (71)		**2** only
7	Bu	**1g**	*t*-$BuMe_2Si$	$SnCl_4$	**2b**; X = H (94)		**2** only
8	Bu	**1h**	PNB	$SnCl_4$	**2h**; X = PNB (26)	**3h**; X = PNB (46)	1:1.8
9	Et	**1a**	H	$BF_3{\cdot}OEt_2$	**2a**; X = H (75)		**2** only
10	Bu	**1b**	H	$BF_3{\cdot}OEt_2$	**2b**; X = H (47)		**2** only
11	Bu	**1c**	Bn	$BF_3{\cdot}OEt_2$	**2c**; X = Bn (81)		**2** only
12	Bu	**1g**	*t*-$BuMe_2Si$	$BF_3{\cdot}OEt_2$	**2b**; X = H (34)		**2** only
13	Bu	**1h**	PNB	$BF_3{\cdot}OEt_2$	**2h**; X = PNB (24)	**3h**; X = PNB (34)	1:1.4

[a] Isolated yields. [b] The ratios were determined by the isolation of each product.

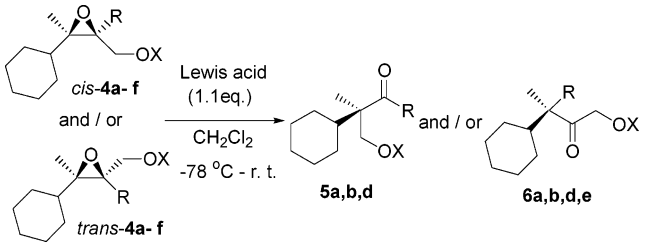
SCHEME 4. Plausible Mechanism for the Difference between $BF_3{\cdot}OEt_2$ and $SnCl_4$ in Cyclic 2,3-Epoxy Alcohols



summarized in Table 1. Initially, we examined the reaction of the cyclic six-membered ring 2,3-epoxy alcohol as the substrate, with $SnCl_4$ as the representative LA, which causes chelation, and $BF_3{\cdot}OEt_2$ as the representative LA, which does not cause chelation. As shown in Table 1, in the case of $SnCl_4$, six-membered ring α-hydroxy ketones **3a** and **3b** were exclusively obtained (entries 1 and 2). On the other hand, in the case of $BF_3{\cdot}OEt_2$, five-membered ring *β*-hydroxy ketones **2a** and **2b** were obtained (entries 9 and 10). These interesting phenomena are explained by Scheme 4. In the case of $SnCl_4$, the tin atom coordinates with both the alcohol and the oxirane ring in a chelation manner. As a result, the oxirane ring and alcohol unit are fixed, and the C2 alkyl group migrates to the C3 carbocation to give the six-membered ring α-hydroxy ketones **3**. On the other hand, in the case of $BF_3{\cdot}OEt_2$, $BF_3{\cdot}OEt_2$ separately coordinates with the two oxygen atoms of the alcohol and oxirane ring. In particular, $BF_3{\cdot}OEt_2$ coordinates with one of the two lone pairs of the oxirane ring, which is outside of the six-membered ring for steric repulsion. The C1−C2 bond then migrates to the C3 carbocation to give the ring-contracted five-membered ring *β*-hydroxy ketones **2**. We next examined several kinds of protecting groups of the alcohol in the presence of $SnCl_4$ and $BF_3{\cdot}OEt_2$. In the case of $SnCl_4$, a clear difference depending on the protecting groups was observed. The trialkylsilyl ether exclusively afforded **2** (entries 5−7), and *tert*-butyldimethylsilyl (TBS) ether **1g** gave the best result compared with trimethylsilyl ether **1e** and triethylsilyl ether **1f**. The benzyl and methyl ether **1c**,**d** preferentially afforded **3c** and **3d** (entries 3 and 4) like that of the alcohols **1a**,**b** (entries 1 and 2). However, the *p*-nitrobenzoyl (PNB) ester **1h** did not show such tendency (entry 8). On the other hand, in the case of $BF_3{\cdot}OEt_2$, *β*-hydroxy ketones **2** were preferentially obtained even when the alcohol was protected with the benzyl group and TBS group (entries 11 and 12). When the alcohol was converted to the PNB ester **1h**, both the α-hydroxy ketone **2h** and *β*-hydroxy ketone **3h** were obtained in the ratio of 1:1.4 (entry 13). These results show that $SnCl_4$ is the best LA for the selective rearrangement. A plausible mechanism for the selectivity depending on the protecting groups of the alcohol will be discussed later (Scheme 5).

