Pergamon

Tetrahedron 54 (1998) 11731–11740

TETRAHEDRON

Effect of $A_{(1,3)}$-*cis* Strain on the Asymmetric Epoxidation of (*E*)- and (*Z*)-6,6-Diethoxy-3-hexen-2-ols and 4-Methyl-6,6-diethoxy-3-hexen-2-ols

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Received 21 November 1997; accepted 9 June 1998

Abstract: The effect of $A_{(1,3)}$-*cis* strain on the diastereoselectivity of epoxidation of (*E*)-and (*Z*)-6,6-diethoxy-3-hexen-2-ols and 4-methyl-6,6-diethoxy-3-hexen-2-ols is analyzed, with some empiric observations provided. Increased $A_{(1,3)}$-*cis* strain results in increased amounts of racemic *threo*-epoxy alcohols, while high *ee*'s are found for the *erythro*-epoxy alcohols. © 1998 Elsevier Science Ltd. All rights reserved.

Asymmetric epoxidation of allylic alcohols is the cornerstone for many synthetic processes. The scope of the reaction has been studied extensively with a large number of allylic alcohols [1,2], with some allylic alcohols functioning poorly. On the basis of experimental data from molybdenum hexacarbonyl and vanadium acetylacetonate-catalyzed epoxidations and *ab initio* calculations, a transition state structure for metal-catalyzed allylic alcohol epoxidations has been proposed (Figure 1) [1] which accounts for the high levels of diastereo- and enantioselectivity observed (*i.e.*, favoring or disfavoring *erythro*/*threo* epoxides). However, some allylic alcohols have shown lower reactivity and poorer diastereo- and/or enantioselectivity (*e.g.*, 1-substituted (*Z*)-allylic alcohols have lower reactivity and poorer regio- and enantioselectivity [1,3].

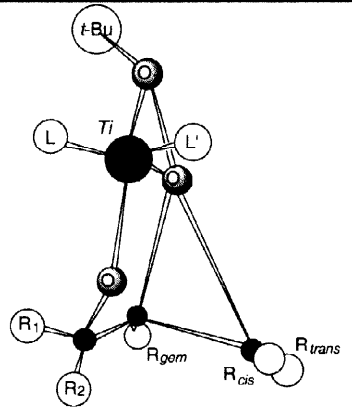

Figure 1. From A.H. Hoveyda, D.A. Evans, and G.C. Fu, *Chem. Rev.*, **1993**, *93*, 1307-1371.

Since our studies on asymmetric syntheses of substituted carbohydrates uses the pivotal epoxy alcohols, we have had the opportunity to further study the subtle substituent effects in the Sharpless asymmetric epoxidation. In spite of the numerous publications on asymmetric epoxidation of allylic alcohols [1,2], there are no reports which describe the effect of $A_{(1,3)}$-*cis* strain on the stereochemical outcome with allylic alcohols containing dissimilar β,β'-substituents. *A priori*, increasing $A_{(1,3)}$-*cis* strain between the R_2 substituent (on carbinol carbon) and the R_{cis} substituent (on the β-carbon) should favor *threo*-epoxide formation. In this communication, we present information on the effect of $A_{(1,3)}$-strain as manifested in the asymmetric epoxidation of (*E*)- and (*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ols (**2**,**4**) *vs.* the earlier results obtained with (*E*)- and (*Z*)-6,6-diethoxy-3-hexen-2-ols (**1**,**3**) [5].

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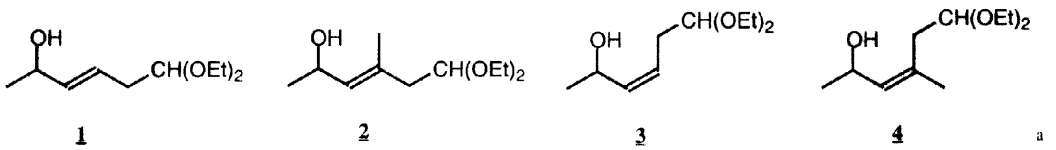
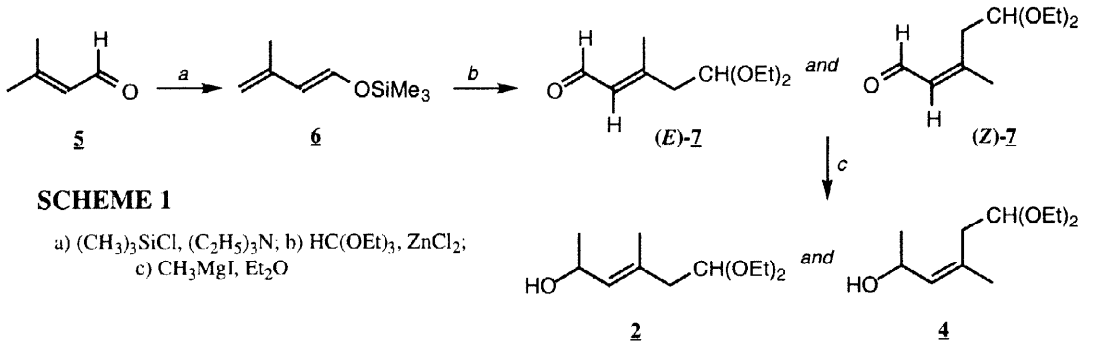
PII: S0040-4020(98)00583-3



