StereoSpecific Synthesis of Aldols

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Abstract

Methods are provided for preparing all four diastereomers of 2-alkyl-3-hydroxyalkanes, 2-alkyl-3-silyloxyalkanes, and the like, with high enantiocontrol, using non-aldol chemistry. The synthetic methods also provide novel, stereospecific routes to polypropinates and chiral 2-substituted-1,3 diols.

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STEREOSPECIFIC SYNTHESIS OF ALDOLS

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FIELD OF THE INVENTION

This invention is directed to processes for making aldos, including 2-substituted-3-silyloxyalkanals and 2-substituted-3-hydroxyalkanals; chiral 1,3-diols; and chiral polypropionates.

BACKGROUND OF THE INVENTION

Aldols (β-hydroxy- and β-alkoxy aldehydes) are useful chemical compounds used in the manufacture of antibiotics and other medicinal compounds, and in various natural products syntheses. The carboxylic acid analogs of certain chiral aldos have been used in liquid crystal applications.

Typically, aldos are prepared by an aldol condensation reaction. For example, the compound named "aldol" (β-hydroxybutyraldehyde) is prepared by condensation of acetaldehyde in sodium hydroxide solution. Schematically, an aldol condensation is expressed by the equation:

\[
\text{CHO} + \text{H} \xrightarrow{\text{base or acid}} \text{C}==\text{C}==\text{O} \rightarrow \text{C}==\text{C}==\text{O}
\]


In general, the known methods for enantiocontrol utilize an aldol reaction with well-designed chiral auxiliaries to produce the desired enantiomers with, at times, quite high selectivity. A few exceptions to this generalization are known, however. In a series of papers, Yamamoto has shown that hindered aluminum-based Lewis acids can promote rearrangements of epoxy silyl ethers to produce various products, including both erythro and three aldos. See Maruoka, K.; Sato, J.; Yamamoto, H. Tetrahedron 1992, 48, 3749; Maruoka, K.; Ooi, T.; Yamamoto, H. J. Am. Chem. Soc. 1989, 111, 6431; 65 and Maruoka, K.; Ooi, T.; Nagahara S.; Yamamoto, H. Tetrahedron 1991, 47, 6983. In each case, however, the group being transferred is originally attached to the epoxide carbon, and not to the adjacent carbon (the carbon that becomes the C2 position, α to the aldehyde).


In a joint paper, Tsuchihashi and Yamamoto reported the migration of phenoxy and vinyl groups in the presence of TiCl4 and Et3SiH to produce primary alcohols. See J. Am. Chem. Soc. 1986, 108, 3827.

Despite the success of such methods, however, the preparation of particular aldos having specific stereoconfigurations at the C2 and C3 positions can be problematic. Thus, new, stereoselective routes to aldos, particularly 2-alkyl-3-silyloxyalkanals and 2-alkyl-3-hydroxyalkanals, are desired.

SUMMARY OF THE INVENTION

It has now been discovered that all four diastereomers of the aldol products, 2-substituted-3-silyloxyalkanals and 2-substituted-3-hydroxyalkanals can be prepared with high enantiocontrol by a unique non-aldol route. The absolute stereoconfiguration at the C2 and C3 positions is introduced by preparing an epoxyalcohol by an asymmetric epoxidation reaction. Treatment of the epoxyalcohol with a silyl reagent, such as a trialkylsilyl triflate, opens the epoxy ring regioselectively with inversion of configuration to form the silyloxyalkanal. Removal of the silyloxy group and replacement with OH gives the 2-substituted-3-hydroxyalkanal.

The method is sufficiently general in scope to allow the synthesis of optically active 2-alkyl- and 2-aryl-3-silyloxyalkanals, and the analogous 2-substituted-3-hydroxyalkanals, and also provides a novel stereospecific route to polypropionates and chiral 2-substituted-1,3-diols, using non-aldol chemistry.

In an exemplary embodiment of the invention, all four diastereomers of 2-methyl-3-(t-butyldimethylsilyloxy)hexanal are prepared in excellent yield from the simple aldehyde, butanal, by the following steps: (a) conversion of the aldehyde to the allylic alcohol, 2-methylhex-2-enol; (b) formation of an epoxyalcohol by Sharpless epoxidation of the allylic alcohol; and (c) treatment of the epoxyalcohol with t-butyldimethylsilyl triflate to form 2-methyl-3-(t-butyldimethylsiloxy)-hexanal.

In another embodiment of the invention, the chiral diol 2-methylhexan-1,3-diol is prepared with high diastereomeric and enantiomeric control by reducing the aldehyde functionality on a 2-methyl-3-silyloxyalkanal, removing the 3-silyloxy group, and replacing it with OH, using a deprotecting agent.

In still another embodiment of the invention, the polypropionate (2S,3S,4S,5R)-5-(triethylsiloxy)-3-hydroxy-2,4-dimethylecyclohexan is made from a silyloxy epoxycarhol that is prepared using the non-aldol chemistry described herein.

DETAILED DESCRIPTION

The present invention provides a new route to optically active 2-alkyl-3-silyloxyalkanals, 2-alkyl-3-hydroxyalkanals, and 2-aryl- analogs thereof, using
non-aldol chemistry, i.e., without the step of an aldol condensation. Thus, the present invention provides a unique synthetic route to optically active compounds of the formula (I):

\[
\begin{array}{c}
R' \\
\text{X} \\
R''
\end{array}
\]

where \( R' \) and \( R'' \) are alkyl or aryl, and \( X \) is a silyloxy group, preferably a trialkysilyloxy group, such as tert-butyldimethylsilyloxy, triethylsilyloxy, trisopropylsilyloxy, trimethylsilyloxy, etc.

The silyloxy group, \( X \), can be easily removed and replaced with a hydroxyl group, \( \text{OH} \), by, e.g., treatment with a deprotecting agent such as hydrogen fluoride-pyridine complex, tetrabutyllammonium fluoride, etc. Thus, the present invention also encompasses a new synthetic route to optically active compounds of the formula (Ia):

\[
\begin{array}{c}
R' \\
\text{OH} \\
R''
\end{array}
\]

where \( R' \) and \( R'' \) are as defined above.

Technically, the \( \text{Si-O} \), rather than the \( \text{O-C} \), bond is broken during deprotection, or else inversion of configuration at the carbon center would be observed. Thus, deprotection actually entails removal of the silyl group and replacement with \( \text{H} \). For ease of discussion, however, and as used herein, the step of deprotecting a protected hydroxy group shall be referred to as “removing the silyloxy group and replacing it with \( \text{OH} \),” or similar language.

The synthetic methods of this invention allow the enantiomeric synthesis of all four diastereomers of compounds of both formulas (I) and (Ia). Stereochemistry at the \( C_2 \) and \( C_3 \) positions is controlled through an asymmetric epoxidation of an allylic alcohol to yield an epoxyalcohol having a predetermined absolute stereoconfiguration. Such an epoxyalcohol is represented by the formula (II):

\[
\begin{array}{c}
R' \\
\text{O} \\
R''
\end{array}
\]

Treatment of the epoxyalcohol with a silyl reagent such as a trialkylsilyl triflate opens the epoxide region-specifically with inversion of configuration to generate the desired 2-alkyl- or 2-aryl-3-silyloxyalkanalan.

Alternatively, the epoxyalcohol is first reacted with a silyl reagent such as a trialkylsilyl halide, to form an epoxy silyl ether of the formula (III):

\[
\begin{array}{c}
R' \\
\text{O} \\
R''
\end{array}
\]

where \( X \) is a silyloxy group. Treatment with a Lewis acid, such as \( \text{BF}_3 \) etherate yields the desired alkanalan.

