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(57) Abstract: The present invention generally relates to methods for the synthesis of catalysts, including epoxidation catalysts, and related compounds and catalyst compositions. Embodiments described herein may provide efficient processes for providing catalysts (e.g., epoxidation catalysts) in large quantities and using simplified methods.



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EPOXIDATION CATALYSTS

Statement Regarding Federally Sponsored Research or Development

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Related Applications

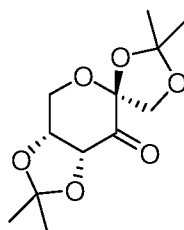
This application claims priority under 35 U.S.C. § 119(e) to co-pending United
10 States Provisional Application Serial No. 61/309,067, filed March 1, 2010, the contents
of which are incorporated herein by reference in its entirety for all purposes.

Field of the Invention

The present invention generally relates to methods for the synthesis of catalysts,
15 including epoxidation catalysts, and related compositions.

Background of the Invention

Optically active epoxides provide useful building blocks in the synthesis of many
biologically active compounds, and much research has been conducted on practical,
20 efficient methods for the synthesis of such epoxides. For example, numerous catalysts
have been developed to perform epoxidation reactions, in which an alkene is converted
to an epoxide by addition of one oxygen atom to a carbon-carbon double bond. In
particular, the "Shi Epoxidation," is an enantioselective epoxidation method developed
by Prof. Yian Shi and coworkers, which utilizes Shi catalyst 1, shown below.

**1**

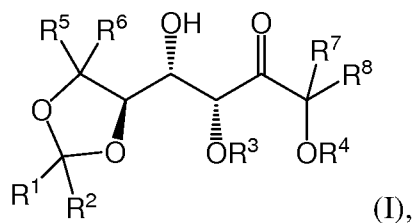
While the Shi Epoxidation method has been shown to be effective for enantioselective
epoxidation reactions, to date, Shi catalyst 1 can only be produced in large quantities as

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one enantiomer. The absence of the availability of the enantiomer of Shi catalyst 1 has hindered the more widespread use of the Shi Epoxidation.

Summary of the Invention

5 The present invention provides methods for synthesizing a catalyst. In one set of embodiments, the method comprises reacting a compound of Formula (I),



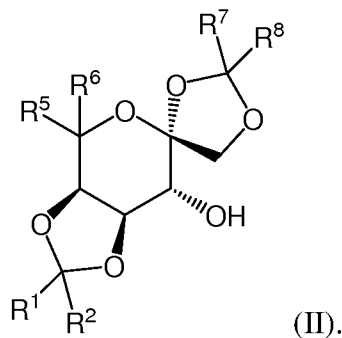
wherein:

R¹ and R² can be the same or different and each can be hydrogen, alkyl, or aryl,
 10 provided that when one of R¹ and R² is hydrogen, the other is alkyl or aryl;

R³ is a protecting group;

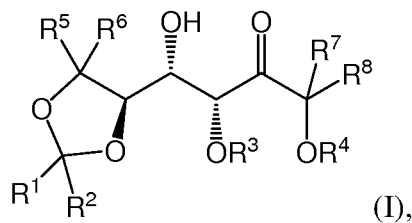
R⁴ is a protecting group that can be removed in the presence of an acid; and

R⁵, R⁶, R⁷, and R⁸ can be the same or different and each can be hydrogen, alkyl, or aryl, to produce a compound of Formula (II),



15

The present invention also relates to compositions comprising a compound having a structure as in Formula (I):



wherein:

20 R¹ and R² can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R¹ and R² is hydrogen, the other is alkyl or aryl;

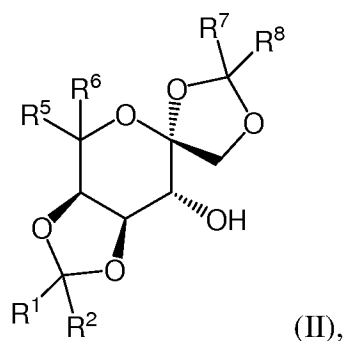
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R^3 is a protecting group;

R^4 is a protecting group that can be removed in the presence of an acid; and

R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl.

5 The present invention also relates to compositions comprising a compound having a structure as in Formula (II):



wherein:

R^1 and R^2 can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R^1 and R^2 is hydrogen, the other is alkyl or aryl; and

R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl.

Brief Description of the Drawings

15 FIG. 1A shows the preparation of compound 2, a TBS-protected dihydroxyacetone.

FIG. 1B shows the synthesis of the ent-Shi ketone.

FIG. 2 shows a proposed mechanism for synthesis of an intermediate compound in the synthesis of the ent-Shi ketone.

20 Other aspects, embodiments and features of the invention will become apparent from the following detailed description when considered in conjunction with the accompanying drawings. The accompanying figures are schematic and are not intended to be drawn to scale. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where

25 illustration is not necessary to allow those of ordinary skill in the art to understand the invention. All patent applications and patents incorporated herein by reference are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

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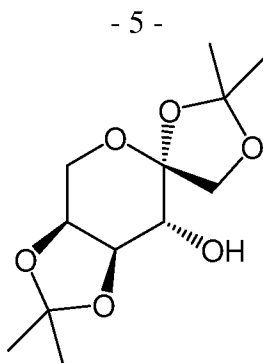
Detailed Description

The present invention generally relates to methods for the synthesis of catalysts, including epoxidation catalysts, and related compounds and catalyst compositions.

5 Some embodiments provide methods for synthesizing large amounts (e.g., greater than 10 grams) of a catalyst composition that may otherwise be difficult to obtain using known methods. In some embodiments, compounds and intermediates useful in the synthesis of catalysts are provided. Embodiments described herein may provide efficient processes for providing catalysts (e.g., epoxidation catalysts) in large quantities and
10 using simplified methods.

Methods for synthesizing the compounds and catalyst compositions described herein are provided. In some cases, the method may comprise reacting an intermediate molecule to produce a compound or catalyst, as described herein. In some cases, the intermediate molecule may be a compound comprising at least one ketal group and/or at
15 least one protecting group. Other intermediate molecules are described herein, including the Examples. Methods described herein may involve one or more chemical transformations, which may be performed sequentially and/or simultaneously. For example, the method may comprise reacting a compound in the presence of a chemical reagent (e.g., acid), wherein multiple chemical transformations may occur in a single
20 reaction step. Those of ordinary skill in the art would be able to select the appropriate set(s) of reaction conditions (e.g., concentration, temperature, pressure, reaction time, solvents, etc.) suitable for use in a particular application. In some cases, the method may further comprise isolating and/or purifying the compound and/or catalyst, for example, by chromatography (e.g., column chromatography, HPLC), crystallization, precipitation,
25 distillation, filtration, solvent extraction, and the like. The method may also comprise characterization of the compound and/or catalyst by mass spectrometry, NMR, and the like.

Some embodiments relate to the synthesis of the following compound,



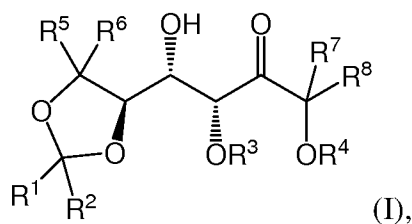
also known as the “ent-Shi ketone” catalyst, which is the enantiomer of a commercially available catalyst known as “Shi ketone.” The ent-Shi ketone catalyst has been shown to be an effective catalyst for enantioselective epoxidation reactions. In some

5 embodiments, methods for synthesizing the ent-Shi ketone catalyst, as described herein, may include fewer synthetic steps and may produce the ent-Shi ketone catalyst in higher yields, relative to known methods. In some cases, the ent-Shi ketone catalyst may advantageously be produced in relatively large amounts, when performing a single iteration of a synthetic scheme. For example, carrying out the synthetic scheme shown

10 in FIG. 1B one time may produce the ent-Shi ketone catalyst in relatively large quantities (e.g., greater than 10 grams). In some embodiments, the method may produce a catalyst (e.g., the ent-Shi catalyst) in an amount of 10 grams or greater, 20 grams or greater, 30 grams or greater, 40 grams or greater, 50 grams or greater, 60 grams or greater, 70 grams or greater, 80 grams or greater, 90 grams or greater, 100 grams or greater, 150 grams or

15 greater, or, in some cases, 200 grams or greater, based upon a single run of a particular synthetic scheme. In one set of embodiments, the ent-Shi ketone catalyst may be produced in quantities ranging from about 50 grams to about 60 grams, based upon a single run of a particular synthetic scheme.