1 2 3 4 a

(*E*)- and (*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ols (**2**,**4**) were synthesized from 3-methyl-2-butenal (**5**) according to Scheme 1. Enal **5** was treated with trimethylchlorosilane, in the presence of triethylamine-sodium iodide in a binary system (acetonitrile/pentane) [6], to afford (*E*)-1-trimethylsilyloxy-3-methyl-1,3-butadiene (**6**, 75% yield). Condensation of **6** with triethyl orthoformate, in the presence of anhydrous zinc chloride, gave a mixture of (*E*)- and (*Z*)-5,5-diethoxy-3-methyl-1-pentenals (**7**, 60% yield) in a 60:40 ratio [7]. Enals **7**, on reaction with methyl magnesium iodide, afforded alcohols (**2**,**4**) in a 65:35 ratio of (*E*/*Z*)-isomers as determined by ^{13}C NMR (60% yield). The individual alcohols were isolated by column chromatography over silica gel.

The stereochemistry for enals **7** and alcohols **2** and **4** was determined by analysis of ^{13}C NMR shift differentials. Using related structures, we have established correlations between the chemical shifts of α-carbon atoms of the R^2 and R^3 substituents and their location relative to the *cis*-proton [8]. Resonances for the α-carbon of the substituent, *cis* to the proton, occur at lower field than that when the substituent is *trans* to the proton (the γ-effect). For example, the ^{13}C NMR spectra for aldehyde (*E*)-**7** showed that the resonance for the methylene group (C-4), *cis* to the proton H-2, is shifted 7.1 ppm to lower field in comparison to that found for the methylene group in the *Z*-isomer. Similarly, the resonance for the methyl group of (*Z*)-**7** is shifted 8.1 ppm to lower field *vs.* that found for the resonance for the methyl group in (*E*)-**7**.



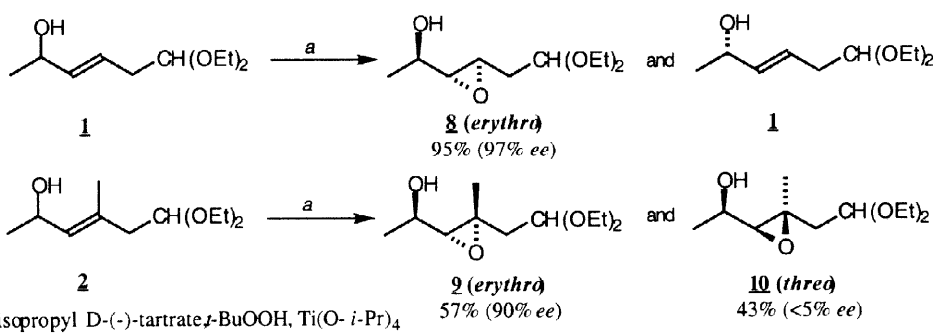
5 6 (*E*)-7 (*Z*)-7

2 4

SCHEME 1

a) $(CH_3)_3SiCl$, $(C_2H_5)_3N$; b) $HC(OEt)_3$, $ZnCl_2$; c) CH_3MgI, Et_2O

Asymmetric Epoxidation: Results and Interpretation



1 **8** (*erythro*) 95% (97% *ee*) 1

2 **9** (*erythro*) 57% (90% *ee*) **10** (*threo*) 43% (<5% *ee*)

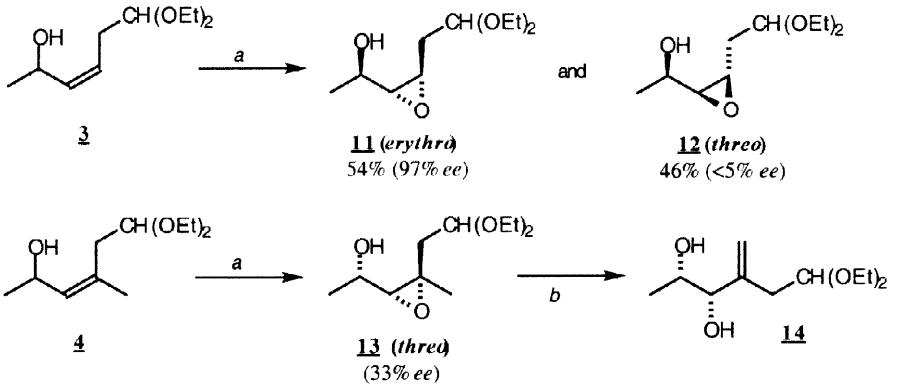
a) Diisopropyl D-(-)-tartrate, *t*-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$

SCHEME 2

Previously [5], epoxidation [*tert*-butyl hydroperoxide (0.55 eq), diisopropyl D-(-)-tartrate (DIPT) and titanium (IV) isopropoxide] of (±)-(*E*)-6,6-diethoxy-3-hexen-2-ol (**1**) afforded a 95:5 ratio of *erythro*- and *threo*-

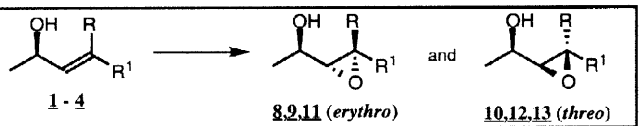
isomers, with the *erythro*-epoxy alcohol (**8**, 97% *ee*) isolated by silica gel chromatography. Its optical purity, was determined by the Mosher method [9]. Under identical reaction conditions, (±)-(*E*)-6,6-diethoxy-4-methyl-3-hexen-2-ol (**2**) afforded a diastereomeric mixture of *erythro*-epoxy alcohol **9** and *threo*-epoxy alcohol **10** in 57:43 ratio in 52% yield (Scheme 2).

