LIPPIAGAL ENANTIOMERS AND THEIR DERIVATIVES AND PRECURSORS, AND ENANTIOMERICALLY IDENTICAL METHODS OF MAKING THE SAME

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ABSTRACT
Enantiomeric compositions of lipilagall and its derivatives and precursors include more than 50 mol % of a first enantiomer based on the total amount of a first and a second enantiomer. A method of making an enantiomeric composition includes catalytic enantiomeric allylation, ring expansion, and intramolecular arylene cyclization.

9 Claims, No Drawings
References Cited

OTHER PUBLICATIONS

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OTHER PUBLICATIONS


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LIPHAGAL ENANTIOMERS AND THEIR DERIVATIVES AND PRECURSORS, AND ENANTIOSELECTIVE METHODS OF MAKING THE SAME

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to and the benefit of U.S. Provisional Patent Application Ser. No. 61/491,631 filed on May 31, 2011, the entire content of which is incorporated herein by reference.

STATEMENT OF FEDERAL SUPPORT

This invention was made with government support under Grant No. GM080269 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

 embodiments of the present invention are directed to liphagal enantiomers, derivatives thereof and precursors thereto, and to enantioselective methods of making the same.

BACKGROUND

Phosphatidylinositol 3-kinases participate in the regulation of numerous biological functions and have been directly implicated in the pathogenesis of diabetes and cancer. Indeed, the PI3K family of enzymes is intimately involved in numerous cellular pathways spanning proliferation, survival, adhesion, movement, differentiation, membrane trafficking, glucose transport, neurite outgrowth, and superoxide production in cells. Many natural and synthetic inhibitors of PI3K's are known, for example, myricetin, quercetin, resveratrol, staurosorpin, viridin, wortmannin, and liphagal (all shown below) but selective inhibition of an individual isoform is rare. As the human genome has numerous kinases, the selective inhibition of one isoform of PI3K, for example, PI3Kα (a lipid kinase isoform that holds a central role in several cancers), would be particularly beneficial. For instance, selective inhibitors of individual isoforms of these enzymes would allow for the targeting of specific diseases spanning cancer, cardiovascular disease, and autoimmune disorders.
Liphagel (the (+) enantiomer shown as compound 271 below), in the racemic form, has an IC₅₀ of 100 nM against PI3Kα, and is at least 10-fold more potent against this isoform of the enzyme compared to any other PI3K, including the γ isoform. While other natural and synthetic inhibitors of PI3Ks are known, they do not show the same selective inhibition of the PI3Kα isoform as liphagel does in the racemic form, and they do not possess the same potency. For example, although the natural product wortmannin (compound 273 shown below) shows an IC₅₀ of 12 nM toward PI3Kα, it has nearly equal potency against several other related enzymes. Additionally, quercitin (compound 274 shown below) and other molecules have been used in chemical genetics studies to understand the roles of certain PI3K’s in cell signaling. Second generation synthetic molecules designed to mimic natural products (e.g., LY294002 (compound 275 shown below)) have also been developed and studied by the pharmaceutical industry. Though somewhat selective, molecules such as LY294002 (compound 275 shown below) lack the potency of liphagel (the (+) enantiomer shown as compound 271 below).

With its unique biological activity and potentially novel mode of action, liphagel shows promise in the development of new therapeutics and as a chemical tool for studying cellular signaling and disease states. Additionally, liphagel (in the racemic form) displays substantial cytotoxicity toward various cancer cell lines. Against LoVo (human colon) cells, liphagel (in the racemic form) displays an IC₅₀ of 0.58 μM, and against another cell line, CaCo (human colon), liphagel (in the racemic form) displays an IC₅₀ value of 0.67 μM. Also, liphagel (in the racemic form) shows some cytotoxicity toward the MDA-468 breast cancer line, i.e., IC₅₀ value of 1.58 μM.

From a structural perspective, liphagel is a tetracyclic meroterpenoid having an unprecedented [6-7-5-6] tetracyclic skeleton and has attracted significant attention from the synthetic organic community. While syntheses for the production of a racemic mixture of (±)-liphagel have been reported, no enantioselective method has been reported to date.

**SUMMARY**

According to some embodiments of the present invention, an enantioenriched composition includes a first enantiomer and optionally a second enantiomer. The first enantiomer is present in an amount greater than 50 mol % based on an amount of the first and second enantiomers, and the second enantiomer is present in an amount of about 0 to about less than 50 mol % based on the amount of the first and second enantiomers. The first and second enantiomers are (+) and (−) enantiomers of one another, and the first enantiomer is selected from compounds represented by Formulae 1 through 22.
third precursor compound; promotion of a photocycloaddition reaction of the third precursor compound to form a fourth precursor compound; exposure of the fourth precursor compound to a Lewis acid to form a fifth precursor compound; arylation of the fifth precursor compound to form a sixth precursor compound; functionalization of an aromatic group on the sixth precursor compound to form a seventh precursor compound; ring expansion of the seventh precursor compound to form an eighth precursor compound; reduction of the eighth precursor compound to form a ninth precursor compound; reduction of steric congestion in the ninth precursor compound to form a tenth precursor compound; intramolecular aryne cyclization of the tenth precursor compound to form a thirteenth precursor compound; stereoselective hydrogenation or substitution of the thirteenth precursor compound to form a fourteenth precursor compound; and oxidation of the fourteenth precursor compound to form a fifteenth compound.

The method may further include functionalization of the fifteenth precursor compound to form a compound of Formula 1, and/or demethylation (or deprotection) of the compound of Formula 1 (or the fifteenth precursor compound) to yield a different compound of Formula 1. For example, demethylation (or deprotection) of the fifteenth precursor compound could result in the formation of a compound of Formula 1 in which all of R₁ény, R₁, and R₂ are hydrogen. Also, in some embodiments, the intramolecular aryne cyclization includes stereoselective substitution of the tenth precursor to form an eleven precursor; reduction of the eleventh precursor to form a twelfth precursor; and exposure of the twelfth precursor to a strong base to form the thirteenth precursor. Additionally, reduction of the steric congestion may be accomplished by epimerization of an ary substituent of the ninth precursor compound to form the tenth precursor compound.

**DETAILED DESCRIPTION**

The potent biological activity of liphagel has prompted more than one attempt at its total synthesis. However, the complex tetracyclic structure of liphagel, which is highlighted by a chiral quaternary carbon center at C(11), makes total synthesis a significant challenge. Additionally, while syntheses of a racemic form of liphagel have been reported, these syntheses are not enantioselective, i.e., they produce compositions including an equal mixture of the (+) and (−) enantiomers. While it is not yet known which of the (+) and (−) enantiomers of liphagel shows the most bioactivity; those of ordinary skill in the art readily recognize that it is uncommon for both enantiomers of a compound to show bioactivity (or the same degree of bioactivity). As such, an enantioselective synthesis of either (or both of) the (+) or the (−) enantiomer(s) of liphagel would not only enable the determination of which enantiomer is bioactive (or the most bioactive), but would enable the production of an enantiomerically pure (or substantially enantiomerically pure, i.e., about 95 wt % to about 100 wt % of the desired enantiomer) composition, the development of derivatives that would potentially also be biologically active, and the development of precursors to the liphagel enantiomers and derivatives that would be useful in the production of the enantiomers and derivatives as well as other products.

According to embodiments of the present invention, a composition includes a major amount of a first enantiomer and a minor amount of a second enantiomer. As used herein, the term “major amount” denotes an amount of the first enantiomer that is greater than the amount of the second enantiomer, and a major amount is any amount greater than 50 mol %. Conversely, the term “minor amount,” as used herein, denotes an amount of the second enantiomer that is less than the amount of the first enantiomer, and a minor amount is any amount less than 50 mol %. In particular, these compositions...
are intended to exclude racemic mixtures of the first and second enantiomers. As used herein, the term “racemic mixture” (or “racemate”) refers to a substantially equimolar mixture of the first and second enantiomers. As used herein, the term “substantially” is intended as a term or approximation, and not degree, so that the term “substantially” is intended to cover a standard deviation from the listed value that may arise, for example, from the uncertainty involved in certain measurements and calculations. In some exemplary embodiments, the first composition includes about 90 mol % to 100 mol % of the first enantiomer, and about 0 mol % to about 10 mol % of the second enantiomer. For example, the composition may include about 95 mol % to about 100 mol % of the first enantiomer, and about 0 mol % to about 10 mol % of the second enantiomer, or the composition may include about 99 mol % to about 100 mol % of the first enantiomer and about 0 mol % to about 1 mol % of the second enantiomer.

Stated somewhat differently, the first enantiomer is present in an enantiomeric excess of greater than 50%, for example about 90% to about 100% or about 95% to about 100%. As used herein, “enantiomeric excess” (or “ee”) is defined as 100%F(−)/F(+) or 100%(F(+)/F(−)) for compositions including more of the (−) enantiomer for a mixture of (+) and (−) enantiomers, with the composition given as the mole or weight fractions F(+) and F(−), such that F(+) = F(−) = 1. When given as a percentage, enantiomeric excess is defined by 100%F(+)/F(−) or 100%F(−)/F(+).

The first and second enantiomers are independently selected from compounds represented by Formula 1 through 22, described in detail below. However, the first and second enantiomers are enantiomers of each other, and therefore while the arrangement of the atoms in space may differ, their chemical formulae are identical. Accordingly, if the first enantiomer is a compound represented by Formula 1, then the second enantiomer is a corresponding compound represented by Formula 2. Similarly, if the second enantiomer is a compound of Formula 1, then the first enantiomer is a corresponding compound represented by Formula 2. As another example, if the first enantiomer is a compound of Formula 13, then the second enantiomer is a corresponding compound represented by Formula 14, and so on. Based on the descriptions of the compounds of Formulae 1 through 22 below, those of ordinary skill in the art would readily recognize which Formulae represent enantiomers within the meaning herein described. As used herein, the term “corresponding compound” refers to the opposite enantiomer, such that the first and second enantiomers are enantiomers of each other, for example, (+) and (−) enantiomers having the same chemical formula but a different (i.e., opposite or mirror-image) arrangement of atoms. Indeed, as can be seen from their structures depicted below, Formula 1 and Formula 2 are (+) and (−) enantiomers of the depicted structure. Accordingly, the term “corresponding compound” denotes that the R groups and other variables are identical in the first and second enantiomers, even though one enantiomer is represented by Formula 1 and the other is represented by Formula 2.

In Formulae 1 and 2, each of R₁ through Rₐ may be independently selected from hydrogen, substituted and unsubstituted hydrocarbyl groups, substituted and unsubstituted heteroatom containing hydrocarbyl groups, and functional groups. Also, any two adjacent groups selected from R₁ through R₁₆ may optionally combine to form a double bond in the respective six-membered or seven-membered ring structure. As used herein, the term “hydrocarbyl groups” refers to univalent hydrocarbon radicals containing from 1 to 30 carbon atoms, for example, from 1 to 24 carbon atoms or 1 to 12 carbon atoms. The term “hydrocarbyl groups” includes linear, branched, cyclic, saturated and unsaturated species, for example, alkyl groups, alkenyl groups, alkynyl groups, aryl groups, and the like. Also, as used herein, the term “substituted,” as in “substituted hydrocarbyl groups,” refers to a hydrocarbyl group in which one or more hydrogen atoms (bonded to a carbon atom) is replaced with one or more non-hydrogen functional groups.

The term “functional groups” would be readily understood to those of ordinary skill in the art. However, some non-limiting examples of suitable functional groups for use in Formula 1 and 2 include halogenos, hydroxyl groups, sulfhydryl groups, alkyl groups, alkoxyl groups (e.g., having from 1 to 24 carbon atoms), alkenyl groups (e.g., having from 1 to 24 carbon atoms), alkynyl groups (e.g., having from 1 to 24 carbon atoms), aryloxyl groups (e.g., having from 5 to 24 carbon atoms), acyl groups including alkyl/acyl groups of the formula —CO—alkyl (e.g., having from 2 to 24 carbon atoms) and aryloxycarbonyl groups of the formula —CO—aryl (e.g., having from 6 to 24 carbon atoms), acyloxyl groups having the formula —O—acyl, alkoxycarbonyl groups having the formula —O—(CO)—O—alkyl (e.g., having from 2 to 24 carbon atoms), carbonyl groups (including aldehyde moieties having the formula —CO—H) and ketone moieties having the formula —CO—R where R is any hydrocarbyl group), aryloxycarbonyl groups having the formula —(CO)—O—aryl (e.g., having from 6 to 24 carbon atoms), haloalkyl groups having the formula —CO—X (where X is a halogen), alkyl carbonyl groups having the formula —O—CO—aryl (e.g., having from 2 to 24 carbon atoms), aryloxycarbonyl groups having the formula —O—CO—O—aryl (e.g., having from 6 to 24 carbon atoms), carboxy 1 groups having the formula —COOH, carboxylato groups having the formula —COO—, carbamoyl groups having the formula —CO—NH, mono-alkyl substituted carbamoyl groups having the formula —CO—NH—alkyl (e.g., the alkyl group having from 1 to 24 carbon atoms), di-alkyl substituted carbamoyl groups having the formula —CO—N—alkyl (e.g., each alkyl group having from 1 to 24 carbon atoms), mono-aryl substituted carbamoyl groups having the formula —CO—NH—aryl (e.g., the aryl group having from 6 to 24 carbon atoms), di-aryl substituted carbamoyl groups having the formula —CO—N—aryl (e.g., each aryl group having from 6 to 24 carbon atoms), di-N(alkyl)-N(aryl) substituted carbamoyl groups having the formula —CO—N(alkyl)(aryl),
thiocarbamoyl groups having the formula \(-\text{CS}\)-NH\(_2\), carbamido groups having the formula \(-\text{NH}-(\text{CO})-\text{NH}_2\), cyano groups, isocyanato groups, cyamato groups, isocyanato groups, isothiocyanato groups, azido groups, formyl groups, thioformyl groups, amino groups, mono-alkyl substituted amino groups (e.g., the alkyl group having from 1 to 24 carbon atoms), di-alkyl substituted amino groups (e.g., the alkyl group having from 1 to 24 carbon atoms), mono-aryl substituted amino groups (e.g., the aryl group having from 6 to 24 carbon atoms), di-aryl substituted amino groups (e.g., each aryl group having from 6 to 24 carbon atoms), alkylamido groups having the formula \(-\text{NH}-(\text{CO})\text{-alkyl}\) (e.g., having from 2 to 24 carbon atoms), arylamido groups having the formula \(-\text{NH}-(\text{CO})\text{-aryl}\) (e.g., having from 6 to 24 carbon atoms), imino groups having the formula \(-\text{CR}=\text{NH}\) (where R is hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), alkyl imino groups having the formula \(-\text{CR}=\text{N-alkyl}\) (where R is hydrogen, alkyl, aryl, aralkyl, alkaryl, etc.), aryl imino groups having the formula \(-\text{CR}=\text{N-aryl}\) (where R is hydrogen, alkyl, aryl, alkaryl, alkaryl, etc.), nitro groups, nitroso groups having the formula \(-\text{NO}\), sulfon groups having the formula \(-\text{SO}_2\), sulfonato groups having the formula \(-\text{SO}_2\text{-O}\), alkysulfanyl groups having the formula \(-\text{S-alkyl}\) (also called, interchangeably, alkylthio groups), arylysulfanyl groups having the formula \(-\text{S-aryl}\) (also called, interchangeably, arylthio groups), alkysulfanyl groups having the formula \(-\text{SO}_2\text{-aryl}\), boryl groups having the formula \(-\text{BH}_2\), boronato groups having the formula \(-\text{B(OR)}_2\) (where R is alkyl or another hydrocarbyl group), phosphino groups having the formula \(-\text{P(O)(OH)}_2\), phosphono groups having the formula \(-\text{P(O)(O)}\) (or \(-\text{P(O)}_2\)), phosphino groups having the formula \(-\text{PO}_2\), and phosphino groups having the formula \(-\text{PH}_2\).