As a first exemplary embodiment of the invention, the enantiomeric synthesis of all four diastereomers of 2-methyl-3-(t-butyldimethylsilyloxy)-hexanal will now be described. In this and the following descriptions and examples, particular reactants, intermediates, and products are identified by bold Arabic numbers, as needed for clarity. Complete reaction conditions (concentrations and amounts of reactants and reagents; temperatures; etc.) are provided in the examples at the end of the specification.

(2S,3R)-2-methyl-3-(t-butyldimethylsilyloxy) hexanal 5

This compound is prepared by first converting the simple aldehyde butanal 1 into E-2-methylhex-2-enol 2 by a Wittig reaction with the phosphonate \( \text{CH}_3\text{CH(COOCH}_3\text{)}\text{PO(OCH}_3\text{)} \) and reduction with disobutyllaluminum hydride (DIBAL):

\[
\begin{array}{c}
\text{PrCHO} \\
\text{OH} \\
\text{Me}
\end{array}
\xrightarrow{\text{MeCHCOOMe}}
\text{OH} \\
\text{DIBAL}
\]

where \( \text{Pr} \) is propyl and \( \text{Me} \) is methyl. (Large quantities of allylic alcohols such as 2 are better prepared using a modified Bayliss-Hillman procedure, as described in Example 1 at the end of the specification.)

The allylic alcohol 2 is converted into the optically active epoxyalcohol (2R,3R)-2-methyl-3-propyl oxypropyranemethan 3, in 94% yield and 95% enantiomeric excess ("ee"), by a Sharpless asymmetric epoxidation reaction, using D-(--)-diisopropyl tartrate as the chiral catalyst:

\[
\begin{array}{c}
\text{OH} \\
\text{tBuOOH} \\
\text{Ti(OiPr)}_4
\end{array}
\xrightarrow{D-(--)-diisopropyl tartrate 94\%}
\]

The desired alkanalan is formed by treating the epoxyalcohol 3 with t-butyldimethylsilyl triflate ("TBSOTT") at low temperature:

\[
\begin{array}{c}
\text{OH} \\
\text{OTBS} \\
\text{Me}
\end{array}
\xrightarrow{1.13 \text{ eq TBSOTT} \text{ molecular sieves 42\textdegree C.}}
\]

Although not bound by theory, it is believed that the mechanism of this novel transformation involves activation of the epoxide oxygen with the silyl triflate, followed by intramolecular hydride transfer to generate the new stereochemical center at the \( C_2 \) position and loss of the trialkysilyl group to give the silyl aldehyde product 5. Such a mechanism may be illustrated by the following equation:
In practice, treating the epoxyalcohol 3 with one equivalent of the silyl triflate yields approximately an 88:12 mixture of the silyl ether 4 and the rearrangement product—the silyloxalkan 5. If an excess of silyl triflate is used, the reaction is driven essentially all the way to the silyloxalkan 5. However, the reaction appears to be somewhat dependent on the concentration of epoxyalcohol. For example, treating a 0.1 molar epoxyalcohol—dichloromethane solution with 1 to about 1.4 equivalents of silyl triflate yields a mixture of the silyl ether 4 and the silyloxalkan 5. If the concentration of epoxyalcohol is increased to about 0.3 molar or higher, however, treatment with even 1.2 equivalents of silyl triflate drives the reaction all the way to the silyloxalkan 5.

In an alternate embodiment, the silyl ether 4 is prepared by reacting the epoxyalcohol with the silyl reagent t-butyldimethylsilyl chloride ("TBSCI"), in the presence of Hunig's base (disopropylethylamine) and dichloromethane (1.3 eq TBSCI 5 eq Hunig's base, 12 h, heat: >90%). The silyl ether 4 is then treated with a Lewis acid, such as BF₃ etherate, which opens the epoxide regioselectively and generates the 2-methyl-3-trialkylsilyloxalkan 5. The yield is only slightly lower than for the one-step process.

Though not bound by theory, it is believed that this alternate route proceeds by a mechanism where the BF₃ complexes with the epoxide, and internal hydride transfer occurs as with the silyl triflate to give the analog of 7, which then internally transfers the silyl group from the oxonium salt to the ROBF₃ group (with loss of BF₃) to give the observed product 5.

Despite the utility of this latter approach, which is less expensive because it employs BF₃, rather then a silyl triflate, the best conditions are direct treatment of the epoxyalcohol 3 with 1.3 equivalents of TBOTf and 1.35 equivalents of Hunig's base, in the presence of molecular sieves, at −42°C. to give the desired product 5 in 87% crude yield. Both capillary GC and NMR analysis show this compound to be a greater than 50:1 mixture at the center α to the aldehyde (the C₂ position). After purification by chromatography (during which, some epimerization occurs at the C₂ position), a 96:4 mixture is isolated in 78% yield.

(2R,3S)-2-methyl-3-(t-butyldimethylsilyloxy)hexanal 9

The enantiomer of 5 is prepared in like manner. The allylic alcohol E-2-methylhex-2-enol 2 is converted into the optically active epoxyalcohol (2S,3S)-2-methyl-3-propoxyiranemethanol 8 (the enantiomer of 3) in 94% yield and 96% enantiomeric excess by Sharpless epoxidation, using the L-(+)-disopropyl tartrate as the chiral catalyst.

Rearrangement using TBOTf as before yields the desired allyl alcohol product 9, as a greater than 99:1 mixture at the C₂ position. After chromatography, a 92:8 mixture is isolated in 87% yield:

The anti aldol products 14 and 16 are prepared in a similar manner, beginning with a Z-allylic alcohol.

(2S,3S)-2-methyl-3-(t-butyldimethylsilyloxy)hexanal 14

Butanal is treated with the bis(trifluoroethoxy)phosphonate reagent of Still* to give the Z-α,β-unsaturated ester, which is not isolated but directly reduced with Super Hydride (LiEt₃BH) in a one pot mixture to give the Z-allylic alcohol (Z)-2-methyl-2-hexen-1-ol 12 in 96% yield as the major component of a 98:2 Z/E mixture:

Sharpless epoxidation of the allylic alcohol 12 with the chiral catalyst D-(-)-disopropyl tartrate gives the desired epoxyalcohol (2R,3S)-2-methyl-3-propoxyiranemethanol 13 in 81% yield and 85% enantiomeric excess:

Rearrangement of the epoxyalcohol with TBOTf and Hunig's base gives the desired anti aldol product (2S,3S)-2-methyl-3-(t-butyldimethylsilyloxy)hexanal 14, as a greater than 50:1 crude mixture (more than 20:1 after column chromatography):

(2R,3R)-2-methyl-3-(t-butyldimethylsilyloxy)hexanal 16

The enantiomer of 14 is prepared in like manner. The allylic alcohol Z-2-methyl-2-hexen-1-ol 12 is converted into the anti aldehyde 16 via the optically active epoxyalcohol (2S,3R)-2-methyl-3-propyloxiranemethanol 15 in comparable yield and stereochemical purity, using L(+)-diisopropyl tartrate as the chiral catalyst:

Thus, E-allylic alcohols give syn aldol products while Z-allylic alcohols give anti aldol products. Through a three-step process—Wittig and reduction; epoxidation; and rearrangement—the simple aldehyde butanal is converted into all four diastereomers of 2-methyl-3-(t-butyldimethylsilyloxy)hexanal in high yield and with excellent enantioselectivity.