The relative configurations of epoxides **9-10** were established by ^{13}C NMR. We have previously shown that ^{13}C NMR shifts can be used to assign the relative configuration of diastereomers, provided that pairs of diastereomeric α-epoxy alcohols are available. The *erythro* and *threo* isomers differ in their ^{13}C NMR spectra with the resonances for -CH(OH)-carbon atom and α-carbon atom of the oxirane ring shifting to lower field by 1.3 and 0.9 ppm, respectively, and the resonances for the β-carbon atom shifting to higher field by 0.3 ppm [8]. By applying these correlations to the spectra of diastereomers (**9**,**10**), the *erythro* configuration was assigned to isomer **9** and *threo* configuration to isomer **10**. Further, the enantiomeric purity was determined for *erythro*-epoxide **9** (90% *ee*) and *threo*-epoxide **10** (5% *ee*).



SCHEME 3 a) Diisopropyl D-(-)-tartrate, *t*-BuOOH (0.5 eq), Ti(O-*i*-Pr)$_4$; b) Ti(O-*i*-Pr)$_4$

Table 1. Asymmetric Epoxidation of Allylic Alcohols 1-4



	Allylic alcohol R	Allylic alcohol R^1	Epoxide Ratio (NMR) *erythro:threo*	Optical purity of epoxides *erythro*	Optical purity of epoxides *threo*
1	H	$CH_2CH(OEt)_2$	93:7	97	-
2	CH_3	$CH_2CH(OEt)_2$	57:43	90	<5
3	$CH_2CH(OEt)_2$	H	54:46	97	<5
4	$CH_2CH(OEt)_2$	CH_3	5:95	-	33

Similarly, (±)-(*Z*)-6,6-diethoxy-3-hexen-2-ol (**3**) afforded a 54:46 ratio of *erythro*-epoxide **11** (97% *ee*) and *threo*-epoxide **12** (racemic). In contrast, (±)-(*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ol (**4**) afforded only one α-epoxy alcohol, the *threo*-epoxide **13**, in 37.5% yield (33% *ee*, determined by Mosher method [9]). Since the second diastereomer of epoxide **13** was not available, the comparative method for assignment of its relative configuration was not applicable. The relative configuration of **13** was determined by conversion to alcohol **14**, previously obtained by rearrangement of *threo*-epoxide **10**. Since the ^1H NMR and ^{13}C NMR spectra of **14** from both sources were identical, which inferred the *relative configuration* of C-2 and C-3 in both epoxides **10** and **13** is *threo*-configuration. The absolute configuration of **13** was determined by ^1H NMR analysis of the Mosher ester. Observations of shift differentials for Mosher esters of diastereomeric epoxy alcohols have shown that the

resonances for the α-methoxy moiety differ by *ca.* 0.05 ppm, with the (*R*)-configuration esters at higher field [5,9,10]. For epoxide **13**, C-2 was assumed to be the (*S*)-configuration.

The analysis of the experimental results for substrates **1-4** is based on the transition state shown in Figure 2 [1]; the model prescribes a preferred stereochemical relationship between the hydroxymethyl group and the double bond, the absolute configuration of the tartrate used and the direction of attack by the oxygen atom of the peroxide. In our analyses, we also considered a modified transition state in which the hydroxy group is not in a planar orientation, but is twisted and located over the plane of the double bond in the case of D-(-)-tartrate [9].

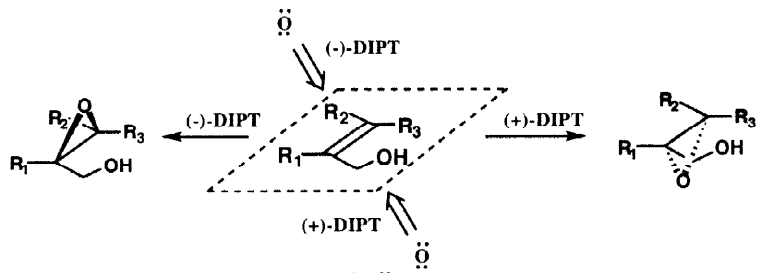
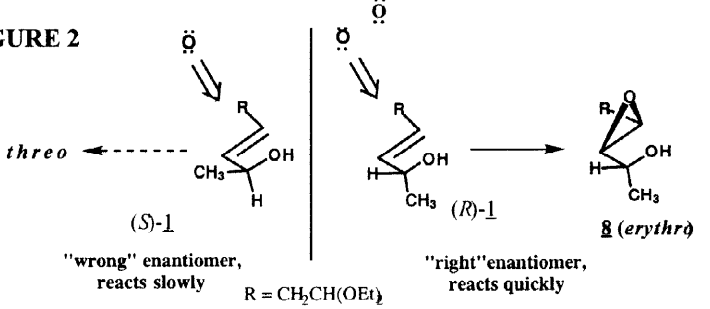


FIGURE 2



The epoxidation of (±)-(*E*)-6,6-diethoxy-3-hexen-2-ol (**1**) is the classic case of asymmetric epoxidation of a racemic allylic alcohol with kinetic resolution. According to the Sharpless paradigm, the substituent on the carbinol center is located either above or below the plane of the olefin. Depending on which enantiomeric tartrate is employed, the steric bulk of the substituent will either affect or not affect the formation of the transition state.

