Very High Chemoselective, Regioselective, and *E*-Stereoselective 1,3-Chirality Transfer Involving Reaction of Acyclic (*E*)- and (*Z*)-γ-Mesyloxy α,β-Enoates and Organocyanocopper–Trifluoroborane Reagents. Efficient Synthetic Routes to Functionalized Chiral α-Alkyl (*E*)-β,γ-Enoates and (*E*)-Allylic Alcohols with High Optical Purity

Toshiro Ibuka,*,† Miwa Tanaka,‡ Shinji Nishii,‡ and Yoshinori Yamamoto*,‡

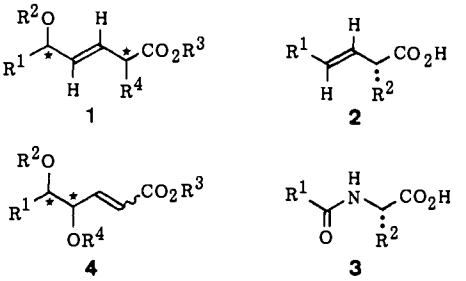
Contribution from the Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606, Japan, and the Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan.
Received October 21, 1988

Abstract: Reaction of γ-mesyloxy (*E*)- or (*Z*)-α,β-enoates with $Me_2Cu(CN)Li_2 \cdot BF_3$ (prepared from MeLi–LiI in ether), $MeCu(CN)Li \cdot BF_3$ (prepared from MeLi–LiBr in ether), and $RCu(CN)Li \cdot BF_3$ (R = Et, *n*-Pr, *n*-Bu) in tetrahydrofuran or mixed solvents involving tetrahydrofuran at −78 °C results in the formation of synthetically useful α-alkyl (*E*)-β,γ-enoates, compounds that are not easily accessible by other means. In all cases the chemical and optical yields are very high. The *E* geometry of the product is not related to the geometry of the starting material. Addition of $BF_3 \cdot Et_2O$ to the organocopper reagent is critical to the clean 1,3-chirality transfer. Other essential factors such as reaction solvent, type of organocopper reagent, and nature of the γ-oxygenated leaving group are discussed. The *E* geometry of the β,γ-double bond of the alkylation products could be determined by ^1H NMR spectroscopy and a chiral shift reagent. The present 1,3-chirality-transfer strategy is a potentially useful method for the synthesis of biologically important compounds such as pheromones, isosteres, and antibiotics.

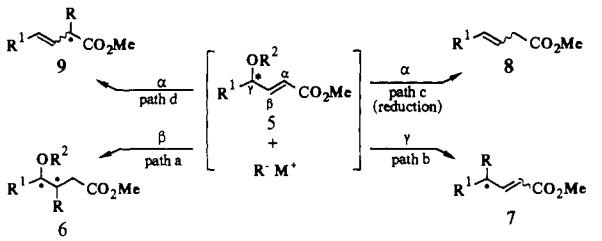
Development of synthetic methods which provide ready access to chiral carbon centers with a high level of regio-, chemo-, and stereocontrol as well as high chemical and optical yields represents a contemporary challenge for synthetic-organic chemists.[1] Recently, great advances have been made in the α-alkylation of esters and their congeners in enantio- or diastereoselective reactions via chiral metal enolates,[2] chiral oxazolines,[3] intra- and extraannular chirality transfer reactions,[4] asymmetric hydrogenations,[5] enzyme-catalyzed reactions,[6] sigmatropic rearrangements such as the Ireland–Claisen rearrangement,[7] and photodeconjugation of α,β-enoates (Chart I).[8]

Chiral α-substituted δ-oxygenated β,γ-enoates **1** bearing an *E* double bond are promising intermediates for the synthesis of natural products since both protected (*E*)-allylic alcohol and ester functions are available for further chemical manipulation (Chart I). However, in contrast to the well-documented methodologies mentioned above,[2-8] chiral syntheses of such α-alkyl (*E*)-β,γ-enoates remain a challenge. In addition, it has recently been suggested that the replacement of the amide bond (CONH) of a peptide **3** with an *E*-double bond (C=C) might provide "isosteres" **2**[9] of pharmacologically active peptides such as enkephalin[10] and substance P[11]. The *E* C=C bond in **2** closely resembles the three-dimensional shape (rigidity, bond angle, and bond length) of the parent amide **3**. In addition, this type of substitution should stabilize the peptide toward enzymatic hydrolysis by peptidases. Except for a few cases,[9a,c] however, published synthetic routes to such peptide mimics give unsatisfactory results with regard to double-bond geometry and/or stereochemistry at the α-position.[9] Clearly development of an efficient route to compounds of type **1** would be extremely valuable. We now detail an efficient regio-, *E*-stereo-, chemo-, and diastereoselective 1,3-chirality-transfer strategy involving organocopper–Lewis acid reagents for converting both (*E*)- and (*Z*)-γ-mesyloxy α,β-enoates **4** to a synthetically important chiral (*E*)-α-alkyl β,γ-enoate **1**, not readily accessible by other means.[12]

Chart I



Scheme I



In addition, we present reliable diagnostic data from ^1H NMR analyses using the chiral shift reagent $Eu(hfc)_3$ which allow un-

† Kyoto University.
‡ Tohoku University.

(1) Evans, D. A. *Science* **1988**, *240*, 420.
(2) (a) For an excellent review, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 1. (b) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318. (c) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735 and references cited. (d) Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 3247. (e) Renaud, P.; Hürzeler, M.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 292. (f) Agami, C.; Couty, F. *Tetrahedron Lett.* **1987**, *28*, 5659.
(3) (a) Evans, D. A.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 1007. (b) Evans, D. A.; Dimare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476. (c) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001.
(4) (a) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256. (b) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81 and references cited.

0002-7863/89/1511-4864$01.50/0

Table I. Chemical Yields and Diastereoselectivity in the Reaction of γ,δ-Dioxygenated α,β-Enoates with Organocopper Reagents[a]

entry	substrate: compd	substrate: leaving group at C-4[b]	substrate: geometry of C=C	reagent	product (% yield): reduction	product (% yield): α-alkylation	diastereoselectivity of α-alkyl product (abs configuration at C-2)[c]
1	**10**	OAc	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)	**13** (5.5)		
2	**11**	OCOPh	*E*	$Me_2Cu(CN)Li_2$ (LiBr)	**13** (46)		
3	**11**	OCOPh	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiBr)	**13** (54)		
4	**12**	OAc	*E*	Me_2CuLi (LiI)	**13** (76)		
5	**12**	OAc	*E*	$Me_2CuLi{\cdot}BF_3$ (LiI)	**13** (58)		
6	**12**	OAc	*E*	*n*-Bu_2CuLi	**13** (57)		
7	**20**	OMs	*E*	$Me_2CuLi{\cdot}BF_3$ (LiI)	**13** (26)	**25** (62)	>99:1 (*R*)
8	**44**	OMs	*E*	Me_2CuLi (LiI)	**13** (25)	**29** (61)	>99:1 (*S*)
9	**44**	OMs	*E*	$Me_2Cu(CN)Li_2$ (LiI)	**13** (11)	**29** (78)	>99:1 (*S*)
10	**21**	OTs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**25** (98)	97:3 (*R*)
11	**45**	OTs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**29** (96)	>99:1 (*S*)
12	**45**	OTs	*E*	$Me_2CuLi{\cdot}BF_3$ (LiI)	**13** (34)	**29** (40)	>99:1 (*S*)
13	**20**	OMs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**25** (97)	>99:1 (*R*)
14	**20**	OMs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiBr)		**25** (81)	>99:1 (*R*)
15	**20**	OMs	*E*	$MeCu(CN)Li{\cdot}BF_3$ (LiI)		**25** (82)	>99:1 (*R*)
16	**20**	OMs	*E*	$MeCu(CN)Li{\cdot}BF_3$ (LiBr)		**25** (98)	>99:1 (*R*)
17	**20**	OMs	*E*	$EtCu(CN)Li{\cdot}BF_3$		**26** (93)	>99:1 (*R*)
18	**20**	OMs	*E*	*n*-$PrCu(CN)Li{\cdot}BF_3$		**27** (97)	>99:1 (*R*)
19	**20**	OMs	*E*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**28** (96)	>99:1 (*R*)
20	**20**	OMs	*E*	*n*-$Bu_2Cu(CN)Li_2{\cdot}BF_3$		**28** (81)	>99:1 (*R*)
21	**22**	OMs	*Z*	$MeCu(CN)Li{\cdot}BF_3$ (LiBr)		**29** (93)	>99:1 (*S*)
22	**23**	OMs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**31** (98)	>99:1 (*R*)
23	**23**	OMs	*E*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**32** (93)	>99:1 (*R*)
24	**24**	OMs	*Z*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**33** (93)	>99:1 (*S*)
25	**24**	OMs	*Z*	*n*-$PrCu(CN)Li{\cdot}BF_3$		**35** (93)	>99:1 (*S*)
26	**24**	OMs	*Z*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**36** (96)	>99:1 (*S*)
27	**43**	OMs	*Z*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**25** (86)	>99:1 (*R*)
28	**43**	OMs	*Z*	*n*-$PrCu(CN)Li{\cdot}BF_3$		**27** (94)	>99:1 (*R*)
29	**43**	OMs	*Z*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**28** (96)	>99:1 (*R*)
30	**44**	OMs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**29** (96)	>99:1 (*S*)
31	**44**	OMs	*E*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**30** (95)	>99:1 (*S*)
32	**46**	OMs	*Z*	$MeCu(CN)Li{\cdot}BF_3$ (LiBr)		**31** (93)	>99:1 (*R*)
33	**47**	OMs	*E*	$Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI)		**33** (98)	>99:1 (*S*)
34	**47**	OMs	*E*	$EtCu(CN)Li{\cdot}BF_3$		**34** (92)	>99:1 (*S*)
35	**47**	OMs	*E*	*n*-$PrCu(CN)Li{\cdot}BF_3$		**35** (94)	>99:1 (*S*)
36	**47**	OMs	*E*	*n*-$BuCu(CN)Li{\cdot}BF_3$		**36** (95)	>99:1 (*S*)

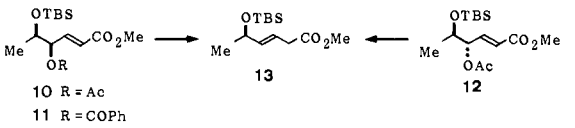
[a] All reactions were carried out at −78 °C for 30 min with 3 molar equiv of reagents. [b] OTs = [(4-methylphenyl)sulfonyl]oxy; OMs = (methylsulfonyl)oxy. [c] Diastereoselectivities were determined by ^1H NMR and/or ^{13}C NMR for isolated compounds with the chiral shift reagent Eu(hfc)$_3$. >99:1 indicates that the other isomer was not detectable.

ambiguous determination of the *E* geometry of the double bond of the β,γ-enoates.