In addition to, or instead of, being substituted with a functional group, the substituted species may be substituted with hydrocarbyl groups, for example, alkyl groups (e.g., having from 1 to 24 carbon atoms, or from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms), alkenyl groups (e.g., having from 2 to 24 carbon atoms, or from 2 to 13 carbon atoms, or from 2 to 6 carbon atoms), alkynyl groups (e.g., having from 2 to 24 carbon atoms, or from 2 to 12 carbon atoms, or from 2 to 6 carbon atoms), aryl groups (e.g., having from 5 to 24 carbon atoms, or from 5 to 14 carbon atoms), alkaryl groups (i.e., aryl with an alkyl substituent, e.g., having from 6 to 24 carbon atoms, or from 6 to 16 carbon atoms), aralkyl groups (i.e., aryl with an aryl substituent, e.g., having from 6 to 24 carbon atoms, or from 6 to 16 carbon atoms), and/or aralkyl groups (i.e., aryl with an aryl substituent, e.g., having from 6 to 24 carbon atoms, or from 6 to 16 carbon atoms).

In other embodiments, each of \(R_5\) through \(R_{20}\) is independently selected from hydrogen, carboxyl groups and alkyl groups. In some exemplary embodiments, each of \(R_5\) through \(R_{20}\) is selected from hydrogen, aldehyde carboxyl groups and methyl groups. For example, in some embodiments, each of \(R_5\) through \(R_{12}\) is hydrogen, each of \(R_{12}\) and \(R_{20}\) is an alkyl group, and \(R_{13}\) is a carboxyl group. For example, in some embodiments, each of \(R_5\) through \(R_{12}\) is hydrogen, each of \(R_{12}\) and \(R_{20}\) is a methyl group, and each of \(R_{13}\) and \(R_{14}\) is an aldehyde carboxyl group. This configuration yields \((+)-\text{liphagal}\) (Formula 1A below) and \((-)-\text{liphagal}\) (Formula 2A below). However, it is understood that although this configuration is depicted as having each of \(R_5\) through \(R_{12}\) as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding derivatives of \((+)-\text{liphagal}\) or \((-)-\text{liphagal}\).
According to some exemplary embodiments of the present invention, (+) and (−) precursors to the enantiomers of Formula 1B and Formula 2B also have the general formula of Formula 1 and Formula 2. However, in these precursors, each of R₁ through R₆, R₁₀ through R₁₂, and R₁₈ is hydrogen, and each of R₈, R₁₂, R₁₆, R₁₉ and R₂₀ is an alkyl group (e.g., a methyl group). This configuration yields a (+)-enantiomer of Formula 1C below and a (−)-enantiomer of Formula 2C below. It is understood that although this configuration is depicted as having each of R₂ through R₇, R₁₅ through R₁₉, R₁₆, and R₁₈ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding derivatives of the (+)-enantiomer or the (−)-enantiomer of Formulae 1C and 2C.

In Formulae 3 and 4, each of R₁ through R₂₀ is as described above with respect to Formulae 1 and 2 (i.e., like reference numerals designate like moieties and/or functional groups throughout). Also, any two adjacent groups selected from R₁ through R₄ may optionally combine to form a double bond in the respective six-membered or seven-membered ring structure. Additionally, R₂₁ and R₂₂ may each be independently selected from the substituents discussed above for R₁ through R₂₀ in Formulae 1 and 2. In some embodiments, however, R₂₁ and R₂₂ may be hydrogen. For example, in some embodiments of the present invention, in Formulae 3 and 4, each of R₁ through R₂₀ is independently selected from hydrogen, carbonyl groups and alkyl groups. In some exemplary embodiments, each of R₁ through R₂₀ is selected from hydrogen, aldehyde carbonyl groups and methyl groups. For example, in some embodiments, each of R₂ through R₇, R₁₀ through R₁₅, R₁₇, R₂₁ and R₂₂ is hydrogen, and each of R₁, R₁₅, R₁₆, R₁₉ and R₂₀ is an alkyl group. In some embodiments, for example, each of R₂ through R₄, R₁₅, R₁₇, R₂₁, and R₂₂ is hydrogen, and each of R₁, R₈, R₁₀, R₁₉ and R₂₀ is a methyl group. This configuration yields the (+)-enantiomer of Formula 3A below and the (−)-enantiomer of Formula 4A below. However, it is understood that although this configuration is depicted as having each of each of R₁ through R₄, R₁₀ through R₁₅, R₁₇, R₁₉, R₂₁ and R₂₂ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulae 3 and 4.
According to other embodiments of the present invention, (+) and (−) precursors (Formulae 5 and 6 below) to the enantiomers of Formulae 3 and 4 have the structures of Formulae 3 and 4 in which the R₇ and R₈ functional groups (or hydrogen atoms) combine to form carbon to carbon double bonds in the seven-membered rings. All of the R groups in the following Formulae 5 and 6 (except for R₂ and R₆, which are absent from Formulae 5 and 6) are as described above with respect to Formulae 3 and 4.

As in Formulae 3 and 4, each of R₁ through R₅ and R₇ through R₁₂ in Formulae 5 and 6 are as described above with respect to R₁ through R₅ in Formulae 1-4 (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from R₁ through R₅, R₇ through R₁₂, R₁₆, and R₂₁ and R₂₂ may optionally combine to form a carbon to carbon double bond in the respective six-membered ring or seven-membered ring. Also, R₂ and R₇ may each be independently selected from the substituents discussed above for R₇ through R₁₀. In some embodiments, however, R₂ and R₇ may be hydrogen. For example, in some embodiments of the present invention, in Formulae 5 and 6, each of R₁ through R₅, and R₇ through R₁₂ is independently selected from hydrogen, carbonyl groups and alkyl groups. In some exemplary embodiments, each of R₁ through R₅, and R₇ through R₁₂ is selected from hydrogen, aldehyde carbonyl groups and methyl groups. For example, in some embodiments, each of R₁ through R₅, R₁₀ through R₁₅, R₁₇, R₂₀, and R₂₂ is hydrogen, and each of R₁, R₈, R₉, R₁₆, R₁₉, and R₂₀ is an alkyl group. In some embodiments, for example, each of R₁ through R₅, R₁₀ through R₁₅, R₁₇, R₁₈, R₂₁, and R₂₂ is hydrogen, and each of R₁, R₈, R₉, R₁₆, R₁₉, and R₂₀ is a methyl group. This configuration yields the (+)-enantiomer of Formula 5A below and the (−)-enantiomer of Formula 6A below. However, it is understood that although this configuration is depicted as having each of each of R₁ through R₅ and R₁₀ through R₁₅, R₁₇, R₁₈, R₂₁, and R₂₂ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulae 5 and 6.

According to another embodiment of the present invention, (+) and (−) precursors to the enantiomers of Formulae 5, 6, 5A and 6A are represented by Formulae 7 and 8 below.
As can be seen from Formulae 7 and 8, these structures are related to their reaction products (i.e., Formulae 5 and 6) in the preservation of the 6-7 ring structure, but differ from their reaction products in the absence of the heteroaromatic ring attached to the seven-membered ring, the presence of an alkene in the six-membered aromatic ring, the absence of $R_{18}$ (in Formula 7) and $R_{18}'$ (in Formula 8), and the inclusion of $R_{23}$ (in Formula 7) and $R_{23}'$ (in Formula 8). However, in Formulae 7 and 8, all of the like numbered $R$ groups (except for $R_6$, $R_7$, and $R_8$ which are absent from Formulae 7 and 8) are as described above with respect to Formulae 1, 2, 3, 4, 5 and 6.

In Formulae 7 and 8, each of $R_1$, through $R_4$, through $R_{19}$, and $R_{20}$ through $R_{23}$ are as described above with respect to $R_1$, through $R_{20}$ (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from $R_1$, through $R_5$, $R_6$ through $R_10$, $R_{15}$, and $R_{21}$ may optionally combine to form a carbon to carbon double bond in the respective six-membered ring or seven-membered ring. Also, $R_{23}$ and $R_{23}'$ may each be independently selected from the substituents discussed above for $R_1$, through $R_{20}$. In some embodiments, however, $R_{21}$, and $R_{23}$ may be hydrogen.

Further, $R_{23}$ is an oxygen containing functional group. For example, $R_{23}$ may be a functional group represented by $-OM$, where $M$ is an alkali metal. In some embodiments, for example, $R_{23}$ may be lithium, sodium or potassium. For example, in some embodiments, $M$ is lithium.

In some exemplary embodiments of the present invention, in Formulae 7 and 8, each of $R_1$, through $R_5$, $R_6$ through $R_7$, and $R_{19}$ through $R_{23}$ is independently selected from hydrogen, carbonyl groups and alkyl groups, and $R_{23}$ is a functional group represented by $-OM$ as defined above. In some exemplary embodiments, each of $R_1$, through $R_5$, $R_6$ through $R_7$, and $R_{19}$ through $R_{23}$ is independently selected from hydrogen, carbonyl groups and alkyl groups, and $R_{23}$ is a functional group represented by $-OM$ as defined above. For example, in some embodiments, each of $R_1$, through $R_5$, $R_6$ through $R_{10}$, $R_{15}$, through $R_{21}$ and $R_{23}$ is hydrogen, each of $R_1$, $R_6$, $R_7$, $R_8$, $R_{15}$, $R_{19}$, and $R_{20}$, is an alkyl group, and $R_{23}$ is a functional group represented by $-OM$ as defined above. In some embodiments, for example, each of $R_1$, through $R_5$, $R_10$ through $R_{15}$, $R_{19}$, and $R_{20}$ is hydrogen, each of $R_1$, $R_6$, $R_7$, $R_8$, $R_{15}$, $R_{19}$, and $R_{20}$ is a methyl group, and $R_{23}$ is a functional group represented by $-OLi$. This configuration yields the (+)-enantiomer of Formula 7A below and the (-)-enantiomer of Formula 8A below. However, it is understood that although this configuration is depicted as having each of each of each of $R_1$ through $R_5$, and $R_10$ through $R_{15}$, $R_{19}$, and $R_{20}$ is hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (-)-enantiomer of Formulae 7 and 8.

According to another embodiment of the present invention, (+) and (-) precursors to the enantiomers of Formulae 7, 8, 7A and 8A are represented by Formulae 9 and 10 below.

As can be seen from Formulae 9 and 10, these structures are related to the structures of their reaction products (i.e., Formulae 7 and 8) in the preservation of the 6-7 ring system, but differ from their reaction products in the presence of $R_{18}$, the inclusion of an X group, and the absence of the alkynyl linkage in the six-membered aromatic ring. However, in For-
formulae 9 and 10, all of the like numbered R groups are as described above with respect to Formulae 7 and 8.

In Formulae 9 and 10, each of R₁ through R₆ and R₁₀ through R₁₂ are as described above with respect to R₁ through R₁₀ (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from R₁ through R₆, R₁₀ through R₁₆, R₁₇, and R₁₈ may optionally combine to form a carbon to carbon double bond in the respective six-membered ring or seven-membered ring. Also, R₂₁ and R₂₂ may each be independently selected from the substituents discussed above for R₁ through R₁₀. In some embodiments, however, R₂₁ and R₂₂ may be hydrogen.

Further, R₂₃ is an oxygen containing functional group. For example, R₂₃ may be a hydroxyl group. Also, X is a halogen, for example, Br, I, Cl or F. In some embodiments, for example, X is Br.

In some exemplary embodiments of the present invention, in Formulae 9 and 10, each of R₁ through R₆, and R₁₀ through R₁₂ is independently selected from hydrogen, carbonyl groups and alkyl groups, R₂₃ is an oxygen containing functional group, and X is a halogen. In some exemplary embodiments, each of R₁ through R₆, and R₁₀ through R₁₂ is selected from hydrogen, aldehyde carbonyl groups and methyl groups, R₂₃ is an oxygen containing functional group, and X is a halogen. For example, in some embodiments, each of R₁ through R₆, R₁₀ through R₁₆, R₁₇ through R₂₁, and R₂₂ is hydrogen, each of R₁₁, R₁₈, R₁₉, R₂₀, and R₂₁ is an alkyl group, R₂₃ is an oxygen containing functional group, and X is a halogen. In some embodiments, for example, each of R₁ through R₆, R₁₀ through R₁₆, R₁₇ through R₂₁, and R₂₂ is hydrogen, each of R₁₁, R₁₈, R₁₉, R₂₀, and R₂₁ is a methyl group, R₂₃ is a hydroxyl group, and X is a halogen (e.g., Br). This configuration yields the (+)-enantiomer of Formula 9A below and the (−)-enantiomer of Formula 10A below. However, it is understood that although this configuration is depicted as having each of R₁ through R₆ and R₁₀ through R₁₆, R₁₇ through R₂₁, and R₂₂ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulae 9 and 10.

As can be seen from Formulae 11 and 12, these structures are related to the structures of their reaction products (i.e., Formulae 9 and 10) in the preservation of the 6-7 ring system, but differ from their reaction products in the presence of a carbonyl group on each of the seven-membered rings at the R₂₃ positions, and the absence of the R₂₁ and R₂₂ groups. However, in Formulae 11 and 12, all of the like numbered R groups are as described above with respect to Formulae 9 and 10.

In Formula 11 and 12, each of R₁ through R₆ and R₁₀ through R₁₂ are as described above with respect to R₁ through R₁₀ (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from R₁ through R₆, R₁₀ through R₁₆, and R₂₁ may optionally combine to form a carbon to carbon double bond in the respective six-membered ring or seven-membered ring. Also, R₂₁ may each be independently selected from the substituents discussed above for R₁ through R₁₀. In some embodiments, however, R₂₁ may be hydrogen.

Also, X is a halogen, for example, Br, I, Cl or F. In some embodiments, for example, X is Br.

Additionally, although not depicted in Formulae 11 and 12, the bonds connecting the seven membered rings to the six membered aromatic rings can have any suitable stereochemistry. For example, the stereochemistry of that bond may be either that depicted in the following Formulae 11A and 12A or that depicted in the following Formulae 11B and 12B.

According to another embodiment of the present invention, (+) and (−) precursors to the enantiomers of Formulae 9, 10, 9A and 10A are represented by Formulae 11 and 12 below.
Similarly, although not depicted in Formulæ 11 and 12, the bond connecting the $R_i$ and $R_{i+1}$ groups to the seven-membered rings can have any suitable stereochemistry. In some embodiments, for example, the stereochemistry of that bond is that depicted in the following Formulæ 11C and 12C.

