Stereochemistry of S_N2' Additions to Acyclic Vinyloxiranes

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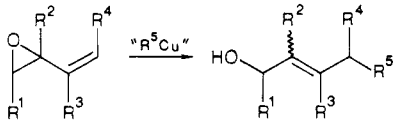
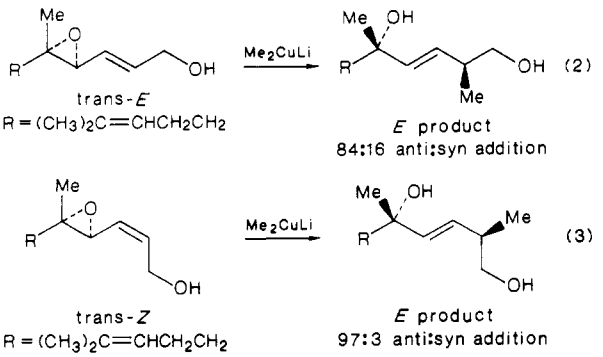
The isomeric *trans*-(*E*)-, *trans*-(*Z*)-, *cis*-(*E*)-, and *cis*-(*Z*)-vinyloxiranes **7**, **9**, **17**, and **19** were prepared from 2-(benzyloxy)ethanol by sequential Swern–Wittig or Swern–Horner–Emmons propionate condensation, DIBAH reduction, Sharpless epoxidation, Swern oxidation, Wittig or Horner–Emmons acetate condensation, and a second DIBAH reduction. Addition of lithium dimethylcuprate and lithium methylcyanocuprate to these epoxides in THF–ether at −20 to 0 °C afforded the allylic alcohols **22**, **25**, *ent*-**23**, and *ent*-**22** as the major products. These products are formed by anti addition to the lower energy conformer (*s*-trans for **7**, **17**, and **19** and *s*-cis for **9**) of the respective vinyloxirane. The conformational preferences of transition-state-like geometries of the vinyloxiranes, calculated with the aid of Still's MACROMODEL program, were in agreement with the observed trends.

The S_N2' addition of organocopper reagents to vinyloxiranes represents a potentially versatile route to a variety of allylic alcohols. First observed in 1970 by Anderson[1] and Johnson[2] with butadiene epoxide and isoprene epoxide, the reaction was subsequently explored by others using cyclic vinyloxiranes with endocyclic or exocyclic double-bond and epoxide combinations (eq 1: $R^1 = R^2 = R^3 = R^4 = H$;[1] $R^1 = R^2 = R^4 = H$, $R^3 = Me$;[2] R^1, R^4 = ring;[3] R^1, R^3 = ring;[4] R^2, R^3 = ring[5,6]).

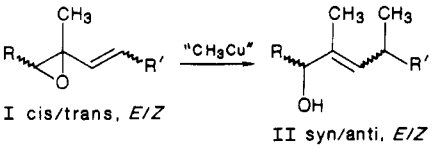


(1)

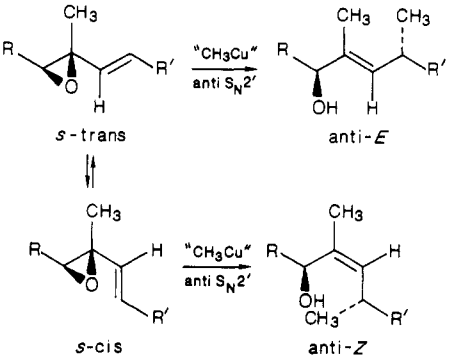
In the first reported study on the stereochemistry of cuprate additions to acyclic vinyloxiranes, we found that allylic alcohol substituents were excellent S_N2' directors (eq 2 and 3).[7] The major products were formed by anti addition to the *s*-trans conformer of the vinyloxiranes.



The present study was undertaken to examine the relationship between substrate and product stereochemistry in S_N2' additions of methylcuprates to vinyloxiranes such as I (eq 4). The substitution pattern of I was selected with a view toward the eventual synthesis of polypropionate and related natural products with alternating CH_3 and OH substitution.



Based on our previous findings, we expected the cuprate additions to preferentially occur anti to the epoxide oxygen via the *s*-trans and/or *s*-cis coplanar conformation of the vinyloxirane (eq 5).[7]

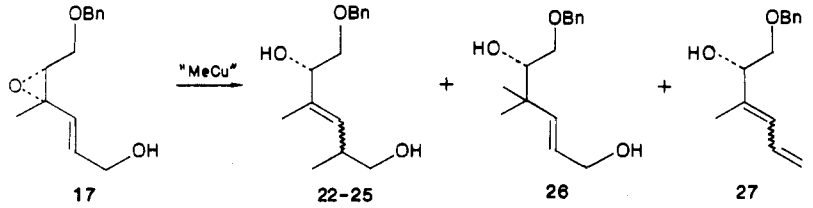


The isomeric vinyloxiranes employed in this study were prepared from 2-(benzyloxy)ethanol (**1**) by parallel reaction sequences in which known variants of the Wittig or Horner–Emmons condensation provided control over double-bond geometry.[8] The Sharpless asymmetric epoxidation reaction was used to introduce the homochiral epoxide substituent.[9] Thus ester **2**, obtained through the Swern–Wittig sequence[10] on alcohol **1**, afforded allylic alcohol **3** upon reduction with DIBAH.[11] Sharpless epoxidation[9] with the reagent derived from L-(+)-diethyl tartrate gave epoxy alcohol **4** of 80–90% ee as determined by ^1H NMR analysis of the O-methyl mandelic ester derivative.[12] A second Swern–Wittig sequence[10] yielded the *E*-conjugated ester **6**, which afforded the allylic alcohol **7**

(1) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978. See also: Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239.
(2) Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4979. See also: Cahiez, C.; Alexakis, A.; Normant, J. R. *Synthesis* **1978**, 528. Asaki, S.; Butsugan, Y. *Chem. Lett.* **1980**, 185. Tamara, M.; Suzukamo, G. *Tetrahedron Lett.* **1981**, *22*, 577. Gras, J.-L. *J. Org. Chem.* **1981**, *46*, 3738.
(3) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675. Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. Marino, J. P.; Abe, H. *Synthesis* **1980**, 872. Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114. Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379. Jaën, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1984**, *49*, 5280. Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.
(4) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907.
(5) Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122.
(6) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106.
(7) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985.
(8) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735.
(9) Cf. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
(10) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
(11) Abbreviations: Bn = CH_2Ph; DIBAH = *i*-Bu_2AlH; KHMDS = $[(CH_3)_3Si]_2NK$; TBAF = Bu_4NF; TBS = *t*-$BuSiMe_2$; TFE = CF_3CH_2.
(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem* **1969**, *34*, 2543.

0022-3263/88/1953-4274$01.50/0

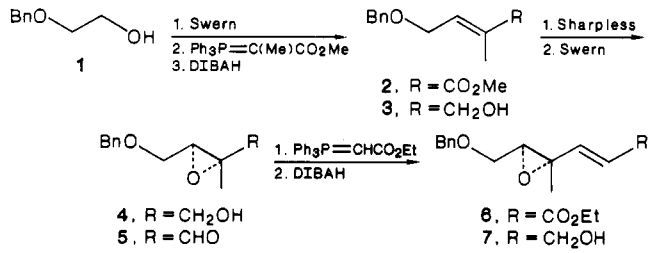
Table I. Additions of Methylcopper Reagents to Vinyloxirane 17



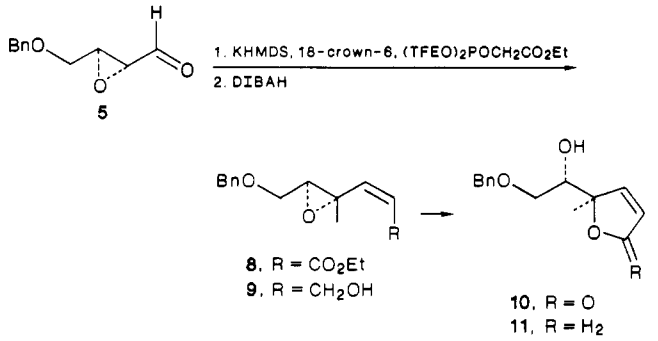
"MeCu"[a]	solvent	temp (°C)	yield (%)	S_N2' (%) (22–25)	S_N2 (%) (26)	elim (%) (27)
$(MeMgBr)_2CuBr$	THF	−20	40	54	46	
$(MeLi)_2CuCN$[b]	Et_2O	−20	55	85	15	
(MeLi)CuCN	Et_2O	−20	65	85	5	10
$(MeLi)_2CuI$	Et_2O	−20	50	75	25	
$(MeLi)_2CuI$	3:1 THF–Et_2O	−20	65	100		
$(MeLi)_2CuI$	4:1 THF–Et_2O	0	74	91	2	7

[a] The stoichiometry of the reagent is shown. [b] Product ratios varied in replicate experiments.

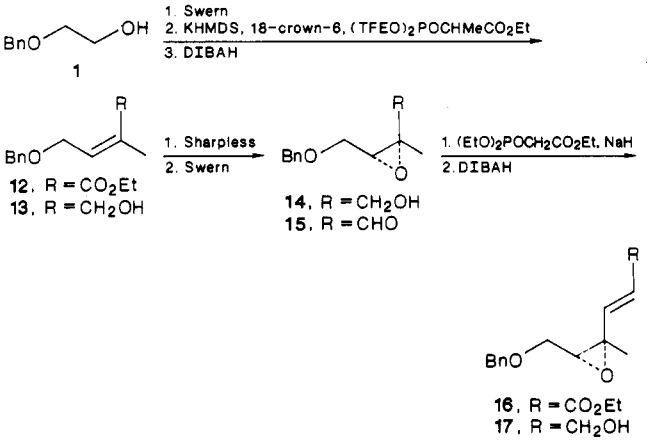
upon reduction with DIBAH.[11] This reduction also gave significant amounts of conjugated aldehyde byproduct unless water was added slowly to the reaction just prior to workup. The acid-sensitive epoxy alcohol **7** was conveniently purified by chromatography on triethylamine-deactivated silica gel.



