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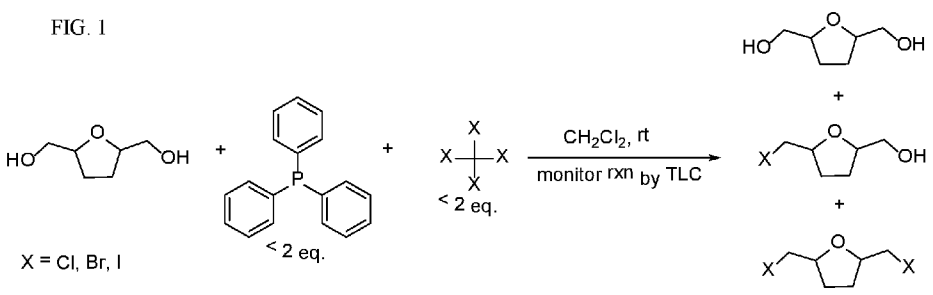
FIG. 1



(57) Abstract: A process for the preparation of diastereomeric mono- and 2,5- bis(halomethyl)tetrahydrofurans from renewable THF-diols is described. Also disclosed are certain derivative compounds that can be prepared from the mono or di-alkyl halide furanic compounds.

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PREPARATION OF MONO- AND DI-ALKYL HALIDE FURANIC COMPOUNDS FROM 2,5-BIS(HYDROXYMETHYL)-TETRAHYDROFURANS (BHMTHF) AND DERIVATIVES THEREOF

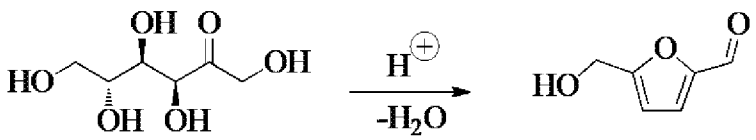
FIELD OF INVENTION

[0001] The present disclosure relates to certain cyclic bi-functional materials that are useful as monomers in polymer synthesis, as well as intermediate chemical compounds. In particular, the present invention pertains to halogenated furanic molecules, particular methods by which such molecules are prepared, and certain derivative compounds or materials that incorporate these molecules.

BACKGROUND

[0002] In recent years, researchers have devoted effort to find ways to employ biomass as feedstock for the production of organic chemicals because of its abundance, renewability, and worldwide distribution. Biomass contains carbohydrates or sugars (i.e., hexoses and pentoses) that can be converted into value added products. Organic compounds that are readily derived from sugars include furans, robust cyclic ethers that possess structural features that can be useful for making certain polymers, pharmaceuticals, or solvents, among other industrial constituents. A related compound that has received considerable attention of late is 5-(hydroxymethyl)furfural (HMF), a major dehydration product of fructose, an abundant, inexpensive monosaccharide (Scheme A).

Scheme A. HMF synthesis from acid-catalyzed dehydration of fructose



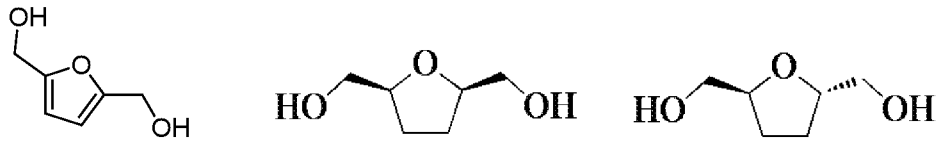
A B

[0003] HMF is a versatile chemical antecedent to various furanic ring-based derivatives that are known intermediates for various chemical syntheses, and are plausible surrogates for aromatic hydrocarbons that derive from petroleum resources. Due to the diverse functionalities of HMF, some have proposed that HMF be used to produce a wide range of commodities such as polymers, solvents, surfactants, pharmaceuticals, and plant protection agents. As substitutes, derivatives of HMF are comparable to benzene-based aromatic compounds or to other compounds containing a furan or tetrahydrofuran (THF). HMF and 2,5-disubstituted furans and THF analogs, therefore, have great potential in the field of intermediate chemicals from renewable agricultural resources.

[0004] HMF itself, however, is rather unstable and tends to polymerize or decompose under thermo-oxidative conditions with prolonged storage at ambient conditions. Thus, one should look to

derivatives of HMF for practical commercial utility. Two derivatives of interest are: furan-2,5-dimethanol (abbreviated as FDM) and 2,5-bis-(hydroxymethyl)-tetrahydrofuran (abbreviated as bHMTHF), also known colloquially as THF-diols, presented in Scheme B.

Scheme B. Chemical structures of FDM and *cis, trans* isomers of bHMTHF



Furan-2,5-dimethanol (FDM) *cis, trans* 2,5-bis-(hydroxymethyl)tetrahydrofuran (bHMTHF)

[0005] These cyclic bifunctional molecules have potential to be chemical feedstock or platforms from which various derivative compounds can be synthesized. These chemical entities can serve as valuable glycolic antecedents for the preparation of polymers, solvents, additives, lubricants, and plasticizers, etc. Furthermore, the inherent, immutable chirality of bHMTHFs makes these compounds useful as potential species for pharmaceutical applications or candidates in the emerging chiral auxiliary field of asymmetric organic synthesis.

[0006] Conventional preparation of halogenated furanic compounds have involved rather complex and exotic conditions. For instance, Peng *et al.* used 1,5-hexadiene and iodine as starting materials in preparing 2,5-bis(iodomethyl)-tetrahydrofuran through a nickel-mediate stereocontrolled synthesis (Peng, Yu; Xu, Xiao-Bo; Xiao, Jian; Wang, Ya-Wen, "Nickel-mediated stereocontrolled synthesis of spiroketals via tandem cyclization-coupling of β-bromo ketals and aryl iodides," Chemical Communications (Cambridge, United Kingdom) (2014), 50(4), pp. 472-474.) Others have used a rather harsh protocol involving reacting bHMTHF with thionyl chloride, a highly toxic and corrosive reagent, and pyridine under high temperatures to make 2,5-bis(chloromethyl)-tetrahydrofuran. (E.g., Cope, Arthur C., Anderson, Burton C., Journal of the American Chemical Society (1955), 77, pp. 995-8; Wiggins, L. F., Wood, D. J. C., Journal of the Chemical Society (1950), pp. 1566-75; Cope, Arthur C., Baxter, Warren N., Journal of the American Chemical Society (1955), 77, pp. 393-6; U.S. Patent No. 6,027355 (Mano *et al.*)) These processes tend to be limited in their production and none of these reactions describe a way of making mono- or bis-(halomethyl)-tetrahydrofuran directly from sugar derived compounds according to a mild, non-toxic protocol. Given the potential uses, a cost efficient and simple process that can make bHMTHFs more accessible and easily manipulated for preparation of derivative would be appreciated by manufacturers of both industrial and specialty chemicals alike as a way to better utilize biomass-derived carbon resources.

SUMMARY OF THE INVENTION

[0007] The present disclosure relates in part to a method for making an alkyl halide, exemplified by brominated furanic molecules, from 2,5-bis-(hydroxymethyl)-tetrahydrofuran (bHMTHF) according

to mild and non-toxic protocols. The method involves contacting 2,5-bis-(hydroxymethyl)-tetrahydrofuran (bHMTHF) with a triphenylphosphine and tetrahalomethanes (CCl_4, CBr_4, CI_4) at a temperature and for a time sufficient to convert the bHMTHF to corresponding mono or 2,5-bis(halomethyl)tetrahydrofurans (HMT). The temperature is in a range from about 0°C to about 50°C, and the duration is at least 4 hours.

[0008] In another aspect, the present disclosure pertains to the halomethyl-tetrahydrofuran compounds made from the synthesis described herein. In particular, the mono or di-alkyl halide furanic compounds have a general structure:

wherein R is either -OH, Cl, Br, or I, and X is Cl, Br, or I when the furanic compound has a *trans* configuration, and that when both R and X are either Cl or I then the furanic compound is not in a *cis* configuration, and X is Br when the furanic compound has a *cis* configuration.

[0009] In yet another aspect, the present disclosure describes a process for making a derivative compound. The process includes contacting either mono- or bis(halomethyl-tetrahydrofurans with a regent that a) displaces nucleophilically, b) eliminates, or c) substitutes at least an alcohol moiety or a halide moiety of the mono- or bis(halomethyl)-tetrahydrofurans under conditions sufficient to produce a derivative compound. In particular, the mono- or bis(halomethyl)-tetrahydrofurans are subjected to a reaction that involves at least: C-nucleophile displacement, N-nucleophile displacement, O-nucleophile displacement, S-nucleophile displacement, dimerization, esterification, etherification, epimerization, fluorination, Gilman's reaction, Grinard reaction, and oxidation.