In some exemplary embodiments of the present invention, in Formulæ 11 and 12, each of $R_i$ through $R_{15}$ and $R_8$ through $R_{21}$ is independently selected from hydrogen, carbonyl groups and alkyl groups, and $X$ is a halogen. In some exemplary embodiments, each of $R_i$ through $R_{15}$ and $R_8$ through $R_{25}$ is selected from hydrogen, aldehyde carbonyl groups and methyl groups, and $X$ is a halogen. For example, in some embodiments, each of $R_2$ through $R_4$, $R_{10}$ through $R_{15}$, $R_{17}$, $R_{18}$, and $R_{23}$ is hydrogen, each of $R_1$, $R_9$, $R_{16}$, $R_{19}$, and $R_{20}$ is an alkyl group, and $X$ is a halogen. In some embodiments, for example, each of $R_2$ through $R_4$, $R_{10}$ through $R_{15}$, $R_{17}$, $R_{18}$, and $R_{23}$ is hydrogen, each of $R_1$, $R_9$, $R_{16}$, $R_{19}$, and $R_{20}$ is a methyl group, and $X$ is a halogen (e.g., $Br$). This configuration yields the (+)-enantiomer of Formula 11D below and the (−)-enantiomer of Formula 12D below. However, although the stereochemistry of the bonds connecting the seven-membered rings to the six-membered aromatic rings, and the bonds connecting the $R_i$ groups to the seven-membered rings are not shown in the below Formulæ 11D and 12D, it is understood that these bonds can have any suitable stereochemistry, as discussed above. It is understood that although this configuration is depicted as having each of $R_2$ through $R_4$ and $R_{10}$ through $R_{15}$, $R_{17}$, $R_{18}$, and $R_{23}$ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulæ 9 and 10.
According to other embodiments of the present invention, (+) and (−) precursors (Formulae 13 and 14 below) to the enantiomers of Formula 11 and 12 have the structures of Formulae 11 and 12 in which the \( R_5 \) and \( R_6 \) functional groups (or hydrogen atoms) combine to form carbon to carbon double bonds in the seven-membered rings. In Formulae 13 and 14, all of the like numbered \( R \) groups are as described above with respect to Formulae 11 and 12.

In Formulae 13 and 14, each of \( R_{17}, R_{18}, R_5 \) and \( R_6 \) through \( R_{21} \) are as described above with respect to \( R_1 \) through \( R_{22} \).

(i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from \( R_6 \) through \( R_{16} \) and \( R_{21} \) may optionally combine to form a carbon to carbon double bond in the respective six-membered rings or seven-membered rings. Also, \( R_{21} \) may be selected from the substituents discussed above for \( R_1 \) through \( R_{22} \). In some embodiments, however, \( R_{21} \) may be hydrogen.

Also, \( X \) is a halogen, for example, \( \text{Br} \), \( I \), \( \text{Cl} \) or \( F \). In some embodiments, for example, \( X \) is \( \text{Br} \).

In some exemplary embodiments of the present invention, in Formulae 13 and 14, each of \( R_5, R_6, R_7 \), and \( R_7 \), \( R_8 \) through \( R_{21} \) is independently selected from hydrogen, carbonyl groups and alkyl groups, and \( X \) is a halogen. In some exemplary embodiments, each of \( R_5, R_6, R_7 \) and \( R_8 \) through \( R_{21} \) is selected from hydrogen, aldehyde carbonyl groups and methyl groups, and \( X \) is a halogen. For example, in some embodiments, each of \( R_5, R_6, R_7, R_{10} \) through \( R_{15}, R_{17}, R_{18}, \) and \( R_{21} \) is hydrogen, each of \( R_6, R_8, R_{10}, R_{12}, \) and \( R_{20} \) is an alkyl group, and \( X \) is a halogen. In some embodiments, for example, each of \( R_5, R_6, R_8, R_{10} \) through \( R_{15}, R_{17}, R_{18}, \) and \( R_{21} \) is hydrogen, each of \( R_6, R_8, R_{10}, R_{12}, \) and \( R_{20} \) is a methyl group, and \( X \) is a halogen (e.g., \( \text{Br} \)). This configuration yields the (+)-enantiomer of Formula 13A below and the (−)-enantiomer of Formula 14A below. It is understood that although this configuration is depicted as having each of \( R_5, R_6, R_7, R_{10} \) through \( R_{15}, R_{17}, R_{18}, \) and \( R_{21} \) as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulae 11 and 12.
In Formula 15 and 16, each of R₈ through R₂₁ are as described above with respect to R₁ through R₁₂ (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from R₈ through R₁₀ and R₂₁ may optionally combine to form a carbon to carbon double bond in the respective six-membered rings or five-membered rings. Also, R₂₄, R₂₅, and R₂₆ may be selected from the substituents discussed above for R₁ through R₂₂. In some embodiments, however, R₂₄, R₂₅, and R₂₆ may be hydrogen.

Also, X’ is either hydrogen or a halogen, for example, Br, I, Cl or F. In some embodiments, for example, X’ is Br. In other embodiments, however, X’ is hydrogen.

In some exemplary embodiments of the present invention, in Formulae 15 and 16, each of R₈ through R₂₁ and R₂₄ through R₂₆ is independently selected from hydrogen, carbonyl groups and alkyl groups, and X’ is hydrogen or a halogen. In some exemplary embodiments, each of R₈ through R₂₁ and R₂₄ through R₂₆ is selected from hydrogen, aldehyde carbonyl groups and methyl groups, and X’ is hydrogen or a halogen. For example, in some embodiments, each of R₁₀ through R₁₅, R₁₇, R₁₈, R₂₁, and R₂₄ through R₂₆ is hydrogen, each of R₉, R₆, R₁₀, and R₂₀, is an alkyl group, and X’ is hydrogen or a halogen. In some embodiments, for example, each of R₁₀ through R₁₅, R₁₇, R₁₈, R₂₁, and R₂₄ through R₂₆ is hydrogen, each of R₉, R₆, R₁₀, and R₂₀, is a methyl group, and X’ is a halogen (e.g., Br). This configuration yields the (+)-enantiomer of Formula 15A below and the (−)-enantiomer of Formula 16B below. Again, it is understood that although this configuration is depicted as having each of X’, R₁₀ through R₁₅, R₁₇, R₁₈, R₂₁, and R₂₄ through R₂₆, as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional precursors to the (+)-enantiomer and the (−)-enantiomer of Formulae 13 and 14.

According to other embodiments of the present invention, (+) and (−) precursors to the enantiomers of Formulae 15 and
In Formulae 17 and 18 below, these structures are precursors to the three ring systems depicted in the previously described Formulae. In Formulae 17 and 18, all of the like numbered R groups are as described above with respect to Formulae 15 and 16.

In Formula 17 and 18, each of R7 through R17, R22, and R24 are as described above with respect to R1 through R22 in Formulae 1-16 (i.e., like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from R7 through R16, R21, R22, R24, R27, and R28 may optionally combine to form a carbon to carbon double bond in the respective six-membered rings or five-membered rings, and/or may optionally combine to form a cyclic or aromatic ring. In particular, in some embodiments, R7 and R27 may optionally combine to form a cyclobutane ring which may be saturated or unsaturated (e.g., monounsaturated as shown in Formulae 17A and 18A below). Also, R23, R27, and R28 may be selected from the substituents discussed above for R1 through R22. In some embodiments, however, R24, and R29 may be hydrogen, and R20, may combine with R2 to form either a carbon to carbon double bond in the five membered ring (e.g., as shown in Formulae 17B and 18B below) or a cyclic or aromatic ring (e.g., a monounsaturated cyclobutane moiety as shown in Formulae 17A and 18A below).

In Formulae 17A and 18A, each of R29 and R30 may be selected from the substituents discussed above for R1 through R22 as well as trialkylsilyl groups. However, in some embodiments, each of R29 and R30 may be selected from hydrogen and trialkylsilyl groups. For example, each of R29 and R30 may be selected from hydrogen and trimethylsilyl groups.

In some exemplary embodiments of the present invention, in Formulae 17, 18, 17A, 17B, 18, 18A and 18B, each of R7 through R16, R21, R24, R27, and R28 is independently selected from hydrogen, carbonyl groups and alkyl groups, and each of R29 and R30 (when present) may be selected from hydrogen and trialkylsilyl groups. In some embodiments, however, R24 and R29 may be hydrogen, R2 may combine with R7 to form either a carbon to carbon double bond in the five membered ring (e.g., as shown in Formulae 17B and 18B above) or a cyclic or aromatic ring (e.g., a monounsaturated cyclobutane moiety as shown in Formulae 17A and 18A above), and each of R29 and R30 (when present) may be selected from hydrogen and trialkylsilyl groups. Also, in some exemplary embodiments, each of R7 through R16, R21, R24, R27, and R28 may be selected from hydrogen, aldehyde carbonyl groups and methyl groups. R27 may combine with R2 to form either a carbon to carbon double bond in the five membered ring or a cyclic or aromatic ring, and each of R29 and R30 (when present) may be selected from hydrogen and trialkylsilyl groups. For example, in some embodiments, each of R10 through R16, R21, R24, and R29 is hydrogen, each of R8, R9, and R19 is an alkyl group, R7 and R27 combine together to form either carbon to carbon double bond in the five membered ring structure or a cyclic or aromatic ring, and each of R29 and R30 (when present) may be selected from hydrogen and trialkylsilyl groups.

In some embodiments, for example, each of R7 through R15, R21, R24, and R29 is hydrogen, each of R8, R9, and R15 is a methyl group, R7 and R27, combine together to form either a carbon to carbon double bond in the five membered ring structure or a monounsaturated cyclobutane moiety, and each of R29 and R30 (when present) may be selected from hydrogen and trimethylsilyl groups. The configuration in which R7 and R27 combine together to form a carbon to carbon double bond in the five membered ring yields the (+)-enantiomer of Formula 17C below and the (−)-enantiomer of Formula 18C below. The configuration in which R7 and R27 combine together to form a monounsaturated cyclobutane moiety in which one of R29 and R30 is a trimethylsilyl group yields the (+)-enantiomer of Formula 17D below and the (−)-enantiomer of Formula 18D below. The configuration in which R7 and R27 combine together to form
a monounsaturated cyclobutane moiety in each of \( R_{23} \) and \( R_{30} \) is hydrogen yields the (+)-enantiomer of Formula 17E below and the (-)-enantiomer of Formula 18E below. It is understood that although these configurations are depicted as having each of \( R_{10} \) through \( R_{15} \), \( R_{21} \), \( R_{28} \), and \( R_{34} \) as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional precursors to the (+)-enantiomer and the (-)-enantiomer of Formulae 15 and 16.

According to other embodiments of the present invention, derivatives of the compounds represented by Formulae 13 and 14 include compounds represented by Formulae 19 and 20, and Formulae 21 and 22, below. These derivatives were serendipitously obtained, as they were unexpectedly produced as a byproduct of the reaction leading to the formation the compounds of Formulae 13 and 14. Although the \( R \) groups in Formulae 19, 20, 21 and 22 are somewhat differently labelled (i.e., they are labelled in 100 series numerals rather than 10 series numerals), \( R \) groups in Formulae 19-22 having 100 series numerals corresponding to the 10 series numerals listed in the above Formulae 1-18, also have the same definitions. For example, \( R_{104} \) in Formulae 19-22 corresponds to \( R_{8} \) in the above Formulae 1-18.

In Formulae 19-22, each of \( R_{101} \) and \( R_{104} \) through \( R_{121} \) are as described above with respect to \( R_{8} \) through \( R_{15} \) in Formulae 1-18 (i.e. like reference numerals designate like moieties and/or functional groups throughout). Additionally, any two adjacent groups selected from \( R_{8} \) through \( R_{15} \) and \( R_{21} \) may optionally combine to form a carbon to carbon double bond in the respective rings. Also, \( R_{104} \) through \( R_{108} \) may be selected from the substituents discussed above for \( R_{8} \) through \( R_{15} \), or may be selected from trialkysilane groups and hydrogen. For example, \( R_{133} \) through \( R_{134} \) may be selected from hydrogen and trimethylsilyl groups. In some embodiments, however, \( R_{131} \) through \( R_{134} \) may be hydrogen.

In some exemplary embodiments of the present invention, in Formulae 19-22, each of \( R_{1} \), and \( R_{4} \) through \( R_{21} \) is inde-
In some embodiments, for example, each of R₁, R₄ through R₆, R₁₀ through R₁₅, R₁₇, R₁₈ and R₂₁ is hydrogen, each of R₉, R₁₁, R₁₆, R₁₉ and R₂₀ is a methyl group, and each of R₁₃ through R₁₄ (when present) may be selected from hydrogen and trimethylsilyl groups. These configurations of Formulae 19-22, in which each of R₁₂₃ through R₁₂₄ (when present) is hydrogen yield the (+)-enantiomers of Formulae 19A, 20A, 21A and 22A below and the (−)-enantiomers of Formulae 19B, 20B, 21B and 22B below. It is understood that although these configurations are depicted as having each of R₁, R₄ through R₆, R₁₀ through R₁₅, R₁₇, R₁₈ and R₂₁ as hydrogen, any or all of these hydrogen atoms could be substituted with the substituents described above, yielding additional derivatives of the (+)-enantiomer and the (−)-enantiomer of Formulae 13 and 14.

Some embodiments of the present invention are directed to methods of enantioselectively synthesizing the enantiomeric compositions described above. These methods are initially understood by devising a retrosynthetic pathway from the ultimate end-product, the enantioselctive composition of liphagal (i.e., a non-racemic mixture of the two enantiomers of liphagal). Such a retrosynthetic pathway is illustrated in the following retrosynthetic Reaction Scheme 1.

**Reaction Scheme 1 - retrosynthetic from (+)-liphagal**

1. **Furan Formation**
2. **Olefin Reduction**
3. **Ring Expansion**
4. **Formylation**
5. **Demethylation**

**Formulas:**
- **Formula 19A**
- **Formula 20A**
- **Formula 21A**
In Scheme 1, looking at a single enantiomer of liphagal (e.g., the (+) enantiomer, represented by Formula 1A above and designated Compound 1 in the above Reaction Scheme 1), a first step in the retrosynthetic method is the simplification of the six-membered aromatic ring of liphagal to dimethoxybenzofuran (designated Compound 2 in the above retrosynthetic Reaction Scheme 1). The product designated Compound 2 is a known precursor to the natural liphagal product. Next in the retrosynthetic scheme is the disconnection of the tetracycle along the benzofuran moiety, which leads back to α-bromoaryl diene (designated Compound 3 in the retrosynthetic Reaction Scheme 1).

Reduction of the sterically hindered tri-substituted olefin to establish the trans ring fusion is a major challenge. The α-bromoaryl diene (Compound 3) could arise from a ring expansion of strained cyclobutene (designated Compound 4 in the retrosynthetic Scheme 1). Excision of the cyclobutene and α-aryl group from the ketone (i.e., Compound 4) reveals chiral cyclopentenone (designated Compound (R)-5, where R designates the enantiomer of Compound 5) in the retrosynthetic Scheme 1. The S enantiomer of Compound 5 (i.e., the enantiomeric enone (S)-5)) has been previously prepared from achiral enol carbonate (designated Compound 6 in the retrosynthetic Scheme 1). However, a synthesis of the R enantiomer, as depicted in Reaction Scheme 1, has not been reported. Palladium-catalyzed enantioselective decarboxylative allylation reactions that employ the t-Bu-PHOS ligand scaffold in conjunction with allyl enol-carbonates, silyl enol-ethers, and racemic β-ketoesters have been used to produce a wide array of α-quaternary substituted ketones. With the strategy developed from this retrosynthetic analysis, a total, enantioselective synthesis of (+) or (−)-liphagal could be created.