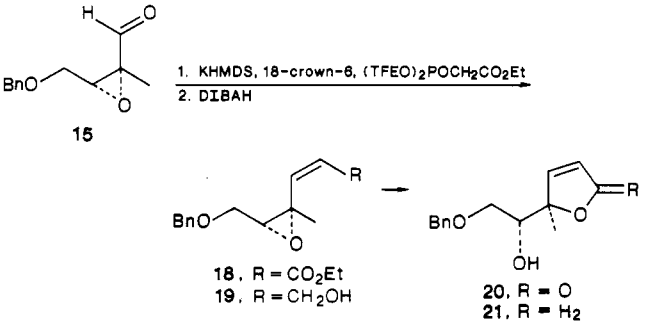
Treatment of epoxy aldehyde **5** with Still's trifluoroethyl phosphonoacetate reagent gave the *Z*-conjugated ester **8**.[13] This ester, in keeping with the *Z* double-bond geometry, was slowly transformed to butenolide **10** upon standing at room temperature. Reduction of ester **8** with DIBAH[11] afforded the *trans*-(*Z*)-vinyloxirane **9** along with a small amount of the dihydrofuran **11** as a byproduct. Both **11** and butenolide **10** appeared homogeneous by TLC and ^1H NMR analysis. They are presumed to arise by internal displacement at the allylic epoxide center and the stereochemistry is assigned accordingly.



Condensation of 2-(benzyloxy)acetaldehyde with Still's ethyl [bis(trifluoroethyl)phosphono]propionate reagent yielded the *Z*-conjugated ester **12**.[13] The derived alcohol **13** afforded epoxy alcohol **14** of 75–85% ee[12] upon Sharpless epoxidation with the L-(+)-tartrate reagent.[9] The Swern–Wittig sequence converted **14** via the aldehyde **15** to the *E*-conjugated ester **16** whose reduction with DIBAH, as for ester **6**, led to the acid labile *E*-allylic alcohol **17**.



The final isomeric vinyloxirane **19** required for these studies was prepared from the cis-epoxy aldehyde **15** by a sequence analogous to that employed for the *trans-Z* isomer **9**. In this case, the butenolide **20** was not observed as a byproduct, but reduction of the ester **18** gave significant amounts of the dihydrofuran **21** in addition to the desired alcohol **19**. Before examining the comparative



behavior of vinyloxiranes **7**, **9**, **17**, and **19**, we conducted a brief survey of additions to the *cis*-(*E*)-vinyloxirane **17** by various organocopper reagents to optimize reaction conditions for the S_N2' addition mode. These results are summarized in Table I. Three different product types were observed; S_N2' (**22–25**), S_N2 (**26**), and elimination (**27**). Conceivably these three products could originate from a common complex, as shown in eq 6.[14] Product identities

(13) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

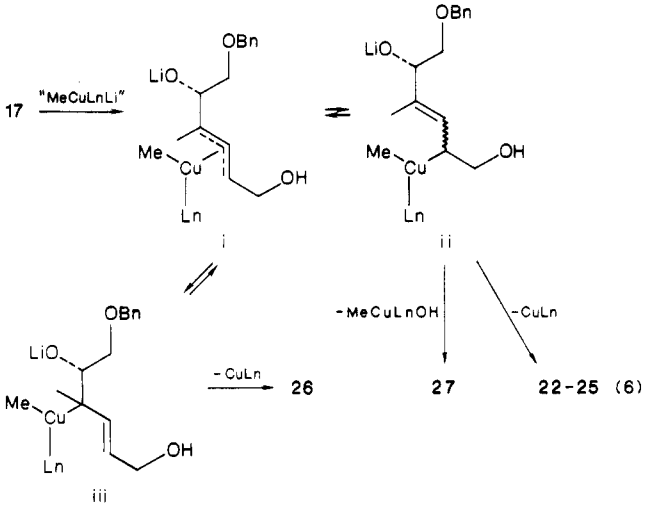
(14) The analogy is drawn to S_N2' additions of organocopper reagents to allylic esters. For leading references, see: Goering, H. L.; Kantner, S. D.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.

Table II. S_N2' Additions of Cuprates to Vinyloxiranes

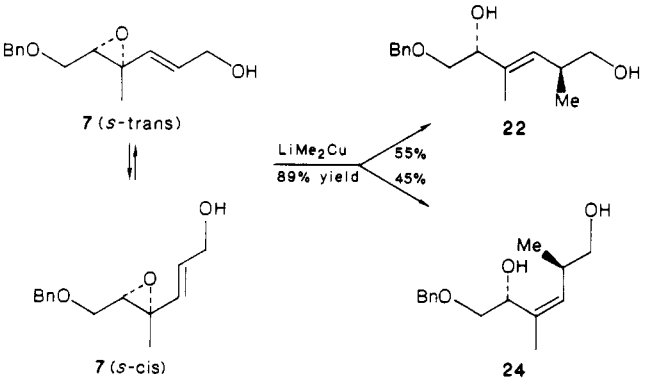
oxirane	RCu[a]	S_N2' products (%) anti *E* **22**	anti *Z* **24**	syn *E* **23**	syn *Z* **25**	yield (%)	mode of addition anti/syn	*s*-trans/*s*-cis
trans-*E* (**7**)	A	55	45	<1	<1	89	99:1	55:45
	B	68	23	7	2	76	91:9	75:25
trans-*Z* (**9**)	A	<1	<1	13	87	88	>99:1	13:87
	B	<1	2	16	82	97	98:2	16:84
cis-*E* (**17**)[b]	A	4	<1	80	16	57	96:4	84:16
	B	3	<1	95	2	76	97:3	98:2
cis-*Z* (**19**)[b]	A	93	6	1	<1	63	99:1	94:6
	B	88	<1	9	2	71	90:10	97:3

[a] A = Me_2CuLi in THF–ether at −20 to 0 °C; B = LiMeCuCN in ether at −20 to 0 °C. [b] The products are *ent*-**22**, **23**, **24**, **25**.

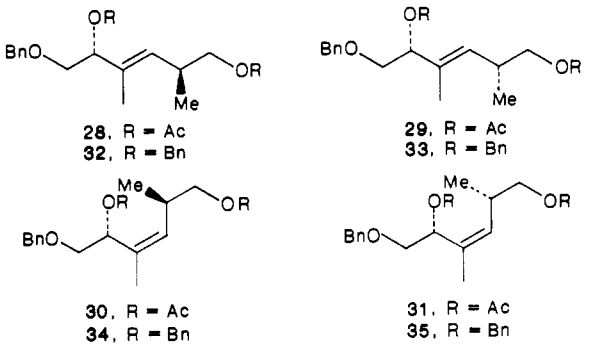
were surmised from the ^1H NMR spectra and ratios were estimated from integration of these spectra and GC analysis.



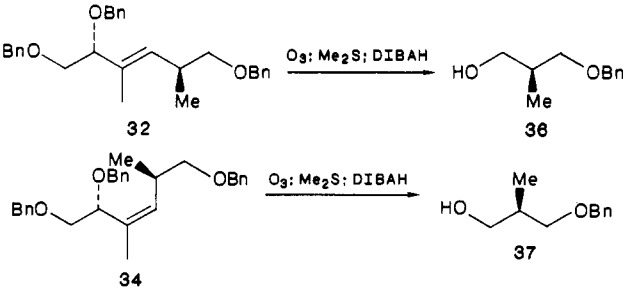
Of the cuprates examined, Me_2CuLi and LiMeCuCN gave the best overall results and they were therefore employed for the comparison studies.[15] Addition of the former to the *trans*-(*E*)-vinyloxirane **7** afforded only two products, the anti-*E* and the anti-*Z* allylic alcohols **22** and **24** as a nearly 1:1 mixture.[16] The latter reagent gave an



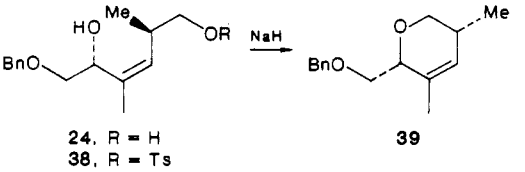
improved 3:1 ratio of **22** and **24** along with a small amount of the diastereomeric syn-*E* and syn-*Z* products **23** and **25**, also in a 3:1 ratio (Table II). Product ratios were obtained from capillary gc analysis of the derived acetates **28** and **30**. Pure samples of the diols were secured through



chromatographic separation on silica gel. The relative stereochemistry of each diol was deduced as follows: The absolute stereochemistry at the secondary carbinol center of both is defined as *R* from consideration of the known preference of the L-(+)-tartrate reagent in the Sharpless epoxidation (**3** → **4**).[9] The absolute stereochemistry of the newly introduced methyl stereocenters in the *E* and *Z* isomers **22** and **24** was established as *S* and *R*, respectively, through ozonolysis–reduction of the derived tribenzyl ethers **32** and **34** leading to the known *S* and *R* alcohols **36** and **37**.[8] The optical rotation of these alcohols, when



corrected for the enantiomeric excess (ee) of the starting vinyloxirane, provided an independent check on the diastereoselectivity (>90:10 favoring the anti mode) of these S_N2' additions.[16] The double-bond geometry was surmised from ^{13}C NMR analysis[17] and by conversion of the *Z* isomer **24** to the cyclic ether **39** via the tosylate **38**.