[0010] Additional features and advantages of the present synthesis process and material compounds will be disclosed in the following detailed description. It is understood that both the foregoing summary and the following detailed description and examples are merely representative of the invention, and are intended to provide an overview for understanding the invention as claimed.

BRIEF DESCRIPTION OF FIGURES

[0011] FIG. 1, is a generic schematic of the present method for preparing a mono or di-alkyl furnaic compound under Appel reaction conditions.

[0012] FIG. 2, is a schematic illustrating the mechanism according to the Appel reaction.

[0013] FIG. 3, is a schematic representing a particular reaction according to an embodiment of the present process for preparing 2,5-bis(bromomethyl)tetrahydrofurans (BMT) diastereomers from bHMTHF diastereomers.

[0014] FIG. 4, is a general schematic that illustrates various synthesis pathways to make derivative compounds, such as thioethers, amines, halides, alkyl/aryl chain extensions, by nucleophilic displacement reactions, for example, from 2,5-bis(bromomethyl)tetrahydrofurans (BMT) diastereomers.

[0015] FIG. 5, is a general schematic that illustrates alternate synthesis pathways in which an alcohol moiety of a tetrahydrofluranic mono-halide (prepared according to the present disclosure) reacts while preserving the halogenated moiety.

[0016] FIG. 6, is a general schematic that illustrates other synthesis pathways in which a halide moiety of a tetrahydrofluranic mono-halide reacts while the alcohol moiety remains.

[0017] FIG. 7, is a gas chromatogram of a product mixture prepared according to an embodiment of the present invention.

[0018] FIG. 8, is a mass spectrum of the brominated furanic compound as eluted in Fig. 7.

DETAILED DESCRIPTION OF THE INVENTION

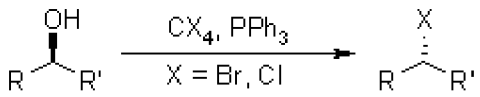
Section I. – Description

A. Preparation of mono and 2,5-bis(halomethyl)tetrahydrofurans

[0019] In the present invention, alkyl-halide furanic compounds can be prepared directly from 2.5-bis-(hydroxymethyl)-tetrahydrofuran (bHMTHF) derived from the hydrogenation of HMF in a simple and elegant reaction that can achieve high yields. One can attain significant levels to near complete conversion of the starting materials (e.g., 50%-98% wt./wt.) and a yield of at least 25% relative to the starting materials of either the desired mono- or di-halogenated furanic compound. Typically, the percent yield is in a range from about 30% to about 60% or greater, such as about 35%, 40%, 45%, 50% 55%, or 63%. With process optimization one can achieve even higher yields, for example, about 65% or 70% to about 75% or 85% or more.

[0020] Whereas previous syntheses involves complicated reactions with toxic reagents and produced di-halogenated *cis*-configured molecules, an advantage of the present reaction over the previously synthesis is the ability to generate both mono and dialkyl furanic halide molecules having both *cis* and *trans*-configured molecules according to a non-toxic reaction protocol under mild conditions. Figure 1 shows a general reaction for preparing mono- and di-halide furanic compounds under Appel reaction conditions according to the present disclosure. The Appel reaction, as illustrated generally in Scheme 1, involves a reaction of triphenylphosphine (PPh_3) and tetrahalomethanes (CX_4: CCl_4, CBr_4, CI_4,) with alcohols is a ready method to convert an alcohol to the corresponding alkyl halide under mild conditions. The yields are normally high.

Scheme 1.



[0021] The reaction proceeds by activation of the triphenylphosphine (PPh_3) by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group, and an S_N2 displacement by halide takes place, proceeding with inversion of configuration if the carbon is

asymmetric. Figure 2 shows this mechanism. Alternative phosphine reagents one may use in the Appel reaction may include commercially available alkyl phosphines, such as tributylphosphine.

[0022] To maximize the amount of mono-halogenated bHMTHF, one can either moderate the amount of CX_4/PPh_3 used or halt the reaction at an earlier time, thus precluding further halogenation to the di-halogenated analogs. It is believed that the reaction is collision controlled. Some amount of di-halogenated species will be present and its concentration increases over time if sufficient halogenating agent is available regardless of the amount of mono-halogenated molecules. To optimize yields of the mono-halogenated species one can limit the amount of halogenating agent available. Hence, to increase the amount of mono-halogenated species one can use one stoichiometric equivalent or less, instead of two or more equivalents, of CX_4/PPh_3.

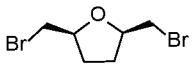
[0023] Figure 3, presents a reaction according to an embodiment of the present process for preparing 2,5-bis(bromomethyl)tetrahydrofurans (BMT) diastereomers from bHMTHF diastereomers. The synthesis process of the present disclosure are equally applicable for the other halide species (i.e., chlorine and iodine).

[0024] The reaction can be performed in a temperature range from about 0°C to about 60°C. In certain embodiments, the temperature is in a range from about 10°C or 12°C to about 40°C or 50°C. Certain desirable temperatures are about 15°C or 18°C to about 22°C or 30°C, specifically ambient room temperature (e.g. ~20°C).

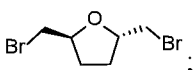
[0025] The duration of the reaction can be at least 3 or 4 hours. Typically, the reaction time is between about 5 hours to about 12 hours. In certain embodiments, the time is about 6 or 7 hours to about 9 or 10 hours; more typically, about 6 to 8 hours.

[0026] The mono or di-alkyl halide furanic compounds have a general structure:

wherein R is either -OH, Cl, Br, or I, and X is Cl, Br, or I when the furanic compound has a *trans* configuration, and that when both R and X are either Cl or I then the molecule is not in a *cis* configuration. X is Br when the furanic compound has a *cis* configuration. The mono or di-alkyl halide furanic compounds are in a 90%:10% ratio of *cis*:*trans* configured molecules. The alkyl halide furanic compounds that can be generated according to the present method of synthesis may include, for example:

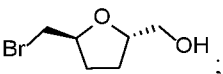
cis 2,5-bis(bromomethyl)tetrahydrofuran 

;

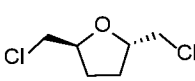
trans 2,5-bis(bromomethyl)tetrahydrofuran 

;

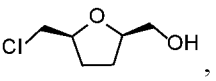
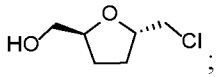
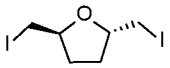
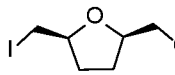
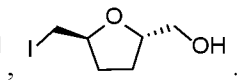
cis and *trans* (5-(bromomethyl)-tetrahydrofuran-2-yl)-methanol 

, 

;

trans 2,5-bis(cloromomethyl)tetrahydrofuran 

;

cis and *trans* (5-(chloromomethyl)-tetrahydrofuran-2-yl)-methanol  ,  ; *trans* 2,5-bis(iodomethyl)tetrahydrofuran  ; and *cis* and *trans* (5-(iodomethyl)-tetrahydrofuran-2-yl)-methanol  ,  .

B. Derivatives of mono- and di-halides of tetrahydrofuranic molecules

[0027] The alkyl halide furanic compounds produced according to the present synthesis process are versatile molecules for further chemical synthesis. The materials can serve as precursor chemicals for various other reactions to generate an array of derivative compounds, such as thioethers, amines, halides, alkyl/aryl chain extensions, all achieved by nucleophilic displacement reactions as illustrated in Figure 4. The example shows 2,5-bis(bromomethyl)-tetrahydrofuran as the starting material, but can apply equally to other halogenated species. The derivative compounds are represented in generic notation.

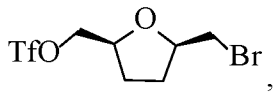
[0028] When in the presence of powerful nucleophiles, such as thiols and amines, the 2,5-bis(bromomethyl)tetrahydrofurans undergoes rapid second order substitutions to form thioethers and secondary or tertiary amine products. Another example of a transformation is to induce a polarity inversion (umpolung) of the 2,5-bis(bromomethyl)tetrahydrofurans with magnesium (Grignard) and lithium dialkylcuprates (Gilman) reagents. This can generate easily powerful carbon centered nucleophiles. In another reaction, when a strong base is added (e.g., hydride, amide, organolithiates) to a solution of 2,5-bis(bromomethyl)-tetrahydrofurans at reduced temperature, an elimination generates a diolefin, 2,5-dimethylenetetrahydrofuran.

[0029] Further illustration of the versatility of tetrahydrofluranic mono-halide molecules are presented in Figure 5 and 6, which show some other representative reactions and compounds. In Figure 5, the tetrahydrofluranic mono-halide undergoes alcohol modifications, in which the alcohol moiety reacts while preserving the halogenated moiety. Figure 6 shows halide displacement reactions, in which the halide moiety reacts while the alcohol moiety remains. Other alternate derivative compounds can be prepared with some of the displacement, elimination, or substitution reactions described in International Patent Application No. PCT/US2014/070012, the contents of which are incorporated herein by reference, *mutandis mutatis*.