Working backwards from the retrosynthetic analysis, in an embodiment of the present invention, as shown in the following Reaction Scheme 2, the forward synthesis of the liphagal enantiomers commences with a palladium-catalyzed decarboxylative allylation of enol carbonate (designated compound 6 in Reaction Scheme 2) to furnish a tetrasubstituted ketone (designated compound 7 in Reaction Scheme 2) in 87% yield and 92% enantiomeric excess. As used herein, as discussed above, "enantiomeric excess" (or "ee") is defined as |F(+)−F(−)| or |F(−)−F(+)| for compositions including more of the (+) enantiomer) for a mixture of (+) and (−) enantiomers, with the composition given as the mole or weight fractions F(+) and F(−), such that F(+)−F(−)−1. When given as a percentage, enantiomeric excess is defined by 100*(F(+)−F(−)) or 100*(F(−)−F(+)). This intermediate was elaborated to the bicyclic compound 5 following the two-step sequence reported in McFadden, et al., "The Catalytic Enantioselective, Protecting Group-Free Total Synthesis of (+)-Dichromone," J. Am. Chem. Soc., vol. 128, pgs. 7738-7739 (2006), the entire content of which is incorporated herein by reference. The synthesis continues with exposure of the enone designated Compound 5 to trimethylsilylacetylene under UV irradiation, which promotes a [2+2] photocycloaddition. Exposure of the crude reaction mixture to BF₃:OEt₂ forms a single silylated cyclobutene product (designated Compound 8a). Subsequent removal of the trimethylsilyl group with TBAF yields the chromatographically stable and pleasantly fragrant cyclobutene designated Compound 8b, which is a compound that contains three contiguous quaternary centers within the strained carbon framework. A microwave-assisted palladium-catalyzed α-arylation with 4-bromoveratrole installs the electron rich aromatic moiety, producing the aryl ketone designated Compound 4 as a single diastereomer.
Upon synthesizing Compound 4 (from Reaction Scheme 2), Lewis acid-mediated ring expansion by selective cleavage of the strained cyclobutane (Compound 4) can be attempted by exposure of the tricyclic ketone (Compound 4) to BF$_3$·OEt$_2$ at 50°C. However, as shown in Reaction Scheme 3 below, this process provides the desired cycloheptadienone product (Compound 9) in modest yield. Serendipitously, it was found that this compound can be isolated alongside a crystalline byproduct (i.e., Compound 10), which is suitable for X-ray diffraction analysis and structure determination. Bridged polycyclic ketone (Compound 10) is presumably the result of a Cargill rearrangement, which proceeds through two concerted [1,2]-carbon-carbon bond migrations. More specifically, activation of the ketone (Compound 4) with BF$_3$ (yielding Compound 11) promotes carbon bond migration to rupture the cyclobutene and produce an allylic carbocation intermediate (Compound 12). The second carbon bond migration forms a [2.2.1] bridged bicyclic core of a Lewis acid complex (Compound 13). Finally, loss of BF$_3$ reveals the isolated product (Compound 10). Importantly, the stereospecific rearrangement mechanism allows assignment of the relative stereochemistry of cyclobutenes (Compound 8 in Reaction Scheme 2) from the unequivocal assignment of the bridged bicyclic (Compound 10 in Reaction Scheme 3).

In addition to BF$_3$·OEt$_2$, it was discovered that AlCl$_3$ also promotes ring expansion of the aryl cyclobutene (Compound 4) without formation of the Cargill product (Compound 10). However, under these reaction conditions, a new side-product was surprisingly found, i.e., an enone (Compound) arising from an intramolecular 1,6-addition of the electron-rich arene fragment of Compound 9 to the cycloheptadienone system. This result suggests that the arene resides in close proximity to the tri-substituted olefin and also indicates that the aromatic moiety should be deactivated before ring expansion to avoid formation of Compound 14. However, while the formation of Compounds 10 and 14 may not be desirable in the total, enantioselective synthesis of a lipophilic enantiomer, these derivatives have structures similar to other precursors in the total synthesis, and therefore would be expected to have similar properties.
Next, as shown in Reaction Scheme 4 below, a functional group handle is installed on the aromatic ring. The functional group could be utilized for eventual benzoifuran formation and could serve to deactivate the aromatic residue of Compound 9 toward unwanted Friedel-Crafts chemistry. It was found that chemoselective aromatic bromination occurs in the presence of the strained cyclobutene, furnishing a bromoarene (Compound 15 shown in Reaction Scheme 4 below). At this stage, crystallization of the crude product increases the enantiomeric excess to >99%. With the deactivated aromatic ketone in hand, it was found that treatment of the bromide (Compound 15) with AlCl₃ furnishes much improved yields of the corresponding ring expanded product (Compound 3). An optimized ring expansion from the [6-5-4] system to the desired [6-7] core (Compound 3) can be accomplished in the absence of a Lewis acid with microwave heating at about 250°C in o-dichlorobenzene. Chemospecific reduction of the diene (Compound 3) with Adams’ catalyst in ethyl acetate furnishes a ketone (Compound 16), leaving the aromatic halide intact.

With the core carbon framework of liphagal (the (+)-enantiomer depicted as Compound 1) secured, the focus now turned to the challenging stereospecific hydrogenation of the tri-substituted olefin to establish the desired [6-7] trans ring fusion. The strategy to effect this transformation was guided by the previous isolation of the 1,6-addition product (Compound 14 in Reaction Scheme 3), which provided evidence that hydrogenation to form a trans ring fusion would be sterically demanding. To alleviate steric congestion, epimerization of the aryl substituent can be carried out, forming a β-oriented α-aryl ketone (Compound 17). The mass recovery for this equilibration averages 97% and a 78% overall yield of Compound 17 may be obtained after three cycles of equilibration (K_{eq}={\text{1.0}}). With the arene substituent further removed from the tri-substituted olefin, the plan was to rigidify the polycyclic system via formation of the fourth ring. This began with a diastereoselective methylation, affording the desired α-methyl cycloheptene (18) in 68% yield. Reduction of this hindered ketone with diisobutyl aluminum hydride (DIBAL) produced an alcohol (Compound 19), a substrate poised for dihydrobenzoifuran formation.

However, initial attempts to form dihydrobenzoifuran (Compound 21) were unsuccessful and prompted an unconventional strategy to accomplish the desired transformation. Formation of the dihydrobenzoifuran (Compound 21) may be accomplished upon exposure of the bromoarene (Compound 19) to lithium diisopropylamide (LDA), proceeding through a putative anion intermediate (Compound 20). This powerful anion capture cyclization strategy generates the highly congested dihydrobenzoifuran product in 83% yield. With the tetracycle (Compound 21) in hand, the key stereospecific hydrogenation of the tri-substituted olefin was tested. Using catalytic Pd/C in ethanol under 1 atm H₂, 97% yield of the saturated homodecalin (Compound 22) can be isolated, and exclusive formation of the [6-7] trans ring fusion is observed.

Having executed the synthesis of the challenging trans fused ring system, the completion of (+)-liphagal required three additional transformations: 1) benzoifuran construction, 2) aldehyde installation, and 3) demethylation, the final two of which are known from previous syntheses (e.g., in Marion, et al., "Liphalag, a Selective Inhibitor of P3 Kinase α Isolated from the Sponge Aka caralliphaga: Structure Elucidation and Biomimetic Synthesis," Org. Lett., vol. 8, no. 2, pgs. 321-324 (2006), and George, et al., "Enantiospecific, Biosynthetically Inspired Formal Total Synthesis of (+)-Liphagal," Org. Lett., vol. 12, no. 10, pgs. 2394-2397 (2010), the entire contents of which are incorporated herein by reference.

Oxidation of the dihydrobenzoifuran (Compound 22) to the benzoifuran (Compound 2) proved surprisingly difficult, and with 2,3-dichloro-5,6-dicyano-1,4-benzquinone (DDQ) a tendency for over-oxidation can be observed. Upon switching to nitrosamine to tetrifuoroaborate, which oxidizes by hydride abstraction, dehydrogenation occurs in 70% yield to give the benzoifuran of Compound 2. Aryl lithiation with n-butyllithiu-ium·TMEDA (tetramethylethylenediamine) and quenching with anhydrous dimethylformamide (DMF) installs the alde-}

hyde functional group in the compound designated Compound 23. Finally, this may be followed by demethylation using boron triiodide to generate (+)-liphagal (Compound 1), which is identical in all respects to data reported in the literature for the natural product.
Reaction Scheme 4 - Completion of the total synthesis of (+)-Liphagal

1. (+)-4 → (+)-15
   - 
   - MeO
   - OMe
   - Br
   - MeO
   - OMe
   - Br
   - MeO
   - OMe
   - Br
   - MeO
   - OMe

  - Reaction with Br₂ (1.8 equiv) in CHCl₃ (65% yield)
  - Recrystallized to > 99% ee

2. (+)-15 → (-)-3
   - μwave
   - o-dichlorobenzene, 250°C, 3h (69% yield)
   - PhO₂ (20 mol %)
   - H₂ (1 atm)
   - EtOAc (69% yield)

3. (+)-16 → (+)-17
   - NaOMe/MeOH
   - 65°C, 4 d (78% yield; three cycles)
   - LDA, THF
   - -78°C → 0°C, then Mel
   - -78°C → 0°C (68% yield)

4. (+)-17 → (+)-18
   - DIBAL
   - PhMe (91% yield)

5. (+)-19 → 20
   - LDA (0 equiv)
   - THF, -20°C
   - (83% yield)

6. (+)-21 → (+)-22
   - Pd/C (19 mol %)
   - H₂ (1 atm)
   - EtOH, 21°C (97% yield)
   - NO²Br⁻
   - MeCN, 0°C (70% yield)
The above described process represents the first catalytic enantioselective total synthesis of (+)-liphagal, and accomplishes this feat in 15 steps from known compounds (and 19 steps from commercially available materials). Applying a combination of catalytic enantioselective alkylation (Compound 6→Compound 7), two-carbon ring expansion via cyclobutene (Compound 15), and an intramolecular arylene cyclization (Compound 19→Compound 20→Compound 21) enables access to the tetra cyclic core of the natural product in enantiomerically enriched form. Judicious choice of the tetracyclic hydrogenation substrate (Compound 21) establishes the critical trans-[6-7] ring fusion and enables completion of the total synthesis.

Given the above discussion of the synthesis of the (+) liphagal enantiomer, those of ordinary skill in the art would readily recognize that a corresponding synthesis method could be used to synthesize the (-) liphagal enantiomer in a similar enantiomerically enriched form. Specifically, those of ordinary skill in the art would recognize that replacing the above disclosed reactants with their enantiomers would yield the (-) liphagal enantiomer in enantiomerically enriched form. For example, to make the (-) enantiomer, the starting reactants, i.e., Compounds 6 and 7 in Reaction Scheme 2 would be replaced with their enantiomers, which are represented by Compounds 6A and 7A, below. Also, the reactant used to effect transformation of Compound 6 to Compound 7 would be replaced with its enantiomer. The reactant depicted in Scheme 2 above is represented by Reactant A below, and the enantiomer of this reactant used in the production of the (-) liphagal enantiomer is depicted as Reactant A' below. The remaining compounds in Schemes 2 through 4 are similarly replaced with their enantiomers, which are described above in Formulae 1 through 22.
Although the above synthesis method is described as yielding the specific structure of the lphaal enantiomers, it is understood that similar methods can be used to prepare the derivatives and precursors (discussed above with respect to Formulae 1 through 22) to the lphaal enantiomers. In particular, according to certain embodiments of the present invention, a method of making an enantiomer represented by Formula 1 includes procedures analogous to those described above with respect to the production of (+) lphaal.

For example, in some embodiments of the present invention, a method of making an enantioselective composition includes enantioselective catalytic alkylation of a first precursor compound to form a second precursor compound; oxidation and condensation of the second precursor compound to form a third precursor compound; promotion of a photocycloadDITION reaction of the third precursor compound to form a fourth precursor compound; exposure of the fourth precursor compound to a Lewis acid to form a fifth precursor compound; arylation of the fifth precursor compound to form a sixth precursor compound; functionalization of an aromatic group on the sixth precursor compound to form a seventh precursor compound; ring expansion of the seventh precursor compound to form an eighth precursor compound; reduction of the eighth precursor compound to form a ninth precursor compound; reduction of steric congestion in the ninth precursor compound to form a tenth precursor compound; intramolecular aryne cyclization of the tenth precursor compound to form a thirteenth precursor compound; stereoselective hydrogenation (or substitution) of the thirteenth precursor compound to form a fourteenth precursor compound; and oxidation of the fourteenth precursor compound to form a fifteenth precursor compound.

The method may further include functionalization of the fifteenth precursor compound to form a compound of Formula 1, and/or deacetylation (or desubstitution) of the compound of Formula 1 (or the fifteenth precursor compound) to yield a different compound of Formula 1. For example, deacetylation (or desubstitution) of the fifteenth precursor compound could result in the formation of a compound of Formula 1 in which all of R₂ₐ, R₁ₙ, and R₂ₐₙ are hydrogen. Also, in some embodiments, the intramolecular aryne cyclization includes stereoselective substitution of the tenth precursor to form an eleventh precursor; reduction of the eleventh precursor to form a twelfth precursor; and exposure of the twelfth precursor to a strong base to form the thirteenth precursor. Additionally, reduction of the steric congestion may be accomplished by epimerization of an aryl substituent of the ninth precursor compound to form the tenth precursor compound. Also, as used herein, the term "strong base" is used in its art-recognized sense, and is not intended to be a term of degree. Some nonlimiting examples of some art-recognized strong bases include hydroxides of alkali and alkaline earth metals, as well as LDA.

In the method of making the enantiomer of Formula 1, according to an embodiment of the present invention, the first precursor compound may be an enol carbonate of Formula 100, below, and is subjected to palladium-catalyzed decarboxylative alkylation to yield the second precursor compound, which can be a tetrasubstituted ketone of Formula 110, below. In Formulae 100 and 110, all like numbered R groups are as described above with respect to R₁ through R₂₂₄, and R₂₀₁ through R₂₀₅ may include the substituents described above with respect to R₁ through R₂₂₄.

In the palladium-catalyzed decarboxylative alkylation, the compound of Formula 100 is reacted with Reactant A (above) (i.e., (R)-t-Bu-PHOX (4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-5-dihydro-(4S)-oxazole)) in the presence of a Pd₃(dba)₃ catalyst in t-butyl methyl ether at a temperature of about 25 to about 30° C., for example about 27° C. Synthesis of the S enantiomer of t-Bu-PHOX has been reported, e.g., in Krout, et al., "Preparation of (S)-tert-ButylPHOX," Org. Synth., vol. 86, pgs. 181-193 (2009), the entire content of which is incorporated herein by reference. Those of ordinary skill in the art would readily understand a method of making the (R) enantiomer from the description of the (S) enantiomer. Also, although Pd₃(dba)₃ and t-butyl methyl ether are disclosed here as the catalyst and solvent in this reaction, it is understood that any suitable palladium catalyst and solvent may be used. Reactant A is present in this reaction in an amount of about 5 to about 10 mol %, for example, about 6.1 mol %, and the palladium catalyst is present in this reaction in an amount of about 1 to about 5 mol %, for example about 2.5 mol %. The reaction yields the compound of Formula 110 in a yield of about 80 to about 90%, for example about 87%, and an enantiomeric excess of about 85 to about 95%, for example about 92%.

