Substituent-Directed Alkyl Addition Reactions of Epoxides. 1. Applications to the Synthesis of 3-Hydroxy-4-methylalkanoic Acids

Lee A. Flippin,* Peter A. Brown, and Keyvan Jalali-Araghi

Department of Chemistry and Biochemistry, San Francisco State University, San Francisco, California 94132

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The addition reactions of 3,4-epoxy-1-alkanol derivatives were studied using $Li(CH_3)_2Cu$ (ether, 0 °C) and 2:1 $(CH_3)_3Al$–*n*-BuLi or 2:1 $(C_2H_5)_3Al$–*n*-BuLi (hexane, 0 °C). In all cases $Li(CH_3)_2Cu$ showed a small (2–3:1) preference for C(4) addition over C(3) addition; however, the mixed organoaluminum–organoaluminate reagents afforded 3-hydroxy-4-methyl-1-alkanol derivatives with high selectivity. For example, reaction of *trans*-1-(benzyloxy)-3,4-epoxyhexane with 2:1 $(CH_3)_3Al$–*n*-BuLi gave a 65:1 ratio of regioisomeric anti β-methyl alcohols **9** and **10** while *cis*-1-(benzyloxy)-3,4-epoxyhexane gave a 9:1 ratio of syn β-methyl alcohols **19** and **20** under the same reaction conditions. *cis*-1-(Benzyloxy)-3,4-epoxypentane reacted with 2:1 $(C_2H_5)_3Al$–*n*-BuLi to give an 11:1 ratio of isomeric β-ethyl alcohols **9** and **23**, which were accompanied by 4 mol % of a hydride addition product, **24**. In no case was any evidence found for *n*-butyl addition in the reactions of the organoaluminum–organoaluminate reagents. Reaction of $(CH_3)_3Al$ with *cis*-1-(benzyloxy)-3,4-epoxypentane afforded only an intramolecular Friedel–Crafts product, **25**; however, *trans*-1-methoxy-3,4-epoxyhexane underwent slow methyl addition with $(CH_3)_3Al$ to give anti β-methyl alcohol **11**. Control experiments performed with *cis*-1-(benzyloxy)-3,4-epoxyhexane showed that 1:1 $(CH_3)_3Al$–*n*-BuLi (hexane, 25 °C) is not reactive under our conditions. Alcohol **15**, prepared by C(4)-selective methyl addition to *trans*-1-(benzyloxy)-3,4-epoxytetradecane, and alcohol **19** were employed in racemic syntheses of the fatty esters derived from cyclodepsipeptide antibiotics of the CDPC 3510 and the polypeptin groups, respectively.

Organometallic addition reactions have long been exploited for the stereospecific transformation of epoxides to β-alkyl alcohols. This general reaction type has proved especially valuable in natural product applications because the large arsenal of stereoselective alkene-forming methods and the many diastereospecific and, more recently, highly enantioselective epoxidation methods that are available combine to provide a diverse array of useful synthetic intermediates.[1] Thus, depending upon an initial choice of substitution pattern, addition of a nucleophilic organometallic reagent to the three-member ring of an epoxide may afford either syn or anti β-alkyl alcohols[2] with very high stereospecificity and with considerable structural latitude (Figure 1). The addition reactions of monosubstituted, geminally disubstituted, and trisubstituted epoxides generally proceed with a decided preference for nucleophilic attack at the least substituted ring carbon; however, addition reactions of vicinally disubstituted epoxides, especially those that possess negligible steric bias near the three-member ring, may exhibit poor regioselectivity.[3] Nearly two decades ago, Rickborn et al.[4] introduced a useful framework for the development of regiocontrolled alkyl and hydride additions to vicinally disubstituted epoxides based on chelation control of the substrates. Thus, bidentate chelation of an organometallic reagent by the epoxide oxygen and a suitably positioned alkoxy substituent was envisioned to alter the substrate conformer population and, consequently, provide a plausible means of differentiating between the epoxide ring carbons. However, at least two factors apparently conspired to attenuate the importance of chelation control in the early experiments that were designed to test this idea: (1) The reactions of 3-methoxycyclohexene oxides are, as Rickborn concluded, undoubtedly influenced by a strong preference for trans-diaxial addition[4,5] regardless of the expected chelation effects on the distribution of substrate conformers. (2) The addition reactions were all performed in ether, presumably because the reagents employed, $Li(CH_3)_2Cu$ and $LiAlH_4$, are both soluble and reactive in that medium; however, efficient coordination of the organometallic reagents by the solvent may also serve to diminish their bidentate chelation by the substrate. In the years following Rickborn's seminal investigations, it has been demonstrated that monocyclic vicinally disubstituted epoxides are versatile candidates for substituent-directed addition reactions. For example, the reactions of monocyclic β-alkoxy epoxides with organocuprate reagents show a clear preference for alkyl addition distal to the alkoxy group, while a dramatic reversal to proximal addition selectivity may be realized by employing β-hydroxy epoxides in alkyl and hydride addition reactions.[6] Aluminum-based

(1) Reviews: (a) Pfenniger, A. *Synthesis* **1986**, 89. (b) Rossitier, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 193–246. (c) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (d) Berti, G. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1973; Vol. 7, pp 93–251.

(2) The use of syn and anti descriptors to denote the relative stereochemistry of adjacent chiral centers in diastereomeric alcohols has been described elsewhere: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. A referee has pointed out that some potential for confusion exists in our use of Masamune's syn/anti structural descriptors because it is also true that the ring-opening processes described in this paper occur with anti stereospecificity. However, the Cahn–Ingold–Prelog structural descriptors, while completely unambiguous, can be quite cumbersome for the purpose of general discussion, particularly when racemic substances containing more than one chiral center are at issue; therefore, we continue to adopt the Masamune syn/anti convention to facilitate discussions of structure and we have endeavored to distinguish this usage very clearly from any description of a syn or anti process.

(3) (a) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185. (b) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173. (c) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5697. (d) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (e) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253. (f) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.

(4) (a) Hartman, B. C.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 4246. (b) Hartman, B. C.; Livinghouse, T.; Rickborn, B. *J. Org. Chem.* **1973**, *38*, 4346.

(5) (a) Inghardt, T.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1988**, *53*, 4542. (b) Grindley, T. B.; Reimer, G. J.; Kralovec, J.; Brown, R. G.; Anderson, M. *Can. J. Chem.* **1987**, *65*, 1065. (c) Deslongschamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 165. (d) Danishefsky, S.; Tsai, M.-Y.; Kitahara, T. *J. Org. Chem.* **1977**, *42*, 394. (e) Williams, N. R. In *Advances in Carbohydrate Chemistry and Biochemistry*; Tipson, R. S., Ed.; Academic Press: New York, 1970; Vol. 25, p 122.

0022-3263/89/1954-3588$01.50/0

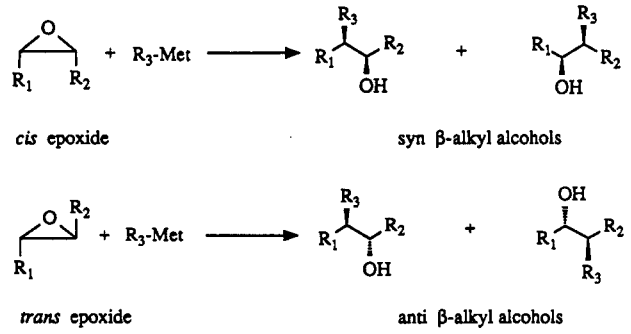


Figure 1. Stereochemistry of organometallic addition reactions of cis and trans epoxides.

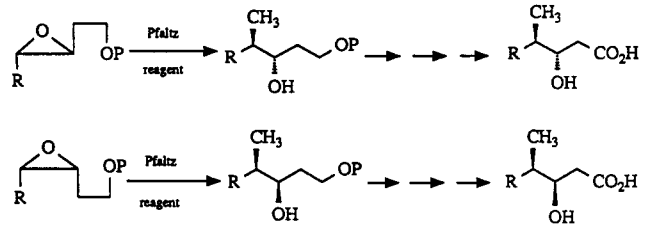


Figure 2. Synthetic approach to anti and syn 3-hydroxy-4-methylalkanoic acids from trans and cis epoxides, respectively.

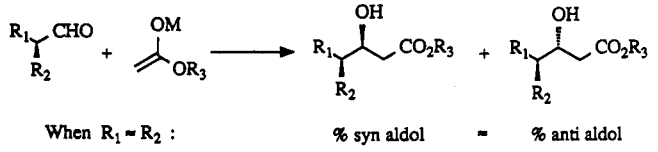


Figure 3. Aldol addition reaction of a chiral aldehyde with an acetic ester enolate. In general, when $R_1 \approx R_2$, the ratio of syn and anti products is close to unity.

reagents including trialkylaluminums,[6c,7] tetraalkylaluminates,[8] and mixed organoaluminum–organoaluminates[9] have also been employed in a variety of alkyl additions to epoxides—some of these have shown very useful regioselectivity in their reactions with vicinally disubstituted substrates that contain remote oxygen functionality. Along these lines, we were particularly attracted to a report by Pfaltz and Mattenberger[9] which describes unusually high regioselectivity for distal methyl addition in the base-catalyzed reactions of trimethylaluminum with (*E*)- or (*Z*)-1-(benzyloxy)-2,3-epoxybutane and (*E*)- or (*Z*)-1-(benzyloxy)-3,4-epoxypentane. If general

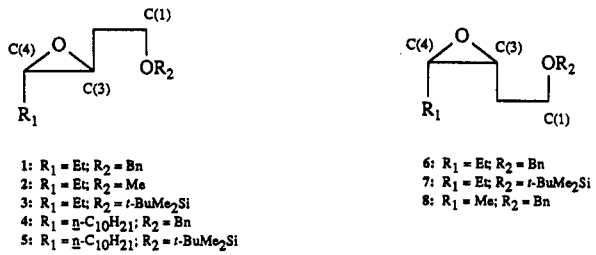


Figure 4. 3,4-Epoxy-1-alkanol derivatives.

in scope, Pfaltz's reaction[10] could provide a useful approach to 3-hydroxy-4-methylalkanoic acids starting from readily available 3,4-epoxy-1-alkanol derivatives (Figure 2).