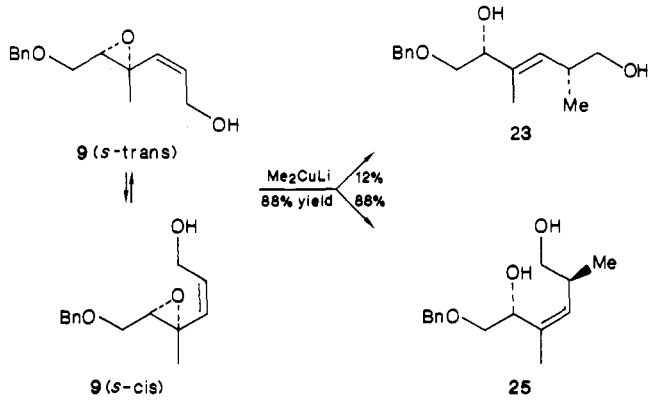


(15) For a recent survey of organocuprate reagents, see: Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

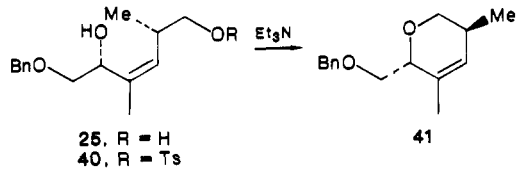
(16) The prefixes syn and anti are used to denote relative stereochemistry of substituents on the zig-zag conformation of the acyclic chain as suggested by Masamune. Masamune, S.; Kaiko, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. Anti addition and syn addition refer to the relationship between the incoming cuprate reagent and the epoxide oxygen. Cis and trans indicate the oxirane stereochemistry whereas *E* and *Z* designate double-bond stereochemistry.

(17) Cf. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

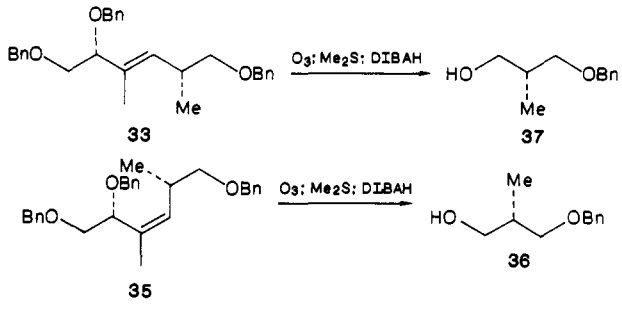
Addition of $LiMe_2Cu$ to the *trans*-(*Z*)-vinyloxirane **9** also gave rise to only two products, the syn-*E* and the syn-*Z* allylic alcohols **23** and **25** in the ratio 12:88 according to GC analysis of the diacetates **29** and **31**.[16] The diastereoisomeric diacetates **28** and **30** were not present. The cyanocuprate reagent afforded a like ratio of **23** and **25** (16:84) along with a small amount of the anti-*Z* product **24**, analyzed as the diacetates.



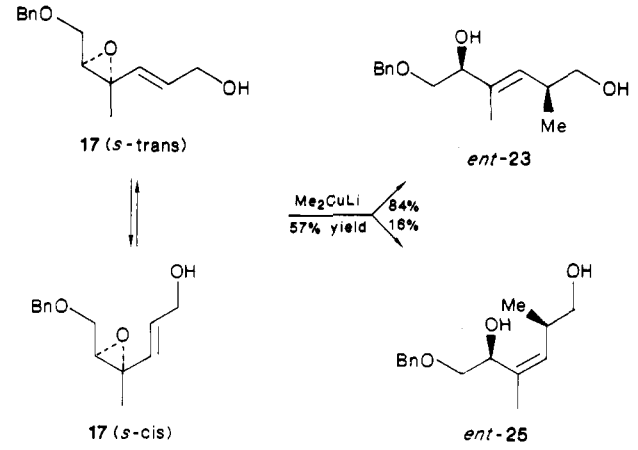
Alcohols **23** and **25** were separated chromatographically and the major isomer **25** was converted via the tosylate **40** to the cyclic ether **41**, epimeric with **39**. Hydroxy tosylate **40** cyclized more readily than **38**, reflecting the diequatorial nature of the substituents in ether **41**. The stereochem-



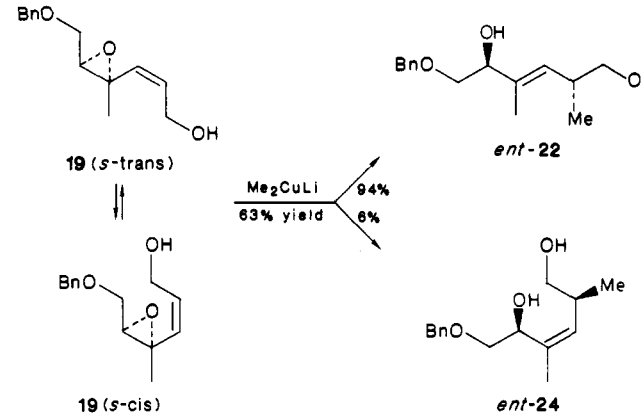
istry of each diol was confirmed as described above through ozonolysis–reduction of the benzyl ethers **33** and **35**, which yielded the *R* and *S* alcohols **37** and **36**, respectively.[8] Thus, both vinyloxiranes **7** and **9** show a high preference for anti S_N2' addition.[16]



The two vinyloxiranes, **17** and **19**, prepared from the cis epoxy alcohol **14**, were examined next. Addition of Me_2CuLi to the cis-*E* isomer **17** yielded the syn-*E* and syn-*Z* products *ent*-**23** and *ent*-**25** as a 5:1 mixture along with a small amount of the anti-*E* product *ent*-**22**, according to capillary GC analysis of the diacetate derivatives.[16,18] The cyanocuprate reagent proved more selective, affording a nearly 50:1 ratio of *ent*-**23** to *ent*-**25** and a small amount of *ent*-**22** (Table II). As expected, the optical rotations of the two major diols were similar in magnitude but opposite in sign from those of their enantiomers obtained from the *trans*-(*Z*)-vinyloxirane **9**. The cis-*Z* vinyloxirane **19** yielded mainly the anti-*E* allylic alcohol



ent-**22** upon addition of Me_2CuLi, along with a small amount of anti-*Z* (*ent*-**24**) and a trace of syn-*E* (*ent*-**23**).[16]



The cyanocuprate reagent showed slightly lower anti:syn selectivity but gave more of the *E* products (Table II). The diastereomeric ratios and the stereochemistry of the products were determined through the acetate and benzyl ether derivatives as before.

The foregoing study reveals two interesting trends. (1) Acyclic vinyloxiranes **7**, **9**, **17**, and **19**, like their previously studied counterparts (eq 2 and 3),[7] show a high anti preference in S_N2' additions of methylcuprates.[19] (2) The ratio of *E*/*Z* allylic alcohol products is significantly influenced by the geometry of the vinyloxirane substrate and, to a lesser degree, by the nature of the cuprate. These ratios must reflect transition-state energies related to the *s*-trans and *s*-cis conformers of the respective vinyloxiranes. In an attempt to gain more insight regarding these trends and with a view toward predicting product-like conformational preferences of other acyclic vinyloxiranes, we carried out molecular modeling calculations on the *s*-cis and *s*-trans conformers of **7**, **9**, **17**, and **19**.[20] The double bond and the epoxide ring were constrained to occupy

(18) The prefix *ent* is used to designate the enantiomer of the numbered compound.

(19) Anti preferences for S_N2' reactions involving cuprates have previously been observed.[3-6,14] For a review, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. For an interesting rationale involving d-orbital bidentate binding, see: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. S_N2' displacements of acyclic homochiral allylic acetates and alcohols with organocuprates have been studied by Goering (Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986; **1985**, *50*, 1597.

(20) The calculations were performed in the "Multiconformer" submode of MacroModel. Fully minimized cis/trans, *E*/*Z* isomers were used as input structures. The dihedral angle of the epoxide carbons and the double bond of each structure was constrained to 0° for the *s*-cis and 180° for the *s*-trans conformers and minimization was allowed to proceed. The ten lowest energy conformers generated for each batch minimization were subjected to a Boltzman distribution analysis to determine the average energy. In each case the highest energy conformer of the ten considered comprised less than 5% of the calculated conformational population.

Table III. S_N2' Additions of Cuprates to TBS-Protected Vinyloxiranes

7TBS trans-*E*
9TBS trans-*Z*
17TBS cis-*E*
19TBS cis-*Z*

22TBS anti-*E*
23TBS syn-*E*
24TBS anti-*Z*
25TBS syn-*Z*

		S_N2' products (%)					mode of addition	
oxirane	RCu[a]	anti *E* **22TBS**	anti *Z* **24TBS**	syn *E* **23TBS**	syn *Z* **25TBS**	yield (%)	anti/syn	*s*-trans/*s*-cis
trans-*E*	A	59	24	14	3	59[b]	83:17	73:27
(**7TBS**)	B	69	14	12	5	89	83:17	81:19
trans-*Z*	A	<1	6	79	15	89[c]	94:6	79:21
(**9TBS**)	B	0	5	48	47	79	95:5	48:52
cis-*E*	A	*d*	*d*	*d*	*d*	~10[e]	*d*	*d*
(**17TBS**)	B	0	0	100	0	~10[e]	100:0	100:0
cis-*Z*	A	*d*	*d*	*d*	*d*	~5[f]	*d*	*d*
(**19TBS**)	B	98	2	0	0	~5[f]	98:2	100:0

[a] A = Me_2CuLi in THF–ether at −20 to 0 °C; B = LiMeCuCN in THF–ether at −20 to 0 °C. [b] 26% elimination. [c] 4% elimination. [d] Not determined. [e] 90% elimination. [f] 95% elimination.

approximately perpendicular planes, as might be expected for a stereoelectronically favored reactant conformation.[19] The results of these calculations are shown in Figure 1.[20] Two significant conclusions can be drawn. (1) Vinyloxirane **7** shows the smallest energy difference between the *s*-trans and *s*-cis conformers. Accordingly, S_N2' additions to **7** would expectedly exhibit the lowest *E*/*Z* selectivity. (2) Vinyloxiranes **7**, **17**, and **19** are calculated to favor the *s*-trans, whereas **9** prefers the *s*-cis conformation. S_N2' additions to **9** should therefore give more of the *Z* product than like additions to **7**, **17**, and **19**. Both of these expectations are concordant with the experimental findings. Thus, although it does not predict product ratios exactly nor does it account for variations in these ratios with different cuprates, the modeling approach nonetheless provides a basis for comparative predictions of geometric preferences.