Rearrangement of Acyclic 2,3-Epoxy Alcohols. Next we tried to apply this method to the acyclic 2,3-epoxy alcohol derivatives, and the effect of the protecting group of the alcohol

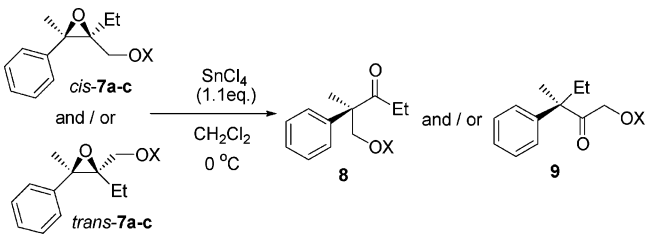
TABLE 2. Rearrangements of Acyclic 2,3-Epoxy Alcohol Derivatives



					product (yield, %)[a]		
entry	R	4	X	Lewis acid	5	6	ratio[b] (5:6)
1	Et	*cis*-**4a**	H	$SnCl_4$		**6a**; X = H (76)	**6** only
2	Et	*trans*-**4a**	H	$SnCl_4$	**5a**; X = H (27)	**6a**; X = H (56)	1:2.1
3	Et	*cis*-**4b**	Bn	$SnCl_4$		**6b**; X = Bn (94)	**6** only
4	Et	*trans*-**4b**	Bn	$SnCl_4$		**6b**; X = Bn (55)	**6** only
5	Et	*cis*-**4c**	TBS	$SnCl_4$	**5a**; X = H (65)		**5** only
6	Et	*trans*-**4c**	TBS	$SnCl_4$	**5a**; X = H (47)		**5** only
7	Me	*cis*-**4d**	H	$SnCl_4$	**5d**; X = H (31)	**6d**; X = H (3)	10.3:1
8	Me	*trans*-**4d**	H	$SnCl_4$	**5d**; X = H (60)		**5** only
9	Me	*cis*-**4e**	Bn	$SnCl_4$		**6e**; X = Bn (91)	**6** only
10	Me	*trans*-**4e**	Bn	$SnCl_4$		**6e**; X = Bn (76)	**6** only
11	Me	*cis*-**4f**	TBS	$SnCl_4$	**5d**; X = H (90)		**5** only
12	Me	*trans*-**4f**	TBS	$SnCl_4$	**5d**; X = H (100)		**5** only
13	Et	*cis*-**4a**	H	$BF_3{\cdot}OEt_2$	**5a**; X = H (46)	**6a**; X = H (50)	0.92:1
14	Et	*trans*-**4a**	H	$BF_3{\cdot}OEt_2$	**5a**; X = H (31)	**6a**; X = H (67)	1:2.2
15	Me	*cis*-**4d**	H	$BF_3{\cdot}OEt_2$	**5d**; X = H (58)	**6d**; X = H (14)	4.1:1
16	Me	*trans*-**4d**	H	$BF_3{\cdot}OEt_2$		**6d**; X = H (100)	**6** only

[a] Isolated yields. [b] The ratios were determined by the isolation of each product.