Over the past several years, we have been interested in the development of effective methods for the synthesis of syn and anti 3-hydroxy-4-methylalkanoic acids.[11] For example, the fatty acid residues of the polypeptin A and CDPC 3510 cyclodepsipeptide groups constitute typical synthetic targets of this genre.[12] In principle, the preparation of virtually any member of this structural class may be accomplished via an aldol-type addition of acetic acid or its equivalent to a 2-methylalkanal; however, most currently available aldol methods are inherently syn-selective and may suffer from diminished selectivity when the facial bias of the aldehyde carbonyl is small, i.e., when $R_1 \approx R_2$ in the vicinity of the α-chiral center (Figure 3).[11,13] Thus, a racemic synthesis of the polypeptin A fatty acid performed via a Reformatsky reaction of ethyl 2-bromoacetate with 2-methylbutanal afforded a 1:1 mixture of the syn and anti diastereomers,[12a] while an aldol method employing the lithium enolate of ethyl 1,3-dithiane-2-carboxylate gave only marginal selectivity, syn:anti = 3.5.[11] A stereospecific synthesis of methyl (3*S*,4*S*)-3-hydroxy-4-methylhexanoate has recently been accomplished in six steps and ca. 8% yield by an unrelated approach; however, the reported procedure requires an unusual amino acid, D-alloisoleucine, as the starting material.[14]

The unsuitability of routine aldol-related methods for a general approach to the 3-hydroxy-4-methylalkanoic acids became further apparent to us after a syn-selective aldol route to methyl 3-hydroxy-4-methyltetradecanoate indicated that the natural fatty acid residue obtained by hydrolytic degradation of CDPC 3510 is, in fact, an anti diastereomer.[15]

(6) (a) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495. (b) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 6195. (c) Roush, W. R.; Adam. M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, 1377. (d) Kobayashi, Y.; Kitano, Y.; Takedo, Y.; Sato, F. *Tetrahedron* **1986**, *42*, 2937. (e) McWhorter, W. W., Jr.; Kang, S. H.; Kishi, Y. *Tetrahedron Lett.* **1983**, 2243. (f) Tius, M.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131. (g) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, 707. (h) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (i) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (j) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, 2719. (k) Fuganti, C.; Graselli, P.; Servi, S.; Zirotti, C. *Tetrahedron Lett.* **1982**, 4269. (l) Viti, S. M. *Tetrahedron Lett.* **1982**, 4541. (m) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (n) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (o) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (p) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347.

(7) (a) Matthews, R. S.; Mihelich, E. D.; McGowan, L. S.; Daniels, K. *J. Org. Chem.* **1983**, *48*, 409. (b) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. (c) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

(8) (a) Negishi, E.; Baba, S.; King, A. O. *J. Chem. Soc., Chem. Commun.* **1976**, 17. (b) Boireau, G.; Abenhaim, D.; Bernardon, C.; Henry-Basch, E.; Sabourault, B. *Tetrahedron Lett.* **1975**, 2521.

(9) (a) Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71. (b) Pfaltz, A.; Mattenberger, A. *Angew. Chem. Suppl.* **1982**, 161.

(10) For synthetic applications of Pfaltz's reaction, see: (a) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744. (b) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767. (c) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459.

(11) Flippin, L. A.; Dombroski, M. A. *Tetrahedron Lett.* **1985**, 2977.

(12) Polypeptin A group: (a) Sogn, J. A. *J. Med. Chem.* **1976**, *19*, 1228. (b) Takahara, Y.; Takeuchi, Y.; Komura, I.; Hirose, Y.; Murao, S. *J. Antibiot.* **1979**, *32*, 115. (c) Takeuchi, Y.; Murai, A.; Takahara, Y.; Kainosho, M. *J. Antibiot.* **1979**, *32*, 121. (d) Sugawara, K.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 1257. CDPC 3510 group: (e) Carr, S. A.; Block, E.; Costello, C. E.; Vesonder, R. F.; Burmeister, H. R. *J. Org. Chem.* **1985**, *50*, 2854.

(13) (a) Nógrádi, M. In *Stereoselective Synthesis*; VCH Publishers: New York, 1987; Chapter 5. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D, Ed.; Academic Press: New York, 1984; Vol. 3, pp 165–174. However, aldol methods that exhibit high double asymmetric induction may provide a useful route to selected 3-hydroxy-4-methylalkanoic acids. See, for example: (c) Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035. (d) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. It is possible that Matteson's boronic ester method could also be adapted to provide a general approach to the 3-hydroxy-4-methylalkanoic acids: (e) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294.

(14) Murai, A.; Amino, Y.; Ando, T. *J. Antibiot.* **1985**, *38*, 1610.

Table I. Product Ratios for the Reactions of 3,4-Epoxy-1-alkanol Derivatives with Organometallic Reagents (Eq 1–5)

entry	epoxide	organometallic reagent[a]	yield,[b] %	products (ratio)[c]
1	1	A	(95)	**9**, **10** (1.8:1)
2	1	B	86	**9**, **10** (65:1)
3	2	A	(95)	**11**, **12** (2:1)
4	2	C	42	**11** (–)[d]
5	3	A	(88)	**13**, **14** (3.3:1)
6	3	B	90	**13**, **14** (50:1)
7	4	A	60	**15**, **16** (2:1)
8	4	B	83	**15**, **16** (>200:1)
9	5	A	(81)	**17**, **18** (2.5:1)
10	5	B	88	**17**, **18** (90:1)
11	6	A	57	**19**, **20** (1.5:1)
12	6	B	59	**19**, **20** (9:1)
13	6	D	–	– (–)[e]
14	7	A	77	**21**, **22** (2.5:1)
15	7	B	(100)	**21**, **22** (5:1)
16	8	C	(86)	**25** (–)[f]
17	8	E	76	**9**, **23**, **24** (22:2:1)

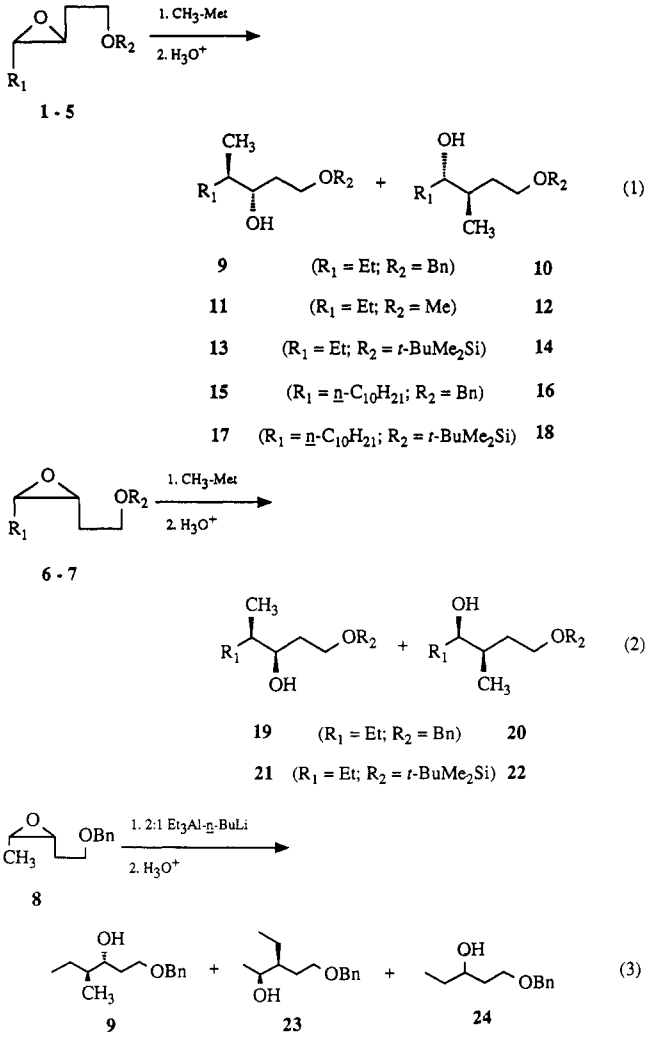
[a] Reagent A: $Li(CH_3)_2Cu$ (ether, 0 °C). Reagent B: 2:1 $(CH_3)_3Al$–*n*-BuLi (hexane, 0 °C). Reagent C: $(CH_3)_3Al$ (hexane, 25 °C). Reagent D: 1:1 $(CH_3)_3Al$–*n*-BuLi (hexane, 25 °C). Reagent E: 2:1 $(CH_3CH_2)_3Al$–*n*-BuLi (hexane, 0 °C). [b] Yields in parentheses are crude product yields. All others refer to total yields of isolated products. [c] All product ratios were determined from the crude reaction mixtures. [d] An approximately 1:1 mixture of **11** and the starting epoxide, **2**, was isolated. [e] An 83% yield of the starting epoxide, **6**, was recovered. [f] Single product.

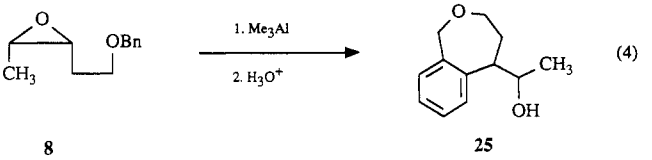
Our aims in this report are (1) to summarize the results of our study of the regioselectivity of selected organometallic additions to (*E*)- and (*Z*)-3,4-epoxy-1-alkanol derivatives and (2) to demonstrate the synthetic versatility of Pfaltz's organoaluminum–organoaluminate method in diastereoselective syntheses of the fatty acid components of both the CDPC 3510 and the polypeptin A groups of cyclodepsipeptides.