The relative stereochemistry of both the syn and anti products can be confirmed by $^1$H NMR analysis of the corresponding acetonide (prepared by reduction of the aldehyde to the primary alcohol, fluoride removal of the TBS group, and acetonide formation). The coupling constants observed for the protons $\alpha$ to the oxygen atoms are those expected for the structures drawn. (2S,3R)-2-methyl-3-(triethylsilyloxy)-4-phenylbutanal 11

As a second exemplary embodiment, a benzylic system is converted into a $\beta$-triethylsilyloxy aldehyde in good overall yield and enantiomeric excess. First, the allylic alcohol E-2-methyl-4-phenylhex-2-enol is epoxidized to the epoxyalcohol (2R,3R)-2-methyl-3-phenyloxiranemethanol 10 using D(-)-diisopropyl tartrate as the chiral catalyst:

The epoxyalcohol 10 is converted into the syn aldol product 11 by reacting it with triethylsilyloxy trflate ("TESOT") in the presence of collidine:

The enantiomer of 11 may be prepared using L(+)-diisopropyl tartrate as the chiral catalyst. Similarly, the anti aldol products may be prepared by starting with the Z-allylic alcohol Z-2-methyl-4-phenylhex-2-enol.

It will be appreciated by those skilled in the art that many other aldols can be prepared by the methods described above. For example, although in each of the examples above the silyloxyalkanal is substituted at the C2 position ($\alpha$ to the aldehyde) with a methyl group, the invention is not so limited. Rather, the synthetic schemes described herein are sufficiently general to afford routes to numerous aldols, substituted at the C2 position with other alkyl and aryl groups.

Similarly, other silyl triflates can be used, including, for example, trisopropylsilyl trflate, trimethylsilyloxy trflate, etc. In short, the invention is not limited to methods for producing the silyloxy hexanals and silyloxy phenylbutanals described above, but is sufficiently broad in scope to afford the preparation of optically active compounds of the formulas (I) and (Ia), shown above.

Chiral 1,3-Diols

As another embodiment of the invention, the non-aldol synthesis of chiral silyloxyalkanals described above provides a route to chirally active 1,3-diols, i.e., compounds having the formula (IV):

where R' and R" are alkyl or aryl. Such compounds are prepared by selecting a silyloxyalkanal having the desired stereoconfiguration at C2 and C3; reducing the aldehyde functionality by, e.g., treatment with NaBH$_4$ or the like; and removing the silyloxy group and replacing it with OH, using any of several known deprotecting agents, such as HF-pyridine complex, tetrabutylammonium fluoride, etc. The following two examples are representative, and in no way limiting, examples of this aspect of the invention.

(2R,3R)-2-methylhexan-1,3-diol 26

This compound is prepared by first reducing the aldehyde functionality of the syn silyloxyalkanal (2S,3R)-2-methyl-3-(triethylsilyloxy)hexanal 21 (which is identical to compound 5 above, except for the identity of the silyloxy group) using NaBH$_4$ in methanol:
The alcohol 24 is then treated with tetrabutylammonium fluoride (on silica gel) to deprotect the hydroxy group at C5, giving the syn 1,3-diol 26:

(2R,3S)-2-methylhexan-1,3-diol 27
This anti diastereomer of 26 is prepared in like manner, starting with the anti silyloxyalkanal (2S,3S)-2-methyl-3-(triethylsilyloxy)hexanal 22:

The two other diastereomers can be prepared in like manner, starting with the appropriate silyloxyalkanal. The stereochemistry of these compounds is verified by converting the diol to an acetone, using 2,2-dimethoxypropane and p-toluensulfonic acid ("TsOH"), as shown for diol 26 by the following equation:

Experimental details are found at the end of the specification.
It will be readily apparent that numerous optically active 1,3-diols can be prepared in this way, form chiral silyloxyalkanals.

Polypropionate
One of the major advantages of the invention is its usefulness in the preparation of polypropionates. In particular, the regioselective opening of the epoxy silyl ether yields a product which can be viewed as a protected aldehyde, and which may be directly converted into an allylic acid, an epoxycarboxhyde and, ultimately, a polypropionate. In contrast, in most known aldol processes, one must first protect the β-hydroxy group and convert the acyl unit into an aldehyde.

As a first exemplary embodiment of this aspect of the invention, the syn aldol product (2S,3R)-2-methyl-3-(t-

Alternatively, the epoxidation of 17 may be carried out using an external source of chirality, as in the Sharpless epoxidations described above. However, epoxidation of chiral allylic alcohols often proceeds with greater stereoselectivity when using a peracid or metal catalyst and the resident chirality present in the alkene.

The preparation of all four diastereomeric epoxides corresponding to 18 may be accomplished by using the methods described above, keeping in mind that Z-allylic alcohols are used to produce anti aldol products, and E-allylic alcohols yield syn aldols.

As a second exemplary embodiment of this aspect of the invention, the 2-triethyloxysilane analog of the allylic alcohol 17 is epoxidized with titanium tetraisopropoxide and t-BuOOH, without a chiral catalyst, to yield the all syn silyloxy epoxycarboxhyde (2S,3R,4R,5R)-5-(triethylsilyloxy)-2,3-epoxy-2,4-dimethyl-1-ocanol 30 as a 10:1 mixture to its diastereomer.
An epoxyalcohol such as 18 or 30 may be treated with a silyl reagent, preferably a trialkylysilyl triflate, to yield a polypropionate, with high enantioccontrol. The silyloxy groups of such a compound may be removed and replaced by hydroxyl groups, in the manner described above. Alternatively, the process (conversion to an allylic alcohol, epoxidation, and rearrangement) may be repeated to form longer polypropionates.

It has also been discovered that a silyloxy epoxyalcohol such as 18, 30, etc. can be converted into a chiral polypropionate using an alkyl or aryl lithium compound and a rare earth catalyst. Thus, alcohol 18 (which is the same as 18 except for the identity of the silyloxy group) is treated with (i) butyl lithium, and (ii) samarium diiodide, to yield the polypropionate (2S,3S,4S,5R)-5-triethylsilyloxy-3-hydroxy-2,4-dimethoxytolanal:

Though not bound by theory, it is believed that the alkyl lithium abstracts a proton from the alcohol, leaving the nucleophile $\text{R} - \text{O}^-$, which attacks the samarium atom, which catalyzes the regioselective opening of the epoxide and the rearrangement to 31. The reaction may also be run using the samarium catalyst:

The following examples describe in detail syntheses illustrative of the present invention. It will be apparent to those skilled in the art that many modifications, both of materials and methods, may be practiced without departure from the purpose and intent of this disclosure.

**EXAMPLES**

All temperatures and boiling points (bp) are uncorrected and rections were carried out under Argon (Ar) with the exclusion of moisture. Dichloromethane (CH$_2$Cl$_2$) was distilled from CaH$_2$. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl radical. Hexamethyldiphosphoramide (HMTP) was distilled under vacuum from CaH$_2$ prior to use. Titanium(TI) isoproxide (Ti(O-iPr)$_4$) was distilled under vacuum and stored frozen at $-23^\circ$ C under nitrogen (N$_2$). Diisopropyl tartrate (()+ or (−)-DIPT) was distilled under vacuum and stored in a desiccator. Commercial t-butylhydroperoxide (TBHP) was dried over 4 Å molecular sieves (pellet form) for 2 days at 0° C and titrated. (See Hanson, R. M.; Sharpless, K. B., J. Org. Chem. 1986, 51, 1922.)

