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(54) Title: MONO- AND DIALKYL ETHERS OF FURAN-2,5-DIMETHANOL AND (TETRA-HYDROFURAN-2,5-DIYL)DIMETHANOL AND AMPHIPHILIC DERIVATIVES THEREOF

(57) Abstract: Linear mono- and dialkyl ethers of furan-2,5-dimethanol (FDM) and/or 2,5-bis(hydroxymethyl)tetrahydrofuran (bHMTHF), methods for their preparation, and derivative chemical compounds thereof are described. In general, the synthesis process entails a reaction of FDM or bHMTHFs in a polar aprotic organic solvent having a permittivity ( ) >8, at a temperature ranging from about -25C to about 100C, with either a) an unhindered Brnsted base with a pKa ?15 or b) a hindered Brnsted base having minimum pKa of about 16, and a nucleophile.

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MONO- AND DIALKYL ETHERS OF FURAN-2,5-DIMETHANOL AND (TETRA-HYDROFURAN-2,5-DIYL)DIMETHANOL AND AMPHIPHILIC DERIVATIVES THEREOF

BENEFIT OF PRIORITY

The present application claims benefit of priority of U.S. Provisional Application No.: 61/918,239, filed December 19, 2013, the contents of which are incorporated herein by reference.

FIELD OF INVENTION

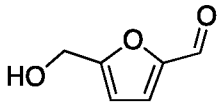
The present disclosure relates to certain cyclic bi-functional materials that are useful as monomers in polymer synthesis, as well as intermediate chemical compounds. In particular, the present invention pertains to ethers of furan-2,5-dimethanol (FDM) and/or (tetrahydrofuran-2,5-diyl)dimethanol (bHMTHF), methods for their preparation, and derivative chemical compounds thereof.

BACKGROUND

Research into renewable, bio-based surrogates for petroleum-based platform chemicals is on the rise in view of growing concerns about the impact of climate change and the gradual depletion of fossil fuels. Sugars are ubiquitous in agricultural materials, and hence are rational precursors for empirical innovations in the "green" materials area. Organic compounds that are readily derived from sugars include furans, robust cyclic ethers that possess structural features which 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), (Figure 1), a salient dehydration product of the abundant, inexpensive monosaccharide, fructose.

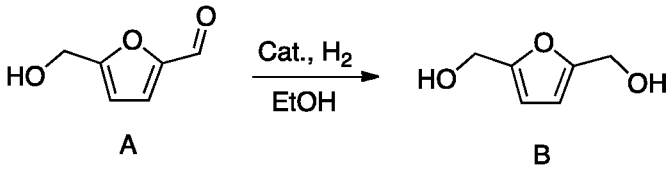
Fig. 1. Chemical structure of HMF



HMF is a versatile chemical antecedent to various furanic ring-based derivatives that are known intermediates for a multitude of chemical syntheses, and as plausible surrogates for aromatic hydrocarbons that derive from petroleum resources. Due to HMF's diverse functionalities, 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 alternates, 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.

HMF itself, however, is rather unsuitable as a chemical intermediate substrate, given its propensity to decompose under thermo-oxidative conditions. Thus, one should look to derivatives of HMF for practical commercial utility. One derivative is furan-2,5-dimethanol (abbreviated as FDM)(Scheme 1), which is produced from partial hydrogenation (aldehyde reduction) of HMF.

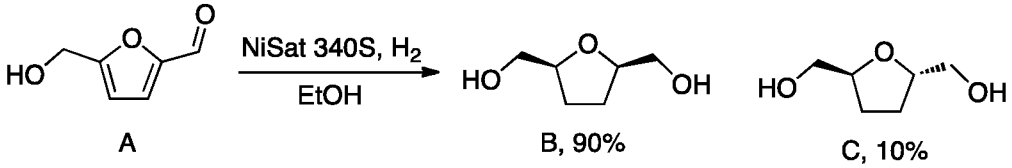
Scheme 1. – FDM **B** from partial hydrogenation of HMF **A**



A B

Another derivative is 2,5-bis(hydroxymethyl)tetrahydrofuran (abbreviated as bHMTHF), a saturated analog produced in a 9:1 cis (**B**):trans (**C**) diastereometic ratio when both the ring and aldehyde moieties of HMF are reduce completely (Scheme 2).

Scheme 2. – bHMTHFs from the exhaustive reduction of HMF



A B, 90% C, 10%

These materials can be of value as a molecular antecedent, for example, to polyesters, polyurethane foams, FDCA, plasticizers, additives, lubricants, and amphiphiles.

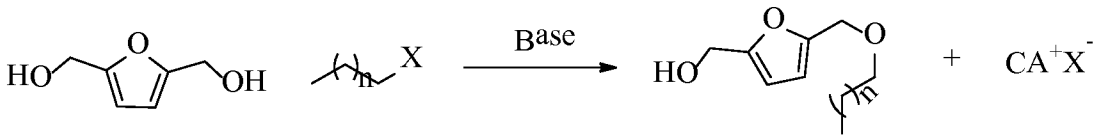
To become market competitive with petroleum products, however, the preparation of HMF derivatives from standard agricultural raw materials, such as sugars, need to become economically feasible in terms of cost. Heretofore, research for chemical derivatives using FDM and/or bHMTHFs has received limited attention due in part to the great cost and relative paucity (e.g., ~$200 per gram commercially) of the compounds. Recently, a need has arisen for a way to unlock the potential of FDM and bHMTHFs and their derivative compounds, as these chemical entities have gained attention 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. Given the potential uses, a cost efficient and simple process that can synthesis derivatives from FDM and/or bHMTHFs 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

The present disclosure describes, in part, linear mono- and di-alkyl ethers of furan-2,5-dimethanol (FDM) and/or 2,5-bis(hydroxymethyl)tetrahydrofuran (bHMTHF), and a process for their synthesis. Generally, the process includes contacting either FDM or bHMTHF in a polar aprotic

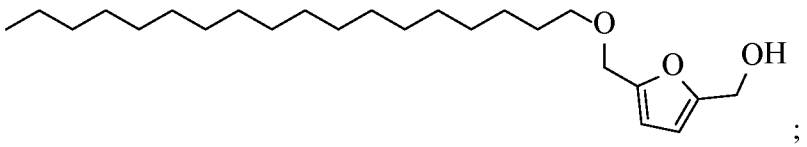
organic solvent having a permittivity (ε) >8, at a temperature ranging from about -25°C to about 100°C, with either a) an unhindered Brønsted base having a difference in pKa (ΔpKa) ≥15 relative to the pKa of a hydroxyl group of either FDM or bHMTHF or b) a hindered Brønsted base and a nucleophile.

In a particular embodiment, the present disclosure provides a method of preparing a mono-ether involving: contacting FDM with a Brønsted base and one or less molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the leaving group (nucleofuge), "n" is an integer from 5 to 25, and "CA" is a conjugate acid. The resultant mono-ether of FDM can be, for example, at least one of the following compounds:

a. (5-((octadecyloxy)methyl)furan-2-yl)methanol



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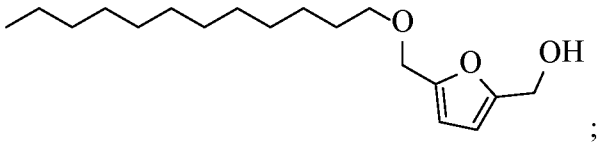
b. (5-((dodecyloxy)methyl)furan-2-yl)methanol



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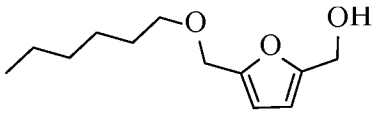
c. (5-((hexyloxy)methyl)furan-2-yl)methanol



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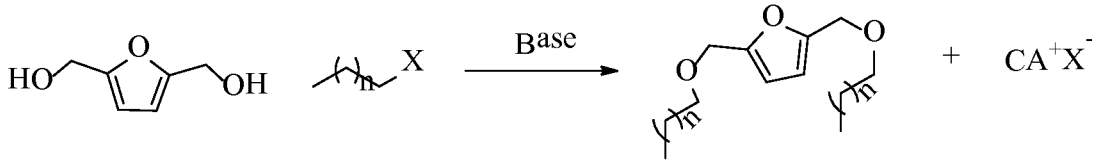
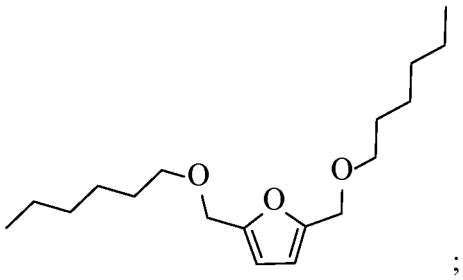
In an embodiment for preparing di-ethers, the method involves: contacting FDM with a Brønsted base and a minimum of 2 molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the nucleofuge, "n" is an integer from 5 to 25, and "CA" is a conjugate acid. The resultant di-ether of FDM can be, for instance, at least one of the following compounds:

a. 2,5-bis((hexyloxy)methyl)furan



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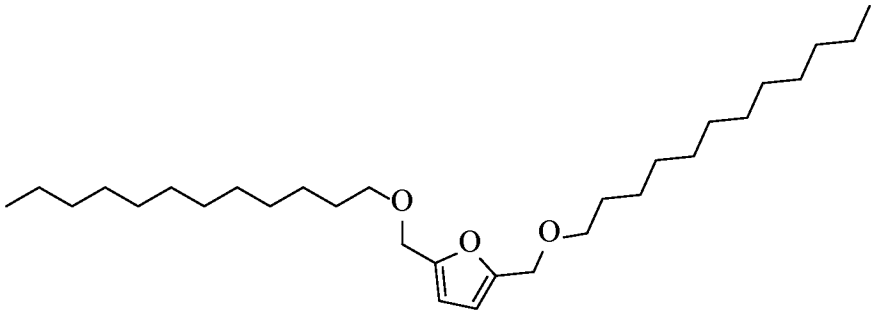
b. 2,5-bis((dodecyloxy)methyl)furan



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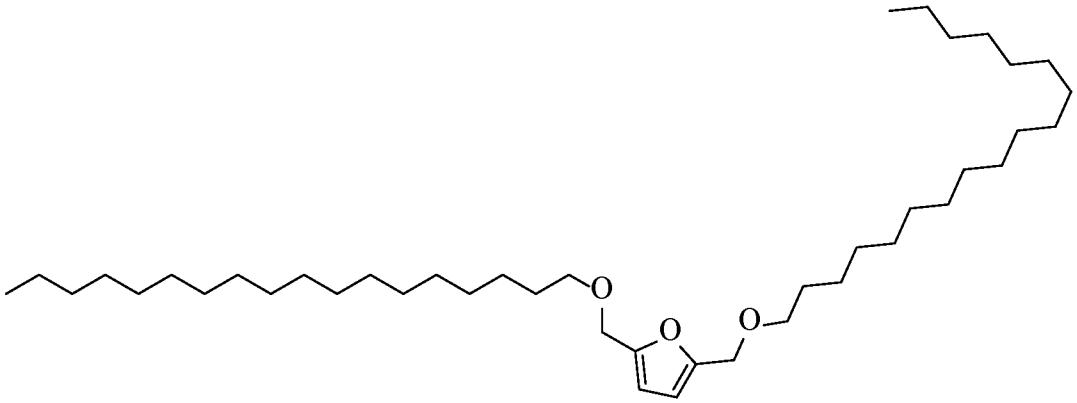
c. 2,5-bis((octadecyloxy)methyl)furan



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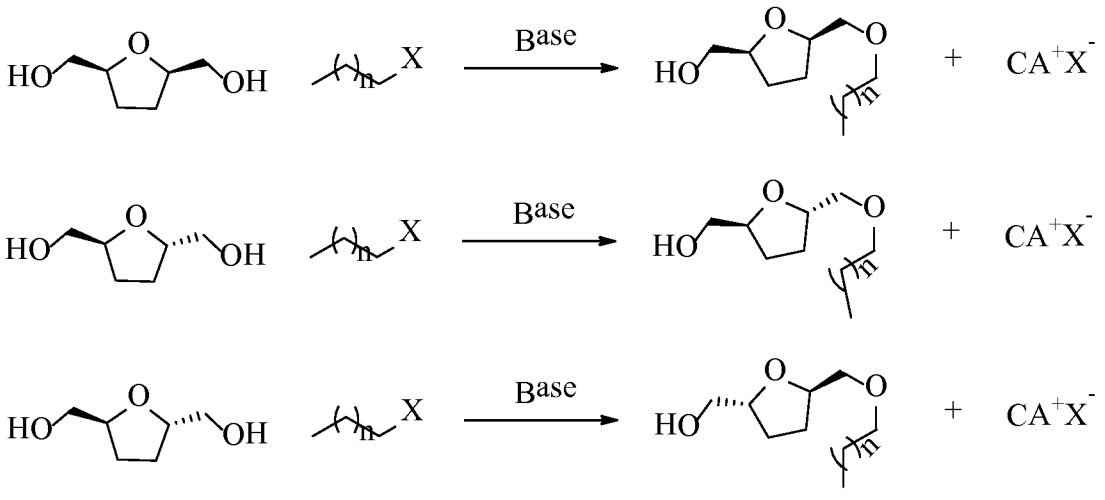
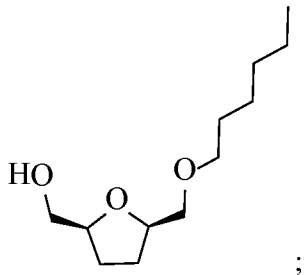
In yet a further embodiment, the present disclosure provides a method of preparing a mono-ether involving: contacting bHMTHFs with a Brønsted base and 1 or less molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the nucleofuge, "n" is an integer from 5 to 25, and "CA" is a conjugate acid. The resultant mono-ether of bHMTHF can be, for example, at least one of the following compounds:

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



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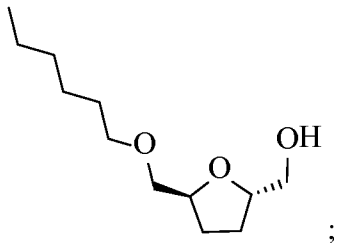
b. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol



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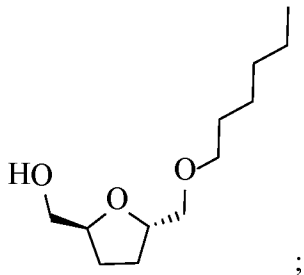
c. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol



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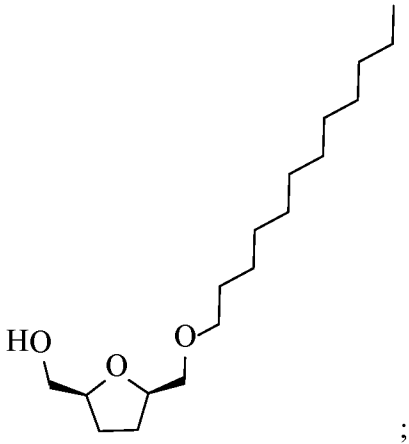
d. ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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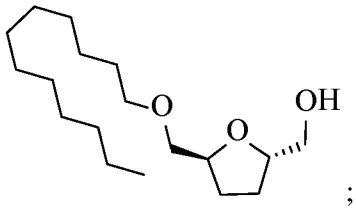
e. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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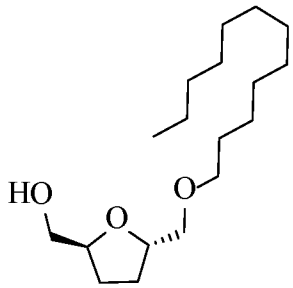
f. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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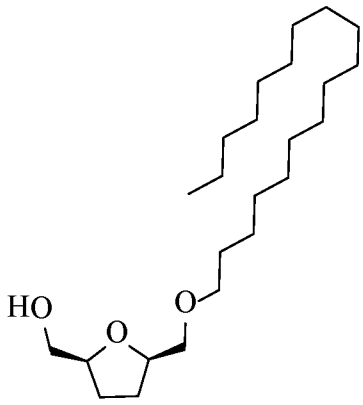
g. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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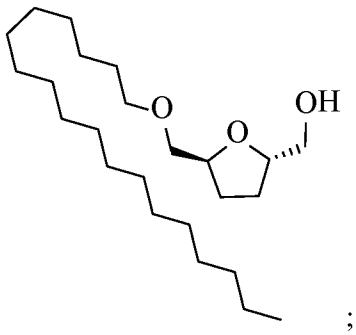
h. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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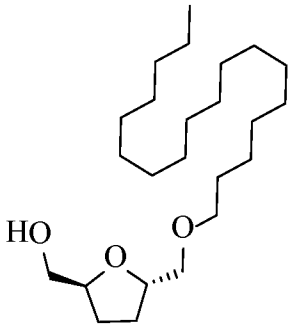
i. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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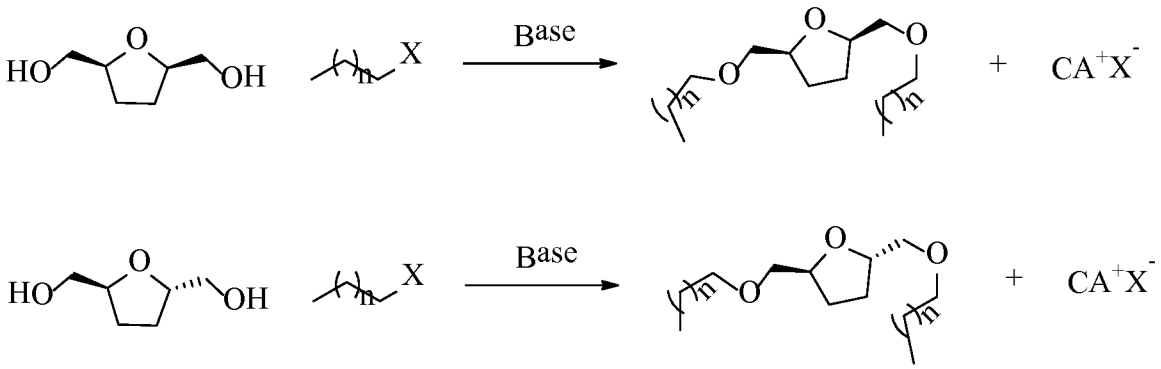
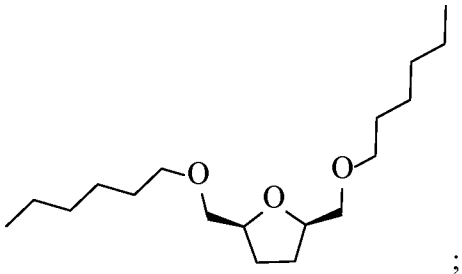
In an embodiment for preparing di-ethers, the method involves: contacting bHMTHFs with a Brønsted base and a minimum of two molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the nucleofuge, "n" is an integer from 5 to 25, and "CA" is a conjugate acid. The resultant di-ethers of bHMTHF can be, for instance, at least one of the following compounds:

a. (2R,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran



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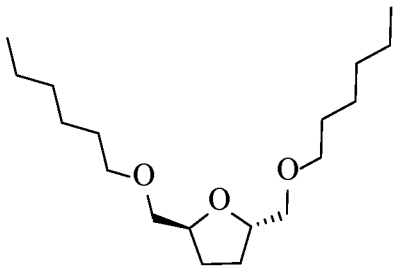
b. (2S,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran



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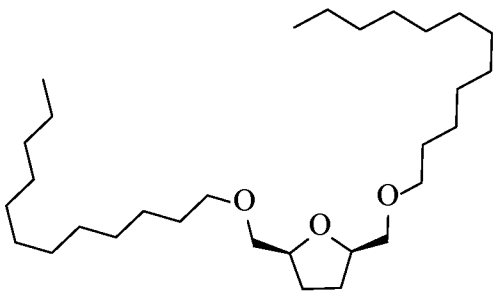
c. (2R,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran



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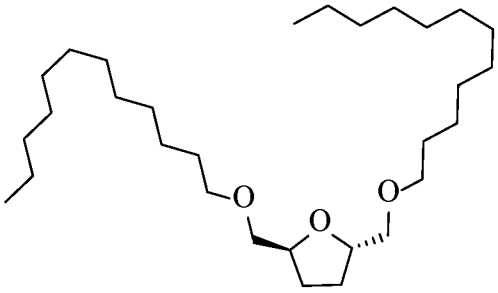
d. (2S,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran



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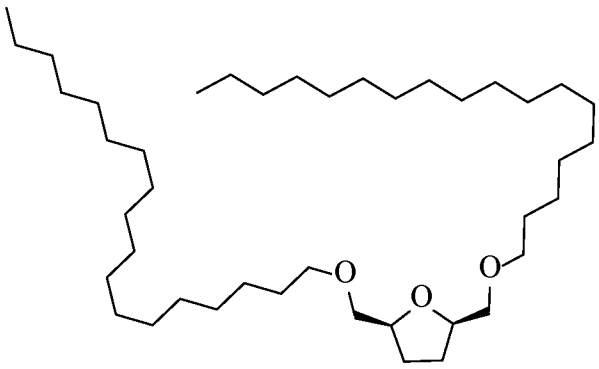
e. (2R,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran



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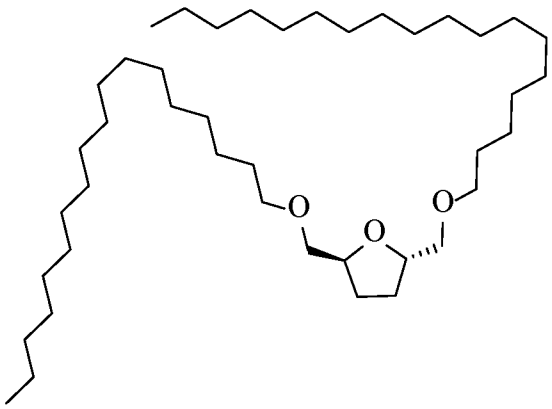
f. (2S,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran



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Additionally, in another aspect, the present disclosure pertains to derivative compounds from the linear mono-ethers of FDM and bHMTHF described above and methods for making the

derivatives. These derivative compounds are amphiphilic variants of the mono-ethers and are valued as precursors or plausible bio-based surfactants, dispersants, and/or hydrophiles.