Results and Discussion

Although the nucleophilic attack of organocopper reagents on simple vinyloxiranes and allylic alcohol derivatives is a well-documented synthetic procedure, application of this strategy has mainly involved rigid 5- and 6-ring carbocycles,[13] except in a few cases.[14] Despite its potential utility for the synthesis of natural products, 1,3-chirality transfer involving γ-oxygenated α,β-enoates has scarcely been studied to date from the viewpoint of regio-, chemo-, and stereocontrol in acyclic systems. Four different reaction products from an acyclic γ-oxygenated α,β-enoate **5** with

Scheme II



(5) (a) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (b) For a review, see: Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985, Vol. 5, p 71. (c) For a nonstereoselective hydrogenation, see: Fujimoto, Y.; Iwadate, H.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1*, 1985, 2701. (d) Nõgrãdi, M. In *Stereoselective Synthesis*; VCH Publishers: Weinheim, **1987**, p 53. (e) Brown, J. M.; James, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 181.

(6) (a) Gu, Q.-M.; Reddy, D. R.; Sih, C. J. *Tetrahedron Lett.* **1986**, *27*, 5203. (b) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5241.

(7) (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479. (b) Ireland, R. E.; Wutz, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (c) Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179. (d) Heathcock, C. H.; Radel, P. A. *J. Org. Chem.* **1986**, *51*, 4322.

(8) (a) Montezaei, R.; Henin, F.; Muzart, J.; Pete, J.-P. *Tetrahedron Lett.* **1985**, *26*, 6079. (b) Piva, O.; Henin, F.; Muzart, J.; Pete, J.-P. *Tetrahedron Lett.* **1986**, *27*, 3001.

(9) (a) Johnson, R. L. *J. Med. Chem.* **1984**, *27*, 1351. (b) Shue, Y.-K.; Carrera, G. M., Jr.; Nadzan, A. M. *Tetrahedron Lett.* **1987**, *28*, 3225. (c) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759 and references cited.

(10) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299 and references cited.

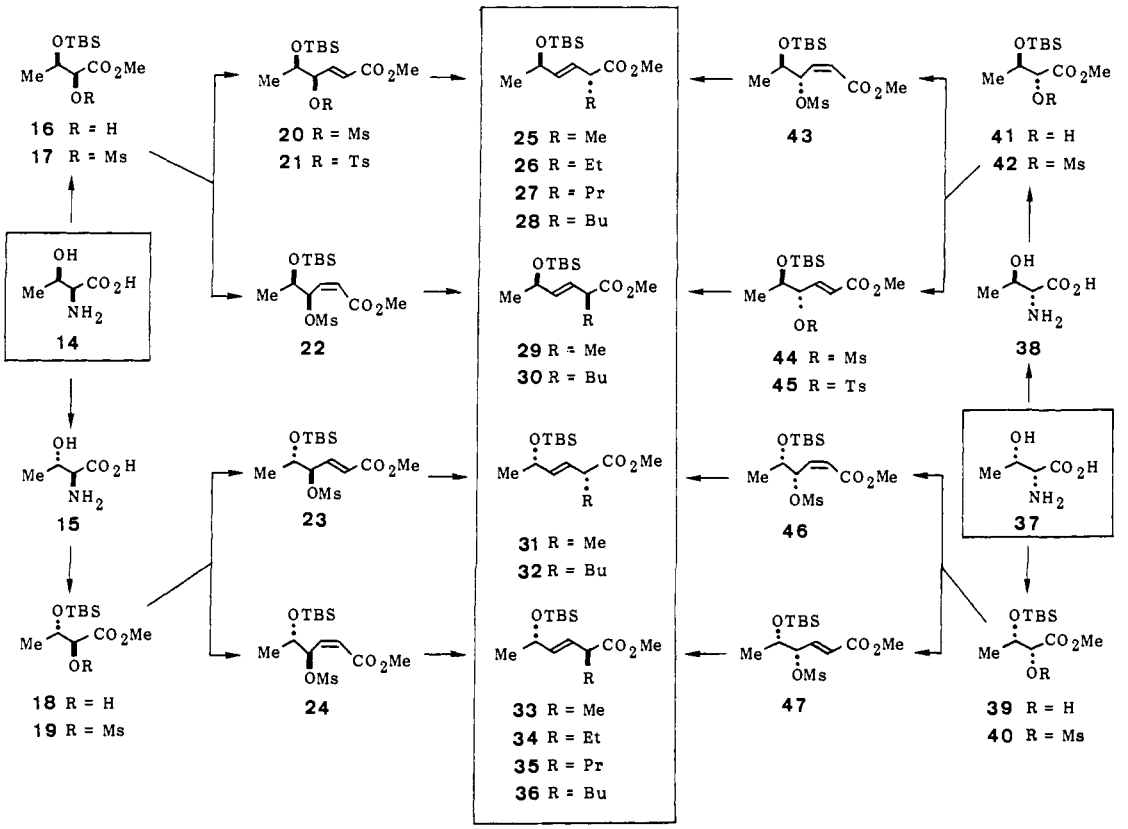
(11) (a) Cox, M. T.; Heaton, D. W.; Horbury, J. *J. Chem. Soc., Chem. Commun.* **1980**, 799. (b) Cox, M. T.; Gormley, J. J.; Havard, C. F.; Petter, N. N. *J. Chem. Soc., Chem. Commun.* **1980**, 800.

(12) For a preliminary communication of a portion of this work, see: Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.

(13) (a) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422. (c) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (d) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892. (e) For regio- and stereochemical of electrophilic additions to allylic alcohols and their derivatives, see: Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666. Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. (f) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898 and references cited. (g) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1988**, *53*, 1140.

(14) (a) Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4919. (b) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. (c) Claesson, A.; Olsson, L.-I. *J. Chem. Soc., Chem. Commun.* **1978**, 621. (d) References 4a. (e) Fleming, I.; Marchi, D. *Synthesis* **1981**, 560. (f) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1985**, *264*, 99. (g) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1985**, 411. (h) Fleming, I.; Thomas, P. *J. Chem. Soc., Chem. Commun.* **1986**, 1456. (i) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985. (j) Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *Tetrahedron Lett.* **1988**, *29*, 913.

Scheme III



an organocopper reagent (R^-M^+) can be envisioned (Scheme I).

Addition of an R group at the β-position provides a 1,4-adduct **6** (path a),[15] S_N2 reaction at the γ-position generates a γ-alkylated product **7** (path b),[16] and reductive elimination of the γ-oxygenated function affords a β,γ-unsaturated ester **8** (path c).[17] Finally, S_N2' attack at the α-position leads to either an *E* or *Z* alkylation product **9** (path d).[12,16] Thus, it is not an easy matter to predict whether a, b, c, or d is the major reaction pathway in the reaction of acyclic γ-oxygenated α,β-enoates with organocopper reagents.

Synthesis of Four Chiral Stereoisomers of the Important Chiral Building Blocks, Methyl (*E*)-2-Alkyl-5-(*tert*-butyldimethylsiloxy)-3-hexenoate, from either L- or D-Threonine via (*E*)- and (*Z*)-γ-Mesyloxy α,β-Enoates. We initiated our studies to determine the scope of the 1,3-chirality-transfer reaction with respect to leaving groups on the γ-position utilizing (*E*)-α,β-enoates. Although extensive studies on the allylic rearrangement of acetates, benzoates, and their analogous derivatives of simple allylic alcohols with organocopper reagents have shown that alkylation at the γ-position is favored,[13] reaction of the acetates (**10**, **12**)[18] and the benzoate **11**[18] with various kinds of organocopper reagents in either ether or tetrahydrofuran (THF) yielded mixtures of products from which only the reduction product **13** could be isolated[19] (Scheme II and Table I, entries 1–6). In these reactions, we did not detect any alkylation product by the TLC, GLC, and ^1H NMR analyses. Thus, regiocontrolled α-alkylation of acyclic γ-acetoxy and γ-benzoyloxy α,β-enoates with ordinary organocuprates or their Lewis acid complexes such as Me_2CuLi and $Me_2CuLi{\cdot}BF_3$ as well as the organocyanocuprate–trifluoroborane reagent via the 1,3-chirality transfer process proved troublesome. Similar reductive elimination reactions of simple cyclic γ-acetoxy and γ-benzoyloxy α,β-enoates[16b,17a,b,20] and γ-oxygenated enones[21] with organocopper reagents such as the classical Gilman reagent have been reported previously. For whatever reason the expected 1,3-chirality transfers were not observed.

The difficulty was overcome by the use of γ-mesyloxy and γ-tosyloxy α,β-enoates. As shown in Scheme III and Table I, all possible stereoisomers (**20**, **22–24**, **43**, **44**, **46**, and **47**), with respect to the two chiral centers and the *E* and *Z* geometries, of methyl 4-mesyloxy-5-(*tert*-butyldimethylsiloxy)-2-hexenoate and two stereoisomer tosylates (**21** and **45**)[18] were readily prepared from L- and D-threonines (**14** and **37**) via the previously reported hydroxy esters (**16**, **18**, **39**, and **41**)[22] and the mesyloxy esters (**17**, **19**, **40** and **42**).[23] In these γ-mesyloxy and γ-tosyloxy α,β-enoates, the δ-hydroxy group was protected with the *tert*-butyldimethylsiloxy group which can withstand a wide range of chemical manipulations and yet be easily removed under mild conditions. Our

(15) (a) Ibuka, T.; Minakata, H.; Mitsui, Y.; Kinoshita, K.; Kawami, Y.; Kimura, N. *Tetrahedron Lett.* **1980**, *21*, 4073. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. (c) Linderman, R. J.; Mckenzie, J. R. *Tetrahedron Lett.* **1988**, *29*, 3911.