Some embodiments involve reacting a compound of Formula (I),



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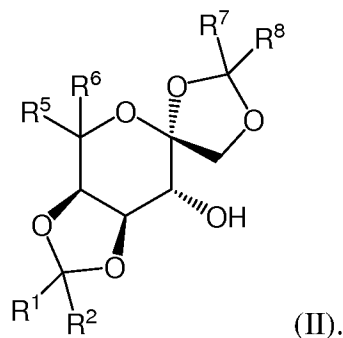
wherein:

R¹ and R² can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R¹ and R² is hydrogen, the other is alkyl or aryl;

R³ is a protecting group;

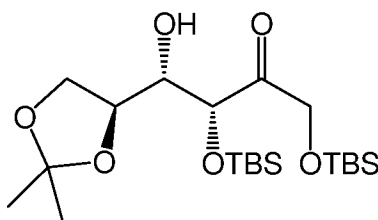
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R^4 is a protecting group that can be removed in the presence of an acid; and R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl, to produce a compound of Formula (II),

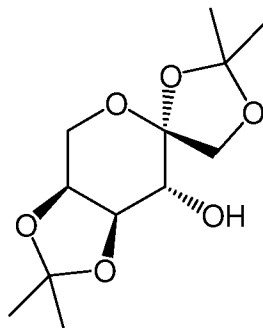


5 In some embodiments, R^1 and R^2 are alkyl; and R^5 , R^6 , R^7 , and R^8 are each hydrogen.

In one set of embodiments, the compound of Formula (I) has the structure,



In one set of embodiments, the compound of Formula (II) has the structure,



10

In some embodiments, the compound of Formula (I) may include at least one protecting group. For example, R^3 and R^4 may each comprise a silicon-containing protecting group. In some embodiments, the protecting group is trimethylsilyl (TMS), tributylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), [2-(trimethylsilyl)ethoxy]methyl (SEM), trimethylsilyl triflate, triethylsilyl triflate, or tri-*t*-butylsilyl triflate. In one set of embodiments, the protecting group is tributylsilyl (TBS). In some cases, the protecting group may be capable of being removed in the presence of an acid.

15

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The phrase “protecting group” as used herein refers to temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively.

5 The field of protecting group chemistry has been reviewed (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

In some embodiments, conversion of a compound of Formula (I) to a compound of Formula (II) may be performed in a one-pot reaction. The term “one-pot” reaction is known in the art and refers to a chemical reaction which can produce a product in one
10 step which may otherwise have required a multiple-step synthesis. One-pot procedures may eliminate the need for isolation (e.g., purification) of intermediates and additional synthetic steps while reducing the production of waste materials (e.g., solvents, impurities). Additionally, the time and cost required to synthesize such compounds can be reduced. For example, one or more chemical transformations may occur in a single
15 reaction vessel to convert of a compound of Formula (I) to a compound of Formula (II), as described more fully below.

In some embodiments, the method may involve exposure of a compound of Formula (I) to an acid. As used herein, an “acid” refers to any species capable of acting as a source of at least one proton. Examples of acids include, but are not limited to,
20 hydrochloric acid, hydrobromic acid, hydrofluoric acid, hydroiodic acid, hypochloric acid, chloric acid, perchloric acid, periodic acid, sulfuric acid, fluorosulfuric acid, nitric acid, phosphoric acid, hexafluorophosphoric acid, chromic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, nitric acid, acetic acid, citric acid, formic acid, and the
25 like. In some embodiments, the acid may be perchloric acid (HClO₄).

The acid may be provided as an aqueous solution comprising at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or, in some cases, at least 90% acid. In some embodiments, the acid may be added to the reaction mixture as a solution comprising about 50% to about 80% acid,
30 about 60% to about 80% acid, or, about 70% to about 80% acid. In some embodiments, the acid may be added to the reaction mixture as a solution comprising 70% acid.

The compound of Formula (I) may be exposed to the acid under reaction conditions suitable for use in a particular application. In some embodiments, the reaction

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mixture may be maintained at any temperature from about -78 °C to about 200 °C. In some embodiments, the acid may be added to the reaction mixture at relatively lower temperatures. For example, the reaction mixture may be maintained at any temperature from about -78 °C to about room temperature. In some embodiments, the reaction mixture may be maintained at about room temperature or lower, at about 15 °C or lower, at about 10 °C or lower, at about 5 °C or lower, or, at about 0 °C or lower. In one set of embodiments, the reaction mixture may be maintained at about 0 °C.

Exposure of a compound of Formula (I) to an acid may result in one or more chemical transformations, including addition of a nucleophile to a carbonyl, removal/addition of protecting group(s), isomerization of protecting group(s), and the like. For example, exposing compound 4 to perchloric acid results in transformation of compound 4 to compound 5. (FIG. 1B) Without wishing to be bound by theory, FIG. 2 shows a proposed mechanism for conversion of compound 4 to compound 5, involving multiple chemical transformations upon exposure to compound 4 to an acid. In some cases, the compound may undergo acid-catalyzed isomerization, such that a protecting group (e.g., cyclic ketal) may moved to a different portion of the compound, as shown in step (a) of FIG. 2. For example, the cyclic ketal of compound 4 may be fully removed from compound 4 upon exposure to acid, and a new cyclic ketal may be formed at a different location of compound 4. Alternatively, the cyclic ketal in compound 4 may be partially removed from compound 4 (e.g., only one carbon-oxygen bond of the cyclic ketal may be cleaved) and may migrate to a different location of compound 4, upon exposure to acid. Upon isomerization of the cyclic ketal, the compound may then cyclize via addition of hydroxyl group to the carbonyl, as shown in step (b) of FIG. 2. Subsequent removal and/or addition of protecting groups at various locations may then produce compound 5, as shown in steps (c)-(e) of FIG. 2.

In some cases, the method may involve the subsequent step of neutralizing the acid. This may be performed, for example, by exposing the reaction mixture to a base. Bases suitable for use in the invention include those having sufficient pKa values to neutralize (e.g., deprotonate) an acidic reagent present within the reaction mixture. In general, a variety of bases may be used in practice of the present invention. Examples of bases include, but are not limited to, alkoxides such as sodium *t*-butoxide, an alkali metal amide such as sodium amide, lithium diisopropylamide or an alkali metal bis(trialkylsilyl)amides such as lithium bis(trimethylsilyl)amide or sodium

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bis(trimethylsilyl) amide, a tertiary amine (e.g. triethylamine, trimethylamine, Et(*i*-Pr)₂N, Cy₂MeN, 4-(dimethylamino)pyridine (DMAP), 2,6-lutidine, N-methylpyrrolidine (NMP), quinuclidine, and the like), 1,5-diazabicycl[4.3.0]non-5-ene (DBN), 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), ammonium salts (e.g., ammonium hydroxide),
5 alkali and alkaline earth carbonates, alkali and alkaline earth bicarbonates, alkali and alkaline earth hydroxides, alkali and alkaline earth hydrides, (e.g. NaH, LiH, KH, K₂CO₃, Na₂CO₃, Tl₂CO₃, Cs₂CO₃, K(*O**t*-Bu), Li(*O**t*-Bu), Na(*O**t*-Bu) K(OPh), Na(OPh)), and the like. In some embodiments, a solution of ammonium hydroxide may be added to the reaction mixture to neutralize, for example, HClO₄.

10 Other suitable bases include quinoline, optionally substituted with alkyl or aryl groups, isoquinoline, optionally substituted with alkyl or aryl groups, imidazole, optionally substituted with alkyl or aryl groups, thiazole, optionally substituted with alkyl or aryl groups, and oxazole, optionally substituted with alkyl or aryl groups. In the above compounds, preferred alkyl substituents may be C₁₋₅ alkyl groups and preferred
15 aryl substituents may be C₆₋₂₀ aryl groups, such as phenyl, substituted phenyl, naphthyl, phenanthryl, and the like. The base may be added in solid form, or as a solution comprising a base (e.g., an aqueous solution). For example, the acid may be neutralized by exposure to an ammonium hydroxide solution.