TABLE 3. Rearrangement of Acyclic 2,3-Epoxy Alcohol Derivatives with C3 Phenyl Group



			product (yield, %)[a]		ratio[b]
entry	7	X	8	9	(8:9)
1	*cis*-**7a**	H	**8a**; X = H (39)	**9a**; X = H (52)	1:1.3
2	*trans*-**7a**	H	**8a**; X = H (42)	**9a**; X = H (53)	1:1.3
3	*cis*-**7b**	Bn	**8b**; X = Bn (13)	**9b**; X = Bn (68)	1:5.2
4	*trans*-**7b**	Bn	**8b**; X = Bn (11)	**9b**; X = Bn (80)	1:7.3
5	*cis*-**7c**	TBS	**8a**; X = H (78)		**8** only
6	*trans*-**7c**	TBS	**8a**; X = H (89)		**8** only

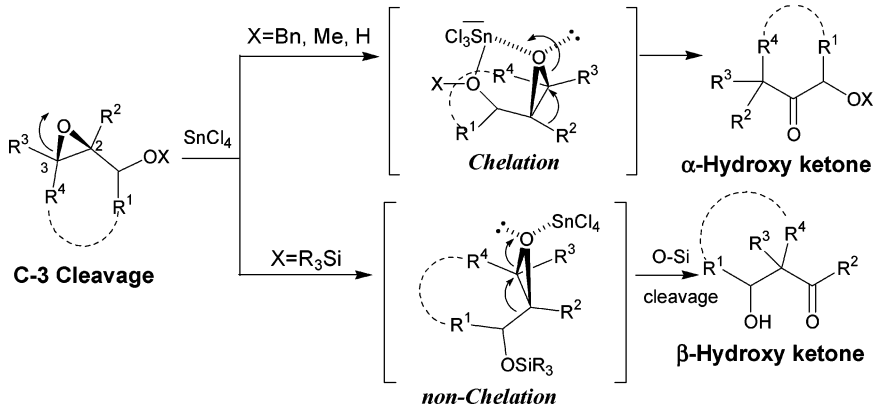
[a] Isolated yields. [b] The ratios were determined by the isolation of each product.

was examined. These results are shown in Table 2. $SnCl_4$ had almost the same reactivity in the acyclic system as in the cyclic system. The epoxy alcohol itself **4a** or the benzyl ethers **4b**,**e** afforded the α-hydroxy ketone **6a** or α-benzyloxy ketones **6b**,**e** as the major products by migration of the R group via the C3 carbocation (entries 1−4, 9, and 10). In contrast, the TBS ethers **4c**,**f** afforded the *β*-hydroxy ketones **5a**,**d** as a single product by migration of the siloxymethyl group and successive cleavage of the O−Si bond (entries 5, 6, 11, and 12). Furthermore, this tendency was observed in both the *cis*- and *trans*-isomers of the 2,3-epoxy alcohol derivatives. However, in the case of **4d** (R = Me and X = H), the *β*-hydroxy ketone **5d** was preferentially obtained (entries 7 and 8). This is the opposite tendency compared with the case of **4a** (R = Et, X = H; entries 1 and 2). This is probably due to the low migration ability of the methyl group, which is often reported in the literature.[2l−n] For the trialkylsilyloxy compounds, every reaction afforded the *β*-hydroxy ketones possibly obtained by the desilylation after the rearrangement because the products are completely different from those derived from the epoxy alcohols without protecting groups. On the other hand, for the reactions by $BF_3{\cdot}OEt_2$, no regular reaction was observed (entries 13−16).