(16) (a) Ibuka, T.; Minakata, H. *Synth. Commun.* **1980**, 119. (b) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

(17) (a) Ibuka, T.; Chu, G.-N.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. (b) Ibuka, T. Aoyagi, T.; Yoneda, F. *J. Chem. Soc., Chem. Commun.* **1985**, 1452. (c) Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 449.

(18) The substrates **10**, **11**, and **21** were prepared from methyl-(*E*,4*R*,5*R*)-4,5-dihydroxy-2-hexenoate, which was obtained from L-threonine according to the literature (Fronza, G.; Fuganti, C.; Grasseli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883). Thus, selective *tert*-butyldimethylsilylation (*t*-Bu(Me)$_2$SiCl, imidazole, CH_2Cl_2, 49%) was followed by acetylation (Ac_2O/pyridine), benzoylation (PhCOCl, CH_2Cl_2, pyridine), and tosylation (TsCl, pyridine, CH_2Cl_2) to give **10** (99%), **11** (98%), and **21** (97%), respectively. By the same procedure, the substrates **12** and **45** were prepared from D-allothreonine in high yields.

(19) Organocopper–Lewis acid reagents (RCu.$AlCl_3$ and RCu.BF_3) undergo 1,4-addition to simple cyclic γ-oxygenated α,β-enones (Ibuka, T.; Minakata, H.; Mitsui, Y.; Kinoshita, K.; Y. *J. Chem. Soc., Chem. Commun.* **1980**, 1193 and ref 16b).

(20) Reaction of acylic γ-acetoxy-α,β-unsaturated carbonyl compounds with lithium dioctylcuprate has been reported to yield a mixture of unidentified products (Descoins, C.; Henrick, C. A.; Siddall, J. B. *Tetrahedron Lett.* **1972**, 3777).

(21) (a) Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975**, 2043. (b) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144. (c) Logusch, E. W. *Tetrahedron Lett.* **1979**, 3365.

(22) Ibuka, T.; Nishii, S.; Yamamoto, Y. *Chem. Express* **1988**, 53.

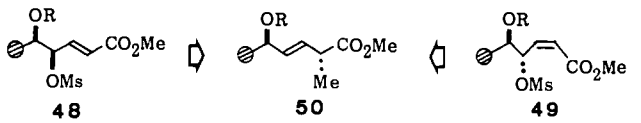
(23) Because space does not permit description of the experimental details, preparative methods and spectroscopic as well as analytical data for all substrates are presented as supplementary materials.

early experiments[12] involved the use of $Me_2Cu(CN)Li_2{\cdot}BF_3$ since the lower order reagent $MeCu(CN)Li{\cdot}BF_3$ was less successful (see Table I, entries 13 and 15). Subsequently, it was found that different chemical yields were obtained not only with different molar ratios of MeLi and CuCN but also with a reagent prepared from MeLi–LiI or MeLi–LiBr complexes. Thus, $Me_2Cu(CN)Li_2{\cdot}BF_3$ was less useful than $MeCu(CN)Li{\cdot}BF_3$ when prepared from a MeLi-LiBr complex (see Table I, entries 14 and 16). Consequently, although the role of inorganic salts (LiI and LiBr) is not perfectly clear,[24] the expressions such as $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI) and $MeCu(CN)Li{\cdot}BF_3$ (LiBr) are intended to indicate that the reagents have been prepared from MeLi as the LiI or LiBr complex, respectively. These representations are used only for convenience, however, since the nature of the reagents and their states of aggregation are not clear.[25] Mesylate **20** gave the α-methylated (*E*)-β,γ-enoate **25** as the major product by treatment with $Me_2CuLi{\cdot}BF_3$ (LiI) in THF–Et_2O (10:1 to 10:2) at −78 °C for 30 min (Table I, entry 7).[26] Comparable results were obtained by reaction of the mesylate **44** with Me_2CuLi (LiI) or the higher order cyanocuprate $Me_2Cu(CN)Li_2$ (LiI) (Table I, entry 8 or 9). Thus, the mesyloxy group at the γ-position exerts a powerful directing effect leading to both 1,3-chirality transfer and high diastereoselectivity since the diastereoselection of the α-methylation products **25** and **29** is over 99% judging from GLC, ^1H NMR with the shift regent $Eu(hfc)_3$, and ^{13}C NMR analyses. Although very high diastereoselectivity was realized with the γ-mesyloxy group, the chemical yield of the α-alkylation product obtained was not satisfactory since the undesired reductive elimination product **13** always accompanied as a byproduct (Table I, entries 7–9). We ultimately found that highly improved yields in the chirality-transfer reaction could be obtained without sacrificing high diastereoselectivity. The following three factors are essential to achieve very high 1,3-chirality transfer.

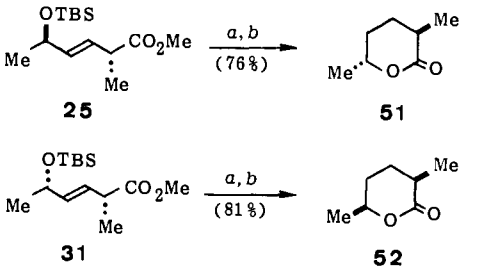
(1) *A γ-mesyloxy or γ-tosyloxy group is essential for clean chirality transfer.* (For the reaction of the tosylates **21**[18] and **45**,[18] see Table I, entries 10–12.)

(2) *THF or a mixed solvent involving THF is the solvent of choice.* In our initial procedure, the ether or *n*-hexane solution of MeLi or BuLi was concentrated to remove as much of the ether or *n*-hexane as possible. Subsequently it was found even if the ether or *n*-hexane were not removed, the chemical and optical yields were unchanged. Consequently, either THF alone or a mixture of THF and ether or *n*-hexane [THF–ether = 10:1 to 10:2 or THF–*n*-hexane = 10:1 to 10:2] could be used equally well. However, reaction in ether alone is too sluggish to be practicable.[27] For example, while the γ-mesyloxy α,β-enoate **20** reacted with $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI) in THF–Et_2O (10:2) at −78 °C after 30 min to afford the 1,3-chirality-transfer product **25** in 97% yield (Table I, entry 13), treatment of the same substrate in ether alone at −78 to −40 °C for 4 h led to complete recovery of unchanged starting material.[28]

Scheme IV



Scheme V[a]



Reagents: (a) H_2/5% $Rh{-}Al_2O_3$; (b) 46% $HF{-}BF_3{\cdot}Et_2O$–MeCN (2:1:97).

(3) *Reagents prepared from CuCN, RLi, and $BF_3{\cdot}Et_2O$ gave satisfactory results.* Reagents formed from CuCN + 2MeLi (LiI) + $BF_3{\cdot}Et_2O$, CuCN + MeLi (LiBr) + $BF_3{\cdot}Et_2O$, or CuCN + RLi + $BF_3{\cdot}Et_2O$ (R = Et, *n*-Pr, *n*-Bu) behave in a satisfactory manner in reaction with the γ-mesyloxy α,β-enoate to yield solely the desired α-alkylation product (Table I, entries 13–36). If the reaction is performed in the absence of $BF_3{\cdot}Et_2O$, a substantial amount of the reductive elimination product is obtained as a byproduct (Table I, entry 9). Although $MeCu(CN)Li{\cdot}BF_3$ (LiBr) and $RCu(CN)Li{\cdot}BF_3$ (R = Et, *n*-Pr, *n*-Bu) could easily be prepared at −78 °C in the usual way,[29] for efficient chirality transfer the complex $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI) should be prepared by a special technique. Thus, an equimolar amount of $BF_3{\cdot}Et_2O$ is added to a solution of $Me_2Cu(CN)Li_2$ (LiI) in THF–Et_2O (ca. 10:2) at −78 °C, and the mixture is allowed to warm to 0 °C over 10–15 min and stirred at this temperature for an additional 10 min and then cooled to −78 °C. This "aging" period is critical to the success of the reaction in the case of $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI) and if omitted, the chirality-transfer product was contaminated with a considerable amount (~10%) of reduction product. Thus, complexation of $Me_2Cu(CN)Li_2{\cdot}$(LiI) with BF_3 seems to be necessary, a phenomenon very recently witnessed by Professor Lipshutz and co-workers.[30]

It has been reported recently that treatment of acyclic (*Z*)-allylic alcohol derivatives[4a] and vinyloxiranes[14i,j] with organocopper reagents led to exclusive or predominant formation of the (*E*)-alkenes. On the other hand, reaction of the *E*-olefinic isomers related to the above substrates under identical conditions led to a mixture of *E*- and *Z*-olefinic isomers.[4a,14i,j] Similarly, treatment of methyl (*E*)-4,5-epoxy-2-hexenoate with methylcopper reagents resulted in a mixture of products.[31] In sharp contrast, as can be seen from Scheme III and Table I, both the (*E*)-α,β-enoates (Table I, entries 10, 11, 13–20, 22, 23, 30, 31, 33–36) and the (*Z*)-α,β-enoates (Table I, entries 21, 24–29, 32) afford the α-alkyl

(24) For effects of inorganic salts or choice of the Cu(I) salt in organocopper reactions, see: (a) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949. (b) Luong-Thi, N. T.; Liviere, H. *Tetrahedron Lett.* **1970**, 1583. (c) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305. (d) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1983**, *48*, 546. (e) Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119. (f) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395. (g) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025, 4029. (h) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273. (i) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251. (j) Lipshutz, B. H.; Ellsworth, E. L.; Behling, J. R.; Campbell, A. L. *Tetrahedron Lett.* **1988**, *29*, 893.

(25) (a) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943. (b) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197. (c) Bertz, S. H.; Dabbagh, G. *J. Am. Chem. Soc.* **1988**, *110*, 3668.

(26) For some recent syntheses of α-alkyl β,γ-enoates, see: (a) Molander, G. A.; LaBell, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259. (b) Majewski, M.; Green, J. R.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 531. (c) Russel, A. T.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2045.

(27) For solvent effects in organocopper reactions, see: (a) Still, W. C.; Macdonald, T. L. *Tetrahedron Lett.* **1976**, 2659. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *J. Org. Chem.* **1977**, *42*, 1099. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (d) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (e) Reference 25a.