We previously reported enhanced anti/syn selectivities for allylic alcohols in comparison to the derived TBS ethers in S_N2' additions of methylcuprates to vinyloxiranes (eq 2 and 3).[7] It was of interest to see if this trend was also operative with alcohols **7**, **9**, **17**, and **19**. Accordingly, the TBS ethers **7TBS**, **9TBS**, **17TBS**, and **19TBS** were prepared and subjected to the cuprate additions. The results are summarized in Table III. The trans-*E* isomer **7TBS** showed higher *s*-trans/*s*-cis selectivity but lower anti/syn diastereoselectivity in comparison to its alcohol counterpart. The trans-*Z* isomer **9TBS** also exhibited a higher *s*-trans/*s*-cis preference than the alcohol **9** and slightly diminished anti/syn selectivity. The enhanced anti/syn ratios observed for alcohols **7** and **9** over **7TBS** and **9TBS** is suggestive of an OH directing effect through coordination with the cuprate or, in the latter case, chelation involving the epoxide oxygen.[7] Neither the cis-*E* nor the cis-*Z* isomers, **17TBS** or **19TBS**, gave useful amounts of S_N2' products. In both cases elimination accounted for over 90% of the reaction. The small amount of S_N2' product isolated showed high anti/syn and *s*-trans/*s*-cis selectivity. However, these product ratios are not meaningful as they may reflect preferential elimination of intermediates (eq 6) that would otherwise have yielded the minor products seen with alcohols **17** and **19**. The origin of the divergent behavior of **17TBS** and **19TBS** is unclear at present.

The foregoing study shows that homochiral acyclic vinyloxiranes can undergo highly selective anti S_N2' additions. The preference for *E* or *Z* products is somewhat reagent dependent but, with the proper choice of substrate geometry, good to excellent selectivity can be realized. Furthermore, relative preferences can be predicted from conformational analysis of appropriately constrained *s*-trans and *s*-cis precursors of the S_N2' products. The trends

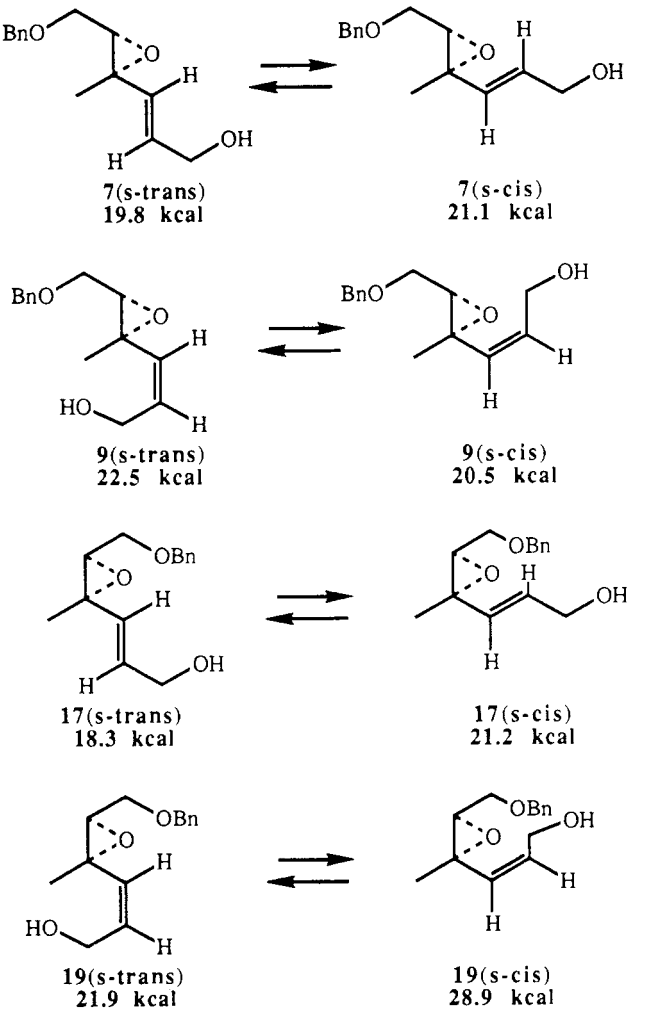


Figure 1. Calculated energies for restricted conformations of vinyloxiranes **7**, **9**, **17**, and **19**.

established for vinyloxiranes **7**, **9**, **17**, and **19** and their TBS derivatives are expected to provide the basis for further applications in natural products synthesis.

Experimental Section[21,22]

2-(Benzyloxy)ethanol (1). To a slurry of 17.7 g (0.74 mol) of sodium hydride in 2 L of dry THF was added 120 mL (2.15 mol) of ethylene glycol over 1.5 h. After addition was complete, the mixture was brought to reflux and 85 mL (0.71 mol) of benzyl bromide was added over 3 h. The mixture was refluxed for 16 h, allowed to cool to room temperature, and diluted with 1 L of ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was distilled to afford 92.8 g (85%) of alcohol **1**, bp 96–100 °C at 1.5 Torr: IR (film) ν 3400, 3100, 3080, 3040, 2930, 2870, 1495, 1455, 1360, 1210, 1110, 1065, 890, 835, 740, 700 cm^{-1}; ^1H NMR (90 MHz) δ 2.34 (m, 1 H, CH_2OH), 3.59 (m, 2 H), 3.74 (m, 2 H), 4.55 (s, 2 H, $PhCH_2O$), 7.33 (m, 5 H, phenyl H).

(*Z*)-Ethyl 4-(Benzyloxy)-2-methyl-2-butenoate (12). To a solution of 6.0 mL (68.7 mmol) of oxalyl chloride in 200 mL of dry CH_2Cl_2 at −78 °C was added 9.8 mL (138.1 mmol) of dimethyl sulfoxide. The mixture was stirred for 10 min and 6.96 g (45.7 mmol) of alcohol **1** in 10 mL of dry CH_2Cl_2 was added over 10 min. The mixture was stirred for 30 min and 30 mL (215 mmol) of Et_3N was added over 20 min. The mixture was allowed to warm to room temperature, diluted with 200 mL of ether, and filtered through a pad of $MgSO_4$. The filtrate was concentrated under reduced pressure to afford a yellow oil.

To a solution of 15.5 g (44.9 mmol) of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate and 25 g (94.5 mmol) of 18-crown-6 in 1 L of dry THF at −78 °C was added 70 mL (44.8 mmol) of 0.64 M KHMDS in toluene. The mixture was stirred for 5 min and the above crude aldehyde in 20 mL of dry THF was added over 15 min. The mixture was stirred for 45 min, allowed to warm to room temperature, and diluted with 1 L of ether. The mixture was poured into 1 L of saturated aqueous NH_4Cl and the phases were separated. The organic phase was washed with water and the combined aqueous phases were extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 19.3 g of a crude amber oil. Flash chromatography on silica gel with hexanes/60% ether–hexanes gradient afforded 0.19 g (2%) of *E* ester **2** and 6.12 g (58%) of *Z* ester **12**: IR (film) ν 3100, 3080, 3040, 2980, 2930, 2860, 1705, 1650, 1495, 1450, 1370, 1350, 1330, 1220, 1140, 1105, 1070, 1025, 945, 830, 740, 700 cm^{-1}; ^1H NMR δ 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.91 (s, 3 H, CH_3), 4.15 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.47 (m, 2 H, $BnOCH_2$), 4.52 (s, 2 H, $PhCH_2O$), 6.16 (m, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.78; H, 7.74. Found: C, 71.55; H, 7.73.

(*Z*)-4-(Benzyloxy)-2-methyl-2-buten-1-ol (13). To a solution of 30 mL (30 mmol) of 20% DIBAH in hexanes in 250 mL of dry CH_2Cl_2 at −78 °C was added 3.10 g (13.26 mmol) of ester **12** in 20 mL of dry CH_2Cl_2 over 20 min. The mixture was stirred for 1.5 h, treated with 1.0 mL of water and 200 mL of saturated aqueous Rochelle's salt, and allowed to warm to room temperature. The layers were separated and the organic phase was washed with Rochelle's salt. The combined aqueous phases were extracted with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with hexanes/80% ether–hexanes gradient afforded 2.14 g (84%) of alcohol **13**: IR (film) ν 3390, 3060, 3030, 2970, 2960, 2910, 2860, 1445, 1360, 1240, 1200, 1105, 1060, 1000, 940, 735, 695 cm^{-1}; ^1H NMR δ 1.82 (s, 3 H, CH_3), 2.11 (br s, 1 H, CH_2OH), 4.02 (d, J = 6.8 Hz, 2 H, $BnOCH_2$), 4.07 (s, 2 H, CH_2OH), 4.50 (s, 2 H, $PhCH_2O$), 5.55 (t, J = 6.8 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.42.