After forming the second precursor compound (e.g., the compound of Formula 110), that compound is subjected to the two-step reaction sequence (i.e., oxidation and condensation) reported in McFadden, et al., "The Catalytic Enantioselective, Protecting Group-Free Total Synthesis of (4R)-Dichlororotenin," J. Am. Chem. Soc., vol. 128, pgs. 7738-7739 (2006), the entire content of which is incorporated by reference. In particular, the second precursor compound (e.g., the compound of Formula 110) is first subjected to a Wacker oxidation using PdCl₂, Cu(OAc)₂, H₂O, dimethylacetamide (DMA) and O₂, and then to condensation using KOH in xylene. This procedure yields the third precursor compound, which can be the compound of Formula 17/8 discussed above (and reproduced below) in a yield of about 85 to about 95%, for example about 92%.
The fifth precursor compound (e.g., the compound of Formula 17A in which R₂₉ is hydrogen) is then subjected to a microwave-assisted palladium-catalyzed α-arylation with 4-bromoacetophenone and NaOT-Bu in THF. This procedure yields the sixth precursor compound, which may be an aryl ketone represented by Formula 15 (described above and reproduced below) in which X' is hydrogen in a yield of about 60% to about 75%, for example about 67%. Although this procedure is described as using 4-bromoacetophenone, it is understood that any suitable haloveratrole could be used, for example, iodoveratrole, fluoroacetophenone, chloroveratrole, etc. Also, although any suitable palladium catalyst can be used in this reaction, in some embodiments the palladium catalyst can be Pd[P(t-Bu)₃]₂. In such embodiments, the amount of the palladium catalyst may be about 3 to about 10 mol %, for example about 5 mol %. Also, although NaOT-Bu and THF are described in this reaction, it is understood that any suitable alternatives may also be used. Additionally, the reaction may be carried out at any suitable temperature, for example a temperature of about 100 to about 140°C, for example 120°C.

Next, a functional group handle is installed on the aromatic ring of the sixth precursor compound (e.g., the compound of Formula 15) to form the seventh precursor compound. Specifically, the sixth precursor compound (e.g., the compound of Formula 15 in which X' is hydrogen) is reacted with a halide (e.g., Br₂) in the presence of a solvent (e.g., trichloromethane). Surprisingly, under these conditions, chemoselective aromatic halogenation (e.g., bromination) occurs in the presence of the strained cyclobutene of Formula 15, yielding the seventh precursor compound, which may be a haloarene (e.g., a bromoarene) compound of Formula 15 in which X' is a halogen (e.g., Br) in a yield of about 60 to about 70%, for example about 65%. Recrystallization may also be performed in order to increase the enantiomeric excess. Indeed, recrystallization can increase the enantiomeric excess to greater than 99%. Also, the haloarene compound of Formula 15 in which X' is a halogen (e.g., Br) may be further treated with a Lewis acid, such as AlCl₃, which surprisingly improves the yield (in the next process of the method) of the ring expanded product, i.e., the eighth precursor compound which may be represented by Formula 13.

The seventh precursor compound, which may be the haloarene product of Formula 15 in which X' is a halogen (e.g., Br), is then subjected to ring expansion to form the eighth precursor compound. Specifically, expansion from the [6-5-4] system in Formula 15 to the [6-7] core in the compounds of Formula 13 is effected in the absence of a Lewis acid by using microwave heating at a temperature of about 200 to about 300°C, for example 250°C, in a solvent (e.g., o-dichlorobenzene). This reaction can be carried out for about...
2 to about 5 hours, for example about 3 hours, and produces the eighth precursor compound (which can be the ring expanded product of Formula 13) in a yield of about 65 to about 75%, for example about 68%.

Chemoselective reduction is then performed on the eighth precursor compound (which can be the compound of Formula 13) using a catalyst (e.g., Adam’s catalyst) in a solvent (e.g., ethyl acetate), producing the ninth precursor compound (which can be the compound of Formula 11B (reproduced below)) while leaving the aromatic halide intact. Specifically, the ninth precursor compound (e.g., the compound of Formula 13) is reduced using PtO₃ and H₂ in ethyl acetate. The PtO₃ may be present in this reaction in an amount of about 15 to about 25 mol %, for example about 20 mol %, and the H₂ may be at about 1 atm pressure. These conditions produce the ninth precursor compound (e.g., the compound of Formula 11B) in a yield of about 65 to about 75%.

Next, epimerization of the aryl substituent of the ninth precursor compound is performed to form the tenth precursor compound, which can be a β-oriented α-aryl ketone represented by Formula 11A (reproduced below). Specifically, the epimerization may be carried out in NaOMe/MeOH at a temperature of about 60 to about 70°C, for example 65°C, for about 3 to about 5 days, for example about 4 days. The mass recovery for this equilibration may average about 95 to about 99%, for example about 97%. An overall yield of the tenth precursor compound (e.g., the compound of Formula 11A) of about 75 to about 85% may be achieved after about three cycles of equilibration (K_eq(avg)=0.76).

Diastereoselective methylation is performed on the tenth precursor compound (e.g., the compound of Formula 11A) to yield the eleventh precursor compound (e.g., an α-substituted cycloheptanone of Formula 11C) in a yield of about 65 to about 75%, for example about 68%. Specifically, the tenth precursor compound (e.g., the compound of Formula 11A) is first treated with lithium diisopropylamide in tetrahydrofuran at a temperature of about −75 to about −85°C, e.g., about −78°C, and is then reacted with a haloide substituent (e.g., an allyl iodide, such as iodomethane) at a similar temperature, i.e., about −75 to about −85°C, e.g., about −78°C, to complete the substitution (e.g., alkylation or methylation).

Although not depicted in Formula 11C, it is understood that, according to this description, the stereochemistry of the bond between the seven-membered ring and the six-membered aromatic ring is the same as that depicted in FIG. 11A.

The eleventh precursor compound (e.g., the hindered ketone of Formula 11C) is then reduced to produce the twelfth precursor compound (e.g., the alcohol represented by Formula 9), which is a substrate poised for dihydrobenzofuran formation. This reduction reaction is carried out using DIBAL (diisobutyl aluminum hydride) in a solvent (e.g., toluene (abbreviated PhMe in the reaction schemes)), and produces the twelfth precursor compound (e.g., the alcohol of Formula 9) in a yield of about 85 to about 95%, for example about 91%.
The twelfth precursor compound (e.g., the bromoarene compound of Formula 9) is then exposed to a base, such as lithium diisopropylamide (LDA), leading to the formation of the thirteenth precursor compound, which can be the dihydrobenzofuran compound represented by Formula 5. Specifically, the twelfth precursor compound (e.g., the compound of Formula 9) is exposed to the base (e.g., LDA) in the presence of a solvent (e.g., THF), and the reaction may be carried out at a temperature of about -15 to about -25°C, for example, -20°C. This reaction may proceed through a putative aryne intermediate represented by Formula 7. Also, this reaction produces the thirteenth precursor compound (e.g., the highly congested dihydrobenzofuran product of Formula 5) in a yield of about 80 to about 90%, for example, about 83%.

Next, the fourteenth precursor compound (e.g., the saturated homodecalin compound of Formula 3) may be oxidized to form the benzofuran compound represented by Formula 1 in which R₁₉ and R₂₀ are each an alkyl group (e.g., a methyl group), and R₄₄ is hydrogen. The oxidation may be carried out using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), however, this may lead to over-oxidation. Therefore, according to another embodiment, the oxidation may be carried out using nitrosium tetrafluoroborate, which oxidizes via hydride abstraction. Using nitrosium tetrafluoroborate, dehydrogenation to produce the benzofuran compound of Formula 1 (in which R₁₉ and R₂₀ are each an alkyl group (e.g., a methyl group), and R₄₄ is hydrogen) may occur in a yield of about 65 to about 75%, for example about 70%. Also, this reaction may occur in the presence of any suitable solvent (e.g., acetonitrile, designated MeCN in the schemes above), and may be performed at any suitable temperature, such as a temperature of about -10 to about 10°C, for example about 0°C.

The thirteenth precursor compound (e.g., the compound of Formula 5) may then be stereoselectively hydrogenated (or substituted) to form the fourteenth precursor compound, which may be the homodecalin product represented by Formula 3. To effect stereoselective hydrogenation, the thirteenth precursor compound (e.g., the compound of Formula 5) may be subjected to a catalyst in a solvent under about 1 atm H₂. In some embodiments, the catalyst is Pd/C and the solvent is ethanol, but the present invention is not limited thereto, and any suitable alternative catalyst and/or solvent may also be used. Additionally, the amount of the catalyst is not particularly limited, but in some embodiments, the amount of the catalyst may be about 15 to about 25 mol %, for example, about 20 mol %. Also, this reaction can be carried out at any suitable temperature, for example a temperature of about 15 to about 25°C. In some embodiments, for example, the reaction temperature may be about 21°C. This reaction can produce the fourteenth precursor compound (e.g., the saturated homodecalin compound of Formula 3) in a yield of about 90 to about 100%, for example about 97%.

As would be understood by those of ordinary skill in the art, stereoselective installation of a substituent other than hydrogen could be accomplished by a number of processes, which would depend on the substituent to be installed. However, in some embodiments, stereoselective installation of a substituent other than hydrogen can be accomplished using standard diastereoselective olefin mono or difunctionalization methods, for example, dihydroxylation, epoxidation, hydroamination, carboamination, Diels-Alder reactions, etc.
A functional group may then be installed at the R₁₉ position in the compound of Formula 1 (in which R₂₀ and R₂₁ are each an alkyl group (e.g., a methyl group), and R₁₈ is hydrogen). Specifically, an aldehyde functional group may be installed through aryl lithiation followed by quenching. The aryl lithiation may be accomplished with n-butyllithium.TMEDA, and the quenching may be accomplished with anhydrous DMF (dimethylformamide). In particular, the aryl lithiation reaction may involve reaction with the n-butyllithium.TMEDA in a solvent (e.g., THF) at a temperature of about -10°C to about 10°C, for example about 0°C. The quenching reaction may be performed using anhydrous DMF, and the quenching may be conducted by ramping the temperature from about 0°C to about room temperature, e.g., from about 0°C to about 21°C, and the reaction may take about 30 minutes to about 1.5 hours, for example about 1 hour. This aldehyde installation procedure is discussed in George, et al., "Enantioselective, Biosynthetically Inspired Formal Total Synthesis of (R)-Liphatol," Org. Lett., vol. 12, no. 10, pgs. 2394-2397 (2010), the entire content of which has been previously incorporated herein by reference. This reaction yields the compound of Formula 1 in which R₁₉ and R₂₀ are each an alkyl group (e.g., a methyl group), and R₁₈ is an aldehyde carbonyl group, and the yield of the reaction is about 65 to about 75%, for example about 70%.

Finally, the compound of Formula 1 (in which R₁₉ and R₂₀ are each an alkyl group (e.g., a methyl group), and R₁₈ is an aldehyde carbonyl group) may be demethylated to produce the compound of Formula 1 in which R₁₉ and R₂₀ are each hydrogen, and R₁₈ is an aldehyde carbonyl group (i.e., derivatives of liphatol). Demethylation may be accomplished with a boron trihalide (e.g., boron triiodide) and the reaction is carried out in a suitable solvent (e.g., dichloromethane). This reaction is discussed in Marion, et al., "Liphatol, a Selective Inhibitor of PI3 Kinase from Isolated from the sponge Akaoralliphasa: Structure Elucidation and Biomimetic Synthesis," Org. Lett., vol. 8, no. 2, pgs. 321-324 (2006), the entire content of which has been previously incorporated herein by reference. This reaction produces the compound of Formula 1 (in which R₁₉ and R₂₀ are each hydrogen and R₁₈ is an aldehyde carbonyl group) in a yield of about 40 to about 50%, for example about 45%.

According to other embodiments of the present invention, methods of making the compounds of Formula 19-22 discussed above generally follow the same procedures as the methods described above to make the compounds of Formulae 1 through 18. However, to make the compounds of Formulae 19-22, the method deviates from the above described method after the microwave-assisted palladium-catalyzed α-arylation of the compound of Formula 17A in which R₂₀ is hydrogen. Specifically, to make a compound represented by Formula 19, a Lewis-acid mediated ring expansion is performed through selective cleavage of the strained cyclobutene of the compound of Formula 17A in which R₂₀ is hydrogen.

Specifically, the tricyclic ketone of Formula 17A in which R₂₀ is hydrogen is exposed to BF₃·OEt₂ in a solvent (e.g., dichloromethane) at a temperature of about 40 to about 60°C, for example about 50°C, yielding the compound of Formula 15 in a yield of about 40 to about 50%, but also yielding the compound of Formula 19 in a yield of about 3 to about 10%. The bridged polycyclic ketone of Formula 19 is presumably the result of a Cargill rearrangement, which proceeds through two concerted [1,2]-carbon-carbon bond migrations (as shown in Reaction Scheme 3 depicted and discussed above). More specifically, activation of the ketone of Formula 17A in which R₂₀ is hydrogen with BF₃ (i.e., as shown in Compound 11 in Reaction Scheme 3 above) promotes bond migration to rupture the cyclobutene and produce an allylic carbocation intermediate (i.e., Compound 12 in Reaction Scheme 3 above). The second carbon bond migration forms a [2,2.1] bridged bicyclic core of a Lewis acid complex (i.e., Compound 13 in Reaction Scheme 3 above). Finally, loss of BF₃ reveals the isolated derivative product of Formula 19. Importantly, the stereospecific rearrangement mechanism allowed assignment of the relative stereochemistry of the cyclobutenes of Formula 17A from the unequivocal assignment of the bridged bicycle of Formula 19.

In the above method of making the compounds of Formula 19, replacing the BF₃ with AlCl₃ also promotes ring expansion of the aryl cyclobutene of Formula 17A, but does not result in the Cargill rearrangement product of Formula 19. Instead, using from 3 to 10 equivalents, for example 5 equivalents, of AlCl₃ in a solvent (e.g., dichloromethane) at a temperature of about 20 to about 30°C, yielded an enone represented by Formula 21 (discussed above and reproduced below). This enone arises from the intramolecular 1,6-addition of the electron-rich arene fragment of the compound represented by Formula 13 (described and depicted above) to the cycloheptadiene system. This suggests that the arene resides in close proximity to the tri-substituted olefin.

Although the above methods are described in connection with the synthesis of a single enantiomer of the desired prod-
ucts, those of ordinary skill in the art would readily recognize the corresponding methods needed to create the opposite enantiomer. Specifically, as discussed above, the same basic methods may be used to make the opposite enantiomers, except that the reactants used would be their opposite enantiomer. For example, to produce an end-product of the opposite enantiomer, the enantiomer of Formula 14 may be used in the methods instead of the enantiomer of Formula 15, etc. This applies to all enantiomers discussed above.

EXAMPLES

The below Examples are presented for illustrative purposes only, and do not limit the scope of the present invention.

Materials and Methods.

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF was distilled over sodium/benzophenone or dried by passage through an activated alumina column under argon prior to use. Methanol was distilled over Mg(OH)₂, prior to use. Other solvents were dried by passage through an activated alumina column under argon. Disopropylamine and triethylamine were distilled over CaH₂ prior to use. Iodomethane was distilled prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Phosphinooxazoline (PHOX) ligands were prepared by the methods described in Krout, et al., “Preparation of (S)-tert-ButylPHOX,” Org. Synth., vol. 86, pgs. 181-193 (2009). All other reagents were purchased from Sigma-Aldrich, Acros Organics, Stem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKA Mag nitrogen modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Analytical LC/MS was performed on an Agilent 6140 single quadrupole LC/MS and a Waters 1290 Infinity UHPLC system. Glove box manipulations were performed under a N₂ atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, p-anisaldehyde, or KMnO₄ staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Automated flash column chromatography was performed on a Teledyne Isco CombiFlash RF system. ¹H NMR spectra were recorded on a Varian Mercury 300 MHz, Varian Inova 500 MHz, or Varian Inova 600 MHz spectrometer and are reported relative to residual CHCl₃ (δ 7.26 ppm) or CD₃OD (δ 7.16 ppm). ¹³C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (at 75 MHz and 125 MHz respectively) and are reported relative to CDCl₃ (δ 77.2 ppm) or CD₃OD (δ 128.4 ppm). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration. Multiplicities are reported as follows: s=singlet, d=doublet, t=triplet, q=quartet, sext=sextet, dd=doublet of doublets, ddd=doublet of doublet of doublets, ddddd=doublet of doublet of doublet of doublets, m=multiplet.