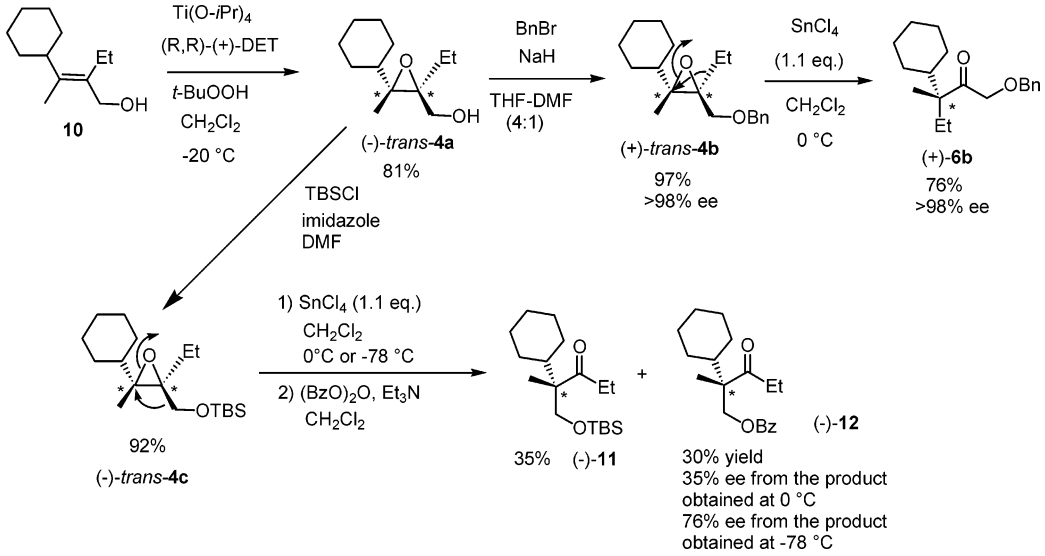
Rearrangements of Acyclic 2,3-Epoxy Alcohols with C3 Phenyl Group. Next we examined the reactivity of the 2,3-epoxy alcohol derivatives with the phenyl group at the C3 position (Table 3). The rearrangement reaction of the substrate must proceed via the more stable C3 carbocation. In these cases, control of the stereochemistry was also achieved to give the *β*-hydroxy ketones **8** and α-hydroxy ketones **9**, depending on the protecting group. Thus, the effect of the protecting group in this $SnCl_4$-promoted rearrangement of the epoxy alcohol derivatives was also observed in the acyclic system bearing a cation stabilizing group, such as the phenyl group. However, the selectivity of two kinds of carbonyl groups in the case of X=H, Bn (entries 1−4) was slightly lower than that observed in Table 2. These results suggest some participation of the stepwise reaction process as a result of the cation stabilizing ability of the phenyl group at the C3 position.

Consideration of the Reaction Mechanism: As shown above, especially in the use of the $SnCl_4$, selective formation of two types of hydroxyl ketones was possible. Thus, the epoxy silyl ethers afforded the *β*-hydroxy ketones as major products, whereas the epoxy alcohols and the epoxy alkyl ethers produced α-hydroxy ketones as the major products. These results are rationalized by the nonchelation and chelation controls. The epoxy silyl ethers form nonchelation intermediates. The hy-

SCHEME 5. Plausible Reaction Mechanism



SCHEME 6. Asymmetric Synthesis of Two Quaternary Carbon Centers in Acyclic System



droxyl or alkyl ether compounds can form the bidentate chelation transition state between two oxygen atoms and the Sn metal. This decreases the migratory aptitude of the alkoxymethyl group, and then the C2 alkyl group, opposite to the alkoxymethyl group, selectively migrates to produce the α-hydroxy ketones. On the other hand, the bulky trialkylsilyl group inhibits the formation of the chelation transition state and makes the LA attack the opposite-side lone pair of the oxygen atom of the oxiran ring. The stereoselective rearrangement of the trialkylsilyloxy group in the *anti*-periplanar position followed by the cleavage of the O−Si bond then occurs to give the *β*-hydroxy ketones (Scheme 5).