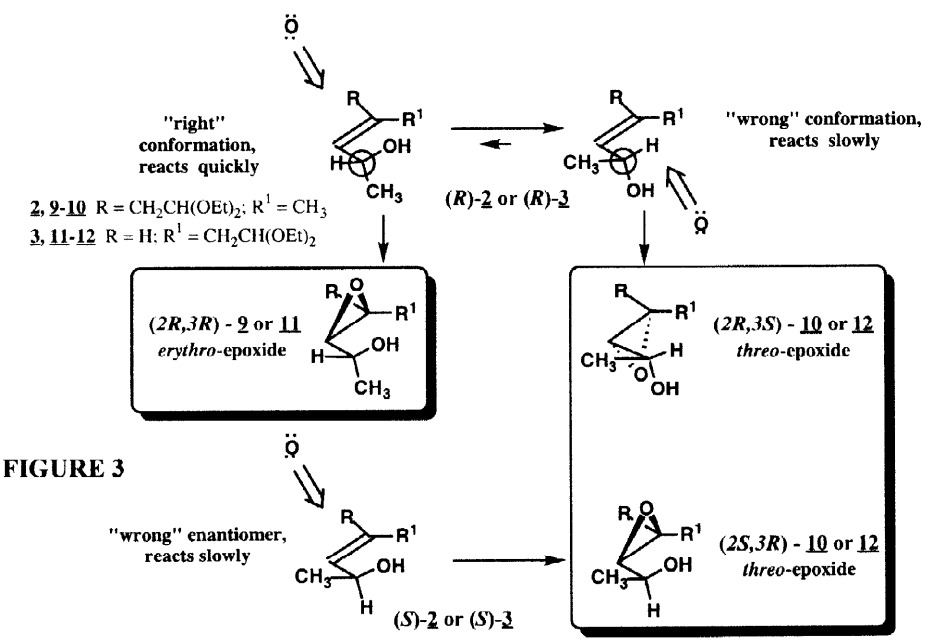


FIGURE 3

With the 4-methyl analog of the above example (*e.g.*, **2** - Figure 3), one enantiomer should react much faster than the other, and yield the *erythro*-epoxide. However with the first enantiomer, there is substantial steric strain between C(1)-CH_3 and C(4)-CH_3 which favors a conformation in which the hydroxy group is located beneath the plane of the olefin. The hydroxy group directs the epoxidation from the "wrong" face (*i.e.*, from the bottom and not the top) and leads to formation of the *threo*-epoxide. Epoxidation, with this conformation, occurs at a slow rate which is comparable to that for the epoxidation of the "wrong" enantiomer. The "wrong" enantiomer also gives the *threo*-epoxide, and thus racemic *threo*-epoxide is formed. Similar events occur for the epoxidation of (±)-(*Z*)-6,6-diethoxy-3-hexen-2-ol (**3**) in which the C(3)-*cis*-$CH_2CH(OEt)_2$ group is responsible for the $A_{(1,3)}$-*cis* strain.

In contrast, (±)-(*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ol (**4**; R=H, R'=$CH_2CH(OEt)_2$) (Figure 4) did not afford the *erythro*-epoxide. That infers either the "right" conformation of the "right" enantiomer does not exist, or, more likely, that this conformation does not react with the epoxidation complex. The steric interaction between the C(4)-CH_3 and $CH(OEt)_2$ moieties forces the acetal group to be positioned, either under or above the plane of the olefin, near C-2. Location below the plane is less likely because of the presence of the bulky C(1)-CH_3, while location above the plane causes steric hindrance to the formation of the epoxidation complex

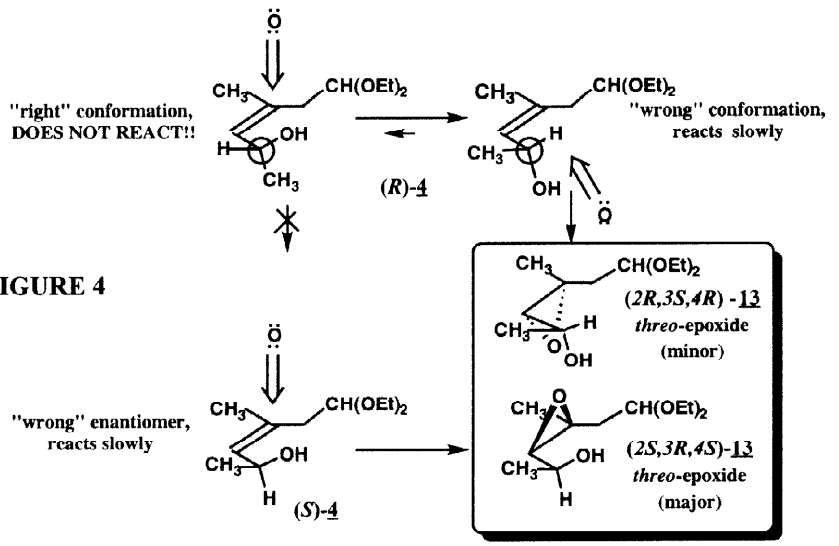


FIGURE 4

In summary, the first example of asymmetric epoxidation of a β,β-disubstituted allylic alcohol with different substituents is reported. The relative effects of the $A_{(1,3)}$-*cis* strain on the outcome of the epoxidations leads to the following conclusions:

- $A_{(1,3)}$-*cis* strain leads to reduction of diastereoselectivity in the asymmetric epoxidation, *i.e.*, increased *threo*-diastereomer formation
- $A_{(1,3)}$ interactions are enhanced if there is a substituent at C-4 (β-carbon atom) which is *trans* to the carbinol group. In some cases, it may result in exclusive formation of *threo*-epoxides.
- $A_{(1,3)}$-*cis* interactions have minimal effect on the enantioselectivity of the asymmetric epoxidations. In all cases, high *ee* are found for *erythro*-diastereomers and low *ee* for the *threo*-diastereomers.