Triethyloxyl trifluoromethanesulfonate (TETSO) and t-butylmethyloxyl trifluoromethanesulfonate (TBTO) were vacuum distilled into a jacketed Vigreux column and stored under N$_2$ in Schlenk flasks. Diisopropylethylamine (DIEA), triethylamine (TEA), and collidine were distilled from CaH$_2$ and stored under N$_2$. Boron trifluoride-etherate (BF$_3$-EtO$_2$) was stirred over CaH$_2$, distilled (67° C at 43 mm Hg) with an excess of diethyl ether (EtO$_2$) and stored at $-23^\circ$ C under N$_2$. Boron trifluoromethanesulfonate (B(O-TfO)$_2$) was prepared by known procedures and distilled immediately before use. (See Olah, G. A.; Faqir, I.; Farns, S. M. F.; Olah, J. A., J. Am. Chem. Soc. 1988, 110, 2560.) Powdered 4 Å molecular sieves were activated by heating to 120° C in a vacuum oven (ca. 1 mm Hg) overnight and cooled under vacuum. Chromatography was conducted on 230–400 mesh silica gel (SiO$_2$), using hexanes (Hex), ethyl acetate (EtOAc), and CH$_2$Cl$_2$ as solvents. Butyraldehyde and chlorotriethylsilane (TESCI) were distilled under vacuum. Potassium hexamethyldisilazide (KHMDS), dimethylaminoipyridine (DMAP), t-butylchlorodimethylsilane (TBSCI), and lithium triisobutylborohydride (1.0M in THF, LiBEt$_3$H) were purchased from Aldrich Chemical Company and used directly. Bis(2,2,2-trifluoroethyl) ethyl 2-phosphonopropionate was made by a known procedure, dried by distillation, and stored at $-23^\circ$ C. (See Still, W. C.; Gennari, C. Tetrahedron Lett. 1983, 24, 4405.) 18-Crown-6 was recrystallized from acetonitrile and evacuated for 3 days (0.01 mm Hg).

$^1$H and $^{13}$C nuclear magnetic resonance (NMR) were recorded on a Bruker AM360, AM500, ARX400 or ARX500 with tetramethylsilane as external standard. Enantiomeric purity were determined by reacting the substrates (ca. 0.05–0.1 mmol) in a sealed NMR tube with 750 $\mu$L of a 10% CD$_2$Cl$_2$ in benzene solution (0.22M) of chiral phosphonamide for 1 day at 25° C. (See Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. Tetrahedron Asym. 1990, 1,437.) The diastereomeric $^{1}$J signals were then integrated and reported relative to 85% H$_2$PO$_4$ (0.00 ppm) as external standard. Infrared (IR) spectra were recorded on a Nicolet 510 FT-IR, Nicolet 205 FT-IR, or a Perkin-Elmer series 1600 spectrometer. Optical rotations were recorded on a Perkin-Elmer 243 Polameter and were run at ambient temperature. Isomeric ratios were determined on a Hewlett-Packard 5890 gas chromatograph/5970 Mass Selective Detector (GC-MS), with a 50 m capillary column, 1.0 ml/min helium flow rate and selective ion monitoring. High resolution mass spectra (MS) were obtained on a VG Autospec at a resolution of 10000 (10% valley).

In the following examples, "ee" denotes enantiomeric excess, and "de" denotes diastereomeric excess.

**Example 1**

(E)-2-Methyl-2-hexen-1-ol (2)

This was prepared by a modified Bayliss-Hilman procedure using ethyl acrylate and DABCO, followed by acetylation and reduction with an ethoxaluminum hydride reagent. (See Basavaiah, D.; Sarma, P. K. S. J. Chem. Soc., Chem. Commun. 1992, 955) to yield 4.732 g of 2 after distillation (bp 96° C at 47 mm Hg, 51% from
butyraldehyde: 1H NMR (CDCl₃, 360.134 MHz) δ 5.34 (1H, t, J = 7.22, 1.33 Hz), 3.93 (2H, d, J = 0.74 Hz), 1.94 (2H, d, J = 8.00, 0.84 Hz), 1.73 (1H, br), 1.59 (3H, dd, J = 0.35, 0.84 Hz), 1.29 (2H, sextet, J = 7.45 Hz), and 0.84 (3H, t, J = 7.39 Hz). 

\[ 1^3 \text{C NMR (CDCl}_3, 90.55 \text{ MHz)} \delta 134.7, 126.4, 69.0, 29.6, 26.13, 13.8, \text{and 13.6.} \]

IR (thin film): 3380 (br), 2959 (s), 2929 (s), 2871 (s), 1458 (m), 1379 (m), 1222 (w), 1073 (s), 1046 (s), 1031 (s), 1000 (s), and 893 (w) cm⁻¹. High Resolution MS (m/z): 96.0940, calcld for C₂H₅O 96.3843 (M-H₂O). Capillary GC-MS shows 96.6% (E) and 3.43% (Z).

Example 2
(Z)-2-Methyl-2-hexen-1-ol (12)
Method A: To bis(2,2,2-trifluoroethyl) ethyl 2-phosphono propionate (1.2975 g, 3.75 mmol) dissolved in THF at 42°C under Ar was added to 0.5 mL of 0.9 M LiBu₂Th in THF (10.0 mL, 10.0 mmol, 2 eq based on phosphonate) and added. The reaction was warmed to 25°C and an additional 10 h. Excess hydride was quenched with 2 mL of EtOAc, and after 10 min., the solution was poured onto 40 mL of distilled H₂O. The layers were separated and the aqueous phase extracted with pentane (4 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried over MgSO₄, concentrated and chromatographed (80 g SiO₂, 97% CH₂Cl₂/3% EtOAc) to yield 256.0 mg (2.24 mmol, 90% of 12) as a clear oil.

Method B**: To a suspension of butyrylphenylphosphonofluorobromide (0.7672 g, 12.0772 mmol, 1 eq) in 50 mL of THF and 5 mL of HMPA at 25°C, was added KHMS (95%, 12.99 mmol, 1 eq) in one portion. After 10 min, the solution was cooled to -78°C and 1-[[(trihydroxypropyl)-oxy]-2-propanone (1.80 g, 11.552 mmol) was added. The reaction was allowed to warm to 25°C over 12 h, at which time 50 mL of saturated NH₄Cl was added. The slurry was poured onto 100 mL of pentane, shaken, and separated. The water phase was extracted with pentane (2 × 50 mL), and the combined organic phases were washed with brine (3 × 20 mL), dried over MgSO₄, concentrated and chromatographed (400 g SiO₂, 97% CH₂Cl₂/R₁ = 0.41) to yield 2.1133 g (92.3%) of the protected allylic alcohol. The product was then dissolved in 75 mL of 3:1 THF:H₂O treated with 340 mg of p-toluene sulfonic acid, and refluxed for 12 h, at which time the solution was partitioned between 100 mL of Et₂O and 100 mL of H₂O. The layers were separated, the aqueous phase extracted with Et₂O (3 × 25 mL), and the combined organic extract washed with 5% NaHCO₃ (3 × 5 mL), brine (2 × 5 mL), dried over MgSO₄, concentrated and chromatographed (200 g SiO₂, 2.4% EtOAc/97.6% CH₂Cl₂) to yield 1.107 g of allylic alcohol 12 (91%, 84% overall).

1H NMR (CDCl₃, 360.134 MHz) δ 5.20 (1H, t, J = 7.48 Hz), 4.02 (2H, s), 2.01 (1H, br), 1.93 (2H, qd, J = 7.30, 1.11 Hz), 1.70 (3H, J = 1.29 Hz), 1.26 (2H, sextet, J = 7.38 Hz), and 0.80 (3H, t, J = 7.37 Hz). 

13C NMR (CDCl₃, 90.55 MHz) δ 134.3, 126.3, 61.3, 28.9, 25.0, 21.0, and 13.6. 