Data for ¹³C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as: [α]D 25° (concentration in g/100 ml, solvent, ee). Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel AD column (4.6 mm×25 cm) obtained from DriCel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral SFC was performed with a Mettler Toledo SFC supercritical CO₂ analytical chromatography system with a Chiralcel AD-H column (4.6 mm×25 cm) with visualization at 244 nm/235 nm. High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+ or FAB+ or on a Agilent 6200 Series TOF with an Agilent G1978A Multi-Mode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed (MM: ESI-APCI+) ionization mode.

Experimental Procedures and Spectroscopic Data.

** Allyl Ketone (+)-7.**

In the glovebox, an oven dried recovery flask was charged with Pd₂(dba)₃ (25.8 mg, 0.0281 mmol), followed by (R)-t-Bu-PHIOX (26.8 mg, 0.0691 mmol). Anhydrous t-butyl methyl ether (37 mL) was added and the solution stirred for 30 min. After this time, enol carbonate 6 (254.1 mg, 1.13 mmol) was added via pipette as a solution in t-butyl methyl ether (−2 mL). The flask was sealed with a yellow WW series Caplug® and stirred at 27°C for 15 h. The reaction was removed from the glovebox and vacuum filtered through silica gel. The majority of t-butyl methyl ether was removed by distillation under nitrogen and the remaining material purified by flash column chromatography on silica gel (2% EtO/pentane) providing allyl ketone (+)-7 (177.8 mg, 87% yield) as a colorless oil in 92% ee as determined by chiral HPLC of enone (+)-5 (vide infra). [α]D 25° (+)-7 (c 1.005, CHCl₃), 92% ee. Other characterization data for this compound matched what has been previously reported.²

2
Diketone (+)-S-1.
A Parr flask was charged with PdCl₂ (7.0 mg, 0.0394 mmol) and Cu(OAc)₂ (38.6 mg, 0.229 mmol), followed by H₂O (0.25 mL). A solution of allyl ketone (+)-S-3 (152.1 mg, 0.843 mmol) in DMA (1.75 mL) was introduced. The reaction was cooled to -78 °C, then evacuated/bubbled (vacuum/O₂) (3×). The reaction was warmed to 22 °C and placed on a Parr Shaker under 1 atm of O₂ for 25 h. At this time additional PdCl₂ (10.3 mg, 0.059 mmol) was added and the reaction restarted on the Parr Shaker under 1 atm of O₂. After 60 h the reaction was directly loaded onto a column of silica gel and purified by flash column chromatography (20:80 Et₂O:pentane eluent) giving diketone (+)-S-1 (105.5 mg, 63% yield) as determined by chiral HPLC of enone (+)-5 (vide infra). [α]D²⁵⁻⁰⁻⁷².⁹ (c 1.05, CHCl₃), 92% ee. Other characterization data for this compound matched what has been previously reported. See McFadden, et al., “The Catalytic Enantioselective Protecting Group-Free Total Synthesis of (+)-Dichromanone,” J. Am. Chem. Soc., vol. 128, pgs. 7738-7739 (2006), the entire content of which has already been incorporated herein by reference.

Silylcyclobutene (+)-S-2.
Enone (+)-S-2 (506.7 mg, 2.84 mmol) was distributed into five quartz test tubes and dissolved in anhydrous acetonitrile (5 mL each) and spectrophotometric grade acetone (1 mL each). To each test tube was added Trimethylsilyl acetylene (2.5 mL, 17.56 mmol) and then capped with a yellow WW Series Caplugs®. The test tubes were inverted (3×) to ensure adequate mixing of the reagents. At this time the reactions were placed in a Luzchem photoreactor and irradiated with ten UVB lamps (~313 nm) for a total of 22.5 h. The test tubes were removed from the photoreactor and the contents concentrated in vacuo. Due to the instability of one isomeric product the crude reaction mixture was immediately advanced to the next step.

The crude reaction mixture was dissolved in anhydrous CH₂Cl₂ and stirred while BF₃·OEt₂ (0.050 mL, 0.405 mmol) was added dropwise. The contents of the reaction were aged for 30 min and then treated with Celite® (5 g). The reaction was vacuum filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (2:98 EtOAc:hexane) providing silylcyclobutene (+)-S-2 (577.4 mg, 73% yield; two stages) as a white waxy solid. Rf = 0.68 (20% EtOAc:hexanes), 1H NMR (CDCl₃, 500 MHz, 7.26 ppm for CHCl₃ in CDCl₃): δ = 8.61 (d, J = 14 Hz, 1H), 3.05 (m, 1H), 2.96 (d, J = 16.2 Hz, 1H), 1.65-1.52 (m, 2H), 1.43-1.35 (m, 3H), 1.32-1.10 (m, 5H), 1.02 (s, 3H), 1.05 (s, 3H), 0.40 (s, 9H); 13C NMR (CDCl₃, 125 MHz, 7.72 ppm for CDCl₃): δ = 216.6, 157.1, 153.3, 64.7, 59.2, 52.1, 38.7, 36.7, 36.3, 33.4, 28.1, 24.9, 22.0, 18.4, -2.1; IR (NaCl, cm⁻¹): ν = 2996, 2956, 2927, 2871, 2845, 1732, 1561, 1456, 1413, 1388, 1378, 1249, 1225, 1213, 1161, 962, 907, 840, 753; HRMS (MM: ESL-APCI+): m/z: C₅3H₂₅O₃Si[M+H]+: calc'd 277.1982, found 277.1989; [α]D²⁵⁺⁺⁷⁷.⁷⁶⁷⁸ (c = 3.39, CHCl₃), 91% ee.

Cyclobutene (+)-S-8.
To a solution of silylcyclobutene (+)-S-2 (253.0 mg, 0.915 mmol) in anhydrous THF was added 1.0 M TBAF in THF (2 mL, 2.0 mmol) under a N₂ atmosphere. The colorless solution
immediately turned reddish-brown. The reaction was stirred and heated to 40°C in an oil bath. Following completion of the reaction, as monitored by TLC, it was concentrated in vacuo and loaded directly onto silica gel with CH₂Cl₂ for flash column chromatography (5:95 EtOAc:hexanes) to afford cyclobutene (−)-8 (176.6 mg, 94% yield) as a white waxy volatile solid. R<sub>f</sub>=0.39 (10% EtOAc/hexane), sublimation point: sp. <23°C. (3 mmHg); <sup>1</sup>H NMR (CDCl₃, 500 MHz): δ=6.37 (m, 1H), 6.32 (m, 1H), 3.06-3.02 (m, 2H), 1.47-1.36 (m, 3H), 1.30 (m, 1H), 1.21-1.12 (m, 2H), 0.95 (s, 3H), 0.94 (s, 3H), 13C NMR (CDCl₃, 125 MHz): δ=77.2 ppm for CDCl₃; δ=216.2, 143.0, 137.8, 65.2, 58.4, 51.9, 38.8, 37.1, 36.1, 33.5, 28.2, 25.1, 22.1, 18.4; IR (NaCl, cm⁻¹): v=3046, 2957, 2924, 2870, 2844, 1733, 1456, 1414, 1388, 1378, 1364, 1212, 1161, 725; HRMS (ESI-APCI<sup>+</sup>) m/z: C<sub>13</sub>H<sub>10</sub>O(M+H)<sup>+</sup> calc’d 205.1587. found 205.1591; [α]<sub>D</sub> = 642.438° (c=1.065, CHCl₃), 91% ee.

Arylcyclobutene (−)-4.

In the glovebox, a 5 mL oven-dried microwave vial was charged with Pd[P(t-Bu)<sub>3</sub>Cl] (1.43 mg, 0.02798 mmol, 5 mol %) and NaOt-Bu (65.6 mg, 0.6826 mmol). A stir bar was added to the vial before it was sealed and removed from the glovebox. A solution of cyclobutene (−)-8 (110.0 mg, 0.5588 mmol) in anhydrous THF was added to the vial under N₂, followed by 4-bromovinyl are (0.085 mL, 0.5908 mmol). The reaction was placed in the microwave reactor and heated to 120°C. For a total of 7.5 h. The reaction was quenched with sat. aq NH₄Cl (0.50 mL) and treated with activated charcoal (0.022 mg) and Celite® (0.310 mg). The heterogeneous mixture was stirred overnight and then vacuum filtered. The residue was purified by flash column chromatography on silica gel (95:5 EtOAc:hexanes) to provide arylycyclobutene (−)-4 (124.0 mg, 67% yield) as a white amorphous solid. R<sub>f</sub>=0.28 (20:80 EtOAc:hexane); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>D<sub>2</sub>SO): δ=6.80 (d, J=2.2 Hz, 1H), 6.74 (dd, J=8.3 Hz, 2.2 Hz, 1H), 6.68 (d, J=2.9 Hz, 0.9 Hz, 1H), 6.05 (app. dd, J=2.9 Hz, 1.5 Hz, 1H), 4.35 (s, 1H), 3.54 (s, 3H), 3.46 (s, 3H), 3.12 (app. dd, J=1.5 Hz, 0.9 Hz, 1H), 1.37-1.18 (m, 3H), 1.09 (app. ddd, J=13.7 Hz, 3.7 Hz, 3.4 Hz, 1H), 1.08-1.02 (m, 1H), 1.07 (app. ddd, J=12.9 Hz, 3.7 Hz, 3.2 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 13C NMR (125 MHz, CD<sub>2</sub>D<sub>2</sub>SO): δ=212.8, 149.93, 149.92, 142.6, 140.4, 126.9, 125.1, 117.1, 112.3, 63.1, 60.7, 57.1, 56.3, 56.0, 40.5, 39.3, 34.0, 33.6, 28.7, 25.9, 20.7, 18.6; IR (NaCl, cm⁻¹): v=2930, 2871, 2842, 1732, 1608, 1588, 1517, 1464, 1253, 1146, 1030, 739; HRMS (ESI<sup>+</sup>) m/z: C<sub>22</sub>H₂₂O₂[M]<sup>+</sup> calc’d 340.2039. found 340.2040; [α]<sub>D</sub> = 512.59° (c=1.015, CHCl₃), 91% ee.

Arylcycloheptadienone (−)-9 and Cargill Rearrangement Adduct (−)-10.

A Schlenk flask was charged with a solution of arylcyclobutene (−)-4 (563 mg, 1.65 mmol) and CH₂Cl₂ (52 mL), BF₃·OEt₂ (1.05 mL, 8.27 mmol) was then introduced. The vessel was sealed and heated with stirring to 50°C behind a blast shield for 20 h. The reaction was cooled to 23°C and added slowly to a suspension of brine (25 mL), sat. aq NaHCO₃ (25 mL), and CH₂Cl₂ (25 mL). After addition was complete, the reaction was stirred vigorously for 5 min. The organic layer was collected, and the aqueous layer was extracted with CH₂Cl₂ (2×30 mL). All organic layers were combined, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane=20:80 EtOAc:hexane=30:70 EtOAc:hexane=40:60 EtOAc:hexane eluent), affording arylcycloheptadienone (−)-9 (242 mg, 43% yield) as a yellow oil. R<sub>f</sub> 0.61 (50:50 EtOAc:hexane); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>D<sub>2</sub>SO): δ= 7.01 (app. d, J=2.0 Hz, 1H), 6.95 (app. dd, J=8.3 Hz, 2.0 Hz, 1H), 6.53 (d, J=8.3 Hz, 1H), 6.17 (d, J=6.8 Hz, 1H), 6.16 (d, J=2.0 Hz, 1H), 5.91 (dd, J=6.8 Hz, 2.0 Hz, 1H), 3.55 (s, 1H), 3.48 (s, 3H), 3.38 (s, 3H), 1.82 (app. td, J=15.2 Hz, 7.2 Hz, 1H),
In addition to (±)-9, several fractions containing a second compound in semipurified form were collected from the flash column above. These fractions were combined and concentrated. The residue was purified by flash column chromatography on silica gel (50:50 CH$_2$Cl$_2$:Petroleum Ether) to afford the pure Cargill rearrangement adduct (±)-10 (28.1 mg, 5.0% yield) as colorless crystals. One of these crystals was suitable for X-ray analysis, allowing for determination of the relative stereochemistry of the compound. R$_f$ 0.74 (50:50 EtOAc:hexane); mp 116-118°C. (C$_5$D$_5$)$_2$; $^1$H NMR (500 MHz, C$_5$D$_5$)$_2$; δ 6.79 (app. d, J=8.3 Hz, 1H), 6.78 (app. s, 1H), 6.57 (app. d, J=8.3 Hz, 1H), 6.32 (app. dd, J=7.1 Hz, 3.9 Hz, 1H), 6.20 (app. dd, J=6.7 Hz, 1.2 Hz, 1H), 3.54 (s, 3H), 3.44 (s, 3H), 2.83 (app. dd, J=3.9 Hz, 0.7 Hz, 1H), 2.23 (s, 2H), 2.04 (app. td, J=13.4 Hz, 3.9 Hz, 1H), 1.47 (app. qt, J=13.7 Hz, J=3.2 Hz, 1H), 1.35 (app. d, J=14.2 Hz, 1H), 1.32-1.13 (m, 2H), 1.28 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.74 (app. d, J=13.9 Hz, 1H); $^{13}$C NMR (125 MHz, C$_5$D$_5$)$_2$; δ 206.5, 150.2, 149.4, 134.6, 134.4, 134.1, 121.0, 113.2, 112.5, 64.0, 56.1, 56.0, 53.4, 40.2, 37.1, 34.3, 32.5, 32.4, 28.1, 26.9, 26.6, 19.6; IR (NaCl, cm$^{-1}$); v=2995, 2934, 2867, 2834, 1772, 1518, 1464, 1267, 1254, 1241, 1147, 1030, 750; HRMS (EI$^+$) m/z: C$_{22}$H$_{22}$O$_3$[M$^+$]$^+$: calc’d 340.2039, found 340.2034.