(2*S*,3*R*)-4-(Benzyloxy)-2,3-epoxy-2-methylbutan-1-ol (14). The procedure of Sharpless was employed.[23] To a slurry of 1.0 g of powdered 3-Å molecular sieves in 50 mL of dry CH_2Cl_2 at −5 °C were added 0.30 mL (1.42 mmol) of L-(+)-diethyl tartrate and 0.30 mL (1.00 mmol) of titanium(IV) isopropoxide. The mixture was cooled to −23 °C and 3.3 mL (14.0 mmol) of 4.25 M *tert*-butyl hydroperoxide in isooctane was added. This mixture was stirred at −23 °C for 25 min and 1.80 g (9.34 mmol) of alcohol **13** in 10 mL of CH_2Cl_2 was added over 10 min. The mixture was stirred at −20 °C for 14 h, allowed to warm to 0 °C, and quenched with 15 mL of water. The mixture was allowed to warm to room temperature, treated with 6 mL of a 30% NaOH–brine solution, and stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford 1.76 g of a pale yellow oil. Flash chromatography on silica gel with hexanes/50% ether–hexanes gradient afforded 1.56 g (80%) of epoxy alcohol **14**: IR (film) ν 3440, 3060, 3020, 2970, 2920, 2860, 1450, 1380, 1305, 1250, 1205, 1125, 1080, 1030, 905, 870, 740, 705 cm^{-1}; ^1H NMR δ 1.39 (s, 3 H, CH_3), 2.22 (m, 1 H, CH_2OH), 3.08 (t, J = 5.7 Hz, 1 H, epoxide H), 3.60 (m, 3 H), 3.75 (dd, J = 5.9, 11.0 Hz, 1 H), 4.54 (AB q, J_{AB} = 11.8 Hz, $\Delta\nu$ = 22.3 Hz, 2 H, $PhCH_2O$), 7.33 (m, 5 H, phenyl H); ^{13}C NMR δ 19.7, 60.3, 61.7, 63.8, 68.1, 73.1, 127.6, 128.2, 137.3; $[\alpha]_D^{24}$ −10.86° (*c* 3.58, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.24; H, 7.77.

Analysis of the *O*-methyl mandelate derivative by ^1H NMR indicated an ee of 80% for this alcohol.

(*E*)-(4*S*,5*R*)-Ethyl 6-(Benzyloxy)-4,5-epoxy-4-methyl-2-hexenoate (16). To a solution of 1.8 mL (20.6 mmol) of oxalyl chloride in 300 mL of dry CH_2Cl_2 at −78 °C was added 3.0 mL (42.3 mmol) of dimethyl sulfoxide. The mixture was stirred for 10 min and a solution of 2.81 g (13.5 mmol) of alcohol **14** in 5 mL of dry CH_2Cl_2 was added over 5 min. The mixture was stirred at −78 °C for 45 min and 12 mL of Et_3N was added over 10 min. The mixture was allowed to warm to room temperature, diluted with 300 mL of ether, and filtered through a pad of $MgSO_4$. The filtrate was concentrated under reduced pressure to afford 3.14 g of crude aldehyde **15**.

To a solution of 8.0 mL (40.3 mmol) of triethyl phosphonoacetate in 250 mL of dry THF at 0 °C was added 0.99 g (41.3 mmol) of sodium hydride. The mixture was stirred at room temperature for 1 h and cooled to −78 °C, and a solution of the above crude aldehyde **15** in 30 mL of dry THF was added over 20 min. The mixture was stirred at −78 °C for 2 h, allowed to warm to room temperature, and diluted with 300 mL of ether. The mixture was washed with saturated aqueous NH_4Cl and the organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 13.1 g of crude oil. Flash chromatography on silica gel with hexanes/40% ether–hexanes gradient afforded 3.14 g (85%) of ester **16**: IR (film) ν 3030, 2980, 2950, 2930, 2860, 1730, 1630, 1490, 1450, 1430, 1370, 1305, 1265, 1245, 1130, 1080, 1025, 920, 740, 700 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.46 (s, 3 H, CH_3), 3.23 (t, J = 5.4 Hz, 1 H, epoxide H), 3.53 (d, J = 5.4 Hz, 2 H, $BnOCH_2$), 4.20 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.52 (AB, J_{AB} = 11.9 Hz, $\Delta\nu$ = 30.7 Hz, 2 H, $PhCH_2O$), 5.99 (d, J = 15.8 Hz, 1 H, vinyl H), 6.81 (d, J = 15.8 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); ^{13}C NMR δ 13.9, 20.8, 58.7, 60.3, 63.9, 67.6, 73.0, 123.6, 127.5, 128.1, 137.5, 144.3, 165.3. $[\alpha]^{24}_D$ +21.80° (*c* 3.27, $CHCl_3$).[24] Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.60; H, 7.36.

(*E*)-(4*S*,5*R*)-6-(Benzyloxy)-4,5-epoxy-4-methyl-2-hexenol (17). To a solution of 2.87 g (10.4 mmol) of ester **16** in 250 mL of dry CH_2Cl_2 at −78 °C was added 22 mL (22 mmol) of 20% DIBAH in hexanes over 10 min. The mixture was stirred for 15 min, treated with 0.5 mL of water and 200 mL of saturated aqueous Rochelle's salt, and allowed to warm to room temperature. The layers were separated, the organic phase was washed with Rochelle's salt, and the combined aqueous phases were extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (deactivated with 5% Et_3N–hexane solution) with hexane/80% ether–hexane

(21) Unless otherwise noted ^1H NMR spectra were run on dilute solutions of sample in $CDCl_3$ on a 300-MHz instrument.

(22) Experimental procedures related to the *cis*-vinyloxiranes **17** and **19** are described. Details for the trans isomers **7** and **9** are available as supplementary material.

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

(24) An ee of 80% is presumed for this product in accord with the ee measured for the starting material, alcohol **14**, and assuming no epimerization of subsequent intermediates derived from **14**.

gradient afforded 1.77 g (73%) of alcohol **17**: IR (film) ν 3440, 3080, 3050, 2990, 2940, 2870, 1500, 1460, 1385, 1210, 1130, 1095, 1030, 975, 875, 740, 700 cm^{-1}; ^1H NMR δ 1.43 (s, 3 H, CH_3), 1.46 (br s, 1 H, CH_2OH), 3.15 (t, J = 5.4 Hz, 1 H, epoxide H), 3.54 (m, 2 H, $BnOCH_2$), 4.11 (br s, 2 H, CH_2OH), 4.53 (AB, J_{AB} = 12.0 Hz, $\Delta\nu$ = 34.1 Hz, 2 H, $PhCH_2O$), 5.60 (dt, J = 1.6, 15.7 Hz, 1 H, vinyl H), 5.87 (dt, J = 5.1, 15.7 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); ^{13}C NMR δ 21.6, 59.2, 62.2, 63.4, 67.9, 72.9, 127.6, 128.2, 133.0, 137.7; $[\alpha]^{24}_D$ +11.79° (c 3.80, $CHCl_3$).[24] Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.49; H, 7.71.

(*E*)-(4*S*,5*R*)-6-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-4,5-epoxy-4-methyl-2-hexene (17TBS). To a solution of 0.44 g (1.88 mmol) of alcohol **17** in 5.0 mL of DMF at 25 °C were added 0.63 g (4.16 mmol) of *tert*-butyldimethylsilyl chloride and 0.57 g (8.37 mmol) of imidazole. The mixture was stirred for 8 h at room temperature, poured into 15 mL of water, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 0.68 g of an amber oil. Flash chromatography on silica gel with hexanes/30% ether–hexane gradient afforded 0.52 g (79%) of silyl ether **17TBS**: IR (film) ν 3085, 3060, 3000, 2950, 2860, 1505, 1465, 1375, 1220, 1130, 1090, 1030, 970, 870, 750 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.43 (s, 3 H, epoxide CH_3), 3.15 (X of ABX, J = 4.8, 5.9 Hz, 1 H, epoxide H), 3.50 (A of ABX, J = 5.9, 11.2 Hz, 1 H, $BnOCH_2$), 3.60 (B of ABX, J = 4.8, 11.2 Hz, 1 H, $BnOCH_2$), 4.16 (dd, J = 1.8, 4.3 Hz, 2 H, CH_2OTBS), 4.53 (AB, J_{AB} = 11.9 Hz, $\Delta\nu$ = 25.6 Hz, 2 H, $PhCH_2O$), 5.61 (dt, J = 1.8, 15.6 Hz, 1 H, vinyl H), 5.81 (dt, J = 4.3, 15.6 Hz, 1 H, vinyl H), 7.31 (m, 5 H, phenyl H).

(*Z*)-(4*S*,5*R*)-Ethyl 6-(Benzyloxy)-4,5-epoxy-4-methyl-2-hexenoate (18). To a solution of 0.40 mL (4.55 mmol) of oxalyl chloride in 20 mL of dry CH_2Cl_2 at −78 °C was added 0.65 mL (9.15 mmol) of dimethyl sulfoxide. The mixture was stirred for 5 min and a solution of 0.71 g (3.40 mmol) of alcohol **14** in 2 mL of dry CH_2Cl_2 was added over 2 min. The mixture was stirred for 20 min and 2.6 mL (18.6 mmol) of Et_3N was added over 1 min. The mixture was allowed to warm to room temperature, diluted with 50 mL of ether, and filtered through a pad of $MgSO_4$. The filtrate was concentrated under reduced pressure to afford the crude aldehyde **15**.

