Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1559-1566, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00222-3

(*S*)-(-)-2-*tert*-Butyl-3-methylene-oxirane: Synthesis and Hydroboration of a Chiral Allene Oxide

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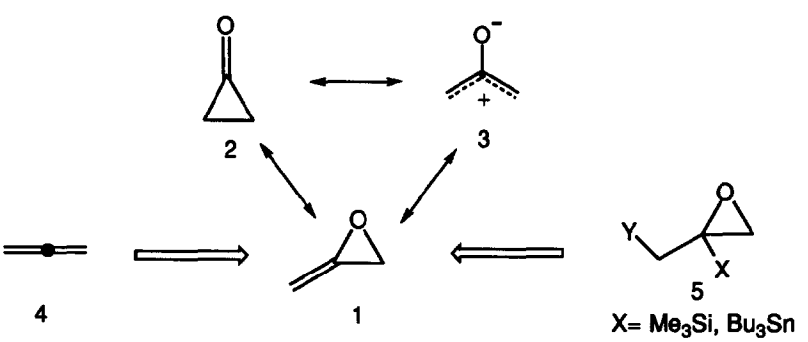
Abstract: The chiral allene oxide, (*S*)-(-)-2-*tert*-butyl-3-methylene-oxirane **12** ((*S*)-(-)-1-*tert*-butylallene oxide) was prepared in a moderate yield and in high enantiomeric excess by a three-step conversion starting from 4,4-dimethyl-2-pentyn-1-ol **6**. The procedure was comprised of hydrostannylation, Sharpless epoxidation and deoxystannylation. The chiral allene oxide **12** has moderate stability for identification and characterization and undergoes hydroboration to afford a chiral diol, (*R*)-4,4-dimethylpentane-1,3-diol **15**.

INTRODUCTION

Allene oxide[1] is a unique and reactive molecule. It is highly strained and has three functional groups; an epoxide, a double bond and an enol ether. Recently, this molecule has gathered both theoretical and experimental attention.[2] Quantum-mechanical calculations dealing with the energy diagram of allene oxide **1** and its valence tautomers, cyclopropanone **2** and oxyallyl **3**, have been reported. They predict that these systems undergo interconversion. The isomerization of **1** to **2** has been experimentally demonstrated. However, the mechanism of the isomerization has not been elucidated.



One difficulty associated with the study of allene oxide is the lack of an adequate synthetic procedure. There have been two main approaches to the synthesis of allene oxides: Peracid oxidation of allene **4** and exocyclic β-elimination of an epoxide **5**. Peracid epoxidation[3] would seem the simplest entry into allene oxides. However, they could rarely be isolated as stable compounds owing to their propensity to react with nucleophiles, undergo further epoxidation or isomerize to the corresponding cyclopropanone. These findings

have shown that only a few allene oxides bearing bulky *tert*-butyl groups could be isolated and characterized, and even these are prone to undergo further reactions. An efficient method of preparing allene oxides has been developed by Chan and coworkers[4] by dehalosilylation of epoxide **5** (X=Me_3Si, Y=Cl). Their approach has an advantage that the epoxide is preformed by a standard technique and a subsequent elimination generating the double bond gave the final allene oxides under mild conditions. This approach has been successfully applied to the preparation and isolation of racemic 2-*tert*-butyl-3-methylene-oxirane **12** (1-*tert*-butylallene oxide) of moderate stability. Kabat[5] recently employed a similar strategy to prepare reactive chiral allene oxides, and they are used as a precursor to chiral α-substituted ketones taking advantage of their susceptibility to nucleophilic addition. There have been several other routes to allene oxides, and the efficient conversion of an endoperoxide to the very stable allene oxide was reported.[6] A chiral allene oxide has also been shown to be an intermediate in the conversion of specific lipoxygenase products of several prostaglandin-like molecules.[7]

