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Tetrahedron 61 (2005) 6726–6742
Tetrahedron

Chemo- and stereoselectivity in titanium-mediated regioselective ring-opening reaction of epoxides at the more substituted carbon

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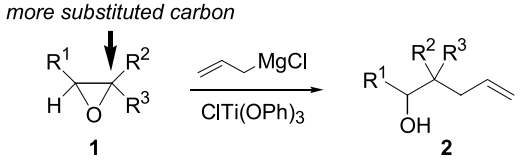
Received 5 April 2005; revised 28 April 2005; accepted 2 May 2005

Abstract—Chemo- and stereoselectivity in the ring-opening reaction of epoxides with a reagent prepared from allylmagnesium halide and chlorotitanium triphenoxide is described. It has been proven that the allylating reagent can also be used for the reaction of epoxides bearing a *tert*-butyl ester, amide, or acetal moiety, and that the epoxide cleavage regioselectively takes place at the more substituted carbon in all cases. Interestingly, while the reaction of acyclic 2,2,3-trialkyl epoxides or 3,3-disubstituted 2,3-epoxy alcohol derivatives with the allyltitanium reagent yielded the allylated products as an almost 1:1 diastereomixture, the ring-opening reaction of 2-substituted 2,3-epoxy alcohol derivatives stereospecifically proceeded through the *anti* pathway. The latter reaction is extremely useful for asymmetric construction of quaternary carbon centers.

1. Introduction

Ring-opening reaction of epoxides is a powerful method for the stereoselective carbon–carbon bond formation,[1] due to the availability of various chiral epoxides in an enantiomerically pure form.[2] Although the ring-opening reaction of epoxides at the less hindered position or at the activated carbon having a vinyl or aryl group is extensively studied,[3,4] considerably less success has been realized in the regioselective ring-opening at the more substituted unactivated carbon, except for intramolecular reactions[5] including rearrangement.[6] If the ring opening at the more substituted carbon of a wide variety of epoxides proceeds in a regioselective manner, it can serve as a synthetically useful method for construction of tertiary and quaternary carbon centers. However, as far as we are aware, only a few examples of such reaction were reported to date, most of which are based on organoaluminium chemistry.[7,8]

In 1990, we reported that an allyltitanium reagent prepared from chlorotitanium triphenoxide and allylmagnesium chloride selectively cleaves the carbon–oxygen bond of epoxides **1** at the more substituted carbon atom to give an allylated product **2** (Scheme 1).[9] When the ring-opening reaction of simple epoxides (not activated by a vinyl or an aryl group) was conducted with an allyltitanium reagent derived from chlorotitanium triisopropoxide,[10] a considerable amount of the undesired reduction product as well as the allylated product at the less hindered carbon were obtained. Formation of the reduction product was attributed to the Meerwein–Ponndorf–Verley reaction with isopropoxide derived from chlorotitanium triisopropoxide. In contrast, our titanium reagent prepared from chlorotitanium triphenoxide prevents the formation of the reduction product. Since our previous study was limited to the reaction of unfunctionalized alkyl epoxides, the chemoselectivity of the ring-opening reaction remains to be seen. Furthermore, although we have already shown that the reaction of cyclic epoxides stereoselectively proceeds through the *anti* pathway (>10:1), the stereochemical course of the reaction with acyclic epoxides has not been investigated. In this paper, we present the chemo- and stereoselectivity in the regioselective ring-opening reaction of epoxides with the allyltitanium reagent. Construction of chiral quaternary carbons from 2-substituted 2,3-epoxy alcohols is also presented.[11]



Scheme 1. Regioselective ring cleavage of epoxides at the more hindered carbon

Keywords: Epoxides; Titanium; Allylation; Quaternary carbon.
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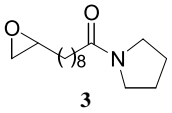
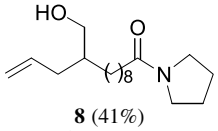
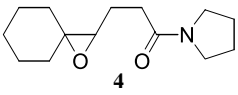
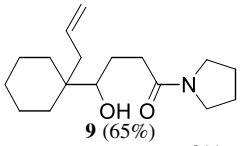
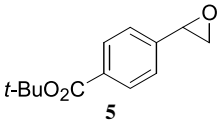
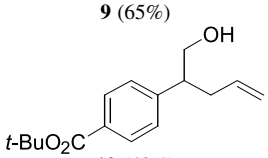
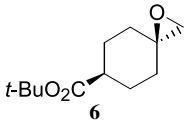
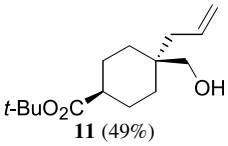
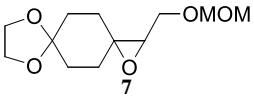
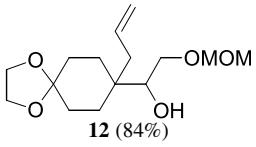
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.05.006

Table 1. Chemoselective epoxide cleavage with the allyltitanium reagent[a]

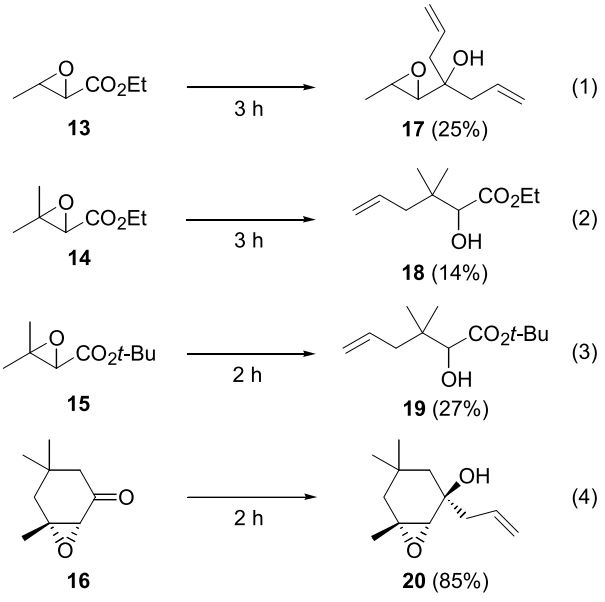
Entry	Epoxides	Reagent (equiv)	Conditions	Product (yield)[b]
1	 **3**	7	−78 °C to rt, 96 h	 **8** (41%)
2	 **4**	5	−78 °C to rt, 24 h	 **9** (65%)
3	 **5**	2	−78 to 0 °C, 1 h	 **10** (48%)
4	 **6**	3	−78 to 0 °C, 3 h	 **11** (49%)
5	 **7**	3	−78 to 0 °C, 4 h	 **12** (84%)

[a] Reagents: allylmagnesium bromide, $ClTi(OPh)_3$, THF.
[b] Isolated yields.

2. Results and discussion

2.1. Reaction of epoxides bearing an electrophilic functionality

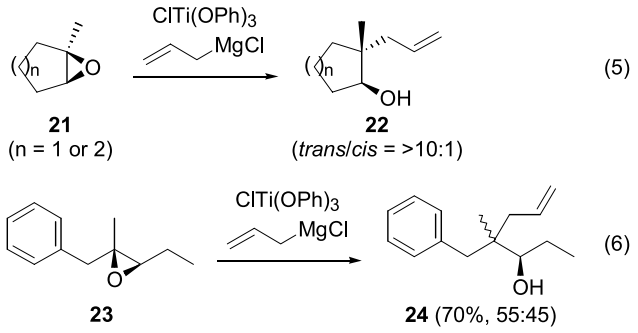
First, we prepared epoxides **3**–**7** bearing an electrophilic functionality through the standard protocol (see the Section 4) and investigated the chemoselectivity of the ring-opening reaction with the allyltitanium reagents (Table 1). Treatment of epoxy amide **3** with allylmagnesium bromide[12] in the presence of chlorotitanium triphenoxide (1 equiv to the Grignard reagent) afforded allylated product **8** in 41% yields (entry 1), as well as the recovered starting material (15%). This is presumably due to the lower reactivity of the monosubstituted epoxides with the titanium reagent. More reactive trisubstituted epoxy amide **4** gave the desired product **9** in a better yield (65%, entry 2). In contrast, the allyltitanium reagent reacted with the carbonyl group of ethyl ester **13** (Eq. 1 in Scheme 2) to give diallylated epoxide **17** in 25% yield. Furthermore, the reaction of β,β-disubstituted-α,β-epoxy esters **14** and **15** afforded low yields of the desired alcohols **18** and **19** (14 and 27% yield, Eqs. 2 and 3). These results clearly show the limitation of the chemoselectivity of the ring-opening reaction of epoxides having an ester moiety. In contrast, the ring-opening reaction of epoxides **5** and **6** (entries 3 and 4) bearing a *tert*-butyl ester apart from the reaction site selectively proceeded in moderate yields (48 and 49%). Allylation of the carbonyl group of epoxy ketone **16** (Eq. 4) with the allyltitanium reagent predominated over the epoxide cleavage, yielding the epoxy alcohol **20**.[13] However, the undesired allylation of the ketone can be readily suppressed by acetalization of the ketone: reaction of epoxide **7** (entry 5) having an ethylene acetal moiety gave the desired alcohol **12** in 84% yield. From these observations, epoxides having an amide, *tert*-butyl ester, and appropriately-protected ketone can be used in the allylative epoxide cleavage at the more hindered carbon with the titanium reagent.



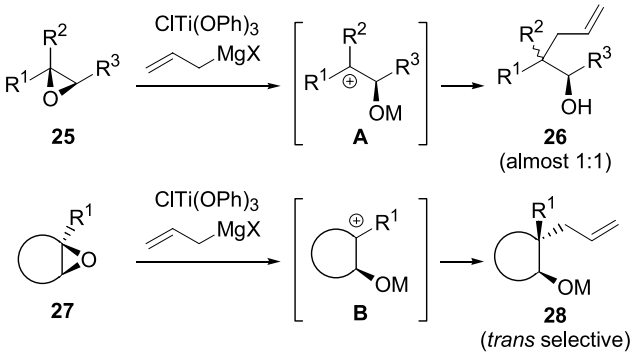
Scheme 2. Reagents and conditions: allylmagnesium bromide, $ClTi(OPh)_3$, THF, −78 to 0 °C.

2.2. Stereoselectivity of the ring-opening of epoxides

In the previous study,[9] we have demonstrated that the allyltitanium-mediated ring-opening reaction of cyclic epoxides **21** stereoselectively proceeds through the *anti* pathway to give the cyclic alcohols **22** (Eq. 5 in Scheme 3).[14] However, the stereochemical course of the reaction of acyclic epoxides was not understood.[15] Thus, we next investigated the reaction of acyclic chiral trisubstituted epoxides **23** (Eq. 6). Unfortunately, the reaction of trialkylepoxide **23** gave the allylated product **24** as a mixture of diastereomers (55:45).



Scheme 3. Stereoselectivity of the epoxide cleavage.



Scheme 4. Stereoselectivity of the reaction of epoxides with the titanium reagent.

Table 2. Stereoselectivity of the reaction of acyclic epoxides

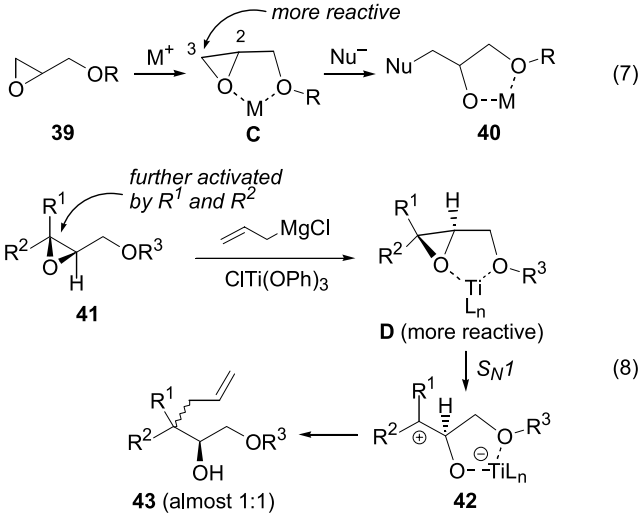
Entry	Epoxy alcohol	Product (yield)[a]	Ratio[b] (*syn*/*anti*)
1	**29** (R=MOM)	**34** (70%)	50:50
2	**30** (R=Bn)	**35** (79%)	54:46
3	**31** (R=MOM)	**36** (83%)	48:52
4	**32** (R=Bn)	**37** (72%)	43:57
5	**33** (R=TBS)	**38** (53%)	48:52

Reagents: allylmagnesium halide, $ClTi(OPh)_3$, THF.
[a] Isolated yields.
[b] Determined by ^1H NMR.

From these results, it is apparent that the titanium-mediated epoxide cleavage proceeds through the S_N1-like pathway including the cationic intermediate **A** (Scheme 4), affording the allylated products **26** as a mixture of diastereomers without stereoselectivity. The good stereoselectivities observed in the reaction of the cyclic epoxides will be attributed to the nucleophilic attack of the allylating reagent from the less hindered side of the cyclic cationic intermediate **B**.

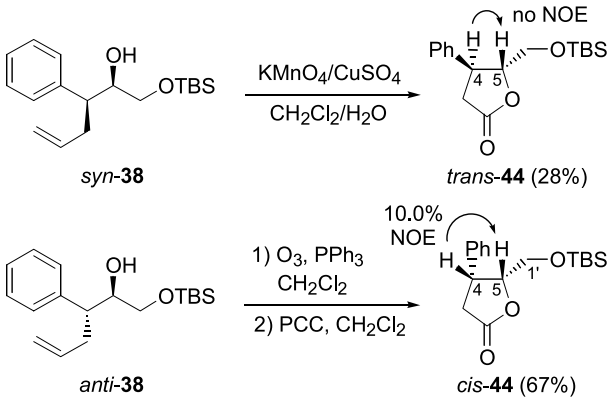
We next investigated the reaction of 2,3-epoxy alcohol derivatives **29**–**33** (Table 2). Treatment of protected 3,3-disubstituted 2,3-epoxy alcohols **29** and **30** with allylmagnesium bromide and chlorotitanium triphenoxide proceeded in good yields (70 and 79%, respectively) but without stereoselectivity. Similarly, 3-substituted 2,3-epoxy alcohol derivatives **31**–**33** also gave almost 1:1 diastereomixtures **36**–**38** (entries 3–5).