Results and Discussion

Initially we wanted to explore three factors that could plausibly relate chelation effects to the regioselectivity of organometallic addition reactions of 3,4-epoxy-1-alkanol derivatives: (1) What is the qualitative dependence, if any, of regioselectivity on the nature of the C(1) hydroxyl protecting group? (2) What effect does epoxide stereochemistry exert on the regioselectivity of addition? (3) How much does solvent basicity affect regioselectivity?

Epoxides **1**–**8** were used in our investigation of these questions (Figure 4). Organometallic addition reactions of compounds **1**–**7** were carried out with $Li(CH_3)_2Cu$ (ether, 0 °C) and with 2:1 $(CH_3)_3Al$–*n*-BuLi (hexane, 0 °C), while for the reaction of compound **8** we employed 2:1 $(C_2H_5)_3Al$–*n*-BuLi (hexane, 0 °C). The reactions of epoxides **2** and **8** with trimethylaluminum (hexane, 25 °C) were also examined. Control experiments employing 0.9–1.1:1.0 $(CH_3)_3Al$–*n*-BuLi (hexane, 25 °C) were performed with epoxide **6**. The reactions of **1**–**7** with $Li(CH_3)_2Cu$ or 2:1 $(CH_3)_3Al$–*n*-BuLi afforded either syn or anti β-methyl alcohols according to the geometry of the starting epoxide (eq 1, 2). The alkyl addition reaction of compound **8** with 2:1 $(C_2H_5)_3Al$–*n*-BuLi was accompanied by a small amount of apparently regioselective hydride addition (eq 3); however, it is remarkable that no products of *n*-butyl addition were observed in the reactions of epoxides **1**–**8** with organoaluminum–organoaluminate reagents. Control experiments with epoxide **6** demonstrated that 1:1 $(CH_3)_3Al$–*n*-BuLi (hexane, 25 °C, 12 h) is completely unreactive under our conditions. It is possible that the negligible reactivity of this organometallic reagent is due to a combination of poor solubility and low intrinsic nucleophilicity since it has been reported that a more lipophilic tetraalkylaluminate, $LiAl(n\text{-}Bu)_4$,[8b] slowly adds to epoxides in pentane at 35 °C. The onset of alkyl addition to epoxide **6** was apparent at short reaction times when as little as 0.1 equiv of excess $(CH_3)_3Al$ was added to the 1:1 $(CH_3)_3Al$–*n*-BuLi reagent. On the other hand, a reaction of epoxide **8** with trimethylaluminum in the absence of *n*-BuLi (hexane, 25 °C, 14 h) failed to yield any detectable methyl addition products but afforded instead the intramolecular Friedel–Crafts product,[16] **25** (eq 4). Epoxide **2** reacted very sluggishly with 2 equiv of tri-

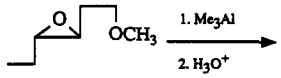




(15) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. Unpublished results.

(16) (a) Taylor, S. K.; Blankespoor, C. L.; Harvey, S. M.; Richardson, L. J. *J. Org. Chem.* **1988**, *53*, 3309. (b) Taylor, S. K.; Davisson, M. E.; Hissom, B. R.; Brown, S. L.; Schramm, S. B.; Harvey, S. M. *J. Org. Chem.* **1987**, *52*, 425. (c) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449. (d) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (e) Namy, J. L.; Boireau, G.; Abenhaim, D. *Bull. Soc. Chim. Fr.* **1971**, 3191.

methylaluminum (hexane, 25 °C, 16 h) to give a 1:1 mixture of starting material and a single β-methyl alcohol, **11**, plus a small amount of an unidentified substance (eq 5).



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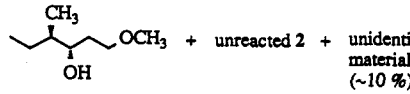


+ unreacted **2** + unidentified material (~10 %) (5)

11

Experiments were carried out at several temperatures in which aliquots were removed from reaction mixtures containing 2:1:1 $(CH_3)_3Al$–*n*-BuLi–epoxide **6**, quenched in aqueous acid, and analyzed by HPLC with the aid of known standards. These runs indicated that the rate of alkyl addition was negligible at −78 °C, slow at −20 °C (ca. 10% completion after 1 h), and rapid at 0 °C (>95% complete after 1 h). Interestingly, there was not a noticeable difference between the regioselectivity of methyl addition to epoxide **6** at −20 °C and at 0 °C. The results of our survey of alkyl addition reactions with 3,4-epoxy-1-alkanol derivatives are summarized in Table I.

Protecting-Group Effects. It seemed unlikely to us that differences in the hydroxyl protecting group of epoxides **1**–**8** would have much of an electronic or steric impact on C(3) or C(4) since these carbon atoms are removed four and five bonds, respectively, from the O–R_2 bond (cf. Figure 4). However, we did expect relatively large perturbations at C(1)–O to accompany the change in R_2 from benzyl to *tert*-butyldimethylsilyl. These suppositions are qualitatively borne out by the small, fairly constant ^{13}C NMR $\Delta\delta$ values for C(4) and C(3), in contrast to the rather large changes in $\delta_{C(1)}$, as a function[17] of the protecting group in our substrates (Table II). Thus, we assumed that the nature of the C(1) hydroxyl protecting group would have little effect on the intrinsic reactivities of C(3) and C(4). On the other hand, it has been convincingly argued that trialkylsiloxy groups normally do not participate in the bidentate chelation of Lewis acids while benzyloxy groups do participate under otherwise identical circumstances.[18] Therefore, we were surprised to find only very small effects on the regioselectivity of alkyl addition in directly comparable Pfaltz reactions of 1-(benzyloxy)-3,4-epoxyalkanes and 1-(*tert*-butyldimethylsiloxy)-3,4-epoxyalkanes. These results suggest that 3,4-epoxy-1-alkanol derivatives **1**–**8** may engage in highly efficient bidentate chelation of a trialkylaluminum[9b,19] in hexane solvent regardless of the nature of the C(1) hydroxyl protecting group. We also found little difference between the regioselectivity of ethereal cuprate additions to comparable benzyl ethers and silyl ethers; however, it is likely that the fairly constant, low level of regioselectivity observed for all of the cuprate reactions may reflect small intrinsic differences between C(3) and C(4) in the absence of chelation control.[20]

(17) (a) Kalinowski, H.-O.; Berger, S.; Braun, S. In *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988; pp 104–112. (b) Lambert, J. R.; Vagenas, A. R. *Org. Magn. Reson.* **1981**, *17*, 265. (c) Lambert, J. R.; Vagenas, A. R. *Org. Magn. Reson.* **1981**, *17*, 270.

(18) (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, 279. (b) Keck, G. E.; Castellano, S. *Tetrahedron Lett.* **1987**, 281.

(19) Although five-coordinate aluminum complexes with square pyramidal geometry at the aluminum atom are unusual, at least two unambiguous examples are known: (a) Robinson, G. H.; Sangokoya, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6852. (b) Kai, Y.; Yasuoka, N.; Kasai, N.; Kakudo, M. *J. Chem. Soc., Chem. Commun.* **1969**, 575.

Table II. Carbon-13 $\delta_{C(1)}$ and $\Delta\delta = \delta_{C(4)} - \delta_{C(3)}$ Values for 3,4-Epoxy-1-alkanol Derivatives

entry	epoxide	R_2	$\delta_{C(1)}$	$\Delta\delta = \delta_{C(4)} - \delta_{C(3)}$
1	**2**	Me	69.4	1.2
2	**1**	Bn	66.8	3.7
3	**4**	Bn	67.2	2.5
4	**6**	Bn	67.7	3.3
5	**8**	Bn	67.4	2.3
6	**3**	*t*-$BuMe_2Si$	60.0	3.9
7	**5**	*t*-$BuMe_2Si$	60.0	2.6
8	**7**	*t*-$BuMe_2Si$	60.5	3.5

Epoxide Stereochemistry. The effect of substrate stereochemistry on the regioselectivity of alkyl addition is readily apparent upon inspection of Table I—the *trans*-3,4-epoxy-1-alkanol derivatives that we studied were uniformly more selective for C(4) alkyl addition than were the corresponding cis diastereomers. Under reaction conditions where chelation control is likely to be dominant, this trend may ultimately stem from the fact that the bicyclic chelate form of a trans substrate incurs only one new eclipsing interaction (between M and a methylene group) while the corresponding bicyclic chelate form of a cis substrate would necessarily suffer two new eclipsing interactions. On the other hand, it is apparent that the cis substrates would enjoy complete relief from new eclipsing interactions if they react via a monodentate complex in which the organometallic reagent coordinates trans to the epoxide substituents (Figure 5). Thus, for example, even in hexane solvent the reaction of a cis epoxide with 2:1 $(CH_3)_3Al$–*n*-BuLi may occur with a significant (20–30%) monodentate component that is intrinsically unselective (leading to ca. 10–15% C(3) addition).

Solvent Effects. The 2:1 $(CH_3)_3Al$–*n*-BuLi reagent is unreactive at 0–25 °C in ether[9a] with epoxides **1** and **6**, and lithium dimethylcuprate does not form in hexane solution under routine preparative conditions;[3e] therefore, we were unable to study the addition reactions of either organometallic reagent in both solvents. Nevertheless, the consistent, low regioselectivity that we observed for the ethereal $Li(CH_3)_2Cu$ reactions suggests that these processes are not significantly chelation-controlled. Presumably, this is because ether can favorably compete with the remote directing group for Li^+ coordination sites and thus allow the reaction to proceed largely via a monodentate pathway. The residual selectivity for C(4) attack in these reactions may conceivably arise from any of several factors including an intrinsic electronic difference between C(3) and C(4), subtle steric differences between the C(3) and C(4) substituents, and persistent contributions from a chelation-control pathway; however, it should be noted that the very similar C(4):C(3) selectivity ratios found in reactions of comparable cis and trans epoxides with $Li(CH_3)_2Cu$ argue against the latter explanation.