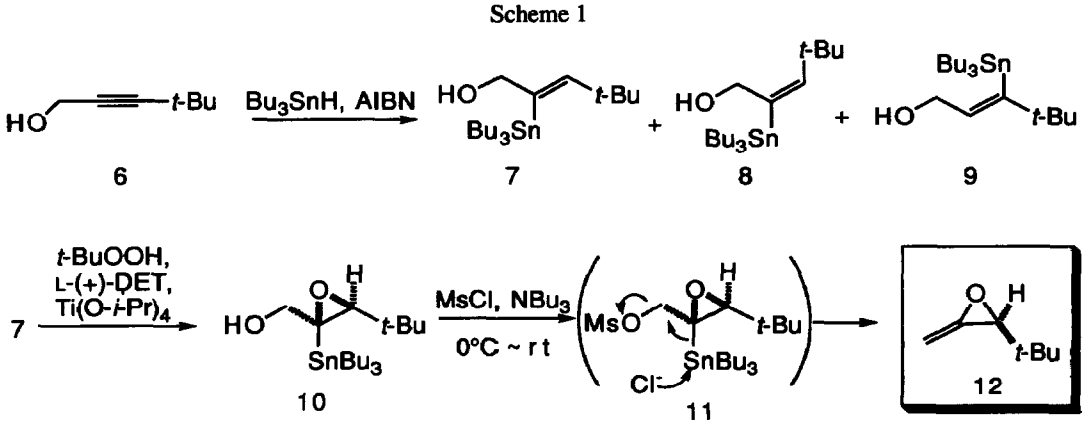
Our work in using deoxystannylation of tin compounds[8] in chiral allene syntheses[9] suggested the possibility of using stannyl epoxide **5** (X=Bu_3Sn, Y=OH) as an entry to allene oxides by β-eliminaton of X and Y. To realize our notion, we chose (*S*)-2-*tert*-butyl-3-methylene-oxirane **12** as our target as the best compromise between its known moderate stability and high reactivity. The chiral allene oxide would not only allow the investigation of the mechanism of rearrangement of allene oxides but also would serve as a chiral synthon in asymmetric synthesis, introducing a chiral three-carbon unit into complex molecules. In the extension of our work on tin chemistry, here we report a highly enantioselective synthesis of allene oxide and its further hydoroboration.

RESULTS AND DISCUSSION

(S)-2-tert-Butyl-3-methylene-oxirane 12: Isolation and characterization.

Scheme 1 shows the synthesis of (*S*)-2-*tert*-butyl-3-methylene-oxirane **12**. It was prepared from 4,4-dimethyl-2-pentyn-1-ol **6** in a three-step protocol: 1) hydrostannylation[10] of **6** to give (*E*)-allylic alcohol **7**, 2) Sharpless asymmetric epoxidation[11] of **7**, and 3) following deoxystannylation[12] of the resulting epoxide **10**. The starting compound, 4,4-dimethyl-2-pentyn-1-ol **6**, was prepared conventionally by the condensation of magnesium salt of 3,3-dimethyl-1-butyne with formaldehyde.

Scheme 1



Free radical addition (AIBN) of tributyltin hydride to 4,4-dimethyl-2-pentyn-1-ol **6** is highly regio- and stereoselective and gave the stannylated allylic alcohol **7** along with a small amount of stereo- **8** and regio-isomer **9** in an essentially quantitative yield (**8**, **7**, and **9** from top to bottom of TLC). A ^{1}H NMR spectrum of the mixture showed that the ratio of **7** to **8** to **9** was 9:1:0.5. These three isomers could be separated by short-path silica gel chromatography and their stereochemical structures are determined from their ^{1}H NMR spectra by examining the H-H and Sn-H coupling constants between vinylic Sn and H.

Sharpless asymmetric epoxidation of the separated allylic alcohol **7** gave chiral epoxide **10** in a good yield (79%). However, it was unnecessary to separate these allylic alcohols **7**, **8**, and **9** for the synthesis of allene oxide, because only (*Z*)-allylic alcohol **7** undergoes Sharpless asymmetric epoxidation and two other isomers were unreactive and recovered unchanged. When the crude mixture of stannylated allylic alcohols was subjected to the Sharpless asymmetric epoxidation by using L-(+)-diethyl tartrate, *t*-BuOOH and Ti(O-*i*-Pr)$_4$, chiral epoxide **10** was obtained and separated by silica gel chromatography. To determine the enantiomeric excess (ee) of epoxide **10**, it was transformed to Mosher's MTPA esters and ee was established to be over 97% ee by comparison of ^{1}H NMR spectra of (*R*)- and (*S*)-MTPA esters of epoxide **10** in the region of -OCH$_2$- ((*R*)- MTPA ester, δ 4.28 (singlet); (*S*)-MTPA ester, δ 4.34, 4.22 (ABq)). The absolute configuration of **10** depicted in Scheme 1 was presumed on the basis of the established stereochemistry of Sharpless asymmetric epoxidation and both ee and absolute configuration of epoxide **10** were finally confirmed by carrying out the further conversion to (*R*)-4,4-dimethylpentane-1,3-diol **15** described in a later section.