EXPERIMENTAL

Thin layer chromatography (TLC) was conducted with Silufol UV_{254} (Kavalier, Czechoslovakia) with spot detection by exposure to heat. Column chromatography was conducted over Silica Gel Merck 60. Optical rotations were determined with a Perkin-Elmer 141 spectropolarimeter. NMR spectra were recorded with a Bruker CXP-200 (200 MHz, ^{1}H; 50 MHz, ^{13}C) or AM-360 (360 MHz, ^{1}H; 90MHz, ^{13}C) spectrometers in acetone-d_6 and resonance values listed as δ (ppm) and coupling constants (*J*) in Hz. Small splitting constants of <1.5 Hz are not reported in the spectra and are sometimes presented as 'br'.

The enantiomeric purity of the epoxy alcohols was determined by the procedure of Mosher [9]. Esterification of epoxy alcohols with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher reagent) was performed directly on nmr samples in deuterated chloroform/pyridine (90:10). Derivatization studies are monitored for disappearance (<1%) of characteristic resonanaces for starting epoxy alcohols; reaction times are 5 to 20 minutes at ambient temperature. The ratio of diastereomeric esters was determined directly (by nmr), without isolation of products. The H-3 (oxirane) protons are typically fully resolved in the diastereomers and are easily quantified for enantiomeric purity. All reagents were obtained from Aldrich Chemicals and used as is.

(*E*)-1-Trimethylsilyloxy-3-methyl-1,3-butadiene (6). A well-stirred suspension of anhydrous sodium iodide (180.0 g, 1.2 mol) and anhydrous acetonitrile (300 ml) was treated sequentially, at ambient temperature, with triethylamine (112 g, 1.1 mol), 3-methyl-2-butenal (**5**; 84 g, 1.0 mol), and pentane (400 ml). Trimethylchlorosilane (109 g, 1.0 mol) was added dropwise to this mixture at 38-40°C. The resultant mixture was stirred at 40-45°C for 4 h, then cooled to ambient temperature. The precipitate was filtered, and washed well with pentane. The filtrate was concentrated and distilled *in vacuo* to afford diene **6** (117 g, 75%): b.p. 56-60°C/35 mmHg, n_D^{20} 1.4496; ^{1}H NMR (200 MHz) δ 0.185 (s, 9H, $Si(CH_3)_3$), 1.79 (br s, 3H, 3-CH_3), 4.66 (br d, 1H, *J* = 2.2 Hz, H-4_b), 4.71(br d, 1H, *J* = 2.2. Hz, H-4_a), 5.77 (d, 1H, *J* = 16.5 Hz, H-2), 6.71 (d, 1H, *J* = 16.5 Hz, H-1); ^{13}C NMR (50MHz) δ -0.5 ($Si(CH_3)_3$), 18.7 (3-CH_3), 107.1 (C-4), 110.4 (C-2), 135.3 (C-3), 138.8 (C-1). Anal. Calcd for $C_8H_{16}OSi$: C, 61.50; H, 10.33; Si, 17.92. Found: C, 61.59; H, 10.24; Si, 17.58.

(*E*)- and (*Z*)-5,5-Diethoxy-3-methyl-2-penten-1-als (7). Silyloxydiene **6** (109.2 g, 0.7 mol) was added dropwise, at ambient temperature, to a solution of 15% anhydrous zinc chloride in ethyl acetate (700 ml) and triethyl orthoformate (104 g, 0.7 mol). The resultant mixture was stirred for 2 h and then treated dropwise with sat. aqueous sodium bicarbonate (600 ml). The precipitate was filtered and washed with diethyl ether (2 x 400 ml); the two-phase filtrate was separated and the organic phase was washed with 5% aqueous potassium carbonate and dried over anhydrous potassium carbonate. Concentration and distillation *in vacuo* gave 78.1 g (60%) of aldehyde **7**, as a mixture of (*E,Z*)-isomers: b.p. 68-70°C/3 mmHg, n_D^{20} 1.4590. *Aldehyde* (*E*)-**7**: ^{1}H NMR (200 MHz) δ 1.13 (t, 6H, *J* = 6.5 Hz, 2 X $OCH_2\mathbf{CH_3}$), 2.21 (br s, 3H, C(3)-CH_3), 2.50 (d, 2H, *J* = 5.8 Hz, H-4_a,4_b), 3.45 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.60 (q, 2H, $O\mathbf{CH_2}CH_3$), 4.69 (t, 1H, *J* = 5.8 Hz, H-5), 5.84 (br d, 1H, *J* = 8.1 Hz, H-2), 9.98 (d, 1H, *J* = 8.1 Hz, CHO); ^{13}C NMR (50 MHz) δ 15.4 (2 X $OCH_2\mathbf{CH_3}$), 18.1 (C(3)-CH_3), 45.1 (C-4), 61.5 ($O\mathbf{CH_2}CH_3$), 61.7 ($O\mathbf{CH_2}CH_3$), 101.7 (C-5), 129.9 (C-2), 159.7 (C-3), 190.3 (C-1). *Aldehyde* (*Z*)-**7**: ^{1}H NMR (200 MHz) δ 1.15 (t, 6H, *J* = 6.5 Hz, 2 X $OCH_2\mathbf{CH_3}$), 1.69 (br s, 3H, C(3)-CH_3), 2.87 (d, 2H, *J* = 5.5 Hz, H-4_a,4_b), 3.47 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.58 (q, 2H, $O\mathbf{CH_2}CH_3$), 4.69 (t, 1H, *J* = 5.8 Hz, H-5), 5.78 (br d, 1H, *J* = 7.8 Hz, H-2), 9.89 (d, 1H, *J* = 7.8 Hz, CHO); ^{13}C NMR (50 MHz) δ 15.5