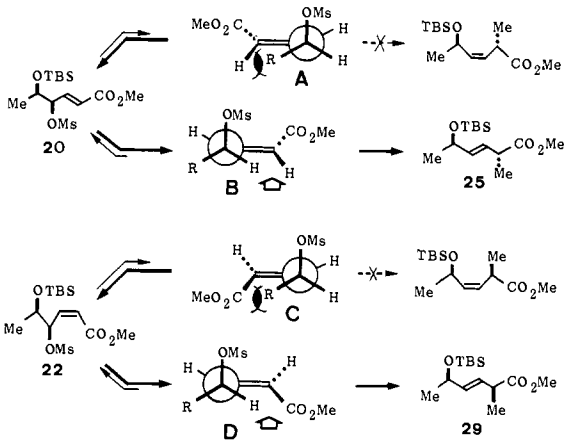
(28) This result is in sharp contrast to the observations of Trost in studies on acyclic allylic alcohol derivatives using RCu(CN)Li in ether alone; see ref, 4a.

(29) (a) Ibuka, T.; Aoyagi, T.; Kitada, K.; Yoneda, F.; Yamamoto, Y. J. *Organomet. Chem.* **1985**, *287*, C18. (b) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (c) For a review on organocopper–Lewis acid reagents, see: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947. (d) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (e) Lipshutz, B. H. *Synthesis* **1987**, 325. (f) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Nguyen, D.; Lipshutz, B. H. *Tetrahedron Lett.* **1988**, *29*, 3045.

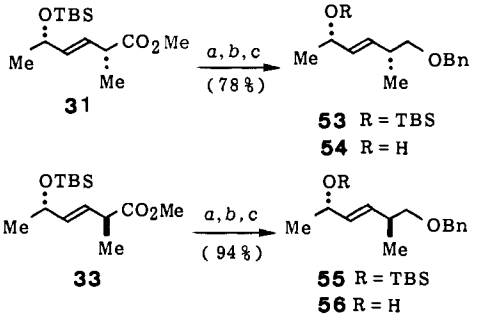
(30) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834.

(31) Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435.

Scheme VI



Scheme VII



Reagents: (a) $LiAlH_4$–Et_2O; (b) NaH–BnBr–DMF; (c) 46% HF–H_2O–MeCN (2:1:97).

(*E*)-β,γ-enoates in very high chemical and optical yields by treatment with alkylcyanocuprate–trifluoroborane reagents under mild conditions as represented in Scheme IV.

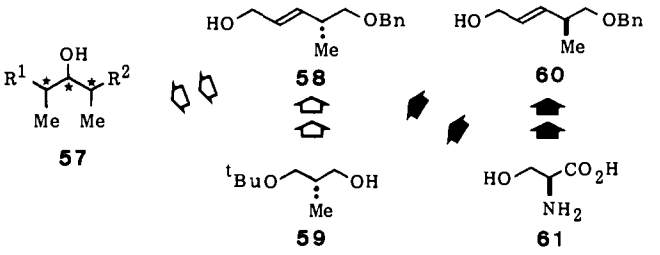
Diastereoselectivities were determined by 200- and/or 400-MHz ^1H NMR with the chiral shift reagent Eu(hfc)$_3$ by monitoring the OCH_3 or CCH_3 signals.[32] While we cannot conclusively rule out the presence of trace quantities of (*Z*)-alkene, the *E* isomer was the only one detected. Thus, the *E* geometry of the products (**25–36**) was easily established from the coupling constant (ca. 15.5 Hz) of the two olefinic protons by ^1H NMR analyses (200 or 400 MHz, $CDCl_3$) using the chiral shift reagent Eu(hfc)$_3$ (Figure 1, supplementary material).

The absolute configuration at the alkylated carbon center was established by conversion of the α-alkyl β,γ-enoate to the corresponding δ-lactone through a two-step sequence of reactions illustrated in Scheme V. For example, the β,γ-enoates **25** and **31** were converted into the known (2*R*,5*R*)-*trans*-2-methyl-5-hexanolide **51**[33] and the corresponding 2*R*,5*S* cis isomer **52**,[33,34] respectively. The latter compound, **52**, is a sex pheromone of the carpenter bee *Xylocopa hirutissima*.[35]

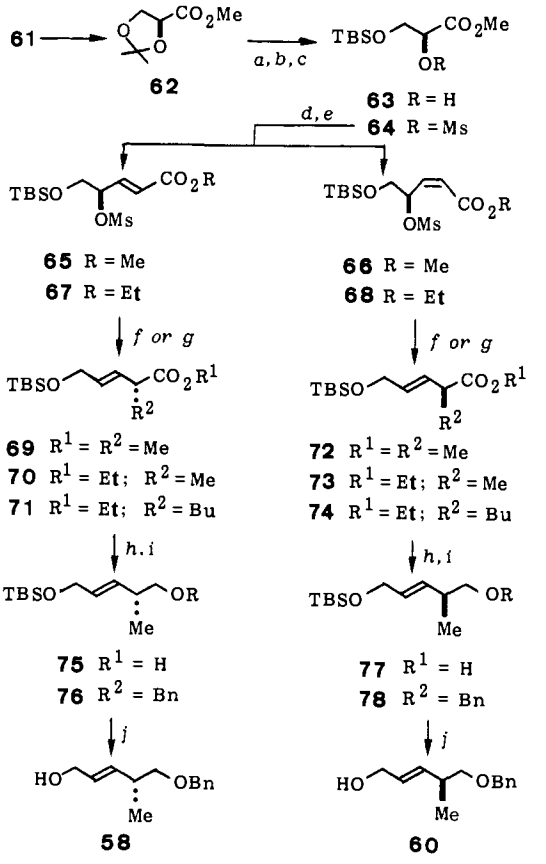
There remains the question of why both the (*E*)- and (*Z*)-α,β-enoates were almost exclusively transformed into the (*E*)-alkenes. This convergent diastereoselection can be explained as follows. Conformers A (*E* series) and C (*Z* series), which would lead to (*Z*)-olefins, are destabilized in comparison with B (*E* series) and D (*Z* series) owing to unfavorable interactions between the bulky R group and the hydrogen or between the R group and the methoxycarbonyl group (Scheme VI). Consequently, the nucleophiles presumably attack anti to the electron-withdrawing mesyloxy group in the conformations B and D.[13e,14,29b,36]

All stereoisomers of α-alkyl (*E*)-β,γ-enoates **25–36** thus obtained from either L- or D-threonine could be transformed into important chiral building blocks. For example, as illustrated in Scheme VII, the β,γ-enoates (**31** and **33**) could be transformed into the chiral allylic alcohols **54** (78% yield from **31**) and **56** (94% yield from **33**) by a three-step sequence of reactions. The allylic alcohols prepared in this way are valuable precursors for further manipulations such as asymmetric epoxidation.[37]

Scheme VIII



Scheme IX[a]



[a] Abbreviations: TBS = *tert*-butyldimethylsilyl; Ms = methylsulfonyl. Reagents: (a) Dowex 50 × 8-MeOH–H_2O (5:50:3); (b) TBSCl–imidazole–DMF; (c) MsCl–pyridine–*p*-DMAP–CH_2Cl_2; (d) DIBAH–CH_2Cl_2; (e) $Ph_3P{=}CHCO_2Et$–CH_2Cl_2, $(i\text{-}PrO)_2P(O)CH_2CO_2Me$–NaH–THF, or $(CF_3CH_2O)_2P(O)CH_2CO_2Me$–KN(TMS)$_2$–THF–18-crown-6; (f) MeCu(CN)Li·BF_3(LiBr); (g) BuCu(CN)Li·BF_3; (h) $LiAlH_4$–Et_2O; (i) BnBr–NaH–DMF; (j) Me_2CO–46% HF (94:4).

(32) For a review on shift reagents, see: Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 173.

(33) (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (c) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 651.

(34) White, D. J.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352.

(35) Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, 4029.

(36) For anti S_N2' reactions, see: (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. (c) Reference 28b.

(37) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Do, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

Table II. Reaction of (*E*)- and (*Z*)-δ-(*tert*-Butyldimethylsiloxy)-γ-[(methylsulfonyl)oxy] α,β-Enoates with $RCu(CN)Li\cdot BF_3$[a]

entry	substrate (geometry)	reagent	product (% yield)	enantioselectivity (absolute config at C-2)[b]
1	**65** (*E*)	$MeCu(CN)Li\cdot BF_3$ (LiBr)[c]	**69** (92)	98:2 (*R*)
2	**67** (*E*)	$MeCu(CN)Li\cdot BF_3$ (LiBr)[c]	**70** (93)	>99:1 (*R*)
3	**67** (*E*)	*n*-$BuCu(CN)Li\cdot BF_3$	**71** (79)	>99:1 (*R*)
4	**66** (*Z*)	$MeCu(CN)Li\cdot BF_3$ (LiBr)[c]	**72** (91)	>99:1 (*S*)
5	**68** (*Z*)	$MeCu(CN)Li\cdot BF_3$ (LiBr)[c]	**73** (95)	>99:1 (*S*)
6	**68** (*Z*)	*n*-$BuCu(CN)Li\cdot BF_3$	**74** (91)	>99:1 (*S*)

[a] All reactions were carried out at least in duplicate at −78 °C for 30 min in a mixture of THF–Et_2O (10:1 to 10:2) except entries 3 and 6 (THF–hexane = 10:1 to 10:2) using 3 molar equiv of reagents. [b] Enantioselectivities were determined by 200- and/or 400-MHz ^1H NMR with $Eu(hfc)_3$. [c] Prepared from a 1.5 M MeLi–LiBr ethereal solution.