Additional features and advantages of the present process 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.

DETAILED DESCRIPTION OF THE INVENTION

Section I. – Description

The present synthetic processes opens a pathway for direct preparation of linear alkyl ethers from the glycols FDM and/or bHMTHF, molecules that arise from the reduction of fructose derived 5-(hydroxymethyl)furfural (HMF) under mild conditions, and their derivative chemical compounds. (Although not necessary, in certain embodiments, the process may also include either first partially reducing HMF to FDM or fully reducing HMF to bHMTHFs in hydrogenation steps prior to selective etherification according to the present reaction process described herein.) The alkyl ethers, in turn, are valuable precursors with bio-based amphiphilic properties that can be used in surfactants, dispersants, and plasticizers.

In general, the process for generating alkyl ethers can be implemented in a single reaction step, in which the FDM or bHMTHF glycol is reacted with either one or two equivalents of a halogenated or sulfonated (leaving group) alkane, depending respectively on whether a mono- or di-ether product is desired. A hindered Brønsted base with a minimum pKa of about 10, preferably about 16, or an unhindered Brønsted base having a difference in pKa (ΔpKa) of $\geq$15 relative to the pKa of a hydroxyl group of either the FDM or bHMTHF is used to deprotonate the -OH moieties of the glycols, enhancing their nucleophilicities by several orders of magnitude towards nucleofuge displacement. (It is believed that with a pronounced difference in the pKa between the Brønsted base and the -OH moieties of the FDM and/or bHMTHF glycols, the Brønsted base should have a limited propensity to react with an alkyl halide or sulfonate in a nucleophilic substitution and/or elimination.) A polar aprotic organic solvent with a dielectric constant of $\geq$10, preferably $\geq$ 30, is employed to augment the basicity of the Brønsted base via charge separation capacities. Typically, the reaction is conducted at a temperature in a range from about -20°C to about 100°C, over a period of about 2 or 3 hours. In some other iterations the time may involve about 4 or 8 hours up to about 12 or 24 hours, as conditions may dictate.

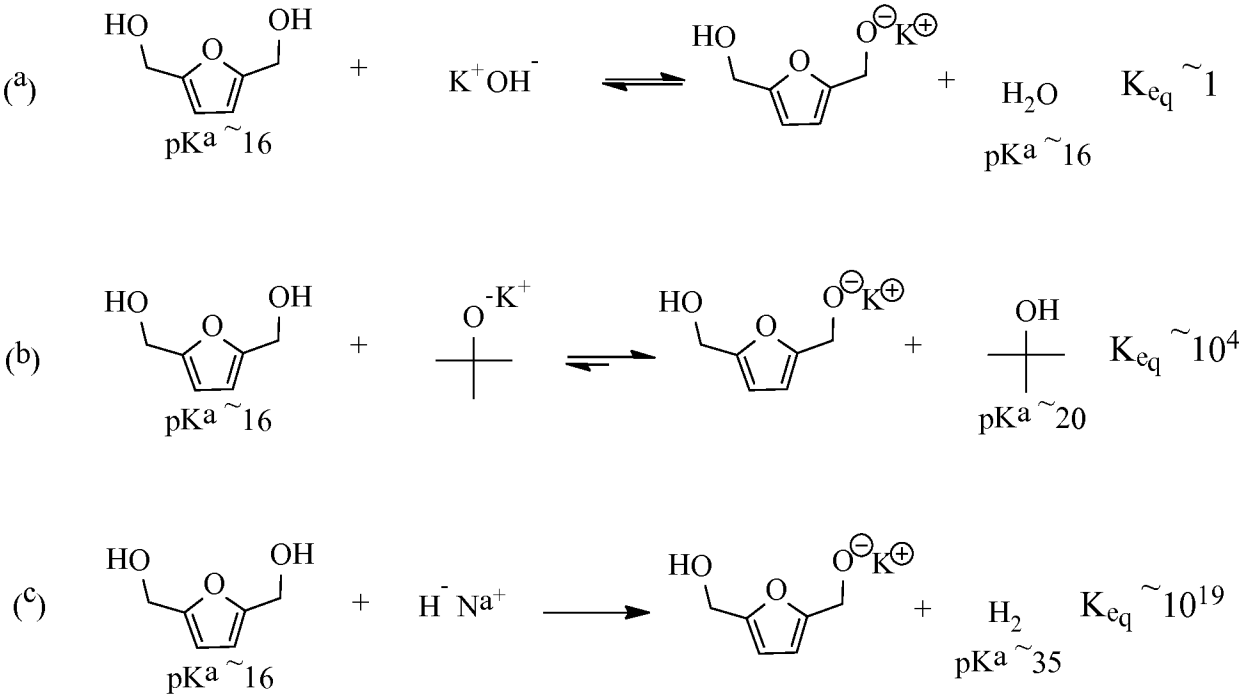
A. Brønsted Bases

As stated, the Brønsted base in the reaction serves to deprotonate the -OH moieties of the glycols. This helps to enhance the corresponding nucleophilicity of the glycols FDM and bHMTHF by about at least 6 or more orders of magnitude (e.g., 8-10-12) and drives halide/sulfonate

displacement on the alkyl reagent. The relative strength of a Brønsted base used in the reaction is of essence in furnishing high conversions of the glycols to, in particular, mono-alkyl ethers.

For some Brønsted bases that have a pKa of at least 10 to about 15, the synthesis reaction usually requires the addition of heat to proceed; hence, reaction temperatures of about 45°C-50°C or greater. This, however, can increase the risk of generating side-products (e.g., product of Brønsted base-nucleophilic substitution with the alkyl halide/sulfonate and/or alkenes formed from Brønsted base- mediated elimination of the alkyl halide/sulfonate) and reducing the overall yield of the desired synthesis. To minimize the generation of side products and counteract this phenomenon, a Brønsted base that has a pKa of at least ~16, typically ≥20, is favored according to certain embodiments of the present process. Brønsted bases with a greater pKa more easily reacts with the -OH moieties of the glycols. This is an advantage that helps one operate effectively the reaction at about ambient room temperatures (e.g., ~18°C -22°C) or lower temperatures. Some suitable Brønsted bases may include, for example, hydroxides (e.g., methoxide, ethoxide, *t*-butoxide, and benzyl oxide). Preferably, Brønsted bases having pKa's ≥ 30 are used, as the equilibrium for deprotonation favors generation of the desired products, such as illustrated in the examples in Scheme 3. Certain favored Brønsted bases of this type may include, for example, metallic hydrides (e.g., lithium, potassium, or sodium hydrides); metal amides (e.g., potassium or sodium amides); lithium diisopropylamide (LDA); organometalic compounds (e.g., alkyl lithium (e.g., methyl-lithium, n-butyl-lithium, or phenyl-lithium), alkyl magnesium, or alkyl cuprate) and Grignard reagents (e.g., ethylmagnesium bromide, phenylmagnesium bromide). In contrast, certain disfavored Brønsted bases may include, for example, nitrogen-centered bases (e.g., tertiary amines, aryl amine), because of low-pKa-favoring reactants and nucleophilic propensities.

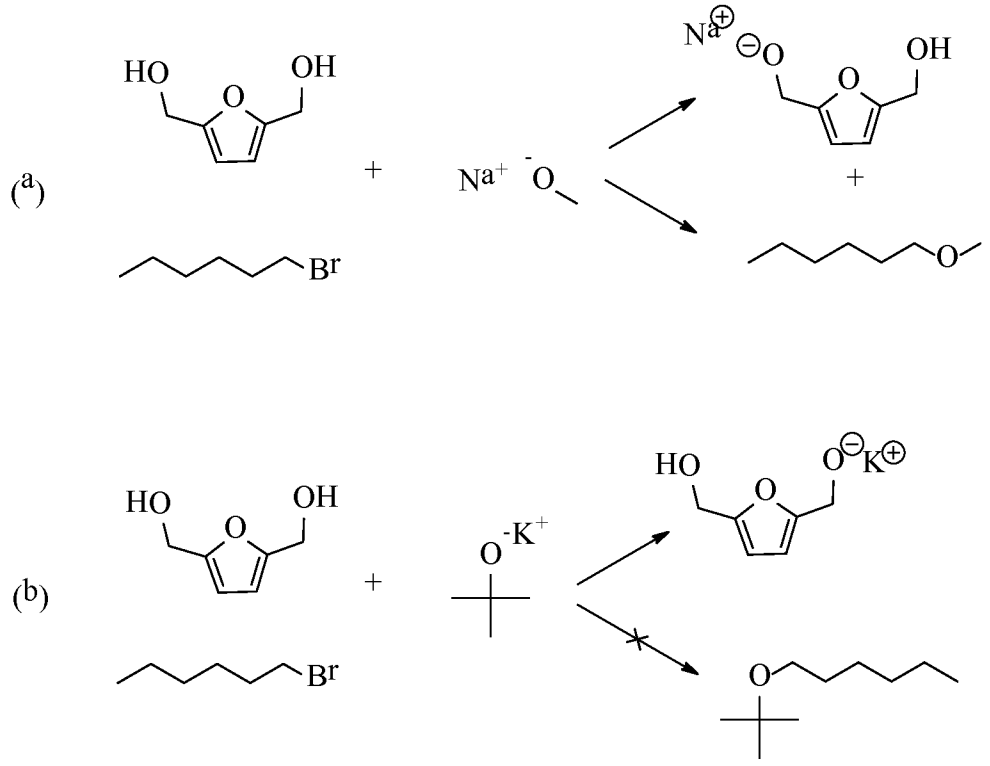
Scheme 3. – Equilibrium constants for various Brønsted base deprotonations of FDM: a) with potassium hydroxide; b) with potassium *t*-butoxide; c) with sodium hydride.



Reaction (a) shows when using a Brønsted base having a pKa ~16, the reaction tends to be at equilibrium between product and reactants. In Reaction (b), when using a Brønsted base having a pKa ~20, the reaction tend to favor the product more, whereas in Reaction (c) when using a Brønsted base having pKa ≥30, the reaction is driven completely towards product formation.

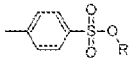
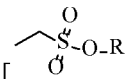
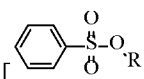
Another factor according to an embodiment of the present invention is to employ a Brønsted base that has molecular bulk. Propitiously, the bulky Brønsted base impedes undesired nucleophilic substitutions of the Brønsted base with the alkyl halide/sulfonate. Hence, a more sterically hindered Brønsted base enhances more effectively the reaction to produce predominantly the ether product. Scheme 4 illustrates this feature. As an example, reaction (a) using an unhindered Brønsted base tends to make a mixed product of both straight-chain and FDM ethers. In contrast, reaction (b) with a more bulky, hindered Brønsted base generates the FDM ethers alone.

Scheme 4. – Examples of Brønsted bases: a) unhindered, nuclephilic base, with sodium methoxide; b) hindered, non-nucleophilic base with potassium *t*-butoxide.



B. Alkyl Halides and Sulfonates

The etherification reaction of the present description can be characterized as a base-mediated, second order substitution reaction between a glycol and activated alkane. To achieve satisfactory yields of the desired ether in a polar aprotic organic solvent most expeditiously, the leaving group affixed to the alkane should exhibit favorable nucleofugal properties. Some species in this context can be, for example, halides (e.g., Cl, Br, I) and sulfonates (e.g., -OTf, -OTs,-OMs). Typically, one can conduct the reaction using straight-chain alkyl halides or sulfonates of 5 to 25 carbons in length. In some reactions, for instance, the alkyl chain lengths may range from about 5 or 8 to about 16 or 18 carbons, or about 6 or 10 to about 20 or 22 carbons (e.g., C_8-C_{18}; C_5-C_{15}; C_6-C_{12}), or any iteration therein between.

One can use a variety of sulfonates, including but not limited to, mesylate (methanesulfonate), CH_3SO_2O- [] (-OMs); triflate (trifluoromethanesulfonate), CF_3SO_2O- [] (-OTfs); tosylate (*p*-toluenesulfonate), $CH_3C_6H_4SO_2O$- [] (-OTs); esylate (ethanesulfonate), $C_2H_5SO_2O$- [] (-OEs); besylate (benzenesulfonate), $C_6H_5SO_2O$- [] (-OBs), and other alkyl and aryl sulfonates without limitation.

As halides, such as bromides, and alcohols are more economically accessible commercial alkane sources, they may be favored for larger scale, industrial uses according to some embodiments.

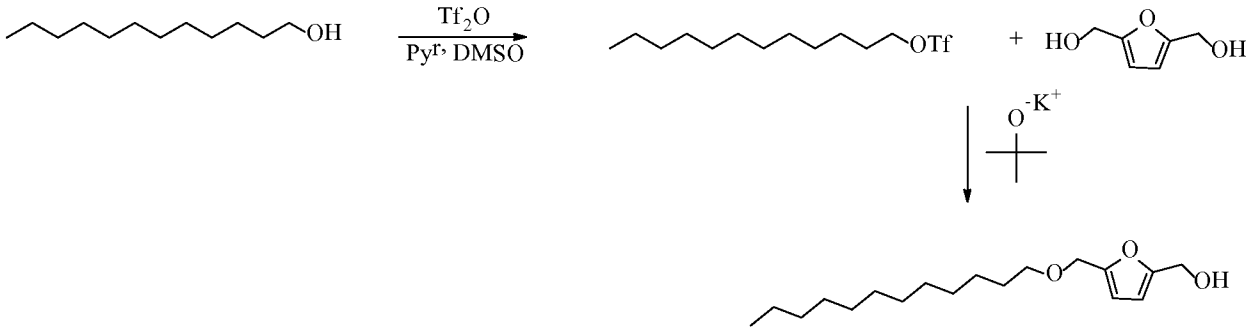
In a situation in which an alkyl halide is unavailable or prohibitively expensive, but the corresponding alcohol available, one may substitute the alcohol for the corresponding sulfonate through a simple sulfonation reaction.

In certain embodiments, the sulfonate is preferably a triflate because it is a powerful leaving group. This reaction exhibits relatively fast kinetics and generates an activated triflic complex. The reaction is usually conducted at a low temperature, less than 0°C (e.g., typically about -10°C or -12°C to about -20°C or -25°C), to control the reaction kinetics more easily. This reaction is essentially irreversible, as the liberated triflate is entirely non-nucleophilic. The triflic complex then reacts readily with the FDM or bHMTHF, forming respectively a FDM or bHMTHF-triflate with concomitant release and protonation of a nucleophilic base (e.g., pyrimidine, dimethyl-aminopyridine, imidazole, pyrrolidine, and morpholine).

The tosylate, mesylate, brosylate, benzenesulfonate, ethylsulfonate or other sulfonate species can be as effective as triflate in imparting leaving groups, and manifesting overall yields that were commensurate with that achieved with triflate. But, these other sulfonates tend to react more slowly in comparison to the triflate. To compensate for this, operations at higher temperatures are typically needed for better yields when using these other species.

Often the conversion can be performed sequentially in a single reaction vessel, prior to executing a displacement reaction with a glycol, such as demonstrated in Scheme 5.

Scheme 5. – Single-vessel sequential sulfonation, displacement reaction between FDM and dodecanol.

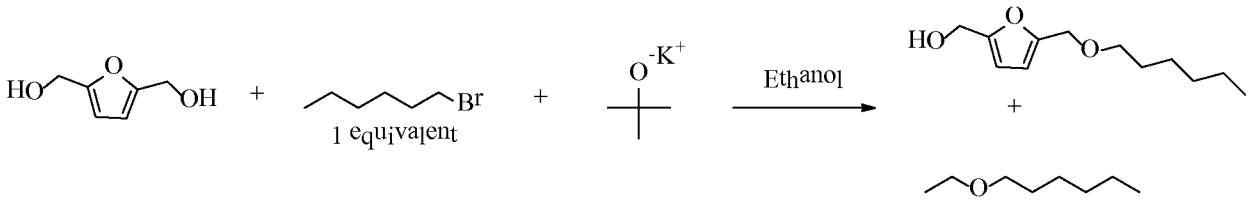


C. Organic Solvents

In the present synthesis process, aprotic solvents are used, as they contain no functionality labile to covalent modifications with the glycol, alkyl halide/sulfonate and Brønsted base of the title reaction, and thus do not interfere with the Sn2-driven process. Furthermore, polar aprotic solvents (i.e., solvents with a permanent dipole moment but without the ability to act as hydrogen bond donors) are favored in the present etherification reactions. Polar aprotic solvents adequately dissolve the glycols and the alkyl halide/sulfonate, a feature for an efficient reaction to occur. The function is dissimilar to apolar solvents like hexane or benzene, which lack the ability to effectuate charge separation of the anionic Brønsted base from its cation counterpart, rendering it inactive. Also, polar

aprotic solvents tend not to react with the alkyl halide/sulfonate (cf., Scheme 6, ethanol, a polar protic solvent, which can generate undesired side products).

Scheme 6. – Solvent etherification potential with ethanol, a polar protic solvent.



In aprotic solvents a greater dielectric constant can help prevent the solvent from reacting with the primary reagents, hence minimizing formation of side-products. The reactions of the present synthesis process are conducted in solvents with a relative permittivity ≥ ε_r 25, typically about 30 or 35. For example, DMSO and DMF exhibit relatively high dielectric constants (e.g., ~30 or 32). Other solvents with high boiling points and dielectric constants, such as NMP and DMA, are effective in cyanide for sulfonate displacement reactions. The reaction to derivatize FDM or bHMTHF with a sulfonate is performed in a solution of solvent having a boiling point ≥ 110°C.