Selective Construction of Optically Active Two Chiral Quaternary Carbon Centers from the Single Isomer. Because many biologically active natural products have chiral quaternary carbon centers, the construction of such structural subunits is one of the important issues in synthetic organic chemistry and has been widely studied.[8] We then tried to apply our method to the asymmetric synthesis of carbonyl compounds bearing chiral quaternary carbon centers. As shown in Scheme 6, we prepared the chiral nonracemic 2,3-epoxy alcohol (−)-*trans*-**4a** using the Katsuki and Sharpless asymmetric epoxidation protocol.[5] This alcohol was protected with the benzyl and TBS group to give (+)-*trans*-**4b** and (−)-*trans*-**4c**, respectively. They were then treated with $SnCl_4$. In the case of the benzyl group (+)-*trans*-**4b**, the reaction proceeded through a chelation intermediate to give the α-benzyloxy ketone (+)-**6b** in good yield without racemization. On the other hand, when the TBS ether (−)-*trans*-**4c** was treated with $SnCl_4$ at 0 °C, the *β*-hydroxy ketone **5a** was obtained by deprotection of the TBS ether of the rearranged product under acidic reaction conditions. This compound **5a** was benzoylated and found to be 35% ee, determined by the HPLC analysis of its benzoylated compound (−)-**12**. This is probably due to the partial racemization through a retro-aldol and aldol mechanism.[9] When the reaction was performed at −78 °C and quenched at the same temperature, the racemization was partly suppressed, and the product was found to be 76% ee after benzoylation (Scheme 6). We already observed the remarkable effect of the reaction temperature on the enantiomeric excess of the *β*-hydroxy ketone derivatives under basic conditions.[10]

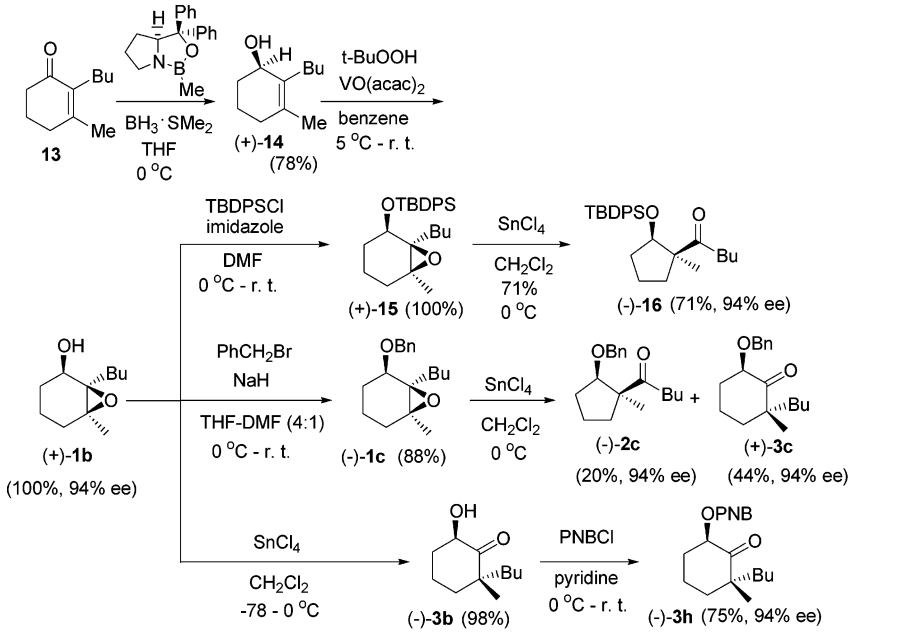
Scheme 7 shows our other application of the method for the selective formation of two types of optically active quaternary carbon centers in the cyclic system. That is, the known α,*β*-

(8) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(9) Racemization through a retro-aldol-type reaction, see: Kimura, T.; Yamamoto, N.; Suzuki, Y.; Kawano, K.; Norimine, Y.; Ito, K.; Nagato, S.; Iimura, Y.; Yonaga, M. *J. Org. Chem.* **2002**, *67*, 6228−6231.

(10) Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K.; Naka, T.; Higuchi, K.; Akiyama, E.; Fujioka, H.; Kita, Y. *Chem.—Eur. J.* **2005**, *11*, 6286−6297.