(2 X $OCH_2\mathbf{CH_3}$), 26.2 (C(3)-CH_3), 38.0 (C-4), 62.4 (OCH_2), 62.6 (OCH_2), 102.2 (C-5), 130.3 (C-2), 159.0 (C-3), 190.5 (C-1). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.72; H, 9.89.

(±)-(*E*)-6,6-Diethoxy-4-methyl-3-hexen-2-ol (2) and **(±)-(*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ol (4)**. A solution of methylmagnesium iodide, prepared from methyl iodide (58 g, 0.41 mol) and magnesium (10 g, 0.41 mol), in diethyl ether (200 ml) was added dropwise at -10°C to a solution of aldehyde **7** (50 g, 0.27 mol) in diethyl ether (300 ml). The resultant mixture was stirred at -10°C for 4 h and at 25°C for 1 h, and then treated at 0°C with sat. aqueous ammonium chloride (200 ml). The mixture was separated and the aqueous phase was extracted with diethyl ether (3 x 200 ml); the combined organic phase was dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (hexane-diethyl ether, gradient elution) to give (*Z*)-allylic alcohol **4** (13.1 g, 24%) [R_f 0.48 (hexane-ethyl acetate, 1:1); n_D^{20} 1.4526; ^{1}H NMR (360 MHz) δ 1.11 (t, 3H, *J* = 6.5 Hz, $OCH_2\mathbf{CH_3}$), 1.12 11 (t, 3H, *J* = 6.5 Hz, $OCH_2\mathbf{CH_3}$), 1.12 (d, 3H, *J* = 6.3 Hz, H-1), 1.72 (d, 3H, *J* = 1.5 Hz, C(4)-CH_3), 2.31 (dd, 1H, *J* = 13.6; 5.2 Hz, H-5_b), 2.40 (dd, 1H, *J* = 13.6; 6.0 Hz, H-5_a), 3.47 ($\mathbf{OCH_2}CH_3$), 3.63 ($\mathbf{OCH_2}CH_3$), 4.44 (m, 1H, H-2), 4.56 (t, 1H, *J* = 5.6 Hz, H-6), 5.26 (br d, 1H, *J* = 8.3 Hz, H-3); ^{13}C NMR (90 MHz) δ 15.4 ($OCH_2\mathbf{CH_3}$), 15.6 ($OCH_2\mathbf{CH_3}$), 23.9 (C-1), 24.5 (C(4)-CH_3), 37.7 (C-5), 61.9 ($\mathbf{OCH_2}CH_3$), 62.4 ($\mathbf{OCH_2}CH_3$), 63.7 (C-2), 102.4 (C-6), 132.6 (C-4), 134.1 (C-3)] and (*E*)-allylic alcohol **2** (19.5 g, 36%) [R_f 0.42 (hexane-ethyl acetate, 1:1); n_D^{20} 1.4522; ^{1}H NMR (360 MHz) δ 1.10 (t, 3H, *J* = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.11 (t, 3H, *J* = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.11 (d, 3H, *J* = 6.5 Hz, H-1), 1.66 (d, 3H, *J* = 1.4 Hz, C(4)-CH_3), 2.20 (br d, 2H, *J* = 5.8 Hz, H-5_a,5_b), 3.43 ($\mathbf{OCH_2}CH_3$), 3.59 ($\mathbf{OCH_2}CH_3$), 4.48 (br m, 1H, H-2), 4.54 (t, 1H, *J* = 5.8 Hz, H-6), 5.24 (br d, 1H, *J* = 8.3 Hz, H-3); ^{13}C NMR (90 MHz) δ 15.6 (2 X $OCH_2\mathbf{CH_3}$), 17.0 (C(4)-CH_3), 24.1 (C-1), 44.4 (C-5), 61.2 ($\mathbf{OCH_2}CH_3$), 61.4 ($\mathbf{OCH_2}CH_3$), 64.3 (C-2), 102.7 (C-6), 131.6 (C-4), 134.1 (C-3)]. Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.92. Found: C, 65.35; H, 10.99.