Some common polar aprotic solvents that are amenable to this process are dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), hexamethylphosphoramide (HMPA), acetone, acetonitrile (ACN), nitromethane, sulfolane, tetrahydrofuran (THF), 1,4-dioxane, and ethyl acetate.

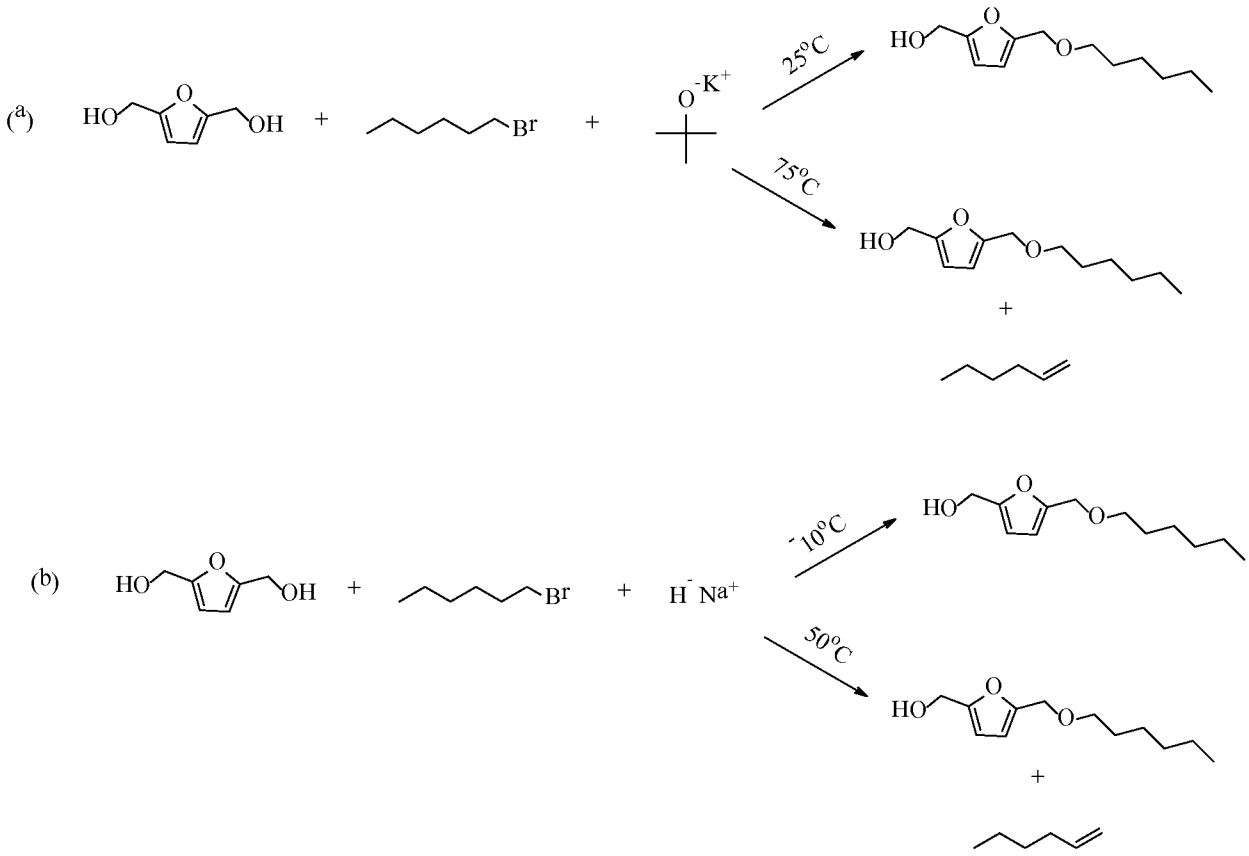
A further consideration when using polar aprotic solvent in the etherification process is to amply charge separate the Brønsted base so that the glycol -OH moieties can be deprotonated. A reflection of the power to charge separate is the permittivity of dielectric constant, represented by ε (no units), with the larger number signifying a greater capacity to sequester the ions. In general, e > 20 is the advantageous for effective charge separation, with exceptions being THF (ε = 7.58) and 1,4-dioxane (ε = 2.21) whose oxygen atoms can coordinate with cations captodatively. The preferred ε is >30. Examples of polar aprotic solvents with propitious ε are DMSO (ε = 46.7), sulfolane (ε = 43.3), DMA (ε = 37.8), acetonitrile (ε = 37.5), DMF (ε = 36.7), nitromethane (ε = 35.9), NMP (ε = 32.0), HMPA (ε = 30.0), acetone (ε = 20.0).

D. Reaction Temperature

One of the advantages of the present synthesis process is that it can be operated in a relatively mild temperature range, and under less harsh conditions than some other conventional reaction processes. Depending on the particular Brønsted base, the reaction temperatures can span between about -25°C or -20°C to about 80°C or 100°C. Typically, the reaction temperature is in a range from about -12°C or -7°C to about 65°C or 70°C, more typically from about -10°C or -5°C to about 40°C or 50°C. In certain embodiments, preferred temperatures may range from about -10°C or -8°C to

about 25°C or 30°C, or about -3°C or 0°C to about 32°C or 35°C, inclusive. Preferably, the reaction can be performed at or below ambient room temperatures (e.g., ≤ about 22°C or 25°C). Because of a potential or tendency to generate olefins from base-mediated elimination of an alkyl halide/sulfonate at elevated temperatures, and potential slow reaction kinetics when uses certain Brønsted bases (Scheme 7), temperature control for the present selective etherification is an important factor. (As aforementioned, a Brønsted base with a pKa lower than 16, which designates that of the -OH moieties of FDM and bHMTHF, tends to favor the reactants at equilibrium; hence the reaction is performed at an elevated temperature (e.g., >25°C, 35°C, or 40°C) to drive the etherification, albeit with a greater risk of forming side products (olefins).)

Scheme 7. – Reaction temperature profiles with a) potassium *t*-butoxide, and b) sodium hydride as Brønsted bases.



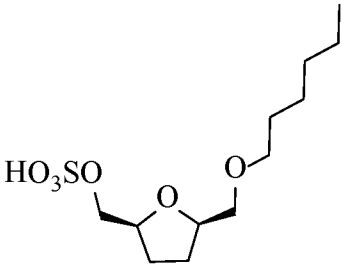
E. Derivatives

In another aspect, various amphiphilic compounds can be synthesized from FDM or bHMTHF ethers as a starting or precursor material. Such derivative materials can be useful as substitutes for existing compounds or new chemical building blocks in surfactant, dispersant, plasticizer or a component in other applications. The derivative amphiphilic compounds can be prepared according to various chemical reactions available for organic synthesis. Preparations of

some representative derivative compounds are further described in the accompanying examples below.

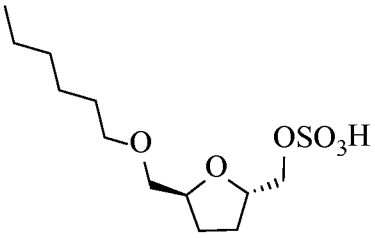
The methods may include: reacting either a mono-ether of bHMTHF or FDM with: a) chlorosulfonic acid to generate a sulfate, or b) trifluoromethanesulfonic anhydride to generate a trifluoromethanesulfonate, respectively, of each glycol species. For the derivatives of bHMTHF mono-ethers, a sulfate product can be, for example, at least one of the following compounds:

a. ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate



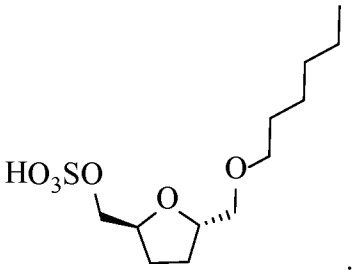
;

b. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate



;

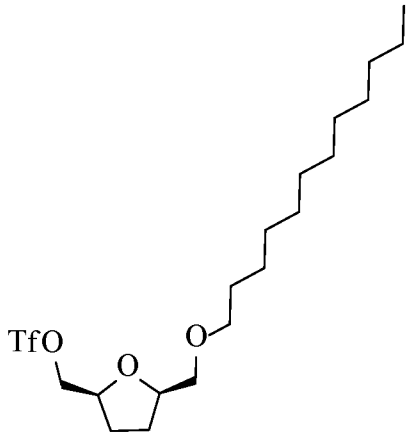
c. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate



.

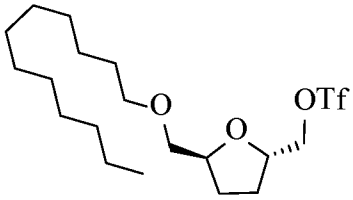
Alternatively, a trifluoromethanesulfonated mono-ether generated from the bHMTHF mono-ether can be, for example, at least one of the following compounds:

a. ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



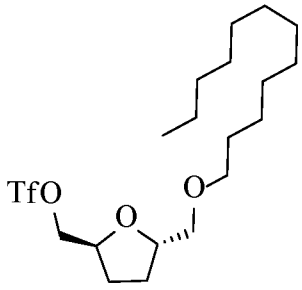
;

b. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



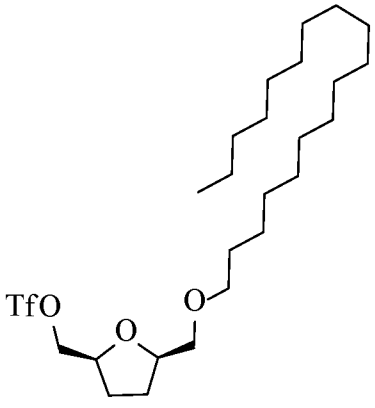
;

c. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



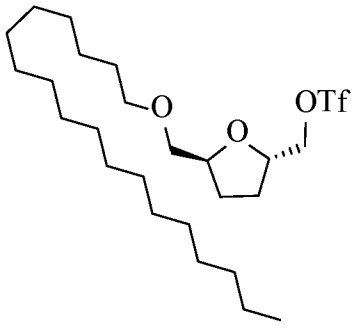
;

d. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



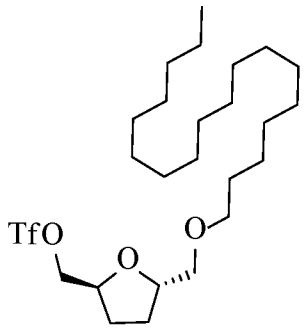
;

e. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



;

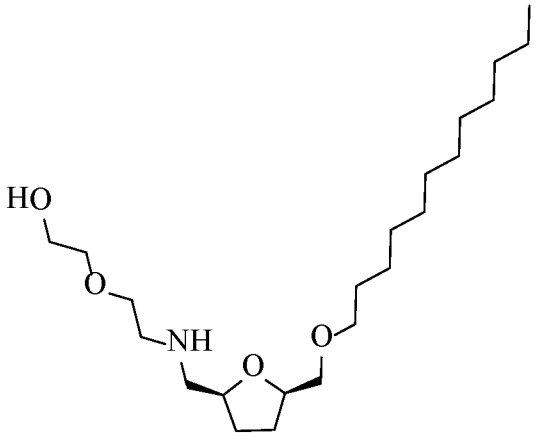
f. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



.

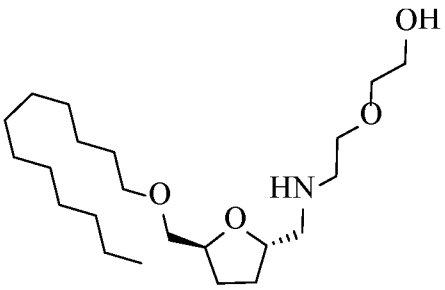
The process may further involve generating an ethoxyethanolamine derivative of the bHMTHF mono-ether sulfonate compound by substitution of a sulfonate group with an ethanolamine. The resultant ethoxyethanolamine prepared can be, for instance, at least one of the following compounds:

a. 2-(2-((((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



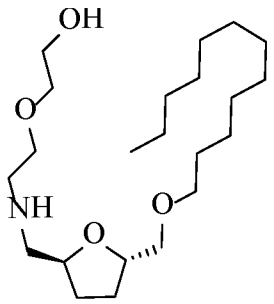
;

b. 2-(2-((((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



;

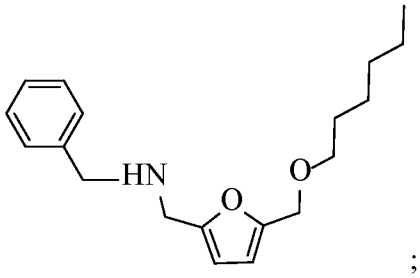
c. 2-(2-((((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



.

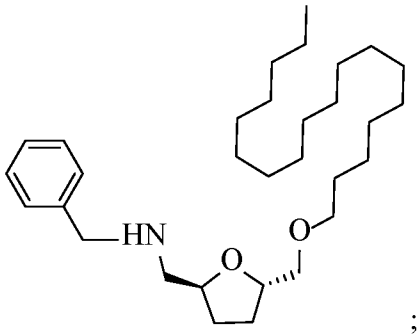
In an alternative embodiment, the process may further include generating a primary amine of a bHMTHF monoether by substitution of a trifluoromethanesulfonate group to form a benzyl-amine, such as one of the following:

a) N-benzyl-1-(5-((hexyloxy)methyl)furan-2-yl)methanamine



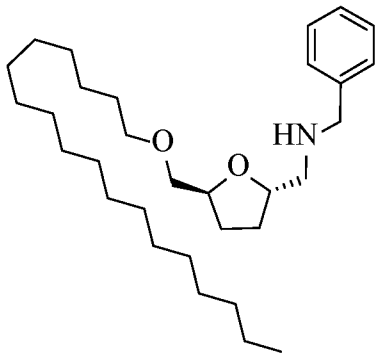
;

b) N-benzyl-1-((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



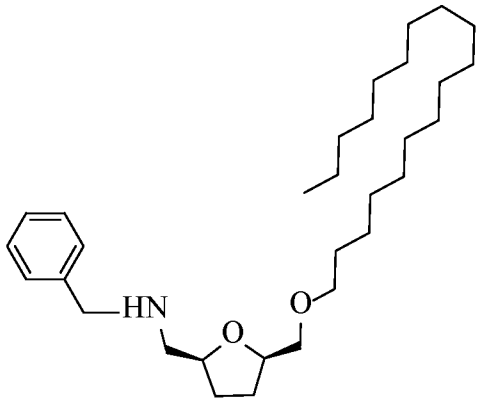
;

c) N-benzyl-1-((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



; and

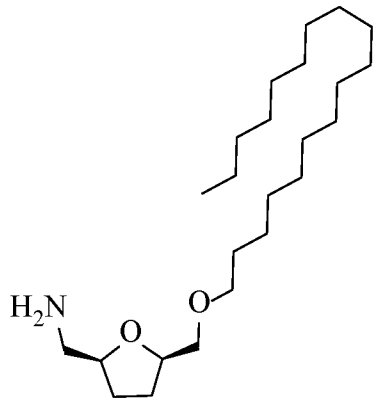
d) N-benzyl-1-((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



.

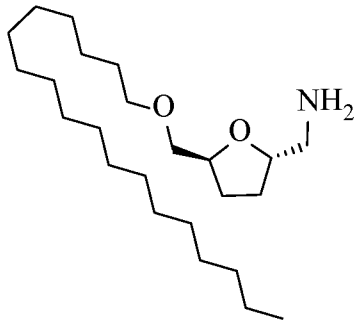
Subsequently, one generates the primary amine by catalytic debenzylation with, for example, a palladium catalyst on carbon. The resultant primary amine can be, for instance, at least one of the following compounds:

a. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



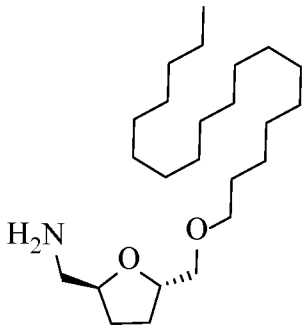
;

b. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



;

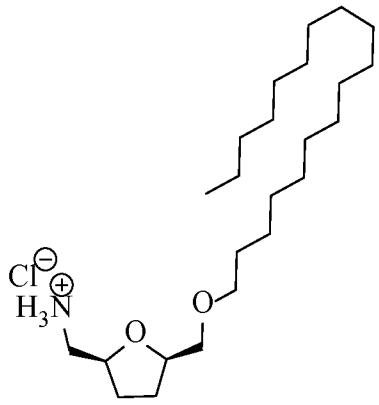
c. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



.

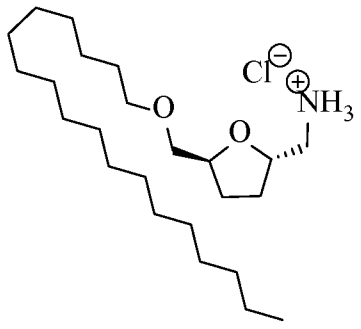
In another alternative embodiment, the process may further include preparing a primary ammonium salt of the bHMTHF monoether by substitution of a trifluoromethanesulfonate group followed by catalytic debenzylation and protonation by a Brønsted acid having a pKa $\leq$ 0 (e.g., HCl, HBr, HI). The resultant primary ammonium group can be, for example, at least one of the following compounds:

a. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



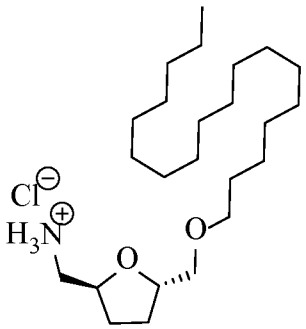
;

b. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



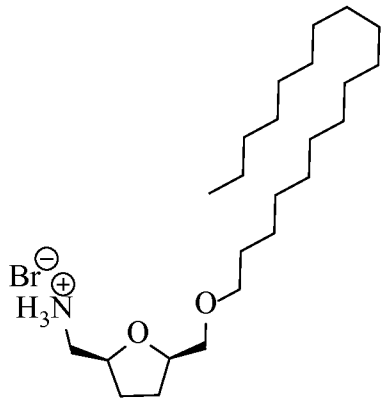
;

c. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



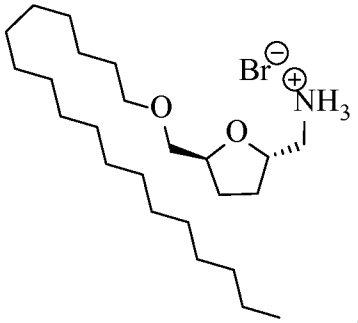
;

d. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



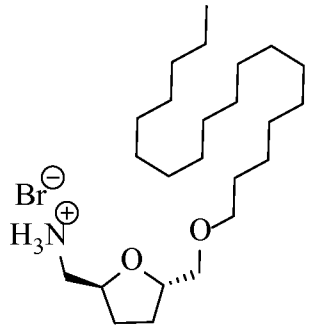
;

e. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



;

f. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



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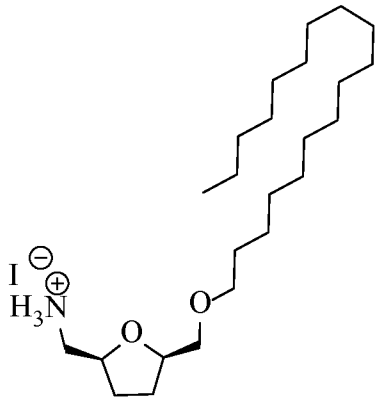
g. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide



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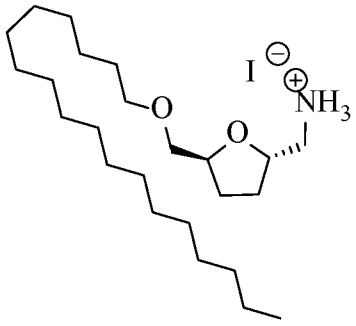
h. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide



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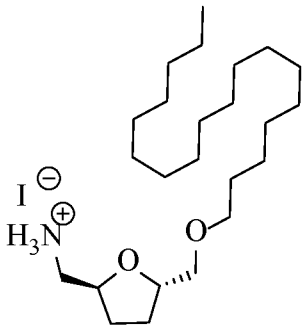
i. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide



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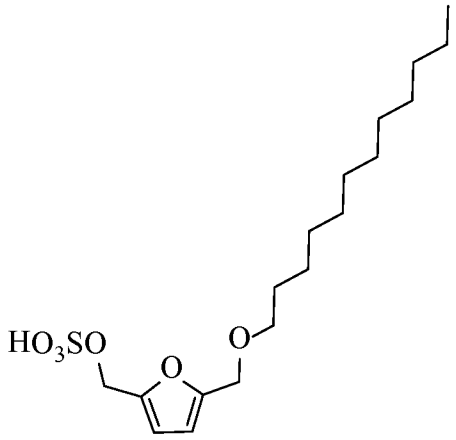
The salt version of the primary amine renders the molecule more amphiphilic with a polar head for cationic surfactants.