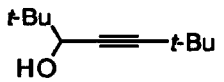
The deoxystannylation of **10** was executed under conditions similar to those for chiral allene synthesis (methanesulfonyl chloride (MsCl) and triethylamine in dichloromethane at 0 °C - room temperature). When no starting epoxide **10** was observed on TLC, no allene oxide was detected. As the 2-*tert*-butyl-3-methylene-oxirane was known to be unisolatable on usual work-up from Chan's report, we took their protocol for isolation of **12**. Therefore the deoxystannylation for generation of **12** was carried out with a slow stream of argon bubbling into the reaction mixture so that volatile **12** could be carried over into a cold trap at -78 °C. We employed the deoxystannylation condition of MsCl, tributylamine and triethyleneglycol dimethylether (triglyme) in respect to their high boiling points and low volatilities. Under this condition the epoxide was treated with a slight excess of MsCl at 0°C to room temperature to give clear oil in a cold trap in 29% yield. The residue was pure (*S*)-2-*tert*-butyl-3-methylene-oxirane **12** which was identical with the one Chan isolated on the basis of its spectroscopic data. This is the first time that a chiral allene oxide was isolated and characterized spectroscopically.

The unique feature of our chiral allene oxide synthesis resides in this double bond forming step by deoxystannylation which proved efficient[13] and proceeded under neutral conditions as reported in our previous work[9]. In contrast to the silylated epoxides of Chan's and Kabat's works where their silylated epoxides were converted to allene oxides in two steps including strong base, the stannylallylic alcohol **10** in our method gave directly allene oxide in a phenomenon similar to our previous allene synthesis and the proposed intermediary mesylate **11** was not detected. Two reasons are speculated as being responsible for the more facile elimination of stannnyl alcohol than of a silyl counterpart in consideration of energetics: 1) the longer and weaker Sn-C bond of higher energy level[14] than Si-C bond, and 2) stronger Sn-Cl bond[15] than Si-Cl bond (Scheme 1).

A few brief comments should be made concerning the usefulness of our methods at this point. The whole sequence of reactions was quite mild and essentially neutral and compatible with many functional groups. The starting material is prepared efficiently from a propargylic alcohol by a simple free radical addition of tin

hydride. Both enantiomeric forms of allene oxides were able to be prepared easily by a choice of enantiomers of tartrates. The deoxystannylation step was simple and efficient. Our method will be reasonably extended for the preparation of a variety of allene oxides.

To extend the scope of our allene oxide synthesis and prepare more stable or more functionalized allene oxide, we have tried some other propargylic alcohols for chiral allene oxides synthesis. However, neither of the di-*tert*-butylpropargyl alcohol **13** nor trimethysilylpropargyl alcohol **14** added tributyltin hydride. These



13

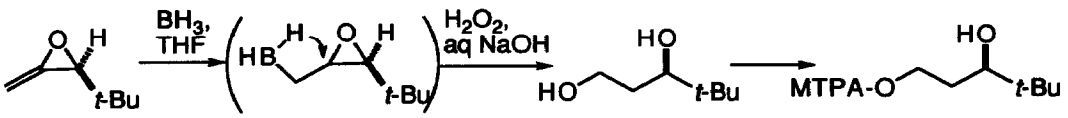
14

findings show that free-radical addition of tributyltin hydride to propargylic alcohols is sensitive to both steric and electronic nature of the propargylic alcohols, and a similar observation was made by Lautens and co-workers[16]. It is inferred that the inertness of these propargylic alcohols was attributed to the instability of stannylated vinyl radical and reversibility of the tin hydride addition.

Hydroboration of (S)-2-tert-Butyl-3-methylene-oxirane 12.