To a solution of 1.31 g (3.96 mmol) of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]acetate and 2.28 g (8.62 mmol) of 18-crown-6 in 100 mL of dry THF at −78 °C was added 8 mL (4.0 mmol) of 0.5 M KHMDS in toluene. The mixture was stirred for 5 min and aldehyde **15** in 5 mL of dry THF was added over 5 min. The mixture was stirred for 45 min, allowed to warm to room temperature, and diluted with 200 mL of ether. The mixture was washed with saturated NH_4Cl and the combined aqueous layers were extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 0.93 g of a pale yellow oil. Flash chromatography on silica gel afforded 0.75 g (80%) of ester **18** upon elution with hexane/60% ether–hexane gradient: IR (film) ν 3080, 3020, 2990, 2940, 2870, 1720, 1645, 1500, 1455, 1410, 1390, 1375, 1310, 1280, 1215, 1175, 1130, 1095, 1075, 1030, 870, 820, 740, 700 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.53 (s, 3 H, CH_3), 3.19 (A of ABX, J_{AB} = 7.3 Hz, J_{AX} = 11.2 Hz, 1 H, $BnOCH_2$), 3.30 (B of ABX, J_{AB} = 7.3 Hz, J_{BX} = 2.5 Hz, 1 H, $BnOCH_2$), 3.70 (dd, X of ABX, J_{AX} = 11.2 Hz, J_{BX} = 2.5 Hz, 1 H, epoxide H), 4.13 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.50 (AB, J_{AB} = 11.9 Hz, $\Delta\nu$ 35.6 Hz, 2 H, $PhCH_2O$), 5.83 (d, J = 11.7 Hz, 1 H, vinyl H), 6.24 (d, J = 11.7 Hz, 1 H, vinyl H), 7.30 (m, 5 H, phenyl H); ^{13}C NMR δ 13.7, 21.7, 58.8, 60.0, 63.8, 69.7, 72.6, 121.7, 127.3, 127.9, 137.7, 143.7, 164.5; $[\alpha]_D$ +133.8° (c 2.84, $CHCl_3$).[24] Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.35.

(*Z*)-(4*S*,5*R*)-6-(Benzyloxy)-4,5-epoxy-4-methyl-2-hexen-1-ol (19). To a solution of 2.67 g (9.67 mmol) of ester **18** in 200 mL of CH_2Cl_2 at −78 °C was added 21 mL of 20% DIBAH in hexanes over 2 min. This mixture was stirred for 15 min and then treated with 0.5 mL of water and 150 mL of aqueous Rochelle's salt. The mixture was allowed to warm to room temperature, the phases were separated, and the organic phase was washed with aqueous Rochelle's salt. The combined aqueous phases were extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1.93 g of crude oil. Flash chromatography on silica gel (deactivated with 5% Et_3N) afforded 1.19 g (53%) of alcohol **19** and 0.51 g of ether **21** upon elution with hexanes/80% ether–hexanes gradient. Alcohol **19**: IR (film) ν 3420, 3100, 3070, 3040, 2980, 2930, 2870, 1495, 1455, 1380, 1300, 1210, 1130, 1090, 1030, 940, 905, 870, 810, 740, 700 cm^{-1}; ^1H NMR δ 1.42 (s, 3 H, CH_3), 2.55 (m, 1 H, CH_2OH), 3.11 (X of ABX, J_{AX} = 5.5 Hz, J_{BX} = 6.1 Hz, 1 H, epoxide H), 3.44 (B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 6.3 Hz, 1 H, $BnOCH_2$), 3.56 (A of ABX, J_{AB} = 10.6 Hz, J_{AX} = 5.5 Hz, 1 H, $BnOCH_2$), 4.16 (m, 2 H, CH_2OH), 4.54 (AB, J_{AB} = 11.8 Hz, $\Delta\nu$ = 19.6 Hz, 2 H, $PhCH_2O$), 5.57 (d, J = 11.4 Hz, 1 H, vinyl H), 5.70 (m, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); ^{13}C NMR δ 23.3, 59.0, 59.6, 61.4, 69.0, 73.3, 127.0, 127.6, 128.2, 132.9, 137.4; $[\alpha]^{23}_D$ +19.89° (c 2.66, $CHCl_3$).[24] Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.66.

Ether **21**: IR (film) ν 3460, 3080, 3040, 2980, 2960, 2880, 1500, 1455, 1370, 1355, 1325, 1210, 1120, 1080, 1020, 970, 940, 910, 880, 820, 740, 700 cm^{-1}; ^1H NMR δ 1.28 (s, 3 H, CH_3), 2.54 (br s, 1 H, $CHOH$), 3.42 (B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 8.0 Hz, 1 H, CH_2OBn), 3.60 (A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 3.6 Hz, 1 H, CH_2OBn), 3.80 (X of ABX, J_{AX} = 3.6 Hz, J_{BX} = 8.0 Hz, 1 H, epoxide H), 4.53 (s, 2 H, $PhCH_2O$), 4.59 (m, 2 H), 5.76 (dt, J = 2.4, 6.2 Hz, 1 H, vinyl H), 5.86 (dt, J = 1.5, 6.2 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); ^{13}C NMR δ 22.2, 71.1, 73.3, 74.5, 75.2, 91.0, 126.4, 127.6, 128.3, 131.3, 138.0; $[\alpha]^{22}_D$ +44.1° (c 4.06, $CHCl_3$).[24] Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.55; H, 7.69.

(*Z*)-(4*S*,5*R*)-6-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-4,5-epoxy-4-methyl-2-hexene (19TBS). The procedure described for **17TBS** was followed with 0.64 g (2.72 mmol) of alcohol **19** in 8.0 mL of DMF, 0.98 g (6.50 mmol) of *tert*-butyldimethylsilyl chloride, and 0.98 g (14.36 mmol) of imidazole. The mixture was stirred for 4 h and after an aqueous workup and chromatography, 0.87 g (91%) of silyl ether **19TBS** was obtained: IR (film) ν 3100, 3050, 3040, 2980, 2920, 2890, 2830, 1490, 1450, 1380, 1300, 1210, 1130, 1095, 1035, 950, 900, 870, 740 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.39 (s, 3 H, epoxide CH_3), 3.06 (X of ABX, J = 4.7, 6.0 Hz, 1 H, epoxide H), 3.38 (A of ABX, J = 6.0, 11.0 Hz, 1 H, $BnOCH_2$), 3.54 (B of ABX, J = 4.7, 11.0 Hz, 1 H, $BnOCH_2$), 4.31 (t, J = 6.2 Hz, 2 H, CH_2OTBS), 4.54 (AB, J_{AB} = 11.8 Hz, $\Delta\nu$ = 31.0 Hz, 2 H, $PhCH_2O$), 5.46 (m, 1 H, vinyl H), 5.60 (m, 1 H, vinyl H), 7.32 (m, 5 H, Phenyl H).

(*E*)-(2*R*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-3-hexene-1,5-diol (*ent*-22). A. Me_2CuLi Addition. The procedure described below for diol *ent*-**23** was followed with 0.544 g (2.32 mmol) of epoxy alcohol **19**, 1.97 g (10.3 mmol) of copper(I) iodide, and 15 mL of 1.4 M ethereal MeLi in 20 mL of THF at 0 °C. Flash chromatography on silica gel afforded 32.4 mg of a mixture of dienes *ent*-**27**, 30.2 mg of ether **21**, 27 mg of S_N2 diol *ent*-**26**, 20 mg of *Z* olefin diol *ent*-**24**, and 313 mg (63%) of *E* olefin diol *ent*-**22** upon elution with hexane–ether gradient: IR (film) ν 3360, 2960, 2930, 2880, 1460, 1375, 1320, 1225, 1205, 1170, 905, 750, 700, 670 cm^{-1}; ^1H NMR δ 0.90 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.63 (s, 3 H, CH_3), 1.95 (br s, 1 H, CH_2OH), 2.63 (m, 1 H, $CHCH_3$), 2.76 (s, 1 H, $CHOH$), 3.50 (m, 4 H), 4.2 (d, J = 7.7 Hz, 1 H, $CHOH$), 4.54 (s, 2 H, $PhCH_2O$), 5.24 (d, J = 9.6 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); $[\alpha]^{22}_D$ +22.0° (c 2.69, $CHCl_3$).[24] GC analysis of the derived diacetates showed 93% *ent*-**28**, 1% *ent*-**29**, 6% *ent*-**30**, and <1% *ent*-**31**.

B. LiMeCuCN Addition. The procedure described for *ent*-**23** was followed with 0.14 g (0.60 mmol) of epoxy alcohol **19**, 0.82 g (9.12 mmol) of CuCN, and 6.5 mL of 1.4 M ethereal MeLi in 20 mL of Et_2O at 0 °C. Flash chromatography on silica gel afforded 10 mg of mixture of dienes *ent*-**27** and 106 mg of a mixture of diols *ent*-**22**–*ent*-**25**. GC analysis of the derived diacetates showed 88% *ent*-**28**, 9% *ent*-**29**, <1% *ent*-**30**, and 2% *ent*-**31**.