For the derivative compounds prepared from a reaction with a mono-ether of FDM, the resultant sulfate product can be for example:

a. (5-((dodecyloxy)methyl)furan-2-yl)methyl hydrogen sulfate



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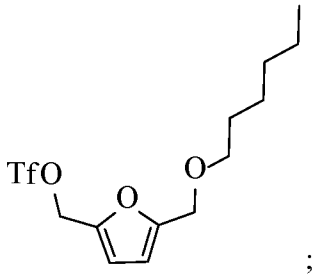
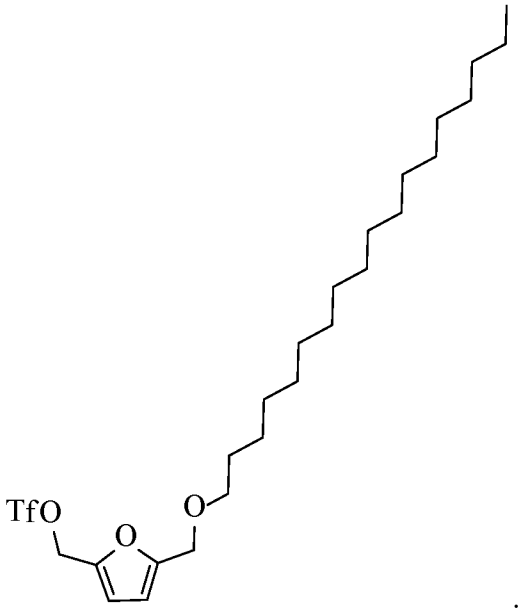
And, the resultant trifluoromethanesulfonate from FDM mono-ether can be, for example, at least one of the following structures:

a. (5-((hexyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate



;

b. (5-((octadecyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate



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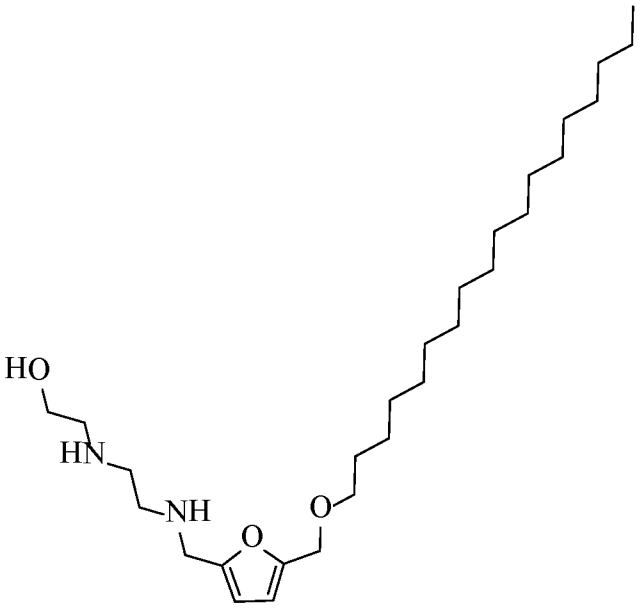
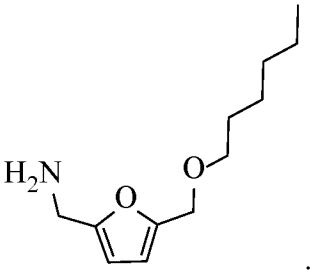
Similar to the process with bHMTHF mono-ethers, the process for preparing a primary ammonium group using FDM mono-ethers also involves substitution of a trifluoromethanesulfonate group followed by catalytic debenzylation and protonation by a Brønsted acid having a pKa $\leq$ 0. The resultant aminoethylethanolamine can be, for example, the following:

a. 2-((2-(((5-((octadecyloxy)methyl)furan-2-yl)methyl)amino)ethyl)amino)-ethanol



According to another embodiment, a primary amine derivative that is prepared using FDM mono-ether as the starting material can be, for example, the following: (5-((hexyloxy)methyl)furan-2-yl)methanamine



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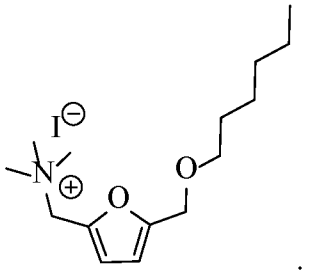
Alternatively, one can also prepare a quaternary trimethylammonium salt such as: 1-(5-((hexyloxy)methyl)furan-2-yl)-N,N,N-trimethylmethanaminium iodide



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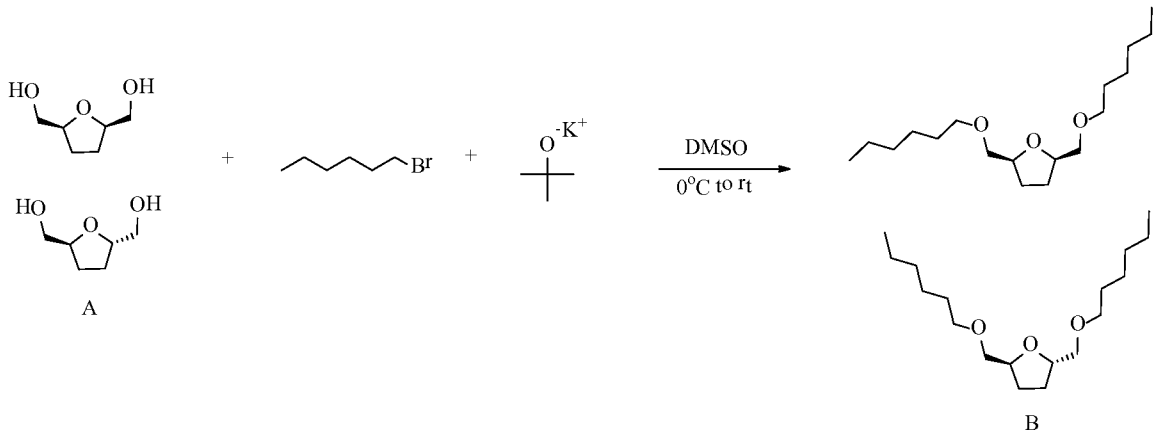
Section II. – Examples

The present synthesis system is further illustrated in the following examples for making: A) bHMTHF di-ethers; B) bHMTHF mono-ethers; C) derivatives of bHMTHF mono-ethers; D) FDM di-ethers; E) FDM mono-ethers; and F) amphiphilic derivatives of FDM mono-ethers .

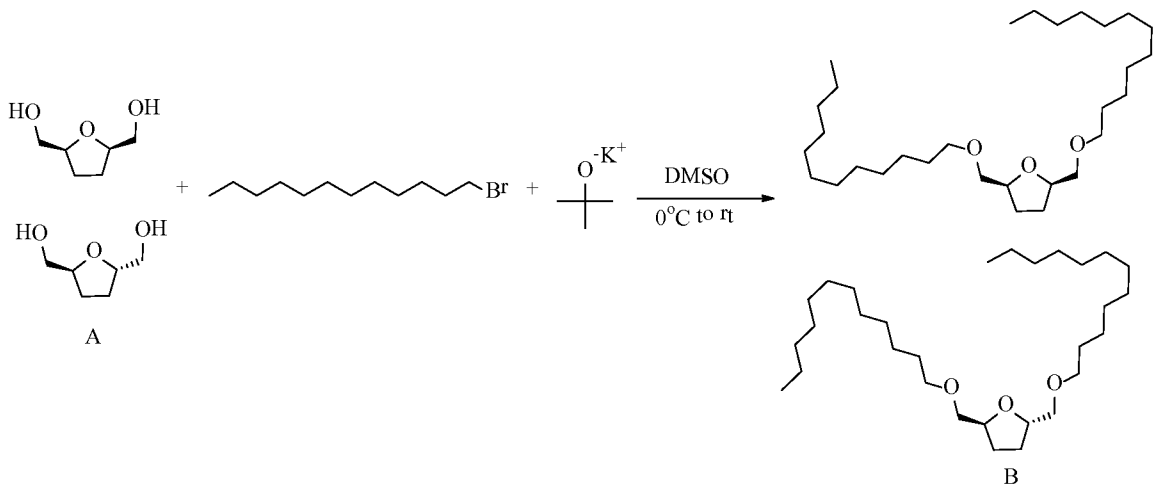
A. bHMTHF Diethers

Example 1: Synthesis of (2R,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran, **B**.



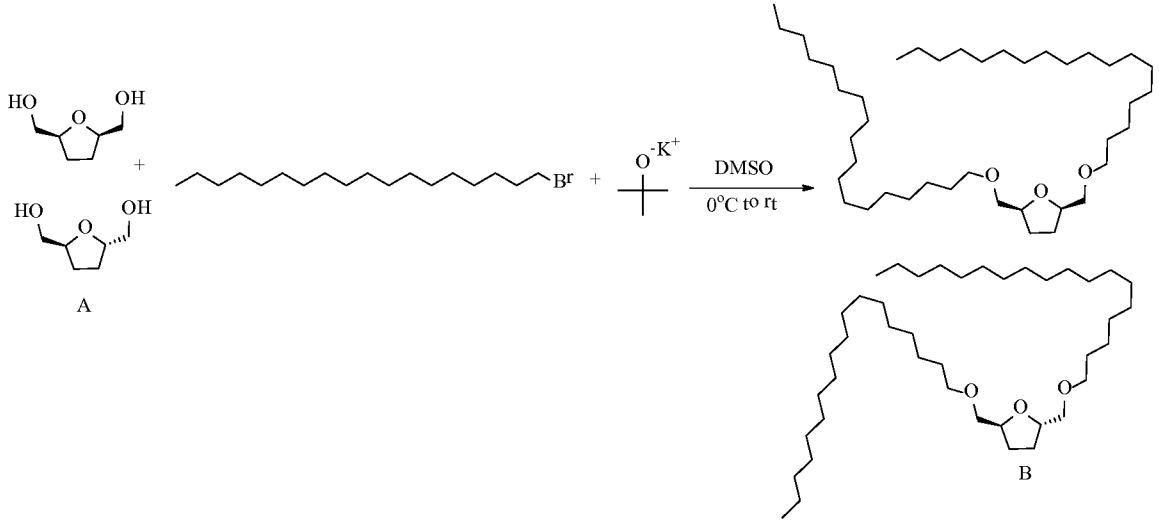
Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 106 mg of potassium *t*-butoxide (0.946 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 117 µL of 1-bromohexane (0.832 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 9:1 hexanes/ethyl acetate. The signature band for **A** (baseline) was patently absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 10% ethyl acetate in hexanes afforded 64 mg of a **B** as light yellow oil after inspissation (56% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$, *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 4.21 (m, 2H), 3.64 (m, 2H), 3.40-3.36 (m, 4H), 2.11 (m, 2H), 1.61 (m, 2H), 1.47 (t, J = 6.2 Hz, 4H), 1.40 (m, 4H), 1.35-1.30 (m, 10H), 0.94 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 87.1, 78.3, 68.9, 33.2, 31.2, 29.8, 25.4, 23.1, 13.3.

Example 2: Synthesis of (2R,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 106 mg of potassium *t*-butoxide (0.946 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 200 μL of 1-bromododecane (0.832 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 10:1 hexanes/ethyl acetate. The signature band for **A** (baseline) was noticeably absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 7% ethyl acetate in hexanes afforded 118 mg of a **B** as a beige solid after concentration (65% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$, *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 4.20 (m, 2H), 3.63 (m, 2H), 3.41-3.38 (m, 4H), 2.09 (m, 2H), 1.59 (m, 2H), 1.49 (t, J = 6.2 Hz, 4H), 1.42 (m, 4H), 1.38-1.30 (m, 34H), 0.92 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 87.4, 78.1, 69.1, 33.0, 31.2, 30.9, 29.8, 28.7, 26.2, 25.4, 24.9, 24.1, 23.3, 22.1, 13.3.

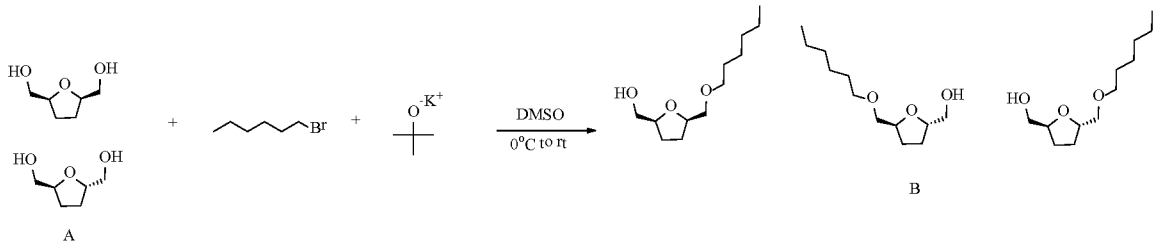
Example 3: Synthesis of (2R,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran and (2S,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 106 mg of potassium *t*-butoxide (0.946 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 277 μL of 1-bromooctadecane (0.832 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 11:1 hexanes/ethyl acetate. The signature band for **A** (baseline) was noticeably absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 5% ethyl acetate in hexanes afforded 132 mg of a **B** as an off-white solid after concentration (55% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$, *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 4.20 (m, 2H), 3.63 (m, 2H), 3.41-3.38 (m, 4H), 2.08 (m, 2H), 1.65 (m, 2H), 1.48 (t, J = 6.2 Hz, 4H), 1.41 (m, 4H), 1.40-1.28 (m, 58H), 0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ *salient peaks corresponding to the cis (meso) derivative in large excess*) δ (ppm) 87.4, 78.1, 69.1, 33.0, 31.2, 30.9, 29.8, 28.7, 26.2, 25.4, 24.9, 24.1, 23.8, 23.3, 22.9, 22.7, 22.5, 22.1, 21.7, 21.3, 13.3.

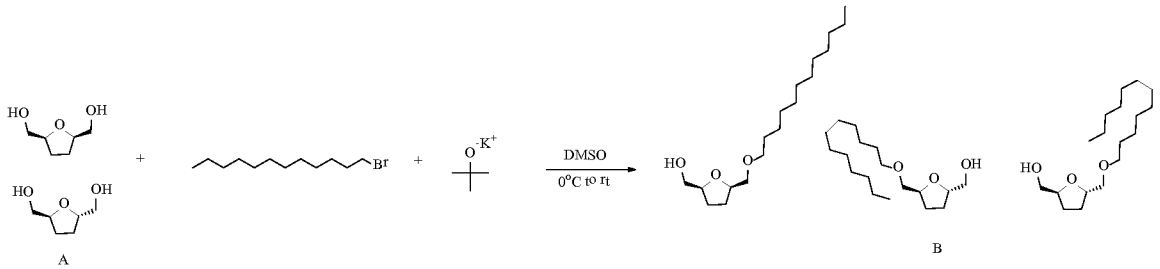
B. bHMTHF Monoethers

Example 4: Synthesis of ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol, ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol, and ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 42 mg of potassium *t*-butoxide (0.378 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 53 µL of 1-bromohexane (0.378 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited two salient bands (cerium molybdate stain) after developing in 3:1 hexanes/ethyl acetate, Rf_1 = 0.54 (targets **B**), Rf_2 = baseline (unreacted THF-diols **A**). Analysis by GC/MS (EI, Initial 70°C, ramp 5°C per minute to 350°C, hold for 60 min.) manifested three salient signals with retention times as follows: a) 12.4 min., m/z 132.1 (M+, unreacted THF-diols), b) 18.7 min., m/z 216.1 (M+, one or more of target monoethers), 19.2 min. m/z 216.1 (M+, one of more of the target mono-ethers).

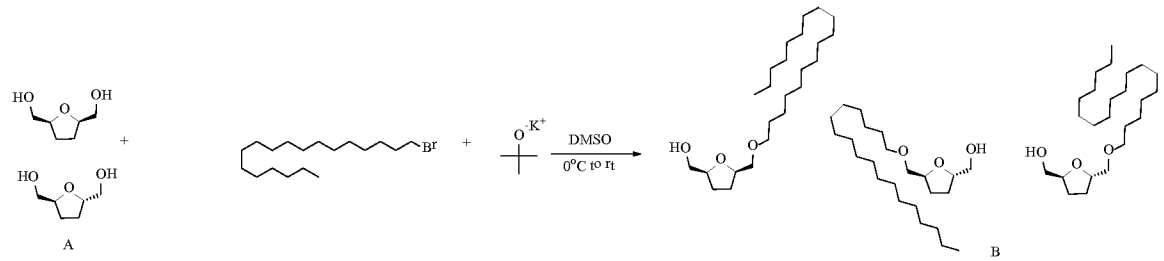
Example 5: Synthesis of ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol, ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol, ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-

diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 42 mg of potassium *t*-butoxide (0.378 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 91 µL of 1-bromododecane (0.378 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited two salient bands (cerium molybdate stain) after developing in 5:1 hexanes/ethyl acetate, Rf_1 = 0.57 (targets **B**), Rf_2 = baseline (residual THF-diols **A**). Analysis by GC/MS (EI, Initial 70°C, ramp 5°C per minute to 350°C, hold for 60 min.) manifested three salient signals with retention times as follows: a) 12.3 min., m/z 132.1 (M+, unreacted THF-diols **A**), b) 25.1 min., m/z 300.2 (M+, one or more of target monoethers), 25.9 min. m/z 300.2 (M+, one of more of the target mono-ethers).

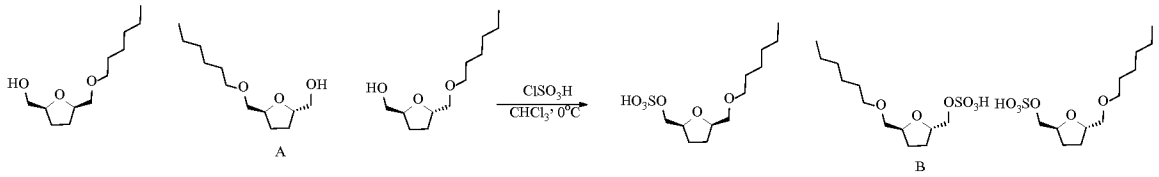
Example 6: Synthesis of ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol, ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol, ((2S,5S)-5((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2R,5S)-tetrahydrofuran-2,5-diyl)dimethanol and ((2S,5S)-tetrahydrofuran-2,5-diyl)dimethanol (0.378 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 42 mg of potassium *t*-butoxide (0.378 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 126 µL of 1-bromododecane (0.378 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 6:1 hexanes/ethyl acetate, Rf_1 = 0.62 (targets **B**) and Rf_2 = baseline (unreacted THF-diols **A**). The signature band for **A** was patently absent, suggesting this reagent had fully converted. Analysis by LC/MS (APCI-, RP 1.7 µm, 2.1 x 50 mm,, mobile phase-gradient 50 to 0% aqueous in CH_3CN, flow rate 0.5 mL/min., M-1) m/z 383.4.