Table III. Reaction of Polyoxygenated α,β-Enoates with Organocopper Reagents[a]

entry	substrate	leaving group at C-4	reagent	product (% isolated yield) reduction	γ-alkylation	α-alkylation	diastereoselectivity (abs configuration)[b]
1	**81**	OAc	$Me_2CuLi\cdot BF_3(LiI)$[c]	**82** (74)			
2	**83**	OMs	$Me_2CuLi(LiI)$[c]	**84** (15)		**85** (68)	95:5 (*S*)
3	**83**	OMs	$Me_2Cu(CN)Li_2\cdot BF_3(LiI)$[c]			**85** (98)	96:4 (*S*)
4	**83**	OMs	*n*-$PrCu(CN)Li\cdot BF_3$[d]			**86** (93)	98:2 (*S*)
5	**83**	OMs	*n*-Bu_2CuLi[d]		**88** (23)	**87** (70)	98:2 (*S*)
6	**83**	OMs	*n*-$Bu_2CuLi\cdot 2BF_3$[d]		**88** (19)	**87** (71)	98:2 (*S*)
7	**83**	OMs	*n*-$Bu_2Cu(CN)Li_2\cdot BF_3$[d]			**87** (94)	>99:1 (*S*)
8	**83**	OMs	*n*-$BuCu(CN)Li\cdot BF_3$[d]			**87** (98)	>99:1 (*S*)
9	**94**	OMs	$MeCu(CN)Li\cdot BF_3(LiBr)$[c]			**95** (96)	>99:1 (*S*)
10	**94**	OMs	*n*-$BuCu(CN)Li\cdot BF_3$[d]			**96** (94)	>99:1 (*S*)

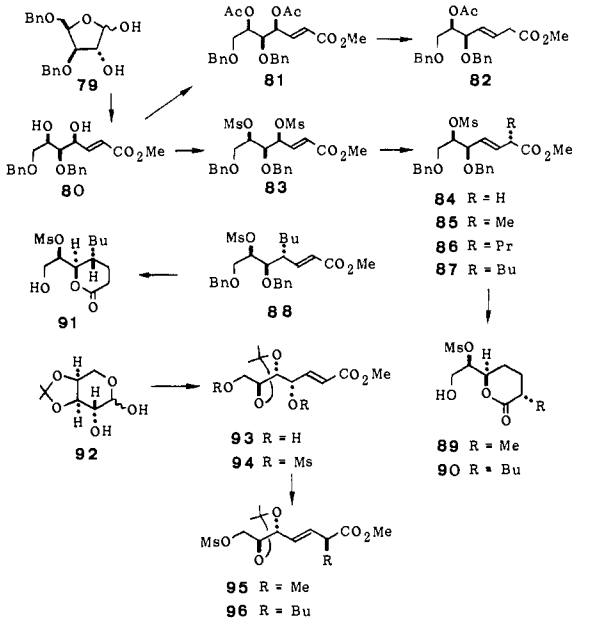
[a] All reactions were carried out at −78 °C for 30 min using 3 molar equiv of reagents. [b] Diastereoselectivities were determined by ^1H NMR (200 and/or 400 MHz). [c] Reactions were carried out in a mixture of THF–Et_2O (ca. 10:2). [d] Reactions were carried out in a mixture of THF–hexane (ca. 10:2).

Synthesis of Chiral Building from L-Serine via the $RCu(CN)\cdot Li\cdot BF_3$-Mediated 1,3-Chirality Transfer. The structural unit **57** with three chiral centers is found in biologically important natural products (Scheme VIII). All possible diastereoisomers of **57** are known as partial structures of antibiotics.[38] A wide variety of methods has been developed to provide **57** in a diastereoisomerically pure form.

In Kishi's synthetic studies on rifamycin S, the asymmetric epoxidation of **58**, which was prepared from chiral alcohol **59**, and subsequent regio- and stereospecific epoxide opening by the Gilman reagent was used to produce the requisite system **57**.[39] Subsequently we expanded the 1,3-chirality-transfer methodology to the synthesis of allylic alcohols **58** and **60** from L-serine (**61**).

The requisite (*E*)-enoates (**65** and **67**) and their *Z* isomers (**66** and **68**) were readily prepared from known (*S*)-2,2-dimethyl-4-(methoxycarbonyl)-1,3-dioxolane (**62**)[40] in five steps according to the usual methods as shown in Scheme IX (see the supplementary material). Reaction of the γ-mesyloxy (*E*)-α,β-enoates (**65** and **67**) and their *Z* isomers (**66** and **68**) with $RCu(CN)Li\cdot BF_3$ (R = Me or Bu) at −78 °C for 30 min furnished (*R*)-α-alkyl β,γ-enoates (**69–71**) and the corresponding *S* isomers (**72–74**), respectively, in satisfactory chemical and optical yields after flash chromatography (Table II). ^1H NMR analysis using the chiral shift reagent $Eu(hfc)_3$ noted above revealed that the geometry of the β,γ-double bond of the products (**69–74**) is *E* and the enantioselectivity is in the range of 98:2 to >99:1. Successive treatment of the α-methyl β,γ-enoates **70** and **73** with lithium aluminum hydride in ether, benzyl bromide–sodium hydride in DMF, and 46% hydrogen fluoride–acetone (4:96) gave the synthetically useful allylic alcohols **58**[39] [76% from **70**, $[\alpha]_D$ +9.57° ($CHCl_3$)] and **60** [86% from **73**, $[\alpha]_D$ −10.1° ($CHCl_3$)], respectively. It has been reported[39] by Professor Kishi that the optical purity of allylic alcohol **58** could not be determined by NMR with either chiral shift reagents or the MTPA method. In the present case, allylic alcohols **58** and **60** are expected to be essentially optically pure since epimerization at the chiral center could not occur during the transformation processes.

Scheme X



Synthesis of Polyfunctional α-Allyl β,γ-Enoates Starting from Pentoses. Chirality transfer involving polyoxygenated α,β-enoates with organocopper reagents was next attempted to see if the presence of other oxygenated functional groups in any way interfered with the selectivity (Scheme X and Table III).

As before, the γ-acetoxy α,β-enoate **81**, derived from D-xylose dibenzyl ether **79** via the known γ,ε-dihydroxy α,β-enoate **80**,[41] gave a mixture of products by treatment with $Me_2CuLi\cdot BF_3$ (LiI). The only compound isolated from the reaction mixture was the reductive elimination product **82** (Table III, entry 1). No evidence

(38) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (b) Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442 and references cited.

(39) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3888 and references cited.

(40) Lok, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115. (b) Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863. (c) Tanner, D.; Somfai, P. *Synth. Commun.* **1986**, *16*, 1517.

(41) Matsuda, F.; Terashima, S. *Tetrahedron* **1988**, *44*, 4721.

for any methylated products was obtained. On the other hand, treatment of mesylate **83**, derived from **80**, with Me_2CuLi (LiI) furnished a mixture of the desired α-methylated product **85** (68% yield) and the unwanted reduction product **84** (15% yield) (Table III, entry 2). Likewise, treatment of mesylate **83** with either Bu_2CuLi or $Bu_2CuLi{\cdot}2BF_3$ yielded the α-butylated product **87** along a small amount of the γ-butylated product **88** (Table III, entries 5 and 6). The stereochemistries of the alkylated products **85**, **87**, and **88** were determined as depicted in Scheme X by ^1H NMR analyses of the lactones **89–91** derived from **85**, **87**, and **88** by a two-step sequence of reactions (i. H_2/10% Pd–C in MeOH; ii. $BF_3{\cdot}Et_2O$ in MeCN). It is apparent from these data that classical Gilman type reagents or their $BF_3{\cdot}Et_2O$ complexes and the γ-acetoxy leaving group are inappropriate for clean and efficient chirality transfer. On the other hand, as described before, 1,3-chirality transfer involving dimesylate **83** with $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI), *n*-PrCu(CN)Li·BF_3, and *n*-BuCu(CN)Li·BF_3 proceeded cleanly to yield the desired alkylation products **85–87** in high chemical and optical yields (Table III, entries 3, 4, 8). The presence of the mesyloxy group at the ϵ-position in **83** does not exert a significant influence upon the course of the 1,3-chirality-transfer reaction. Similarly, dimesylate **94**, prepared from L-arabinose monoacetonide **92**[42] via the dihydroxy α,β-enoate **93**, furnished alkylation products **95** and **96** by treatment with MeCu(CN)Li·BF_3 (LiBr) and *n*-BuCu(CN)Li·BF_3, respectively. Clearly, only the γ-mesyloxy group in **94** is involved in the reaction (Table III, entries 9 and 10). Thus, organocyanocuprate–trifluoroborane reagents differentiate the two mesyloxy groups of **83** and **94** and this high chemoselectivity allows for the selective synthesis of chiral materials such as **85–87**, **95**, and **96**.

Conclusion

We have demonstrated that reactions of a variety of both (*E*)- and (*Z*)-γ-mesyloxy α,β-enoates with organocyanocopper–trifluoroborane reagents provide a highly efficient route to synthetically useful chiral (*E*)-α-alkyl β,γ-enoates. THF or mixed solvents containing THF along with percentages of ether and/or *n*-hexane are highly preferred solvents over those rich in Et_2O as clean reactions occur in this media at −78 °C within a short period of time. The (*E*)-α-alkyl β,γ-enoates thus obtained provide easy access to chiral allylic alcohols that have great promise as intermediates for the synthesis of natural products. Finally, this chirality-transfer strategy may be applied to the synthesis of potentially useful isosteres.

Experimental Section

General Methods. Ethereal MeLi (as complexed with LiI or LiBr) was purchased from Aldrich. EtLi and *n*-PrLi were prepared by reaction of EtBr and *n*-PrBr with metallic Li in the usual way. *n*-BuLi was purchased from Nacalai Chemicals. CuI was purchased from Mitsuwa chemicals and purified by a published method.[43] CuCN was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at 50 °C.

General Procedure for Reductive Elimination of γ-Acetoxy- and γ-Benzoyloxy (*E*)-α,β-Enoates with Organocopper or Organocopper–Trifluoroborane Reagents.

Methyl (*E*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-3-hexenoate (13) from Methyl (*E*,5*R*,4*S*)-4-Acetoxy-5-(*tert*-butyldimethylsiloxy)-2-hexenoate (12) by Treatment with Me_2CuLi (LiI) (Table I, Entry 4). The following procedure is representative for all reductive elimination reactions. To a stirred slurry of CuI (285 mg, 1.5 mmol) in 10 mL of dry THF at 0 °C was added by syringe 2.5 mL (3 mmol) of 1.2 M MeLi–LiI in ether and the mixture was stirred at 0 °C for 10 min. A solution of γ-acetoxy α,β-enoate **12** (158 mg, 0.5 mmol) in dry THF (2.5 mL) was added dropwise to the above reagent at −78 °C with stirring. Stirring was continued for 30 min followed by quenching with 3 mL of a 2:1 saturated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products. The mixture was purified by flash chromatography over silica gel with *n*-pentane–AcOMe (50:1) to give 98 mg (76% yield) of the reductive elimination product **13** as a colorless oil. **13**: Kugelrohr distillation, 80 °C (1 mmHg); $[\alpha]^{26}_D$ −2.19° (*c* 0.548, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2870, 1730, 1472, 1464, 1440, 1362, 1254, 1168, 1080, 997, 972, 943, 835 cm^{-1}; ^1H NMR (200 MHz) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.21 (d, J = 6.35 Hz, 3 H), 3.05 (m, 2 H), 3.68 (s, 3 H), 4.30 (m, 1 H), 5.53–5.75 (m, 2 H); nominal mass spectrum, m/z 258 (M^+), 243, 201, 173, 159, 89 (base peak), 75; exact mass spectrum, m/z calcd for $C_{13}H_{26}O_3Si$ 258.1652, found 258.1666. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.16; H, 10.41.