In contrast to the well established nucleophilic addition to allene oxide, electrophilic addition has not been reported so far. Allene oxides have an electron rich and strained enol moiety and we expected that an allene oxide would undergo an electrophilic addition. Our speculation was realized by hydroboration of the chiral allene oxide **12**, which is shown in Scheme 2. The hydroboration was performed by treating oxide **12** with

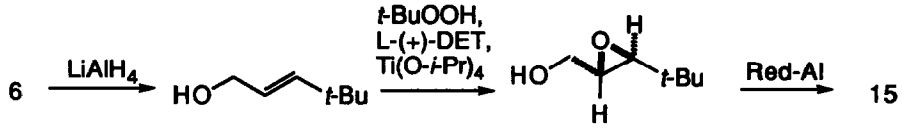
Scheme 2



12 15

BH_3•THF in a usual way. Subsequent oxidative work-up gave (*R*)-4,4-dimethylpentane-1,3-diol **15** in 15% yield from stannylepoxide **10**. The yield of hydroboration was estimated to be ca 50% considering 29% yield of the allene oxide formation step. The absolute configuration of chiral 4,4-dimethylpentane-1,3-diol **15** was established to be *R*-configuration by comparison of the sign of its specific rotation with those in the literature[17] and of the authentic sample prepared from by the standard procedure (Scheme 3). The enantiomeric excess was established to be over 97% ee by its transformation into Mosher's MTPA esters and comparison of their ^1H NMR spectra. Only the primary alcohol was acylated by acid chloride of MTPA and the secondary alcohol remained intact. Scheme 2 shows the reaction path of the hydroboration and further derivatization to MTPA ester.

Scheme 3



As allene oxides are well recognized to be highly reactive species, we have tried several asymmetric reactions of chiral allene oxide **12**, including cycloaddition or complexation with transition metals, however, polymeric or unidentified materials were obtained in these experiments.

In conclusion, we have shown that a chiral allene oxide, (*S*)-(-)-2-*tert*-butyl-3-methylene-oxirane **12** was prepared in moderate yield and in high optical purity by a three-step conversion starting from 4,4-dimethyl-2-pentyn-1-ol **6** and the resulting chiral allene oxide was hydroborated to give a chiral diol, (*R*)-4,4-dimethyl-pentan-1,3-diol **15**. Our synthesis of an allene oxide from propargylic alcohol is quite simple and would find use in the preparation of a variety of allene oxides.

EXPERIMENTAL SECTION

General. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sieves type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished at an aspirator pressure using a rotary evaporator. TLC was performed with a Merck pre-coated TLC plate silica gel 60 F_{254}, and compound visualization was effected with a 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Gravity chromatography was done with Merck silica gel 60 (70-230 mesh). ^1H NMR and ^{13}C NMR spectra were measured as $CDCl_3$ solutions at 200 and 50.3 MHz. *J* values are given in Hz. High-resolution mass spectra (HR-LSIMS) were recorded on a HITACHI M-90 instrument.

4,4-Dimethyl-2-pentyn-1-ol (6). A solution of 3,3-dimethyl-1-butyne (3.34 g, 40.7 mmol) in THF (70 mL) was cooled to 0 °C, and a solution of 3 M EtMgBr in Et_2O (15 mL, 45 mmol) was added dropwise, and the mixture was stirred for 3 h at room temperature. Formaldehyde gas (generated from pyrolysis of paraformaldehyde (7.5 g) at 110 °C) was passed into the reaction mixture at -78 °C and the resulting solution was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl (80 mL) was added to the mixture and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl and dried. The solvent was removed and the residue was distilled under reduced pressure to give **6** (2.89 g, 63%), bp 44-46 °C/4 mmHg. ^1H NMR: δ 4.25 (s, 2), 1.61 (s, 1), 1.26 (s, 9). ^{13}C NMR: δ 27.39, 30.96, 51.13, 76.96, 94.49. Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.51; H, 10.79.

(*Z*)-4,4-Dimethyl-2-tributylstannylpent-2-en-1-ol (7), (*E*)-4,4-Dimethyl-2-tributylstannylpent-2-en-1-ol (8), and (*Z*)-4,4-Dimethyl-3-tributylstannylpent-2-en-1-ol (9). A mixture of alcohol **6** (1.0 g, 8.9 mmol) and Bu_3SnH (3.12 g, 10.7 mmol) was heated with AIBN (a catalytic amount) at 80 °C for 4 h. ^1H NMR spectrum and TLC of the mixture showed the existence of three components, and the resulting mixture was used for the next epoxidation. The three components were purified by short-path silica gel chromatography (hexane saturated with MeCN as eluent) to give **7** as major isomer