The origin of the high selectivity for C(4) addition to 3,4-epoxy-1-alkanol derivatives under reaction conditions that do involve chelation control may be rationalized in stereoelectronic terms. Thus, in the transition-state structure for C(4) addition, C–O bond cleavage leads smoothly to the placement of a nonbonded electron pair in a boat-equatorial orbital on oxygen; however, in the transition-state structure for C(3) addition to a bicyclic chelate intermediate, the oxygen lone pair would develop in an orbital that is intraannular and presumably of higher

(20) The *tert*-butyldimethylsiloxy group has recently been shown to be capable of coordination to Li^+ in the solid state: Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. However, we believe it is unlikely that a benzyloxy group and a *tert*-butyldimethylsiloxy group would coordinate to Li^+ with essentially identical facility in ether solution.

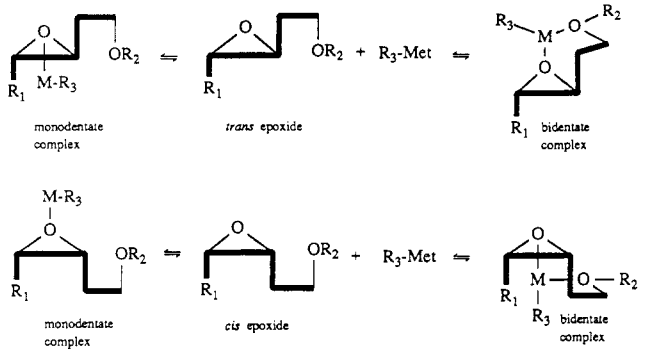


Figure 5. Coordination states of *trans*- and *cis*-3,4-epoxy-1-alkanol derivatives with an organometallic reagent, R_3-Met.

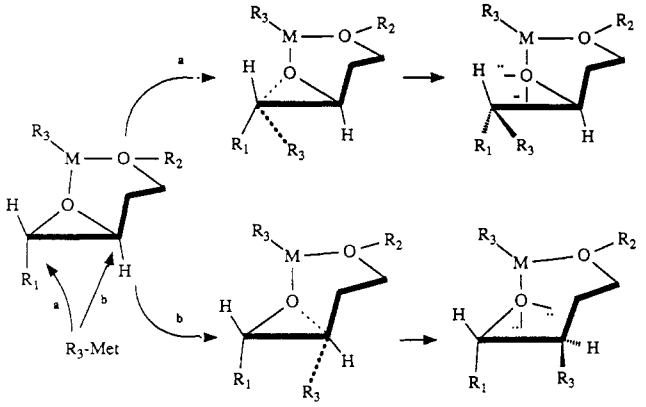


Figure 6. Transition states and products for C(4) addition (pathway a) and C(3) addition (pathway b) to a *trans*-3,4-epoxy-1-alkanol derivative.

potential energy. In the latter event, the transition-state geometry would require extensive reorganization in order to produce a reasonable structure (Figure 6).[21]

Synthesis of 3-Hydroxy-4-methylalkanoic Acids. Intermediates **19** and **15** (Table I) are properly functionalized for use in short racemic syntheses of the fatty acid components of the polypeptin group cyclodepsipeptides and CDPC 3510, respectively. Our syntheses of the methyl esters of these cyclodepsipeptide degradation products are summarized in Scheme I.

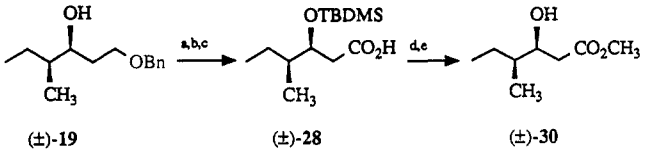
Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were obtained with a GE-Nicolet QE spectrometer operated at 300 MHz and 75 MHz, respectively. All spectra were recorded by using $CDCl_3$ as the solvent; tetramethylsilane (δ = 0.00 ppm) was employed as an internal reference for all ^{1}H NMR spectra, while $CDCl_3$ (δ = 77.0 ppm) was used as the reference for ^{13}C NMR spectra. Thin-layer chromatography was performed with Eastman Kodak 250-μm silica gel plates. Column chromatography was performed with Merck 60-mesh silica gel. High-pressure liquid chromatography was carried out with a Waters 6000A chromatograph with UV detection at 254 nm or with RI detection. GLC separations were carried out with a Varian Aerograph Model 920 thermal conductivity instrument. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley or Multichem Laboratories, Inc. (Lowell, MA).

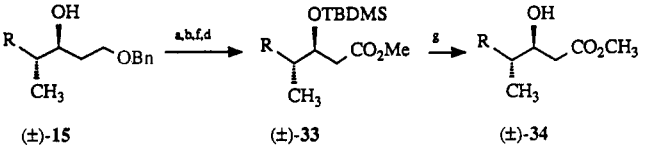
Materials. Dimethylformamide (DMF), methylene chloride, and hexane were dried over CaH_2 and distilled under a nitrogen atmosphere before use. Ether and tetrahydrofuran (THF) were distilled from sodium–benzophenone under a nitrogen atmosphere. (*Z*)-3-Alken-1-ol derivatives were prepared by silylation[22] or alkylation of an appropriate 3-alkyn-1-ol, followed by partial hydrogenation using nickel boride–ethylenediamine[23] as the catalyst. (*E*)-3-Hexen-1-ol derivatives were prepared by silylation or alkylation of commercially obtained (*E*)-3-hexen-1-ol. (*E*)-3-Tetradecen-ol was prepared by the method of Negishi.[8a]

Scheme I

A. Polypeptin group fatty ester:



B. CDPC 3510 fatty ester (R = n-$C_{10}H_{21}$):



[a] TBDMSCl, imidazole (DMF). [b] H_2 (1 atm), 5% Pd–C (ether, 25 °C). [c] Catalyst $RuCl_3$, $NaIO_4$ (CCl_4–CH_3CN–H_2O). [d] CH_2N_2 (ether). [e] Aqueous HF, 48% (THF). [f] PDC (DMF). [g] *n*-BuN^+F^- (THF).

3,4-Epoxyalkan-1-ol Derivatives. General. The following procedure is typical.

(3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxyhexane (6). To a stirred solution of 6.880 g (36.2 mmol) of (*Z*)-1-(benzyloxy)-3-hexene in 100 mL of CH_2Cl_2 at 0 °C was added 9.37 g of 87 mol % *m*-chloroperoxybenzoic acid in small portions. The temperature was maintained below 5 °C during the addition period, and then the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was diluted with 200 mL of pentane and filtered through a plug of silica gel. The filtrate was washed with dilute aqueous sodium bisulfite and saturated aqueous Na_2CO_3, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 7.47 g of a colorless oil. The crude product was distilled with a Kugelrohr apparatus to afford 6.530 g (87% yield) of **6**: bp(0.5 Torr) = 90–95 °C; ^{1}H NMR δ 7.40–7.25 (m, 5 H), 4.54 (s, 2 H), 3.64 (t, J = 6.5 Hz, 2 H), 3.09 (dt, J = 7.1, 4.6 Hz, 1 H), 2.91 (m, 1 H), 1.89 (m, 1 H), 1.78 (m, 1 H), 1.56 (m, 2 H), 1.03 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 138.4, 128.4, 127.6, 73.1, 67.7, 58.1, 54.8, 28.5, 21.2, 10.5.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.64; H, 8.67.

(3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxyhexane (1): prepared from (*E*)-1-(benzyloxy)-3-hexene in 93% yield; bp(0.4 Torr) = 92–100 °C; ^{1}H NMR δ 7.40–7.25 (m, 5 H), 4.49 (s, 2 H), 3.62 (t, J = 6.5 Hz, 2 H), 2.80 (m, 1 H), 2.64 (m, 1 H), 1.90–1.71 (m, 2 H), 1.51 (m, 2 H), 0.98 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 138.1, 128.0, 127.2, 72.7, 66.8, 59.4, 55.7, 32.4, 24.8, 9.5.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.58; H, 8.63.

(3*RS*,4*RS*)-1-Methoxy-3,4-epoxyyhexane (2): prepared from (*E*)-1-methoxy-3-hexene in 63% yield; bp = 138–142 °C; ^{1}H NMR δ 3.52 (t, J = 6.0 Hz, 2 H), 3.35 (s, 3 H), 2.83 (m, 1 H), 1.57 (m, 2 H), 1.00 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 69.4, 59.7, 58.5, 55.9, 32.4, 25.0, 9.6.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.30; H, 10.71.

(3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (3): prepared from (*E*)-1-(*tert*-butyldimethylsiloxy)-3-hexene in 60% yield; ^{1}H NMR δ 3.77 (t, J = 6.2 Hz, 3 H), 2.83 (td, J = 6.0, 3.0 Hz, 1 H), 2.67 (td, J = 6.0, 4.0 Hz, 1 H), 1.75 (m, 2 H), 1.58 (m, 2 H), 1.02 (t, J = 7.5 Hz, 3 H), 0.92 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR δ 60.0, 59.8, 55.9, 35.5, 25.8, 25.1, 18.2, 9.7, −5.5.

Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.28; H, 11.33. Found: C, 62.35; H, 11.38.