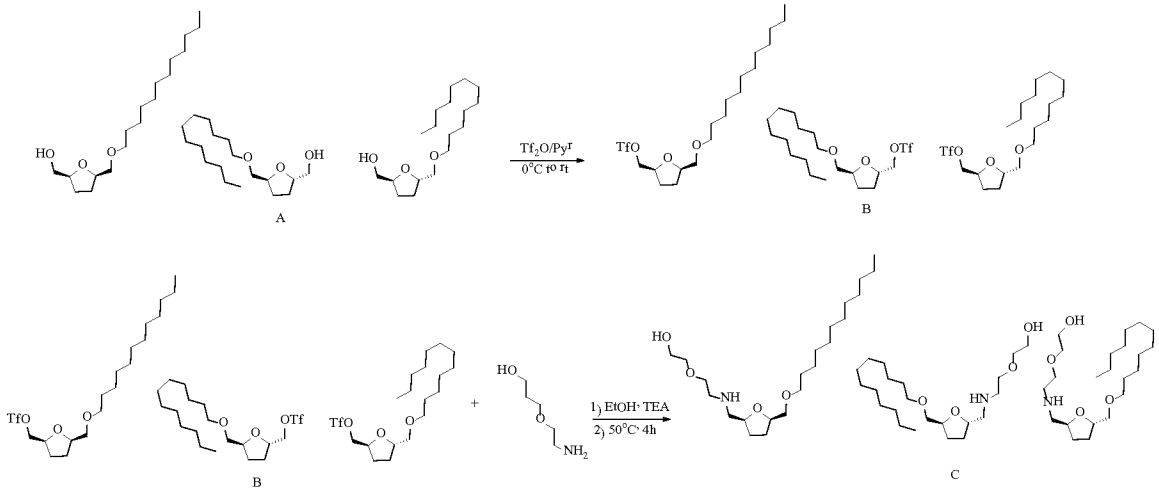
C. Derivatives of bHMTHF monoethers

Example 7: Synthesis of potassium ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl sulfate and diastereomers, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a 0.5" PTFE coated tapered magnetic stir bar was charged with 50 mg of a 9:1 mixture of ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methanol and diastereomers **A** (0.231 mmol) and 5 mL of anhydrous $CHCl_3$. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 15.4 µL of chlorosulfonic acid (26.9 mg, 0.231 mmol) was added dropwise over 15 minutes. The mixture was then warmed to room temperature and continued to react for 1 hour. After this time, the solvent and resultant HCl was removed via rotary evaporation and high vacuum. The light yellow oily residue dissolved in a minimum amount of isopropanol and placed in a freezer. After about 3 days, suspended crystals were observed, which were filtered and dried, affording 16 mg (24% of theoretical) of **B**. Elemental analysis (C, H): Predicted for $C_{12}H_{24}O_6S$ (C, 48.63; H, 8.16); Found (C, 48.66; H, 8.23).

Example 8: Synthesis of 2-(2-((((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran2yl)methyl)amino)-ethoxy)ethanol and diastereomers **C** (plausible non-ionic surfactant)

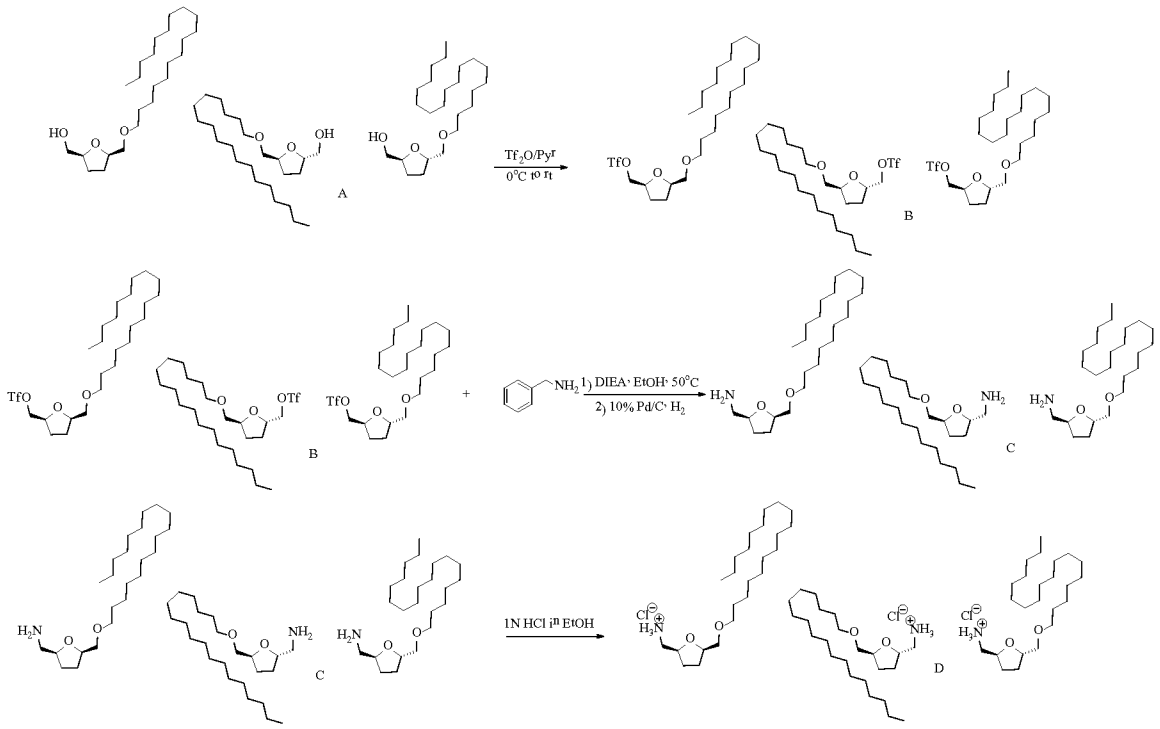


Experimental: An oven dried, single neck 25 mL round bottomed flask equipped with a 0.5" PTFE coated octagonal magnetic stir bar was charged with 200 mg of a 9:1 mixture of ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol and diastereomers **A** (0.666 mmol), 107 µL of pyridine (1.33 mmol) and 5 mL of anhydrous methylene chloride. The flask was then immersed in an

ice-brine bath (~-10°C) and, while stirring, 112 μL of triflic anhydride (0.666 mmol) was added dropwise over 15 minutes. The mixture was then warmed to room temperature and continued to react for 2 hour. After this time, an aliquot was removed and spotted on a silica gel TLC plate that was developed using a 25% ethyl acetate eluent. One spot appeared on the plate (cerium molybdate visualization) with an Rf = 0.57. The absence of the band corresponding to the starting alcohol, Rf = 0.44, signified complete conversion. Excess solvent was then evaporated, furnishing 261 mg of a light yellow oil (90%) specifying **B**. This material was used in the subsequent step without further purification.

A single neck 50 mL round bottomed flask equipped with a 5/8" octagonal PTFE coated magnetic stir bar and was charged with 250 mg of B (0.578 mmol), 69 mg of 3-(2-aminoethoxy)propan-1-ol, 81 μL of triethylamine (0.578 mmol) and 10 mL of absolute ethanol. A reflux condenser was outfitted to the flask, and while stirring, the solution was heated to 50°C, 4 hours. After this time, an aliquot was extracted and analyzed by TLC (cerium molybdate visualization), demonstrating that **B** had entirely disappeared. The mixture was poured directly onto a short-path, pre-fabricated column comprised of neutral alumina, where flash chromatography with absolute ethanol afforded 96 mg of **C** as a viscous, pale yellow oil (43%). ^{1}H NMR (400 MHz, $CDCl_3$, *salient peaks corresponding to the cis* (*meso*) *species*) δ (ppm) 4.12 (m, 1H), 4.03 (m, 1H), 3.64-3.62 (m, 4H), 3.53 (t, *J* = 5.4 Hz, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 3.30 (t, J = 5.4 Hz), 2.75-2.72 (m, 3H), 2.59 (m, 1H), 2.01 (m, 2H), 1.71 (m, 2H), 1.47 (t, *J* = 5.6 Hz, 2H), 1.38 (m, 2H), 1.33-1.27 (m, 16H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, salient peaks (*cis*, *meso*)) δ (ppm) 84.1, 82.2, 77.8, 73.6, 69.0, 68.4, 63.2, 55.9, 50.0, 32.4, 31.9, 31.4, 30.8, 30.6, 30.5, 30.2, 29.9, 29.7, 29.6, 29.3, 29.1, 16.0.

Example 9: Synthesis of ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride and diastereomers **D** (plausible cationic surfactants)



Experimental: An oven dried, 25 mL single neck round bottomed flask equipped with a tapered 1 cm PTFE coated magnetic stir bar was charged with 150 mg of **A** (0.390 mmol), 94 μL of pyridine (1.17 mmol) and 10 mL of anhydrous methylene chloride. The flask was then immersed in brine/ice bath (~ -10°C), and while vigorously stirring, 66 μL of triflic anhydride (0.390 mmol) was added dropwise over 10 minutes. The ice bath was then removed and reaction continued at room temperature for 2 h. After this time, an aliquot was removed, spotted on a silica gel TLC plate and developed with 20% ethyl acetate in hexanes, indicating (cerium molybdate visualization) a single band with an R_f = 0.52. The signature band for A, R_f = 0.39, was patently absent, indicating this reagent had fully converted. Solids were then filtered and filtrate concentrated *in vacuo* overnight, furnishing 173 mg of **B** as a light brown oil (88%). This product was used in the next step without further purification.

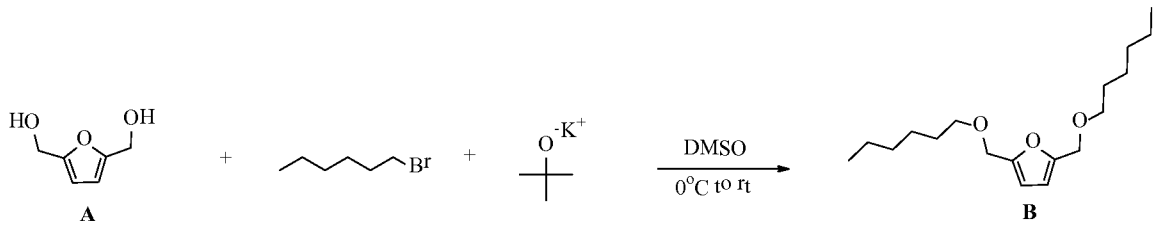
A single neck, 50 mL round bottomed flask equipped with a 1 cm PTFE coated magnetic stir bar was charged with 175 mg of **B** (0.339 mmol), 65 μL of Hunig's base (0.373 mmol), 37 μL of benzylamine and 10 mL of ethanol. The neck was capped with a reflux condenser, and while vigorously stirring, the mixture was heated to 50°C for 2hrs. After this time, TLC (UV and cerium molybdate visualization) indicated a single band and full consumption of both reagents. The mixture was then diluted with 10 mL of water and 10 mL of methylene chloride and layers partitioned by liquid-liquid extraction. The aqueous layer was extracted with 5 mL volumes of methylene chloride (x2), organic layers combined and dried, affording a pale yellow waxy solid. This material was charged to a 25 mL round bottomed flask equipped with a 0.5" PTFE coated magnetic stir bar, along with 100 mg of 10% Pd/C and 10 mL of absolute ethanol. The neck was capped with a rubber septum and a balloon filled with H_2 was inserted via a 9 inch, 16" needle; the mixture was stirred vigorously

and monitored by TLC (UV-vis visualization). After 2 h, the reaction was deemed complete; catalyst filtered through a pad of Celite and filtrate concentrated under vacuum overnight, affording 74 mg of **C** (52%) as light yellow, loose oil. This material was used in the supervening step without further purification.

A single neck, 10 mL round bottomed flask equipped with a 0.5" octagonal PTFE coated magnetic stir bar was charged with 50 mg of **C** (0.130 mmol) and 2 mL of a 1N ethanolic HCl solution. The mixture was stirred for 15 minutes, after which time excess solvent was removed first with a rotary evaporator (50°C, 30 mmHg) then under high vacuum (< 1 torr) for 1 week. After this time, a yellow semi-solid corresponding to **D** was observed, weighing 49 mg (88%). ^{1}H NMR (400 MHz, d^6-DMSO/D_2O, *salient signals corresponding to the cis (meso) derivative*) δ (ppm) 4.52 (m, 1H), 4.13 (m, 1H), 3.62-3.60 (m, 2H), 3.32-3.28 (m, 4H), 2.03 (m, 2H), 1.75 (m, 2H), 1.59 (m, 2H), 1.48 (m, 2H), 1.30-1.25 (m, 28H), 0.95 (t, J = 6.2 Hz, 3H). 13C NMR (100 MHz, d^6-DMSO/D_2O salient signals corresponding to the *cis* (meso) derivative) δ (ppm) 85.1, 81.2, 77.3, 72.2, 49.2, 32.6, 32.2, 31.9, 31.5, 31.2, 30.5, 30.3, 30.0, 29.8, 29.6, 29.3, 29.1, 28.9, 28.8, 28.6, 28.3, 28.0, 27.9, 13.1.

D. FDM diethers

Example 10: Synthesis of 2,5-bis((hexyloxy)methyl)furan, **B**

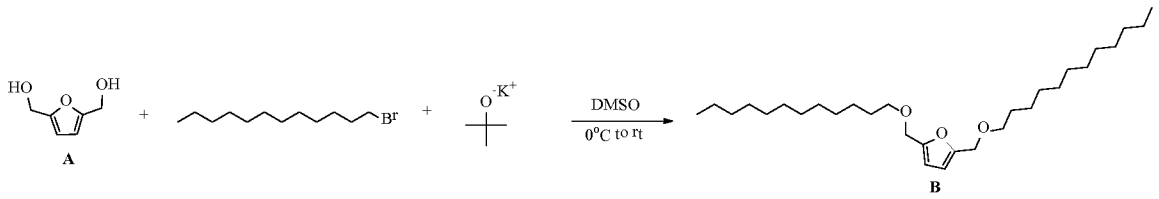


A **B**

Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of FDM **A** (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 219 mg of potassium *t*-butoxide (1.95 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 240 μL of 1-bromohexane (1.72 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 9:1 hexanes/ethyl acetate. The signature band for FDM **A** (baseline) was patently absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica

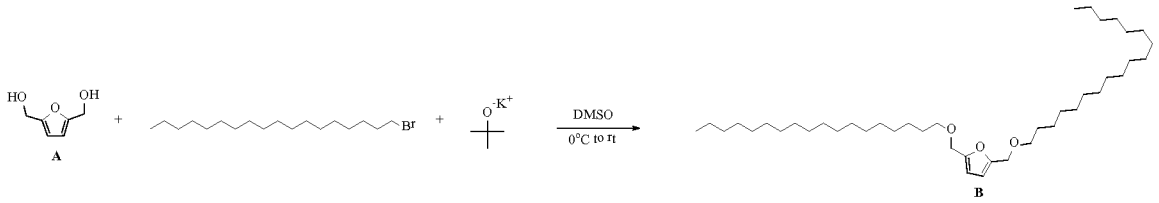
gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 13% ethyl acetate in hexanes afforded 124 mg of a **B** as light yellow oil after concentration *in vacuo* (53% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.32 (s, 2H), 4.63 (s, 4H), 3.40-3.36 (m, 4H), 2.10 (m, 2H), 1.59 (m, 2H), 1.48 (t, J = 6.0 Hz, 4H), 1.42 (m, 4H), 1.35-1.30 (m, 10H), 0.91 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.23, 108.3, 71.6, 68.1, 32.6, 31.4, 29.8, 25.4, 13.3.

Example 11: Synthesis of 2,5-bis((dodecyloxy)methyl)furan, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of FDM **A** (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 219 mg of potassium *t*-butoxide (1.95 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 412 µL of 1-bromododecane (1.72 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 10:1 hexanes/ethyl acetate. The signature band for FDM **A** (baseline) was noticeably absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 9% ethyl acetate in hexanes afforded 139 mg of a **B** as a beige solid after concentration (39% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.42 (2, 2H), 4.67 (s, 4H), 3.42-3.39 (m, 4H), 2.06 (m, 2H), 1.58 (m, 2H), 1.47 (t, J = 6.4 Hz, 4H), 1.40 (m, 4H), 1.38-1.30 (m, 34H), 0.91 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.4, 108.5, 73.4, 69.9, 33.0, 31.2, 30.9, 29.8, 28.7, 26.2, 25.4, 24.9, 24.1, 23.3, 22.1, 13.3.

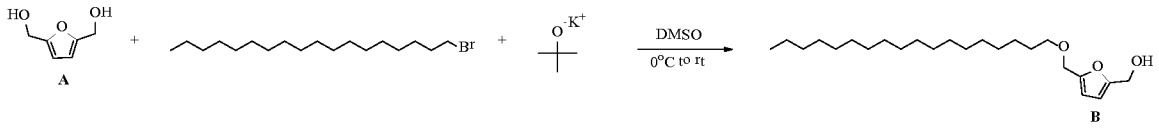
Example 12: Synthesis of 2,5-bis((octadecyloxy)methyl)furan, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of FDM A (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 219 mg of potassium *t*-butoxide (1.95 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 586 μL of 1-bromooctadecane (1.72 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited a single band (cerium molybdate stain) after developing in 11:1 hexanes/ethyl acetate. The signature band for FDM **A** (baseline) was noticeably absent, suggesting this reagent had fully converted. Here, the mixture was diluted with 5 mL of water and 5 mL of methylene chloride and partitioned and the aqueous layer extracted with 3-5 mL volumes of methylene chloride. The organic phases were combined, dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. The oily residue was dissolved in a minimum amount of methylene chloride and added to 20 g of silica gel, which was then dried under vacuum, furnishing product adsorbed silica gel. This material was added to a pre-fabricated silica gel column, where flash chromatography with hexanes to 6% ethyl acetate in hexanes afforded 171 mg of a **B** as an off-white solid after concentration (35% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 6.40 (s, 2H), 4.52 (s, 4H), 3.41-3.38 (m, 4H), 2.08 (m, 2H), 1.65 (m, 2H), 1.48 (t, J = 6.2 Hz, 4H), 1.41 (m, 4H), 1.40-1.28 (m, 58H), 0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.7, 108.6, 73.6, 69.0, 33.0, 31.2, 30.9, 29.8, 28.7, 26.2, 25.4, 24.9, 24.1, 23.8, 23.3, 22.9, 22.5, 22.1, 21.7, 21.3, 13.3.