In some cases, the method may comprise a protection or deprotection reaction.

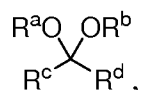
20 For example, the compound of Formula (I) may be exposed to a protecting group precursor, which may interact with a portion of the compound to produce a compound comprising a protecting group. In some cases, the compound of Formula (I) may comprise at least one protecting group and may be exposed to conditions under which the protecting group may be at least partially removed. In some embodiments, the
25 protecting group may be removed from the compound. In some embodiments, the protecting group may be partially removed from the compound. For example, the protecting group may be attached to the compound via at least two bonds, and one of the bonds may be cleaved during a deprotection step. Some embodiments may involve migration of a protecting group from one location of the compound to another, different
30 location of the compound.

In some cases the protection or deprotection reaction may be performed in the absence of additional chemical transformations. In some embodiments, the protection or deprotection reaction may be performed simultaneously with another chemical

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transformation. For example, a compound of Formula (I) may be exposed to an acid and a protecting group precursor at the same time, and may undergo both removal/addition of a protecting group and addition of a nucleophile to a carbonyl.

Some embodiments involve exposure of a compound of Formula (I) to a species
5 capable of forming an acetal or a ketal as a protecting group. As used herein, the terms “acetal” and “ketal” are given their ordinary meaning in the art and refer to carbonyl-protecting groups having the formula,



wherein R^{a} , R^{b} , and R^{c} are carbon-containing groups, R^{d} is hydrogen in the case of an
10 acetal, and R^{d} is a carbon-containing group in the case of a ketal. In some cases, the species may be capable of forming a cyclic acetal or a cyclic ketal, i.e., where R^{a} and R^{b} are joined together to form a ring. In some embodiments, acetals may be produced by reacting an aldehyde species with an alcohol. In some embodiments, ketals may be produced by reacting a ketone species with an alcohol.

15 In some embodiments, the compound of Formula (I) may comprise at least one hydroxyl group capable of forming an acetal or a ketal upon exposure to an aldehyde species or a ketone species. For example, the compound may comprise two hydroxyl groups, each attached to adjacent atoms of the compound (e.g., a vicinal diol), which may react with a ketone species to form a cyclic ketal. In some embodiments, the ketone
20 species may be acetone. As described herein, some embodiments may involve acid-catalyzed isomerization of a cyclic ketal.

In some embodiments, the compound of Formula (I) may be exposed to conditions suitable to remove one or more protecting groups. For example, the compound may comprise a silicon-containing protecting group and may be exposed to a
25 fluoride-containing species capable of removing the silicon-containing protecting group from the compound. Examples of fluoride-containing species include, but are not limited to, sodium fluoride (NaF) and tetra-n-butylammonium fluoride (TBAF). In some cases, the compound may comprise a TBS group, which may then be removed upon exposure to, for example, TBAF.

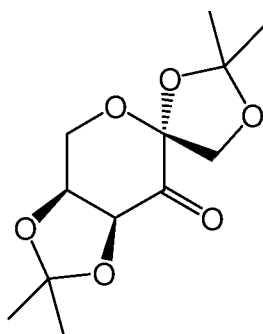
30 In one set of embodiments, the act of reacting a compound of Formula (I) comprises (i) exposure to HClO_4 and acetone; (ii) exposure to ammonium hydroxide solution; and (iii) exposure to tetra-n-butylammonium fluoride (TBAF).

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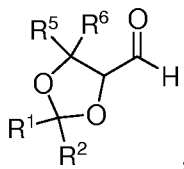
The method may further comprise exposing the compound of Formula (II) to an oxidant. As used herein, the terms “oxidant” or “oxidizing agent” are given their ordinary meaning in the art and refer to a species capable of oxidizing or increasing the oxidation number of a substrate. In some embodiments, the oxidant may comprise a transition metal. For example, the oxidant may comprise ruthenium.

Examples of oxidants include halogens (e.g., iodine), peroxides, sulfoxides, ozone, osmium tetroxide, ruthenium(III) trichloride, chlorite, chlorate, perchlorate, hexavalent chromium compounds, nitric acid, nitrous oxide, permanganate salts, and the like.

In one set of embodiments, the compound of Formula (II) is oxidized to produce the ent-Shi catalyst, i.e., a compound having the structure,

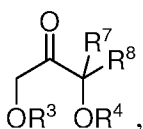


In some embodiments, the method may further comprising synthesizing a compound of Formula (I). In some embodiments, the compound may be synthesized via an aldol reaction. In some embodiments, the compound may be synthesized via an asymmetric aldol reaction. The method may involve performing an aldol reaction between an aldehyde species having the formula,



wherein R^1 and R^2 can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R^1 and R^2 is hydrogen, the other is alkyl or aryl; and

R^5 and R^6 can be the same or different and each can be hydrogen, alkyl, or aryl, and a carbonyl species having the formula,



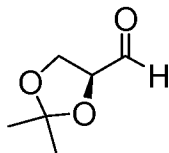
wherein R^3 is a protecting group;

R^4 is a protecting group that can be removed in the presence of an acid; and

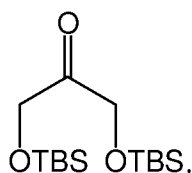
- 12 -

R^7 and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl.

In some embodiments, the aldehyde species has the following structure,



In some embodiments, the carbonyl species has the following structure,



5

The aldol reaction may be performed under conditions suitable for use in a particular application. In some embodiments, the aldol reaction may be performed in the presence of one or more asymmetric (e.g. chiral) species capable of enhancing the formation of a particular desired product. For example, the aldol reaction may be performed in the presence of a chiral catalyst, chiral auxiliary, and/or chiral substrates. Those of ordinary skill in the art would be able to select the appropriate chiral species to produce a particular, desired product (e.g., syn aldol product, anti aldol product). In some embodiments, a syn aldol product may be the desired product. In some embodiments, an anti aldol product may be the desired product. In an illustrative embodiment, an asymmetric aldol reaction may be performed in the presence of *O*-tert-butyl-L-threonine.

The aldol reaction may be performed in the presence of one or more solvents, including organic solvents, aqueous solvents, and combinations thereof. In some embodiments, the solvent may be a polar aprotic solvent. Examples of polar aprotic solvents include N-methylpyrrolidinone (NMP), dimethylformamide (DMF), dimethylacetamide, and dimethyl sulfoxide, and the like.

In some embodiments, the aldol reaction mixture may be maintained at any temperature from about -78 °C to about 200 °C. For example, the aldol reaction mixture may be maintained at any temperature from about -78 °C to about 50 °C. In some embodiments, the aldol reaction mixture may be maintained at about 50 °C or lower, at about 30 °C or lower, at about 10 °C or lower, at about 5 °C or lower, or, at about 0 °C or lower. In one set of embodiments, the reaction mixture may be maintained at about room temperature.

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Upon reaction, the contrast agent may be subjected to one or more purification steps. Purification and isolation may be performed using methods known to those skilled in the art, including separation techniques like chromatography, or combinations of various separation techniques as are known the art. In one embodiment, high
5 performance liquid chromatography (HPLC) may be used with a solvent, or mixture of solvents, as the eluent, to recover the product. In some cases, the eluent may include a mixture of water and acetonitrile, such as a 45:55 water:acetonitrile mixture. The content of water may vary from, for example, about 1% to about 50 %. In some cases, HPLC may be performed using a C18 column.

10 Any of the compounds or intermediates described herein product may be further processed using one or more purification techniques. Purification and isolation may be performed using methods known to those skilled in the art, including separation techniques like chromatography, recrystallization, distillation, or combinations of various separation techniques as are known the art. In some cases, the compound or intermediate
15 may be purified using column chromatography. Any solvent, or mixture of solvents, may be uses the eluent to recover the product. In some cases, the eluent may include hexane, ethyl acetate, and/or a mixture of hexane and ethyl acetate, such as a 1:1 hexane:ethyl acetate mixture, a 2:1 hexane:ethyl acetate mixture, a 20:1 hexane:ethyl acetate mixture, or the like.