***Erythro*-(2*R*,3*R*,4*R*)-6,6-Diethoxy-4-methyl-3,4-epoxyhexan-2-ol (9)** and ***threo*-6,6-diethoxy-4-methyl-3,4-epoxyhexan-2-ol (10).** A suspension of powdered activated 4Å molecular sieves (5.0 g) in anhydrous dichloromethane (300 ml), under argon, was cooled to -20°C and treated with titanium (IV) isopropoxide (2.84 g, 10.0 mmol), diisopropyl D-(-)-tartrate (3.51 g, 15.0 mmol), and *tert*-butyl hydroperoxide (13.6 ml, 4.4 M solution in dichloromethane). The mixture was stirred at -20°C for 0.5 h and then a solution of alcohol **2** (20.2 g, 100.0 mmol) in anhydrous dichloromethane (20 ml) was added dropwise and the mixture stirred at -20°C for 18 hours. The reaction was quenched at -20°C with water (40 ml) and stirred for an additional 3 hr, while the temperature reached ambient temperature. The resultant suspension was filtered and the filtercake washed with diethyl ether (3 x 100 ml). The combined filtrate was dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and the residue purified by column chromatography over silica gel (hexane-diethyl ether, gradient elution) to give epoxide **9** (5.3 g, 45%, based on the reacted enantiomer of the allylic alcohol **2**) [R_f 0.27 (hexane-diethyl ether, 1:1); $[\alpha]_D^{20}$+10.0° (*c* 1.0; methanol); ^{1}H NMR (360 MHz) δ 1.11 (t, 3H, *J* = 6.7 Hz, $OCH_2\mathbf{CH_3}$), 1.13 (t, 3H, *J* = 6.7 Hz, $OCH_2\mathbf{CH_3}$), 1.20 (d, 3H, *J* = 6.3 Hz, H-1), 1.32 (s, 3H, C(4)-CH_3), 1.66 (dd, 1H, *J* = 14.0; 5.9 Hz, H-5_b), 1.85 (dd, 1H, *J* = 14.0; 5.1 Hz, H-5_a), 2.57 (d, 1H, *J* = 8.0 Hz, H-3), 3.47 (q, 2H, $\mathbf{OCH_2}CH_3$), 3.51 (dq, 1H, *J* = 8.3; 6.3 Hz, H-2), 3.59 (q, 2H, $\mathbf{OCH_2}CH_3$), 4.61 (dd, 1H, *J* = 5.9 Hz; 5.1 Hz; H-6); ^{13}C NMR (90 MHz) δ 15.6 ($OCH_2\mathbf{CH_3}$), 17.6 (C(4)-CH_3), 21.4 (C-1), 43.5 (C-5), 59.4 (C-4), 61.1 ($\mathbf{OCH_2}CH_3$), 61.8 ($\mathbf{OCH_2}CH_3$), 65.7 (C-2), 67.2 (C-3), 101.3 (C-6). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.48; H, 10.17]. Key resonances [^{1}H

NMR (360 MHz)] for analysis of diastereomeric Mosher esters are δ 2.890 (d, J = 8.3 Hz, H-3 for *2R,3R,4R*-isomer), 2.806 (d, J = 8.2 Hz, H-3 for *2S,3S,4S*-isomer), 2.749 (d, J = 8.1 Hz, H-3 in epoxide **9**).

Later fractions yielded epoxide **10** (4.0 g) [R_f 0.25 (hexane:diethyl ether, 1:1); $[\alpha]_D^{20}$ -0.7° (*c* 1.0; methanol); ^{1}H NMR (360 MHz) δ 1.12 (t, 3H, J = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.14 (t, 3H, J = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.15 (d, 3H, J = 6.5 Hz, H-1), 1.25 (s, 3H, C(4)-CH_3), 1.54 (dd, 1H, J= 13.9; 6.6 Hz, H-5_b), 1.93 (dd, 1H, J = 13.9; 4.7 Hz, H-5_a), 2.65 (d, 1H, J= 8.0 Hz, H-3), 3.47 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.51 (dq, 1H, J= 8.0; 6.5 Hz, H-2), 3.60 (q, 2H, $O\mathbf{CH_2}CH_3$), 4.60 (dd, 1H, J = 6.6; 4.7 Hz; H-6); ^{13}C NMR (90 MHz) δ 15.5 ($OCH_2\mathbf{CH_3}$), 18.1 (C(4)-CH_3), 20.1 (C-1), 43.8 (C-5), 58.3 (C-4), 61.2 ($O\mathbf{CH_2}CH_3$), 61.8 ($O\mathbf{CH_2}CH_3$), 67.4 (C-2), 68.4 (C-3), 101.2 (C-6). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.40; H, 10.21]. Key resonances [^{1}H NMR (360 MHz)] for analysis of diastereomeric Mosher esters are δ 2.962 (d, J = 8.7 Hz, H-3 for *2R,3S,4S*-isomer), 2.913 (d, J = 8.6 Hz, H-3 for *2S,3R,4R*-isomer), 2.852 (d, J = 8.1 Hz, H-3 in epoxide **10**).