E. FDM mono-ethers

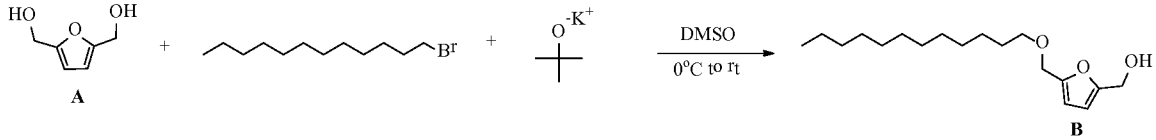
Example 13: Synthesis of (5-((octadecyloxy)methyl)furan-2-yl)methanol, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg FDM **A** (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 87 mg of potassium *t*-butoxide (0.780 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14"

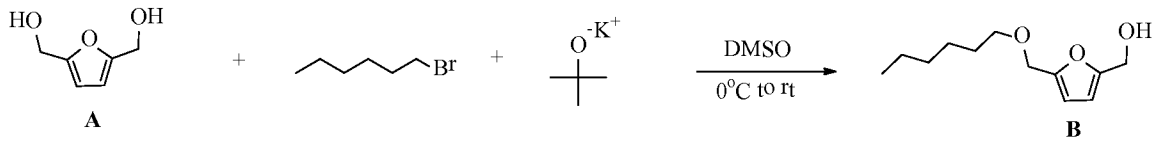
needle. While vigorously stirring and under an argon blanket, 266 µL of 1-bromooctadecane (0.780 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited three bands (cerium molybdate stain) after developing in 6:1 hexanes/ethyl acetate, Rf_1 = 0.91 (FDM di-ether) and Rf_2 = 0.60, and baseline (unreacted FDM **A**). The signature band for **A** was patently absent, suggesting this reagent had fully converted. Analysis by LC/MS (APCI-, RP 1.7 µm, 2.1 x 50 mm, mobile phase-gradient 50 to 0% aqueous in CH_3CN, flow rate 0.5 mL/min., M-1) divulged a m/z of 379.3.

Example 14: Synthesis of (5-((dodecyloxy)methyl)furan-2-yl)methanol, **B**



Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg FDM **A** (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 87 mg of potassium *t*-butoxide (0.780 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed via a 14" needle. While vigorously stirring and under an argon blanket, 187 µL of 1-bromododecane (0.780 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited two salient bands (cerium molybdate stain) after developing in 5:1 hexanes/ethyl acetate, Rf_1 = 0.91 (FDM-diether) , Rf_2 = 0.55 (targets **B**), Rf_3 = baseline (FDM **A**). Analysis by GC/MS (EI, Initial 70°C, ramp 5°C per minute to 350°C, hold for 60 min.) manifested three salient signals with retention times as follows: a) 11.3 min., m/z 128.1 (M+, FDM **A**), b) 24.2 min., m/z 296.2 (M+, FDM-monoether **B**).

Example 15: Synthesis of (5-((hexyloxy)methyl)furan-2-yl)methanol, **B**



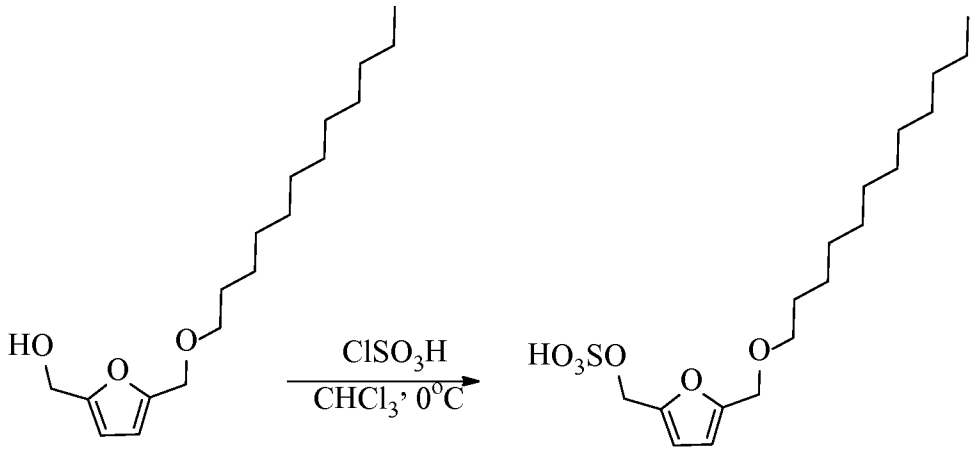
Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg FDM **A** (0.780 mmol) and 5 mL of anhydrous DMSO. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 87 mg of potassium *t*-butoxide (0.780 mmol) added in portions and the mixture stirred for 30 minutes at this temperature. At this time, the neck was stoppered with a rubber septum and an argon gas inlet affixed

via a 14" needle. While vigorously stirring and under an argon blanket, 109 μL of 1-bromohexane (0.780 mmol) was added via syringe. The mixture was then warmed to room temperature and continued to react overnight. After this time, an aliquot was removed and spotted on a silica gel TLC plate, which exhibited three bands (cerium molybdate stain) after developing in 3:1 hexanes/ethyl acetate, Rf_1 = 0.89 (FDM di-ether), Rf_2 = 0.57 (target **B**), Rf_3 = baseline (unreacted FDM **A**). Analysis by GC/MS (EI, Initial 70°C, ramp 5°C per minute to 350°C, hold for 60 min.) manifested three salient signals with retention times as follows: a) 11.3 min., m/z 128.1 (M+, unreacted THF-diols), b) 17.6 min., m/z 212.1 (M+, FDM mono-ether, **B**).

F. Amphiphilic derivatives of FDM mono-ethers

Generally, various derivative species can also be made from FDM-monoethers, and the preparation of the FDM derivatives employ the same or similar reaction protocols, *mutatis mutandis*, as that used to synthesize the derivatives from bHMTHF as a starting material, such as described in the foregoing examples. Hence, as a person of ordinary skill will comprehend, rather than repeat the entire series of examples for synthesis of derivatives from FDM mono-ethers, the following examples are of alternative compounds that illustrate certain variance in synthesis. Each of the compounds in these variant examples is expected to parallel that of a derivative bHMTHF mono-ether (e.g., non-hydrolyzable amphiphiles with potential applications as surfactants, dispersants, plasticizers, etc).

Example 16: Synthesis of (5-((dodecyloxy)methyl)furan-2-yl)methyl hydrogen sulfate, **B**.

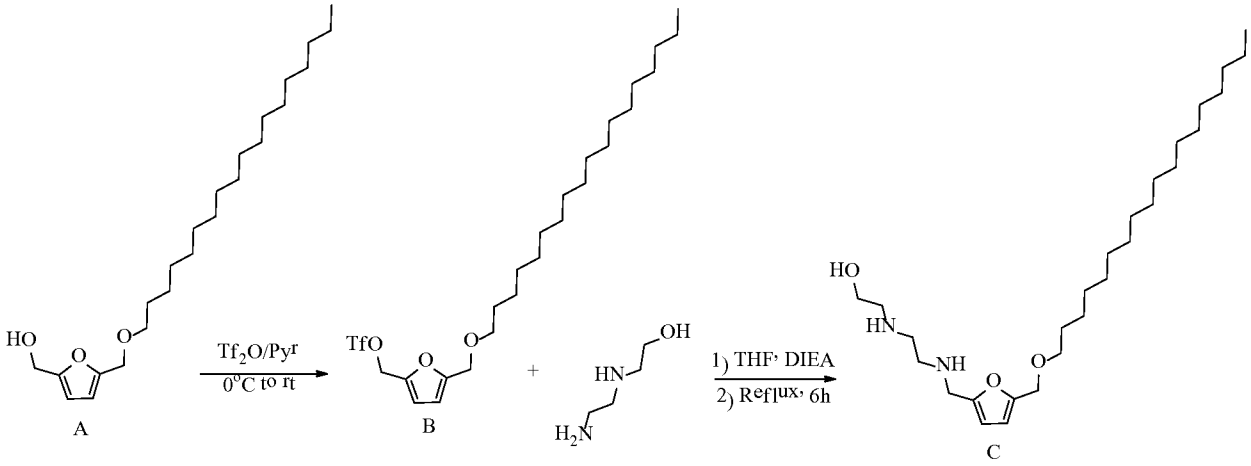


A B

Experimental: An oven dried, single neck 10 mL round bottomed flask equipped with a 0.5" PTFE coated tapered magnetic stir bar was charged with 100 mg of (5-((dodecyloxy)methyl)furan-2-yl)methanol **A** (0.337 mmol) and 5 mL of anhydrous $CHCl_3$. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 22.5 μL of chlorosulfonic acid (39.2 mg, 0.231 mmol) was added dropwise over 15 minutes. The mixture was then warmed to room temperature and continued to react for 1 hour. After this time, the solvent and resultant HCl was removed via rotary evaporation

and high vacuum. The light yellow oily residue dissolved in a minimum amount of isopropanol and placed in a freezer overnight. An abundance of suspended crystals were manifest that were filtered and dried, affording 55 mg (43% of theoretical) of **B**. Elemental analysis (C, H): Predicted for $C_{18}H_{32}O_6S$ (C, 57.42; H, 8.57); Found (C, 57.51; H, 8.60).

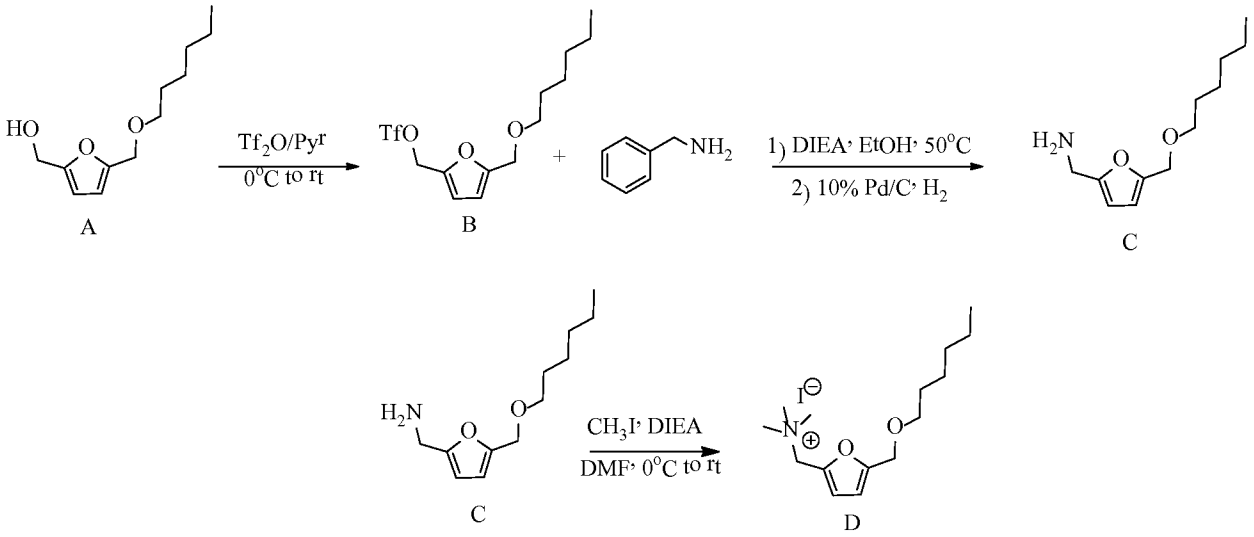
Example 17: Synthesis of 2-((2-(((5-((octadecyloxy)methyl)furan-2-yl)methyl)amino)ethyl)amino)-ethanol, **C**



Experimental: An oven dried, single neck 25 mL round bottomed flask equipped with a 0.5" PTFE coated octagonal magnetic stir bar was charged with 100 mg of a (5-((octadecyloxy)methyl)furan-2-yl)methanol **A** (0.263 mmol), 42 µL of pyridine (0.526 mmol) and 5 mL of anhydrous methylene chloride. The flask was then immersed in an ice-brine bath (~-10°C) and, while stirring, 44.2 µL of triflic anhydride (0.263 mmol) was added dropwise over 15 minutes. The mixture was then warmed to room temperature and continued to react for 2 hour. After this time, an aliquot was removed and spotted on a silica gel TLC plate that was developed using a 25% ethyl acetate eluent. One spot appeared on the plate (cerium molybdate visualization) with an Rf = 0.54. The absence of the band corresponding to the starting alcohol, Rf = 0.41, signified complete conversion. Excess solvent was then evaporated, furnishing 110 mg of a light yellow oil (82%) specifying (5-((octadecyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate, **B**. This material was used in the subsequent step without further purification. A single neck 50 mL round bottomed flask equipped with a PTFE coated magnetic stir bar and was charged with 100 mg of (5-((octadecyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate **B** (0.195 mmol), 20.3 mg of 2-((2-aminoethyl)amino)ethanol (0.195 mmol), 67.9 µL of diisopropyl-ethylamine (0.390 mmol) and 10 mL of anhydrous THF. A reflux condenser was outfitted to the flask, and while stirring, the solution was heated to reflux for 6 hours. After this time, an aliquot was extracted and analyzed by TLC (cerium molybdate visualization), demonstrating that **B** had entirely disappeared. The mixture was poured directly onto a short-path, pre-fabricated column comprised of neutral alumina, where flash

chromatography with absolute ethanol afforded 31 mg of 2-((2-(((5-((octadecyloxy)methyl)-furan-2-yl)methyl)amino)ethyl)amino)ethanol **C** as a loose, pale yellow oil (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.38 (d, J = 8.2 Hz, 1H), 6.16 (d, J = 8.2 Hz, 1H), 4.51 (s, 2H), 3.62 (m, 3H), 3.45 (m, 2H), 3.32 (t, J = 6.0 Hz, 2H), 2.94 (m, 2H), 2.80 (m, 2H), 2.61 (m, 4H), 1.59 (m, 2H), 1.42 (m, 2H), 1.33-1.29 (m, 28H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.9, 149.1, 108.2, 107.0, 73.5, 68.2, 62.1, 51.6, 50.9, 47.8, 46.6, 30.3, 30.0, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.8, 28.7, 28.6, 28.4, 28.2, 28.0, 21.8, 13.8

Example 18: Synthesis of 1-(5-((hexyloxy)methyl)furan-2-yl)-N,N,N-trimethylmethanaminium iodide, **D**



Experimental: An oven dried, 25 mL single neck round bottomed flask equipped with a tapered 1 cm PTFE coated magnetic stir bar was charged with 125 mg of (5-((hexyloxy)methyl)furan-2-yl)methanol **A** (0.589 mmol), 94 µL of pyridine (1.18 mmol) and 10 mL of anhydrous methylene chloride. The flask was then immersed in brine/ice bath (~ -10°C), and while vigorously stirring, 99.1 µL of triflic anhydride (0.589 mmol) was added dropwise over 10 minutes. The ice bath was then removed and reaction continued at room temperature for 2 hrs. After this time, an aliquot was removed, spotted on a silica gel TLC plate and developed with 20% ethyl acetate in hexanes, indicating (cerium molybdate visualization) a single band with an R_f = 0.52. The signature band for A, R_f = 0.39, was patently absent, indicating this reagent had fully converted. Solids were then filtered and filtrate concentrated *in vacuo* overnight, furnishing 183 mg of (5-((hexyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate **B** as a beige oil (90%). This product was used in the next step without further purification.

A single neck, 25 mL round bottomed flask equipped with a 1 cm PTFE coated magnetic stir bar was charged with 150 mg of (5-((hexyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate **B** (0.436 mmol), 152 µL of Hunig's base (0.871 mmol), 48 µL of benzylamine (0.436 mmol) and 10 mL

of ethanol. The neck was capped with a reflux condenser, and while vigorously stirring, the mixture was heated to 50°C for 2h. After this time, TLC (UV and cerium molybdate visualization) indicated a single band and full consumption of both reagents. The mixture was then diluted with 10 mL of water and 10 mL of methylene chloride and layers partitioned by liquid-liquid extraction. The aqueous layer was extracted with 5 mL volumes of methylene chloride (x2), organic layers combined and dried, affording a pale yellow waxy solid. This residue was charged to a 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar, along with 100 mg of 10% Pd/C and 10 mL of absolute ethanol. The neck was capped with a rubber septum and a balloon filled with H_2 was inserted via a 9 inch, 16" needle; the mixture was stirred vigorously and monitored by TLC (UV-vis visualization). After 1.5 h, the reaction was deemed complete; catalyst filtered through a pad of Celite and filtrate concentrated under vacuum overnight, affording 71 mg of (5-((hexyloxy)methyl)furan-2-yl)methanamine **C** (77%) as colorless, loose oil. This product was used in the next step without further purification.

A single neck, 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 50 mg of (5-((hexyloxy)methyl)furan-2-yl)methanamine **C** (0.237 mmol) and 5 mL of anhydrous DMF. The flask was capped with a rubber septum affixed to an argon inlet and immersed in a saturated brine/ice bath mixture (~0°C). While vigorously stirring and under argon, 74 µL of methyl iodide (167 mg, 1.18 mmol) the mixture was added dropwise over 10 minutes. Upon complete addition, the ice bath was withdrawn and the mixture stirred at room temperature overnight. After this time, 15 mL of diethyl ether was added, which induced the precipitation of a white solid. The solid was filtered, washed with 5 mL of diethyl ether (x 3) and dried high vacuum (< 1 torr) for 1 week. After this time, a 55 mg of 1-(5-((hexyloxy)methyl)furan-2-yl)-N,N,N-trimethylmethanaminium iodide **D** was obtained as a fine white powder (61% of theoretical). ^{1}H NMR (400 MHz, d^6-DMSO) δ (ppm) 6.29 (d, J = 8.2 Hz, 1H), 6.10 (d, J = 8.2 Hz, 1H), 4.42 (s, 2H), 4.30 (s, 2H), 3.51 (s, 9H), 3.40 (t, J = 6.2 Hz, 2H), 1.48-1.46 (m, 4H), 1.33-1.31 (m, 4H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ (ppm) 152.7, 151.4, 109.0, 108.2, 73.6, 70.0, 68.8, 50.6, 30.8, 30.1, 23.4, 22.5, 15.8.

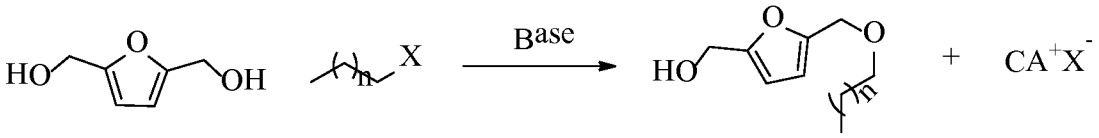
The present invention has been described in general and in detail by way of examples. Persons of skill in the art understand that the invention is not limited necessarily to the embodiments specifically disclosed, but that modifications and variations may be made without departing from the scope of the 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 process for preparing linear mono- and di-alkyl ethers of either furan-2,5-dimethanol (FDM) or 2,5-bis(hydroxymethyl)tetrahydrofuran (bHMTHF) comprising: contacting either FDM or bHMTHF in a polar aprotic organic solvent with a permittivity (ε) >8, at a temperature ranging from about -25°C to about 100°C, with either a) an unhindered Brønsted base having a difference in pKa (ΔpKa) ≥15 relative to the pKa of a hydroxyl group of either said FDM or bHMTHF, or b) a hindered Brønsted base and a nucleophile.
2. The process according to claim 1, wherein said FDM and bHMTHF are reduction products derived from 5-(hydroxymethyl)furfural (HMF).
3. The process according to claim 1, wherein said unhindered Brønsted base is a metallic hydride.
4. The process according to claim 3, wherein said unhindered Brønsted base is at least one of a lithium, sodium, or potassium hydride.
5. The process according to claim 1, wherein said unhindered Brønsted base is an organometallic base.
6. The process according to claim 5, wherein said unhindered Brønsted base is at least one of an alkyl lithium, alkyl magnesium, or alkyl cuprate compound.
7. The process according to claim 1, wherein said unhindered Brønsted base is a metal amide or Grignard reagent.
8. The process according to claim 1, wherein said hindered Brønsted base is at least one of sodium or potassium *t*-butoxide, or lithium diisopropylamide.
9. The process according to claim 1, wherein said hindered Brønsted base has a pKa of at least 16.
10. The process according to claim 9, wherein said hindered Brønsted base has a pKa ≥ 20.
11. The process according to claim 1, wherein said polar, aprotic organic solvent has a permittivity (ε) ≥30.
12. The process according to claim 1, wherein said polar, aprotic organic solvent is at least one of: dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), hexamethylphosphoramide (HMPA), acetone, acetonitrile (ACN), nitromethane, sulfolane, tetrahydrofuran (THF), 1,4-dioxane, and ethyl acetate.
13. The process according to claim 1, wherein said nucleophile is at least one of: an alkyl halide or sulfonate with an alkyl chain length between C_5-C_{25}.
14. The process according to claim 13, wherein said alkyl halide or sulfonate has an alkyl chain length between C_8-C_{18}.
15. The process according to claim 13, wherein said halide is at least one of: Cl, Br, or I.