(48%), along with two minor isomers **8** and **9**. **7.** TLC (hexane/EtOAc (9/1)) *Rf* 0.47. ^{1}H NMR: δ 6.36 (t, 1, $^4J_{H-H}$ = 1.1, $^3J_{Sn-H}$ = 139.6, 133.4), 4.15 (br d, 2, J_{H-H} = 5.2, $^3J_{Sn-H}$ = 39.6), 1.7-1.2 (m, 12), 1.06 (s, 9), 1.2-0.8 (m, 15), 0.90 (t, 9, *J* = 7.4). ^{13}C NMR: δ 154.73 (J_{Sn-C} = 22.4), 137.01, 73.27 (J_{Sn-C} = 40.6), 34.05, 30.58, 29.29 (J_{Sn-C} = 19.2), 27.50 (J_{Sn-C} = 63.0), 13.70, 12.01 (J_{Sn-C} = 339.8, 324.7). HR-LSIMS *m/z* 347.1399 [M-Bu]$^+$ (calcd for $C_{15}H_{31}OSn$, 347.1395). **8.** TLC (hexane/EtOAc (9/1)) *Rf* 0.54. ^{1}H NMR: δ 5.46 (t, 1, $^4J_{H-H}$ = 2.3, $^3J_{Sn-H}$ = 83.4, 79.4), 4.53 (dd, 2, J_{H-H} = 5.2, 2.3, $^3J_{Sn-H}$ = 39.6) 1.7-1.2 (m, 12), 1.08 (s, 9), 1.1-0.8 (m, 15). HR-LSIMS *m/z* 347.1398 [M-Bu]$^+$ (calcd for $C_{15}H_{31}OSn$, 347.1395). **9.** TLC (hexane/EtOAc (9/1)) *Rf* 0.34. ^{1}H NMR: δ 6.20 (t, 1, $^3J_{H-H}$ = 6.8, $^3J_{Sn-H}$ = 138.4, 132.4), 4.11 (t, 2, $^3J_{H-H}$ = 6.8), 1.6-1.2 (m, 12), 1.04 (s, 9), 1.1-0.8 (m, 15). HR-LSIMS *m/z* 347.1400 [M-Bu]$^+$ (calcd for $C_{15}H_{31}OSn$, 347.1395).

(2*R*,3*S*)-1-(3-*tert*-Butyl-2-tributylstannyl-oxirane-2-yl)methanol (10). The suspension of powdered 4A molecular sieves (250 mg) in CH_2Cl_2 (20 mL) was cooled (-20 °C). L-(+)-Diethyl tartrate (31 mg) and Ti(O-iPr)4 (35 mg) were added sequentially with stirring. The mixture was stirred at -20 °C as tBuOOH (1.6 mL, 3.0 M in isooctane) was added and the resulting mixture was stirred at -20 °C for 30 min. The crude mixture of three isomeric allylic alcohols **7**, **8** and **9** (prepared from 0.25 g of **6**) dissolved in CH_2Cl_2 (4 mL) was then added dropwise over 20 min at -40 °C. After stirring for 1 h at -20 °C the temperature was allowed to rise to 0 °C over 2 h. Then the mixture was slowly poured into an ice-cold aqueous solution (100 mL) of $FeSO_4.7H_2O$ (3 g) and tartaric acid (1 g). The mixture was allowed to warm to room temperature and stirred for 30 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was treated with 30% NaOH saturated with NaCl and the mixture was stirred vigorously for 30 min at 0 °C. The phases are separated and aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, concentrated and purified by chromatography (hexane/EtOAc (19/1)) to give epoxide **10** (0.35 g, 38% from **6**). TLC (hexane/EtOAc (4/1)) *Rf* 0.51. ^{1}H NMR: δ 3.69 (dd, 1, *J* = 12.0, 4.8), 3.60 (dd, 1, *J* = 12.0, 8.0), 2.80 (s, 1, $^3J_{Sn-H}$ = 10.0), 1.79 (dd, 1, *J* = 8.0, 4.8), 1.60-1.20 (m, 12), 0.96 (s, 9), 0.90 (t, 9, *J* = 7.4), 1.1-0,9 (m, 6). ^{13}C NMR δ 69.23, 68.85, 62.90 (J_{Sn-C} = 382.1, 365.4), 31.28, 29.25, 29.06 (J_{Sn-C} = 19.1), 27.49, 26.80, 13.67, 11.18 (J_{Sn-C} = 335.1, 319.9). $[\alpha]^{23.5}_D$ = +10.7 (*c* = 4.5, $CHCl_3$). HR-LSIMS *m/z* 443.1942 [M+Na]$^+$ (calcd for $C_{19}H_{40}O_2SnNa$, 443.1945).