20 In some embodiments, a compound or intermediate may be purified using recrystallization, a process which may be repeated until desired purity of product is obtained. In one embodiment, the compound or intermediate is recrystallized at least once, two times, three times, or four or more times to achieve the desired level of purity. For example, the compound or intermediate may be obtained at purities of greater than or
25 equal to 50 %, 80 %, 85 %, 90 %, 95 %, 97 %, 98 % , 98.5 %, 99.8%. Recrystallization may be achieved using a single solvent, or a combination of solvents. In some cases, recrystallization is achieved by dissolving the compound or intermediate in a solvent such as hexane at elevated temperatures, and then cooling the solution to produce a precipitate. For example, the compound may be recrystallized from hexane.

30 FIG. 1B shows an illustrative embodiment, wherein ent-Shi ketone 6 (the ent-Shi ketone catalyst) is synthesized from L-ascorbic acid. As shown in FIG. 1B, L-ascorbic acid may be converted to (S)-glyceraldehyde 3, using the methods described in U.S. Publication No. 2007/0073068, the contents of which are incorporated herein by

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reference in its entirety for all purposes. An asymmetric aldol reaction may then be performed between (S)-glyceraldehyde 3 and compound 2, in the presence of *O*-tert-butyl-L-threonine and NMP, to produce aldol compound 4. Compound 4 may then be reacted as described herein. In one set of embodiments, the act of reacting compound 4

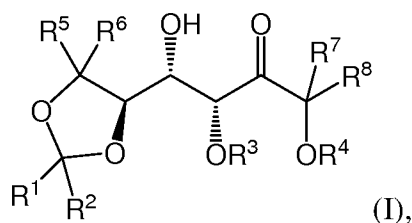
5 comprises (i) exposure to HClO₄ and acetone; (ii) exposure to ammonium hydroxide solution; and (iii) exposure to tetra-n-butylammonium fluoride (TBAF), to produce compound 5, which may then be oxidized to produce ent-Shi ketone 6.

In some embodiments, the ent-Shi ketone catalyst may be synthesized from (S)-glyceraldehyde in three steps with an overall yield of at least 10%, at least 20%, or at

10 least 30%. In some cases, the ent-Shi ketone catalyst may be synthesized from (S)-glyceraldehyde in three steps with an overall yield of about 35%. In some embodiments, the ent-Shi ketone catalyst may be synthesized from L-ascorbic acid in six steps with an overall yield of at least 5%, at least 10%, or at least 13%. In some cases, the ent-Shi ketone catalyst may be synthesized from L-ascorbic acid in six steps with an overall

15 yield of about 13.2%.

Some embodiments provide novel compounds or intermediates. In some case, compositions are provided comprising a compound having a structure as in Formula (I):



wherein:

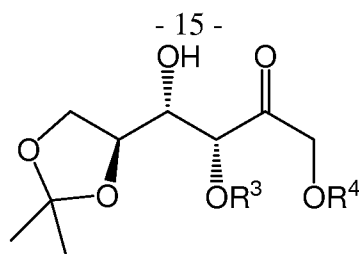
20 R¹ and R² can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R¹ and R² is hydrogen, the other is alkyl or aryl;

R³ is a protecting group;

R⁴ is a protecting group that can be removed in the presence of an acid; and

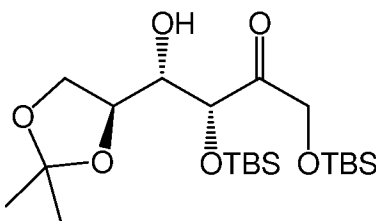
25 R⁵, R⁶, R⁷, and R⁸ can be the same or different and each can be hydrogen, alkyl, or aryl.

In some embodiments, the compound has the following structure,

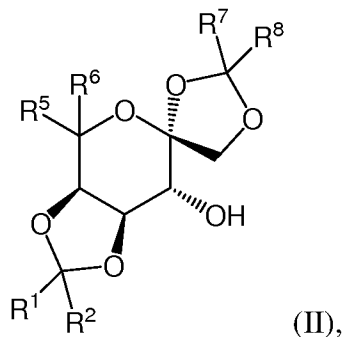


In some embodiments, R^3 and R^4 each comprise a silicon-containing protecting group, such as trimethylsilyl (TMS), tributylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBDMS) triisopropylsilyl (TIPS), [2-(trimethylsilyl)ethoxy]methyl (SEM), trimethylsilyl triflate, triethylsilyl triflate, or tri-*t*-butylsilyl triflate.

In some embodiments, the compound of Formula (I) has the structure,



In other embodiments, compositions comprising a compound having a structure as in Formula (II):



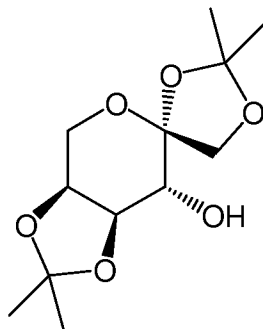
wherein:

R^1 and R^2 can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R^1 and R^2 is hydrogen, the other is alkyl or aryl; and

R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl, are provided.

In one set of embodiments, the compound has the following structure,

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Suitable silicon compounds or silicon-containing compounds which may be used in methods of the invention may include those which are capable of forming a covalent bond with an oxygen atom. For example, the silicon-containing compound may form a covalent bond with an oxygen atom to form a silyl ether. In some embodiments, the silicon compound has the formula R^3SiX , wherein R^3 can be optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and X can be halide, triflate, or the like. In some embodiments, the silicon compound is trimethylsilyl (TMS), tributylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBDMS) triisopropylsilyl (TIPS), [2-(trimethylsilyl)ethoxy] methyl (SEM), trimethylsilyl triflate, triethylsilyl triflate, or tri-*t*-butylsilyl triflate. In some embodiments, the

Solvents which may be used in methods of the invention include inert solvents such as benzene, *p*-cresol, toluene, xylene, diethyl ether, glycol monomethyl or dimethyl ether, petroleum ether, hexane, cyclohexane, methylene chloride, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran (THF), dimethyl sulfoxide, dimethylformamide, hexamethyl-phosphoric triamide, ethyl acetate, pyridine, triethylamine, picoline, mixtures thereof, or the like. Preferred solvents may include benzene, toluene, xylene, ether, hexane, petroleum ether, methylene chloride, chloroform, or tetrahydrofuran. In a particular embodiment, toluene is the preferred solvent.

The products which may be produced by methods of the present invention may undergo further reaction(s) to afford desired derivatives thereof. Such permissible derivatization reactions can be carried out in accordance with conventional procedures known in the art. For example, potential derivatization reactions include cleavage of the oxygen-silicon bond of a silyl ether of an allylic alcohol to afford the allylic alcohol. Suitable reagents which can cleave an oxygen-silicon bond to deprotect an alcohol are known, such as tetrabutylammonium fluoride (TBAF), for example.

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As used herein, the term “reacting” refers to the forming of a bond between two or more components to produce a stable, isolable compound. For example, a first component and a second component may react to form one reaction product comprising the first component and the second component joined by a covalent bond. That is, the term “reacting” does not refer to the interaction of solvents, catalysts, bases, ligands, or other materials which may serve to promote the occurrence of the reaction with the component(s). A “stable, isolable compound” refers to isolated reaction products and does not refer to unstable intermediates or transition states.

In the compounds and compositions of the invention, the term “alkyl” refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some embodiments, a straight chain or branched chain alkyl may have 30 or fewer carbon atoms in its backbone, and, in some cases, 20 or fewer. In some embodiments, a straight chain or branched chain alkyl may have 12 or fewer carbon atoms in its backbone (e.g., C₁-C₁₂ for straight chain, C₃-C₁₂ for branched chain), 6 or fewer, or 4 or fewer. Likewise, cycloalkyls may have from 3-10 carbon atoms in their ring structure, or 5, 6 or 7 carbons in the ring structure. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, cyclobutyl, hexyl, cyclohexyl, and the like.