Reaction of (*E*)- and (*Z*)-γ-Mesyloxy α,β-Enoates with Organocopper or Organocopper–Trifluoroborane Reagents. General Procedure Using $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiI). Methyl (*E*,2*R*,5*R*)-2-Methyl-5-(*tert*-butyldimethylsiloxy)-3-hexenoate (25) from 20 (Table I, Entry 13). To a stirred slurry of CuCN (136 mg, 1.2 mmol) in 14 mL of dry THF at −78 °C was added by syringe 4 mL (2.4 mmol) of 0.76 M MeLi–LiI in ether, and the mixture was allowed to warm to 0 °C and stirring was continued at 0 °C for 10 min. $BF_3{\cdot}Et_2O$ (0.18 mL, 1.2 mmol) was added to the above mixture at −78 °C and the mixture was allowed to warm to 0 °C and to stir at this temperature for an additional 10 min. The reagent thus prepared was cooled to −78 °C, where a solution of mesylate **20** (176 mg, 0.4 mmol) in dry THF (6 mL) was added with stirring. Stirring was continued for 30 min at −78 °C folllowed by quenching with 3 mL of a 2:1 saturated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure yielded an oily residue, which was purified by flash chromatography over silica gel. Elution with *n*-hexane–EtOAc (10:1) gave **25** (106 mg, 97% yield) as a colorless oil. **25**: Kugelrohr distillation, 90 °C (1 mmHg); $[\alpha]^{26}_D$ −30.01° (*c* 0.559, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2880, 1728, 1463, 1437, 1374, 1364, 1254, 1171, 1084, 1057, 994, 970, 914, 837 cm^{-1}; ^1H NMR (200 or 400 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.20 (d, J = 6.35 Hz, 3 H), 1.25 (d, J = 7.08 Hz, 3 H), 3.13 (m, 1 H), 3.67 (s, 3 H), 4.26 (m, 1 H), 5.50–5.72 (m, 2 H); diastereoselection, >99:1, $Eu(hfc)_3$; ^{13}C NMR (100 MHz) δ −4.73, −4.53, 17.03, 18.30, 24.42, 25.92, 42.21, 51.70, 69.02, 127.56, 136.23, 175.02. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.87; H, 10.54.

General Procedure Using MeCu(CN)Li·BF_3 (LiBr). Methyl (*E*,5*R*,2*S*)-2-Methyl-5-(*tert*-butyldimethylsiloxy)-3-hexenoate (29) from 22 (Table I, Entry 21). To a stirred slurry of CuCN (54 mg, 0.6 mmol) in 2 mL of dry THF at −78 °C was added by syringe 0.4 mL (0.6 mmol) of 1.5 M MeLi–LiBr in ether and the mixture was allowed to warm to −20 °C and to stir at this temperature for 10 min. $BF_3{\cdot}Et_2O$ (0.074 mL, 0.6 mmol) was added to the above mixture at −78 °C and the mixture was stirred for 5 min. A solution of α,β-enoate **22** (70.4 mg, 0.2 mmol) in dry THF (1 mL) was added dropwise to the above reagent at −78 °C with stirring. Stirring was continued for 30 min followed by quenching with 3 mL of a 2:1 saturated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure yielded an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1). Kugelrohr distillation (85 °C/1 mmHg) gave **29** (52 mg, 93% yield) as a colorless oil of better than 99% optical purity [^1H NMR (200 MHz), $Eu(hfc)_3$]. **29**: $[\alpha]^{24}_D$ +31.30° (*c* 0.973, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1730, 1466, 1437, 1374, 1364, 1254, 1168, 1097, 974, 840 cm^{-1}; ^1H NMR (200 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.20 (d, J = 6.35 Hz, 3 H), 1.26 (d, J = 7.08 Hz, 3 H), 3.12 (m, 1 H), 3.67 (s, 3 H), 4.28 (m, 1 H), 5.54 (dd, J = 15.36, 4.64 Hz, 1 H), 5.67 (m, 1 H); ^{13}C NMR (100 MHz) δ −4.74, −4.52, 17.27, 18.29, 24.42, 25.90, 42.31, 51.68, 69.02, 127.59, 136.22, 175.06. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.79; H, 10.59.

General Procedure Using RCu(CN)Li·BF_3 (R = Et, *n*-Pr, *n*-Bu). The following procedure is representative for all reactions of (*E*)- and (*Z*)-γ-mesyloxy α,β-enoates with EtCu(CN)Li·BF_3, *n*-PrCu(CN)Li·BF_3, and *n*-BuCu(CN)Li·BF_3.

Methyl (*E*,2*R*,5*R*)-2-Propyl-5-(*tert*-butyldimethylsiloxy)-3-hexenoate (27) from 20 (Table I, Entry 18). To a stirred slurry of CuCN (61 mg, 0.68 mmol) in 3 mL of dry THF at −78 °C was added by syringe 0.38 mL (0.68 mmol) of a 1.8 M solution of PrLi in *n*-hexane and stirring was continued for 10 min. $BF_3{\cdot}Et_2O$ (0.082 mL, 0.68 mmol) was added to the above mixture at −78 °C and stirring was continued for 5 min. A solution of **20** (80 mg, 0.227 mmol) in THF (0.8 mL) was added dropwise to the above reagent at −78 °C and the stirring was continued for 30 min. A mixture of saturated NH_4Cl (2 mL) and 28% NH_4OH (1 mL) was added to the above mixture at −78 °C, and the mixture was allowed to warm to ambient temperature and the stirring was continued for 30 min. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried

(42) For a synthesis of D-3,4-*O*-isopropylidenearabinose, see: (a) Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1976**, *52*, 95. (b) Schmidt, R. R.; Haier, M. *Synthesis* **1982**, 747.

(43) Kauffmann, G. B.; Tetter, L. A. *Inorg. Synth.* **1963**, *7*, 9.

over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (20:1 to 10:1) to give **27** (66 mg, 97% yield) as a colorless oil. **27**: diastereoselective, >99:1, $Eu(hfc)_3$; Kugelrohr distillation, 140 °C (1 mmHg); $[\alpha]^{23}_D$ −42.77° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2870, 1729, 1464, 1437, 1373, 1363, 1254, 1165, 1087, 1074, 995, 971, 837 cm^{-1}; ^1H NMR (200 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 0.90 (t, *J* = 7.08 Hz, 3 H), 1.20 (d, *J* = 6.35 Hz, 3 H), 2.99 (m, 1 H), 3.66 (s, 3 H), 4.26 (m, 1 H), 5.53–5.63 (m, 2 H). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.92; H, 10.89.

Methyl (*E*,2*R*,5*R*)-2-Propyl-5-(*tert*-butyldimethylsiloxy)-3-hexenoate (27) from (*Z*)-Enoate (43) (Table I, Entry 28). By a procedure identical with that described for the preparation of **27** from (*E*)-α,β-enoate **20**, 80 mg (0.227 mmol) of (*Z*)-enoate **43** was converted into 64 mg (94% yield) of **27** by treatment with $PrCu(CN)Li\cdot BF_3$ (0.68 mmol) at −78 °C for 30 min. **27**: a colorless oil; Kugelrohr distillation, 140 °C (1 mmHg); diastereoselection, >99:1, $Eu(hfc)_3$; $[\alpha]^{23}_D$ −43.17° (*c* 0.63, $CHCl_3$). The IR ($CHCl_3$) and ^1H NMR (200 MHz, $CDCl_3$) were identical with those of **27** which was prepared from (*E*)-α,β-enoate **20**. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.15; H, 10.86.

(2*R*,5*R*)-*trans*-2-Methyl-5-hexanolide (51). A mixture of **25** (50 mg, 0.184 mmol), 5% Rh–Al_2O_3 (5 mg), and MeOH (2 mL) was subjected to catalytic hydrogenation at atmospheric pressure for 30 min. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to leave an oily residue (50 mg), which, without purification, was used for the next step. To a solution of the above oil (50 mg) in MeCN (2.43 mL) were added $BF_3\cdot Et_2O$ (0.05 mL) and 46% HF (0.05 mL), and the mixture was stirred at 0 °C for 2 h. The mixture was made basic with a 5% $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$ and concentrated under reduced pressure to leave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to yield a crystalline residue. Recrystallization from cold *n*-pentane gave **51** (18 mg, 76% yield) as colorless crystals. **51**: mp 50 °C (lit.[32a] mp 49–50 °C); $[\alpha]^{21}_D$ +50.1° (*c* 0.47, $CHCl_3$) [lit.[32a] $[\alpha]^{23}_D$ +54.9° ($CHCl_3$)]; IR ($CHCl_3$) 2980, 2950, 2880, 1723, 1463, 1386, 1364, 1332, 1188, 1139, 1099, 1030, 1010, 971, 939 cm^{-1}; ^1H NMR (400 MHz) δ 1.30 (d, *J* = 7.32 Hz, 3 H), 1.37 (d, *J* = 6.35 Hz, 3 H), 1.51–1.64 (m, 2 H), 1.89–2.07 (m, 2 H), 2.39–2.48 (m, 1 H), 4.40–4.48 (m, 1 H); exact mass spectrum, *m*/*z* calcd for $C_7H_{12}O_2$ 128.0836, found 128.0838.