Example 3
(E)-4-Phenyl-2-methyl-2-buten-1-ol (20)
This was synthesized according to a known procedure in 79% yield. 1H NMR (CDCl₃, 300.135 MHz) δ 7.1-7.3 (5H, m), 5.7 (1H, t, J = 5.39, 1.39 Hz), 4.00 (2H, s), 3.35 (2H, d, J = 7.31 Hz), 1.73 (3H, q, J = 0.36 Hz), and 1.40 (1H, br). 13C NMR (CDCl₃, 90.55 MHz) δ 140.9, 135.6, 128.4, 128.2, 125.9, 124.6, 68.6, 33.8, and 13.7. IR (thin film): 3323 (br), 3084 (m), 3061 (m), 3026 (s), 2975 (m), 2914 (s), 2959 (s), 1602 (m), 1494 (s), 1453 (s), 1072 (m), 1029 (m), 1016 (s), 866 (w), 741 (s), and 698 (s) cm⁻¹. High Resolution MS (m/z): 162.1029, calcld for C₉H₁₄O₂ 162.1045. Capillary GC-MS shows 90.8% (E) and 9.2% (Z).

Example 4
(2S,3S)-2-Methyl-3-propyloxiranemethanol (8)
This is a representative procedure for the synthesis of epoxy alcohols.

1H NMR (CDCl₃, 360.134 MHz) δ 3.66 (1H, dd, J = 12.2, 4.6 Hz), 3.54 (1H, dd, J = 12.3, 8.3 Hz), 3.02 (1H, J = 5.4 Hz), 2.06 (1H, dd, J = 8.3, 4.8 Hz), 1.6-1.0 (4H, m), 1.26 (3H, s), and 0.96 (3H, t, J = 7.3 Hz). 

13C NMR (CDCl₃, 90.55 MHz) δ 65.4, 60.8, 60.0, 30.1, 19.7, 14.2, and 13.9. IR (thin film): 3426 (br), 2961 (s), 2932 (s), 2874 (s), 1466 (s), 1383 (m), 1074 (s), 1036 (s), 889 (m), and 685 (w) cm⁻¹. High Resolution MS (m/z): 130.0998, calcld for C₇H₁₀O₂ 130.0994. 

Example 5
(2R,3R)-2-Methyl-3-propyloxiranemethanol (3)
Using the same procedure for the preparation of 8 from (−)-DIPT and allylic alcohol 2 gave 3 in 94% yield. The 1H NMR, 13C NMR, IR and high resolution MS were identical to 8. [a]d +26.0° (c = 1.05, CH₂Cl₂). P NMR (10% Cd₂ as benzene, 145.786 MHz) δ 133.5 (2.7%), and 137.2 (97.5%), 95.5% ee.
Example 6

(2R,3S)-2-Methyl-3-propyloxiranemethanol (13)

Using the same procedure for the preparation of 8, (–)-DPIT and alcohol 12, with a 36 h reaction time, gave 13 in 81% yield. 1H NMR (CDCl₃, 360.134 MHz) δ 5.57 (1H, d, J = 11.80 Hz), 3.51 (1H, d, J = 11.80 Hz), 2.73 (1H, t, J = 6.19 Hz), 2.00 (1H, br), 1.5–1.3 (4H, m), 1.27 (3H, s), and 0.84 (3H, t, J = 7.30 Hz). 13C NMR (CDCl₃, 90.55 MHz) δ 68.4, 63.9, 60.8, 30.0, 20.1, 19.9, and 13.9. IR (thin film): 3436 br, 2985 (s), 2938 (s), 1466 (m), 1381 (m), 1300 (w), 1267 (w), 1175 (m), 1044 (s), 889 (m), and 853 (m) cm⁻¹. High resolution MS (m/z): 130.0997, calcd for C₇H₁₄O₃ 130.0994, [M⁺] = –14.5° (c = 0.615, CH₂Cl₂). –P NMR (100% CD₂Cl₂ in benzene, 145.786 MHz) δ 133.5 (92.8%) and 132.4 (7.4%), 85.5% ee.

Example 7

(2R,3R)-2-Methyl-3-propyloxiranemethanol (15)

Using the same procedure as for the preparation of 13, (+)-DPIT and allylic alcohol 12 gave 15 in 79% yield. 1H NMR, 13C NMR IR and high resolution MS are identical to 13. [α]D = +13.9° (c = 1.35, CH₂Cl₂).

Example 8

(2R,3R)-2-Methyl-3-phenylmorphoxiranemethanol (10)

Using the same procedure as for the preparation of 8, (–)-DPIT and allylic alcohol 20 gave 75% yield of epoxy alcohol 10. 1H NMR (CDCl₃, 360.134 MHz) δ 7.2–7.4 (5H, m), 3.69 (1H, dd, J = 6.66, 12.29 Hz), 3.58 (1H, dd, J = 8.20, 12.29 Hz), 3.28 (1H, t, J = 6.35 Hz), 2.96 (1H, dd, J = 6.46, 14.76 Hz), 2.86 (1H, dd, J = 6.25, 14.77 Hz), 1.92 (1H, dd, J = 8.37, 4.72 Hz), and 1.41 (3H, s). 13C NMR (CDCl₃, 99.55 MHz) δ 137.6, 128.6, 128.6, 126.1, 65.3, 61.3, 60.2, 34.6, and 14.4. IR (thin film): 3424 (br), 3086 (w), 3062 (w), 3028 (m), 2997 (w), 2984 (m), 2926 (s), 2868 (m), 1604 (w), 1493 (s), 1454 (s), 1384 (m), 1072 (m), 1063 (s), 891 (w), 853 (w), 741 (m), and 700 (s) cm⁻¹. [α]D = +22.1° (c = 2.65, CHCl₃).

Example 9

(2R,3R)-2-[t-butyldimethylsilyl]oxy)methyl-2-methyl-3-propyloxiranemethanol (4)

Alcohol 3 (51.1 mg, 0.3925 mmol) in 3 mL of CH₂Cl₂ was treated successively with DPEA (102 μL, 0.5888 mmol, 1.5 eq), DMAP (19.3 mg, 150.512 mmol, 1.3 eq) and refluxed for 12 h. The solution was poured onto 20 mL of 0.2M pH 7 phosphate buffer and 30 mL of low boiling petroleum ether, shaken, and separated. The aqueous phase was extracted with petroleum ether (3 × 10 mL), washed with pH 7 buffer (1 × 10 mL), and dried with MgSO₄. The solution was evaporated to yield 3.20 mg of aldehyde 16 (slight contamination of silanol, 95% + yield). 1H NMR (CDCl₃, 360.134 MHz) δ 7.48 (1H, d, J = 2.0 Hz), 3.89 (1H, q, J = 4.80 Hz), 2.44 (1H, qdd, J = 7.02, 5.40, 2.35 Hz), 1.5–1.3 (4H, m), 1.02 (3H, d, J = 7.02 Hz), 0.86 (3H, t, J = 7.31 Hz), 0.82 (9H, s), 0.01 (3H, s), and –0.01 (3H, s).

Example 10

(2R,3R)-2-[triethylsilyloxy]methyl-2-methyl-3-propyloxiranemethanol (19)

Epoxy alcohol 3 (714.5 mg, 5.4882 mmol) was weighed into a dry, 50 mL, 1 neck round bottom flask equipped with a magnetic stirbar. The flask was flushed with Ar, treated successively with 30 mL of CH₂Cl₂, DPEA (1.4 mL, 8.3233 mmol, 1.5 eq), and DMAP (ca. 50 mg). TESCl was added quickly and a mildly exothermic reaction ensued. After 1 h, the mixture was poured into 100 mL of petroleum ether and 50 mL of 0.2M pH 7 phosphate buffer. The layers were separated, extracted with petroleum ether (2 × 50 mL), washed with 0.2M pH 7 phosphate buffer (1 × 10 mL), brine (1 × 10 mL), dried over MgSO₄, concentrated and distilled via short path (bp = 72–75°C at 0.09 mm Hg) to give 1.3055 g of pure silyl epoxide 19 (97.3%). 1H NMR (CDCl₃, 500.135 MHz) δ 3.58 (1H, d, J = 11.11 Hz), 3.52 (1H, d, J = 11.10 Hz), 2.80 (1H, t, J = 5.99 Hz), 1.6–1.4 (4H, m), 1.24 (3H, s), 1.0–0.9 (9H, m), and 0.60 (9H, q, J = 7.82 Hz). 13C NMR (CDCl₃, 90.55 MHz) δ 66.7, 61.0, 60.8, 30.3, 19.8, 14.2, 13.9, 6.7, and 4.3. IR (thin film): v = 2992 (s), 2919 (s), 2876 (m), 1458 (m), 1416 (w), 1381 (m), 1240 (m), 1101 (s), 1007 (m), 820 (m), and 745 (s) cm⁻¹. High resolution MS (m/z): 215.1456, calcd for C₈H₁₄O₃Si 215.1467 (M+H₃Si).