(3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxytetradecane (4): pre-

(21) Hine, J. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: New York, 1977; Vol. 15, pp 1–61.
(22) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(23) Brown, C. A.; Ahuja, V. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

pared from (*E*)-1-(benzyloxy)-3-tetradecene in 79% yield. An analytical sample of compound **4** was obtained by semipreparative HPLC (μ-Porasil; 19:1 hexane–ether): ^{1}H NMR δ 7.40–7.26 (m, 5 H), 4.53 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 3.61 (t, J = 5.8 Hz, 2 H), 2.83 (dt, J = 5.5, 2.3 Hz, 1 H), 2.72 (dt, J = 5.5, 2.3 Hz, 1 H), 1.97–1.65 (m, 2 H), 1.58–1.18 (m, 18 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 138.4, 128.4, 127.6, 73.1, 67.2, 58.9, 56.4, 33.7, 32.7, 32.1, 31.9, 29.7, 29.5, 29.4, 29.3, 26.0, 22.7, 14.1.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.98; H, 10.84.

(3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxytetradecane (5): prepared from (*E*)-1-(*tert*-butyldimethylsiloxy)-3-tetradecene and purified by column chromatography (silica gel; 49:1 hexane–ether) in 86% yield: ^{1}H NMR δ 3.74 (t, J = 5.8 Hz, 2 H), 2.76 (dt, J = 5.7, 2.1 Hz, 1 H), 2.70 (dt, J = 5.7, 2.1 Hz, 1 H), 1.81–1.65 (m, 2 H), 1.55–1.20 (m, 18 H), 0.92–0.83 (m, 12 H), 0.06 (s, 6 H); ^{13}C NMR δ 60.0, 58.9, 56.3, 35.6, 32.1, 31.9, 29.6, 29.4, 29.3, 26.0, 25.9, 25.7, 22.7, 14.1, −2.9.

Anal. Calcd for $C_{20}H_{42}O_2Si$: C, 69.90; H, 12.32. Found: C, 69.95; H, 12.36.

(3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (7): prepared from (*Z*)-1-(*tert*-butyldimethylsiloxy)-3-hexene in 78% yield: ^{1}H NMR δ 3.73 (dd, J = 7.0, 5.6 Hz, 2 H), 3.00 (m, 1 H), 2.84 (m, 1 H), 1.80–1.45 (m, 4 H), 1.05 (t, J = 7.5 Hz, 3 H), 0.98 (s, 9 H), 0.03 (s, 6 H).

Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.28; H, 11.33. Found: C, 62.15; H, 11.40.

(3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxypentane (8): prepared[9] from (*Z*)-1-(benzyloxy)-3-pentene in 90% yield: bp(0.5 Torr) = 90–95 °C; ^{1}H NMR δ 7.40–7.32 (m, 5 H), 4.55 (s, 2 H), 3.65 (t, J = 6.0 Hz, 2 H), 3.07 (m, 2 H), 1.85 (m, 2 H), 1.85 (m, 2 H), 1.27 (d, J = 6.0 Hz, 3 H); ^{13}C NMR δ 138.3, 128.2, 127.4, 72.9, 67.4, 54.5, 52.2, 28.2, 13.1.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.40.

Reaction of 3,4-Epoxyalkan-1-ol Derivatives with Li(CH$_3$)$_2$Cu. General. The following procedure is illustrative.

Reaction of (3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxyhexane (6) with Li(CH$_3$)$_2$Cu. In a one-neck 50-mL round-bottom flask equipped with a magnetic stirrer, rubber septum, and a nitrogen inlet were placed 0.6925 g (3.64 mmol) of CuI and 25 mL of dry ether. The stirred suspension was cooled to 0 °C under a dry nitrogen atmosphere, and 5.2 mL of a 1.40 M solution of methyllithium in ether was added. After 10 min, 0.3765 g (1.83 mmol) of epoxide **6** in ca. 0.5 mL of ether was added in one portion to the Li(CH$_3$)$_2$Cu solution. The reaction mixture was maintained at 0 °C for 1 h and allowed to stand overnight at room temperature; it was then poured into 100 mL of ice-cold 3 M HCl and extracted with several portions of ether. The combined ether layers were washed with water until the aqueous layer was neutral to pHydrion paper, dried (MgSO$_4$), filtered, and concentrated with a rotary evaporator to afford 0.3785 g of a yellow oil. Column chromatography of the crude material (silica gel; 19:1 hexane–ether) gave 0.1250 g (31% yield) of (3*RS*,4*RS*)-1-(benzyloxy)-3-hydroxy-4-methylhexane (**19**) and 0.1060 g (26% yield) of (3*RS*,4*RS*)-1-(benzyloxy)-4-hydroxy-3-methylhexane (**20**). Analysis of the crude product mixture by HPLC (μ-Porasil; 2:1 hexane–ether) and ^{13}C NMR gave a diastereomer ratio **19**:**20** = 1.5.

(3*RS*,4*RS*)-1-(Benzyloxy)-3-hydroxy-4-methylhexane (19): ^{1}H NMR δ 7.38–7.25 (m, 5 H), 4.52 (s, 2 H), 3.72 (m, 2 H), 3.65 (td, J = 9.0, 4.3 Hz, 1 H), 2.70 (d, J = 4.0 Hz, 1 H), 1.87–1.06 (m, 5 H), 0.90 (t, J = 7.8 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 138.0, 128.4, 127.6, 74.4, 73.3, 69.7, 40.5, 33.7, 25.6, 13.7, 11.8.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.75; H, 10.19.

(3*RS*,4*RS*)-1-(Benzyloxy)-4-hydroxy-3-methylhexane (20): ^{1}H NMR δ 7.37–7.24 (m, 5 H), 4.50 (s, 2 H), 3.61–3.41 (m, 3 H), 2.15 (br s, 1 H), 1.73 (m, 2 H), 1.54 (m, 1 H), 1.43 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 3 H); ^{13}C NMR 138.3, 128.4, 127.7, 127.6, 76.1, 73.1, 68.5, 35.5, 33.6, 27.0, 13.3, 10.8.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.32; H, 10.04.

Reaction of (3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxyhexane (1) with Li(CH$_3$)$_2$Cu. Epoxide **1**, 0.5013 g (2.43 mmol), gave 0.5128 g (95% yield) of a 1.8:1 mixture of **9** and **10**, respectively. Analytical samples of **9** and **10** were obtained by semipreparative HPLC (μ-Porasil; 2:1 hexane–ether).

(3*RS*,4*SR*)-1-(Benzyloxy)-3-hydroxy-4-methylhexane (9): ^{1}H NMR δ 7.40–7.25 (m, 5 H), 4.55 (s, 2 H), 3.74 (dt, J = 9.2, 5.1 Hz, 1 H), 3.65 (ddd, J = 12.9, 6.1; 2.1 Hz, 2 H), 2.59 (br s, 1 H), 1.72 (m, 2 H), 1.49 (m, 2 H), 1.15 (m, 1 H), 0.90 (t, J = 7.1 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 138.2, 128.4, 128.1, 127.7, 75.2, 73.4, 69.8, 40.5, 32.7, 24.9, 14.6, 11.6.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.38; H, 10.02.

(3*RS*,4*SR*)-1-(Benzyloxy)-4-hydroxy-3-methylhexane (10): ^{1}H NMR δ 7.40–7.25 (m, 5 H), 4.52 (s, 2 H), 3.62–3.45 (m, 2 H), 3.32 (ddd, J = 8.9, 5.6, 3.7 Hz, 1 H), 2.10 (br s, 1 H), 1.73 (m, 2 H), 1.58 (m, 2 H), 1.40 (heptet, J = 6.7 Hz, 1 H), 0.96 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 138.2, 129.5, 128.3, 127.6, 77.2, 73.1, 68.4, 36.2, 32.2, 27.0, 16.3, 10.2.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.42; H, 9.99.

Reaction of (3*RS*,4*RS*)-1-Methoxy-3,4-epoxyhexane (2) with Li(CH$_3$)$_2$Cu. Epoxide **2**, 0.3512 g (2.70 mmol), gave 0.3764 g (95% yield) of a 2:1 mixture of **11** and **12**. Analytical samples of **11** and **12** were obtained by preparative GLC (10% Carbowax 20M column, oven temperature = 160 °C).

(3*RS*,4*SR*)-1-Methoxy-3-hydroxy-4-methylhexane (11): ^{1}H NMR δ 3.70–3.60 (m, 2 H), 3.60–3.52 (m, 1 H), 3.36 (s, 3 H), 2.85 (br s, 1 H), 1.68 (q, J = 6.0 Hz, 2 H), 1.55–1.40 (m, 2 H), 1.15 (m, 1 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.87 (d, J = 7.0 H, 3 H); ^{13}C NMR 74.7, 71.9, 58.6, 40.3, 32.0, 24.8, 14.3, 11.5.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.45; H, 12.20.

(3*RS*,4*SR*)-1-Methoxy-4-hydroxy-3-methylhexane (12): ^{1}H NMR δ 3.55–3.38 (m, 3 H), 3.34 (s, 3 H), 2.49 (br s, 1 H), 1.73–1.65 (m, 2 H), 1.64–1.50 (m, 2 H), 1.49–1.30 (m, 1 H), 0.97 (t, J = 7.5 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 76.8, 70.7, 58.3, 36.1, 32.3, 26.8, 16.2, 10.1.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.49; H, 12.38.

Reaction of (3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (3) with Li(CH$_3$)$_2$Cu. Epoxide **3**, 0.3175 g (1.38 mmol), gave 0.2985 g (88% yield) of a 3.3:1 mixture of **13** and **14**. Analytical samples of **13** and **14** were obtained by preparative GLC (10% Carbowax 20M column, oven temperature = 165 °C).

(3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-4-methylhexane (13): ^{1}H NMR δ 3.92 (m, 1 H), 3.81 (m, 1 H), 3.67 (m, 1 H), 3.33 (br s, 1 H), 1.65–1.40 (m, 4 H), 1.25–1.10 (m, 1 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.07 (s, 6 H); ^{13}C NMR δ 75.8, 63.2, 40.5, 34.7, 25.9, 25.0, 18.2, 14.5, 11.6, −5.5.

Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.39; H, 12.25.

(3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-4-hydroxy-3-methylhexane (14): ^{1}H NMR δ 3.75 (m, 1 H), 3.63 (m, 1 H), 3.48 (m, 1 H), 2.59 (br s, 1 H), 1.75–1.30 (m, 5 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR δ 76.4, 61.1, 36.1, 35.2, 27.1, 25.9, 18.3, 16.5, 10.2, −5.4.

Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.22; H, 12.18.

Reaction of (3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxytetradecane (4) with Li(CH$_3$)$_2$Cu. Epoxide **4**, 0.3800 g (1.19 mmol), gave 0.2390 g (60% yield) of a 2:1 mixture of **15** and **16**, respectively. Analytical samples of **15** and **16** were obtained by semipreparative HPLC (μ-Porasil; 4:1 hexane–ether).

(3*RS*,4*SR*)-1-(Benzyloxy)-3-hydroxy-4-methyltetradecane (15): ^{1}H NMR δ 7.41–7.27 (m, 5 H), 4.57 (s, 2 H), 3.74 (dt, J = 9.2, 5.1 Hz, 1 H), 3.70–3.60 (m, 2 H), 1.77–1.67 (m, 2 H), 1.56–1.18 (m, 19 H), 0.92–0.82 (m, 6 H); ^{13}C NMR δ 138.0, 128.4, 127.7, 75.5, 73.4, 69.8, 42.0, 38.8, 32.6, 32.3, 31.9, 30.0, 29.7, 29.3, 27.3, 22.7, 15.0, 14.1.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.90; H, 11.50.

(3*RS*,4*SR*)-1-(Benzyloxy)-4-hydroxy-3-methyltetradecane (16): ^{1}H NMR δ 7.38–7.27 (m, 5 H), 4.52 (s, 2 H), 3.62–3.45 (m, 2 H), 3.44–3.34 (m, 1 H), 1.92 (br s, 1 H), 1.80–1.40 (m, 3 H), 1.40–1.18 (m, 18 H), 0.94–0.84 (m, 6 H); ^{13}C NMR δ 138.3, 128.4,

127.7, 127.6, 75.7, 73.1, 68.3, 36.5, 34.2, 32.2, 31.9, 29.8, 29.7, 29.3, 26.0, 22.7, 16.2, 14.1.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 78.66; H, 11.50.

Reaction of (3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxytetradecane (5) with $Li(CH_3)_2Cu$. Epoxide **5**, 0.0950 g (0.28 mmol), gave 0.0801 g (81% yield) of a 2.5:1 mixture of **17** and **18**, respectively. Individual samples of **17** and **18** were obtained by column chromatography (silica gel; 19:1 hexane–ether).

(3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-4-methyltetradecane (17): ^1H NMR δ 3.90 (dt, J = 10.1, 4.6 Hz, 1 H), 3.86–3.75 (m, 1 H), 3.70–3.61 (m, 1 H), 3.38 (d, J = 4.2 Hz, 1 H), 1.65–1.03 (m, 21 H), 0.93–0.83 (m, 15 H), 0.08 (s, 6 H); ^{13}C NMR δ 76.1, 63.2, 38.8, 34.5, 32.4, 31.9, 30.0, 29.7, 29.3, 27.3, 25.9, 22.7, 18.2, 15.0, 14.1, −5.5.

(3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-4-hydroxy-3-methyltetradecane (18): ^1H NMR δ 3.83–3.72 (m, 2 H), 3.67–3.57 (m, 1 H), 3.35 (s, 1 H), 1.68–1.18 (m, 21 H), 0.92–0.82 (m, 15 H), 0.04 (s, 6 H); ^{13}C NMR δ 75.6, 61.0, 36.4, 35.0, 34.4, 32.1, 29.8, 29.6, 29.5, 29.3, 26.0, 25.7, 18.2, 16.4, 14.0, −5.5.

Reaction of (3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (7) with $Li(CH_3)_2Cu$. Epoxide **7**, 0.4480 g (1.94 mmol), gave 0.3680 g (77% yield) of a 2.5:1 mixture of **21** and **22**. Analytical samples of **21** and **22** were obtained by preparative GLC.

(3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-4-methylhexane (21): ^1H NMR δ 3.90 (m, 1 H), 3.82 (m, 1 H), 3.73 (m, 1 H), 3.02 (br s, 1 H), 1.78–1.30 (m, 4 H), 1.22–1.08 (m, 1 H), 0.91 (t, J = 7.7 Hz, 3 H), 0.90 (s, 9 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.08 (s, 6 H); ^{13}C NMR δ 75.1, 63.1, 40.5, 35.8, 25.5, 18.2, 13.9, 11.8, −5.5.

Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.19; H, 12.30.

(3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-4-hydroxy-3-methylhexane (22): ^1H NMR δ 3.74 (m, 1 H), 3.65 (m, 1 H), 3.45 (m, 1 H), 2.48 (br s, 1 H), 1.80–1.60 (m, 2 H), 1.55–1.40 (m, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.90 (s, 9 H), 0.87 (d, J = 7.0 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR δ 76.1, 61.4, 36.6, 35.6, 26.9, 25.9, 18.3, 13.5, 10.8, −5.4.

Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.48; H, 12.20.

Reaction of 3,4-Epoxyalkan-1-ol Derivatives with 2:1 Trimethylaluminum–*n*-Butyllithium. General. The following procedure is typical.

Reaction of (3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxyhexane (6) with 2:1 TMA–*n*-BuLi. In a one-neck 100-mL round-bottom flask equipped with an ice bath, magnetic stirrer, rubber septum, and a nitrogen inlet were placed 40 mL of dry hexane and 0.7400 g (3.60 mmol) of **6**. The reaction vessel was purged with dry nitrogen, and 3.60 mL of a 2.0 M solution of trimethylaluminum in hexane was added, followed by dropwise addition of 1.50 mL of a 2.41 M solution of *n*-butyllithium in hexane. The white suspension was stirred for 1 h at 0 °C and allowed to stand overnight at room temperature. Aqueous 1 M HCl was carefully added (**CAUTION**: Vigorous gas evolution!), and the reaction mixture was extracted with 3 × 50 mL portions of ether. The combined organic layers were washed with an additional portion of 1 M HCl and 3 × 50 mL portions of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to afford 0.7795 g of a colorless oil. Analysis of the crude product by HPLC (μ-Porasil; 2:1 hexane–ether), ^1H NMR, and ^{13}C NMR with the aid of authentic standards showed that it consisted of a 9:1 mixture of **19** and **20**, respectively. Column chromatography of 0.7450 g of the crude product (silica gel; 19:1 hexane–ether) gave 0.4501 g (59% yield) of pure **19**.

Reaction of (3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxyhexane (1) with 2:1 TMA–*n*-BuLi. The general procedure gave a 65:1 mixture of **9** and **10**, respectively, in 86% isolated yield. The diastereomer ratio was determined from the crude product mixture by HPLC (μ-Porasil; 2:1 hexane–ether; UV detection) and ^1H NMR analysis with the aid of authentic standards.

Reaction of (3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (3) with 2:1 TMA–*n*-BuLi. The general procedure gave a 50:1 mixture of **13** and **14** in 90% yield. The diastereomer ratio was determined from the crude product mixture by GLC (10% Carbowax 20M, oven temperature = 165 °C) and ^1H NMR analysis with the use of authentic standards.

Reaction of (3*RS*,4*RS*)-1-(Benzyloxy)-3,4-epoxytetradecane (4) with 2:1 TMA–*n*-BuLi. The general procedure gave a ca. 250:1 ratio of **15** and **16**, respectively, in 83% yield. HPLC (μ-Porasil; 4:1 hexane–ether; UV detection) and ^1H NMR analysis of the diastereomer ratio were performed using the crude product mixture with the aid of authentic standards.

Reaction of (3*RS*,4*RS*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxytetradecane (5) with 2:1 TMA–*n*-BuLi. The general procedure gave a 90:1 mixture of **17** and **18**, respectively, in 88% yield. The diastereomer ratio was estimated from ^1H NMR, ^{13}C NMR, and HPLC (RI detection) analysis of the crude product mixture with the aid of authentic standards.

Reaction of (3*RS*,4*SR*)-1-(*tert*-Butyldimethylsiloxy)-3,4-epoxyhexane (7) with 2:1 TMA–*n*-BuLi. The general procedure gave a 5:1 mixture of **21** and **22**, respectively, in quantitative yield. The diastereomer ratio was determined by ^1H NMR and ^{13}C NMR analysis of the crude product mixture.

Reaction of (3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxypentane (8) with 2:1 Triethylaluminum–*n*-BuLi. To a 25-mL round-bottom flask equipped with an ice bath, magnetic stirrer, rubber septum, and a nitrogen inlet were added 0.6402 g (3.3 mmol) of epoxide **8**, 8 mL of hexane, and 7.7 mL of a 1 M solution of triethylaluminum in hexane. To the mixture was added 1.7 mL of a 2.41 M solution of *n*-BuLi in hexane over 5 min. The cloudy suspension was stirred vigorously for 5 h at 0 °C under a dry nitrogen atmosphere and quenched by the cautious addition of 10 mL of 3 M HCl. The reaction mixture was extracted with 3 × 50 mL portions of ether, and the combined organic layers were washed with 20 mL of 3 M HCl and 3 × 50 mL of water, dried ($MgSO_4$), and concentrated with a rotary evaporator to give 0.5189 g (76% yield) of an 11:1 mixture of **9** and **23**, respectively. The product mixture contained an additional 4 mol % of a hydride addition product, 1-(benzyloxy)-3-hydroxypentane, **24**. Analytical samples of the three products were obtained with an HPLC (μ-Porasil; 2:1 hexane–ether).