It is well known that ring-opening reaction of 2,3-epoxy alcohol derivatives **39** with a nucleophilic metal reagent such as titanium,[16] aluminum,[17] and other nucleophiles[18] regioselectively proceeds at the 3-position to form 1,2-diols such as **40** (Eq. 7 in Scheme 5).[19] Also in the reaction of 2,3-epoxy alcohol derivatives **29**–**33** (Table 2), the ring-opening reaction regioselectively took place at the 3-position. In these cases, two alkyl substituents (entries 1 and 2) or a phenyl group (entries 3–5) at the 3-position further facilitates the S_N1-type ring-opening reaction of **41** at this position to form the cationic intermediate **42** through the intermediate **D** (Eq. 8). Accordingly, the low stereoselectivity of the ring-opening reaction is understandable. In order to realize the stereoselective ring-opening reaction of acyclic epoxides, it is essential to suppress the S_N1-type reaction. This difficulty has been overcome by accelerating the ring-opening reaction at the 2-position of the epoxy alcohols as described later (Section 2.3).



Scheme 5. Ring-opening reaction at the 3-position of protected 2,3-epoxy alcohol.

Stereochemical assignments for the synthesized alcohols were readily made by their transformation into the lactone derivatives as shown in Scheme 6. The allylated diol derivative *syn*-**38**, formed by the reaction of the protected

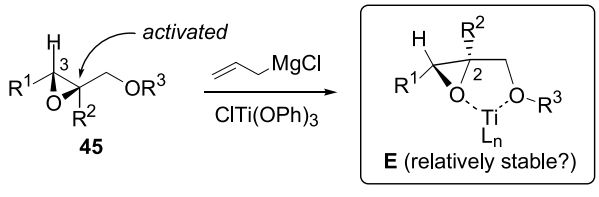


Scheme 6. Determination of stereochemistries of *syn*-**38** and *anti*-**38**.

epoxy alcohol **33** with titanium reagent, was treated with $KMnO_4$ and $CuSO_4$ in CH_2Cl_2 to give the corresponding lactone *trans*-**44** in a one-pot manner. Irradiation of the signal of 4-H led to no NOE enhancement of the signals of 5-H.[20] In contrast, 10% of NOE was observed between 4-H and 5-H of the lactone *cis*-**44** derived from *anti*-**38** as shown in Scheme 6. Stereochemistries of other allylated products including those described later were also confirmed in a similar manner.

2.3. Asymmetric construction of quaternary carbon centers by stereospecific ring-opening reaction

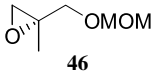
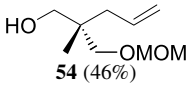
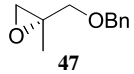
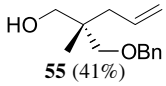
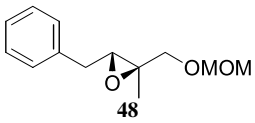
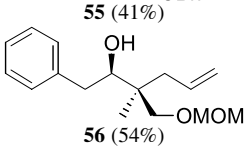
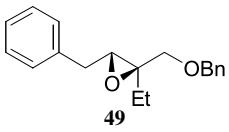
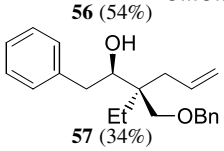
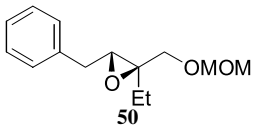
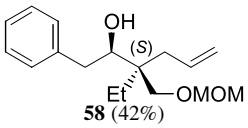
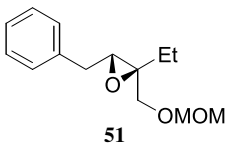
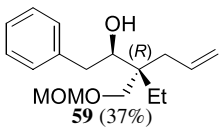
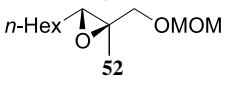
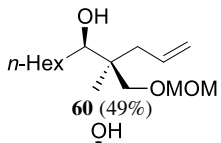
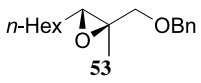
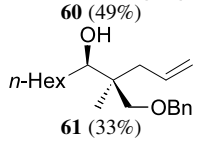
As described in Section 2.2, it was extremely difficult to realize the stereospecific ring-opening reaction of the protected 2,3-epoxy alcohols at the 3-position, due to the high reactivity at this position to form the carbocation intermediate. In contrast, if the relatively unreactive 2-position of the protected 2,3-epoxy alcohols **45** can be appropriately activated (Scheme 7), the intermediate **E** may be more stable than the intermediate **D** (Scheme 5) and unreactive toward the unfavorable S_N1-like ring-opening reaction. Furthermore, if the allylating reagent approaches from the back side of the C_2–O bond of the intermediate **E**, the ring-opening reaction would proceed through the stereospecific *anti* pathway. Therefore, we next turned our attention to the ring-opening reaction of 2-substituted 2,3-epoxy alcohols.



Scheme 7. Ring-opening reaction at the 2-position of protected 2,3-epoxy alcohol.

The results with the protected 2-substituted 2,3-epoxy alcohols **46–53** are summarized in Table 3. As we expected, the reaction of **46** with the allylmagnesium chloride[12] and chlorotitanium triphenoxide yielded 1,3-diol derivative **54** bearing a quaternary carbon center as a single isomer (entry 1). The corresponding benzyl ether **47** also afforded

Table 3. Construction of chiral quaternary carbon centers from 2-substituted 2,3-epoxy alcohols[a]

Entry	Epoxy alcohol	Product (yield)[b]
1	 **46**	 **54** (46%)
2	 **47**	 **55** (41%)
3	 **48**	 **56** (54%)
4	 **49**	 **57** (34%)
5	 **50**	 **58** (42%)
6	 **51**	 **59** (37%)
7	 **52**	 **60** (49%)
8	 **53**	 **61** (33%)

[a] Reagents: allylmagnesium chloride, $ClTi(OPh)_3$, THF, −78 to 0 °C.
[b] Isolated yields.

55 under the identical reaction conditions (entry 2). Reaction of 2,3-disubstituted 2,3-epoxy alcohols **48–53** yielded the allylated product **56–61** bearing two contiguous stereocenters including a chiral quaternary carbon (entries 3–8).[21] Although the yields are moderate, all the reactions proceeded in a stereospecific manner. The ring-opening reaction of epoxide **50** derived from (*E*)-allylic alcohol afforded the desired product **58** with (*S*)-configuration, which is opposite to that obtained with the corresponding (*Z*)-allylic alcohol derivative **51**, both via the *anti* pathway. Stereochemistries of the products were readily confirmed by the NOE analysis of the corresponding lactone derivatives.[22] These results clearly demonstrate that the allylation proceeds through the S_N2-type stereospecific reaction, not through the stereoselective S_N1 reaction, the latter of which would produce the same diastereomer from both of the (*E*)- and (*Z*)-allylic alcohol derivatives **50** and **51**.

3. Conclusion

In conclusion, we have demostrated the chemo- and stereoselectivity in the ring-opening reaction of epoxides with allylmagnesium halide[23] and chlorotitanium

triphenoxide. The ring cleavage of the functionalized epoxides chemoselectively proceeded in the presence of a *tert*-butyl ester, amide, or acetal moiety, and the more substituted carbon of the epoxides regioselectively reacted to give the allylated product. Although the ring-opening reaction proceeds through the S_N1 pathway in most cases, it has been proven that *anti*-selective ring-opening reaction of epoxides is possible when using 2-substituted 2,3-epoxy alcohol derivatives, presumably due to the relatively low reactivity of the epoxy alcohol at the 2-position. This is the first example of the asymmetric construction of quaternary carbon centers by a stereospecific ring-opening reaction of readily available chiral acyclic epoxides using a titanium reagent. Since the products obtained have three distinguishable functional groups around the chiral quaternary stereocenter, this reaction would serve as an extremely useful method for the synthesis of complex molecules having a chiral quaternary carbon.

4. Experimental

4.1. General methods

All reactions were carried out under a positive pressure of argon, and glassware and syringes were dried in an electric oven at 100 °C prior to use. THF was distilled from sodium benzophenone ketyl under N_2. Other solvents and reagents were used without further purification. Melting points are uncorrected. ^{1}H NMR spectra (270, 300 or 500 MHz) were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublet, t=triplet, m=multiplet). For flash chromatography, silica gel 60 (230–400 mesh, Merck) was employed. Known epoxides **13**,[24] **14**,[24] and **47**[25] were prepared according to the literature. Compound **16** was purchased from Aldrich and used without purification.

4.2. Allyltitanium-mediated ring-opening reaction of epoxides

4.2.1. General procedure: synthesis of (±)-10-(hydroxymethyl)-1-pyrrolidinyltridec-12-en-1-one (8) (Table 1, entry 1). A solution of chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) was added dropwise to a solution of allylmagnesium bromide (1.0 M in Et_2O; 3.5 mL, 3.5 mmol) at −78 °C, and the mixture was stirred for 30 min at −50 °C. To the stirred mixture was slowly added a solution of epoxide **3** (127 mg, 0.50 mmol) in THF (1 mL) at −78 °C, and the mixture was stirred for 96 h with warming to room temperature. After the mixture was diluted with Et_2O (30 mL), saturated aqueous KF (5 mL) was added under stirring, and precipitate was filtered off. The filtrate was washed with 2 N NaOH, water, and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH (200:1; hexane–EtOAc was used in other cases) to give **8** (61 mg, 41% yield) as a colorless oil; IR (KBr) cm^{-1} 3415 (OH), 1626 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.66 (m, 23H), 3.39–3.59 (m, 6H, 2′-CH_2, 5′-CH_2 and OCH_2), 4.99–5.09 (m, 2H, 13-CH_2), 5.75–5.89 (m, 1H, 12-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.9, 26.1, 26.8, 29.3 (2C), 29.4, 29.8, 30.5, 34.8, 35.8, 40.3, 45.6, 46.6, 65.5, 116.0, 137.2, 171.9; MS (FAB) *m*/*z* (%): 296 (MH^+, 100); HRMS (FAB) calcd for $C_{18}H_{34}NO_2$ (MH^+): 296.2590; found: 296.2573.

4.2.2. (±)-4-Hydroxy-4-[1-(prop-2-enyl)cyclohexyl]-1-pyrrolidinylbutan-1-one (9) (Table 1, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **4** (119 mg, 0.50 mmol) was converted into **9** (91 mg, 65% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.5 mL, 2.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 5.0 mL, 2.5 mmol) at −78 to 0 °C for 24 h. In this reaction, allylmagnesium bromide was added dropwise to a solution of chlorotitanium triphenoxide: colorless oil; IR (KBr) cm^{-1} 3470 (OH), 1643 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.66 (m, 6H), 1.77–2.46 (m, 14H), 3.41–3.53 (m, 5H, 2′-CH_2, 5′-CH_2 and 4-H), 5.01–5.13 (m, 2H, CH=CH_2), 5.78–5.92 (m, 1H, CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (2C), 26.1 (2C), 27.9, 28.5 (2C), 30.7, 35.3, 37.0, 40.2, 46.2, 46.5, 70.2, 116.8, 136.9, 176.3; MS (FAB) *m*/*z* (%): 280 (MH^+, 100); HRMS (FAB) calcd for $C_{17}H_{30}NO_2$ (MH^+): 280.2277; found: 280.2280.

4.2.3. *tert*-Butyl (±)-4-[1-(hydroxymethyl)but-3-enyl]-benzoate (10) (Table 1, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **5** (55 mg, 0.25 mmol) was converted into **10** (32 mg, 48% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 0.5 mL, 0.50 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 1.0 mL, 0.50 mmol) at −78 to 0 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 3452 (OH), 1714 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (br s, 1H, OH), 1.59 (s, 9H, CMe_3), 2.37–2.43 (m, 1H, 2′-CHH), 2.48–2.54 (m, 1H, 2′-CHH), 2.93–2.99 (m, 1H, 1′-H), 3.75–3.84 (m, 2H, OCH_2), 4.96–5.04 (m, 2H, 4′-CH_2), 5.65–5.73 (m, 1H, 3′-H), 7.27 (d, J=7.9 Hz, 2H, Ph), 7.95 (d, J=7.9 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 36.4, 48.2, 66.6, 80.9, 116.7, 127.9 (2C), 129.7 (2C), 130.6, 135.8, 146.9, 165.6; MS (FAB) *m*/*z* (%): 285 (MNa^+, 40.5), 207 (100); HRMS (FAB) calcd for $C_{16}H_{22}NaO_3$ (MNa^+): 285.1467; found: 285.1446.

4.2.4. *tert*-Butyl (±)-(1*R,4*R**)-4-allyl-4-(hydroxymethyl)cyclohexanecarboxylate (11) (Table 1, entry 4).** By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **6** (106 mg, 0.50 mmol) was converted into **11** (62 mg, 49% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3446 (OH), 1728 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.23 (m, 2H, 2-CHH and 6-CHH), 1.44 (s, 9H, CMe_3), 1.52–1.66 (m, 4H, 3-CH_2 and 5-CH_2), 1.72–1.81 (m, 2H, 2-CHH and 6-CHH), 2.09–2.16 (m, 1H, 1-H), 2.19 (d, J=8.5 Hz, 2H, CH_2CH=CH_2), 3.34 (s, 2H, CH_2OH), 5.05 (m, 2H, CH=CH_2), 5.75–5.89 (m, 1H, CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (2C), 28.1 (3C), 30.9 (2C), 36.2, 37.3, 43.9, 70.9, 79.9, 117.4, 134.8, 175.4; MS (FAB) *m*/*z* (%): 255 (MH^+, 50), 181 (100); HRMS (FAB) calcd for $C_{15}H_{27}O_3$ (MH^+): 255.1960; found: 255.1965.

4.2.5. (±)-4-(1-Hydroxy-2-methoxymethoxy)ethyl-4-(prop-2-enyl)cyclohexan-1-one 1,1-ethylene acetal (12) (**Table 1**, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **7** (122 mg, 0.50 mmol) was converted into **12** (120 mg, 84% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 4 h: colorless oil; IR (KBr) cm^{-1} 3504 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46–1.76 (m, 8H), 2.14 (dd, $J=13.9$, 7.5 Hz, 1H, C*H*HCH=CH_2), 2.34 (dd, $J=13.9$, 7.0 Hz, 1H, CH*H*CH=CH_2), 2.52 (br s, 1H, OH), 3.37 (s, 3H, OMe), 3.46–3.52 (m, 1H, 1′-H), 3.71–3.79 (m, 2H, 2′-CH_2), 3.93 (s, 4H, OC_2H_4O), 4.66 (s, 2H, OCH_2O), 5.05–5.10 (m, 2H, CH=CH_2), 5.81–5.94 (m, 1H, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 28.6, 30.1, 30.3, 36.3, 38.1, 55.3, 64.1 (2C), 69.2, 74.0, 96.9, 108.7, 117.4, 134.9; MS (EI) *m/z*: 286 (M^+). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.06; H, 9.02.