Example 11

(2R,3R)-3-[t-Butyldimethylsilyloxy]-2-methylhexan-1-ol (16)

This is a representative procedure for the rearrangement of epoxy alcohols with trialkylsilyl trifluoromethanesulfonate. Epoxy alcohol 15 (74.3 mg, 0.4647 mmol) was dissolved in 4.0 mL of CH₂Cl₂ which was treated with 100 mg of 4 Å molecular sieves, DPEA (129 μL, 0.7419 mmol, 1.3 eq) and cooled to –42°C. TBSOTf (157.2 μL, 0.6849 mmol, 1.3 eq) was then added drop wise and stirred for 80 min at which time the solution was poured onto 20 mL of Et₂O and shaken with 5 mL of pH 5.5 phosphate buffer. The layers were separated and the aqueous phase extracted with Et₂O (2 × 5 mL). The combined organic phases were washed with H₂O (3 × 2 mL), 5% NaHCO₃ (2 × 2 mL), brine (1 × 2 mL), dried over MgSO₄ and the solvent evaporated to yield 132.0 mg of aldehyde 16 (slight contamination of silanol, 95% + yield).

Example 12

(2S,3S)-3-(t-Butyldimethylsilyloxy)-2-methylhexan-1-ol (14)

Epoxy alcohol 13, 1.25 eq TBSOTf, and 1.30 eq DPEA were reacted as in the preparation of 16 to give the crude aldehyde 14 in 95% + yield. 1H NMR, 13C
<table>
<thead>
<tr>
<th>Example 13</th>
<th>Example 17</th>
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<tbody>
<tr>
<td>(2S,3R)-3-(butyldimethylsiloxy)-2-methylhexanal (5)</td>
<td>(2S,3R)-3-(Triethylsiloxy)-2-methylhexanal (21)</td>
</tr>
<tr>
<td>Epoxy alcohol 1.4, eq. TBSOTf, and 1.35 eq. DIPEA were reacted as in the preparation of 16 to give crude aldehyde (&gt;50:1 de, 95%+; which was then chromatographed (5% EtOAc/95% Hex/1% TEA) to give in 5% yield). 1HN NMR (CDCl3, 500.135 MHz) δ: 7.8 (1H, d, J = 7.3 Hz), 3.95 (1H, q, J = 5.03 Hz), 2.43 (1H, qdd, J = 6.95, 5.03, 2.30 Hz), 1.5–1.2 (4H, m), 0.36 (3H, s), 0.89 (6H, t, J = 8.0 Hz), 0.85 (3H, s, J = 7.14 Hz), and 0.54 (9H, q, J = 7.80 Hz). 13C NMR (CDCl3, 90.55 MHz) δ: 205.1, 73.3, 51.3, 37.2, 18.1, 14.1, 10.3, 6.4, and 5.1. IR (thin film): 2917, 2970, 2929, 2877 (s), 1726 (s), 1459 (s), 1415 (w), 1379 (w), 1239 (m), 1155 (w), 1074 (s), 1038 (m), 1005 (w), and 741 (s) cm⁻¹. High resolution MS (m/z): 215.1467, calculated for C11H22O3Si 215.1457 (M-C2H3). [α]D = +14.7° (c = 0.89, CH2Cl2). 1H NMR integration of δ 9.69 to δ 9.72 indicated a 90:9.7 ratio.</td>
<td>Method A: Silyl epoxide 19 (97.8 mg, 0.587 mmol) was dissolved in 0.5 mL of CH2Cl2 and treated successively with 34 mg of powdered 4 Å molecular sieves and DIPEA (21 μL, 0.12 mmol, 0.30 eq). The solution was cooled to −42°C and treated with TESOTT (22 μL, 0.10 mmol). After 60 min, the solution was poured onto Et2O (20 ml) and 10 ml of 1 M pH 5.5 buffer. The layers were separated, extracted with Et2O (3 × 5 ml), washed with H2O (3 × 1 ml), 5% NaHCO3 (2 × 1 ml), brine (1 × 5 ml), dried over MgSO4, and concentrated to yield 98.5 mg of virtually pure aldehyde 21. 1HN NMR shows &lt;50:1 de. Method B: Silyl epoxide 19 (143.9 mg, 0.587 mmol) was dissolved in 5 ml of CH2Cl2 and cooled to −78°C in an inert atmosphere. BF3-Et2O (72 μL, 0.59 mmol, 1.00 eq) was added and the solution stirred for 1 h. Then 2 mL of saturated Na2CO3 was added and the cooling bath removed. After reaching 25°C, the layers were separated, extracted with Et2O (4 × 1 ml), washed with H2O (3 × 1 ml), brine (2 × 1 ml), dried over MgSO4, concentrated, and chromatographed (70 g SiO2, 95% Hex/1% TEA/4% EtOAc, Rf = 0.50) to yield 125.0 mg of aldehyde 21 (86%, 94:6 de). Method C: To a stirring solution of silyl epoxide 19 (37.0 mg, 0.1514 mmol), 23 mg of mol. sieves, and DIPEA (2.6 μL, 0.151 mmol, 1.0 eq) in 1.5 mL of CH2Cl2 at −42°C, NaHCO3 (50 mg) was added. This solution was stirred for 1 h. After addition of 5.0 mL of 1 M HCl, the mixture was poured onto 5% NaHCO3, separated, extracted with Et2O (2 × 5 ml), brine (1 × 1 ml), dried over MgSO4, and concentrated to give 36.4 mg of aldehyde 21 (95%+, &gt; 20:1 de). 1HN NMR (CDCl3, 500.135 MHz) δ: 7.81 (1H, d, J = 1.01 Hz), 4.06 (1H, dt, J = 10.98, 6.35, 2.37 Hz), 2.78 (1H, qdd, J = 6.96, 3.65, 1.00 Hz), 1.5–1.1 (4H, m), 0.93 (3H, s), 0.51 (6H, s), 0.6–0.4 (9H, m). 1H NMR integration of δ 9.64 to the contaminant δ 9.71 indicated a 93.6:6.4 ratio.</td>
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at −23°C. For 12 h, then was recooled to −78°C. and 1.0M LiEt₃BH in THF was added (2.0 ml, 2.0 mmol, 4.4 eq based on phosphate). The temperature gradually warmed to 25°C over 4 h and stirred an additional 8 h when 200 μl of EtOAc was added. The solution was poured onto 10 ml of 0.2M pH 7 phosphate buffer, and extracted with 3:1 pentane:Et₂O (3 × 10 ml). The extracts were washed with 5% NaHCO₃ (2 × 1 ml), brine (1 × 1 ml), dried over MgSO₄, concentrated, and chromatographed (80 g SiO₂, 1% TEA/CH₂Cl₂) to give 68.4 mg of isomERICally pure alcohol 17 (72%).