(3*RS*,4*RS*)-1-(Benzyloxy)-3-ethyl-4-hydroxypentane (23): ^1H NMR δ 7.45–7.25 (m, 5 H), 4.50 (s, 2 H), 3.83 (m, 1 H), 3.58 (dt, J = 9.5, 5.3 Hz, 1 H), 3.48 (m, 1 H) 2.75 (br s, 1 H), 1.76 (sextet, J = 6.8 Hz, 1 H), 1.55–1.18 (m, 2 H), 1.10 (d, J = 6.4 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.78; H, 9.83.

(3*RS*)-1-(Benzyloxy)-3-hydroxypentane (24): ^1H NMR δ 7.45–7.25 (m, 5 H), 4.52 (s, 2 H), 3.80–3.59 (m, 3 H) 2.87 (br s, 1 H), 1.75 (m, 2 H), 1.60–1.45 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.44; H, 9.08.

Reaction of (3*RS*,4*RS*)-1-Methoxy-3,4-epoxyhexane (2) with Trimethylaluminum. To a 25-mL round-bottom flask equipped with an ice bath, magnetic stirrer, rubber septum, and a nitrogen inlet were added 0.3112 g (2.39 mmol) of epoxide **2** and 5 mL of dry hexane. To this solution was added 2.4 mL of a 2.0 M solution of trimethylaluminum in hexane, and the reaction temperature was maintained at 0 °C for 2 h. The reaction mixture was allowed to stand at room temperature for 16 h and quenched by careful addition of 20 mL of 1 M HCl. The reaction mixture was extracted with 3 × 50 mL portions of ether, and the combined ether layers were washed with an additional portion of 1 M HCl and 3 × 50 mL portions of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 0.3089 g of a colorless oil. GLC analysis of the crude product mixture (20% Carbowax 20M; column temperature = 180 °C; TC detection) with the aid of authentic standards indicated that it primarily consisted of a 1:1 mixture of the starting epoxide and **11**. An unidentified product (ca. 10 mol %) was also observed; however, no **12** was detected in the mixture.

Reaction of (3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxypentane (8) with Trimethylaluminum. Reaction of epoxide **8**, 0.1012 g (0.53 mmol), in 1 mL of hexane with 0.5 mL of a 2 M solution of trimethylaluminum in hexane (25 °C, 14 h) afforded after workup 0.0871 g of a light yellow oil, **25**: ^1H NMR δ 7.6–7.2 (m, 5 H), 4.51 (m, 2 H), 3.30–3.70 (m, 3 H), 1.7–1.3 (m, 2 H), 1.46 (d, J = 6.8 Hz, 3 H).

Attempted Reaction of (3*RS*,4*SR*)-1-(Benzyloxy)-3,4-epoxyhexane (6) with 1:1 $(CH_3)_3Al$–*n*-BuLi. In a 50-mL

round-bottom flask equipped with a magnetic stirrer, a rubber septum, and a nitrogen inlet were placed 0.3045 g (1.48 mmol) of epoxide **6** and 10 mL of hexane. To this solution was added 0.76 mL of a 2 M solution of trimethylaluminum in hexane. *n*-BuLi, 0.69 mL of a 2.40 M solution in hexane, was added dropwise over several minutes. The reaction mixture was allowed to stand at room temperature for 12 h. Routine workup of the reaction mixture afforded 0.2527 g of a colorless oil. ^{1}H NMR analysis showed that recovered material was unchanged epoxide **6**. No trace of **19** or **20** was detected in the material by analytical HPLC (μ-Porasil; 9:1 hexane–ether; UV detection).

(3*RS*,4*RS*)-1-(Benzyloxy)-3-(*tert*-butyldimethylsiloxy)-4-methylhexane (26). (3*RS*,4*RS*)-1-(Benzyloxy)-3-hydroxy-4-methylhexane, **19**, was treated according to the method of Corey and Venkateswarlu[20] to give silyl ether **26** in 94% yield: ^{1}H NMR δ 7.38–7.26 (m, 5 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 3.72 (td, *J* = 7.1, 2.1 Hz, 2 H), 1.71 (m, 2 H), 1.56 (m, 1 H), 1.40 (m, 1 H), 1.06 (m, 1 H), 0.87 (t, *J* = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR δ 138.6, 128.3, 127.6, 127.5, 72.9, 67.7, 40.4, 25.9, 14.3, 12.3, −4.5.

Anal. Calcd for $C_{20}H_{36}O_2Si$: C, 71.37; H, 10.78. Found: C, 71.55; H, 10.80.

(3*RS*,4*SR*)-1-(Benzyloxy)-3-(*tert*-butyldimethylsiloxy)-4-methyltetradecane (31). (3*RS*,4*SR*)-1-(Benzyloxy)-3-hydroxy-4-methyltetradecane, **15**, was silylated as above to give silyl ether **31** in 91% yield: ^{1}H NMR δ 7.36–7.24 (m, 5 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.73 (dt, *J* = 8.4, 3.8 Hz, 1 H), 3.60–3.46 (m, 2 H), 1.75–1.55 (m, 3 H), 1.35–1.17 (m, 18 H), 0.92–0.83 (m, 15 H), 0.03 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR δ 138.7, 128.3, 127.6, 127.4, 73.0, 72.8, 67.9, 44.1, 38.9, 33.0, 31.9, 31.8, 30.0, 29.7, 29.4, 27.6, −4.3, −4.6.

Anal. Calcd for $C_{28}H_{52}O_2Si$: C, 74.93; H, 11.68. Found: C, 74.80; H, 11.87.

(3*RS*,4*RS*)-1-Hydroxy-3-(*tert*-butyldimethylsiloxy)-4-methylhexane (27). A 25-mL round-bottom flask was charged with 10 mL of ether, 0.5 g of 10% Pd–C, and 1.3280 g (40 mmol) of compound **26**. Hydrogen was bubbled into the stirred solution at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated with a rotary evaporator to give 0.9705 g (99% yield) of analytically pure **27**: ^{1}H NMR δ 3.73 (m, 3 H), 2.1 (s, 1 H), 1.68 (q, *J* = 5.7 Hz, 2 H), 1.64–1.42 (m, 2 H), 0.89 (t, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 75.3, 60.9, 40.4, 34.4, 25.9, 25.7, 24.0, 15.0, 12.2, −4.3, −4.5.

Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.24; H, 12.25.

(3*RS*,4*SR*)-1-Hydroxy-3-(*tert*-butyldimethylsiloxy)-4-methyltetradecane (32). Benzyl ether **31**, 0.6360 g (1.42 mmol), was hydrogenolyzed (1 atm of H_2; room temperature; 2 h) with 0.45 g of 10% Pd–C to afford 0.4961 g (97% yield) of analytically pure **32**: ^{1}H NMR δ 3.81–3.70 (m, 3 H), 1.70–1.50 (m, 4 H), 1.34–1.20 (m, 18 H), 0.92–0.83 (m, 15 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR δ 75.0, 61.0, 38.7, 33.3, 33.2, 31.9, 29.9, 29.6, 29.3, 25.9, 25.7, 22.7, 18.0, 14.1, 13.7, 11.0, −4.3, −4.6.

Anal. Calcd for $C_{21}H_{46}O_2Si$: C, 70.32; H, 12.93. Found: C, 70.33; H, 13.02.

(3*RS*,4*RS*)-3-(*tert*-Butyldimethylsiloxy)-4-methylhexanoic Acid (28). Ruthenium Tetraoxide Method.[24] A 25-mL round-bottom flask was charged with 7 mL of a 3:2:2 mixture of water, acetonitrile, and CCl_4, ca. 10 mg of $RuCl_3$, and 0.8770 g (4.1 mmol) of $NaIO_4$. To the vigorously stirred mixture was added 0.2585 g (1.05 mmol) of compound **27**. After 2 h at room temperature, the reaction mixture was poured into a separatory funnel containing 10 mL of methylene chloride and 1 mL of saturated NaCl solution. The phases were separated, and the aqueous layer was extracted with 4 × 10 mL portions of methylene chloride. The combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to afford 0.2535 g of a dark oil. A portion of the crude product (0.2355 g) was distilled with a Kugelrohr apparatus to give 0.2340 g (92% yield) of **28**: bp(0.8 Torr) = 100–105 °C; ^{1}H NMR δ 11.5 (br s, 1 H), 4.06 (td, *J* = 6.1, 3.7 Hz, 1 H), 2.45 (d, *J* = 6 Hz, 2 H), 1.65–1.40 (m, 2 H), 1.03 (m, 1 H), 0.89 (t, *J* = 7.5 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, *J* = 7.0 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR δ 177.5, 72.9, 40.7, 38.8, 25.8, 24.5, 18.0, 14.3, 12.0, −4.6.

Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 60.01; H, 10.81.

Methyl (3*RS*,4*RS*)-3-(*tert*-Butyldimethylsiloxy)-4-methylhexanoate (29). Methylation of acid **28**, 0.1995 g (0.77 mmol), with an ethereal solution of diazomethane afforded 0.2090 g (99% yield) of **29**: ^{1}H NMR δ 4.10 (td, *J* = 6.3, 3.1 Hz, 1 H), 3.66 (s, 3 H), 2.39 (m, 2 H), 1.57 (m, 1 H), 1.42 (m, 1 H), 1.24 (m, 2 H), 1.09–0.95 (m, 1 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.85 (s, 9 H), 0.84 (t, *J* = 6.9 Hz, 3 H), 0.09 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR δ 75.2, 60.9, 40.4, 34.5, 25.9, 24.0, 15.0, 12.2, −4.3, −4.5.

Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.20; H, 10.97.