(*R*)-MTPA Ester of Epoxide 10. To a mixture of **10** (42 mg), DMAP (12 mg) and Et_3N (0.066 mL) in CH_2Cl_2 (0.3 mL), (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA-Cl) (0.030mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 5 min and then quenched with 3-(dimethylamino)propylamine (0.030 mL). The residue was condensed and passed through a short plug of silica gel to give (*R*)-MTPA ester of **10** (48 mg, 78%). TLC (hexane/EtOAc (4/1)) *Rf* 0.2. ^{1}H NMR: δ 7.6-7.3 (m, 5), 4.28 (s, 2, $^3J_{Sn-H}$ = 24.4), 3.55 (q, 3, *J* = 1.4), 2.56 (s, 1, $^3J_{Sn-H}$ = 7.8), 1.5-1.1 (m, 12), 0.88 (s, 9), 1.1-0.8 (m, 15). HR-LSIMS *m/z* 579.1736 [M-Bu]$^+$ (calcd for $C_{25}H_{38}F_3O_4Sn$, 579.1741).

(*S*)-MTPA Ester of Epoxide 10. The (*S*)-MTPA ester was prepared by (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in a similar way to the (*R*)-MTPA ester. ^{1}H NMR: δ 7.6-7.3 (m, 5), 4.34, 4.22 (ABq, 2, *J* = 11.4), 3.55 (q, 3, *J* = 1.4), 2.62 (s, 1, $^3J_{Sn-H}$ = 8.3), 1.6-1.2 (m, 6), 0.92 (s, 9), 1.1-0.8 (m, 6), 0.89 (t, 9, *J* = 7.6).

(*S*)-2-*tert*-Butyl-3-methylene-oxirane (12). A mixture of **10** (0.48 g, 1.1 mmol) and tributylamine (0.25 g, 1.32 mmol) in triglyme (5 mL) was cooled to 0 °C and MsCl (0.16 g, 1.32 mmol) was

added with a slow stream of argon bubbled into the solution. The mixture was allowed to room temperature overnight with bubbling continued so that any volatile products would be carried over into a cold trap. Then, a colorless liquid was collected in the cold trap. The distillate was dissolved in $CDCl_3$ (1 mL) containing CH_2Cl_2 (0.010 mL) as an internal standard for ^1H NMR analysis. The NMR integration showed the yield of **12** was 29%. ^1H NMR: δ 4.36 (dd, 1, *J* = 3.2, 0.8), 4.23 (d, 1, *J* = 3.2), 3.41 (s, 1), 0.99 (s, 9). ^{13}C NMR: δ 144.06, 70.90, 68.31, 31.92, 25.98. $[\alpha]^{11}_D$ = -12 (*c* = 0.7, $CDCl_3$).

(*R*)-4,4-Dimethyl-pentane-1,3-diol (15). To a $CDCl_3$ solution of (*S*)-2-*tert*-butyl-3-methylene-oxirane (prepared as described starting from 1.0 mmol of epoxide **10**) in THF (1 mL) was added BH_3•THF (2.0 mL of 1.0 M solution) at -78 °C. The temperature was allowed to rise to room temperature and the mixture was stirred for a few minutes. To the mixture was added H_2O (0.3 mL), 3N NaOH and 30% H_2O_2 (0.5 mL) sequentially and stirring was continued for 30 min, and then the residue was extracted with EtOAc. The organic layer was dried and concentrated and purified by chromatography (hexane/EtOAc (1/1)) to give diol **15** (16 mg, 15% from **10**). ^1H NMR: δ 3.77-3.95 (m, 2), 3.50 (dd, 1, *J* = 9.8, 3.0), 2.45 (br s, 2), 1.50-1.80 (m, 2), 0.91 (s, 9). $[\alpha]^{24}_D$ = +18.0 (*c* = 0.4, $CHCl_3$).

Alternative synthesis of (*R*)-4,4-Dimethylpentane-1,3-diol (15).

(*E*)-4,4-Dimethyl-2-penten-1-ol (16). A THF (10 mL) solution of 4,4-dimethyl-2-pentyn-1-ol **6** (336 mg, 3.0 mmol) and $LiAlH_4$ (285 mg, 7.5 mmol) was refluxed for 4 h and quenched with H_2O. A mixture was extracted with EtOAc and condensed to give crude (*E*)-4,4-dimethyl-2-penten-1-ol **16**. ^1H NMR: δ 5.72 (dt, 1, *J* = 15.5, 1.0), 5.54 (dt, 1, *J* = 15.6, 5.6), 4.11 (dd, 2, *J* = 5.6, 1.0), 1.4 (br s, 1), 1.02 (s, 9).