4.2.6. (±)-4-[(2*R,3*S**)-3-Methyloxiran-2-yl]-1,6-heptadien-4-ol (17).** By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **13** (130 mg, 1.0 mmol) was converted into **17** (43 mg, 25% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.2 mL, 1.2 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 2.6 mL, 1.3 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, $J=5.5$ Hz, 3H, CMe), 1.91 (s, 1H, OH), 2.25–2.42 (m, 4H, 3-CH_2 and 5-CH_2), 2.68 (d, $J=2.4$ Hz, 1H, 2′-H), 3.05 (qd, $J=5.5$, 2.4 Hz, 1H, 3′-H), 5.09–5.18 (m, 4H, 1-CH_2 and 7-CH_2), 5.82–5.95 (m, 2H, 2-H and 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 41.5, 44.4, 51.0, 63.7, 70.6, 118.3, 119.2, 132.7, 133.0; MS (FAB) *m/z* (%): 175 (MLi^+, 25), 160 (100); HRMS (FAB) calcd $C_{10}H_{16}LiO_2$ (MLi^+): 175.1310; found: 175.1311.

4.2.7. Ethyl (±)-2-hydroxy-3,3-dimethyl-5-hexenoate (18). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **14** (144 mg, 1.0 mmol) was converted into **18** (26 mg, 14% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3469 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, $J=6.9$ Hz, 3H, CMe), 1.38 (s, 3H, CMe), 1.43 (s, 3H, CMe), 2.24 (d, $J=2.4$ Hz, 2H, 4-CH_2), 3.33 (s, 1H, 2-H), 4.20–4.34 (m, 2H, OCH_2), 5.09–5.17 (m, 2H, 6-CH_2), 5.80–5.94 (m, 1H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 24.2, 43.6, 59.4, 60.1, 61.3, 118.7, 133.5, 168.5; MS (FAB) *m/z* (%): 193 (MLi^+, 100); HRMS (FAB) calcd for $C_{10}H_{18}LiO_3$ (MLi^+): 193.1416; found: 193.1425.

4.2.8. *tert*-Butyl (±)-2-hydroxy-3,3-dimethyl-5-hexenoate (19). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **15** (86 mg, 0.50 mmol) was converted into **19** (29 mg, 27% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3516 (OH), 1716 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 3H, CMe), 0.95 (s, 3H, CMe), 1.51 (s, 9H, CMe_3), 2.03 (dd, $J=13.4$, 7.3 Hz, 1H, 4-C*H*H), 2.20 (dd, $J=13.4$, 7.9 Hz, 1H, 4-CH*H*), 2.86 (d, $J=6.7$ Hz, 1H, OH), 3.76 (d, $J=6.7$ Hz, 1H, 2-H), 5.06–5.90 (m, 2H, 6-CH_2), 5.81–5.89 (m, 1H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 23.3, 28.1 (3C), 38.1, 43.4, 76.8, 82.7, 117.8, 134.7, 173.8; MS (FAB), *m/z* (%): 215 (MH^+, 100). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.86; H, 10.30.

4.2.9. (±)-(1*R,2*S**,6*S**)-4,4,6-Trimethyl-2-(prop-2-enyl)-7-oxabicyclo[4.1.0]heptan-2-ol (20).** By the general procedure for the allyltitanium-mediated ring-opening reaction, isophorone oxide **16** (154 mg, 1.0 mmol) was converted into **20** (167 mg, 85% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.0 mL, 2.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.0 mL, 2.0 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3498 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3H, CMe), 1.03 (s, 3H, CMe), 1.22 (d, $J=14.6$ Hz, 1H), 1.30 (d, $J=14.6$ Hz, 1H), 1.36 (s, 3H, CMe), 1.57 (dd, $J=14.6$, 1.8 Hz, 1H), 1.62 (d, $J=14.6$ Hz, 1H), 1.82 (s, 1H, OH), 2.27 (dd, $J=13.4$, 7.9 Hz, 1H, 1′-C*H*H), 2.42 (dd, $J=13.4$, 7.3 Hz, 1H, 1′-CH*H*), 2.77 (s, 1H, 1-H), 5.20–5.26 (m, 2H, CH=CH_2), 5.92–6.00 (m, 1H, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.4, 29.5, 31.7, 43.3, 44.7, 45.8, 59.5, 63.8, 70.7, 120.2, 132.5; MS (FAB) *m/z* (%): 219 (MNa^+, 13.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{20}NaO_2$ (MNa^+): 219.1361; found: 219.1381.

4.2.10. (3*R*,4*R*)- and (3*R*,4*S*)-4-Benzyl-4-methylhept-6-en-3-ol (24). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **23** (176 mg, 1.0 mmol) was converted into an inseparable mixture of *syn*-**24** and *anti*-**24** (55:45 by ^1H NMR; 153 mg, 70% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.5 mL, 3.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 6.0 mL, 3.0 mmol) at −78 to 0 °C for 4 h: colorless oil; IR (KBr) cm^{-1} 3500 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 1.5H, 4-Me), 0.88 (s, 1.5H, 4-Me), 1.01 (dd, $J=14.8$, 7.3 Hz, 3H, CMe), 1.25–1.76 (m, 2H, 2-CH_2), 1.81–2.26 (m, 2H, 5-CH_2), 2.52 (d, $J=13.0$ Hz, 0.5H, PhC*H*H), 2.61 (d, $J=13.2$ Hz, 0.5H, PhC*H*H), 2.73 (d, $J=13.2$ Hz, 0.5H, PhCH*H*), 2.82 (d, $J=13.0$ Hz, 0.5H, PhCH*H*), 3.26 (t, $J=11.8$ Hz, 1H, 3-H), 5.06–5.13 (m, 2H, 7-CH_2), 5.84–6.05 (m, 1H, 6-H), 7.16–7.29 (m, 5H, Ph); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.32 (0.5C), 12.35 (0.5C), 21.4 (0.5C), 22.0 (0.5C), 24.7 (0.5C), 24.8 (0.5C), 41.4 (0.5C), 41.5 (0.5C), 42.3 (0.5C), 42.4 (0.5C), 42.5 (0.5C), 42.7 (0.5C), 79.1 (0.5C), 79.2 (0.5C), 118.0 (1C), 126.5 (1C), 128.4 (2C), 131.3 (2C), 136.1 (0.5C), 136.3 (0.5C), 139.26 (0.5C), 139.29 (0.5C); MS (FAB) *m/z* (%): 241 (MNa^+, 18), 142 (100); HRMS (FAB) calcd for $C_{15}H_{22}NaO$ (MNa^+): 241.1568; found: 241.1572.

4.2.11. (2*S*,3*R*)- and (2*S*,3*S*)-3-Benzyl-1-(methoxymethoxy)-3-methylhex-5-en-2-ol (34) (**Table 2**, entry 1). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **29** (111 mg, 0.50 mmol) was converted into an inseparable mixture of *syn*-**34** and *anti*-**34** (50:50 by ^1H NMR; 92 mg, 70% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 0.75 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in

THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3560 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 1.5H, CMe), 0.91 (s, 1.5H, CMe), 1.79–1.86 (m, 0.5H, 4-C*H*H), 2.03–2.10 (m, 0.5H, 4-C*H*H), 2.18–2.31 (m, 1H, 4-CH*H*), 2.46–2.62 (m, 2H, PhC*H*H and OH), 2.82–2.93 (m, 1H, PhCH*H*), 3.37 (d, J=0.4 Hz, 1.5H, OMe), 3.39 (d, J=0.4 Hz, 1.5H, OMe), 3.46–3.66 (m, 2H, 1-C*H*H and 2-H), 3.72–3.83 (m, 1H, 1-CH*H*), 4.65 (s, 1H, OCH_2O), 4.68 (s, 1H, OCH_2O), 5.05–5.13 (m, 2H, 6-CH_2), 5.82–6.02 (m, 1H, 5-H), 7.18–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (0.5C), 21.1 (0.5C), 40.62 (0.5C), 40.64 (0.5C), 41.1 (0.5C), 41.3 (0.5C), 42.3 (0.5C), 42.5 (0.5C), 50.58 (0.5C), 50.63 (0.5C), 71.36 (0.5C), 71.39 (0.5C), 72.7 (1C), 98.9 (0.5C), 99.0 (0.5C), 117.3 (0.5C), 117.5 (0.5C), 126.3 (1C), 128.0 (1C), 128.3 (1C), 128.6 (1C), 128.8 (1C), 136.6, (1C), 140.2 (0.5C), 140.4 (0.5C); MS (FAB) *m*/*z* (%): 265 (MH^+, 18), 151 (100); HRMS (FAB) calcd for $C_{16}H_{25}O_3$ (MH^+): 265.1804; found: 265.1810.

4.2.12. (2*S*,3*R*)- and (2*S*,3*S*)-3-Benzyl-1-benzyloxy-3-methylhex-5-en-2-ol (35) (Table 2, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **30** (134 mg, 0.5 mmol) was converted into an inseparable mixture of *syn*-**35** and *anti*-**35** (54:46 by ^1H NMR; 123 mg, 79% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 0.75 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3528 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 1.5H, CMe), 0.88 (s, 1.5H, CMe), 1.75–1.83 (m, 0.5H, 4-C*H*H), 1.99–2.07 (m, 0.5H, 4-C*H*H), 2.15–2.31 (m, 1H, 4-CH*H*), 2.44–2.60 (m, 1.5H, PhCH_2), 2.81–2.91 (m, 0.5H, PhCH_2), 3.45–3.69 (m, 3H, 1-CH_2 and 2-H), 4.53 (d, J=1.5 Hz, 1H, OCH_2Ph), 4.56 (d, J=2.4 Hz, 0.5H, OCH_2Ph), 5.00–5.10 (m, 2H, 6-CH_2), 5.80–6.00 (m, 1H, 5-H), 7.15–7.39 (m, 10H, Ph); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.6 (0.5C), 21.1 (0.5C), 39.9 (0.5C), 40.1 (0.5C), 40.4 (0.5C), 40.6 (0.5C), 41.6 (0.5C), 42.1 (0.5C), 71.0 (1C), 73.39 (0.5C), 73.41 (0.5C), 73.8 (0.5C), 73.9 (0.5C), 117.5 (0.5C), 117.7 (0.5C), 125.8 (1C), 127.6 (3C), 127.7 (1C), 128.4 (2C), 130.78 (1C), 130.83 (1C), 134.6 (1C), 135.0 (1C), 137.75 (0.5C), 137.80 (0.5C), 138.2 (1C); MS (FAB) *m*/*z* (%): 333 (MNa^+, 33), 174 (100); HRMS (FAB) calcd for $C_{21}H_{26}NaO_2$ (MNa^+): 333.1830; found: 333.1836.

4.2.13. (2*R*,3*S*)- and (2*R*,3*R*)-1-(Methoxymethoxy)-3-phenylhex-5-en-2-ol (36) (Table 2, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **31** (146 mg, 0.75 mmol) was converted into an inseparable mixture of *syn*-**36** and *anti*-**36** (48:52 by ^1H NMR; 147 mg, 83% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.25 mL, 2.25 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.5 mL, 2.25 mmol) at −78 to −20 °C for 120 h: colorless oil; IR (KBr) cm^{-1} 3474 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.27–2.89 (m, 4H, 3-H, 4-CH_2 and OH), 3.23–3.64 (m, 5H, OMe and 1-CH_2), 3.86–3.92 (m, 0.5H, 2-H), 4.00–4.05 (m, 0.5H, 2-H), 4.54–4.63 (m, 2H, OCH_2O), 4.85–5.06 (m, 2H, 6-CH_2), 5.54–5.73 (m, 1H, 5-H), 7.13–7.39 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4 (0.5C), 36.5 (0.5C), 48.2 (0.5C), 49.2 (0.5C), 55.41 (0.5C), 55.43 (0.5C), 71.4 (1C), 72.5 (0.5C), 74.0 (0.5C), 96.95 (0.5C), 97.04 (0.5C), 116.1 (0.5C), 116.4 (0.5C), 126.67 (0.5C), 126.74 (0.5C), 128.27 (1C), 128.30 (1C), 128.5 (1C), 128.9 (1C), 136.4 (0.5C), 136.6 (0.5C), 140.4 (0.5C), 141.2 (0.5C); MS (FAB) *m*/*z* (%): 237 (MH^+, 13.3), 126 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1490.

4.2.14. (2*R*,3*S*)- and (2*R*,3*R*)-1-Benzyloxy-3-phenylhex-5-en-2-ol (37) (Table 2, entry 4). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **32** (120 mg, 0.50 mmol) was converted into an inseparable mixture of *syn*-**37** and *anti*-**37** (43:57 by ^1H NMR; 102 mg, 72% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to −20 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (br s, 0.4H, OH), 2.36–2.88 (m, 3.6H, 3-H, 4-H and OH), 3.15–3.48 (m, 2H, 1-CH_2), 3.88–3.93 (m, 0.4H, 2-H), 4.05–4.06 (m, 0.6H, 2-H), 4.35–4.51 (m, 2H, OCH_2Ph), 4.84–5.03 (m, 2H, 6-CH_2), 5.52–5.72 (m, 1H, 5-H), 7.11–7.36 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3 (0.5C), 36.4 (0.5C), 48.0 (0.5C), 49.2 (0.5C), 72.2 (0.5C), 72.7 (0.5C), 72.8 (0.5C), 73.2 (0.5C), 73.3 (0.5C), 73.8 (0.5C), 116.0 (0.5C), 116.4 (0.5C), 126.6 (0.5C), 126.7 (0.5C), 127.67 (1.5C), 127.72 (1.5C), 128.2 (1.5C), 128.3 (1.5C), 128.4 (1.5C), 128.9 (1.5C), 136.5 (0.5C), 136.6 (0.5C), 137.8 (0.5C), 137.9 (0.5C), 140.4 (0.5C), 141.2 (0.5C); MS (FAB) *m*/*z* (%): 283 (MH^+, 21), 150 (100); HRMS (FAB) calcd for $C_{19}H_{23}O_2$ (MH^+): 283.1698; found: 283.1690.

4.2.15. (2*R*,3*S*)-1-(*tert*-Butyldimethylsiloxy)-3-phenylhex-5-en-2-ol (*syn*-38) and Its (2*R*,3*R*)-isomer (*anti*−38) (Table 2, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **33** (264 mg, 1.0 mmol) was converted into a diastereomixture of *syn*-**38** and *anti*-**38** by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.0 mL, 2.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.0 mL, 2.0 mmol) at −78 to 0 °C for 1 h. The diastereomixture was purified by column chromatography over silica gel with hexane–Et_2O (20:1) to give, in the order of elution, *syn*-**38** (78 g, 25% yield) and *anti*-**38** (86 mg, 28% yield).