Friedel-Crafts Adduct (±)-14.
A solution of aryl cyclobutene (±)-4 (50 mg, 0.147 mmol, 1.0 equiv) in CHCl$_3$ (15.0 mL) was treated with AlCl$_3$ (98.0 mg, 0.735 mmol, 5.0 equiv, weighed in the glovebox). As the reaction stirred for 48 h, it went from peach-colored to maroon. After the reaction was complete, it was added dropwise to a solution of brine (20 mL) and sat. aq NaHCO$_3$ (20 mL) at 23°C. The suspension was then extracted with CHCl$_3$ (2x20 mL). All organic layers were combined, dried (Na$_2$SO$_4$), filtered, and concentrated to ~500 µL total volume. The brown oil was purified by preparative TLC (20:80 EtOAc:hexane eluent), affording the Friedel-Crafts adduct (±)-14 (8.3 mg, 17% yield) as a yellow powder. R$_f$ 0.24 (20:80 EtOAc:hexane); mp 152-155°C. (CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.09 (s, 1H), 6.64 (s, 1H), 6.04 (app. dd, J=12.6 Hz, 5.5 Hz, 3.6 Hz, 1H), 5.66 (app. dd, broad, J=12.6 Hz, 1.9 Hz, 3.6 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.35 (app. dd, broad, J=1.6 Hz, 1Hz, 1H), 2.84 (app. d, broad, J=1.9 Hz, 1H), 2.84 (app. dd, J=9.0 Hz, 1.6 Hz, 1H), 1.72-1.58 (m, 1H), 1.54-1.26 (m, 4H), 1.43 (s, 3H), 1.26 (s, 3H), 1.24-1.00 (m, 1H), 1.19 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$); δ 148.8, 148.4, 142.9, 139.5, 135.5, 128.7, 110.2, 107.6, 73.1, 57.5, 56.3, 55.9, 46.4, 40.8, 39.9, 38.9, 37.5, 29.6, 26.9, 20.7, 18.4; IR (NaCl, cm$^{-1}$); v=2932, 1659, 1605, 1504, 1464, 1402, 1295, 1206, 1096, 1036, 914, 857, 755; HRMS (EI$^+$) m/z: C$_{22}$H$_{24}$O$_3$[M$^+$]$^+$: calc’d 340.2039, found 340.2039. $^1$H-nOesy-1D spectra were obtained for (±)-14 (300 MHz, CDCl$_3$); the results are shown below:

10% Pd/C/H$_2$ (1 atm)
EtOH, 23°C. Parr Shaker (77% yield)
shaker for 40 h. At this time, more 10% w/v Pd/C (114 mg, 0.106 mmol, 15 mol %) was carefully added. The reaction was continued under H₂ (now 3 atm) for 20 h. Once the reaction was complete, it was filtered through celite over glass frits with the aide of EtOAc. The filtrate was concentrated and purified by flash chromatography on silica gel (hexane→20:80 EtOAc/hexane eluent), giving γδ-unsaturated aryl cycloheptanone (+)-S-3 (188 mg, 77% yield) as a colorless oil. Rf 0.31 (20:80 EtOAc/hexane); 1H NMR (300 MHz, CDCl₃): δ 7.17 (app. dd, J=2.1 Hz, 1H), 7.09 (app. dd, J=8.2 Hz, 2.1 Hz, 1H), 6.59 (app. d, J=8.2 Hz, 11H), 5.77 (app. dd, J=8.2 Hz, 5.2 Hz, 2 Hz, 11H), 3.85 (s, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.60 (app. dd, J=13.8 Hz, 7.4 Hz, 1H), 2.30-1.86 (m, 5H), 1.60-1.42 (m, 1H), 1.36-1.20 (m, 1H), 1.27 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H), 0.98-0.68 (m, 1H); 13C NMR (75 MHz, CDCl₃): δ 210.0, 153.5, 150.1, 149.7, 130.5, 123.5, 123.5, 115.3, 112.3, 71.8, 56.2, 55.9, 42.0, 41.0, 40.2, 37.8 (C2), 33.8, 33.7, 28.4, 23.7, 18.6; IR (NaCl, cm⁻¹): ν=2933, 1695, 1603, 1588, 1515, 1464, 1379, 1252, 1146, 1029, 756; HRMS (EI⁺) m/z: C₂₃H₂₃O₃Br[M⁺]⁺: calc’d 420.1123, found 420.1119; [α]₂₀ D+519.57° (c 2.16, CHCl₃), >99% ee.

Bromoaryl dienone (+)-3.
A round bottom flask was charged with bromoaryl cyclobutene (+)-15 (214.5 mg, 0.512 mmol) and dissolved in o-dichlorobenzene (o-PhCl₂) (15 mL) with the aide of mild heating from a heat gun. The clear and colorless solution was distributed between two 20 mL microwave vials. The round bottom flask was rinsed with o-PhCl₂ (15 mL×2, 9 mL×1) and again distributed between the three microwave vials (total=18 mL each). The solutions were sealed, placed under Ar, and degassed by the method of freeze-pump-thaw (3×). At this time, the microwave vials were individually irradiated (3 h) in a microwave reactor at 250°C. Following irradiation the clear yellow-orange solutions were combined and loaded directly onto silica gel for purification by flash column chromatography (10:90→20:80→30:70 EtOAc/hexanes) yielding bromoaryl dienone (+)-3 (147.0 mg, 68% yield) as a yellow solid, in addition to recovered bromoaryl cyclobutene (+)-15 (26.0 mg, 12% yield) as a white solid. Rf 0.28 (20:80 EtOAc/hexane); mp 146-147°C. (EtOAc/hexane)(racemate), mp 144-147°C. (EtOAc/hexane)(95% ee); 1H NMR (300 MHz, CDCl₃): δ 7.21 (s, 1H), 7.03 (s, 1H), 6.70 (dd, J=12.4 Hz, 8.8 Hz, 1H), 6.30 (d, J=8.8 Hz, 1H), 6.08 (d, J=12.4 Hz, 1H), 4.16 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 1.35 (s, 3H), 1.55 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H); 1H NMR (75 MHz, CDCl₃): δ 188.7, 168.4, 148.4, 148.0, 137.6, 129.5, 128.1, 120.4, 118.0, 115.8, 112.4, 66.3, 56.1, 55.8, 42.8, 38.4, 37.9, 35.4, 33.5, 31.5, 25.3, 17.0; IR (NaCl, cm⁻¹): ν=2934, 1644, 1572, 1509, 1463, 1440, 1377, 1267, 1248, 1230, 1159, 1090, 837; HRMS (EI⁺) m/z C₂₃H₂₂O₂Br[M⁺]⁺: calc’d 418.1144, found 418.1156; [α]₂₀ D+437.31° (c 0.985, CHCl₃), 95% ee.
Bromoaryl\(\alpha,\beta,\gamma\)-Unsaturated Cycloheptanone (+)-16.

A round-bottom flask containing bromoaryl dieneone (–)-3 (400 mg, 0.952 mmol) in EtOAc (ACS grade, 50 mL) was degassed with argon for 5 min. Then, PO\(_4\) (43.2 mg, 0.190 mmol, 20 mol %) was carefully added. The reaction was cooled to –78°C, then evacuated/backfilled (vacuum/H\(_2\) (1 atm)) (3×). With vigorous stirring, the reaction was warmed to 23°C under H\(_2\) (1 atm). After 30 min, the reaction was concentrated, and the residue was taken up in PhH. It was purified by flash chromatography on silica gel (10:90 EtOAc:hexane eluent), giving bromoaryl\(\gamma,\delta\)-unsaturated cycloheptanone (+)-16 (277 mg, 69% yield) as a white solid. R\(_f\)=0.41 (20:80 EtOAc/hexane); mp 114-116°C (EtOAc/hexane/racemate, mp 121-123°C (EtOAc/hexane) (95% ee); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.58 (s, 1H), 7.02 (s, 1H), 6.00 (dd, J=9.9 Hz, 4.4 Hz, 1H), 4.68 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.71-2.49 (m, 2H), 2.43-2.32 (m, 2H), 1.79-1.57 (m, 2H), 1.51-1.39 (m, 2H), 1.36-1.24 (m, 2H), 1.28 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H); \(^1^C\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 210.0, 153.8, 148.6, 147.8, 128.2, 122.7, 118.4, 115.6, 115.0, 66.0, 56.7, 56.2, 43.9, 41.5, 39.7, 37.8, 36.4, 33.7, 33.3, 27.5, 23.4, 17.9; IR (NaCl, cm\(^{-1}\)): \(\nu\) = 2936, 2845, 1716, 1609, 1600, 1567, 1506, 1463, 1440, 1374, 1254, 1212, 1159, 1039, 732; HRMS (FAB\(^+\)) \(m/z\): C\(_{22}\)H\(_{18}\)BrO\(_4\) [M+H]\(^+\) calc'd 420.1300, found 420.1303; [\(\alpha\)]\(_D\)\(^{25}\) +162.47° (c 1.250, CHCl\(_3\)), 95% ee.

\[\text{NaOMe/MeOH} \rightarrow \] 65°C, 4d, glovebox (78% yield after three cycles of equilibration)

\(+\)-16

\[i. \text{LDA, THF, } -78 \rightarrow 0^\circ\text{C; ii. MeI, } -78 \rightarrow 0^\circ\text{C; (68% yield)} \]

\(+\)-17

\(\beta\)-Bromoaryl Ketone (+)-17.

In a glovebox\(^4\), a 20 mL oven-dried scintillation vial was charged with a solution of bromoaryl\(\gamma,\delta\)-unsaturated cycloheptanone (+)-16 (138.1 mg, 0.327 mmol) in MeOH (1 mL) and 1M NaOMe (5 mL, 5 mmol) in MeOH. The reaction mixture was heated to 65°C in the glovebox with stirring for 86 h. The reaction was removed from the glovebox and quenched with AcOH (0.30 mL) under vigorous stirring. The mixture was diluted with H\(_2\)O (3.0 mL) and the volatiles concentrated in vacuo. Brine (3.0 mL) was added and the aqueous phase extracted with EtOAc (4×3 mL). The organic layers were combined, dried (MgSO\(_4\)), vacuum filtered, and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Si, 5 μm, 9.4×250 mm, 89:2 EtOAc:hexanes, 7 mL/min, monitored at 254 nm) affording bromoaryl\(\gamma,\delta\)-unsaturated cycloheptanone (+)-16 (73.4 mg, 53% yield) as a white solid and \(\beta\)-bromoaryl ketone (+)-17 (61.6 mg, 44% yield) as a colorless oil. Retention times: bromoaryl\(\gamma,\delta\)-unsaturated cycloheptanone (+)-16 7.5 min, \(\beta\)-bromoaryl ketone (+)-17 8.8 min. This procedure was repeated twice more with the recovered bromoaryl\(\gamma,\delta\)-unsaturated cycloheptanone (+)-16 to yield \(\beta\)-bromoaryl ketone (+)-17 (109.0 mg, 78% yield after three cycles of equilibration) as a colorless oil. R\(_f\)=0.33 (20:80 EtOAc:hexanes); \(^1^H\) NMR (CDCl\(_3\), 300 MHz, 7.26 ppm for CHCl\(_3\) in CDCl\(_3\)): \(\delta\) = 7.20 (s, 1H), 6.99 (s, 1H), 5.97 (dd, J=3.4 Hz, 3.4 Hz, 1H), 5.28 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.77 (m, 1H), 2.66-2.51 (m, 2H), 2.33 (m, 1H), 1.67-1.19 (m, 11H), 1.15 (s, 3H), 0.92 (m, 1H); \(^1^C\) NMR (CDCl\(_3\), 75 MHz, 77.2 ppm for CDCl\(_3\)): \(\delta\) = 211.1, 155.7, 148.4, 147.5, 128.8, 121.9, 117.4, 115.3, 114.9, 62.3, 56.2, 56.1, 43.5, 43.1, 39.7, 38.2, 37.7, 33.9, 32.2, 24.8, 24.6, 18.2; IR (NaCl, cm\(^{-1}\)): \(\nu\) = 2933, 1706, 1602, 1570, 1506, 1466, 1439, 1375, 1308, 1266, 1209, 1160, 1029; HRMS (MM: ESI-APCI\(^+\)) \(m/z\): C\(_{22}\)H\(_{18}\)BrO\(_4\) [M+H]\(^+\) calc'd 421.1373; found 421.1356; [\(\alpha\)]\(_D\)\(^{25}\) =–212.15° (c=0.74, CHCl\(_3\)), >99% ee.
Bromoaryl Methyl Ketone (−)-18.

To a solution of freshly distilled i-Pr₂NH (0.025 mL, 0.1768 mmol) in anhydrous THF (0.20 mL) cooled to −78 °C, was added 2.3 M n-BuLi (0.062 mL, 0.1439 mmol) dropwise via syringe. The contents were stirred for 30 min at −78 °C, before addition of β-bromoaryl ketone (−)-17 (57.8 mg, 0.1371 mmol) as a solution in anhydrous THF (1 mL). The pear-shaped flask containing β-bromoaryl ketone (−)-17 was rinsed with THF (0.20 mL) and added to the reaction mixture at −78 °C. The stirred solution was aged for 30 min at −78 °C, followed by 30 min in an ice-water bath. The reaction mixture was cooled to −78 °C and Mel (0.025 mL, 0.4015 mmol) was added dropwise. The reaction stirred for 15 min at −78 °C, followed by 15 min in an ice-water bath. The reaction was allowed to warm to 23 °C and additional Mel (0.050 mL, 0.8030 mmol) was added. Stirring continued for 30 min before quenching with H₂O (5 drops). The volatiles were removed in vacuo and the residue dissolved in EtOAc and diluted with Brine. The organic layer was collected and the aqueous layer extracted with EtOAc (3×2 mL). All organic layers were combined, dried (Na₂SO₄), vacuum filtered, and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Sil, 5 µm, 9.4×250 mm, 8:92 EtOAc/Hexanes, 7 mL/min, monitored at 254 nm) affording bromoaryl methyl ketone (−)-18 (40.6 mg, 68% yield) as a colorless oil and β-bromoaryl ketone (−)-17 (10.6 mg, 18% yield) as a colorless oil. Retention times: bromoaryl methyl ketone (−)-18 5.45 min, β-bromoaryl ketone (−)-17 7.7 min. Rₜ=0.45 (20:80 EtOAc:Hexanes); ¹H NMR (CDCl₃, 300 MHz, 7.26 ppm for CHCl₃): δ=7.22 (s, 1H), 6.99 (s, 1H), 5.93 (dd, J₁=2.4 Hz, J₂=8.7 Hz, 1H), 5.35 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.79-2.48 (m, 2H), 2.29 (m, 1H), 1.72-1.35 (m, 4H), 1.33 (s, 3H), 1.26 (m, 1H), 1.19 (s, 3H), 1.17-1.10 (m, 6H), 0.96 (s, 3H), 1.3C NMR (CDCl₃, 75 MHz, 77.2 ppm for CDCl₃): δ=213.3, 155.6, 148.5, 147.7, 129.2, 121.4, 117.5, 115.5, 115.0, 61.3, 56.3, 56.2, 47.2, 43.4, 40.0, 38.2, 38.1, 34.0, 33.5, 32.0, 24.7, 18.4, 17.7; IR (NaCl, cm⁻¹): ν=2952, 2868, 2843, 2706, 1602, 1503, 1462, 1441, 1377, 1308, 1262, 1207, 1162, 1032, 845, 795, 734; HRMS (ESI-APCI⁺): m/z: C₂₅H₂₅O₂Br[M+H]⁺; calc'd 435.1529, found 435.1526; [α]D²⁵(calc)=−190.14° (c=0.815, CHCl₃), >99% ee.

Aryl alcohol (−)-19.