SCHEME 7. Selective Synthesis of Optically Active Five-Membered and Six-Membered Ring Skeletons



unsaturated ketone **13**[11] was converted to the epoxy alcohol (+)-**1b** by asymmetric reduction using the method of Corey et al.,[12] followed by *cis*-selective epoxidation by the Sharpless and Michaelson procedure.[13] The protection of the hydroxyl function of (+)-**1b** with TBDPS, a stable protecting group under acidic conditions, and the benzyl group afforded the optically active epoxy alcohol derivatives (+)-**15** and (−)-**1c** in good yields, respectively. Three different types of optically active 2,3-epoxy alcohol derivatives (+)-**15**, (−)-**1c**, and (+)-**1b** were then treated with $SnCl_4$. As we already described above, the six-membered ring product (−)-**3b** was exclusively obtained in the case of the 2,3-epoxy alcohol (+)-**1b** without the protecting group. The ee value of (−)-**3b**, 94% ee, was deduced by the HPLC analysis of its benzoate (−)-**3h**. In contrast, the five-membered ring product (−)-**16** was exclusively obtained in the case of the TBDPS ether (+)-**15**, whereas the benzyl ether (−)-**1c** afforded a 1:2 mixture of the five-membered ring product (−)-**2c** and six-membered ring one (+)-**3c**. No racemization occurred in every rearranged product. This fact also indicates that our method is applicable to the construction of the quaternary asymmetric carbon centers of cyclic systems as well as acyclic systems.

Conclusion

We have found that the LA-promoted rearrangement of 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives, which are supposed to have only a slight difference in the stability of carbocation at the C2 and the C3 positions, proceeds through the C3 carbocation. Moreover, when we used $SnCl_4$ as a LA, control of the stereochemistry of the rearranged products was achieved via the chelation or nonchelation transition state only by changing the type of protecting group of the alcohol. Thus, we have succeeded in selectively producing two types of rearranged products from the single carbon skeleton. A detailed mechanistic investigation and applications of this method including natural product synthesis are now in progress in our laboratory.

Experimental Section

General Procedure for the Rearrangement Reaction of 2,3-Epoxy Alcohol Derivatives using BF_3·Et_2O or $SnCl_4$: BF_3·Et_2O or $SnCl_4$ (1.1 mmol) was added to a stirred solution of the 2,3-epoxy alcohol derivatives (1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C or −78 °C under N_2, and the mixture was gradually warmed to rt. After the completion of the reaction (TLC check), saturated aqueous $NaHCO_3$ was added to the solution, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (2/1∼20/1) as the eluent to give the rearranged product.

(1*RS*,3*RS*)-2-Methyl-2-pentanoylcyclopentanol (2b; Entry 10 in Table 1): BF_3·Et_2O (47 μL, 0.37 mmol) was added to a stirred solution of **1b** (61.8 mg, 0.34 mmol) in CH_2Cl_2 (3.4 mL) at 0 °C under N_2, and the mixture was gradually warmed to rt. After the completion of the reaction (TLC check), saturated aqueous $NaHCO_3$ was added to the solution, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (7/1) as the eluent to give **2b** (29.1 mg, 47%) as a colorless oil. IR (KBr): 3441, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 6.9 Hz), 1.16 (s, 3H), 1.20−1.36 (m, 2H), 1.49−2.02 (m, 8H), 2.16 (br s, 1H), 2.41−2.56 (m, 2H), 4.29 (t, 1H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 13.9, 16.7, 18.3, 22.3, 25.7, 30.2, 32.8, 37.7, 57.1, 75.5, 216.7. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.47; H, 10.83.

(1*RS*,3*RS*)-3-Butyl-3-methyl-2-oxacyclohexanol (3b; Entry 2 in Table 1): $SnCl_4$ (1.0 M in CH_2Cl_2, 0.22 mL, 0.22 mmol) was added to a stirred solution of **1b** (36.0 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C under N_2, and the mixture was gradually warmed to rt. After the completion of the reaction (TLC check), saturated

(11) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700−12704.
(12) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.
(13) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

aqueous $NaHCO_3$ was added to the solution, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (7/1) as the eluent to give **3b** (35.3 mg, 98%) as a colorless oil. IR (KBr): 3479, 1705 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7.2 Hz), 0.92−1.00 (m, 2H), 1.09 (s, 3H), 1.21−1.94 (m, 9H), 2.38−2.45 (m, 1H), 3.77 (d, 1H, J = 3.6 Hz), 4.28−4.36 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 18.9, 22.0, 23.2, 26.0, 37.2, 37.3, 40.7, 48.4, 72.4, 215.8. HRMS (FAB) calcd for $C_{11}H_{20}O_2Li$ $[M + Li]^+$, 191.1624; found, 191.1622.