Compound syn-**38**. Colorless oil; $[\alpha]_D^{27}$ −18.8 (*c* 0.43, $CHCl_3$); IR (KBr) cm^{-1} 3469 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ −0.03 (s, 6H, $SiMe_2$), 0.87 (s, 9H, CMe_3), 2.36–2.47 (m, 1H, OH), 2.63–2.74 (m, 2H, 4-CH_2), 2.81–2.90 (m, 1H, 3-H), 3.24 (dd, J=9.9, 6.6 Hz, 1H, 1-C*H*H), 3.37 (dd, J=9.9, 3.1 Hz, 1H, 1-CH*H*), 3.71–3.79 (m, 1H, 2-H), 4.84–4.97 (m, 2H, 6-CH_2), 5.54–5.67 (m, 1H, 5-H), 7.12–7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 (2C), 18.2, 25.8 (3C), 36.6, 49.1, 65.2, 75.0, 115.9, 126.6, 128.3 (2C), 128.4 (2C), 136.8, 141.4; MS (FAB) *m*/*z* (%): 329 (MNa^+, 100); HRMS (FAB) calcd for $C_{18}H_{30}NaO_2Si$ (MNa^+): 329.1913; found: 329.1911.

Compound anti-**38**. Colorless oil; $[\alpha]_D^{27}$ −39.1 (*c* 0.55, $CHCl_3$); IR (KBr) cm^{-1} 3466 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.88 (s, 9H, CMe_3), 2.20 (br s, 1H, OH), 2.43–2.63 (m, 2H, 4-CH_2), 2.78–2.85 (m, 1H, 3-H), 3.39 (dd, J=10.1, 7.3 Hz, 1H,

1-C*H*H), 3.57 (dd, $J=10.1$, 4.2 Hz, 1H, 1-CH*H*), 3.86–3.88 (m, 1H, 2-H), 4.91–5.05 (m, 2H, 6-CH_2), 5.59–5.72 (m, 1H, 5-H), 7.18–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.43, −5.38, 18.2, 25.8 (3C), 36.4, 47.9, 65.3, 73.8, 116.2, 126.6, 128.2 (2C), 128.9 (2C), 136.6, 140.8; MS (FAB) *m/z* (%): 329 (MNa^+, 100); HRMS (FAB) calcd for $C_{18}H_{30}NaO_2Si$ (MNa^+): 329.1913; found: 329.1913.

4.2.16. (4*S*,5*R*)-5-(*tert*-Butyldimethylsiloxy)methyl-4-phenyloxolan-2-one (*trans*-44). To a mixture of powdered $KMnO_4$ (800 mg) and $CuSO_4$ (400 mg) were added H_2O (40 μL) and CH_2Cl_2 (2.0 mL) under stirring. A solution of *syn*-**38** (61 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL) was added to the mixture and the mixture was stirred under reflux for 5 days. The mixture was filtered through Celite with CH_2Cl_2, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (10:1) to give *trans*-**44** (17 mg, 28% yield) as a colorless oil; $[\alpha]_D^{28}$ −16.7 (*c* 0.59, $CHCl_3$); IR (KBr) cm^{-1} 1770 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.85 (s, 9H, CMe_3), 2.67 (dd, $J=17.7$, 7.3 Hz, 1H, 3-C*H*H), 3.04 (dd, $J=17.7$, 9.2 Hz, 1H, 3-CH*H*), 3.66–3.71 (m, 1H, 4-H), 3.73 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-C*H*H), 3.92 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-CH*H*), 4.49–4.51 (m, 1H, 5-H), 7.23–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, 18.3, 25.8 (3C), 37.3, 42.1, 63.1, 86.8, 126.9 (2C), 127.5, 129.1 (2C), 140.9, 176.2; MS (FAB) *m/z* (%): 307 (MH^+, 36), 181 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3Si$ (MH^+): 307.1729; found: 307.1725.

4.2.17. (4*R*,5*R*)-5-(*tert*-Butyldimethylsiloxy)methyl-4-phenyloxolan-2-one (*cis*-44). Ozone was bubbled through a solution of *anti*-**38** (45 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at −78 °C until a blue color persisted (30 min). To this mixture was added PPh_3 (115 mg, 0.44 mmol) at −78 °C and the mixture was stirred for 2 h at 0 °C. Concentration under reduced pressure gave an oily residue, which was purified by short column chromatography over silica gel with hexane–EtOAc (3:1) to give the corresponding lactol. Pyridinium chlorochromate (39 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added to a solution of the lactol in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred for 5 days at room temperature. The mixture was filtered through Celite with CH_2Cl_2, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give *cis*-**44** (31 mg, 67% yield) as a colorless oil; $[\alpha]_D^{28}$ −95.9 (*c* 0.78, $CHCl_3$); IR (KBr) cm^{-1} 1774 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.09 (s, 3H, SiMe), −0.05 (s, 3H, SiMe), 0.85 (s, 9H, CMe_3), 2.73 (dd, $J=17.1$, 9.2 Hz, 1H, 3-C*H*H), 3.13 (dd, $J=17.1$, 10.4 Hz, 1H, 3-CH*H*), 3.41 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-C*H*H), 3.64 (dd, $J=11.6$, 3.7 Hz, 1H, 1′-CH*H*), 3.90–3.96 (m, 1H, 4-H), 4.70–4.73 (m, 1H, 5-H), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.91, −5.89, 18.1, 25.7 (3C), 34.1, 43.8, 62.0, 82.7, 127.5, 127.9 (2C), 128.6 (2C), 136.4, 176.7; MS (FAB) *m/z* (%): 307 (MH^+, 25), 181 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3Si$ (MH^+): 307.1729; found: 307.1734.

4.2.18. (2*S*)-2-(Methoxymethoxymethyl)-2-methylpent-4-en-1-ol (54) (Table 3, entry 1). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **46** (106 mg, 0.80 mmol) was converted into **54** (64 mg, 46% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 2.8 mL, 5.6 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 11.2 mL, 5.6 mmol) at −78 to 0 °C for 2 h: colorless oil; $[\alpha]_D^{28}$ +8.6 (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3524 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H, CMe), 2.18 (dd, $J=14.0$, 7.9 Hz, 1H, 3-C*H*H), 2.20–2.28 (m, 1H, 3-CH*H*), 2.54 (br s, 1H, OH), 3.38 (s, 3H, OMe), 3.46 (s, 2H, 1-CH_2), 3.52 (s, 2H, 1′-CH_2), 4.80 (s, 2H, OCH_2O), 5.11–5.16 (m, 2H, 5-CH_2), 5.83–5.92 (m, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 38.0, 39.2, 50.5, 70.4, 72.2, 99.4, 117.6, 128.4; MS (FAB) *m/z* (%): 175 (MH^+, 35), 90 (100); HRMS (FAB) calcd for $C_9H_{19}O_3$ (MH^+): 175.1334; found: 175.1329.

4.2.19. (2*S*)-2-(Benzyloxymethyl)-2-methylpent-4-en-1-ol (55) (Table 3, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **47** (89 mg, 0.50 mmol) was converted into **55** (45 mg, 41% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 4 h: colorless oil; $[\alpha]_D^{24}$ +18.0 (*c* 0.80, $CHCl_3$); IR (KBr) cm^{-1} 3507 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3H, CMe), 2.24 (dd, $J=14.0$, 7.9 Hz, 1H, 3-C*H*H), 2.29–2.33 (m, 1H, 3-CH*H*), 2.45 (d, $J=4.9$ Hz, 1H, OH), 3.27–3.63 (m, 4H, 1-CH_2 and 1′-CH_2), 4.42 (s, 2H, PhCH_2), 5.02–5.08 (m, 2H, 6-CH_2), 5.83–5.90 (m, 1H, 5-H), 7.30–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 38.2, 38.8, 70.0, 73.4, 77.4, 117.7, 127.3, 128.8 (2C), 132.2 (2C), 135.5, 137.0; MS (FAB) *m/z* (%): 221 (MH^+, 45), 90 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_2$ (MH^+): 221.1542; found: 221.1550.

4.2.20. (2*R*,3*S*)-3-(Methoxymethoxymethyl)-3-methyl-1-phenylhex-5-en-2-ol (56) (Table 3, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **48** (111 mg, 0.50 mmol) was converted into **56** (71 mg, 54% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 2 h: colorless oil; $[\alpha]_D^{24}$ +10.6 (*c* 1.02, $CHCl_3$); IR (KBr) cm^{-1} 3492 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3H, CMe), 2.24 (dd, $J=14.0$, 7.9 Hz, 1H, 4-C*H*H), 2.29–2.33 (m, 1H, 4-CH*H*), 2.45 (d, $J=4.9$ Hz, 1H, OH), 2.57 (dd, $J=13.4$, 10.4 Hz, 1H, 1-C*H*H), 2.93 (dd, $J=13.4$, 1.2 Hz, 1H, 1-CH*H*), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 2H, 1′-CH_2), 3.71–3.73 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 6-CH_2), 5.85–5.93 (m, 1H, 5-H), 7.20–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 38.1, 39.9, 41.1, 55.5, 73.4, 77.4, 96.8, 117.9, 126.2, 128.4 (2C), 129.3 (2C), 134.3, 140.0; MS (FAB) *m/z* (%): 265 (MH^+, 15), 172 (100); HRMS (FAB) calcd for $C_{16}H_{25}O_3$ (MH^+): 265.1804; found: 265.1812.

4.2.21. (2*R*,3*S*)-3-(Benzyloxymethyl)-3-ethyl-1-phenylhex-5-en-2-ol (57) (Table 3, entry 4). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **49** (141 mg, 0.50 mmol) was converted into **57** (55 mg, 34% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL,

3.5 mmol) at −78 to 0 °C for 6 h: colorless oil; $[\alpha]_D^{26}$ +45.5 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3483 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J*=6.4 Hz, 3H, CMe), 1.13 (q, *J*=6.4 Hz, 2H, C*H*$_2$Me), 2.18 (dd, *J*=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.20–2.32 (m, 1H, 4-CH*H*), 2.52 (d, *J*=4.9 Hz, 1H, OH), 2.64 (dd, *J*=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.82 (dd, *J*=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.40–3.56 (m, 2H, 1′-CH_2), 3.64–3.68 (m, 1H, 2-H), 4.47 (s, 2H, PhC*H*$_2$), 5.12–5.16 (m, 2H, 6-CH_2), 5.84–5.93 (m, 1H, 5-H), 7.12–7.40 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 22.5, 37.1, 39.0, 41.9, 70.7, 75.9, 78.4, 117.1, 125.9, 127.7 (2C), 127.9 (2C), 130.7 (2C), 131.0 (2C), 138.3, 138.4, 138.6 (2C); MS (FAB) *m*/*z* (%): 347 (MNa^+, 48), 126 (100); HRMS (FAB) calcd for $C_{22}H_{28}NaO_2$ (MNa^+): 347.1987; found: 347.1990.

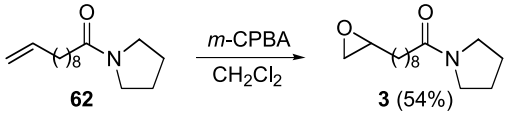
4.2.22. (2*R*,3*S*)-3-Ethyl-3-(methoxymethoxymethyl)-1-phenylhex-5-en-2-ol (58) (Table 3, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **50** (118 mg, 0.50 mmol) was converted into **58** (58 mg, 42% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 3 h: colorless oil; $[\alpha]_D^{24}$ +12.6 (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3546 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, *J*=6.4 Hz, 3H, CMe), 1.05 (q, *J*=6.4 Hz, 2H, 3-C*H*$_2$Me), 2.14 (dd, *J*=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.20–2.29 (m, 1H, 4-CH*H*), 2.43 (d, *J*=4.9 Hz, 1H, OH), 2.50 (dd, *J*=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.90 (dd, *J*=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.28 (s, 3H, OMe), 3.43–3.51 (m, 2H, 1′-CH_2), 3.69–3.76 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.14 (m, 2H, 6-CH_2), 5.80–5.93 (m, 1H, 5-H), 7.25–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.5, 37.6, 38.9, 41.6, 56.3, 72.0, 78.4, 96.0, 117.4, 126.6, 129.3 (2C), 128.9 (2C), 136.1, 138.6; MS (FAB) *m*/*z* (%): 279 (MH^+, 30), 184 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3$ (MH^+): 279.1960; found: 279.1952.

4.2.23. (2*R*,3*R*)-3-Ethyl-3-(methoxymethoxymethyl)-1-phenylhex-5-en-2-ol (59) (Table 3, entry 6). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **51** (118 mg, 0.50 mmol) was converted into **59** (52 mg, 37% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 3 h: colorless oil; $[\alpha]_D^{28}$ +34.4 (*c* 0.90, $CHCl_3$); IR (KBr) cm^{-1} 3560 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J*=6.4 Hz, 3H, CMe), 1.08 (q, *J*=6.4 Hz, 2H, 3-C*H*$_2$Me), 2.20 (dd, *J*=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.29–2.33 (m, 1H, 4-CH*H*), 2.45 (d, *J*=4.9 Hz, 1H, OH), 2.57 (dd, *J*=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.93 (dd, *J*=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 2H, 1′-CH_2), 3.71–3.77 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 6-CH_2), 5.86–5.92 (m, 1H, 5-H), 7.23–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.7, 37.8, 38.9, 41.0, 56.1, 72.3, 77.9, 95.9, 117.3, 126.6, 129.0 (2C), 129.1 (2C), 136.1, 138.7; MS (FAB) *m*/*z* (%): 279 (MH^+, 26), 184 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3$ (MH^+): 279.1960; found: 279.1971.

4.2.24. (4*S*,5*R*)-4-(Methoxymethoxymethyl)-4-methylundec-1-en-5-ol (60) (Table 3, entry 7). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **52** (108 mg, 0.50 mmol) was converted into **60** (63 mg, 49% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 6 h: colorless oil; $[\alpha]_D^{26}$ +18.4 (*c* 1.02, $CHCl_3$); IR (KBr) cm^{-1} 3486 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3H, CMe), 0.97 (s, 3H, CMe), 1.16–1.46 (m, 10H), 2.22–2.36 (m, 2H, 3-CH_2), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 3H, 5-H and 1′-CH_2), 4.63 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 1-CH_2), 5.85–5.93 (m, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 15.8, 22.9, 24.2, 30.4, 31.0, 34.1, 35.9, 41.1, 55.5, 72.7, 76.7, 98.8, 120.2, 130.6; MS (FAB) *m*/*z* (%): 259 (MH^+, 34), 183 (100); HRMS (FAB) calcd for $C_{15}H_{31}O_3$ (MH^+): 259.2273; found: 259.2286.