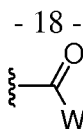
The term “heteroalkyl” refers to an alkyl group as described herein in which one or more carbon atoms is replaced by a heteroatom. Suitable heteroatoms include oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of heteroalkyl groups include, but are not limited to, alkoxy, amino, thioester, and the like.

The terms “alkenyl” and “alkynyl” refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The terms “heteroalkenyl” and “heteroalkynyl” refer to unsaturated aliphatic groups analogous in length and possible substitution to the heteroalkyls described above, but that contain at least one double or triple bond respectively.

As used herein, the term “halogen” or “halide” designates -F, -Cl, -Br, or -I.

The terms “carboxyl group,” “carbonyl group,” and “acyl group” are recognized in the art and can include such moieties as can be represented by the general formula:



wherein W is H, OH, O-alkyl, O-alkenyl, or a salt thereof. Where W is O-alkyl, the formula represents an “ester.” Where W is OH, the formula represents a “carboxylic acid.” The term “carboxylate” refers to an anionic carboxyl group. In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a “thiolcarbonyl” group. Where W is a S-alkyl, the formula represents a “thiolester.” Where W is SH, the formula represents a “thiolcarboxylic acid.” On the other hand, where W is alkyl, heteroalkyl, aryl, or heteroaryl, the above formula represents a “ketone” group. Where W is hydrogen, the above formula represents an “aldehyde” group.

The term “aryl” refers to aromatic carbocyclic groups, optionally substituted, having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple fused rings in which at least one is aromatic (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl). That is, at least one ring may have a conjugated pi electron system, while other, adjoining rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. The aryl group may be optionally substituted, as described herein. “Carbocyclic aryl groups” refer to aryl groups wherein the ring atoms on the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups and polycyclic or fused compounds (e.g., two or more adjacent ring atoms are common to two adjoining rings) such as naphthyl groups. In some cases, the

The terms “heteroaryl” refers to aryl groups comprising at least one heteroatom as a ring atom.

The term “heterocycle” refers to refer to cyclic groups containing at least one heteroatom as a ring atom, in some cases, 1 to 3 heteroatoms as ring atoms, with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, nitrogen, phosphorus, and the like. In some cases, the heterocycle may be 3- to 10-membered ring structures or 3- to 7-membered rings, whose ring structures include one to four heteroatoms. The term “heterocycle” may include heteroaryl groups, saturated heterocycles (e.g., cycloheteroalkyl) groups, or combinations thereof. The heterocycle may be a saturated molecule, or may comprise one or more double bonds. In some case, the heterocycle is a nitrogen heterocycle, wherein at least one ring comprises at least one nitrogen ring atom. The heterocycles may be fused to other rings to form a

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polycyclic heterocycle. The heterocycle may also be fused to a spirocyclic group. In some cases, the heterocycle may be attached to a compound via a nitrogen or a carbon atom in the ring.

Heterocycles include, for example, thiophene, benzothiophene, thianthrene, furan, tetrahydrofuran, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, dihydropyrrole, pyrrolidine, imidazole, pyrazole, pyrazine, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, triazole, tetrazole, oxazole, isoxazole, thiazole, isothiazole, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, oxazine, piperidine, homopiperidine (hexamethyleneimine), piperazine (e.g., N-methyl piperazine), morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, other saturated and/or unsaturated derivatives thereof, and the like. The heterocyclic ring can be optionally substituted at one or more positions with such substituents as described herein. In some cases, the heterocycle may be bonded to a compound via a heteroatom ring atom (e.g., nitrogen). In some cases, the heterocycle may be bonded to a compound via a carbon ring atom. In some cases, the heterocycle is pyridine, imidazole, pyrazine, pyrimidine, pyridazine, acridine, acridin-9-amine, bipyridine, naphthyridine, quinoline, benzoquinoline, benzoisoquinoline, phenanthridine-1,9-diamine, or the like.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula: $N(R')(R'')(R''')$ wherein R' , R'' , and R''' each independently represent a group permitted by the rules of valence. An example of a substituted amine is benzylamine.

Any of the above groups may be optionally substituted. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds, "permissible" being in the context of the chemical rules of valence known to those of ordinary skill in the art. It will be understood that "substituted" also includes that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In some cases, "substituted" may generally refer to replacement of a hydrogen with a substituent

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as described herein. However, "substituted," as used herein, does not encompass replacement and/or alteration of a key functional group by which a molecule is identified, e.g., such that the "substituted" functional group becomes, through substitution, a different functional group. For example, a "substituted phenyl group" must still comprise the phenyl moiety and can not be modified by substitution, in this definition, to become, e.g., a pyridine ring. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms.

Examples of substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF₃, -CN, aryl, aryloxy, perhaloalkoxy, aralkoxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroaralkoxy, azido, amino, halide, alkylthio, oxo, acylalkyl, carboxy esters, -carboxamido, acyloxy, aminoalkyl, alkylaminoaryl, alkylaryl, alkylaminoalkyl, alkoxyaryl, arylamino, aralkylamino, alkylsulfonyl, -carboxamidoalkylaryl, -carboxamidoaryl, hydroxyalkyl, haloalkyl, alkylaminoalkylcarboxy-, aminocarboxamidoalkyl-, cyano, alkoxyalkyl, perhaloalkyl, arylalkyloxyalkyl, and the like.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used.

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Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and
5 equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not
10 mutually inconsistent, is included within the scope of the present invention.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should
15 be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to
20 “A and/or B,” when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, “or” should be understood
25 to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will
30 refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e. “one or the other but not both”) when preceded by terms of exclusivity, such as

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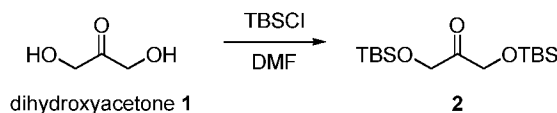
“either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

EXAMPLES

Example 1

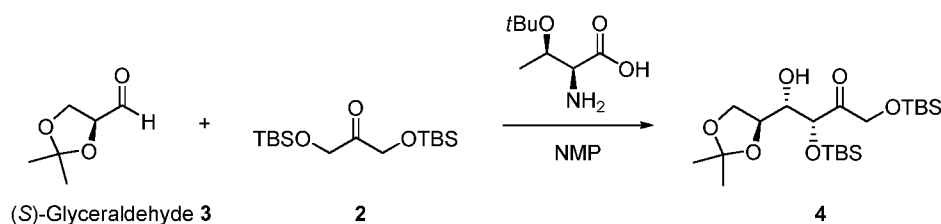


The following example describes a procedure for the TBS-protection of dihydroxyacetone (Preparation of Compound 2), as described in Sodeoka et al., *J. Am. Chem. Soc.* **1990**, *112*, 4906, the contents of which are incorporated herein by reference. To a solution of dihydroxyacetone **1** (250.00g, 2.78mol) and imidazole (472.34g,

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6.94mol; 2.5equiv) in DMF (1250mL) TBS-Cl (1045.70g, 6.94mol; 2.5 equiv) was added over about 40min between 0 to 30 °C. Then, the mixture was stirred at room temperature until dihydroxyacetone was disappeared (typical reaction time is 4 to 5 hours. Reaction progress was monitored by TLC.). After completion of the reaction, ice-water (1500mL) was added to the reaction mixture and extracted with ethyl acetate (1500mL). The aqueous layer was separated and organic layer was washed with water (1500mL), then 20% NaCl aq. (1500mL). The organic layer was evaporated to dryness and the residue was purified by distillation (bp. 135-138 °C at 3mmHg) to give **2** as colorless oil (849.83g, 96% yield).