(+)-3-Cyclohexyl-3-methyl-2-oxo-1-benzyloxypentane ((+)-6b): Colorless oil; $[\alpha]^{25}_D$ +2.51 (*c* 0.47, $CHCl_3$). IR (KBr): 1712 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.75 (t, 3H, J = 7.5 Hz), 0.87−1.74 (m, 13H), 2.17 (s, 3H), 4.23 (d, 2H, J = 2.5 Hz), 4.61 (s, 2H), 7.29−7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 8.8, 14.7, 26.5, 26.7, 26.8 (2C), 28.5, 29.6, 45.1, 53.5, 71.9, 73.0, 127.6, 127.7 (2C), 128.2 (2C), 137.3, 211.5. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.99; H, 9.67.

(−)-(1*S*,2*R*)-(1-[2-(*tert*-Butyldiphenylsilanyloxy)-1-methyl-cyclopentyl]-pentan-1-one ((−)-16): Colorless oil; $[\alpha]^{25}_D$ −11.9 (*c* 0.91, $CHCl_3$). IR (KBr): 1703, 1427 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 7.2 Hz), 1.09 (s, 9H), 1.15−1.24 (m, 2H), 1.26 (s, 3H), 1.31−1.70 (m, 7H), 1.88−1.94 (m, 1H), 2.25−2.34 (m, 2H), 4.42 (t, 1H, J = 6.6 Hz), 7.32−7.46 (m, 6H), 7.61−7.68 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 13.9, 17.9, 19.3, 20.3, 22.3, 26.0, 27.0 (3C), 33.3, 34.4, 37.6, 59.1, 78.0, 127.4 (2C), 127.5 (2C), 129.5, 129.6, 133.6, 134.6, 135.9 (4C), 214.5. Anal. Calcd for $C_{27}H_{38}O_2Si$: C, 76.72; H, 9.06. Found: C, 76.42; H, 9.15. HPLC analysis: 94% ee (Daicel Chiralpak OD-H; hexane only, 0.5 mL/min, 20 °C).

(−)-(1*R*,2*S*)-(1-Benzyloxy-2-methyl-2-pentanoylcyclopentane ((−)-2c). Colorless oil; $[\alpha]^{25}_D$ −54.1 (*c* 0.94, $CHCl_3$). IR (KBr): 1703 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 7.5 Hz), 1.20−1.34 (m, 2H), 1.23 (s, 3H), 1.48−1.75 (m, 6H), 1.92−2.04 (m, 2H), 2.39−2.57 (m, 2H), 4.14 (t, 1H, J = 6.6 Hz), 4.42 (A in ABq, 1H, J = 12.0 Hz), 4.53 (B in ABq, 1H, J = 12.0 Hz), 7.25−7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.9, 17.6, 20.3, 22.4, 26.1, 30.1, 35.0, 37.5, 58.1, 71.7, 82.8, 127.4, 127.5 (2C), 128.3 (2C), 138.8, 214.7. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.64; H, 9.68. HPLC analysis: 94% ee (Daicel Chiralpak OD-H; hexane only, 0.5 mL/min, 20 °C).