4.2.25. (4*S*,5*R*)-4-(Benzyloxymethyl)-4-methylundec-1-en-5-ol (61) (Table 3, entry 8). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **53** (131 mg, 0.50 mmol) was converted into **61** (50 mg, 33% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 8 h: colorless oil; $[\alpha]_D^{24}$ +29.0 (*c* 0.90, $CHCl_3$); IR (KBr) cm^{-1} 3523 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H, CMe), 0.95 (s, 3H, CMe), 1.12–1.34 (m, 10H), 2.18–2.26 (m, 2H, 3-CH_2), 2.40 (d, *J*=5.4 Hz, 1H, OH), 3.20 (dd, *J*=13.4, 5.4 Hz, 1H, 5-H), 3.46 (s, 2H, 1′-CH_2), 4.50 (s, 2H, PhC*H*$_2$), 5.06–5.12 (m, 2H, 1-CH_2), 5.78–5.83 (m, 1H, 2-H), 7.22–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 15.3, 22.2, 24.8, 30.2, 30.4, 34.7, 36.0, 40.6, 68.6, 74.2, 77.4, 117.9, 127.04, 127.07, 130.1 (2C), 132.6 (2C), 136.4; MS (FAB) *m*/*z* (%): 305 (MH^+, 40), 91 (100); HRMS (FAB) calcd for $C_{20}H_{33}O_2$ (MH^+): 305.2481; found: 305.2476.

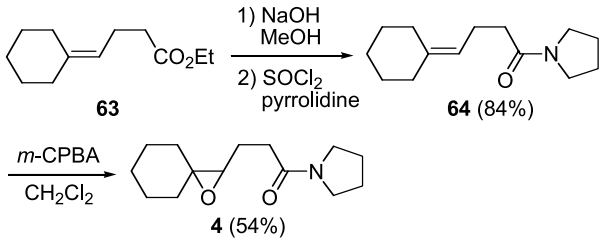
4.3. Preparation of epoxides



62 **3** (54%)

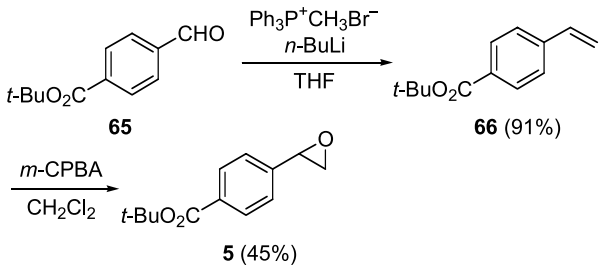
4.3.1. (±)-9-(Oxiran-2-yl)-1-pyrrolidinylnonan-1-one (3). To a stirred solution of 1-pyrrolidinylundec-10-en-1-one **62**[26] (2.50 g, 10.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of 75% *m*-CPBA (3.08 g, 13.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred for 4 h at room temperature. Saturated $Na_2S_2O_3$ was added to the mixture and stirring was continued for 30 min. Organic layer was separated and washed with saturated $NaHCO_3$ (×2), water, and brine, and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (3:2) to give **3** (1.43 g, 54% yield) as a colorless oil; IR (KBr) cm^{-1} 1643 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.66 (m, 14H, 7×CH_2), 1.80–2.00 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.22–2.28 (m, 2H, 2-CH_2), 2.45–2.48 (m, 1H, OC*H*H), 2.73–2.76 (m, 1H, OCH*H*), 2.88–2.93 (m, 1H, OCH), 3.39–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.9, 25.9, 26.1, 29.31 (2C), 29.35, 29.4, 32.4, 34.8, 45.5, 46.6, 47.1, 52.4, 171.8; MS (FAB) *m*/*z* (%): 254 (MH^+,

100); HRMS (FAB) calcd for $C_{15}H_{28}NO_2$ (MH^+): 254.2120; found: 254.2101.



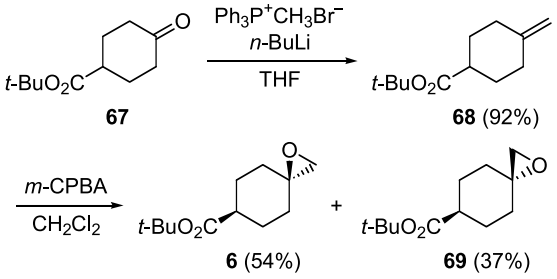
4.3.2. 4-Cyclohexylidene-1-pyrrolidinylbutan-1-one (64). To a stirred solution of ethyl 4-cyclohexylidenebutyrate **63**[27] (5.00 g, 25.5 mmol) in MeOH (60 mL) was added 5 N NaOH (20 mL), and the mixture was stirred under reflux for 3 h. The mixture was concentrated under reduced pressure and diluted with Et_2O. The mixture was made acidic with 10% HCl and extracted with Et_2O (×3). The extract was washed with brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave a crude carboxylic acid, which was used in the next reaction without further purification. To a mixture of this crude carboxylic acid and DMF (1 mL) in CH_2Cl_2 (60 mL) was added dropwise thionyl chloride (2.23 mL, 30.6 mmol) at −78 °C. The mixture was stirred under reflux for 30 min and, after cooling, pyrrolidine (5.11 mL, 61.2 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was diluted with Et_2O and made acidic with 5% HCl. The whole was extracted with Et_2O (×2) and the extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with $CHCl_3$–Et_2O (10:1) to give **64** (4.74 g, 84% yield) as a colorless oil; IR (KBr) cm^{-1} 1642 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 6H), 1.74–2.00 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.05–2.16 (m, 4H, 2×CH_2), 2.24–2.39 (m, 4H, 2×CH_2), 3.39–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2), 5.10 (t, J=7.2 Hz, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 24.4, 26.1, 26.9, 27.8, 28.6 (2C), 35.3, 37.1, 45.6, 46.6, 119.8, 140.7, 171.4; MS (FAB) m/z (%): 222 (MH^+, 36), 182 (100); HRMS (FAB) calcd for $C_{14}H_{24}NO$ (MH^+): 222.1858; found: 222.1852.

4.3.3. (±)-3-(1-Oxaspiro[2.5]oct-2-yl)-1-pyrrolidinylpropan-1-one (4). By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **64** (2.50 g, 11.3 mmol) was converted into **4** (1.45 g, 54% yield) by the reaction with 75% *m*-CPBA (3.13 g, 13.6 mmol) at room temperature for 1 h: colorless oil; IR (KBr) cm^{-1} 1640 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48–1.64 (m, 6H), 1.73–2.01 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.07–2.38 (m, 8H, 4×CH_2), 2.90–2.93 (m, 1H, OCH), 3.40–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 24.4, 26.2, 27.0, 27.9, 28.6 (2C), 35.2, 37.0, 45.5, 46.5, 47.7, 52.9, 172.0; MS (FAB) m/z (%): 238 (MH^+, 46), 90 (100); HRMS (FAB) calcd for $C_{14}H_{24}NO_2$ (MH^+): 238.1807; found: 238.1810.



4.3.4. *tert*-Butyl 4-vinylbenzoate (66). To a stirred solution of methyltriphenylphosphonium bromide ($Ph_3P^+CH_3Br^-$; 1.90 g, 5.32 mmol) in THF (8 mL) was added dropwise *n*-BuLi (1.55 M solution in hexane; 3.43 mL, 5.32 mmol) at −78 °C. The mixture was gradually warmed until a red color persisted. After the mixture was cooled to −78 °C, a solution of aldehyde **65**[28] (1.02 g, 4.94 mmol) in THF (8 mL) was added dropwise to the mixture under stirring. After the mixture was stirred for 2 h at 0 °C, saturated NH_4Cl was added to the mixture. Organic layer was separated and washed with saturated NH_4Cl and brine, dried, and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (20:1) to give **66** (914 mg, 91% yield) as a colorless oil; IR (KBr) cm^{-1} 1709 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9H, CMe_3), 5.36 (d, J=11.0 Hz, 1H, CH=C*H*H), 5.84 (d, J=17.7 Hz, 1H, CH=CH*H*), 6.75 (dd, J=17.7, 11.0 Hz, 1H, C*H*=CH_2), 7.44 (d, J=8.5 Hz, 2H, Ph), 7.94 (d, J=8.5 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 80.9, 116.1, 125.9 (2C), 129.7 (2C), 131.2, 136.1, 141.4, 165.5; MS (FAB) m/z (%): 205 (MH^+, 68), 154 (100); HRMS (FAB) calcd for $C_{13}H_{17}O_2$ (MH^+): 205.1229; found: 205.1227.

4.3.5. *tert*-Butyl (±)-4-(oxiran-2-yl)benzoate (5). By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **66** (905 mg, 4.43 mmol) was converted into **5** (443 mg, 45% yield) by the reaction with 75% *m*-CPBA (1.22 g, 5.32 mmol) in the presence of 0.5 M $NaHCO_3$ (20 mL) at room temperature overnight: colorless oil; IR (KBr) cm^{-1} 1710 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H, CMe_3), 2.76–2.79 (m, 1H, C*H*H), 3.16–3.20 (m, 1H, CH*H*), 3.89–3.91 (m, 1H, CH), 7.32 (d, J=8.4 Hz, 2H, Ph), 7.96 (d, J=8.4 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 51.4, 52.0, 81.1, 125.2 (2C), 129.6 (2C), 131.8, 142.3, 165.4; MS (FAB) m/z (%): 221 (MH^+, 100); HRMS (FAB) calcd for $C_{13}H_{17}O_3$ (MH^+): 221.1178; found: 221.1182.



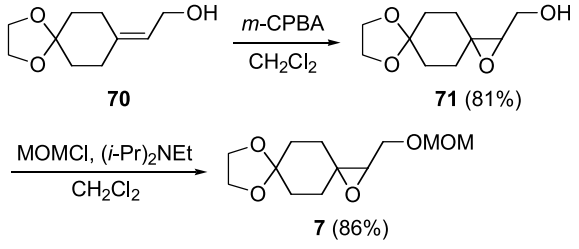
4.3.6. *tert*-Butyl (±)-4-methylenecyclohexanecarboxylate (68). By a procedure identical with that described for the synthesis of the alkene **66**, the ketone **67**[29] (2.00 g,

10.1 mmol) was converted into **68** (1.83 g, 92% yield) by the reaction with $Ph_3P^+CH_3Br^-$ (4.32 g, 12.1 mmol) and *n*-BuLi (1.55 M solution in hexane; 7.81 mL, 12.1 mmol) at 0 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 1725 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, CMe_3), 1.50–1.58 (m, 2H), 1.93–1.98 (m, 2H), 2.01–2.07 (m, 2H), 2.03–2.37 (m, 3H, 1-H and 2×CH), 4.63 (s, 2H, C=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (3C), 30.2 (2C), 33.7 (2C), 43.5, 79.9, 107.7, 148.0, 174.9; MS (FAB) *m/z* (%): 219 (MNa^+, 10.5), 55 (100).

4.3.7. *tert*-Butyl (±)-(3*R,6*R**)-1-oxaspiro[2.5]octane-6-carboxylate (6) and its (3*R**,6*S**)-Isomer (69).** By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **68** (1.75 g, 8.92 mmol) was converted into, in the order of elution, **69** (707 mg, 37% yield) and **6** (1.03 g, 54% yield) by the reaction with 75% *m*-CPBA (2.67 g, 11.6 mmol) in the presence of 0.5 M $NaHCO_3$ (40 mL) at room temperature for 2 h.

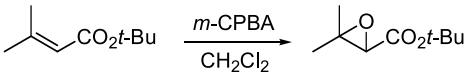
Compound **6**. Colorless needles; mp 32–35 °C; IR (KBr) cm^{-1} 1724 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39–1.41 (m, 2H), 1.45 (s, 9H, CMe_3), 1.78–1.87 (m, 4H), 1.89–1.97 (m, 2H), 2.26–2.32 (m, 1H, 6-H), 2.64 (s, 2H, 2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5 (2C), 28.0 (3C), 31.9 (2C), 42.7, 53.8, 57.6, 80.1, 174.4; MS (FAB) *m/z* (%): 235 (MNa^+, 7.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_3$ (MH^+): 213.1491; found: 213.1467.

Compound **69**. Colorless needles; mp 35–38 °C; IR (KBr) cm^{-1} 1726 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H, CMe_3), 1.49–1.52 (m, 2H), 1.67–1.76 (m, 4H), 2.02–2.05 (m, 2H), 2.30–2.36 (m, 1H, 6-H), 2.60 (s, 2H, 2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 (2C), 28.0 (3C), 32.1 (2C), 42.3, 54.6, 58.6, 80.2, 174.5; MS (FAB) *m/z* (%): 235 (MNa^+, 9.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_3$ (MH^+): 213.1491; found: 213.1493.

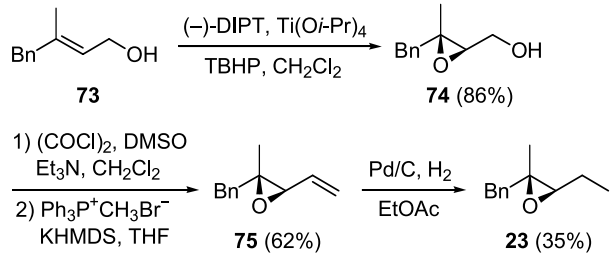


4.3.8. (±)-2-(Hydroxymethyl)-1-oxaspiro[2.5]octan-6-one 6,6-ethylene acetal (71). By a procedure identical with that described for the synthesis of the epoxide **3**, the allyl alcohol **70**[30] (3.20 g 17.4 mmol) was converted into **71** (2.83 g, 81% yield) by the reaction with 75% *m*-CPBA (4.80 g, 20.8 mmol) at room temperature overnight: colorless oil; IR ($CHCl_3$) cm^{-1} 3421 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.54–1.95 (m, 8H), 3.05 (dd, J=6.7, 4.3 Hz, 1H, 2-H), 3.72 (dd, J=12.0, 7.0 Hz, 1H, OC*H*H), 3.86 (dd, J=12.0, 4.0 Hz, 1H, OCH*H*), 3.98 (t, J=2.7 Hz, 4H, OCH_2CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 32.0, 32.8 (2C), 61.0, 62.0, 63.6, 64.38, 64.40, 108.1; MS (EI) *m/z*: 200 (M^+). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 7.94.