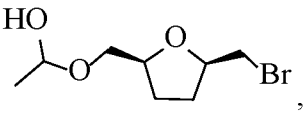
[0030] The following molecules present some representative derivative compounds that can be prepared from mono and bis(halomethyl)tetrahydrofurans according to some of the nucleophilic displacement, elimination or substitution reactions disclosed in the forgoing section above. Examples of some derivatives may include either a *cis* or *trans*-configured molecule. For purposes of

illustration, the following compounds numbered 1-27 and 35, depicted *cis* configured derivative molecules, and compounds 28-34, 36, 37, show *trans* configured molecules:

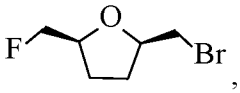
1. ((2S,5R)-5-(bromomethyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



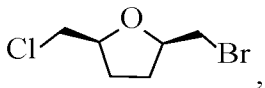
2. 1-(((2S,5R)-5-(bromomethyl)tetrahydrofuran-2-yl)methoxy)ethan-1-ol



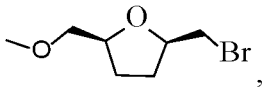
3. (2R,5S)-2-(bromomethyl)-5-(fluoromethyl)tetrahydrofuran



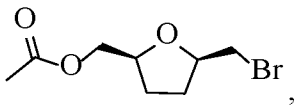
4. (2R,5S)-2-(bromomethyl)-5-(chloromethyl)tetrahydrofuran



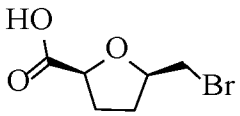
5. (2R,5S)-2-(bromomethyl)-5-(methoxymethyl)tetrahydrofuran



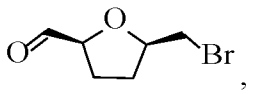
6. ((2S,5R)-5-(bromomethyl)tetrahydrofuran-2-yl)methyl acetate



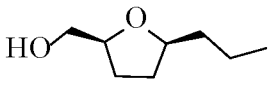
7. (2S,5R)-5-(bromomethyl)tetrahydrofuran-2-carboxylic acid



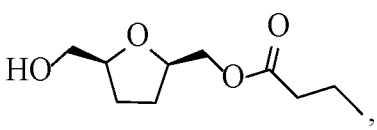
8. (2S,5R)-5-(bromomethyl)tetrahydrofuran-2-carbaldehyde



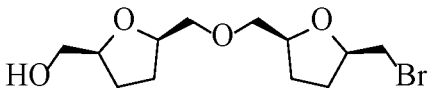
9. ((2S,5S)-5-propyltetrahydrofuran-2-yl)methanol



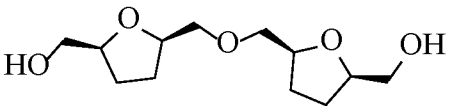
10. ((2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl butyrate



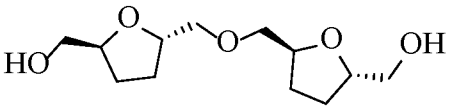
11. ((2S,5R)-5-((((2S,5R)-5-(bromomethyl)tetrahydrofuran-2-yl)methoxy)methyl)-tetrahydrofuran-2-yl)methanol



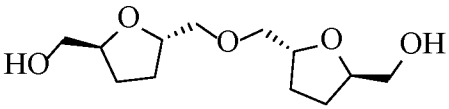
12. ((2R,5S)-5-((((2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methoxy)methyl)-tetrahydrofuran-2-yl)methanol



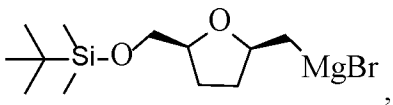
13. ((2S,2'S,5S,5'S)-(oxybis(methylene))bis(tetrahydrofuran-5,2-diyl))dimethanol



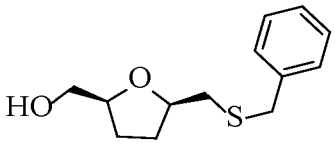
14. ((2R,5R)-5-((((2S,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methoxy)methyl)-tetrahydrofuran-2-yl)methanol



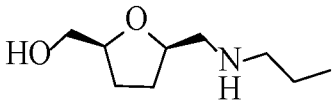
15. (((2R,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)methyl)magnesium bromide



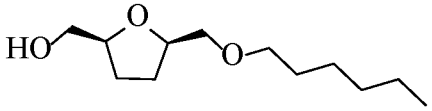
16. ((2S,5R)-5-((benzylthio)methyl)tetrahydrofuran-2-yl)methanol



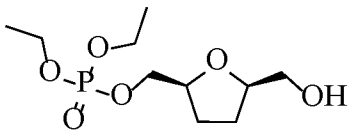
17. ((2S,5R)-5-((propylamino)methyl)tetrahydrofuran-2-yl)methanol



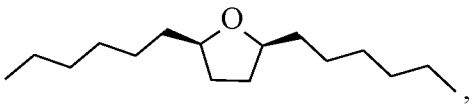
18. ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol



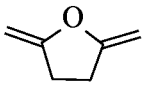
19. Diethyl (((2S,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl) phosphate



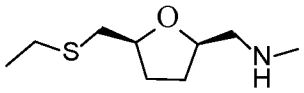
20. (2R,5S)-2,5-dihexyltetrahydrofuran



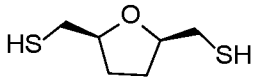
21. 2,5-dimethylenetetrahydrofuran



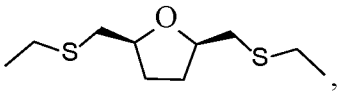
22. 1-((2R,5S)-5-((ethylthio)methyl)tetrahydrofuran-2-yl)-N-methylmethanamine



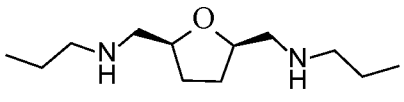
23. ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol



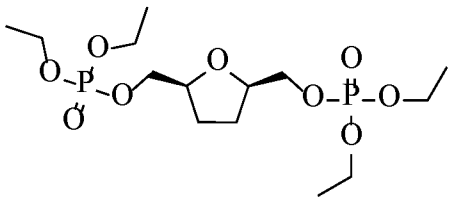
24. (2R,5S)-2,5-bis((ethylthio)methyl)tetrahydrofuran



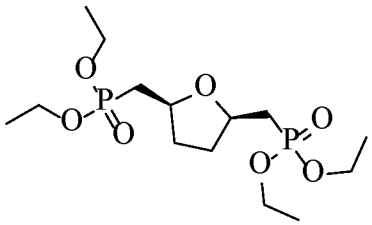
25. N,N'-(((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene))bis(propan-1-amine)



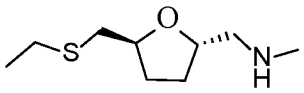
26. Tetraethyl (((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene)) bis(phosphate)



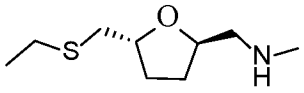
27. Tetraethyl (((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene))bis(phosphonate)



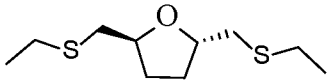
28. 1-((2S,5S)-5-((ethylthio)methyl)tetrahydrofuran-2-yl)-N-methylmethanamine



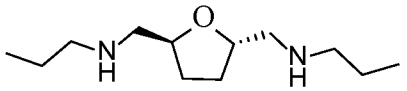
29. 1-((2R,5R)-5-((ethylthio)methyl)tetrahydrofuran-2-yl)-N-methylmethanamine



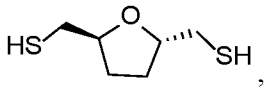
30. (2S,5S)-2,5-bis((ethylthio)methyl)tetrahydrofuran



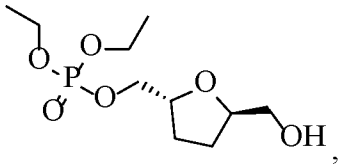
31. N,N'-(((2S,5S)-tetrahydrofuran-2,5-diyl)bis(methylene))bis(propan-1-amine)



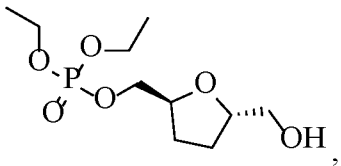
32. ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol



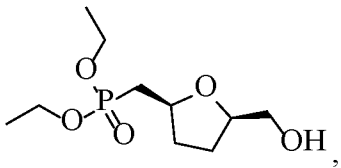
33. Diethyl (((2R,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl) phosphate



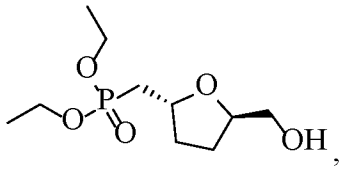
34. Diethyl (((2S,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl) phosphate



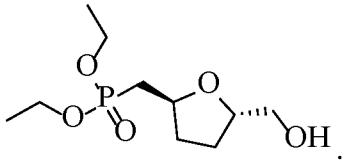
35. Diethyl (((2S,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)phosphonate



36. Diethyl (((2R,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)phosphonate



37. Diethyl (((2S,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)phosphonate



Section II. – Examples

A.