To a solution of bromoaryl methyl ketone (−)-18 (40.6 mg, 0.0932 mmol) in anhydrous PhMe was added a freshly prepared 1M solution of DIBAL-H (0.380 mL, 0.380 mmol) in PhMe at 21 °C. The reaction aged for 30 min before it was quenched with sat. Na₂SO₄, Celite® (2:1) and stirred for an additional 30 min. The heterogeneous mixture was filtered and concentrated in vacuo. The residue was purified by HPLC (Zorbax Rx-Sil, 5 µm, 9.4×250 mm, 25:75 EtOAc:Hexanes, 7 mL/min, monitored at 254 nm) affording aryl alcohol (−)-19 (37.3 mg, 91% yield) as a colorless oil. Rₜ=0.28 (20:80 EtOAc:Hexanes); ¹H NMR (CDCl₃, 500 MHz, 7.26 ppm for CHCl₃ in CDCl₃): δ=7.36 (s, 1H), 7.03 (s, 1H), 5.76 (dd, J₁=2.9 Hz, J₂=8.7 Hz, 1H), 3.95 (d, J=3.5 Hz, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.41 (dd, J₁=3.9 Hz, J₂=4.6 Hz, J₃=8.7 Hz, 1H), 2.32-2.06 (m, 3H), 1.72 (d, J=4.9 Hz, 1H), 1.69 (s, 3H), 1.68-1.60 (m, 1H), 1.44 (m, 1H), 1.37-1.19 (m, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.05 (d, J=6.4 Hz, 3H), 0.92 (dd, J₁=4.5 Hz, J₂=13.0 Hz, J₃=13.0 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz, 77.2 ppm for CDCl₃): δ=156.1, 147.9, 147.6, 134.5, 122.2, 116.9, 115.5, 114.5, 81.6, 56.2, 56.2, 54.6, 42.9, 40.0, 39.9, 39.8, 37.9, 34.0, 33.8, 32.4, 24.6, 20.7, 18.0; IR (NaCl, cm⁻¹): ν=3543, 2953, 2928, 2868, 2839, 1602, 1570, 1503, 1464, 1439, 1385, 1357, 1293, 1261, 1246, 1207, 1157, 1034, 757; HRMS (El⁺) m/z: C₂₅H₂₅O₂Br[M⁺]: calc'd 436.1613, found 436.1600; [α]D²⁵(calc)=+82.61° (c=0.145, CHCl₃), >99% ee.
Dimethoxy dihydrobenzofuran (−21).

Preparation of LDA: To a solution of freshly distilled i-Pr₂NH (0.55 mL, 3.89 mmol) in anhydrous THF (3.4 mL) cooled to −78°C, was added −2.2 M n-BuLi (1.60 mL, 3.52 mmol) dropwise via syringe. The contents were stirred for 30 min at −78°C before use. This solution was titrated according to the method of Chong⁵ and found to be 0.52 M.

A solution of aryl alcohol (+)-19 (36.7 mg, 0.0839 mmol) in anhydrous THF (2.8 mL) was stirred and cooled to −20°C. This colorless solution was added freshly prepared LDA dropwise via syringe. Following completion of the reaction (20 min, monitored by TLC) it was quenched with H₂O (one drop) at −20°C and allowed to warm to 22°C. The crude reaction was filtered through Celite®, concentrated in vacuo, and purified by flash column chromatography on silica gel (10:90 to 20:80 EtOAc/hexanes) yielding dimethoxy dihydrobenzofuran (−21) (25.0 mg, 83% yield) as a white solid. Rₜ=0.56 (20:80 EtOAc/hexanes); ¹H NMR (CDCl₃, 300 MHz, 7.26 ppm for CH₃Cl in CDCl₃): δ = 6.82 (s, 1H), 6.48 (s, 1H), 5.76 (dd, J₁ = 2.2 Hz, J₂ = 8.5 Hz, 1H), 4.18 (dd, J₁ = 7.1 Hz, J₂ = 10.8 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 3.09 (d, J₁ = 7.1 Hz, 1H), 2.61 (m, 1H), 2.20-1.90 (m, 2H), 1.74-1.56 (m, 2H), 1.53-1.43 (m, 2H), 1.52 (m, 2H), 1.12 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H), 1.09 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz, 77.2 ppm for CH₃Cl in CDCl₃): δ = 155.2, 149.9, 142.2, 119.5, 114.1, 95.7, 94.7, 59.9, 57.7, 57.5, 56.1, 43.2, 40.9, 40.7, 37.7, 35.0, 34.1, 34.1, 28.1, 23.1, 22.2, 18.3, 16.3; IR (NaCl, cm⁻¹): ν = 2949, 2928, 2868, 2845, 1618, 1496, 1464, 1453, 1389, 1340, 1224, 1193, 1167, 1121, 1099, 987; HRMS (FAB+) m/z: C₂₃H₂₃O₃[M⁺]: calc'd 356.2352, found 356.2359; [α]₅₀° = +99.55° (c=1.25, CHCl₃), >99% ee.

trans-Fused Dihydrobenzofuran (−22).

To an oven-dried 25 mL Schlenk flask was added dimethoxy dihydrobenzofuran (−21) (24.9 mg, 0.0698 mmol) as a solution in EtOH (7 mL). The flask was evacuated and backfilled with N₂ (3x) before addition of Pd/C (14.4 mg, 0.01535 mmol, 10 wt%, 19 mol%). The rubber septum was replaced under a positive N₂ flow by a three-way Teflon stopcock connected to a H₂ balloon. The heterogeneous mixture was cooled to −78°C before it was evacuated and backfilled with H₂ (3x). The −78°C cold bath was removed and the reaction was allowed to warm to 21°C. After stirring for 12 h the contents of the flask were filtered, concentrated in vacuo, and purified by flash column chromatography on silica gel (10:90 EtOAc/hexanes) affording trans-fused dihydrobenzofuran (−22) (24.3 mg, 97% yield) as a white solid. Rₜ=0.53 (10:90 EtOAc/hexanes); ¹H NMR (CDCl₃, 500 MHz, 7.26 ppm for CH₃Cl in CDCl₃): δ = 6.82 (s, 1H), 6.44 (s, 1H), 4.15 (dd, J₁ = 7.7 Hz, J₂ = 10.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.79 (d, J = 7.6 Hz, 1H), 2.25 (m, 1H), 2.02 (m, 1H), 1.66 (m, 2H), 1.55 (m, 1H), 1.39 (m, 3H), 1.29-1.16 (m, 3H), 1.14 (d, J = 6.5 Hz, 3H), 1.00 (dd, J₁ = 2.4 Hz, J₂ = 12.1 Hz, 1H), 0.94 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz, 77.2 ppm for CH₃Cl in CDCl₃): δ = 155.2, 149.9, 142.2, 119.5, 114.1, 95.7, 94.7, 59.9, 57.7, 57.5, 56.1, 43.2, 40.9, 40.7, 37.7, 35.0, 34.1, 34.1, 28.1, 23.1, 22.2, 18.3, 16.3; IR (NaCl, cm⁻¹): ν = 2949, 2928, 2868, 2845, 1618, 1496, 1464, 1453, 1389, 1340, 1224, 1193, 1167, 1121, 1099, 987; HRMS (FAB+) m/z: C₂₃H₂₃O₃[M⁺]: calc'd 356.2352, found 356.2359; [α]₅₀° = +40.47° (c=1.03, CHCl₃), >99% ee.
Dimethoxybenzofuran (+)-23.

To a solution of trans-fused dihydrobenzofuran (+)-22 (5.4 mg, 0.0150 mmol) in anhydrous MeCN at 0°C, was added dropwise a freshly prepared 0.128 mg/µl solution of NOBF₄⁻ (20 µl, 0.0219 mmol) in anhydrous MeCN. The reaction solution turned brown following addition of the NOBF₄⁻ solution, however this color slowly faded. Analysis of the mixture by LC/MS indicated that trans-fused dihydrobenzofuran (+)-22 remained. Additional NOBF₄⁻ (150 µl, 0.164 mmol) was added at 0°C, however analysis of the mixture by LC/MS again indicated that trans-fused dihydrobenzofuran (+)-22 remained. A final aliquot of NOBF₄⁻ (75 µl, 0.083 mmol) was added at 0°C before the reaction was quenched by the addition of urea (40 mg, 0.67 mmol) and H₂O (100 µl). The reaction solution was diluted with EtOAc, filtered through Celite®, and concentrated in vacuo. The residue was purified by flash pipette chromatography on silica gel (5:95 EtOAc:hexanes) providing dimethoxybenzofuran (+)-23 (3.7 mg, 70% yield) as a white solid. Rf = 0.53 (20:80 EtOAc:hexanes); ¹H NMR (CDCl₃, 500 MHz, 7.26 ppm for CHCl₃ in CDCl₃); δ = 7.16 (s, 1H), 6.93 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.18 (s, 3H), 2.60 (m, 1H), 2.16 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.66-1.44 (m, 6H), 1.41 (d, J = 7.1 Hz, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 0.98 (s, 3H), 0.95 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz, 77.2 ppm for CDCl₃): δ = 156.0, 148.6, 147.0, 145.0, 125.5, 120.5, 105.7, 95.1, 57.2, 56.3, 53.8, 42.2, 40.5, 39.7, 35.4, 35.0, 33.9, 33.5, 24.5, 22.2, 22.1, 20.4, 19.1; IR (NaCl, cm⁻¹): v = 2930, 2867, 1623, 1488, 1466, 1439, 1389, 1316, 1281, 1211, 1197, 1166, 1136, 1115; HRMS (EI+) m/z: C₂₃H₃₂O₃[M⁺]: calc’d 356.2352; found 356.2353; [α]₂₅D = +16.85° (c = 0.16, CHCl₃), >99% ee.

O,O’-Dimethylpiperazal (-)-24.

Preparation of n-BuLi·TMEDA: To a stirred solution of TMEDA (380 µl, 2.5 mmol) in anhydrous THF (5 ml) was added a ~2.0 M solution of n-BuLi (1.20 ml, 2.4 mmol) at 21°C. The contents stirred for 30 min prior to use. This solution was titrated according to the method of Chong⁶ and found to be 0.33 M.

A two dram vial containing dimethoxybenzofuran (+)-23 (3.7 mg, 0.01037 mmol) in anhydrous THF (500 µl) was cooled to 0°C before dropwise addition of n-BuLi·TMEDA (80 µl, 0.0264 mmol). After stirring for 30 min at 0°C, DME (7.5 µl, 0.0972 mmol) was introduced and the reaction was allowed to warm to 21°C. After 20 min the reaction was quenched by the addition of sat. aq NaHCl (25 ml) and filtered through MgSO₄ prior to HPLC purification (Zorbax RX-Sil, 5 µm, 9.4×250 mm, 5:95 EtOAc:hexanes, 6 ml/min, monitored at 254 nm) providing O,O’-dimethylpiperazal (-)-24 (2.8 mg, 70% yield) as a faint yellow solid. Rf = 0.50 (20:80 EtOAc:hexanes); NMR (CDCl₃, 500 MHz, 7.26 ppm for CHCl₃ in CDCl₃); δ = 10.56 (s, 1H), 7.47 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.31 (s, J = 7.0 Hz, 1H), 2.55 (m, 1H), 2.18 (dd, d, J = 3.3 Hz, J = 7.2 Hz), 1.74 (m, 1H), 1.64-1.48 (m, 6H), 1.46 (d, J = 7.2 Hz, 3H), 1.37 (s, 3H), 1.26 (dd, d, J = 2.8 Hz, J = 13.5 Hz, J = 13.5 Hz, 3H), 0.99 (s, 3H), 0.96 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz, 77.2 ppm for CDCl₃): δ = 188.6, 159.1, 149.7, 148.1, 146.5, 125.5, 124.8, 115.0, 113.3, 63.0, 57.5, 53.7, 42.1, 40.5, 39.7, 35.0, 35.0, 33.7, 33.5, 24.2, 22.2, 20.4, 19.1; IR (NaCl, cm⁻¹): v = 2933, 2866, 1600, 1584, 1464, 1435, 1388, 1330, 1240, 1124, 1054, 979; HRMS (MM-ESI-APCI+) m/z: C₂₃H₃₂O₃[M⁺]: calc’d 385.2373. Found 385.2371; [α]₂₅D = -16.36° (c = 0.280, CHCl₃), >99% ee.
Liphagal (+)-1.

In the glovebox\(^4\), a two dram vial containing 0, O'-dimethyl-liphagal (-)-24 (1.7 mg, 0.00442 mmol) dissolved in anhydrous CH\(_2\)Cl\(_2\) was cooled to -55°C. before addition of a freshly prepared 0.01M solution of B\(_2\)I\(_3\) (885 µL, 0.00885 mmol) in anhydrous CH\(_2\)Cl\(_2\). After 5 min at -55°C, the vial was warmed to 0°C, over 45 min. After 20 min at 0°C, the vial was removed from the glovebox and immediately quenched with H\(_2\)O:MeCN (50 µL:300 µL) resulting in a cloudy mixture. The volatiles were removed under a stream of Ar. The yellow residue was dissolved in MeCN, filtered through a Kimwipe\(^\text{®}\) plug, and purified by reversed-phase HPLC (Eclipse XDB-C18, 5 µm, 9.4x250 mm, 80:20 MeCN:0.1% AcOH/H\(_2\)O, 5 mL/min, monitored at 254 nm) yielding liphagal (+)-1 (0.7 mg, 45% yield) as a yellow oil/film. Reten-

\(^{1}H\) NMR of (+)-liphagal, CDCl\(_3\)^\(^{1}\)

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<td>0.98</td>
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1. The values for Andersen's Synthetic Liphagal have been referenced to residual CHCl\(_3\) at δ = 7.26

\(^{13}C\) NMR of (+)-liphagal, CDCl\(_3\)^\(^{2}\)

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1. The values for Andersen’s Synthetic Lippafl have been referenced to CDCl₃ at δ = 77.2

Methods for the Determination of Enantiomeric Excess.

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<th>Method</th>
<th>Retention Time (min)</th>
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<td>Enantiomeric Excess</td>
<td>Chiral HPLC</td>
<td>3% EtOH/Hex</td>
<td>Major (R)</td>
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<td>Chiralcel AD Column</td>
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<tr>
<td></td>
<td>(R),(+)-5</td>
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| 2.    |            |       |        |        |                      |
|       |            | Enantiomeric Excess | Chiral SFC | 30% IPA/CO₂ | Major (R) | 4.6 |
|       |            |                   | Chiralcel AD-H Column | monitor@235/244 nm |         |     |
|       | (R),(+)-15 |       |        |        |                      |

While the present invention has been illustrated and described with reference to certain exemplary embodiments, those of ordinary skill in the art will understand that various modifications and changes may be made to the described embodiments without departing from the spirit and scope of the present invention, as defined in the following claims.

What is claimed is:

1. A method for preparing a compound of Formula 17A:

![Formula 17A](image)

comprising treating a compound of Formula 17B:

![Formula 17B](image)

under [2+2] photocycloaddition conditions with a compound represented by the Formula (1):

![Formula 1](image)

wherein:

R₂₉ and R₃₀ are independently selected from hydrogen, alkyl group and carbonyl group;
2. A method for preparing a compound of Formula 18A:

comprising treating a compound of Formula 18B:

under [2+2] photocycloaddition conditions with a compound represented by the Formula (1):

$$R_{30} \quad R_{30}$$

wherein:

- $R_{30}$-$R_{14}$ and $R_{24}$ are independently hydrogen or an alkyl group;
- $R_{21}$ and $R_{28}$ are hydrogen; and
- $R_{29}$ and $R_{30}$ are independently hydrogen or trialkysilyl group.

3. The method of claim 1 or 2, wherein $R_{24}$ is hydrogen.

4. The method of claim 1 or 2, wherein the compound of Formula (1) is trimethylsilyl acetylene.

5. The method of claim 1 or 2, wherein the photocycloaddition conditions comprise UV radiation.

6. The method of claim 1 or 2, wherein the UV radiation comprises UVB radiation.

7. The method of claim 1 or 2, wherein the photocycloaddition conditions comprise a solvent.

8. The method of claim 7, wherein the solvent comprises acetone.

9. The method of claim 1 or 2, wherein the method further comprises treating a compound of Formula 17A or 17B with a Lewis acid.

* * * * *