Example 2



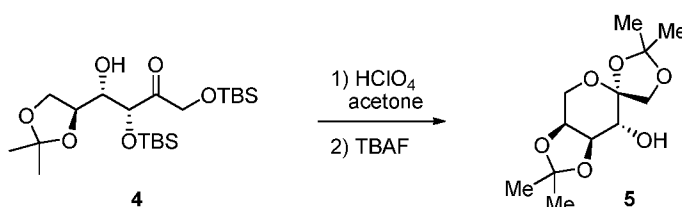
Compound **4** was synthesized according to the procedure described in Barbas et al., *Org. Lett.* **2007**, 9, 3445, with slight modifications for large scale synthesis. A solution of (*S*)-glyceraldehyde **3** was prepared according to method described in U.S. Publication No. 2007/0073068, and used without purification. The solution of (*S*)-glyceraldehyde **3** (100g (assumed net quantity), 768.4mmol) and **2** (489.63g, 1536.8mmol; 2.0equiv) in *N*-methylpyrrolidone (142.5mL) and water (7.5mL), *O*-tert-butyl-L-threonine (26.93g, 153.7mmol; 0.2equiv) was stirred at room temperature until **3** was no longer detectable by TLC (reaction time was about 24-72 hours and yield was about 70-95%; however, this may vary due to the quality and/or solubility of catalyst). This reaction mixture was diluted with *n*-hexane (2000mL) and washed with water (1000mL), water (500mL), water (500mL), 0.1M HCl aq. (500mL), 5% NaHCO₃ aq. (500mL), and 10% NaCl aq. (500mL). The organic layer was evaporated to dryness and the residue was purified by silica gel column chromatography (silica gel 2kg; *n*-hexane / ethyl acetate = 200/1 (4020mL), 100/1 (4040mL), 50/1 (4080mL), 20/1 (4200mL), 10/1 (4400mL), 4/1 (5000mL) to give **4** as colorless oil (258.62g, 75% yield).

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Excess TBS-protected dihydroxyacetone **2** was recovered as colorless oil (282.00g, 58% based on the initial amount), and can be re-used after distillation (90% yield).

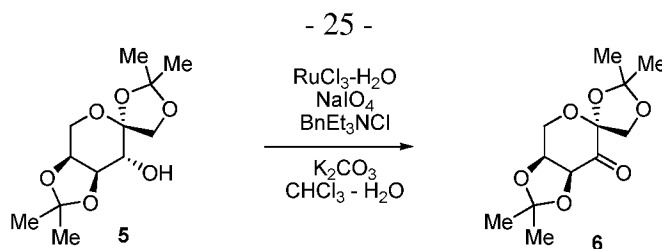
Also, excess *O*-*tert*-butyl-L-threonine was also recovered by concentrating the 1st to 3rd aqueous layers and adding 2-PrOH (500mL) to the residue. The mixture was stirred for 10 hours at room temperature, upon which a precipitate formed. The precipitate was filtered and washed with 2-PrOH to give *O*-*tert*-butyl-L-threonine as white powder (27.06g, 53%).

Example 3



The following example describes the synthesis of compound **5**. To a solution of aldol product **4** (238.46g, 531.4mmol) in acetone (1900mL) and water (2.3mL) 70% HClO₄ (7.63g, 53.14mmol) was added at 0 °C and stirred at the same temperature for 1.5 hour. The reaction mixture was quenched with 28% NH₄OH (7.4mL, 53.14mmol). A 1M tetrabutyl- ammonium fluoride in THF solution (1062.8mL, 1062.8mmol, 2equiv) was then added, and the mixture was stirred for 9 hours at room temperature. After removal of solvent, the residue was diluted with ethyl acetate (2400mL) and washed with water (1200mL) and 20% NaCl aq. (1200mL). The aqueous layers were reextracted with ethyl acetate (2400mL), and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was evaporated dryness and the remaining residue was purified by silica gel column chromatography (silica gel 1kg; *n*-hexane/ethyl acetate = 20/1 (4200mL), 2/1 (3000mL), 1/1 (4000mL)) to give white powder (130.15g, 94.1%), which contained about 10-20% impurities. To this powder *n*-hexane (1440mL) was added and refluxed until powder was dissolved. The solution was gradually cooled to 0 °C, upon which a precipitate formed. The precipitate was filtered and washed with cold *n*-hexane (240mL) to give *ent*-Shi alcohol **5** as white powder (87.07g, 63%).

Example 4



The following example describes the preparation of *ent*-Shi ketone 6.

To a solution of Shi alcohol **5** (187.00g, 718.5mmol) in CHCl₃ (655mL) and purified water (655mL) RuCl₃·H₂O (4.47g, 21.6mmol, 3mol%), NaIO₄ (230.51g, 1077.7mmol, 150mol%), BnNEt₃Cl (8.18g, 35.9mmol, 5mol%) and K₂CO₃ (14.89g, 107.8mmol, 15mol%) were added and the mixture was refluxed for 1.5 hours with vigorous stirring

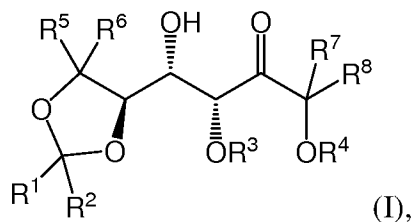
After starting material was disappeared, the mixture was cooled to room temperature. To this mixture 2-PrOH (47mL) was added and stirred for 1 hour, then the mixture was filtered with celite and the residue was washed with CH₂Cl₂ (935mL). The aqueous layer of the filtrate was removed and the organic layer was washed with 1M HCl aq. (560mL), water (560mL), 20% Na₂SO₃ aq. (560mL), and 10% NaCl aq. (560mL). The aqueous layers were reextracted with CH₂Cl₂ (560mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness. To the residue *n*-hexane (1580mL) was added and the mixture was refluxed for 0.5 hours. Then the mixture was filtered and washed with hot *n*-hexane (300mL). The filtrate was gradually cooled to -20 °C without stirring and stand for overnight. The precipitate was filtered and washed with cold *n*-hexane (370mL) to give *ent*-Shi ketone **6** as a colorless needle (163.23g, 88%).

20 What is claimed:

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1. A method for synthesizing a catalyst, comprising:

reacting a compound of Formula (I),



(I),

wherein:

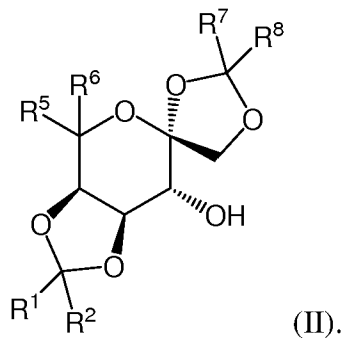
5 R¹ and R² can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R¹ and R² is hydrogen, the other is alkyl or aryl;

R³ is a protecting group;

R⁴ is a protecting group that can be removed in the presence of an acid; and

10 R⁵, R⁶, R⁷, and R⁸ can be the same or different and each can be hydrogen, alkyl, or aryl,

to produce a compound of Formula (II),



(II).

15 2. A method as in claim 1, wherein:

R¹ and R² are alkyl; and

R⁵, R⁶, R⁷, and R⁸ are each hydrogen.

3. A method as in any preceding claim, wherein R³ and R⁴ each comprise a silicon-
20 containing protecting group.

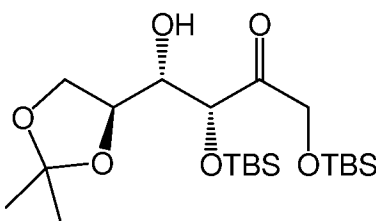
4. A method as in any preceding claim, wherein the protecting group is trimethylsilyl (TMS), tributylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), tert-

- 27 -

butyldimethylsilyl (TBDMS) triisopropylsilyl (TIPS), [2-(trimethylsilyl)ethoxy]methyl (SEM), trimethylsilyl triflate, triethylsilyl triflate, or tri-*t*-butylsilyl triflate.

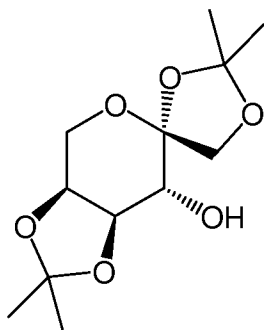
5. A method as in any preceding claim, wherein the protecting group is tributylsilyl (TBS),

6. A method as in any preceding claim, wherein the compound of Formula (I) has the structure,



10

7. A method as in any preceding claim, wherein the compound of Formula (II) has the structure,



15 8. A method as in any preceding claim, wherein the act of reacting comprises exposure to an acid.