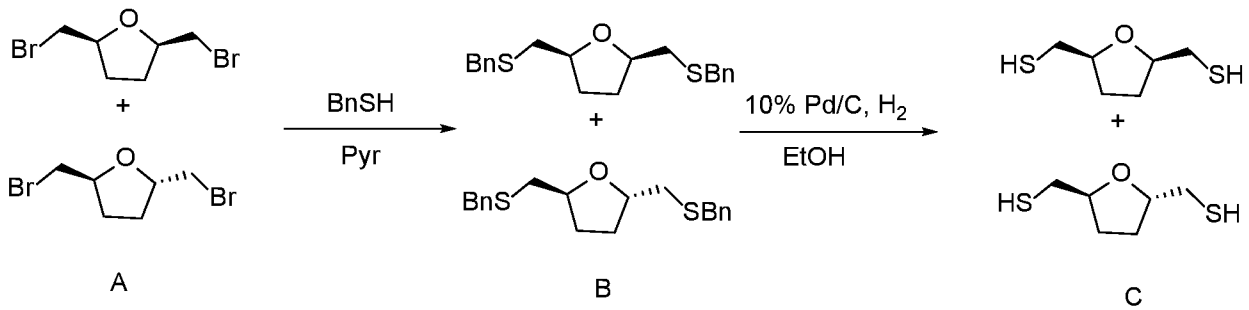
[0031] Example 1. Preparation of 2,5- bis(halomethyl)tetrahydrofurans

[0032] Experimental: A flame-dried, 50 cc three-necked round-bottomed flask equipped with a PTFE magnetic stir bar was charged with 1.00 g of a 9:1 cis/trans diastereomeric mixture of bHMTHFs (7.57 mmol), 5.95 g of triphenylphosphine (22.7 mmol, 3 eq.), 7.53 g of carbon tetrabromide (22.7 mmol, 3 eq.), and 25 mL of dry methylene chloride. The leftmost neck of the flask was capped with a rubber septum imbued with five 12" stainless steel needles, the centermost neck stoppered with a thermowell adapter, and the leftmost affixed to an argon inlet. Stirring commenced at room temperature while under an argon blanket. The reactants were observed to readily dissolve in methylene chloride and appeared as a light yellow tinged solution. After approximately 3 h, prodigious solids were observed suspended in the methylene chloride solution. The reaction proceeded overnight, after which time the solids were filtered and vestigial solution analyzed by GC/MS, ^{31}P NMR, ^{1}H NMR, and ^{13}C NMR. Purification entailed pouring the diluted crude solution onto a pre-fabricated column with hexane/ethyl acetate as the eluting solvents. Gradient flash chromatography furnished the target compounds at a 2:1 hexanes/ethyl acetate proportion, $R_f = 0.44$, as 1.02 g of a colorless liquid (52% yield).

[0033] Figure 7 shows the gas chromatogram of the results with a peak at 8.909 minutes represents the 2,5-bis(bromomethyl)tetrahydrofuran, and a second peak at 15.791 minutes represents any remaining unreacted bHMTHF. Figure 8 presents the corresponding mass spectrum of the compound eluting at 8.909 minutes in Figure 7. The molecular ion, representing the relative molar mass of the targets) is ostensible at m/z 255.9 along with salient signals denoting concerted bromine atom losses (M-Br = 170.0 m/z; M-2Br = 96.1 m/z).

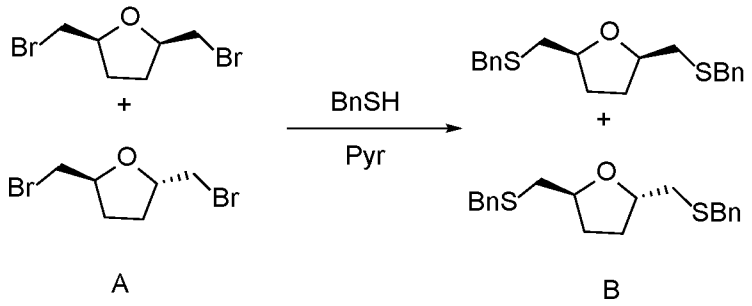
B.

[0034] Example 2. Preparation of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol



A B C

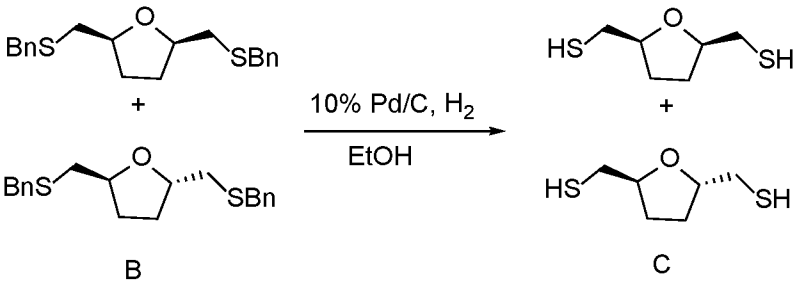
Step 1: Synthesis of (2R,5S)-2,5-bis((benzylthio)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((benzylthio)methyl)tetrahydrofuran, B



A B

[0035] Experimental: A flame-dried, 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 500 mg of a 9:1 mixture of (2R,5S)-2,5-bis(bromomethyl)tetrahydrofuran and (2S,5S)-2,5-bis(bromomethyl)tetrahydrofuran **A** (1.94 mmol), 382 μL benzyl mercaptan (4.85 mmol), 2 mL pyridine, and 10 mL of chloroform. With vigorous stirring, the mixture was refluxed overnight. After this time, the deep yellow solution was dried under reduced pressure and vestigial yellow oil taken up in 2 mL of methylene chloride and charged to a pre-fabricated silica gel column, where flash chromatography with a hexanes/ethyl acetate gradient furnished 476 mg of a 9:1 mixture of (2R,5S)-2,5-bis((benzylthio)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((benzylthio)methyl)tetrahydrofuran as a pale yellow oil (71%). ^{1}H NMR (*primary cis isomer*, 400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, J = 7.2 Hz, 4H), 7.27 (m, 4H), 7.12 (d, J = 7.0 Hz, 2H), 4.18 (m, 2H), 3.61 (s, 4H), 2.80 (dd, J = 9.2 Hz, J = 5.6 Hz, 2H), 2.59 (dd, J = 9.0 Hz, J = 5.6 Hz, 2H), 1.96 (m, 2H), 1.71 (m, 2H); ^{13}C NMR (*primary cis isomer*, 100 MHz, $CDCl_3$) δ (ppm) 140.9, 131.1, 130.6, 129.3, 81.6, 45.0, 39.7, 34.8 ppm.

Step 2: Synthesis of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol, C

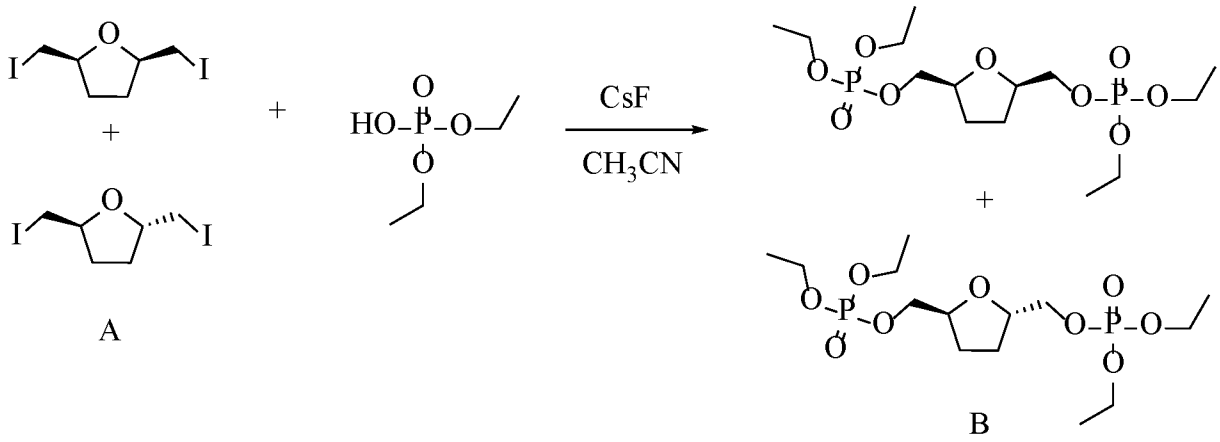


B C

[0036] Experimental: A 75 cc 316 SS Parr reactor equipped with a glass enclosed magnetic stir bar was charged with 400 mg of a 9:1 mixture of bis((benzylthio)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((benzylthio)methyl)tetrahydrofuran B (1.16 mmol), 500 mg of 10% Pd/C and 25 mL of absolute ethanol. The vessel was sealed, purged with volumes of H_2 (500 psi each), charged with H_2 to a pressure of 1000 psi and the solution stirred (500 rpm) at room temperature for 4 h. After this time, the catalyst was filtered and residual solution dried under reduced pressure, furnishing a yellow oil. The oil was taken up 2 mL of methylene chloride and charged to a pre-fabricated silica gel column, where flash chromatography with a gradient hexanes/ethyl acetate eluent furnished 156 mg of a 9:1

mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanethiol as a pale, loose oil (82%). ^{1}H NMR (*principal cis isomer*, 400 MHz, $CDCl_3$) δ (ppm) 4.12 (m, 2H), 2.85 (dd, J = 9.4 Hz, J = 6.4 Hz, 2H), 2.60 (dd, J = 9.4 Hz, J = 6.4 Hz, 2H), 1.93 (m, 2H), 1.66 (m, 2H), 1.25 (broad s, 2H); ^{13}C NMR (*principal cis isomer*, 100 MHz, $CDCl_3$) δ (ppm) 83.9, 39.4, 32.5.

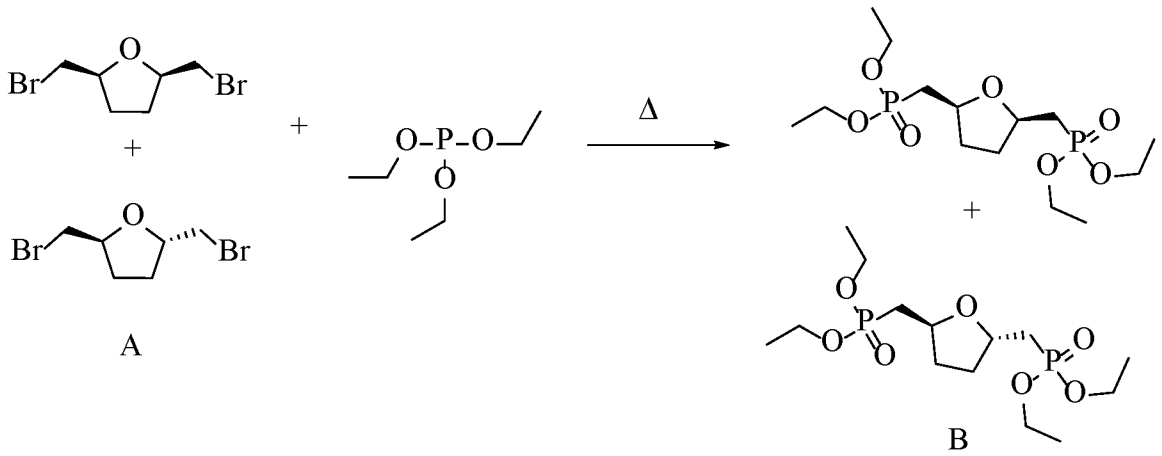
[0037] Example 3. Preparation of tetraethyl (((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene)) bis(phosphate) and tetraethyl (((2S,5S)-tetrahydrofuran-2,5-diyl)bis(methylene)) bis(phosphate), B.



A B

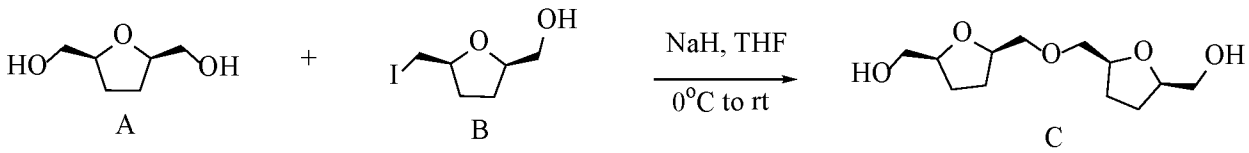
[0038] Experimental: A flame-dried, 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 100 mg of a 9:1 mixture of (2R,5S)-2,5-bis(iodomethyl)tetrahydrofuran and (2S,5S)-2,5-bis(iodomethyl)tetrahydrofuran **A** (0.284 mmol), 131 mg of diethyl hydrogen phosphate (0.852 mmol), 129 mg of cesium fluoride (0.852 mmol) and 10 mL of dry acetonitrile. The mixture was stirred vigorously for 8 hours. After this time, the acetonitrile was evaporated under reduced pressure and residual yellow oil uptaken in 1 mL of methylene chloride and charged to a pre-fabricated silica gel column, where flash chromatography with a hexanes/ethyl acetate gradient furnished 61 mg of tetraethyl (((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene)) bis(phosphate) and tetraethyl (((2S,5S)-tetrahydrofuran-2,5-diyl)bis(methylene)) bis(phosphate)a 9:1 mixture of as a colorless oil (53%). ^{1}H and ^{13}C NMR validated the identities and purities of title compounds, B.

[0039] Example 4. Preparation of tetraethyl (((2R,5S)-tetrahydrofuran-2,5-diyl)bis(methylene))-bis(phosphonate) and tetraethyl (((2S,5S)-tetrahydrofuran-2,5-diyl)bis(methylene))bis(phosphonate), B



[0040] Experimental: A three neck, flame-dried 10 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 200 mg of a 9:1 mixture of (2R,5S)-2,5-bis(bromomethyl)tetrahydrofuran and (2S,5S)-2,5-bis(bromomethyl)tetrahydrofuran (0.775 mmol) and 2 mL of triethylphosphite. An argon inlet was attached to the flask, and while vigorously stirring and under argon, the mixture was heated to 125°C. The reaction was monitored by TLC (5:1 hexanes/ethyl acetate, cerium molybdate visualization), and deemed complete after 4 hours. The solution was then cooled to room temperature and charged to a pre-fabricated silica gel column, where flash chromatography using gradient hexanes---->ethyl acetate afforded 182 mg of the title compound B as a loose colorless oil (63%). %). ^{1}H, ^{13}C, and ^{31}P NMR validated the identities and purities of title compounds, B.

[0041] Example 5. Preparation of ((2R,5S)-5-((((2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)methoxy)-methyl)tetrahydrofuran-2-yl)methanol, C



[0042] Experimental: A flame-dried, 100 mL boiling flask was charged with 1 g of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol (A, 7.57 mmol)) and 25 mL of anhydrous THF. The flask was immersed in a saturated brine/ice bath (~ -10°C) and 302 mg of sodium hydride (60 wt.% in mineral oil, 7.57 mmol) added in 5 portions (~60 mg) over 15 min. After complete addition, the resultant suspension was stirred for 15 min, furnishing an intense green color. A septum was then placed over the neck of the flask, and 1.86 g of ((2R, 5S)-5-(iodomethyl)tetrahydrofuran-2-yl)methanol (B, 7.57 mmol) dissolved in 10 mL of THF was added dropwise via syringe over 15 min. After addition, the brine/ice bath was removed and reaction stirred overnight. After this time, solids were filtered and filtrate poured over a pre-fabricated silica gel column, where flash chromatography with a gradient hexanes---->hexanes/ethyl acetate furnished 1.08 g of the title compound as a colorless oil (58%).

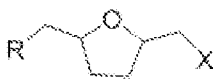
The structure was of the product was validated by NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.00 (broad s, 2H), 4.02 (m, 2H), 3.82 (m, 2H), 3.66-3.61 (m, 4H), 3.47-3.51 (m, 4H), 2.02 (m, 4H), 1.74 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 88.8, 85.4, 77.2, 65.1, 30.8, 29.4.

[0043] The present invention has been described in general and in detail by way of examples. Persons of skill in the art understand that the invention is not limited necessarily to the embodiments specifically disclosed, but that modifications and variations may be made without departing from the scope of the invention as defined by the following claims or their equivalents, including other equivalent components presently known, or to be developed, which may be used within the scope of the present invention. Therefore, unless changes otherwise depart from the scope of the invention, the changes should be construed as being included herein.