**Example 19**

**Example 19**

(2R,3S,4S,5R)-5-(4-Butyl-2,5-dihydroxy-2,4-dimethyl-1-oxan-10 (18)

Allylic alcohol 17 (200.0 mg, 0.7005 mmol) was dissolved in 5 ml of CH₂Cl₂ and cooled to −5°C under Ar with a Brine/ice bath. Then, m-CPPBA (65% purity, 223 mg, 0.8406 mmol, 1.2 eq) in 2 ml of CH₂Cl₂ was added dropwise. Within 10 min, the acid byproduct precipitated, and after 30 min the reaction was complete. The mixture was diluted to 40 ml with pentane and washed vigorously with 10% NaOH (2 × 10 ml), H₂O (2 × 1 ml), 5% NaHCO₃ (1 × 2 ml), brine (2 × 1 ml), dried over MgSO₄, and concentrated to give a 12:1 mixture of epoxide alcohol 18 and its diastereomer. The mixture was chromatographed (100 g SiO₂, 4% EtOAc/96% CH₂Cl₂) to yield 189.0 mg of 18 (90%).

**Example 20**

(2S,3R,4S)-3-(Triethylsilyloxy)-2-methylhexan-1-ol (24)

Aldehyde 21 (87.0 mg, 0.3559 mmol) in 2.0 ml of 55% methanol at 0°C was treated with sodium borohydride (6.4 mg, 0.1692 mmol, 1 eq hydride) for 1 h at which time 2.0 ml of 0.5M pH 7 phosphate buffer was added with simultaneous removal of cooling bath Upon reaching 25°C, the slightly turbid mixture was extracted with Et₂O (3 × 10 ml), washed with brine (2 × 1 ml), dried over MgSO₄, concentrated, and chromatographed (35 g SiO₂, 2% EtOAc/1% TEA/97% CH₂Cl₂, Rf = 0.18) to give 65.7 mg of alcohol 25 (75%) as a clear oil. **Example 21**

(2S,3S)-3-(Triethylsilyloxy)-2-methylhexan-1-ol (25)

Aldehyde 22 and 2.5 eq sodium borohydride were reacted as in the preparation of 24 to give 47% alcohol 25 after chromatography (35 g SiO₂, 2% EtOAc/1% TEA/97% CH₂Cl₂, Rf = 0.34).

**Example 22**

Aldehyde 26 (100.0 mg, 0.4057 mmol) was dissolved in 2.0 ml of EtOAc and treated with 767 mg of tetrabutylammonium fluoride on silica (1.2 mmol/g, 0.8112 mmol, 2.0 eq) and stirred at 25°C for 3 h at which time alumina (acidic, ca. 1 g) was added. The slurry was filtered through a pad of Celite, concentrated and chromatographed (25 g SiO₂, 60% CH₂Cl₂/40% EtOAc) to yield 27.9 mg of diol 26 (25%, 0.0211 mmol) was dissolved in 5.0 ml of THF, and treated with 2,2-dimethoxypropane (64 µl, 0.5159 mmol, 2.0 eq) and a crystal of p-toluenesulfonic acid. After 67 h at 25°C, 200 mg of NaHCO₃ was added. The mixture was poured onto 1.0 M of 0.10M pH 7 phosphate buffer, extracted with EtOAc (3 × 10 ml), washed with H₂O (1 × 1 ml), 5% NaHCO₃ (2 × 1 ml), brine (1 × 1 ml), dried over MgSO₄ and concentrated to give 30.0 mg of acetone 28 as a clear liquid (89%).

**Example 23**

Alcohol 25 was converted to the intermediate diol 27 (85%) and acetone 29 (85%) as in the preparation of 28.

**Example 24**

Aldehyde 26 (10.0 mg, 0.0344 mmol) was dissolved in 2.0 ml of EtOAc and treated with 767 mg of tetrabutylammonium fluoride on silica (1.2 mmol/g, 0.0041 mmol, 1 eq) and stirred at 25°C for 3 h at which time alumina (acidic, ca. 1 g) was added. The slurry was filtered through a pad of Celite, concentrated and chromatographed (25 g SiO₂, 60% CH₂Cl₂/40% EtOAc) to yield 27.9 mg of diol 26 (25%, 0.0211 mmol) was dissolved in 5.0 ml of THF, and treated with 2,2-dimethoxypropane (64 µl, 0.5159 mmol, 2.0 eq) and a crystal of p-toluenesulfonic acid. After 67 h at 25°C, 200 mg of NaHCO₃ was added. The mixture was poured onto 1.0 M of 0.10M pH 7 phosphate buffer, extracted with EtOAc (3 × 10 ml), washed with H₂O (1 × 1 ml), 5% NaHCO₃ (2 × 1 ml), brine (1 × 1 ml), dried over MgSO₄, and concentrated to give 30.0 mg of acetone 28 as a clear liquid (89%).

**Example 25**

Aldehyde 26 (10.0 mg, 0.0344 mmol) was dissolved in 2.0 ml of EtOAc and treated with 767 mg of tetrabutylammonium fluoride on silica (1.2 mmol/g, 0.0041 mmol, 1 eq) and stirred at 25°C for 3 h at which time alumina (acidic, ca. 1 g) was added. The slurry was filtered through a pad of Celite, concentrated and chromatographed (25 g SiO₂, 60% CH₂Cl₂/40% EtOAc) to yield 27.9 mg of diol 26 (25%, 0.0211 mmol) was dissolved in 5.0 ml of THF, and treated with 2,2-dimethoxypropane (64 µl, 0.5159 mmol, 2.0 eq) and a crystal of p-toluenesulfonic acid. After 67 h at 25°C, 200 mg of NaHCO₃ was added. The mixture was poured onto 1.0 M of 0.10M pH 7 phosphate buffer, extracted with EtOAc (3 × 10 ml), washed with H₂O (1 × 1 ml), 5% NaHCO₃ (2 × 1 ml), brine (1 × 1 ml), dried over MgSO₄, and concentrated to give 30.0 mg of acetone 28 as a clear liquid (89%).

**Example 26**

Aldehyde 26 (10.0 mg, 0.0344 mmol) was dissolved in 2.0 ml of EtOAc and treated with 767 mg of tetrabutylammonium fluoride on silica (1.2 mmol/g, 0.0041 mmol, 1 eq) and stirred at 25°C for 3 h at which time alumina (acidic, ca. 1 g) was added. The slurry was filtered through a pad of Celite, concentrated and chromatographed (25 g SiO₂, 60% CH₂Cl₂/40% EtOAc) to yield 27.9 mg of diol 26 (25%, 0.0211 mmol) was dissolved in 5.0 ml of THF, and treated with 2,2-dimethoxypropane (64 µl, 0.5159 mmol, 2.0 eq) and a crystal of p-toluenesulfonic acid. After 67 h at 25°C, 200 mg of NaHCO₃ was added. The mixture was poured onto 1.0 M of 0.10M pH 7 phosphate buffer, extracted with EtOAc (3 × 10 ml), washed with H₂O (1 × 1 ml), 5% NaHCO₃ (2 × 1 ml), brine (1 × 1 ml), dried over MgSO₄, and concentrated to give 30.0 mg of acetone 28 as a clear liquid (89%).
Example 24

(2S,3S,4R,5R)-5-(Triethylsilyloxy)-2,3-epoxy-2,4-dimethyl-1-octanol (30)