(*E*,2*R*,5*S*)-1-(Benzyloxy)-2-methyl-5-(*tert*-butyldimethylsiloxy)-3-hexene (53). To a stirred suspension of $LiAlH_4$ (95 mg, 2.5 mmol) in dry Et_2O (15 mL) at 0 °C was added a solution of ester **31** (170 mg, 0.625 mmol) in 5 mL of dry Et_2O. The mixture was heated under reflux for 15 min. The excess reagent was decomposed with wet Et_2O. The inorganic precipitates were removed by filtration through Celite. The usual workup of the filtrate led to a colorless oil (150 mg, 98% yield), which was used without further purification for the next step. To a stirred suspension of NaH (29.5 mg, 1.23 mmol) in dry DMF (3 mL) was added a solution of the above oil in 2 mL of dry DMF at 0 °C. Benzyl bromide (0.3 mL) was added to the above mixture and the mixture was stirred for 5 h at ambient temperature. The mixture was poured into ice–water and extracted with ether. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) gave benzyl ether **53** (170 mg, 81% yield) as a colorless oil. **53**: $[\alpha]^{29}_D$ −2.6° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2870, 1473, 1465, 1456, 1375, 1364, 1255, 1150, 1128, 1090, 995, 971, 941, 905, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.042 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.03 (d, *J* = 6.83 Hz, 3 H), 1.20 (d, *J* = 6.35 Hz, 3 H), 2.46 (m, 1 H), 3.33 (m, 2 H), 4.26 (m, 1 H), 4.50 (s, 2 H), 5.49–5.52 (m, 2 H), 7.22–7.35 (m, 5 H). Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.90; H, 10.46.

(*E*,2*R*,5*S*)-1-(Benzyloxy)-5-hydroxy-2-methyl-3-hexene (54). A mixture of silyl ether **53** (40 mg, 0.12 mmol), MeCN (0.96 mL), and 46% HF (0.04 mL) was stirred at 0 °C for 15 min. The mixture was made alkaline with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give allylic alcohol **54** (25.6 mg, 97% yield) as a colorless oil. **54**: $[\alpha]^{20}_D$ +4.11° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3600, 3400, 2970, 2930, 2870, 1452, 1365, 1086, 1072, 1030, 971 cm^{-1}; ^1H NMR (200 MHz) δ 1.04 (d, *J* = 6.59 Hz, 3 H), 1.26 (d, *J* = 6.35 Hz, 3 H), 1.53 (s, 1 H), 2.49 (m, 1 H), 3.33 (m, 1 H), 4.27 (m, 2 H), 4.51 (s, 2 H), 5.59 (m, 2 H), 7.24–7.40 (m, 5 H); nominal mass spectrum, *m*/*z* 220 (M^+), 202, 91 (base peak), 82; exact mass spectrum, *m*/*z* calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1460.

(*E*,2*R*)-2-Methyl-5-(*tert*-butyldimethylsiloxy)pent-3-en-1-ol (75) and Its *E*,2*S* Isomer (77). (i) To a stirred suspension of $LiAlH_4$ (62 mg, 1.62 mmol) in 15 mL of dry Et_2O was added a solution of ester **70** (220 mg, 0.81 mmol) in 5 mL of dry Et_2O. The mixture was stirred at 0 °C for 2 h. The excess reagent was decomposed with wet Et_2O, and the inorganic salts were removed by filtration through Celite. The organic layer was washed with water and dried over $MgSO_4$ and concentrated under reduced pressure to leave an oily residue. The crude product was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1). Kugelrohr distillation (120 °C/1 mmHg) gave 170 mg (91% yield) of alcohol **75** as a colorless oil. **75**: $[\alpha]^{22}_D$ +20.8° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 3590, 3420, 1473, 1465, 1393, 1382, 1364, 1255, 1127, 1092, 1070, 1029, 974, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 1.02 (d, *J* = 6.84 Hz, 3 H), 2.38 (m, 1 H), 3.46 (m, 2 H), 4.16 (m, 2 H), 5.46–5.73 (m, 2 H). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.72; H, 11.50. (ii) By a procedure identical with that described for the preparation of **75**, 200 mg (0.0775 mmol) of ester **72** were reduced with $LiAlH_4$ (118 mg, 3.1 mmol) at 0 °C to yield 176 mg (98% yield) of alcohol **77** as a colorless oil (Kugelrohr distillation, 120 °C/1 mmHg). **77**: $[\alpha]^{20}_D$ −19.56° (*c* 0.838, $CHCl_3$). The IR ($CHCl_3$) and ^1H NMR (200 MHz, $CDCl_3$) were identical with those of **75**. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.71; H, 11.18.

(*E*,2*R*)-1-(Benzyloxy)-2-methyl-5-(*tert*-butyldimethylsiloxy)-3-pentene (76). To a stirred suspension of NaH (73 mg, 3 mmol) in DMF (4 mL) at 0 °C was added 140 mg (0.6 mmol) of alcohol **75** in DMF (4 mL), and the mixture was stirred for 10 min. Benzyl bromide (0.35 mL, 3 mmol) was added to the above mixture, which was stirred for 5 h at ambient temperature. The mixture was then poured into ice–water and extracted with ether. The extract was washed with water and dried over $MgSO_4$ and concentrated under reduced pressure to leave a colorless oil. The oil in *n*-hexane–EtOAc (5:1) was chromatography on a silica gel column and the column was eluted with *n*-hexane–EtOAc (5:1) to give an oil. The oil was Kugelrohr distilled (150 °C/1 mmHg) to give benzyl ether **76** (180 mg, 92% yield) as a colorless oil. **76**: $[\alpha]^{20}_D$ +2.68° (*c* 0.823, $CHCl_3$); IR ($CHCl_3$) 1497, 1466, 1456, 1363, 1255, 1094, 974, 839 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 1.04 (d, *J* = 6.83 Hz, 3 H), 2.51 (m, 1 H), 3.32 (m, 2 H), 4.14 (m, 2 H), 4.51 (s, 2 H), 5.51–5.70 (m, 2 H), 7.25–7.35 (m, 5 H). Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.33; H, 10.28.

(*E*,4*R*)-5-(Benzloxy)-4-methyl-2-penten-1-ol (58). To a stirred solution of silyl ether **76** (100 mg, 0.31 mmol) in 2.88 mL of acetone at 0 °C was added 0.12 mL of 46% HF and the mixture was stirred for 1 h. The mixture was made alkaline with a 5% $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil which was purified by flash chromatography (silica gel, *n*-hexane–EtOAc = 3:1) to give 58 mg (91% yield) of **58** as a colorless oil; Kugelrohr distillation, 160 °C (1 mmHg); $[\alpha]^{20}_D$ +9.57° (*c* 0.71, $CHCl_3$) [lit.[38] $[\alpha]_D$ +9.90° ($CHCl_3$)]; IR ($CHCl_3$) 3600, 3500, 1497, 1454, 1361, 1091, 1075, 1030, 998, 972 cm^{-1}; ^1H NMR (200 MHz) δ 1.04 (d, *J* = 6.84 Hz, 3 H), 1.55 (s, 1 H), 2.52 (m, 1 H), 3.34 (m, 2 H), 4.08 (m, 2 H), 4.51 (s, 2 H), 5.58–5.77 (m, 2 H), 7.16–7.41 (m, 5 H); exact mass spectrum, *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1298.

Methyl (*E*,5*R*,6*R*)-6-Acetoxy-5,7-bis(benzyloxy)-3-heptenoate (82). To a stirred slurry of CuI (85.5 mg, 0.45 mmol) in 4.5 mL of dry THF in an argon atmosphere was added by syringe 1.286 mL of 0.7 M MeLi–LiI in ether at 0 °C and the stirring was continued for 10 min. $BF_3\cdot Et_2O$ (0.056 mL) was added to the above solution at 0 °C and stirring was continued for 5 min. A solution of **81** (70.5 mg, 0.15 mmol) in 2 mL of dry THF was added to the above reagent at −78 °C and stirring was continued for 30 min. The usual workup led to a colorless oil which was flash chromatographed over silica gel. Elution with *n*-hexane–EtOAc (4:1) gave 45 mg (74% yield) of **82** as a colorless oil; IR ($CHCl_3$) 3040, 2980, 2900, 1734, 1501, 1457, 1442, 1377, 1171, 1056, 1031, 977 cm^{-1}; ^1H NMR (200 MHz) δ 2.08 (s, 3 H), 3.10 (m, 2 H), 3.60 (s, 3 H), 4.08 (dd, *J* = 7.32, 5.86 Hz, 1 H), 4.34–4.66 (m, 4 H), 5.13 (m, 1 H), 5.49 (m, 1 H), 5.85 (m, 1 H), 7.23–7.36 (m, 10 H); nominal mass spectrum, *m*/*z* 412 (M^+), 353, 321, 304, 261, 244, 219, 215, 202, 155, 129, 91 (base peak), 65; exact mass spectrum, *m*/*z* calcd for $C_{24}H_{28}O_6$ 412.1886, found 412.1887.