CLAIMS

We Claim:

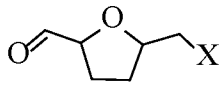
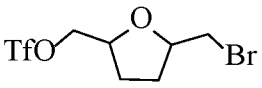
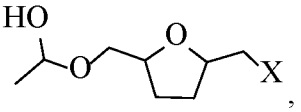
1. A method of preparing a mono or di-alkyl halide furanic compound, comprising: contacting 2,5-bis-(hydroxymethyl)-tetrahydrofuran (bHMTHF) with a triphenylphosphine and tetrahalomethane at a temperature and for a time sufficient to convert said bHMTHF to a corresponding mono or 2,5-bis(halomethyl)tetrahydrofurans (HMT).
2. The method according to claim 1, wherein said tetrahalomethane is at least one of CCl_4, CBr_4, and CI_4.
3. The method according to claim 1, wherein said temperature is in a range from about 0°C to about 60°C.
4. The method according to claim 1, wherein said reaction time is at least 3 hours.
5. The method according to claim 1, wherein said method generates either mono- or di-alkyl halide furanic compound at a yield of at least 25% relative to starting materials.
6. The method according to claim 5, wherein said method generates either mono- or di-alkyl halide furanic compound at a yield of at least 40%-50%.
7. The method according to claim 1, wherein said mono or di-alkyl halide furanic compounds are in a 90%:10% ratio of *cis*:*trans* configured molecules.
8. A mono or di-alkyl halide furanic compound having a general structure comprising:

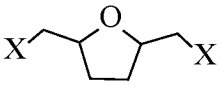
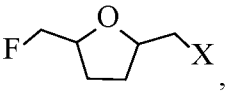
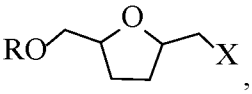


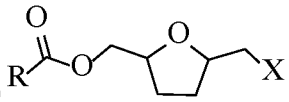
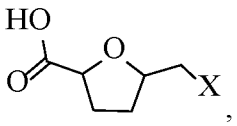
wherein R is either -OH, Cl, Br, or I, and X is Cl, Br, or I when said furanic compound has a *trans* configuration, and that when both R and X are either Cl or I then said furanic compound is not in a *cis* configuration, and X is Br when said furanic compound has a *cis* configuration.
9. The alkyl halide furanic compound according to claim 8, wherein said alkyl halide furanic compound is selected from the group consisting of: *cis* 2,5-bis(bromomethyl)tetrahydrofuran, *trans* 2,5-bis(bromomethyl)tetrahydrofuran, *cis* and *trans* (5-(bromomethyl)-tetrahydrofuran-2-yl)-methanol, *trans* 2,5-bis(cloromomethyl)tetrahydrofuran, *cis* and *trans* (5-(chloromomethyl)-tetrahydrofuran-2-yl)-methanol, *trans* 2,5-bis(iodomethyl)tetrahydrofuran, and *cis* and *trans* (5-(iodomethyl)-tetrahydrofuran-2-yl)-methanol.
10. A process for making a derivative compound, comprising: contacting either mono- or bis-(halomethyl)-tetrahydrofurans with a regent that a) displaces nucleophilically, b) eliminates, or c) substitutes at least an alcohol moiety or a halide moiety of said mono- or bis-(halomethyl)-tetrahydrofurans under conditions sufficient to produce a derivative compound.
11. The process according to claim 10, wherein said mono- or bis(halomethyl)-tetrahydrofurans are subjected to a reaction selected from the group consisting of: C-nucleophile displacement, N-nucleophile displacement, O-nucleophile displacement, S-nucleophile

displacement, dimerization, esterification, etherification, epimerization, fluorination, Gilman's reaction, Grinard reaction, and oxidation.

12. The process according to claim 10, wherein said derivative compound has a general structure selected from the group consisting of:

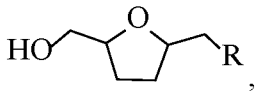
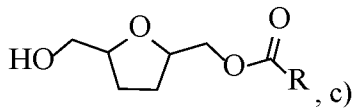
a)  , b)  , c)  ,

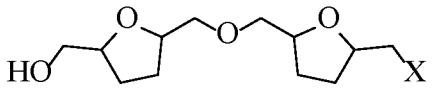
d)  , e)  , f)  ,

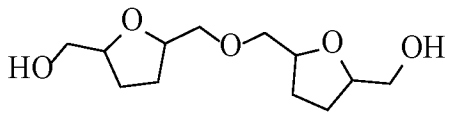
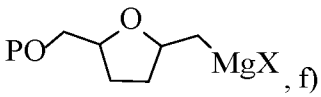
g)  , h)  ,

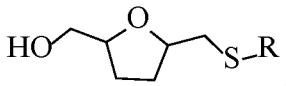
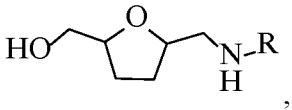
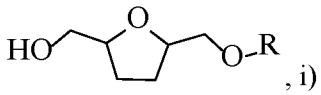
wherein X = Cl, Br, and R = alkyl, alkenyl, alkynyl, allyl aryl, benzyl.

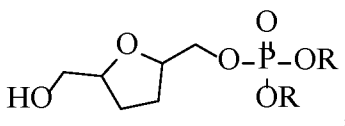
13. The process according to claim 10, wherein said derivative compound has a general structure selected from the group consisting of:

a)  , b)  , c)

 ,

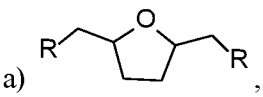
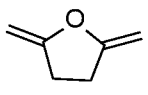
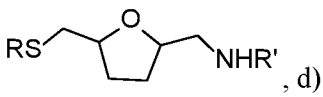
d)  , e)  , f)

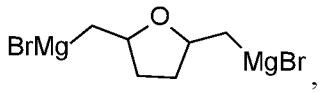
 , g)  , h)  , i)

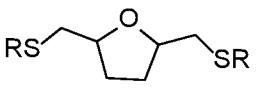
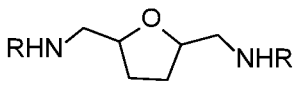
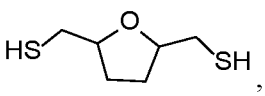
 ,

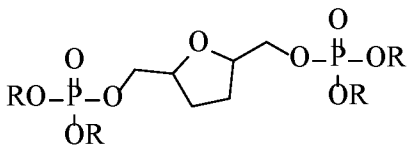
wherein X = Cl, Br, I; R = alkyl, alkenyl, alkynyl, allyl, phenyl, benzyl; and P = protecting group.

14. The process according to claim 10, wherein said derivative compound has a general structure selected from the group consisting of:

a)  , b)  , c)  , d)

 ,

e)  , f)  , g)  ,


h)

wherein R = alkyl, alkenyl, alkynyl, allyl, phenyl, benzyl.

FIG. 1

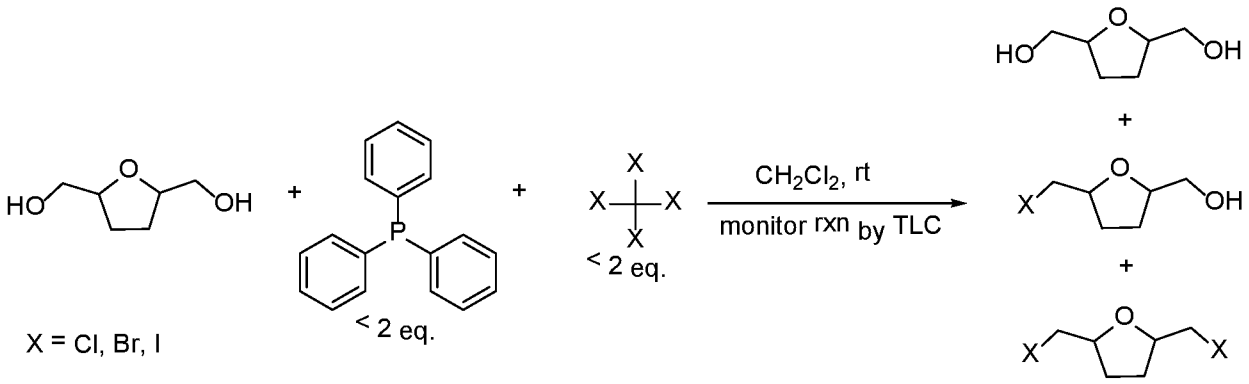


FIG. 2.