4.3.9. (±)-2-(Methoxymethoxymethyl)-1-oxaspiro-[2.5]octan-6-one 6,6-ethylene acetal (7). To a stirred mixture of the alcohol **71** (1.50 g, 7.49 mmol) and $(i\text{-Pr})_2NEt$ (2.61 mL, 15.0 mmol) in CH_2Cl_2 (40 mL) was added MOMCl (0.85 mL, 11.2 mmol) at room temperature and the stirring was continued overnight. 5% HCl was added to the mixture and the whole was extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ (×2) and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (3:1) to give **7** (1.58 g, 86% yield) as a colorless oil; $[\alpha]_D^{25}$ + 0.36 (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1265, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–1.95 (m, 8H), 3.06 (dd, J= 6.0, 5.1 Hz, 1H, 2-H), 3.38 (s, 3H, OMe), 3.65 (dd, J=11.4, 6.0 Hz, 1H, OC*H*H), 3.73 (dd, J=11.4, 5.1 Hz, 1H, OCH*H*), 3.97 (t, J=2.5 Hz, 4H, OCH_2CH_2O), 4.65 (d, J=6.6 Hz, 1H, OC*H*HO), 4.68 (d, J=6.6 Hz, 1H, OCH*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 32.0, 32.7, 32.8, 55.3, 61.1, 61.8, 64.37, 64.40, 66.0, 96.6, 108.2; MS (EI) *m/z*: 244 (M^+). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.08.



4.3.10. *tert*-Butyl (±)-2,3-epoxy-3-methylbutyrate (15). By a procedure identical with that described for the synthesis of the epoxide **3**, the enoate **72**[31] (1.27 g, 8.13 mmol) was converted into **15** (1.01 g, 72% yield) by the reaction with 75% *m*-CPBA (2.39 g, 10.4 mmol) under reflux overnight: colorless oil; IR (KBr) cm^{-1} 1710 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, CMe), 1.41 (s, 3H, CMe), 1.50 (s, 9H, CMe_3), 3.22 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 24.3, 28.1 (3C), 59.7, 59.9, 82.2, 167.6; MS (FAB) *m/z* (%): 173 (MH^+, 5), 154 (100); HRMS (FAB) calcd for $C_9H_{17}O_3$ (MH^+): 173.1178; found: 173.1188.

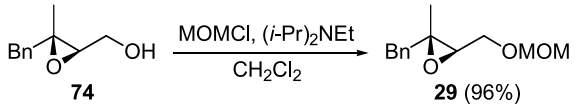


4.3.11. (2*R*,3*R*)-2,3-Epoxy-3-methyl-4-phenylbutan-1-ol (74). To a stirred mixture of molecular sieves 4A (2.50 g) in CH_2Cl_2 (150 mL) were added dropwise D-(−)-diisopropyl tartrate [D-(−)-DIPT; 1.50 mL, 7.05 mmol] and $Ti(Oi\text{-Pr})_4$ (1.39 mL, 4.70 mmol) at −20 °C. After stirring for 30 min, *tert*-butylhydroperoxide (TBHP; 2.6 M solution in toluene, 36.2 mL, 94.1 mmol) was added dropwise to the mixture. After the mixture was stirred for 1 h, a solution of **73**[32] (7.63 g, 47.0 mmol) in CH_2Cl_2 (50 mL) was slowly added to the mixture over 1 h at −30 °C. After 5 h, 10% NaOH saturated with sodium chloride were added to the mixture, and the mixture was vigorously stirred at 10 °C for 30 min. Anhydrous $MgSO_4$ (6.5 g) and Celite (1.0 g) were added to the mixture, and vigorous stirring was continued

for additional 30 min. The mixture was filtered through Celite, and the filtrate was dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (2:1) to give **74** (7.21 g, 86% yield) as a colorless oil; $[\alpha]_D^{24}+21.4$ (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3462 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H, CMe), 2.60 (br s, 1H, OH), 2.74 (d, $J=14.6$ Hz, 1H, 4-C*H*H), 2.80 (d, $J=14.6$ Hz, 1H, 4-CH*H*), 3.23 (d, $J=4.2$ Hz, 1H, 2-H), 4.10–4.18 (m, 2H, 1-CH_2), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 34.1, 58.0, 63.3, 66.6, 126.3, 128.3 (2C), 128.6 (2C), 136.8; MS (FAB) *m*/*z* (%): 201 (MNa^+, 100); HRMS (FAB) calcd for $C_{11}H_{14}NaO_2$ (MNa^+): 201.0891; found: 201.0889.

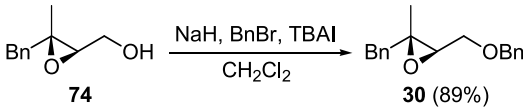
4.3.12. (2*R*,3*R*)-2,3-Epoxy-2-methyl-1-phenylpent-4-ene (75). To a stirred solution of oxalyl chloride (2.9 mL, 33.7 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added dropwise a solution of DMSO (4.78 mL, 67.3 mmol) in CH_2Cl_2 (15 mL). After stirring for 30 min, a solution of the alcohol **74** (3.00 g, 16.8 mmol) in CH_2Cl_2 (25 mL) was added to the above reagent at −78 °C, and the mixture was stirred for 1 h at this temperature. Triethylamine (18.8 mL, 134.7 mmol) was added to the above solution at −78 °C, and the mixture was stirred for 2 h at −30 °C. Saturated NH_4Cl was added to the mixture, and the whole was extracted with CH_2Cl_2. The extract was washed successively with NH_4Cl, $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by short column chromatography over silica gel with hexane–EtOAc (7:1) gave a crude aldehyde as an oil, which was used in the next reaction without further purification. By a procedure identical with that described for the synthesis of the alkene **66**, this aldehyde was converted into **75** (1.70 g, 62% yield) by the reaction with $Ph_3P^+CH_3Br^-$ (8.27 g, 23.1 mmol) and KHMDS (0.50 M solution in toluene, 46.3 mL, 23.1 mmol) at 0 °C for 15 min: colorless oil; $[\alpha]_D^{26}+35.2$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H, CMe), 2.72 (d, $J=14.2$ Hz, 1H, 1-C*H*H), 2.84 (d, $J=14.2$ Hz, 1H, 1-CH*H*), 3.56 (s, 1H, 3-H), 5.21–5.32 (m, 2H, 5-CH_2), 5.90–5.98 (m, 1H, 4-H), 7.22–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 33.8, 61.9, 68.7, 113.8, 126.3, 128.3 (2C), 128.6 (2C), 136.8, 140.0; MS (FAB) *m*/*z* (%): 175 (MH^+, 42), 96 (100); HRMS (FAB) calcd for $C_{12}H_{15}O$ (MH^+): 175.1123; found: 175.1140.

4.3.13. (2*R*,3*R*)-2,3-Epoxy-2-methyl-1-phenylpentane (23). To a mixture of **75** (1.00 g, 5.76 mmol) and 5% Pd/C (100 mg) in EtOAc (35 mL) was stirred for 9 h under hydrogen atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated and purified by column chromatography over silica gel with hexane–EtOAc (20:1) to give **23** (355 mg, 35% yield) as a colorless oil; $[\alpha]_D^{24}+8.6$ (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, $J=7.5$ Hz, 3H, CH_2CH_3), 1.20 (s, 3H, CMe), 1.51–1.64 (m, 2H, CH_2Me), 2.74–2.92 (m, 2H, $PhCH_2$), 7.20–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 16.2, 21.5, 42.5, 60.7, 61.1, 125.8, 127.6 (2C), 128.3 (2C), 134.1; MS (FAB) *m*/*z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1358.



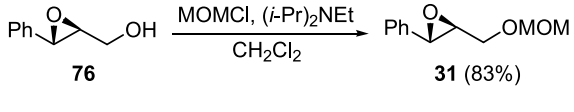
74 **29** (96%)

4.3.14. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-3-methyl-4-phenylbutan-1-ol (29). By a procedure identical with that described for the synthesis of **7**, the alcohol **74** (650 mg, 3.65 mmol) was converted into **29** (776 mg, 96% yield) by the reaction with MOMCl (1.12 mL, 13.1 mmol) and $(i\text{-Pr})_2NEt$ (2.86 mL, 16.4 mmol) at room temperature for 24 h: colorless oil; $[\alpha]_D^{24}+23.6$ (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H, CMe), 2.83 (d, $J=14.1$ Hz, 1H, 4-C*H*H), 2.91 (d, $J=14.1$ Hz, 1H, 4-CH*H*), 3.04 (t, $J=5.5$ Hz, 1H, 2-H), 3.37 (s, 3H, OMe), 3.60–3.75 (m, 2H, 1-CH_2), 4.62–4.68 (m, 2H, OCH_2O), 7.21–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 44.4, 55.3, 60.4, 60.5, 66.3, 96.5, 126.6, 128.4 (2C), 129.6 (2C), 136.8; MS (FAB) *m*/*z* (%): 223 (MH^+, 12), 132 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_3$ (MH^+): 223.1334; found: 223.1340.



74 **30** (89%)

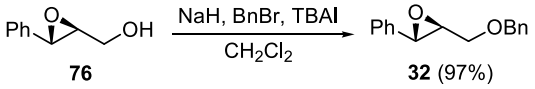
4.3.15. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-3-methyl-4-phenylbutan-1-ol (30). 60% NaH (297 mg, 7.43 mmol) was washed with dry hexane and suspended in THF (10 mL). To this suspension were successively added tetrabutylammonium iodide [$(n\text{-Bu})_4NI$; 250 mg, 0.68 mmol], BnBr (0.88 mL, 7.43 mmol), and a solution of the alcohol **74** (1.20 g, 6.76 mmol) in THF (10 mL) at room temperature. After stirring for 4 h, H_2O was added to the mixture at 0 °C. The whole was extracted with EtOAc and the extract was washed with brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (30:1) to give **30** (1.62 g, 89% yield) as a colorless oil; $[\alpha]_D^{24}+10.6$ (*c* 1.02, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (s, 3H, CMe), 2.80 (d, $J=14.0$ Hz, 1H, 4-C*H*H), 2.87 (d, $J=14.0$ Hz, 1H, 4-CH*H*), 3.03 (m, 1H, 2-H), 3.58–3.71 (m, 2H, 1-CH_2), 4.56–4.64 (m, 2H, OCH_2Ph), 7.25–7.34 (m, 10H, 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 44.6, 59.4, 60.0, 67.1, 78.7, 125.3 (2C), 126.8 (2C), 127.4 (2C), 128.4, 128.7 (3C), 136.8, 137.8; MS (FAB) *m*/*z* (%): 223 (MH^+, 26), 90 (100); HRMS (FAB) calcd for $C_{18}H_{21}O_2$ (MH^+): 269.1542; found: 269.1538.



76 **31** (83%)

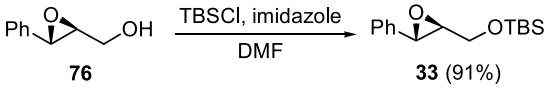
4.3.16. (2*S*,3*S*)-2,3-Epoxy-*O*-methoxymethyl-3-phenylpropan-1-ol (31). By a procedure identical with that described for the synthesis of **7**, the alcohol **76**[26] (1.50 g, 10.0 mmol) was converted into **31** (1.61 g, 83% yield) by the reaction with MOMCl (1.14 mL, 15.0 mmol) and $(i\text{-Pr})_2NEt$ (3.48 mL, 20.0 mmol) at room temperature for 12 h: colorless oil; $[\alpha]_D^{26}$ −39.9 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.23–3.25 (m, 1H, 2-H), 3.39 (s, 3H, OMe), 3.71 (dd, $J=11.6$, 5.5 Hz, 1H, 1-C*H*H), 3.81 (d, $J=$

3.1 Hz, 1H, 3-H), 3.88 (dd, J=11.6, 3.1 Hz, 1H, 1-CH*H*), 4.69 (d, J=6.7 Hz, 1H, OC*H*HO), 4.71 (d, J=6.7 Hz, 1H, OCH*H*O), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.1, 60.9, 67.3, 96.7, 125.7 (2C), 128.3, 128.5 (2C), 136.8; MS (FAB) m/z (%): 217 (MNa^+, 10.2), 176 (100); HRMS (FAB) calcd for $C_{11}H_{14}NaO_3$ (MNa^+): 217.0841; found: 217.0861.



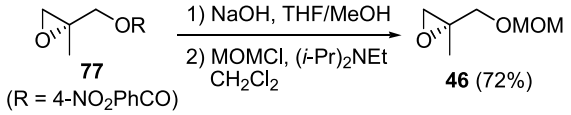
76 **32** (97%)

4.3.17. (2*S*,3*S*)-*O*-Benzyl-2,3-epoxy-3-phenylpropan-1-ol (32). By a procedure identical with that described for the synthesis of **30**, the alcohol **76**[26] (1.20 g, 8.00 mmol) was converted into **32** (1.86 g, 97% yield) by the reaction with 60% NaH (352 mg, 8.80 mmol), (n-Bu)$_4$NI (29.6 mg, 0.08 mmol), and BnBr (1.05 mL, 8.83 mmol) at room temperature for 3 h: colorless oil; $[\alpha]_D^{28}$ −38.9 (c 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23–3.27 (m, 1H, 2-H), 3.59–3.65 (m, 1H, 3-H), 3.79–3.86 (m, 2H, 1-CH_2), 4.58–4.67 (m, 2H, PhC*H*$_2$), 7.24–7.37 (m, 10H, 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 61.2, 69.8, 73.4, 125.7 (2C), 127.8 (2C), 128.2, 128.4 (2C), 128.5 (3C), 136.8, 137.8; MS (FAB) m/z (%): 263 (MNa^+, 41), 176 (100); HRMS (FAB) calcd for $C_{16}H_{16}NaO_2$ (MNa^+): 263.1048; found: 263.1048.



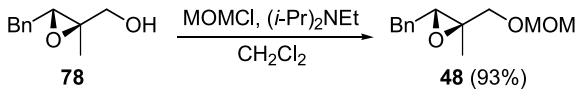
76 **33** (91%)

4.3.18. (2*S*,3*S*)-*O*-(*tert*-Butyldimethylsilyl)-2,3-epoxy-3-phenylpropan-1-ol (33). To a stirred solution of the alcohol **76**[26] (2.00 g, 13.3 mmol) in DMF (50 mL) were successively added imidazole (2.26 g, 33.2 mmol) and TBSCl (2.41 g, 16.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–Et_2O (40:1) to give **33** (3.22 g, 91% yield) as a colorless oil; $[\alpha]_D^{28}$ −28.8 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.105 (s, 3H, SiMe), 0.113 (s, 3H, SiMe), 0.92 (s, 9H, CMe_3), 3.14–3.15 (m, 1H, 2-H), 3.80 (d, J=1.8 Hz, 1H, 3-H), 3.83 (dd, J=12.2, 4.3 Hz, 1H, 1-C*H*H), 3.96 (dd, J=12.2, 3.1 Hz, 1H, 1-CH*H*), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2C), 18.4, 25.9 (3C), 55.8, 62.7, 63.0, 125.7 (2C), 128.1, 128.4 (2C), 137.2; MS (FAB) m/z (%): 265 (MH^+, 32), 207 (100); HRMS (FAB) calcd for $C_{15}H_{25}O_2Si$ (MH^+): 265.1624; found: 265.1629.