Methyl (3*RS*,4*SR*)-3-(*tert*-Butyldimethylsiloxy)-4-methyltetradecanoate (33). Pyridinium Dichromate Method.[25] In a 50-mL round-bottom flask were placed 10 mL of dry DMF, 1.010 g (2.8 mmol) of compound **32**, and 4.24 g (11.3 mmol) of pyridinium dichromate. The solution was allowed to stand overnight at room temperature and was poured into 200 mL of water in a separatory funnel. The mixture was extracted with 4 × 100 mL portions of ether, and the combined ether layers were washed with 200 mL of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 0.671 g of a yellow oil. The crude product was methylated with an ethereal solution of diazomethane to give a crude ester. Column chromatography of the crude material (silica gel; 19:1 hexane–ether) gave a 62% yield of **33**: ^{1}H NMR δ 4.12 (dt, *J* = 8.2, 4.3 Hz, 1 H), 3.67 (s, 3 H), 2.45–2.26 (m, 2 H), 1.67–1.57 (m, 1 H), 1.45–1.20 (m, 18 H), 0.91–0.84 (m, 15 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR δ 173.0, 72.9, 51.3, 39.1, 37.8, 32.8, 31.9, 29.8, 29.6, 29.5, 29.3, 27.5, 25.7, 22.6, 14.0, 13.8.

Anal. Calcd for $C_{22}H_{46}O_3Si$: C, 68.33; H, 11.99. Found: C, 68.58; H, 12.03.

Methyl (3*RS*,4*RS*)-3-Hydroxy-4-methylhexanoate (30). To a stirred solution of 0.5770 g (2.1 mmol) of compound **29** in 4 mL of acetonitrile was added 0.5 mL of aqueous 48% HF. The reaction mixture was allowed to stand at room temperature for 8 h, and ca. 1 g of sodium carbonate was added. After 1 h the mixture was diluted with 10 mL of ether, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 0.2740 g of an oil. A portion of the crude product (0.2645 g) was distilled with a Kugelrohr apparatus to afford 0.2245 g (76% yield) of **30**:[14] bp(0.4 Torr) = 98–100 °C; ^{1}H NMR δ 3.95 (ddd, *J* = 10.6, 4.5, 1.0 Hz, 1 H), 3.70 (s, 3 H), 2.80 (br s, 1 H), 2.46 (dd, *J* = 16.5, 10.6 Hz, 1 H), 2.45 (dd, *J* = 16.5, 1.0 Hz, 1 H), 1.60–1.36 (m, 2 H), 1.23–1.09 (m, 1 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR δ 173.8, 71.0, 51.7, 39.8, 38.6, 25.4, 13.8, 11.7.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.40; H, 9.83.

Methyl (3*RS*,4*SR*)-3-Hydroxy-4-methyltetradecanoate (34). To a 25-mL round-bottom flask were added 0.0900 g (0.23 mmol) of compound **33**, 1.5 mL of dry THF, and 0.93 mL of a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF. The reaction mixture was stirred at room temperature for 2 h and poured into 200 mL of ether in a separatory funnel. The ethereal solution was washed with 50 mL of ice-cold aqueous 15% acetic acid, 200 mL of saturated $NaHCO_3$, and 100 mL of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to afford 0.0850 g of a light yellow oil. The crude material was purified by column chromatography (silica gel; 19:1 hexane–ether) to give 0.0481 g (77% yield) of **34**:[12e] ^{1}H NMR δ 3.87 (ddd, *J* = 9.2, 5.7, 3.2 Hz, 1 H), 3.72 (s, 3 H), 2.85 (s, 1 H), 2.49 (dd, *J* = 16.3, 3.2 Hz, 1 H), 2.40 (dd, *J* = 16.3, 9.3 Hz, 1 H), 1.67–1.53 (m, 1 H), 1.52–1.10 (m, 18 H), 0.92–0.84 (m, 6 H); ^{13}C NMR δ 174.0, 71.8, 51.8, 38.1, 37.6, 32.3, 31.9, 29.9, 29.6, 29.4, 27.1, 22.7, 14.9, 14.1.

Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.23; H, 11.81.

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(24) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(25) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

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Supplementary Material Available: Preparative detail and complete spectral and analytical data for (*E*)-3-tetradecen-1-ol, 1-(benzyloxy)-3-hexyne, 1-(benzyloxy)-3-pentyne, (*E*)-1-(benzyloxy)-3-hexene, (*E*)-1-(benzyloxy)-3-tetradecene, (*E*)-1-methoxy-3-hexene, (*E*)-1-(*tert*-butyldimethylsiloxy)-3-tetradecene, (*Z*)-1-(benzyloxy)-3-hexene, (*Z*)-1-(*tert*-butyldimethylsiloxy)-3-hexene, and (*Z*)-1-(benzyloxy)-3-pentene (4 pages). Ordering information is given on any current masthead page.

Study of Reactions Leading to Sulfine Formation. 3. Competition of Reaction Pathways in the Reaction of Methoxide Ion with Methyl 1-Naphthylmethanesulfinates[1]

John L. Kice* and Harvinder Lotey

Department of Chemistry, University of Denver, Denver, Colorado 80208

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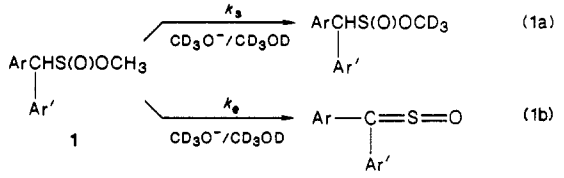
In CD_3O^-/CD_3OD methyl 1-naphthylmethanesulfinates, $NpCH_2S(O)OCH_3$ (**2**), undergo both exchange of CH_3O by CD_3O by substitution at the sulfinyl group and elimination to form the sulfine, NpCH=S=O. With use of methyl (2-methoxy-1-naphthyl)methanesulfinate (**2a**) it has been shown that formation of the sulfine takes place by an $(E1cB)_{irrev}$ mechanism. The rates of substitution (k_s) and elimination (k_e) of a series of **2** have been determined in CD_3O^-/CD_3OD by ^1H NMR spectroscopy, and the effect of several reaction variables on the competition between substitution and elimination has been examined. Salient results are as follows: (1) the rate of elimination is markedly increased by the presence of electron-withdrawing substituents on the aromatic ring, but the rate of substitution is increased only modestly by the same substituents; (2) substituents at the 2-position of the naphthyl group cause a large decrease in k_s (steric hindrance to substitution at S=O) but have little effect on k_e (elimination rate not sensitive to steric requirements of ortho substituents); (3) the activation energy for elimination is almost 9 kcal/mol greater than the activation energy for substitution. This large difference in activation energy contrasts with the 1–2 kcal/mol difference for elimination vs substitution found[14] with alkyl halides.

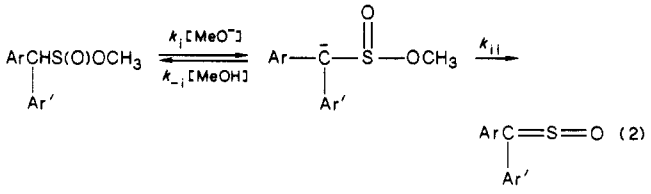
When treated with CD_3O^- in CD_3OD a methyl diarylmethanesulfinate (**1**) can undergo two reactions: (a) replacement of the CH_3O group by CD_3O via nucleophilic substitution at the sulfinyl group (eq 1a) and (b) elimination to form the corresponding sulfine (eq 1b).[2] This



(1a)

(1b)

latter elimination takes place[1b,2] by an $(E1cB)_{irrev}$ mechanism (eq 2, $k_{ii} > k_{-i}$[MeOH]) rather than the $(E1cB)_{rev}$ mechanism ($k_{ii} < k_{-1}$[MeOH]) that is observed in analogous sulfene-forming eliminations of arylmethanesulfonates[3,4] with leaving groups of comparable pK_a.



(2)

We originally planned to explore the effect of various reaction variables on the competition between substitution (k_s) and sulfine-forming elimination (k_e) by measuring (k_s/k_e) for various **1** under a variety of reaction conditions. However, because the exchange reaction (eq 1a) turned out to be considerably slower than sulfine formation (eq 1b) the 1-CD_3O^- system proved to be a less than optimal one for this purpose. To have adequate experimental flexibility in such studies it is necessary to have a system where $k_s > k_e$ under most reaction conditions.

Comparison of the rate constant for eq 1a with that for the analogous exchange involving a phenylmethanesulfinate ($PhCH_2S(O)OCH_3 + CD_3O^- \rightarrow PhCH_2S(O)OCD_3 + CH_3O^-$) showed the latter process was ~40 times faster. This suggested that the proper substrate for studies of the competition between substitution and sulfine-forming elimination would be a methyl *monoarylmethanesulfinate* that gave a reasonably stable sulfine upon elimination. Since 2-methoxynaphthalene-1-thiocarbaldehyde *S*-oxide (**8a**) was known[5] and had been isolated as a pure compound, methyl (2-methoxy-1-naphthyl)methanesulfinate (**2a**) was chosen for initial examination. When this showed that $k_s > k_e$ for **2a**, additional 1-naphthylmethanesulfinates (**2b–e**) were prepared and studied in similar fashion. The present paper reports the results of this work and what has been learned from it about the effect of various reaction variables on the competition between substitution at S=O and sulfine-forming elimination for such sulfinate esters.

Results

Synthesis of Methyl 1-Naphthylmethanesulfinates (2). Esters **2a–d** were prepared from (chloromethyl)-naphthalenes **3a–d** via the five-step sequence shown in

(1) (a) This research supported by the National Science Foundation, Grant CHE-8610116. (b) Paper 2: Kice, J. L.; Lotey, H. *J. Org. Chem.* **1988**, *53*, 3593.
(2) Kice, J. L.; Rudzinski, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 2414.
(3) King, J. F.; Beatson, R. P. *Tetrahedron Lett.* **1975**, *973*.
(4) Davy, M. B.; Douglas, K. T.; Loran, J. S.; Stettner, A.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1196.
(5) Strating, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bays* **1964**, *83*, 631.

0022-3263/89/1954-3596$01.50/0