To a solution of (4R,5R)-(Z)-2,4-dimethyl-5-(triethylsilyloxy)oct-2-ene-1-ol (124.0 mg, 0.4328 mmol) and 30 mg of powdered molecular sieves in 4.0 mL of CH₂Cl₂ at –42 °C was added (TiO₂-iPr₆) (146 μL, 0.6491 mmol, 1.5 eq) and the reaction was kept at –23 °C for 3 wk after which 2.0 mL of ½ saturated Rochelle’s salt was added and stirred overnight. The layers were separated, extracted with Et₂O (3×15 mL), washed with H₂O (2×1 mL), 5% NaHCO₃ (1×5 ml), brine (1×2 mL) dried over MgSO₄ and concentrated to give 125.1 mg of a mixture. 1H NMR of the crude shows 50% conversion yielding a 10:1 mixture of 30 to its diastereomer. Chromatography (40 g SiO₂, 6% Et₂OAc/94% CH₂Cl₂) gave 42.8 mg of starting material (34.5%), 43.0 mg of epoxy alcohol 30 (33%), and 3.0 mg of the minor epoxy alcohol. Spectral properties of 30: 1H NMR (CDCl₃, 360.134 MHz) δ 3.62 (1H, br), 3.58 (1H,m) 3.46 (1H,d,J=10.189 Hz), 2.57 (1H,d,J=9.51 Hz), 1.62 (1H,m), 1.5–1.3 (3H,m), 1.40 (3H,s), 1.30–1.15 (1H,m), 1.08 (3H,d,J=7.04 Hz), 0.94 (3H,d,J=7.91 Hz), 0.90 (3H,t,J=7.00 Hz), and 0.61 (6H,q,J=7.91 Hz). 13C NMR (CDCl₃, 90.55 MHz) δ 75.8, 66.6, 64.5, 61.9, 39.8, 35.3, 20.5, 19.7, 15.5, 14.2, 6.8 and 6.7. IR (thin film): 3451 (br), 2360(s), 2277(s), 1458(s), 1379(s), 1240(s), 1146(s), 1096(s), 1006(s), 892(m), 843(m), 782(m), and 750(s) cm⁻¹. [α]D= +29.1° (c=2.28, CH₂Cl₂).

Example 25

(2S,3S,4S,5R)-5-(Triethylsilyloxy)-3-hydroxy-2,4-dimethylcyclooctanol (31):

(2R,3S,4S,5R)-5-(Triethylsilyloxy)-2,3-epoxy-2,4-dimethyl-1-octanol (21.0 mg, 69.4 μmol) in 300 μL of THF at 0 °C was deprotonated with 1.05 eq of n-butyllithium. After 15 min, 0.1M samarium diiodide (764 μmol, 1.1 eq) was added and the reaction was allowed to warm to 25 °C over night. Then 1 mL of ½ saturated Rochelle’s salt was added, stirred an additional 1 h, and poured onto 5 mL of Et₂O and 1 mL of H₂O. The layers were separated, extracted with ether (3×5 mL), washed with 5% NaHCO₃ (2×1 mL), brine (1×1 mL), dried over MgSO₄ and concentrated to give 31.47 g of crude.

We claim:

1. A method for making an optically active compound of the formula (I)

\[
\begin{align*}
\text{X} & \quad \text{O} \\
\text{R} & \quad \text{H}
\end{align*}
\]

where X is a silyloxy group and R’ and R” are independently selected from the group consisting of alkyl and aryl, comprising the steps of:

(a) preparing an optically active epoxy alcohol of the formula (II)

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

where R’ and R” are as defined above; and

2. A method as recited in claim 1, wherein the silyloxy is a trialkylsilyleoxy group.

3. A method as recited in claim 2, wherein the trialkylsilyleoxy group is selected from the group consisting of t-butyldimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, triisobutylsilyloxy, and trimethylsilyloxy.

4. A method as recited in claim 1, wherein the Lewis acid is BF₃.

5. A method for converting an aldehyde into an optically active compound of the formula (I)

\[
\begin{align*}
\text{X} & \quad \text{O} \\
\text{R} & \quad \text{H}
\end{align*}
\]

where X is a silyloxy group and R’ and R” are independently selected from the group consisting of alkyl and aryl, comprising the steps of:

(a) converting the aldehyde into an allylic alcohol using a Wittig reaction and reduction;

(b) preparing an optically active epoxy alcohol by asymmetric epoxidation of the allylic alcohol; and

(c) treating the epoxy alcohol with either

(i) a silyl triflate, or

(ii) a trialkylsilyleoxy halide and a Lewis acid.

6. A method as recited in claim 5, wherein the silyloxy is selected from the group consisting of t-butyldimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, triisobutylsilyloxy, and trimethylsilyloxy.

7. A method for making an optically active compound of the formula (Ia)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

where R’ and R” are independently selected from the group consisting of alkyl and aryl, comprising the steps of:

(a) preparing an optically active epoxy alcohol of the formula (II)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

where R’ and R” are as defined above;

(b) preparing a 3-silyloxyalkanol of the formula (I)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

where X is a silyloxy group and R’ and R” are as defined above, by treating the epoxy alcohol with at least one reagent selected from the group consisting of (i) silyl triflates and (ii) trialkylsilyl halides and Lewis acid; and
23 (c) removing the 3-silyloxy group and replacing it with OH, by treating the 3-silyloxyalkanal with a deprotecting agent.
8. A method as recited in claim 7, wherein the deprotecting agent comprises hydrogen fluoride-pyridine complex.
9. A method as recited in claim 7, wherein the deprotecting agent comprises tetrabutylammonium fluoride.
10. A method for making an optically active 2-methyl-3-silyloxyhexanal, comprising the steps of:
   (a) preparing an allylic alcohol;
   (b) preparing an optically active epoxyalcohol by asymmetric epoxidation of the allylic alcohol using a chiral catalyst; and
   (c) treating the epoxy alcohol with either
      (i) a silyl triflate, or
      (ii) a trialkylsilyl halide and a Lewis acid.
11. A method as recited in claim 10, wherein the silyloxyhexanal comprises a (2R,3R)-2-methyl-3-silyloxyhexanal, the allylic alcohol comprises an E-allylic alcohol, and the chiral catalyst comprises L-(+)-diisopropyl tartrate.
12. A method as recited in claim 10, wherein the silyloxyhexanal comprises a (2R,3S)-2-methyl-3-silyloxyhexanal, the allylic alcohol comprises an E-allylic alcohol, and the chiral catalyst comprises L-(+)-diisopropyl tartrate.
13. A method as recited in claim 10, wherein the silyloxyhexanal comprises a (2S,3S)-2-methyl-3-silyloxyhexanal, the allylic alcohol comprises a Z-allylic alcohol, and the chiral catalyst comprises D-(−)-diisopropyl tartrate.
14. A method as recited in claim 10, wherein the silyloxyhexanal comprises a (2R,3R)-2-methyl-3-silyloxyhexanal, the allylic alcohol comprises a Z-allylic alcohol, and the chiral catalyst comprises L-(+)-diisopropyl tartrate.
15. A method as recited in claim 10, wherein the silyloxyhexanal is a 2-methyl-3-(trialkylsilyloxy)alkanal.
16. A method for making an optically active 1,3-diol, comprising the steps of
   (a) preparing an optically active 2-silyloxyalkanal;
   (b) reducing the aldehyde on the 2-silyloxyalkanal; and
   (c) removing the silyloxy group and replacing it with OH.
17. A method for making a chiral polypropionate, comprising the steps of:
   (a) preparing a chiral silyloxy epoxy alcohol; and
   (b) treating the alcohol with
      (i) an alkyl lithium or aryl lithium compound, and
      (ii) a rare earth catalyst.
18. A method as recited in claim 17, wherein the rare earth catalyst comprises samarium dildide.
19. A method as recited in claim 17, wherein the rare earth catalyst comprises a samarium compound having the formula
\[
\begin{array}{c}
\text{Ph} \\
\mid \\
N \\
\mid \\
\text{O} \\
\mid \\
\text{Sn} \\
\mid \\
I \\
\end{array}
\]