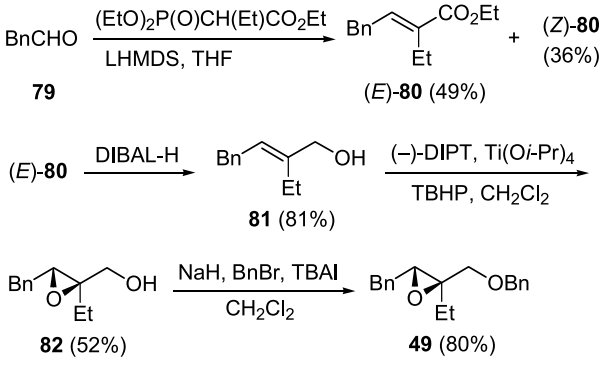
77 (R = 4-NO_2PhCO) **46** (72%)

4.3.19. (*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methylpropan-1-ol (46). To a stirred solution of **77**[26] (3.52 g, 14.8 mmol) in THF/MeOH (4:1, 30 mL) was added 10% NaOH (10 mL), and the mixture was stirred at 0 °C for 3 h. The whole was extracted with EtOAc, and the extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated to give a crude alcohol, which was used in the next reaction without further purification. By a procedure identical with that described for the synthesis of **7**, this alcohol was converted into **46** (1.41 g, 72% yield) by the reaction with MOMCl (3.37 mL, 44.4 mmol) and (i-Pr)$_2$NEt (12.9 mL, 74.0 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}$ −5.6 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H, CMe), 2.53 (s, 2H, 3-CH_2), 3.34 (s, 3H, OMe), 3.40 (s, 2H, 1-CH_2), 5.13 (s, 2H, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 51.3, 51.5, 67.2, 77.0, 98.9; MS (FAB) m/z (%): 133 (MH^+, 100); HRMS (FAB) calcd for $C_6H_{13}O_3$ (MH^+): 133.0865; found: 133.0859.



78 **48** (93%)

4.3.20. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methyl-4-phenylbutan-1-ol (48). By a procedure identical with that described for the synthesis of **7**, the alcohol **78**[33] (1.50 g, 8.42 mmol) was converted into **48** (1.74 g, 93% yield) by the reaction with MOMCl (0.96 mL, 12.6 mmol) and (i-Pr)$_2$NEt (2.92 mL, 16.8 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{23}$ +1.5 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3H, CMe), 2.86 (dd, J=14.6, 6.1 Hz, 1H, 4-C*H*H), 2.90–3.02 (m, 1H, 4-CH*H*), 3.10–3.20 (m, 1H, 3-H), 3.33 (s, 3H, OMe), 3.53 (d, J=11.0 Hz, 1H, 1-C*H*H), 3.56 (d, J=11.0 Hz, 1H, 1-CH*H*), 4.61 (s, 2H, OCH_2O), 7.22–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 34.7, 55.3, 59.8, 61.2, 71.7, 96.5, 126.6, 128.6 (2C), 128.7 (2C), 137.7; MS (FAB) m/z (%): 223 (MH^+, 13.4), 45 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_3$ (MH^+): 223.1334; found: 223.1330.



4.3.21. Ethyl (*E*)-2-ethyl-4-phenylbut-2-enoate [(*E*)-80] and its (*Z*)-isomer [(*Z*)-80]. To a stirred solution of triethyl phosphonobutyrate (28.4 mL, 120 mmol) in THF (120 mL) was added dropwise LHMDS (1.02 M solution in toluene; 118 mL, 120 mmol) at −78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of 60% phenylacetaldehyde (19.5 mL, 100 mmol) in THF (30 mL) was added dropwise to the mixture at −78 °C. The mixture was stirred for 5 h at 0 °C, and saturated NH_4Cl was added to the mixture. The organic layer was separated and washed with saturated NH_4Cl and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (30:1) to give, in the order of

elution, (*Z*)-**80** (7.95 g, 36% yield) and (*E*)-**80** (10.8 g, 49% yield).

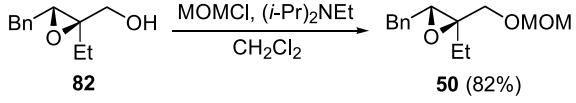
Compound (*E*)-**80**. Colorless oil; IR (KBr) cm^{-1} 1709 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, $J=7.3$ Hz, 3H, CMe), 1.28 (t, $J=7.3$ Hz, 3H, CMe), 2.44 (q, $J=7.3$ Hz, 2H, CH_2Me), 3.54 (d, $J=7.9$ Hz, 2H, 4-CH_2), 4.19 (q, $J=7.3$ Hz, 2H, OCH_2), 6.86 (t, $J=7.9$ Hz, 1H, 3-H), 7.19–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.2, 20.1, 34.5, 60.4, 126.4, 128.5 (2C), 128.6 (2C), 134.6, 139.1, 139.5, 167.7; MS (FAB) *m*/*z* (%): 219 (MH^+, 100); HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (MH^+): 219.1385; found: 219.1380.

Compound (*Z*)-**80**. Colorless oil; IR (KBr) cm^{-1} 1712 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, $J=7.3$ Hz, 3H, CMe), 1.33 (t, $J=7.3$ Hz, 3H, CMe), 2.32 (q, $J=7.3$ Hz, 2H, CH_2Me), 3.77 (d, $J=7.3$ Hz, 2H, 4-CH_2), 4.26 (q, $J=7.3$ Hz, 2H, OCH_2), 5.97 (t, $J=7.3$ Hz, 1H, 3-H), 7.19–7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 14.3, 27.5, 35.8, 60.2, 126.1, 128.5 (2C), 128.6 (2C), 134.3, 137.9, 140.4, 168.2; MS (FAB) *m*/*z* (%): 219 (MH^+, 100); HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (MH^+): 219.1385; found: 219.1393.

4.3.22. (*E*)-2-Ethyl-4-phenylbut-2-en-1-ol (81). To a stirred solution of (*E*)-**80** (9.00 g, 41.2 mmol) in THF (150 mL) was added dropwise DIBAL-H (0.93 M solution in hexane; 133 mL, 124 mmol) at −78 °C, and the mixture was stirred for 1 h at this temperature. Saturated NH_4Cl was added to the mixture, and the precipitate was filtered off. The filtrate was dried and concentrated to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give **81** (5.89 g, 81% yield) as a colorless oil; IR (KBr) cm^{-1} 3323 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, $J=7.6$ Hz, 3H, CMe), 1.31 (br, 1H, OH), 2.24 (q, $J=7.6$ Hz, 2H, CH_2Me), 3.42 (d, $J=7.3$ Hz, 2H, 4-CH_2), 4.10 (s, 2H, 1-CH_2), 5.58 (t, $J=7.3$ Hz, 1H, 3-H), 7.18–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 21.0, 33.5, 66.5, 124.3, 125.9, 128.3 (2C), 128.4 (2C), 141.0, 141.4; MS (FAB) *m*/*z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1367.

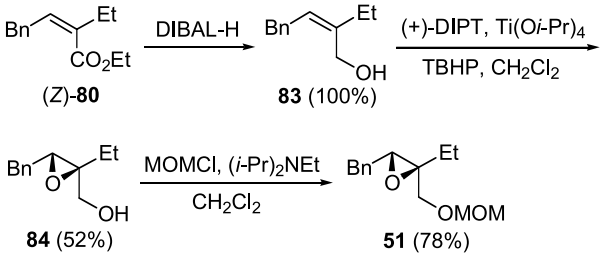
4.3.23. (2*R*,3*R*)-2,3-Epoxy-2-ethyl-4-phenylbutan-1-ol (82). By a procedure identical with that described for the synthesis of **74**, the alcohol **81** (4.41 g, 25.0 mmol) was converted into **82** (2.50 g, 52% yield) by the reaction with TBHP (2.6 M solution in toluene; 19.2 mL, 50.0 mmol), D-(−)-DIPT (0.80 mL, 3.75 mmol), Ti(O*i*-Pr)$_4$ (0.74 mL, 2.50 mmol), and molecular sieves 4A (1.5 g) at −30 °C for 5 h: colorless oil; $[\alpha]_D^{24}+12.3$ (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3434 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, $J=6.4$ Hz, 3H, CMe), 1.42 (q, $J=6.4$ Hz, 2H, CH_2Me), 2.43 (br s, 1H, OH), 2.83 (dd, $J=14.2$, 6.4 Hz, 1H, 4-C*H*H), 2.90 (dd, $J=14.2$, 6.1 Hz, 1H, 4-CH*H*), 2.93–3.05 (m, 1H, 3-H), 3.74 (s, 2H, 1-CH_2), 7.22–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 25.0, 36.1, 59.3, 69.0, 71.4, 124.9, 128.3 (2C), 128.8 (2C), 137.5; MS (FAB) *m*/*z* (%): 199 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO_2$ (MLi^+): 199.1310; found: 199.1321.

4.3.24. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-2-ethyl-4-phenylbutan-1-ol (49). By a procedure identical with that described for the synthesis of **30**, the alcohol **82** (0.76 g, 3.95 mmol) was converted into **49** (0.89 g, 80% yield) by the reaction with 60% NaH (174 mg, 4.35 mmol), $(n\text{-Bu})_4NI$ (148 mg, 0.40 mmol), and BnBr (0.52 mL, 4.37 mmol) at room temperature for 6 h: colorless oil; $[\alpha]_D^{24}+12.6$ (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J=6.2$ Hz, 3H, CMe), 1.32 (q, $J=6.2$ Hz, 2H, CH_2Me), 2.81 (dd, $J=14.2$, 6.4 Hz, 1H, 4-C*H*H), 2.92–3.04 (m, 1H, 4-CH*H*), 3.13–3.25 (m, 1H, 3-H), 3.48–3.59 (m, 2H, 1-CH_2), 4.54–4.62 (m, 2H, PhCH_2), 7.20–7.37 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 24.5, 34.7, 59.8, 61.4, 69.9, 73.2, 126.0 (2C), 127.4 (2C), 128.5 (4C), 128.8 (2C), 136.9, 137.9; MS (FAB) *m*/*z* (%): 283 (MH^+, 13.3), 90 (100); HRMS (FAB) calcd for $C_{19}H_{23}O_2$ (MH^+): 283.1698; found: 283.1688.



82 **50** (82%)

4.3.25. (2*R*,3*R*)-2,3-Epoxy-2-ethyl-*O*-methoxymethyl-4-phenylbutan-1-ol (50). By a procedure identical with that described for the synthesis of **7**, the alcohol **82** (0.82 g, 4.27 mmol) was converted into **50** (0.83 g, 82% yield) by the reaction with MOMCl (0.97 mL, 12.8 mmol) and $(i\text{-Pr})_2NEt$ (3.73 mL, 21.4 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}+7.3$ (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J=5.9$ Hz, 3H, CMe), 1.36 (q, $J=5.9$ Hz, 2H, CH_2Me), 2.82 (dd, $J=14.2$, 6.4 Hz, 1H, 4-C*H*H), 2.93–3.05 (m, 1H, 4-CH*H*), 3.15–3.27 (m, 1H, 3-H), 3.36 (s, 3H, OMe), 3.50 (d, $J=11.0$ Hz, 1H, 1-C*H*H), 3.53 (d, $J=11.0$ Hz, 1H, 1-CH*H*), 4.59 (s, 2H, OCH_2O), 7.20–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 24.8, 34.9, 56.1, 59.6, 61.7, 71.3, 96.8, 126.8, 128.5 (2C), 128.8 (2C), 137.7; MS (FAB) *m*/*z* (%): 237 (MH^+, 23), 151 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1487.



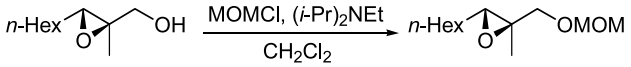
(*Z*)-**80** **83** (100%)

84 (52%) **51** (78%)

4.3.26. (*Z*)-2-Ethyl-4-phenylbut-2-en-1-ol (83). By a procedure identical with that described for the synthesis of **81**, the ester (*Z*)-**80** (7.10 g, 32.5 mmol) was converted into **83** (5.73 g, 100% yield) by the reaction with DIBAL-H (0.93 M solution in hexane; 105 mL, 97.6 mmol) at −78 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 3319 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, $J=7.3$ Hz, 3H, CMe), 1.28 (br s, 1H, OH), 2.21 (q, $J=7.3$ Hz, 2H, CH_2Me), 3.46 (d, $J=7.9$ Hz, 2H, 4-CH_2), 4.26 (s, 2H, 1-CH_2), 5.52 (t, $J=7.9$ Hz, 1H, 3-H), 7.17–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 27.8, 33.6, 60.3, 125.5, 125.9, 128.2 (2C), 128.4 (2C), 140.96, 141.02; MS (FAB) *m*/*z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1360.

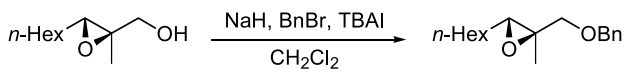
4.3.27. (2*S*,3*R*)-2,3-Epoxy-2-ethyl-4-phenylbutan-1-ol (84). By a procedure identical with that described for the synthesis of **74**, the alcohol **83** (3.52 g, 20.0 mmol) was converted into **84** (2.01 g, 52% yield) by the reaction with TBHP (2.6 M solution in toluene; 23.1 mL, 60.0 mmol), L-(+)-DIPT (0.64 mL, 3.00 mmol), Ti(O*i*-Pr)$_4$ (0.59 mL, 2.00 mmol), and molecular sieves 4A (1.3 g) at −20 °C for 12 h: colorless oil; $[\alpha]_D^{24}$ −21.6 (*c* 0.92, $CHCl_3$); IR (KBr) cm^{-1} 3440 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=6.4 Hz, 3H, CMe), 1.44 (q, *J*=6.4 Hz, 2H, C*H*$_2$Me), 2.50 (br s, 1H, OH), 2.83 (dd, *J*=14.2, 6.1 Hz, 1H, 4-C*H*H), 2.91 (dd, *J*=14.2, 6.4 Hz, 1H, 4-CH*H*), 2.90–3.01 (m, 1H, 3-H), 3.80 (s, 2H, 1-CH_2), 7.21–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 25.1, 36.1, 59.6, 69.4, 71.2, 124.9, 127.2 (2C), 128.0 (2C), 135.5; MS (FAB) *m*/*z* (%): 199 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO_2$ (MLi^+): 199.1310; found: 199.1301.