(2*S*,3*S*)-4,4-Dimethyl-2,3-epoxy-2-penten-1-ol (17). A suspension of powdered 4A molecular sieves (16 mg) in CH_2Cl_2 (2 mL) was cooled (-20 °C) . L-(+)-Diethyl tartrate (7 mg) and Ti(O-iPr)4 (8.1 mg) were added sequentially with stirring. The mixture was stirred at -20 °C as *t*-BuOOH (0.38 mL, 3.0 M in isooctane) was added and the resulting mixture was stirred at -20 °C for 30 min. The crude (*E*)-4,4-dimethyl-2-penten-1-ol **16** (65 mg) dissolved in CH_2Cl_2 (0.25 mL) was then added dropwise over 20 min at -40 °C. After stirring for 2.5 h at -40 °C and then 1 h at -20 °C, the mixture was slowly poured into an ice-cold aqueous solution (1 mL) of $FeSO_4.7H_2O$ (0.3 g) and tartaric acid (0.1 g). The mixture was allowed to warm to room temperature and stirred for 30 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was treated with 30% NaOH saturated with NaCl and the mixture was stirred vigorously for 30 min at 0 °C. The phases separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, concentrated and purified by chromatography (hexane/EtOAc (2/1)) to give epoxide **17** (39 mg, 53%). ^1H NMR: δ 3.98 (dd, 1, *J* = 12.4, 2.6), 3.62 (dd, 1, *J* = 12.4, 4.4), 3.04 (dt, 1, *J* = 4.4, 2.6), 2.76 (d, 1, *J* = 2.6), 1.66 (br s, 1), 0.95 (s, 9).

(*R*)-4,4-Dimethylpentane-1,3-diol (15). Red-Al^R toluene solution (0.093 mL, 0.315 mmol) was added to DME (1.5 mL) solution of **17** (39 mg, 0.3 mmol) at 0 °C. The solution was stirred at 0°C for 2 h and at room temperature for 1 h, then treated with Et_2O (4 mL) and 1N HCl (1 mL). After stirring for 30 min the organic layer was separated, dried and condensed (26 mg). The residue was purified by chromatography to give pure diol **15** (24 mg, 61%). ^1H NMR: δ 3.77-3.95 (m, 2), 3.50 (dd, 1, *J* = 10.0, 3.0), 2.36 (br s, 2), 1.46-1.80 (m, 2), 0.92 (s, 9). $[\alpha]^{24}_D$ = +15.4 (*c* = 1.1, $CHCl_3$).

(*S*)-MTPA Ester of 1,3-diol 15. To a mixture of **15** (8 mg, 0.69 mmol), DMAP (7.7 mg) and Et_3N (11.5 mg) in CH_2Cl_2 (0.4 mL), (*S*)-MTPA-Cl (26 mg) was added at 0 °C. The resulting mixture was stirred at room temperature for 5 min and then quenched with 3-(dimethylamino)propylamine (0.010 mL). The

residue was condensed and passed through a short plug of silica gel to give (*S*)-MTPA ester of **15** (22 mg, 96%). ^{1}H NMR: δ 7.4-7.6 (m, 4), 4.48-4.56 (m, 2), 3.56 (s, 3), 2.24 (dd, 1 *J* = 10.9, 1.8), 1.85-2.03 (m, 1), 1.67 (s, 9), 1.50-1.66 (m,1), 0.86 (s, 9).

(*R*)-MTPA Ester of 1,3-diol 15. (*R*)-MTPA ester was prepared from (*R*)-MTPA-Cl in a way similar to (*S*)-isomer. ^{1}H NMR: δ 7.35-7.6 (m, 5), 4.65-4.40 (m, 2), 3.56 (q, 3, *J* = 1.4), 3.22 (br d, 1, *J* = 12.0), 2.0-1.8 (m, 1), 1.7-1.5 (m, 1), 0.86 (s, 9). HR-LSIMS *m/z* 349.1618 $[M+H]^+$ (calcd for $C_{17}H_{24}F_3O_4$, 349.1625).

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(*Received in Japan* 23 *May* 1994)