(*E*)-(2*S*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-3-hexene-1,5-diol (*ent*-23). A. Me_2CuLi Addition. To a slurry of 0.715 g (3.75 mmol) of CuI in 20 mL of THF at 0 °C was added 5.4 mL of 1.4 M MeLi in ether. To this mixture was added a solution of 0.201 g (0.859 mmol) of vinyloxirane **17** in 2 mL of THF. The mixture was stirred for 12 h at 0 °C, quenched with 1:1 3% NH_4OH–saturated NH_4Cl, and allowed to warm to room temperature. The mixture was poured into 25 mL of EtOAc and the phases were separated. The organic phase was washed with saturated NH_4Cl

until there was no color change in the aqueous phase. The combined aqueous phases were saturated with NaCl and extracted with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a dark amber oil. Flash chromatography on silica gel afforded 11.7 mg of a mixture of diene alcohols **27**, 22.9 mg of *Z* olefin diol *ent*-**25**, 3.3 mg of S_N2 diol **26**, and 121 mg (56%) of *E* olefin diol *ent*-**23** upon elution with hexane–ether gradient. *ent*-**23**: IR (film) ν 3360, 2960, 2930, 2870, 1455, 1370, 1320, 1220, 1200, 1170, 900, 750, 700, 670 cm^{-1}; ^1H NMR δ 0.92 (d, J = 6.7 Hz, 3 H, CH_3), 1.64 (s, 3 H, vinyl CH_3), 1.74 (br s, 1 H, CH_2OH), 2.18 (d, J = 2.4 Hz, 1 H, CHO*H*), 2.64 (m, 1 H, C*H*CH_3), 3.54 (m, 4 H, CH_2OBn and CH_2OH), 4.21 (m, 1 H, C*H*OH), 4.54 (s, 2 H, $PhCH_2O$), 5.26 (d, J = 9.6 Hz, 1 H, vinyl H), 7.32 (m, 5 H, phenyl H); $[\alpha]^{23}_D$ −6.35° (*c* 1.70, $CHCl_3$).[24]

B. LiMeCuCN Addition. To a slurry of 1.04 g (11.6 mmol) of CuCN in 20 mL of dry Et_2O at −78 °C was added 8.5 mL of 1.4 M ethereal MeLi. The mixture was warmed to 0 °C and 0.18 g (0.78 mmol) of epoxy alcohol **17** in 2 mL of Et_2O was added over 3 min. The mixture was stirred at 0 °C for 8 h and quenched with saturated NH_4Cl. The phases were separated and the organic layer was diluted with 50 mL of EtOAc. The extracts were washed with saturated NH_4Cl until the aqueous layer remained colorless and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 170 mg of an amber oil. Flash chromatography on silica gel with hexanes–ether gradient afforded 15 mg of a mixture of diene alcohols *ent*-**27** and 157 mg of a mixture of alcohols *ent*-**22**–*ent*-**26**. GC analysis of the derived diacetates showed 3% *ent*-**28**, 95% *ent*-**29**, <1% *ent*-**30**, and 2% *ent*-**31**.

(*E*)- and (*Z*)-(5*R*)-6-(Benzyloxy)-4-methyl-1,3-hexadien-5-ol (*ent*-27) from Ether 17TBS. A. Me_2CuLi Addition. To a slurry of 0.35 g (1.85 mmol) of CuI in 15 mL of dry THF at 0 °C was added 2.8 mL of 1.4 M ethereal MeLi. The mixture was stirred for 5 min and a solution of 0.14 g (0.41 mmol) of ether **17TBS** in 3 mL of THF was added over 5 min. The mixture was stirred for 3 h at 0 °C and quenched with saturated NH_4Cl. The phases were separated and the organic phase was diluted with 50 mL of EtOAc. This solution was washed with saturated NH_4Cl until the aqueous layer remained colorless, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 138 mg of a crude amber oil. The oil was taken up in 5 mL of dry THF and 1.5 mL of Bu_4NF (1 M in THF) was added. The mixture was stirred at room temperature for 3 h and washed twice with water. The aqueous phases were extracted three times with EtOAc and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with hexanes–ether gradient afforded 98 mg of a mixture of diene alcohol *ent*-**27** and 10 mg of a mixture of diols *ent*-**22**–*ent*-**25**. (*E*)-*ent*-**27**: ^1H NMR δ 1.74 (s, 3 H, CH_3), 2.50 (s, 1 H, CHO*H*), 3.50 (m, 2 H, $BnOCH_2$), 4.28 (m, 1 H, C*H*OH), 4.56 (s, 2 H, $PhCH_2O$), 5.11 (d, J = 10.1 Hz, 1 H, vinyl H), 5.20 (d, J = 16.9 Hz, 1 H, vinyl H), 6.15 (d, J = 11.0 Hz, 1 H, vinyl H), 6.57 (dt, J = 10.4, 16.8 Hz, 1 H, vinyl H), 7.33 (m, 5 H, phenyl H).

B. LiMeCuCN Addition. To a slurry of 0.99 g (11.0 mmol) of CuCN in 15 mL of dry Et_2O at −78 °C was added 8.0 mL of 1.4 M ethereal MeLi. The mixture was allowed to warm to 0 °C and 0.23 g (0.67 mmol) of ether **17TBS** in 2 mL of Et_2O was added over 2 min. The mixture was stirred for 6 h at 0 °C and quenched with saturated NH_4Cl. The phases were separated and the organic phase was diluted with 50 mL of EtOAc and washed with saturated NH_4Cl until the aqueous layer remained colorless. The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 159 mg of an amber oil. The oil was taken up in 5 mL of THF and 2.0 mL of Bu_4NF (1 M in THF) was added. The mixture was stirred at room temperature for 4 h and washed twice with water. The combined aqueous phases were extracted three times with EtOAc and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with hexanes–ether gradient afforded 89 mg of a mixture of diene alcohols *ent*-**27** and 7.3 mg of a mixture of diols *ent*-**22**–*ent*-**25**. GC analysis of the derived diacetates showed only *ent*-**29** to be present.

(*E*)- and (*Z*)-(5*R*)-6-(Benzyloxy)-4-methyl-1,3-hexadien-5-ol (*ent*-27) from Ether 19TBS. A. Me_2CuLi Addition. The procedure described in part A above for *ent*-**27** was followed with 0.19 g (0.54 mmol) of ether **19TBS**, 0.44 g (2.29 mmol) of CuI, and 3.2 mL of 1.4 M ethereal MeLi in 10 mL of dry THF at 0 °C. The TBS ether was cleaved with 2.0 mL of Bu_4NF (1 M in THF). Flash chromatography afforded 81 mg of a mixture of diene alcohols *ent*-**27** and 5 mg of a mixture of diols *ent*-**22**–*ent*-**25**.

B. LiMeCuCN Addition. The procedure described in part B above for *ent*-**27** was followed with 0.19 g (0.54 mmol) of ether **19TBS**, 0.73 g (8.15 mmol) of CuCN, and 6.0 mL of 1.4 M ethereal MeLi in 15 mL of Et_2O at 0 °C. The TBS ether was cleaved with 2.5 mL of Bu_4NF (1 M in THF). Flash chromatography afforded 87 mg of a mixture of diene alcohols *ent*-**27** and 9 mg of a mixture of diols *ent*-**22**–*ent*-**25**. GC analysis of the derived diacetates showed 98% *ent*-**28** and 2% *ent*-**30**.

(*E*)-(2*R*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-3-hexene-1,5-diyl Diacetate (*ent*-28). The procedure employed below for diacetate *ent*-**29** was followed with 140 mg (0.56 mmol) of diol *ent*-**22**, 0.16 mL (1.7 mmol) of acetic anhydride, and 0.28 mL of dry pyridine in 10 mL of dry CH_2Cl_2. The mixture was quenched after 24 h. Flash chromatography on silica gel afforded 144 mg (78%) of diacetate *ent*-**28** upon elution with hexane/40% ether–hexane gradient: IR (film) ν 3470, 3110, 3080, 3040, 2960, 2950, 2880, 1740, 1500, 1465, 1375, 1235, 1100, 1030, 910, 855, 740, 705 cm^{-1}; ^1H NMR δ 0.95 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.63 (s, 3 H, vinyl CH_3), 1.99 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.73 (m, 1 H, C*H*CH_3), 3.57 (m, 2 H), 3.87 (m, 2 H), 4.53 (AB, J_{AB} = 12.2 Hz, $\Delta\nu$ = 9.2 Hz, 2 H, $PhCH_2O$), 5.25 (d, J = 9.3 Hz, 1 H, vinyl H), 5.31 (m, 1 H), 7.29 (m, 5 H, phenyl H); $[\alpha]^{23}_D$ +26.9° (*c* 3.81, $CHCl_3$).[24] Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.06; H, 7.91.

(*E*)-(2*S*,5*S*)-6-(Benzyloxy)-2,4-dimethyl-3-hexene-2,5-diyl Diacetate (*ent*-29). To a solution of 76.2 mg (0.30 mmol) of diol *ent*-**23** in 5 mL of dry CH_2Cl_2 at 0 °C were added 1.0 mL of dry pyridine and 0.5 mL (5.3 mmol) of acetic anhydride. The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was slowly quenched with 0.5 mL of water and diluted with 25 mL of ether. The mixture was washed with saturated aqueous $CuSO_4$ until the washings appeared colorless. The combined aqueous phases were extracted with ether and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel afforded 71.7 mg (71%) of diacetate *ent*-**29** upon elution with hexane/40% ether–hexane gradient: IR (film) ν 3470, 3100, 3070, 3040, 2970, 2940, 2880, 1740, 1500, 1465, 1375, 1235, 1100, 1030, 910, 850, 740, 700 cm^{-1}; ^1H NMR δ 0.96 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.63 (s, 3 H, vinyl CH_3), 1.98 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.73 (m, 1 H, C*H*CH_3), 3.55 (m, 2 H), 3.84 (m, 2 H), 4.53 (AB, J_{AB} = 12.2 Hz, $\Delta\nu$ = 10.3 Hz, 2 H, $PhCH_2O$), 5.24 (d, J = 9.4 Hz, 1 H, vinyl H), 5.30 (m, 1 H), 7.30 (m, 5 H, phenyl H); $[\alpha]^{22}_D$ +26.6° (*c* 3.06, $CHCl_3$).[24] Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.98; H, 7.76.