(+)-(1*RS*,3*RS*)-1-Benzyloxy-3-butyl-3-methyl-2-oxocyclohexane ((+)-3c): Colorless oil; $[\alpha]^{26}_D$ +45.8 (*c* 1.98, $CHCl_3$). IR (KBr): 1717 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 7.5 Hz), 1.05 (s, 3H), 1.19−1.90 (m, 11H), 2.23−2.30 (m, 1H), 4.12 (dd, 1H, J = 6.9, 11.3 Hz), 4.45 (d, 1H, J = 12.3 Hz), 4.80 (d, 1H, J = 12.3 Hz), 7.26−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.9, 19.5, 22.1, 23.2, 26.1, 34.9, 37.2, 40.4, 49.6, 71.7, 78.9, 127.7, 127.9 (2C), 128.4 (2C), 138.1, 213.3. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.74; H, 9.60. HPLC analysis: 94% ee (Daicel Chiralpak OD-H; hexane only, 0.5 mL/min, 20 °C).

(−)-(2*S*)-1-(*tert*-Butyldimethylsilanyloxy)-2-cyclohexyl-2-methyl-pentan-3-one ((−)-11) and (−)-(1*S*)-2-Cyclohexyl-2-methyl-3-oxo pentyl benzoate ((−)-12). The crude rearranged products obtained from (−)-*trans*-**4a** (1 mmol) were subjected to benzoylation using benzoic anhydride (2 mmol), triethylamine (2 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2CH_2 (10 mL) at 0 °C under N_2. After being stirred for 16 h, H_2O was added to the reaction mixture, and the solution was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (9/1) as the eluent to give **(−)-11** and **(−)-12** in the yield shown in Scheme 3.

(−)-11: Colorless oil. IR (KBr): 1705, 1450, 1256, 1084, 839 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.00 (t, 3H, J = 7.2 Hz), 1.05 (s, 3H), 1.07−1.31 (m, 6H), 1.47−1.80 (m, 5H), 2.43−2.51 (m, 2H), 3.47 (A in ABq, 1H, J = 9.3 Hz), 3.79 (B in ABq, 1H, J = 9.3 Hz). $[\alpha]^{25}_D$ − 9.93 (*c* 0.38, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ −5.7 (2C), 7.8, 14.2, 18.1, 25.8 (3C), 26.5, 26.8, 26.9, 27.4, 28.4, 32.2, 42.2, 56.2, 69.0, 215.8. HRMS (FAB) calcd for $C_{18}H_{37}O_2Si$ $[M + H]^+$, 313.2563; found, 313.2569. **(−)-12:** Colorless oil. IR (KBr): 1722, 1450, 1269, 1113, 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80−1.44 (m, 4H), 1.05 (t, 3H, J = 7.2 Hz), 1.21 (s, 3H), 1.48−1.87 (m, 6H), 2.44−2.62 (m, 2H), 4.38 (A in ABq, 1H, J = 10.9 Hz), 4.50 (B in ABq, 1H, J = 10.9 Hz), 7.42 (t, 2H, J = 7.5 Hz), 7.56 (t, 2H, J = 7.5 Hz), 7.94 (d, 2H, J = 6.9 Hz). $[\alpha\ ]^{25}_D$ −9.01 (*c* 0.50, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 8.0, 15.1, 26.4, 26.7, 26.8, 27.7, 28.0, 31.4, 43.0, 54.4, 69.8, 128.5 (2C), 129.5 (2C), 129.9, 133.1, 166.3, 213.8. HRMS (FAB) calcd for $C_{19}H_{27}O_3$ $[M + H]^+$, 303.1960; found, 303.1960. HPLC analysis (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 99/1, 0.4 mL/min, 20 °C).

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Supporting Information Available: Full experimental details including the physical data and ^1H and ^{13}C NMR spectra of **1d**, **1e**, **1f**, **2d**, **3a**, **3b**, **3d**, *cis*-**4d**, **6a**, **8b**, **9a**, **10**, (−)-*trans*-**4a**, (+)-*trans*-**4b**, (+)-**6b**, (−)-*trans*-**4c**, (−)-**11**, (−)-**12**, (+)-**14**, (+)-**1b**, (+)-**15**, (−)-**16**, (−)-**1c**, (−)-**2c**, (+)-**3c**, (−)-**3b**, and (−)-**3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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