Methyl (*E*,5*R*,6*R*)-5,7-Bis(benzyloxy)-6-[(methylsulfonyl)oxy]-3-heptenoate (84) and Methyl (*E*,5*R*,6*R*,2*S*)-5,7-Bis(benzyloxy)-6-[(methylsulfonyl)oxy]-2-methyl-3-heptenoate (85). To a stirred slurry of CuCN (62 mg, 0.32 mmol) in 3 mL of dry THF in an argon atmosphere was added by syringe 0.51 mL (0.64 mmol) of 1.26 M MeLi–LiI in ether at 0 °C and the mixture was stirred for 10 min. A solution of **83** (54 mg, 0.1 mmol) in 2 mL of dry THF was added to the above reagent at −78 °C and the stirring was continued for 30 min. A mixture of saturated NH_4Cl (2 mL) and 28% NH_4OH (2 mL) was added to the above mixture at −78 °C and the mixture was allowed to warm to room temperature. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried

over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel. Elution with *n*-hexane–EtOAc (4:1) gave 37 mg (68% yield) of **85** and further elution gave 7 mg (15% yield) of **84**. **85**: a colorless oil; IR ($CHCl_3$) 2980, 2890, 1730, 1498, 1455, 1437, 1356, 1177, 1117, 1031, 975, 927 cm^{-1}; ^1H NMR (200 MHz) δ 1.26 (d, J = 7.08 Hz, 3 H), 2.96 (s, 3 H), 3.21 (m, 1 H), 3.68 (s, 3 H), 4.11 (m, 1 H), 4.33–4.64 (m, 6 H), 4.72 (m, 1 H), 5.50 (ddd, J = 15.62, 7.57, 0.98 Hz, 1 H), 5.93 (ddd, J = 15.62, 7.81, 0.98 Hz, 1 H), 7.21–7.38 (m, 10 H); diastereoselection, >95:5; nominal mass spectrum, m/z 462 (M^+), 371, 354, 275, 265, 233, 216, 181, 169, 141, 105, 91 (base peak), 81, 79; exact mass spectrum, m/z calcd for $C_{24}H_{30}O_7S$ 462, 1711, found 462.1701. **84**: a colorless oil; IR ($CHCl_3$) 3080, 3040, 2880, 1735, 1455, 1437, 1354, 1175, 1111, 974, 916 cm^{-1}; ^1H NMR (200 MHz) δ 2.96 (s, 3 H), 3.12 (dd, J = 6.59, 1.22 Hz, 2 H), 3.70 (s, 3 H), 4.13 (t, J = 6.83 Hz, 1 H), 4.34–4.66 (m, 4 H), 4.74 (m, 1 H), 5.51 (ddt, 15.62, 7.57, 1.47 Hz, 1 H), 5.94 (m, 1 H), 7.23–7.38 (m, 10 H); nominal mass spectrum, m/z 448 (M^+), 413, 357, 352, 340, 309, 261, 251, 219, 202, 181, 155, 107, 105, 91 (base peak), 81, 79; exact mass spectrum, m/z calcd for $C_{23}H_{28}O_7S$ 448.1555, found 448.1567.

Methyl (*E*,5*R*,6*R*,2*S*)-2-Butyl-5,7-bis(benzyloxy)-6-[(methylsulfonyl)oxy]-3-heptenoate (87) and Methyl (*E*,4*R*,5*R*,6*R*)-4-Butyl-5,7-bis(benzyloxy)-6-[(methylsulfonyl)oxy]-2-heptenoate (88). To a stirred slurry of CuI (122 mg, 0.64 mmol) in 4 mL of dry THF at −78 °C in an argon atmosphere was added by syringe 0.85 mL (1.28 mmol) of a 1.5 M solution of *n*-BuLi in *n*-hexane and the mixture was stirred for 20 min. A solution of **83** (173 mg, 0.32 mmol) in 2 mL of dry THF was added dropwise to the above reagent at −78 °C and the stirring was continued for 30 min. A mixture of NH_4Cl (2 mL) and 28% NH_4OH (2 mL) was added at −78 °C and the mixture was allowed to warm to room temperature. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was flash chromatography over silica gel. Elution with *n*-hexane–EtOAc (4:1) gave 112 mg (70% yield) of **87** and further elution gave 37 mg (23% yield) of **88**. **87**: a colorless syrup; diastereoselection, >98:2; IR ($CHCl_3$) 3050, 2960, 2880, 1730, 1498, 1457, 1438, 1356, 1174, 1105, 1029, 972, 905 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (tripletoid m, 3 H), 2.96 (s, 3 H), 3.06 (m, 1 H), 3.68 (s, 3 H), 4.11 (m, 1 H), 4.33–4.63 (m, 4 H), 4.73 (m, 1 H), 5.49 (ddd, J = 15.62, 7.56, 0.73 Hz, 1 H), 5.84 (ddd, J = 15.62, 8.79, 0.73 Hz, 1 H), 7.26–7.38 (m, 10 H); nominal mass spectrum, m/z 504 (M^+), 413, 396, 317, 307, 302, 275, 258, 211, 183, 130, 91 (base peak). **88**: a colorless syrup; diastereoselection, >99:1; IR ($CHCl_3$) 2960, 2890, 1719, 1660, 1501, 1456, 1441, 1359, 1174, 1094, 973, 924 cm^{-1}; ^1H NMR (200 MHz) δ 0.85 (tripletoide m, 3 H), 2.89 (s, 3 H), 3.73 (s, 3 H), 4.41–4.75 (m, 4 H), 5.69 (d, J = 15.87 Hz, 1 H), 6.91 (dd, J = 15.87, 10.25 Hz, 1 H), 7.20–7.45 (m, 10 H); nominal mass spectrum, m/z 504 (M^+), 472, 413, 381, 317, 275, 246, 211, 181, 155, 105, 91 (base peak); exact mass spectrum, m/z calcd for $C_{27}H_{36}O_7S$ 504.2179, found 504.2175.

Methyl (*E*,5*R*,6*R*,2*S*)-2-Butyl-5,7-bis(benzyloxy)-6-[(methylsulfonyl)oxy]-3-heptenoate (87). To a stirred slurry of CuCN (54 mg, 0.6 mmol) in 5 mL of dry THF at −78 °C in an argon atmosphere was added dropwise by syringe 0.75 mL (1.2 mmol) of 1.6 M *n*-BuLi in *n*-hexane and the stirring was continued for 20 min. $BF_3{\cdot}Et_2O$ (0.074 mL, 0.6 mmol) was added to the above solution at −78 °C and the mixture was stirred for 5 min. A solution of **83** (108 mg, 0.2 mmol) in dry THF (3 mL) was added to the above reagent at −78 °C with stirring and the stirring was continued for 30 min. A mixture of saturated NH_4Cl (1 mL) and 28% NH_4OH (1 mL) was added to the above reaction mixture at −78 °C and the mixture was allowed to warm to room temperature and the stirring was continued for 30 min. The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue which was purified by flash chromatography over silica gel. Elution with *n*-hexane–EtOAc (3:1) gave **87** (93 mg, 94% yield) as a colorless oil; diastereoselection, >99:1; IR ($CHCl_3$) 2950, 2880, 1730, 1456, 1363, 1177, 1106, 974, 928 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (tripletoid m, 3 H), 2.96 (s, 3 H), 3.06 (m, 1 H), 3.68 (s, 3 H), 4.11 (m, 1 H), 4.33–4.63 (m, 4 H), 4.73 (m, 1 H), 5.49 (ddd, J = 15.62, 7.56, 0.73 Hz, 1 H), 5.84 (ddd, J = 15.62, 8.79, 0.73 Hz, 1 H), 7.26–7.38 (m, 10 H). The spectral data [IR ($CHCl_3$) and ^1H NMR (200 MHz, $CDCl_3$)] were identical with those of an authentic sample of **87**.

(6*R*,3*S*)-6-[(1*R*)-2-Hydroxy-1-[(methylsulfonyl)oxy]ethyl]-3-methyl-1-oxacyclohexan-2-one (89). A mixture of **85** (26 mg, 0.06 mmol), 10% Pd–C (5 mg), 5% HCl (0.05 mL), and methanol (2 mL) was subjected to catalytic hydrogenation at atmospheric pressure for 30 min. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was used for the next step. To a solution of the above oil (16 mg) in 4 mL of MeCN was added 0.08 mL of $BF_3{\cdot}Et_2O$ and the mixture was stirred for 2.5 h at 20 °C. The mixture was made alkaline with 5% $NaHCO_3$ and extracted with chloroform. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give 10 mg (66% yield) of **89**: IR ($CHCl_3$) 3600–3200, 2970, 1732, 1463, 1362, 1344, 1174, 1102, 1038, 1010, 975, 923 cm^{-1}; ^1H NMR (200 MHz) δ 1.31 (d, J = 7.04 Hz, 3 H), 1.57–1.68 (m, 1 H), 1.80–1.91 (m, 1 H), 1.99–2.05 (m, 1 H), 2.07–2.13 (m, 1 H), 2.44–2.54 (m, 1 H), 3.21 (s, 3 H), 3.97 (d, J = 4.64 Hz, 2 H), 4.61 (ddd, J = 11.68, 4.04, 3.72 Hz, 1 H), 4.69 (m, 1 H); nominal mass spectrum, m/z 253 (MH^+), 252 (M^+), 143, 125, 113 (base peak), 85; exact mass spectrum calcd for $C_9H_{16}O_6S$ 252.0667, found 252.0663.

Methyl (*E*,5*R*,2*S*,6*S*)-5,6-*O*-Isopropylidene-7-[(methylsulfonyl)-oxy]-2-methyl-3-heptenoate (95). By a procedure identical with that described for the preparation of **25**, 170 mg (0.423 mmol) of enoate **94** was converted to 131 mg (96% yield) of **95** by treatment with MeCu(CN)Li·BF_3 (LiBr) (1.27 mmol) at −78 °C for 30 min followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1): colorless oil; diastereoselection, >99:1; $[\alpha]^{23}_D$ −25.0° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3050, 3030, 2970, 1732, 1456, 1437, 1363, 1342, 1178, 1082, 1065, 994, 965, 873, 820 cm^{-1}; ^1H NMR (200 MHz) δ 1.30 (d, J = 7.08 Hz, 3 H), 1.38 (s, 3 H), 1.51 (s, 3 H), 3.06 (s, 3 H), 3.22 (m, 1 H), 3.69 (s, 3 H), 4.06–4.21 (m, 2 H), 4.40 (dt, J = 6.84, 4.64 Hz, 1 H), 4.72 (dt, J = 7.32, 0.74 Hz, 1 H), 5.55 (ddd, J = 15.38, 7.08, 0.97 Hz, 1 H), 6.00 (ddd, J = 15.38, 7.33, 0.97 Hz, 1 H); nominal mass spectrum, m/z 322 (M^+), 307, 265, 264, 263, 205, 169, 157, 109, 97; exact mass spectrum, m/z calcd for $C_{13}H_{22}O_7S$ 322.1085, found 322.1112.

Acknowledgment. We acknowledge support by the Ministry of Education, Science, and Culture (Japan). We thank Professor Louis A. Carpino, Department of Chemistry, University of Massachusetts, for reading the manuscript.

Supplementary Material Available: Synthetic methods and spectral data ($[\alpha]_D$, IR, ^1H NMR, ^{13}C NMR, and MS) for **10**, **11**, **17**, **19–26**, **28–36**, **40**, **42–44**, **46**, **47**, **52**, **55**, **56**, **60**, **63–74**, **78**, **81**, **83**, **85**, **86**, **90**, **91**, **93**, **94**, and **96** and Figure 1 showing the ^1H NMR spectra of two olefinic protons in **30** (22 page). Ordering information is given on any current masthead page.