4.3.28. (2*S*,3*R*)-2,3-Epoxy-2-ethyl-*O*-methoxymethyl-4-phenylbutan-1-ol (51). By a procedure identical with that described for the synthesis of **7**, the alcohol **84** (0.91 g, 4.73 mmol) was converted into **51** (0.87 g, 78% yield) by the reaction with MOMCl (1.08 mL, 14.2 mmol) and (*i*-Pr)$_2$NEt (4.13 mL, 23.7 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{24}$ −11.1 (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J*=5.9 Hz, 3H, CMe), 1.38 (q, *J*=5.9 Hz, 2H, C*H*$_2$Me), 2.83–2.96 (m, 1H, 4-C*H*H), 3.03 (dd, *J*=14.2, 6.1 Hz, 1H, 4-CH*H*), 3.17–3.29 (m, 1H, 3-H), 3.36 (s, 3H, OMe), 3.54 (d, *J*=11.0 Hz, 1H, 1-C*H*H), 3.58 (d, *J*=11.0 Hz, 1H, 1-CH*H*), 4.57 (s, 2H, OCH_2O), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 24.9, 35.2, 56.1, 59.4, 61.6, 71.0, 96.6, 126.9, 128.5 (2C), 128.8 (2C), 137.7; MS (FAB) *m*/*z* (%): 237 (MH^+, 15), 151 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1501.



85 **52** (89%)

4.3.29. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methylnonan-1-ol (52). By a procedure identical with that described for the synthesis of **7**, the alcohol **85**[34] (1.50 g, 8.71 mmol) was converted into **52** (1.68 g, 89% yield) by the reaction with MOMCl (0.99 mL, 13.1 mmol) and (*i*-Pr)$_2$NEt (3.03 mL, 17.4 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}$ +14.4 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.9 Hz, 3H, CMe), 1.30–1.60 (m, 10H), 1.32 (s, 3H, CMe), 2.89 (t, *J*=6.0 Hz, 1H, 3-H), 3.37 (s, 3H, OMe), 3.52 (s, 2H, 1-CH_2), 4.64 (s, 2H, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.5, 22.5, 26.4, 28.2, 29.1, 31.7, 55.3, 59.4, 61.2, 72.0, 96.5; MS (FAB) *m*/*z* (%): 217 (MH^+, 100); HRMS (FAB) calcd for $C_{12}H_{25}O_3$ (MH^+): 217.1804; found: 217.1801.



85 **53** (95%)

4.3.30. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-2-methylnonan-1-ol (53). By a procedure identical with that described for the synthesis of **30**, the alcohol **85**[34] (1.30 g, 7.55 mmol) was converted into **53** (1.88 g, 95% yield) by the reaction with 60% NaH (330 mg, 8.30 mmol), (*n*-Bu)$_4$NI (27.9 mg, 0.076 mmol), and BnBr (0.99 mL, 8.30 mmol) at room temperature for 4 h: colorless oil; $[\alpha]_D^{24}$ +18.2 (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 1603 (Ph); ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.9 Hz, 3H, CMe), 1.30–1.60 (m, 10H), 1.33 (s, 3H, CMe), 2.85 (t, *J*=6.0 Hz, 1H, 3-H), 3.43 (d, *J*=10.9 Hz, 1H, 1-C*H*H), 3.50 (d, *J*=10.9 Hz, 1H, 1-CH*H*), 4.52 (d, *J*=12.0 Hz, 1H, PhC*H*H), 4.58 (d, *J*=12.0 Hz, 1H, PhCH*H*), 7.24–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 22.5, 26.4, 28.2, 29.1, 31.7, 59.6, 61.0, 73.0, 74.7, 127.4 (3C), 128.1 (2C), 137.9; MS (FAB) *m*/*z* (%): 263 (MH^+, 100); HRMS (FAB) calcd for $C_{17}H_{27}O_2$ (MH^+): 263.2011; found: 263.2020.

4.3.31. (±)-(1*R,2*R**,6*S**)-4,4,6-Trimethyl-2-(prop-2-enyl)-7-oxabicyclo[4.1.0]heptan-2-ol (86).** To a stirred mixture of isophorone oxide **16** (154 mg, 1.0 mmol) in THF (5 mL) was added dropwise allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) at −78 °C, and the mixture was stirred for 4 h at room temperature. 5% HCl was added to the mixture, and diluted organic layer was separated and washed with $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave an oily residue, which was purified by flash column chromatography over silica gel with hexane–EtOAc (5:1) to give, in the order of elution, **20** (33 mg, 17% yield) and **86** (109 mg, 56% yield). Compound **86**: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H, CMe), 1.02 (s, 3H, CMe), 1.24–1.27 (m, 1H, C*H*H), 1.33 (s, 3H, CMe), 1.36 (d, *J*=14.0 Hz, 1H, C*H*H), 1.53 (d, *J*=14.6 Hz, 1H, CH*H*), 1.64 (dd, *J*=14.6, 1.8 Hz, 1H, CH*H*), 1.66 (s, 1H, OH), 2.28 (dd, *J*=14.0, 6.7 Hz, 1H, 1′-C*H*H), 2.33–2.37 (m, 1H, 1′-CH*H*), 2.82 (s, 1H, 1-H), 5.12–5.17 (m, 2H, CH=C*H*$_2$), 5.75–5.83 (m, 1H, C*H*=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 28.9, 29.4, 31.8, 41.0, 42.8, 46.0, 61.5, 63.5, 69.9, 118.4, 132.8; MS (FAB) *m*/*z* (%): 219 (MNa^+, 18.7), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_2$ (MH^+): 197.1542; found: 197.1559.

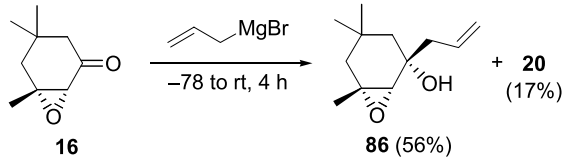
Acknowledgements

This work was supported by the Asahi Glass Foundation and Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. (a) Smith, J. G. *Synthesis* **1984**, 629–656. (b) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503–1511. (c) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1163.
2. (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) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431.

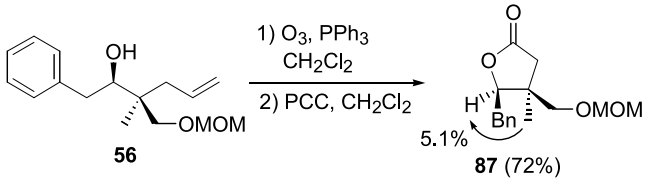
3. For representative examples for the reaction of epoxides at the activated carbon having two substituents, see: (a) Naruta, Y.; Maruyama, K. *Chem. Lett.* **1987**, 963–966. (b) Fujimura, O.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1705–1706. (c) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907–12908. For a recent study on the regioselective ring-opening reaction of chiral epoxides, see: (d) Brandes, B. D.; Jacobsen, E. N. *Synlett* **2001**, 1013–1015.
4. For construction of chiral quaternary carbons, see: (a) Balasubramaniam, R. P.; Moss, D. K.; Wyatt, J. K.; Spence, J. D.; Gee, A.; Nantz, M. H. *Tetrahedron* **1997**, *53*, 7429–7444. (b) Ishibashi, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 3775–3778.
5. (a) Nugent, W. A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561–8562. (b) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929–9930. (c) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929–9930. (d) Aggarwal, V. K.; Bethel, P. A.; Giles, R. *Chem. Commun.* **1999**, 325–326. (e) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206–3208. (f) Taylor, S. K.; Ivanovic, M.; Simons, L. J.; Davis, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 743–747.
6. For representative examples, see: (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 3827–3829. (b) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891–5894. (c) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707–1712. (d) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D. *J. Org. Chem.* **1993**, *58*, 5944–5951. (e) Okada, K.; Katsura, T.; Tanino, H.; Kakoi, H.; Inoue, S. *Chem. Lett.* **1994**, 157–160. (f) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949–8950. (g) 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. (h) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629–633. (i) Marson, C. M.; Khan, A.; Porter, R. A.; Cobb, A. J. A. *Tetrahedron Lett.* **2002**, *43*, 6637–6640. (j) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544–9545. (k) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554–9555.
7. (a) Lundeen, A. J.; Oehlschlager, A. C. *J. Organomet. Chem.* **1970**, *25*, 337–344. (b) Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 5849–5850. (c) Fukumasa, M.; Furuhashi, K.; Umezawa, J.; Takahashi, O.; Hirai, T. *Tetrahedron Lett.* **1991**, *32*, 1059–1062. (d) Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* **2001**, *66*, 5388–5394. (e) Zhao, H.; Pagenkopf, B. L. *Chem. Commun.* **2003**, 2592–2593. (f) Davis, C. E.; Bailey, J. L.; Lockner, J. W.; Coates, R. M. *J. Org. Chem.* **2003**, *68*, 75–82.
8. Ring-opening reaction of epoxides at the more substituted carbon atom with an equimolar amount of a transition metal complex and iodomethane was also reported, see: Hase, T.; Miyashita, A.; Nohira, H. *Chem. Lett.* **1988**, 219–222.
9. Tanaka, T.; Inoue, T.; Kamei, K.; Murakami, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1990**, 906–908.
10. For the epoxide cleavage at the allylic or benzylic position by titanium reagents prepared by chlorotitanium triisopropoxide, see: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986; pp 218–219. (b) Krause, N.; Seebach, D. *Chem. Ber.* **1988**, *121*, 1315–1320.
11. A portion of this study was already reported in a preliminary communication: Ohno, H.; Hiramatsu, K.; Tanaka, T. *Tetrahedron Lett.* **2004**, *45*, 75–78.
12. In some cases, we examined both allylmagnesium chloride and bromide in the ring-opening reaction, and similar results were obtained.
13. The stereochemistry of **20** is opposite to that of **86** which was obtained by the reaction with allylmagnesium bromide. This stereochemical outcome can be explained by the chelating ability of the titanium reagent to the oxygen atom of the epoxide, which allows the allylation of the ketone from the side of the epoxide oxygen.



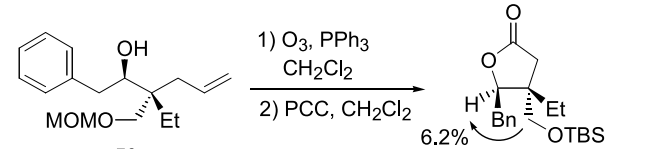
14. Stereoselective reactions of cyclic epoxides such as substituted cyclohexene oxides with a titanium reagent were already reported, see Ref. 10b. See also, (a) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189–4192. (b) Alvarez, E.; Nuñez, M. T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 3429–3431. (c) Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett.* **1991**, 774–776.
15. For titanium-mediated stereospecific ring-opening reactions of acyclic epoxides, see: (a) Sutowardoyo, K.; Emziane, M.; Sinou, D. *Tetrahedron Lett.* **1989**, *30*, 4673–4676. (b) Raifeld, Y. E.; Nikitenko, A. A.; Arshava, B. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1083–1084. (c) Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* **1999**, *29*, 1017–1024. (d) Sasaki, M.; Hatta, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2004**, *45*, 1911–1913.
16. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560. (b) Dai, L.-X.; Lou, B.-L.; Zhang, Y.-Z.; Guo, G.-Z. *Tetrahedron Lett.* **1986**, *27*, 4343–4346. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185–5187. (d) Gao, L.-X.; Murai, A. *Chem. Lett.* **1989**, 357–358. (e) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931–6934. (f) Sutowardoyo, K. I.; Emziane, M.; Lhoste, P.; Sinou, D. *Tetrahedron* **1991**, *47*, 1435–1446. (g) Urabe, H.; Aoyama, Y.; Sato, F. *Tetrahedron* **1992**, *48*, 5639–5646. (h) Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 5413–5415.
17. (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597–3600. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377–1380. (c) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599–602. (d) Ahn, K. H.; Kim, J. S.; Jin, C. S.; Kang, D. H.; Han, D. S.; Shin, Y. S.; Kim, D. H. *Synlett* **1992**, 306–308. (e) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971–7974. (f) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1999**, *40*, 1041–1044.
18. (a) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206–6209. (b) Martín, R.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367–6374. (c) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789–1791.
19. For a recent theoretical study, see: Infante, I.; Bonini, C.; Lelj, F.; Righi, G. *J. Org. Chem.* **2003**, *68*, 3773–3780.
20. Only a relatively small NOE enhancement was observed between 4-H and the siloxymethyl group.
21. Halohydrin is one of the representative side products irrespective of the Grignard reagent used, the stereochemistry

of which is not determined. No stereo- or regioisomer of the allylated product was detected in the reaction mixture.

22. Relative stereochemistries of the quaternary carbons were determined by NOE experiment of the corresponding lactones. Typical examples are shown below.



56 **87** (72%)



59 **88** (62%)

23. We investigated the titanium-mediated ring-opening reaction of epoxides with benzyl-, crotyl-, or vinylmagnesium halide; however, a complex mixture of unidentified products was obtained in every case.
24. MacPeek, D. L.; Starcher, P. S.; Phillips, B. *J. Am. Chem. Soc.* **1959**, *81*, 680–683.
25. Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191–195.
26. Coan, S. B.; Papa, D. *J. Am. Chem. Soc.* **1955**, *77*, 2402–2404.
27. Rae, I. D.; Umbrasas, B. N. *Aust. J. Chem.* **1975**, *28*, 2669–2680.
28. (a) Widmer, U. *Synthesis* **1983**, 135–136. (b) Kotake, Y.; Iijima, A.; Yoshimatsu, K.; Tamai, N.; Ozawa, Y.; Koyanagi, N.; Kitoh, K.; Nomura, H. *J. Med. Chem.* **1994**, *37*, 1616–1624.
29. Kimura, M.; Diwan, P. V.; Yanagi, S.; Kon-no, Y.; Nojima, H.; Kimura, I. *Biol. Pharm. Bull.* **1995**, *18*, 407–410.
30. (a) Urrutia, A.; Rodriguez, J. G. *Tetrahedron* **1999**, *55*, 11095–11108. (b) Srikrishna, A.; Kumar, P. P. *Tetrahedron* **2000**, *56*, 8189–8195.
31. Mayr, H.; von der Bruggen, U. *Chem. Ber.* **1988**, *121*, 339–345.
32. Cavero, M.; Motherwell, W. B.; Potier, P.; Weibel, J.-M. *Chem. Commun.* **2002**, 2394–2395.
33. Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379–7388.
34. Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.,* **1994**, *59*, 4461–4472.