***Threo*-(2*S*,3*R*,4*S*)-6,6-diethoxy-4-methyl-3,4-epoxyhexan-2-ol (13)** was obtained in similar way from (±)-(*Z*)-6,6-diethoxy-4-methyl-3-hexen-2-ol (**4**) to afford epoxide **13**: R_f 0.32 (hexane:diethyl ether, 1:1); $[\alpha]_D^{20}$ +6.0° (*c* 2.0; methanol); ^{1}H NMR (360 MHz) δ 1.11 (t, 3H, J = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.12 (t, 3H, J = 6.6 Hz, $OCH_2\mathbf{CH_3}$), 1.18 (d, 3H, J = 6.5 Hz, H-1), 1.27 (s, 3H, C(4)-CH_3), 1.77 (dd, 1H, J = 14.1; 6.4 Hz, H-5_b), 1.83 (dd, 1H, J = 14.1; 5.0 Hz, H-5_a), 2.52 (d, 1H, J = 8.1 Hz, H-3), 3.45 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.58 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.55 (dq, 1H, J = 8.1; 6.5 Hz, H-2), 4.67 (dd, 1H, J = 6.4; 5.0 Hz; H-6); ^{13}C NMR (90 MHz) δ 15.4 ($OCH_2\mathbf{CH_3}$), 15.7 ($OCH_2\mathbf{CH_3}$), 20.0 (C-1), 23.4 (C(4)-CH_3), 37.9 (C-5), 59.1 (C-4), 61.5 ($O\mathbf{CH_2}CH_3$), 62.3 ($O\mathbf{CH_2}CH_3$), 66.8 (C-2), 69.5 (C-3), 101.4 (C-6). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.58; H, 10.19]. Key resonances [^{1}H NMR (360 MHz)] for analysis of diastereomeric Mosher esters are δ 2.857 (d, J = 8.5 Hz, H-3 for *2S,3R,4S*-isomer), 2.890 (d, J = 8.7 Hz, H-3 for *2R,3S,4R*-isomer), 2.72 (d, J = 8.0 Hz, H-3 in epoxide **13**).

(2*S*,3*R*)-6,6-Diethoxy-4-C-methyleno-hexan-2,3-diol (14). A solution of *threo*-(2*S*,3*R*,4*S*)-6,6-diethoxy-4-methyl-3,4-epoxyhexan-2-ol (**13**; 2.2 g (10 mmol), titanium (IV) isopropoxide (2.84 g, 10 mmol), and anhydrous benzene (80 ml) was heated at reflux for 1 h, then cooled to ambient temperature. The reaction mixture was diluted with diethyl ether (30 ml) and treated with sat. sodium bicarbonate (2 ml). The resultant suspension was filtered through a Celite pad and the pad washed further with diethyl ether. The combined filtrate was dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and the residue purified by chromatography over silica gel (chloroform-methanol, 20:1) to afford diol **14** (1.35 g, 62%): R_f 0.33 (hexane-diethyl ether, 1:1); $[\alpha]_D^{20}$ +2.0° (*c* 1.0; methanol); ^{1}H NMR (360 MHz) δ 1.04 (d, 3H, J=6.1 Hz, H-1), 1.12 (t, 6H, J = 6.5 Hz, 2 X $OCH_2\mathbf{CH_3}$), 2.31 (dd, 1H, J = 15.0, 5.9 Hz, H-5_b), 2.39 (dd, 1H, J = 15.0, 5.5 Hz, H-5_a), 3.46 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.62 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.69 (m, 1H, J = 6.3 Hz, H-2), 3.77 (br d, 1H, J = 6.4 Hz, H-3), 4.64 (t, 1H, J = 5.7 Hz, H-6), 5.01 (br s, 1H, =CH_2), 5.09 (br s, 1H, =CH_2). ^{13}C NMR (90 MHz) δ 15.5 ($OCH_2\mathbf{CH_3}$), 19.6 (C-1), 36.6 (C-5), 61.4 ($O\mathbf{CH_2}CH_3$), 61.8 ($O\mathbf{CH_2}CH_3$), 69.4 (C-2), 80.8 (C-3), 103.2 (C-6), 114,7 (=CH_2), 146.2 (C-4). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.58; H, 10.1.

(2*R*,3*R*)-6,6-Diethoxy-4-C-methyleno-hexan-2,3-diol (15) was obtained in a similar procedure from *erythro*-(2*R*,3*R*,4*R*)-6,6-diethoxy-4-methyl-3,4-epoxyhexan-2-ol (**9**) (85%): R_f 0.31 (hexane-diethyl

ether, 1:1); $[\alpha]_D^{20}$ -8.50° (*c* 1.0; methanol); ^{1}H NMR (360 MHz) δ 1.08 (d, 3H, *J*=6.2 Hz, H-1), 1.12 (t, 6H, *J* = 6.5 Hz, 2 X $OCH_2\mathbf{CH_3}$), 2.30 (dd, 1H, *J* = 14.8, 6.1 Hz, H-5_b), 2.37 (dd, 1H, *J* = 14.8, 5.7 Hz, H-5_a), 3.47 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.62 (q, 2H, $O\mathbf{CH_2}CH_3$), 3.67 (m, 1H, *J* = 6.3 Hz, H-2), 3.73 (br d, 1H, *J* = 6.5 Hz, H-3), 4.64 (t, 1H, *J* = 5.8 Hz, H-6), 5.02 (br s, 1H, $=CH_2$), 5.11 (br s, 1H, $=CH_2$). ^{13}C NMR (90 MHz) δ 15.5 (2 X $OCH_2\mathbf{CH_3}$), 18.4 (C-1), 36.9 (C-5), 61.7 ($O\mathbf{CH_2}CH_3$), 61.9 ($O\mathbf{CH_2}CH_3$), 69.1 (C-2), 79.9 (C-3), 103.5 (C-6), 114.3 ($=CH_2$), 146.1 (C-4). Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.51; H, 10.19.

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