9. A method as in any preceding claim, wherein the acid is HClO_4 .

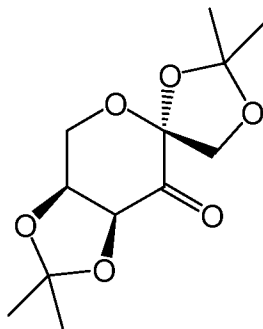
20 10. A method as in any preceding claim, further comprising the act of neutralizing the acid.

11. A method as in any preceding claim, wherein the act of neutralizing comprises exposure to a base.

- 28 -

12. A method as in any preceding claim, wherein the act of neutralizing comprises exposure to an ammonium hydroxide solution.
- 5 13. A method as in any preceding claim, further comprising exposing the compound of Formula (I) to a species capable of forming an acetal or a ketal.
14. A method as in any preceding claim, further comprising exposing the compound of Formula (I) to a species capable of forming a cyclic ketal.
- 10 15. A method as in any preceding claim, further comprising exposing the compound of Formula (I) to a fluoride-containing species.
16. A method as in any preceding claim, wherein the fluoride-containing species is sodium fluoride (NaF) or tetra-n-butylammonium fluoride (TBAF).
- 15 17. A method as in any preceding claim, wherein the act of reacting comprises:
(i) exposure to HClO_4 and acetone;
(ii) exposure to ammonium hydroxide solution; and
20 (iii) exposure to tetra-n-butylammonium fluoride (TBAF).
18. A method as in any preceding claim, further comprising the act of exposing the compound of Formula (II) to an oxidant.
- 25 19. A method as in any preceding claim, wherein the oxidant comprising a transition metal.
20. A method as in any preceding claim, wherein the oxidant comprises ruthenium.
- 30 21. A method as in any preceding claim, wherein the compound of Formula (II) is oxidized to produce a compound having the following structure,

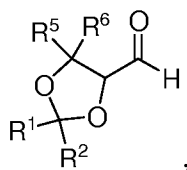
- 29 -



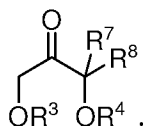
22. A method as in any preceding claim, further comprising synthesizing a compound of Formula (I) via an aldol reaction.

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23. A method as in any preceding claim, wherein the aldol reaction comprises: reacting an aldehyde species having the formula,

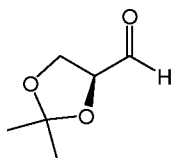


with a carbonyl species having the formula,



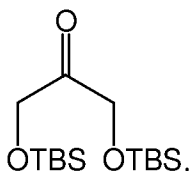
10

24. A method as in any preceding claim, wherein the aldehyde species has the following structure,



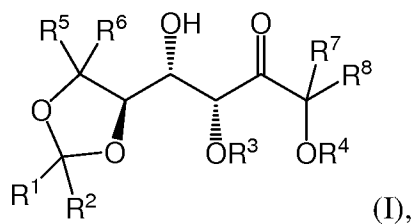
15

25. A method as in any preceding claim, wherein the carbonyl species has the following structure,



- 30 -

26. A composition, comprising:
a compound having a structure as in Formula (I):



5 wherein:

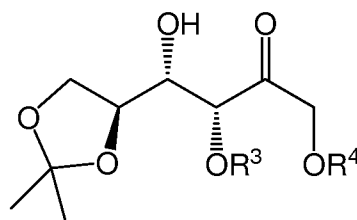
R^1 and R^2 can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R^1 and R^2 is hydrogen, the other is alkyl or aryl;

R^3 is a protecting group;

R^4 is a protecting group that can be removed in the presence of an acid; and

10 R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl.

27. A composition as in claim 26, wherein the compound has the following structure,

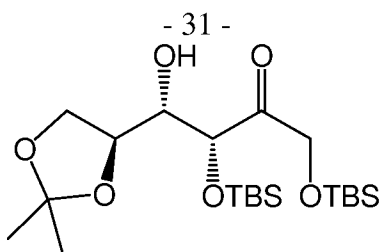


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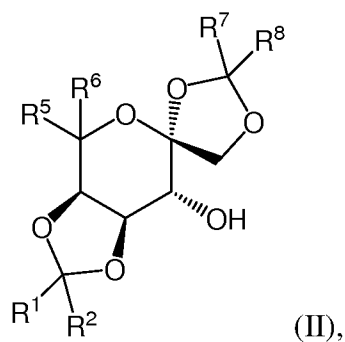
28. A composition as in any preceding claim, wherein R^3 and R^4 each comprise a silicon-containing protecting group.

29. A composition as in any preceding claim, wherein the protecting group is
20 trimethylsilyl (TMS), tributylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBDMS) triisopropylsilyl (TIPS), [2-(trimethylsilyl)ethoxy]methyl (SEM), trimethylsilyl triflate, triethylsilyl triflate, or tri-*t*-butylsilyl triflate.

30. A composition as in any preceding claim, wherein the compound of Formula (I)
25 has the structure,



31. A composition, comprising:
a compound having a structure as in Formula (II):

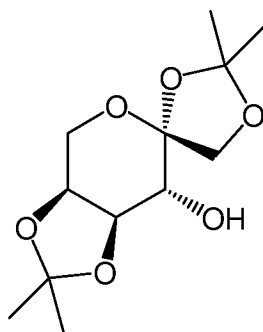


wherein:

R^1 and R^2 can be the same or different and each can be hydrogen, alkyl, or aryl, provided that when one of R^1 and R^2 is hydrogen, the other is alkyl or aryl; and

R^5 , R^6 , R^7 , and R^8 can be the same or different and each can be hydrogen, alkyl, or aryl.

32. A composition as in claim 31, wherein the compound has the following structure,



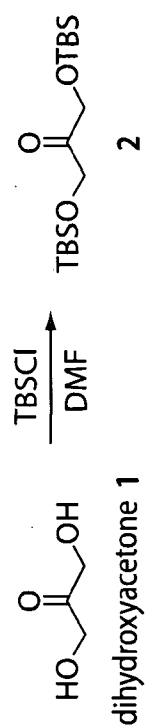


Fig. 1A

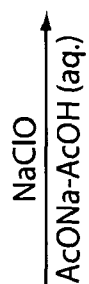
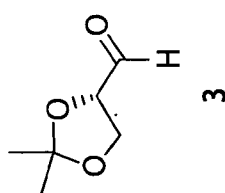
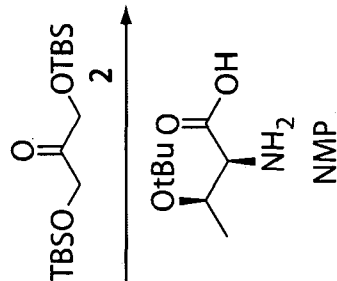
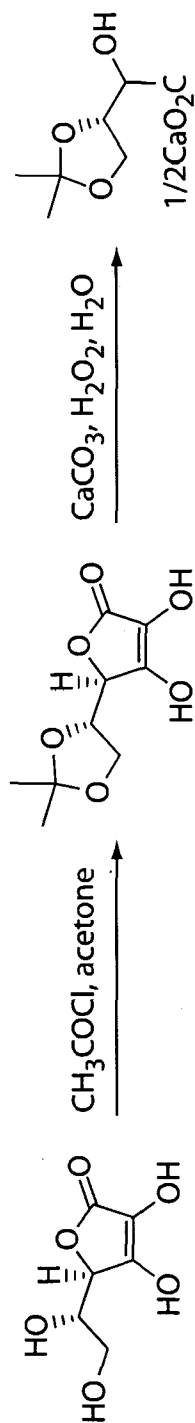
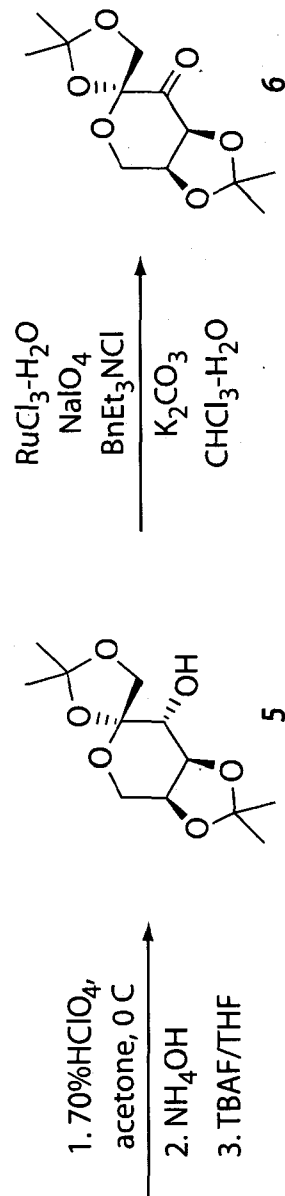