(*E*)-(2*S*,5*R*)-3,5-Dimethyl-1,2,6-tris(benzyloxy)-3-hexene (*ent*-32). The procedure employed below for ether *ent*-**33** was followed with 130 mg (0.52 mmol) of diol *ent*-**22**, 0.04 mL (0.13 mmol) of tris[2-(2-methoxyethoxy)ethyl]amine, 145 mg (2.60 mmol) of potassium hydroxide, and 0.2 mL (1.7 mmol) of benzyl bromide in 5 mL of dry benzene. Flash chromatography on silica gel afforded 147 mg (66%) of tribenzyl ether *ent*-**32** upon elution with hexane/50% ether–hexane gradient: IR (film) ν 3080, 3020, 3000, 2940, 2870, 1450, 1365, 1325, 1220, 1100, 1180, 910, 740, 690, 670 cm^{-1}; ^1H NMR δ 0.98 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.61 (s, 3 H, vinyl CH_3), 2.81 (m, 1 H, C*H*CH_3), 3.32 (m, 2 H), 3.60 (m, 2 H), 3.94 (m, 1 H), 4.50 (m, 6 H, $PhCH_2O$), 5.27 (d, J = 9.3 Hz, 1 H, vinyl H), 7.30 (m, 15 H, phenyl H); $[\alpha]^{22}_D$ +19.6° (*c* 2.67, $CHCl_3$).[24] Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.77; H, 7.85.

(*E*)-(2*S*,5*S*)-3,5-Dimethyl-1,2,6-tris(benzyloxy)-3-hexene (*ent*-33). To a solution of 250 mg (0.998 mmol) of diol *ent*-**23** in 3 mL of dry benzene at room temperature were added 0.10 mL (0.31 mmol) of tris[2-(2-methoxyethoxy)ethyl]amine, 250 mg (4.45 mmol) of crushed potassium hydroxide pellets, and 0.30 mL (2.52 mmol) of benzyl bromide. The mixture was stirred at room temperature for 18 h and concentrated under reduced pressure. The residue was taken up in 20 mL of water and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography

on silica gel afforded 289 mg (67%) of ether *ent*-**33** upon elution with hexane/60% ether–hexane gradient: IR (film) ν 3080, 3020, 2990, 2940, 2870, 1455, 1370, 1320, 1220, 1100, 1180, 910, 740, 690, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 9.7 Hz, 3 H, CH_3), 1.62 (s, 3 H, vinyl CH_3), 2.79 (m, 1 H), 3.30 (m, 2 H), 3.60 (m, 2 H), 3.94 (m, 1 H), 4.49 (m, 6 H, $PhCH_2O$), 5.30 (d, J = 9.3 Hz, 1 H, vinyl H), 7.31 (m, 15 H, phenyl H); $[\alpha]^{23}_D$ +29.3° (*c* 3.07, $CHCl_3$).[24] Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.81; H, 7.90.

(*S*)-3-(Benzyloxy)-2-methyl-1-propanol (36) A. From Olefin Ether 32. Ozone was bubbled through a stirred solution of 0.305 g (0.709 mmol) of (*E*)-alkene **32** in 18 mL of CH_2Cl_2 at −78 °C until a blue color persisted. Nitrogen was then bubbled through until the blue color disappeared and 0.27 mL (3.5 mmol) of methyl sulfide was added dropwise. The mixture was allowed to stir at −78 °C for 15 min and 0.780 mL (0.780 mmol) of 1 M lithium tris[1,1-diethylpropyloxy]aluminum hydride in THF was added dropwise. The solution was stirred for 0.5 h and 1.5 mL of water was added. The mixture was allowed to warm to room temperature and was filtered through Celite–$MgSO_4$. Concentration and chromatography on silica gel (elution with 25% EtOAc–hexanes) afforded 0.064 g (50%) of the alcohol **36** as an oil: IR (film) ν 3400, 2900, 1725, 1450, 1270, 1910, 1060, 1020, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 2.08 (m, 1 H, $CHCH_3$), 2.6 (br s, 1 H, OH), 3.3–3.6 (m, 4 H, H1, H3), 4.50 (s, 2 H, $PhCH_2O$), 7.3 (m, 5 H, phenyl H); $[\alpha]^{25}_D$ −10.7° (*c* 2.05, $CHCl_3$).

B. From Olefin Ether *ent*-33. The procedure described above was employed with 214 mg (0.49 mmol) of (*E*)-alkene *ent*-**33**[24] in 20 mL of dry CH_2Cl_2. Flash chromatography on silica gel afforded 57.4 mg (65%) of alcohol **36** upon elution with hexanes/50% ether–hexanes gradient: IR (film) ν 3400, 3090, 3070, 3040, 2970, 2930, 2870, 1495, 1455, 1370, 1220, 1095, 1040, 750, 700 cm^{-1}; ^1H NMR δ 0.87 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 2.06 (m, 1 H, $CHCH_3$), 2.56 (m, 1 H, OH), 3.53 (m, 4 H), 4.51 (s, 2 H, $PhCH_2O$), 7.32 (m, 5 H, phenyl H); $[\alpha]^{24}_D$ −13.2° (*c* 2.27, $CHCl_3$).

(*R*)-3-(Benzyloxy)-2-methyl-1-propanol (37). A. From Olefin Ether 34. This alcohol was prepared from the (*Z*)-alkene **34** as described for the *S* isomer **36**: yield 38%; $[\alpha]^{25}_D$ +10.4° (*c* 1.45, $CHCl_3$) [lit.[8] $[\alpha]_D$ + 17.2° (*c* 3.24, $CHCl_3$)].

B. From Olefin Ether *ent*-32. The ozonolysis procedure employed for alcohol **36** was followed with 107 mg (0.248 mmol) of (*E*)-alkene *ent*-**32**[24] in 20 mL of dry CH_2Cl_2. Flash chromatography on silica gel afforded 31.3 mg (70%) of alcohol **37** upon elution with hexane/60% ether–hexane gradient: IR (film) ν 3400, 3100, 3070, 3040, 2970, 2920, 2870, 1495, 1460, 1375, 1220, 1095, 1040, 750, 700 cm^{-1}; ^1H NMR δ 0.90 (d, J = 7.1 Hz, 3 H, CH_3), 2.07 (m, 1 H), 2.60 (m, 1 H, OH), 3.55 (m, 4 H), 4.51 (s, 2 H, $PhCH_2$), 7.35 (m, 5 H, phenyl H); $[\alpha]^{23}_D$ +13.0° (*c* 1.56, $CHCl_3$) [lit.[8] $[\alpha]_D$ + 17.2° (*c* 3.24, $CHCl_3$)].

(2,*R*,5*S*)-2-[(Benzyloxy)methyl]-5,6-dihydro-3,5-dimethyl-2*H*-pyran (41). To a solution of 0.200 g (0.80 mmol) of diol **40** in 1.5 mL of dry CH_2Cl_2 at room temperature were added 0.167 g (0.88 mmol) of *p*-TsCl and 0.557 mL (4.0 mmol) of triethylamine. The mixture was allowed to stir for 1 week, 2 mL of water was added, and the layers were separated. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with 1:1 ether–hexane afforded 0.125 g (62%) of pyran **41**: ^1H NMR δ 0.86 (d, J = 7.1 Hz, 3 H, $CHCH_3$), 1.58 (s, 3 H, vinyl CH_3), 2.41 (br s, 1 H, $CHCH_3$), 3.12 (B of ABX, J_{AB} = 10.8 Hz, J_{BX} = 9.1 Hz, 1 H, $ROCH_2$), 3.53 (A of ABX, J_{AB} = 10.5 Hz, J_{AX} = 6.0 Hz, 1 H, $ROCH_2$), 3.63 (B of ABX, J_{AB} = 10.5 Hz, J_{BX} = 2.8 Hz, 1 H, $ROCH_2$), 3.96 (A of ABX, J_{AB} = 10.8 Hz, J_{AX} = 4.4 Hz, 1 H, $ROCH_2$), 4.11 (br s, 1 H, ROCH), 4.59 (AB, J_{AB} = 12.3 Hz, $\Delta\nu$ = 10.9 Hz, 2 H, $PhCH_2O$), 5.45 (br s, 1 H, vinyl H), 7.33 (m, 5 H, phenyl H). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.34; H, 8.71.

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Supplementary Material Available: Experimental details for compounds **2–9**, **22–26**, **28**, **30–35**, **37**, **7TBS**, and **9TBS** (16 pages). Ordering information is given on any current masthead page.

Total Synthesis of Pseudomonic Acid C

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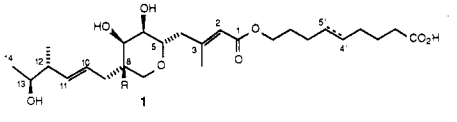
Two approaches to the synthesis of aldehyde **28**, a key intermediate in the total synthesis of pseudomonic acid C, were developed. One asymmetric route from the chiral hydroxy ester **11** proceeded in 13 steps via the hydroxy lactone **17**. A shorter approach involved the Lewis acid catalyzed cycloaddition of formaldehyde to the chiral diene **23a** to give **22a**, which was separated from its diastereomer and then converted into **28** in seven steps. The introduction of the C-8 side chain was initially accomplished by Julia coupling of **28** with the sulfone anion derived from **40** to give the olefin **34**. The stereoselective preparation of **34** was also carried out, via the ester **46a**, by a novel ester enolate Claisen rearrangement of the silyl-protected glycolate ester **44**. A third approach directed toward the synthesis of the side chain entailed controlling the C-10 stereochemistry of the benzyl-protected glycolate ester **48** by reduction of a precursor propargyl ketone **27** with Alpine borane. Ester enolate Claisen rearrangement then gave the ester **46b** with excellent stereocontrol.

The pseudomonic acids are structurally novel C-glycopyranoside antibacterials that have been isolated over the last 15 years.[1] The major constituent of the fermentation broth of *Pseudomonas fluorescens* is the epoxy triol pseudomonic acid A (mupirocin; **1a**), while the simplest member, pseudomonic acid C (**1c**), makes up only 2% of the culture medium. Although they are active mainly against Gram-positive bacteria,[2] the pseudomonic acids have generated a great deal of interest due to their ability



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Pseudomonic Acid A : R=H; C10,11 epoxide
B : R=OH; C10,11 epoxide
C : R=H
D : R=H; C4',5' olefin

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