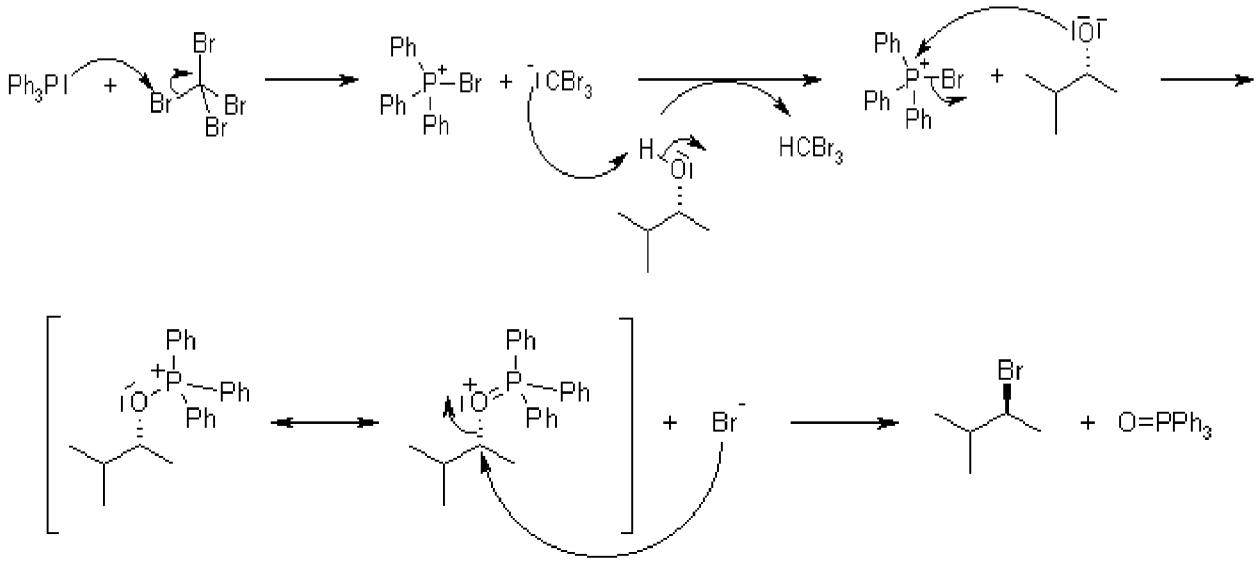
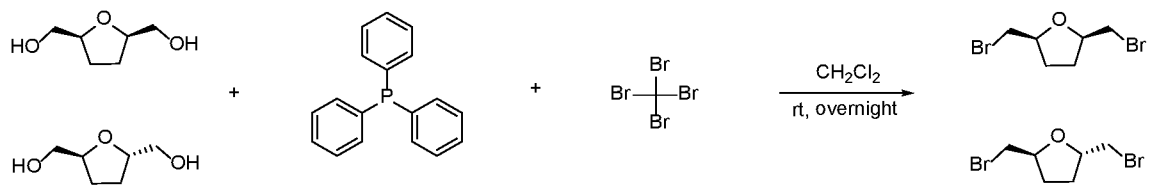


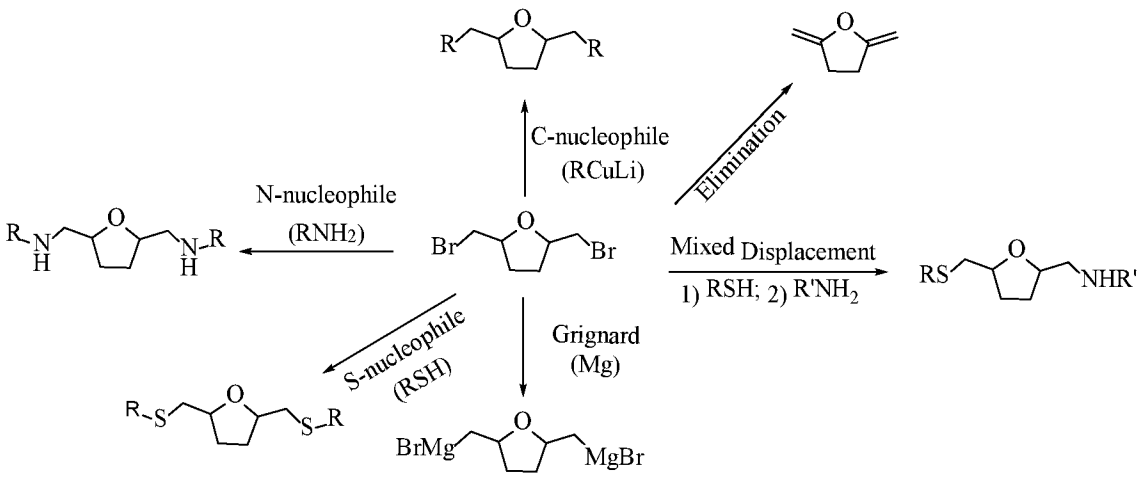
FIG. 3.



9:1 cis/trans bHMTHFs

9:1 cis/trans BMTs

FIG. 4.



R = alkyl, alkenyl, alkynyl, allyl, phenyl, benzyl

FIG. 5.

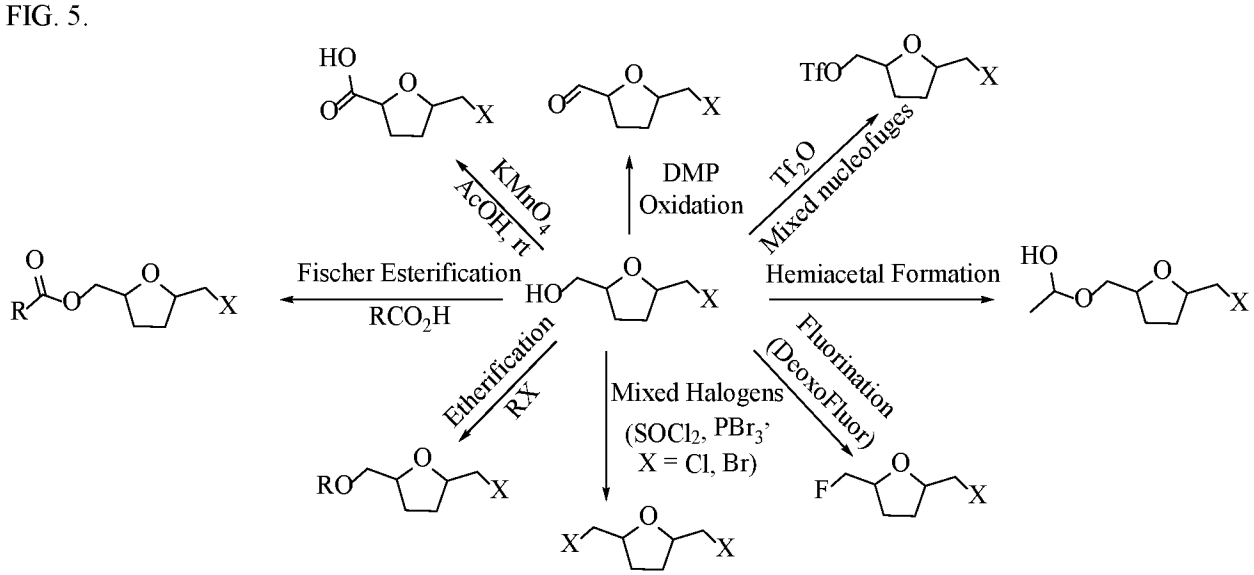
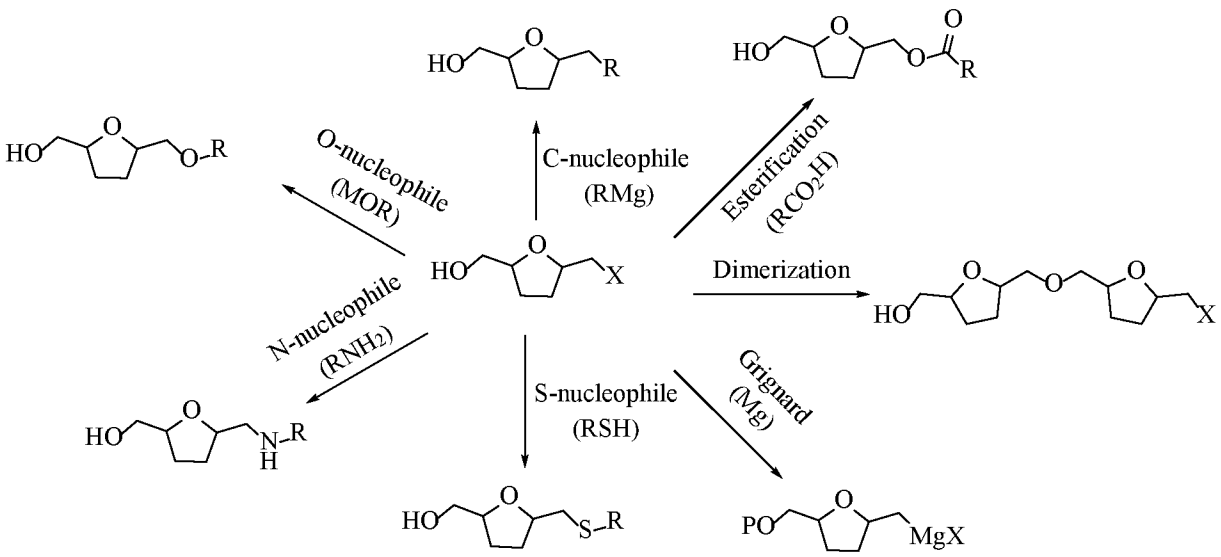


FIG. 6.