Fig. 1B



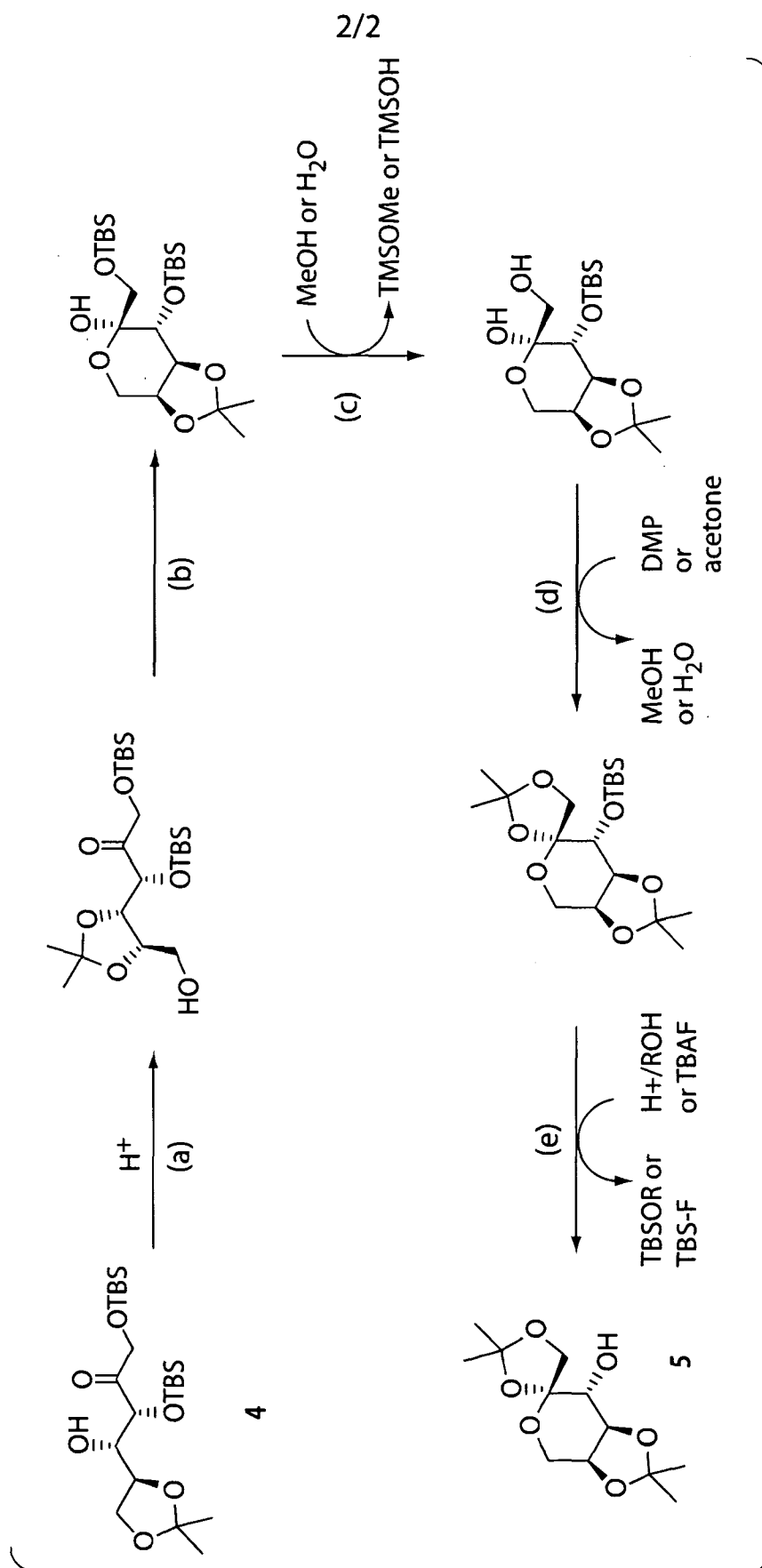


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/026439

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D317/26 C07D493/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMASASTRY S S V ET AL: "Water-compatible organocatalysts for direct asymmetric syn-aldol reactions of dihydroxyacetone and aldehydes.", ORGANIC LETTERS 17 APR 2008 LNKD-PUBMED:18351769, vol. 10, no. 8, 17 April 2008 (2008-04-17), pages 1621-1624, XP002632696, ISSN: 1523-7060 compound 17 in Table 3 ----- -/--	26-30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 April 2011

Date of mailing of the international search report

11/07/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/026439

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-30

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/026439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHAO M -X ET AL: "Practical synthesis of an L-fructose-derived ketone catalyst for asymmetric epoxidation of olefins", JOURNAL OF ORGANIC CHEMISTRY 20060707 US LNKD- DOI:10.1021/J0060335K, vol. 71, no. 14, 7 July 2006 (2006-07-07), pages 5377-5379, XP002632697, ISSN: 0022-3263 whole document, specially compound 7 in page 5378 -----	1-30
A	WANG Z -X ET AL: "An efficient catalytic asymmetric epoxidation method", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 19971119 US LNKD- DOI:10.1021/JA972272G, vol. 119, no. 46, 19 November 1997 (1997-11-19), pages 11224-11235, XP002632698, ISSN: 0002-7863 whole document, specially compound ent-6 in page 11225: "the enantiomer ent-1 is prepared in the same way" and figures (3)-(5) -----	1-30
A	BESSIERES B ET AL: "Iodomethyl group as a hydroxymethyl synthetic equivalent: Application to the syntheses of D-manno-hept-2-ulose and L-fructose derivatives", JOURNAL OF ORGANIC CHEMISTRY 20030516 US, vol. 68, no. 10, 16 May 2003 (2003-05-16), pages 4100-4103, XP002632699, ISSN: 0022-3263 Scheme 3 in page 4102 -----	1-25
A	BACH T ET AL: "Photochemical deconjugation of chiral 3-methyl-2-butenates derived from carbohydrate-based alcohols: the influence of the sugar backbone on the facial diastereoselectivity.", THE JOURNAL OF ORGANIC CHEMISTRY 18 MAY 2001 LNKD- PUBMED:11348126, vol. 66, no. 10, 18 May 2001 (2001-05-18), pages 3427-3434, XP002632700, ISSN: 0022-3263 Scheme 3, page 4102 ----- -/--	1-25

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/026439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	UTSUMI NAOTO ET AL: "Mimicking aldolases through organocatalysis: syn-selective aldol reactions with protected dihydroxyacetone", ORGANIC LETTERS, vol. 9, no. 17, August 2007 (2007-08), pages 3445-3448, XP002632701, ISSN: 1523-7060 cited in the application Scheme 2 page 3448	1-30
A	----- MORGENLIE S: "SYNTHESIS OF DI-O-ISOPROPYLIDENE DERIVATES OF L-FRUCTOSE", CARBOHYDRATE RESEARCH, PERGAMON, GB, vol. 107, 1 January 1982 (1982-01-01), pages 137-141, XP002051786, ISSN: 0008-6215, DOI: DOI:10.1016/S0008-6215(00)80782-X synthesis of 9 from 8 -----	1-30

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30

Synthesis of compound (II) from compound (I) and compositions comprising intermediates (I): Differs from D2 on account of the starting material used (I). The problem which this invention had to solve over D2 was the provision of a further method for the preparation of (II) (and thus of ent-Shi catalyst). Compositions comprising a compound of formula (I) is considered part of this invention as intermediates which were not known for the synthesis of (II).

2. claims: 31, 32

Compositions comprising a compound of formula (II): overlaps with D2 and D3 when e.g. compound 7 in D2 is in solution (e.g. after adding PCC and CH₂Cl₂ to transform it to the ketone).