X = Cl, Br, I
R = alkyl, alkenyl, alkynyl, allyl, phenyl, benzyl
P = protecting group

FIG. 7.

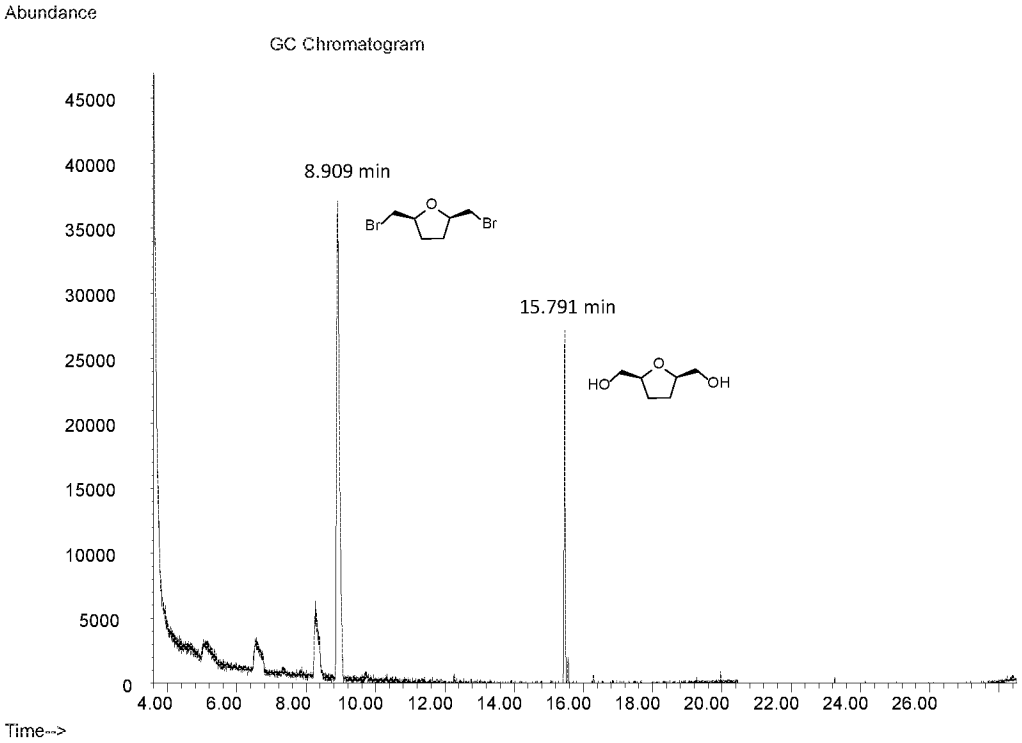
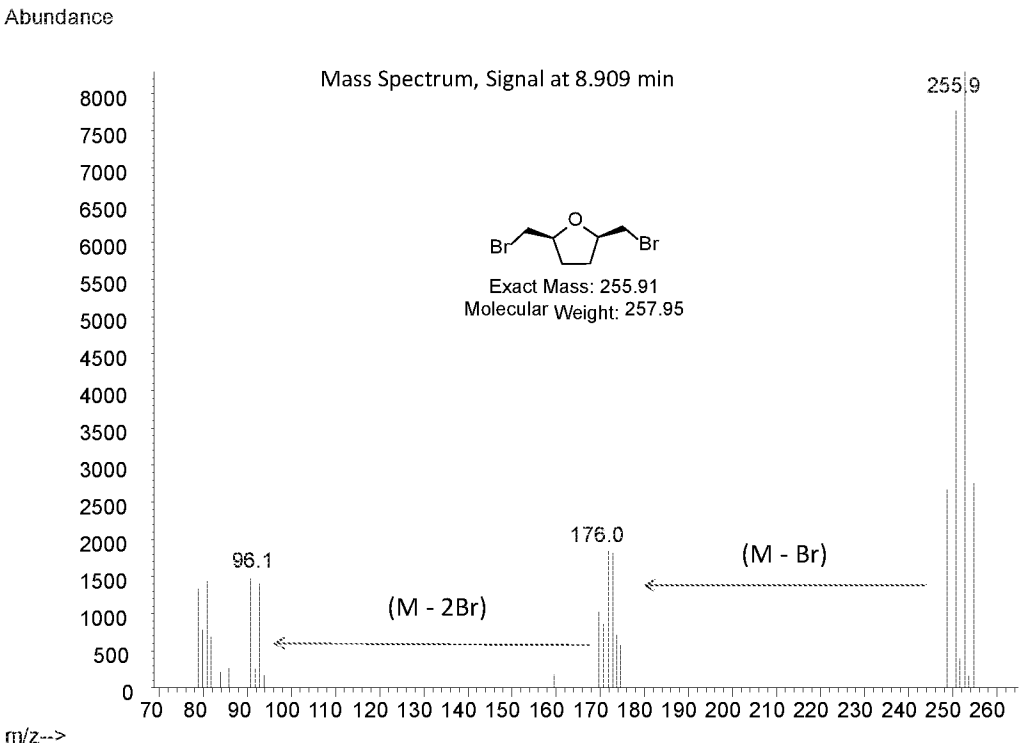


FIG. 8.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Br
O
Br
Exact Mass: 255.91
Molecular Weight: 257.95
176.0
96.1
(M - Br)
(M - 2Br)
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260
m/z-->

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/039005

A. CLASSIFICATION OF SUBJECT MATTER

C07D 307/08(2006.01)i, C07D 307/12(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 307/08; C07D 307/12; C07D 307/14; C09K 3/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & STN(Registry, Caplus, Casreact) & Google & Keywords: bHMTHF, HMT, triphenylphosphine, tetrahalomethane, furan, derivative compound

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEWTH, F. H. et al., "38. The conversion of sucrose into furan compounds. Part IV. Some aminotetrahydrofuran derivatives", Journal of the Chemical Society (Resumed), 1948, pp. 155-158 See page 156.	8-14
Y		1-7
Y	HOOZ, J. et al., "A rapid, mild procedure for the preparation of alkyl chlorides and bromides", Canadian Journal of Chemistry, 1968, Vol. 46, No. 1, pp. 86-87 See page 86; and eq. [5].	1-7
A	WO 2015-057365 A2 (ARCHER DANIELS MIDLAND COMPANY) 23 April 2015 See claims 1-26; and schemes 1, 2, 4.	1-14
A	ZANG, Y. et al., "Synthesis and oxygen permeation of novel polymers of phenylacetylenes having two hydroxyl groups via different lengths of spacers", Polymer, 2015, Vol. 56, pp. 199-206 See abstract; and scheme 1.	1-14
A	US 2012-0261618 A1 (BLOOM, P. D. et al.) 18 October 2012 See the whole document.	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2017 (20.03.2017)	**20 March 2017 (20.03.2017)**

Name and mailing address of the ISA/KR
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2016/039005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015-057365 A2	23/04/2015	AU 2014-334822 A1	10/03/2016
		CA 2922405 A1	23/04/2015
		CN 105555773 A	04/05/2016
		EP 3057946 A2	24/08/2016
		JP 2016-535084 A	10/11/2016
		KR 10-2016-0083865 A	12/07/2016
		MX 2016005015 A	24/06/2016
		US 2016-0207894 A1	21/07/2016
		WO 2015-057365 A3	11/06/2015
US 2012-0261618 A1	18/10/2012	AU 2009-319998 A1	03/06/2010
		AU 2009-319998 B2	16/07/2015
		BR PI0914384 A2	18/10/2016
		CN 102177146 A	07/09/2011
		CN 102177146 B	10/02/2016
		CN 103626639 A	12/03/2014
		CN 103626639 B	07/12/2016
		CN 105801528 A	27/07/2016
		EP 2350035 A2	03/08/2011
		EP 2350035 A4	25/07/2012
		EP 2350035 B1	13/01/2016
		ES 2566649 T3	14/04/2016
		MX 2011004526 A	14/12/2011
		US 2014-0200299 A1	17/07/2014
		US 2014-0239230 A1	28/08/2014
		US 2016-0297788 A1	13/10/2016
		US 8709286 B2	29/04/2014
		US 9416119 B2	16/08/2016
		US 9422258 B2	23/08/2016
		WO 2010-062689 A2	03/06/2010
		WO 2010-062689 A3	22/07/2010