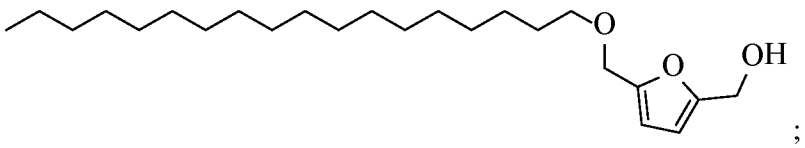
16. The process according to claim 13, wherein said sulfonate is at least one of: a -OTf (triflate), -OMs (mesylate), -OTs (tosylate), -OBs (brosylate), or -OEs (esylate).
17. The process according to claim 1, wherein said temperature is in a range from about -10°C to about 70°C.
18. The process according to claim 1, wherein said temperature is in a range from about -5°C to about 35°C.
19. The process according to claim 1, wherein said mono- and diethers of FDM and bHMTHF have linear hydrocarbon chain lengths of C_5-C_{25}.
20. The process according to claim 19, wherein said mono- and diethers of bHMTHF and FDM have linear hydrocarbon chain lengths of C_6-C_{18}.
21. A method of preparing a mono-ether comprising: contacting FDM with a Brønsted base and 1 or less molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the leaving group, "n" is an integer from 5 to 25, and "CA" is a conjugate acid of the base.

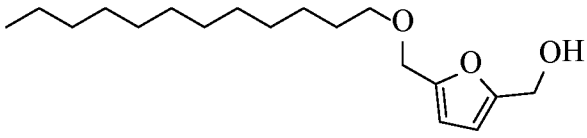
22. A mono-ether of FDM prepared according to claim 21, wherein said mono-ether of FDM is at least one of the following compounds:

a. (5-((octadecyloxy)methyl)furan-2-yl)methanol



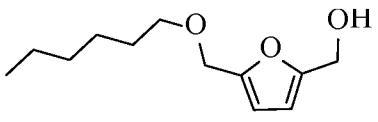
;

b. (5-((dodecyloxy)methyl)furan-2-yl)methanol



; and

a. (5-((hexyloxy)methyl)furan-2-yl)methanol



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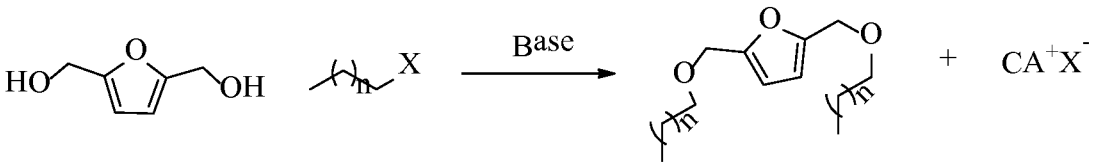
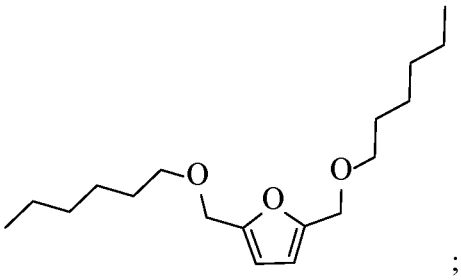
23. A method of preparing a di-ether comprising: contacting FDM with a Brønsted base and a minimum of 2 molar equivalents of an alkyl-X species according to the following:



wherein: "X" is the leaving group, "n" is an integer from 5 to 25, and "CA" is a conjugate acid of the base.

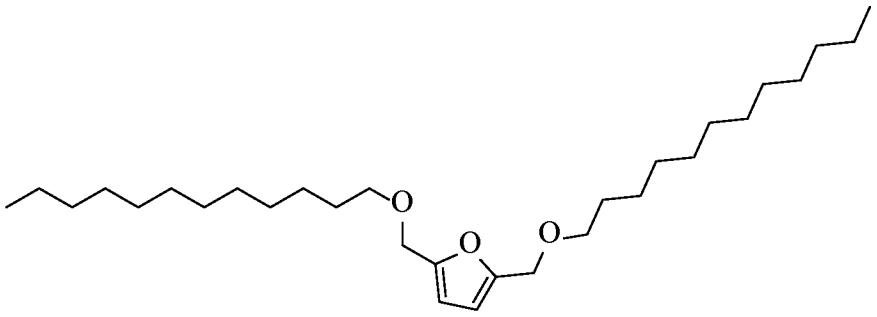
24. A di-ether of FDM prepared according to claim 23, wherein said di-ether of FDM is at least one of the following compounds:

a. 2,5-bis((hexyloxy)methyl)furan



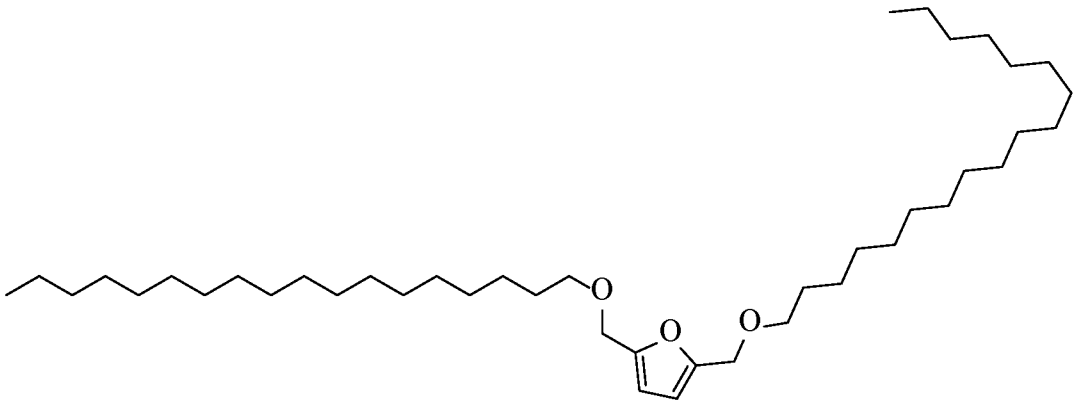
;

b. 2,5-bis((dodecyloxy)methyl)furan



; and

c. 2,5-bis((octadecyloxy)methyl)furan



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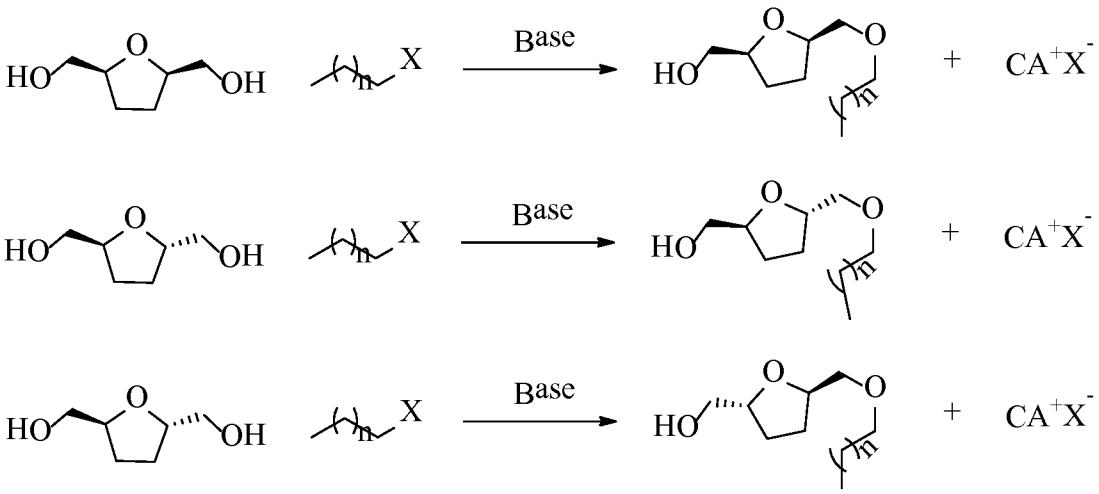
25. A method of preparing a mono-ether comprising: contacting bHMTHFs with a Brønsted base and 1 or less molar equivalents of an alkyl-X species according to at least one of the

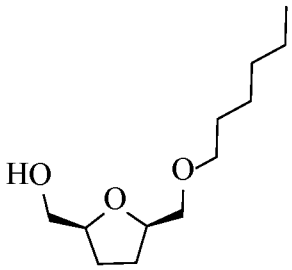
following:



wherein: "X" is the leaving group, "n" is an integer from 5 to 25, and "CA" is a conjugate acid.

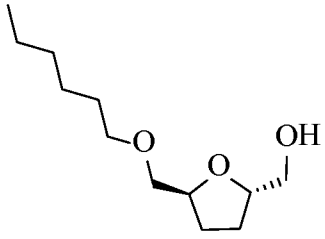
26. A mono-ether of bHMTHF prepared according to claim 25, wherein said mono-ether of bHMTHF is at least one of the following compounds:

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



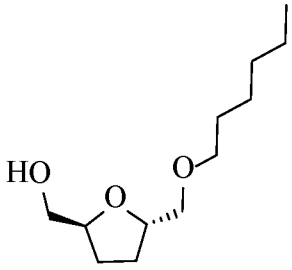
;

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



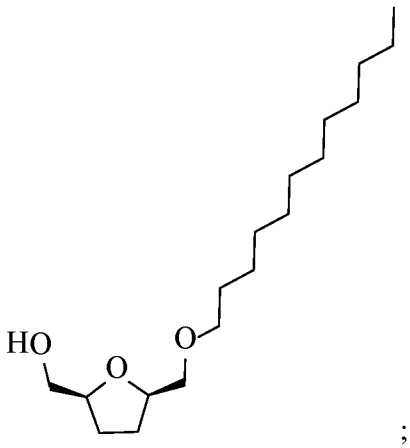
;

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



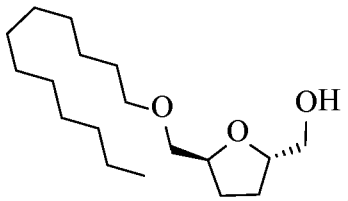
;

d. ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



;

e. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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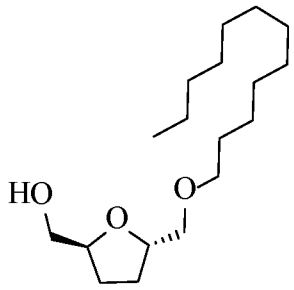
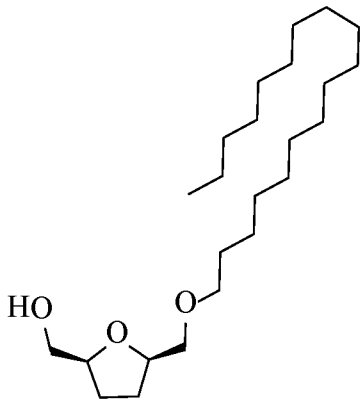
f. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methanol



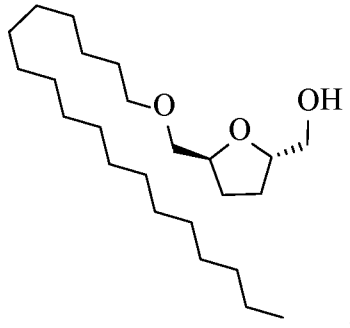
;

g. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



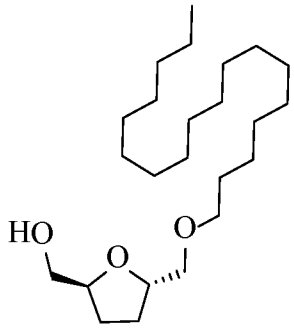
;

h. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



;

i. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanol



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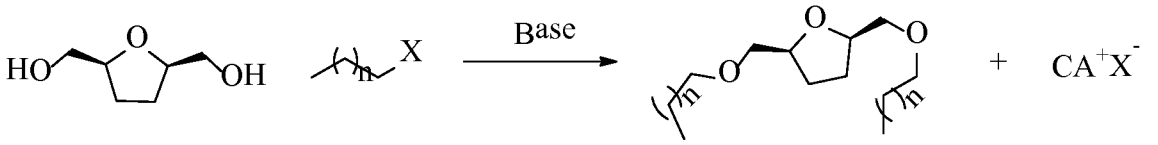
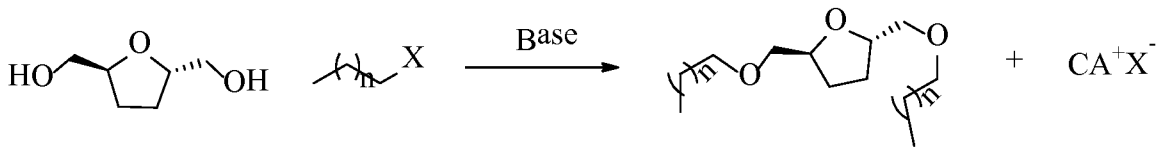
27. A method of preparing a di-ether comprising: contacting bHMTHFs with a Brønsted base and a minimum of 2 molar equivalents of an alkyl-X species according to the following:

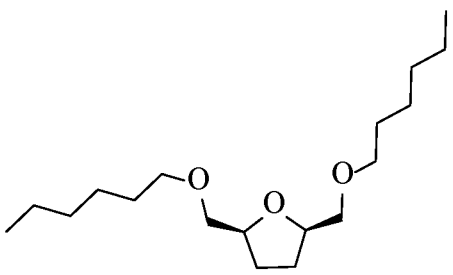




wherein: "X" is the leaving group, "n" is an integer from 5 to 25, and "CA" is a conjugate acid.

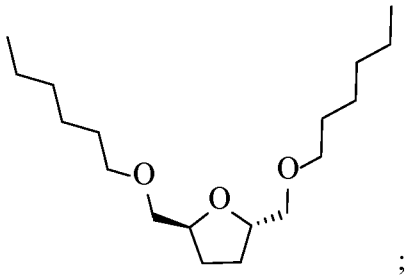
28. A di-ether of bHMTHF prepared according to claim 27, wherein said di-ether of bHMTHF is at least one of the following compounds:

a. (2R,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran



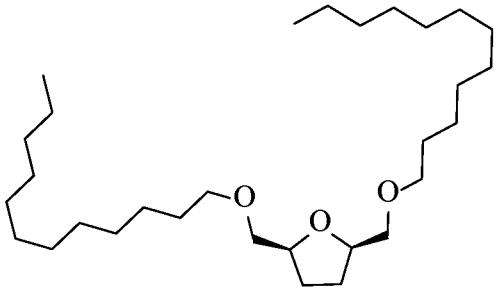
;

b. (2S,5S)-2,5-bis((hexyloxy)methyl)tetrahydrofuran



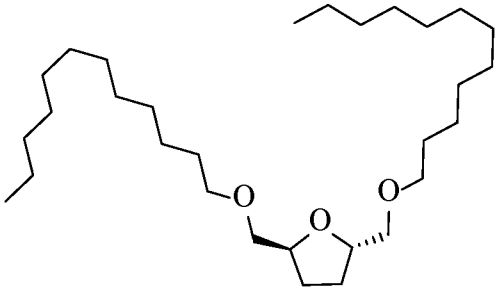
;

c. (2R,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran



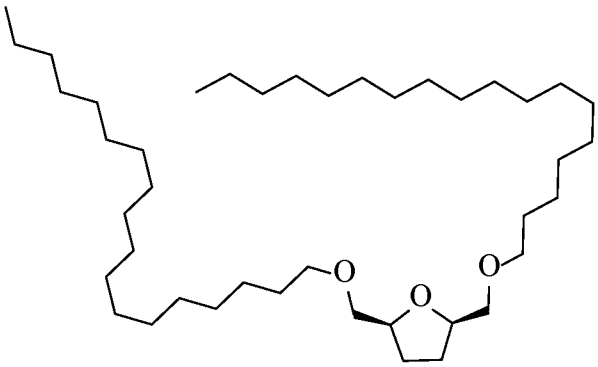
;

d. (2S,5S)-2,5-bis((dodecyloxy)methyl)tetrahydrofuran



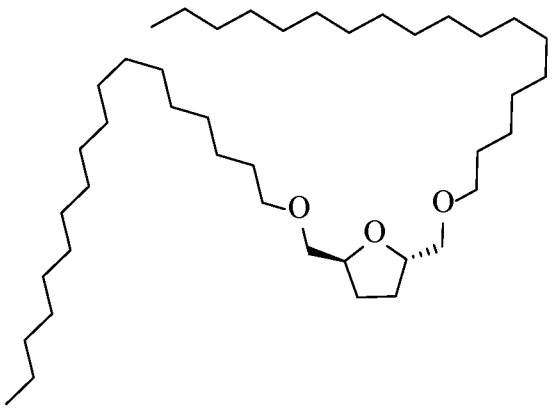
;

e. (2R,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran

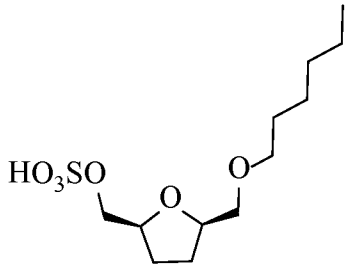


; and

f. (2S,5S)-2,5-bis((octadecyloxy)methyl)tetrahydrofuran

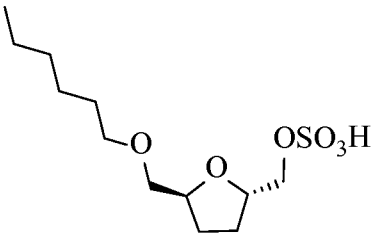


29. A process for preparing a derivative compound from a mono-ether, the process comprising contacting a mono-ether of bHMTHF with a) chlorosulfonic acid to generate a sulfate, or b) trifluoromethanesulfonic anhydride to generate a trifluoromethanesulfonate.
30. A sulfate prepared according to claim 29, wherein said sulfate is at least one of the following compounds:
    a. ((2S,5R)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate



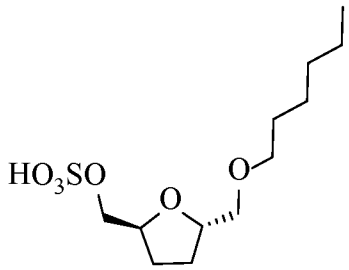
;

    b. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate



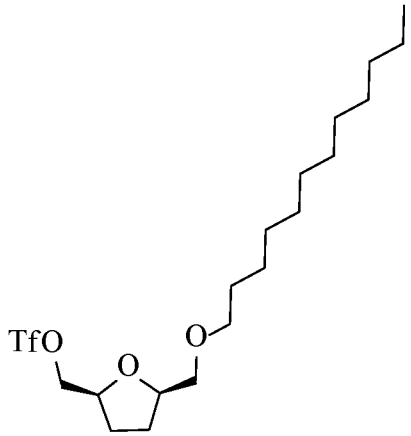
;

    c. ((2S,5S)-5-((hexyloxy)methyl)tetrahydrofuran-2-yl)methyl hydrogen sulfate

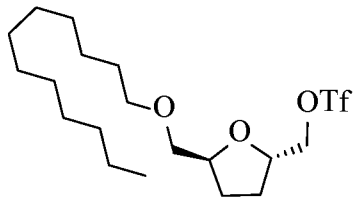


31. A trifluoromethanesulfonated monoether generated according to claim 29, wherein said trifluoromethanesulfonated monoether is at least one of the following compounds:

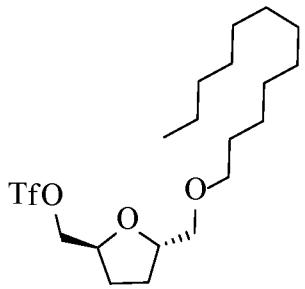
a. ((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



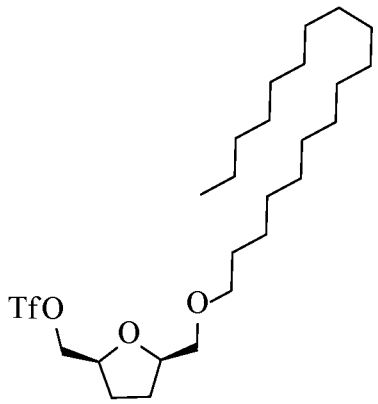
b. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



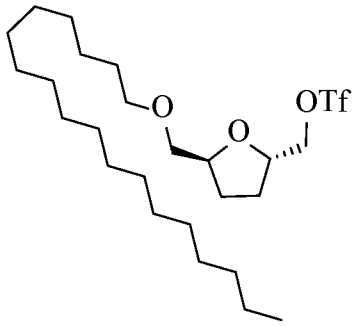
c. ((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



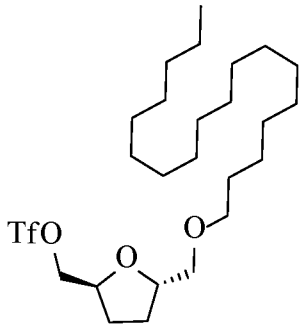
d. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



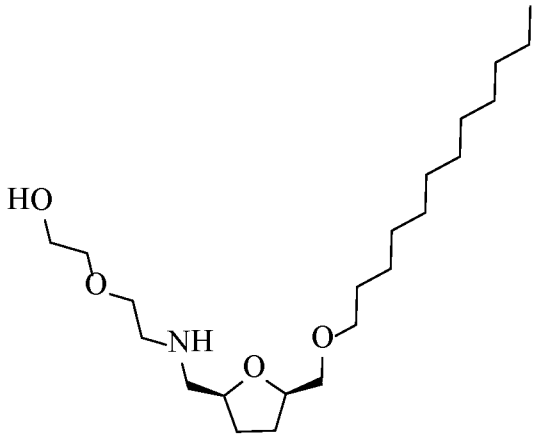
e. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



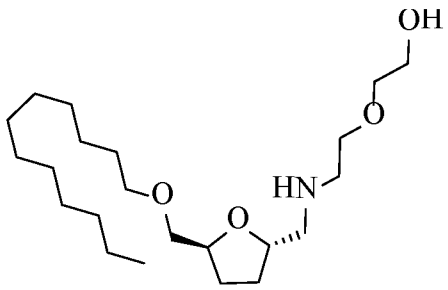
f. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methyl trifluoromethanesulfonate



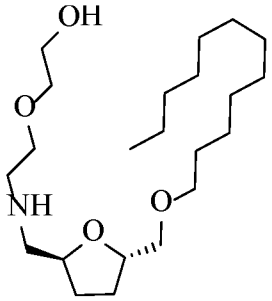
32. The process according to claim 29, further comprising generating an ethoxyethanolamine derivative of a bHMTHF mono-ether sulfonate compound by substitutions of a sulfonate group with an ethnaolamine.
33. A ethoxyethanolamine prepared according to claim 32, wherein said ethoxyethanolamine is at least one of the following compounds:
    a. 2-(2-((((2S,5R)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



    b. 2-(2-((((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



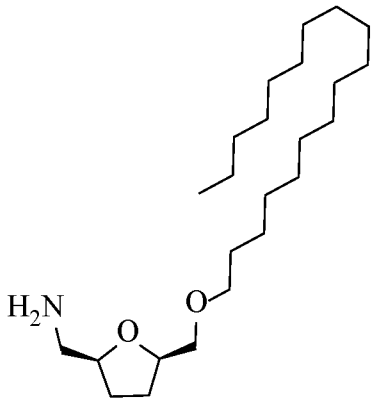
c. 2-(2-((((2S,5S)-5-((dodecyloxy)methyl)tetrahydrofuran-2-yl)methyl)amino)ethoxy)-ethanol



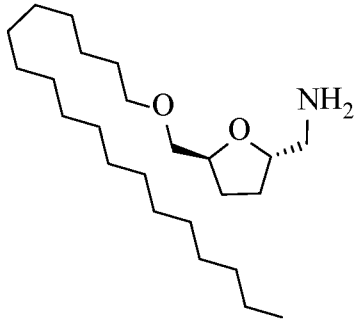
34. The process according to claim 29, further comprising generating a primary amine of a bHMTHF monoether by substitution of a trifluoromethanesulfonate group followed by catalytic debenzylation.

35. A primary amine prepared according to claim 34, wherein said primary amine is at least one of the following compounds:

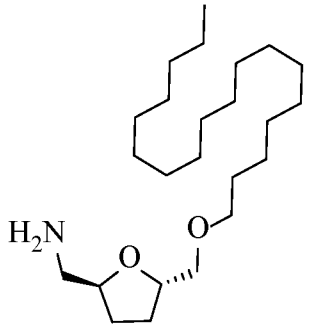
a. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



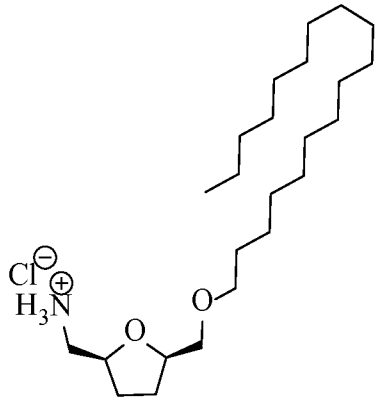
b. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine



c. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanamine

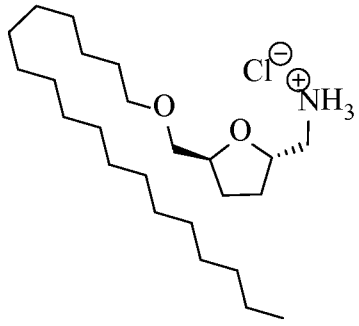


36. The process according to claim 29, further comprising preparing a primary ammonium salt of said bHMTHF monoether by substitution of a trifluoromethanesulfonate group followed by catalytic debenzylation and protonation by a Brønsted acid having a pKa ≤ 0.
37. An primary ammonium salt according to claim 36, wherein said primary ammonium salt is at least one of the following compounds:
    a. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



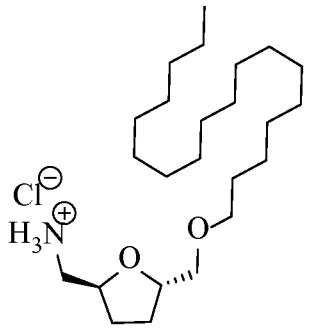
;

    b. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



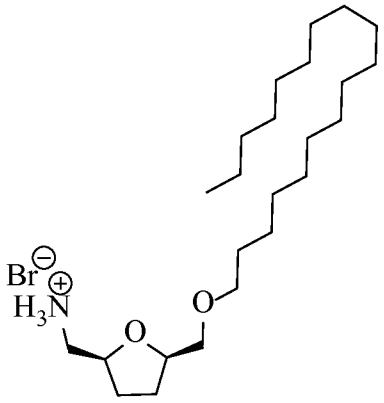
;

    c. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium chloride



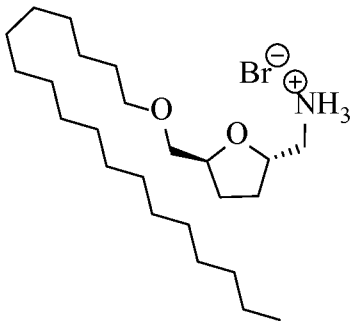
;

d. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



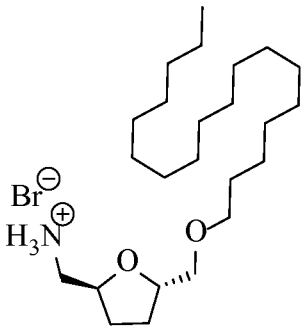
;

e. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



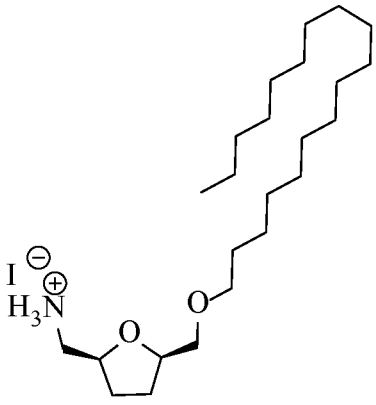
;

f. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium bromide



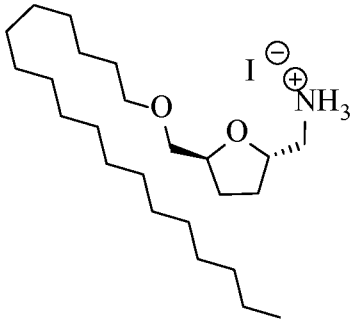
;

g. ((2S,5R)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide



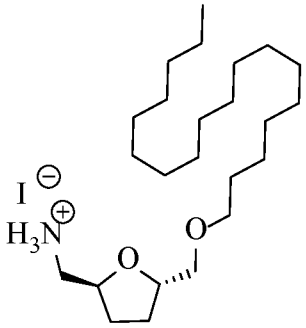
;

h. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide



;

i. ((2S,5S)-5-((octadecyloxy)methyl)tetrahydrofuran-2-yl)methanaminium iodide

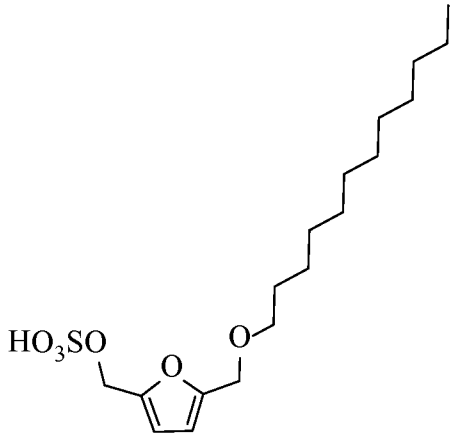


.

38. A process for preparing a derivative compound from a mono-ether, the process comprising contacting a mono-ether of FDM with a) chlorosulfonic acid to generate a sulfate or b) trifluoromethanesulfonic anhydride to generate a trifluoromethanesulfonate.

39. A sulfate made according to claim 38, wherein said sulfate is the following compound:

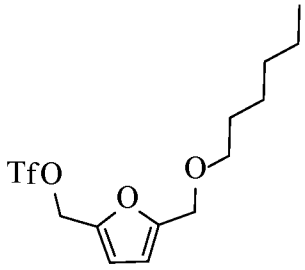
(5-((dodecyloxy)methyl)furan-2-yl)methyl hydrogen sulfate



.

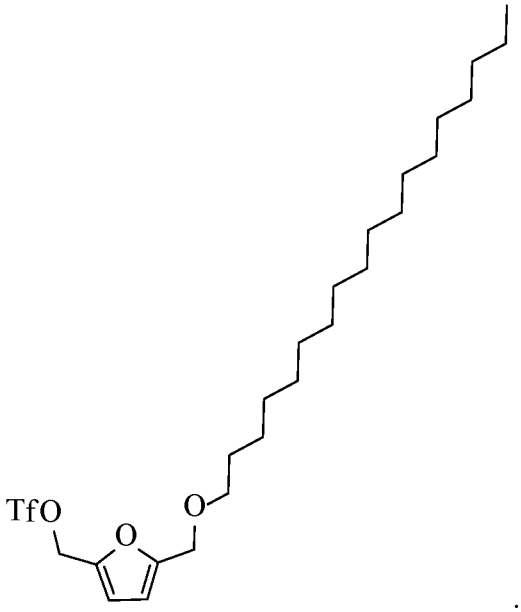
40. A trifluoromethanesulfonate made according to claim 38, wherein said the trifluoromethanesulfonate is at least one of the following structures:

a. (5-((hexyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate



; and

b. (5-((octadecyloxy)methyl)furan-2-yl)methyl trifluoromethanesulfonate

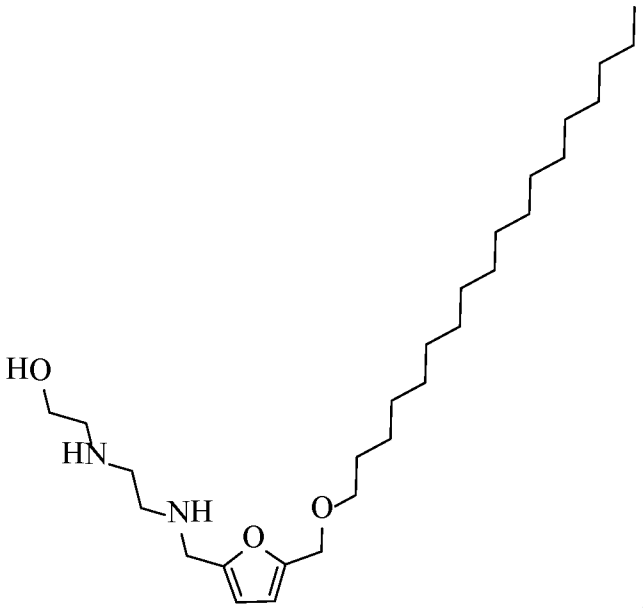


.

41. The process according to claim 38, further comprising preparing a primary ammonium derivative of said FDM monoether by substitution of a trifluoromethanesulfonate group followed by catalytic debenzylation and protonation by a Brønsted acid having a pKa $\leq$ 0.

42. A aminoethylethanolamine, wherein said the aminoethylethanolamine is the following:

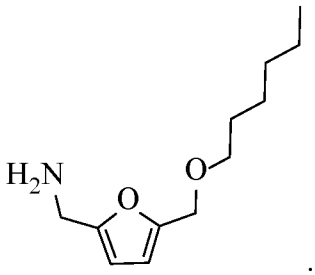
2-((2-(((5-((octadecyloxy)methyl)furan-2-yl)methyl)amino)ethyl)amino)-ethanol



.

43. A primary amine, wherein said primary amine is the following:

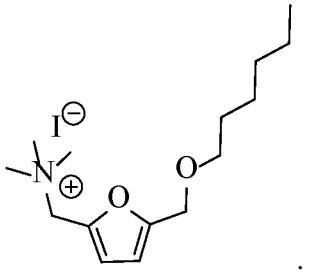
(5-((hexyloxy)methyl)furan-2-yl)methanamine



.

44. A quaternary trimethylammonium salt, wherein said quarternary trimethyl-ammonium salt is the following:

1-(5-((hexyloxy)methyl)furan-2-yl)-N,N,N-trimethylmethanaminium iodide



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INTERNATIONAL SEARCH REPORT

14/070021 13.04.2015

International application No.
PCT/US2014/070021

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 307/12 (2015.01)
CPC - C07D 307/12 (2015.01)
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)
IPC(8) - C07D 307/12, 307/36 (2015.01)
CPC - C07D 307/12, 307/36 (2015.01) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 549/502 (keyword delimited)

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

PatBase, Orbit, STN, PubChem, Google Scholar.
Search terms used: furan, tetrahydrofuran, ether, hexyloxy, dodecyloxy, octadecyloxy, lithium, magnesium, potassium, sodium, cuprate, hydride, Bronsted, halide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PubChem. Compound Summary for CID 10917601. Create Date: 2006-10-26. [retrieved on 23 January 2015]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/10917601>. entire document	24
X	PubChem. Compound Summary for CID 70458981. Create Date: 2012-12-01. [retrieved on 26 March 2015]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/70458981>. entire document	26
A	PubChem. Compound Summary for CID 14785823. Create Date: 2007-02-09. [retrieved on 23 January 2015]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/14785823>. entire document	1-28
A	PubChem. Compound Summary for CID 13793778. Create Date: 2007-02-08. [retrieved on 23 January 2015]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/13793778>. entire document	1-28
A	US 5,208,352 A (CHEN et al) 04 May 1993 (04.05.1993) entire document	1-28
A	US 2013/0303791 A1 (HOWARD et al) 14 November 2013 (14.11.2013) entire document	1-28

☐ Further documents are listed in the continuation of Box C. ☐

* 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
26 March 2015	13 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

14/070021 13.04.2015

International application No.
PCT/US2014/070021

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-28

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

<Continued from Box III: Observations where unity of invention is lacking>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: Claims 1-28 are drawn to a process for preparing linear mono- and di-alkyl ethers of either furan-2,5-dimethanol (FDM) or 2,5-bis(hydroxymethyl)tetrahydrofuran (bHMTHF); and a mono- or di-ether of FDM or bHMTHF.

Group II: Claims 29-44 are drawn to a process for preparing a derivative compound from a mono-ether, and derivatives thereof.

The inventions listed in Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, processes for preparing linear mono- and di-alkyl ethers, are not present in Group II; the special technical features of Group II, processes for preparing a derivative compound from a mono-ether, are not present in Group I.

The Groups I and II share the technical features of a mono-ether of FDM and bHMTHF. However, these shared technical features do not represent a contribution over the prior art.

Specifically, "Compound Summary for CID 14785823" to PubChem teaches a mono-ether of bHMTHF (Pg. 1, AGNPC002JLE...Also known as:...[5-(hexadecoxymethyl)oxolan-2-yl]methanol...; Pg. 3, see 2D structure shown...).

Additionally, "Compound Summary for CID 13793778" to PubChem teaches a mono-ether of FDM (Pg. 1, AGNPC00O0FK...Also known as:...2-Furanmethanol, 5-(butoxymethyl)...; Pg. 3, see 2D structure shown...).

The inventions listed in Groups I and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105814030 A
(43)申请公布日 2016.07.27

(21)申请号 201480067612.0

(22)申请日 2014.12.12

(30)优先权数据
61/918,239 2013.12.19 US

(85)PCT国际申请进入国家阶段日
2016.06.12

(86)PCT国际申请的申请数据
PCT/US2014/070021 2014.12.12

(87)PCT国际申请的公布数据
WO2015/094970 EN 2015.06.25

(71)申请人 阿彻丹尼尔斯米德兰德公司
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(72)发明人 肯尼斯·斯滕斯鲁德

(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
代理人 高瑜 郑霞

(51)Int.Cl.
C07D 307/12(2006.01)

权利要求书15页 说明书35页

(54)发明名称

呋喃-2,5-二甲醇和(四氢呋喃-2,5-二基)二甲醇的单-和二烷基醚以及其两亲衍生物

(57)摘要

描述了呋喃-2,5-二甲醇(FDM)和/或2,5-双(羟甲基)四氢呋喃(bHMTHF)的直链的单-和二烷基醚、其制备方法、以及其衍生化合物。总体上，该合成方法需要FDM或bHMTHF在具有>8的电容率()的一种极性非质子有机溶剂中、在范围从约-25C至约100C的温度下，与或者a)具有pKa≥15的不受阻的布朗斯特碱，或b)具有约16的最小pKa的受阻的布朗斯特碱，和亲核体的反应。

CN 105814030 A

1.一种用于制备或者呋喃-2,5-二甲醇(FDM)或者2,5-双(羟甲基)四氢呋喃(bHMTHF)的直链单-和二-烷基醚的方法,该方法包括:使或者FDM或者bHMTHF在具有>8的电容率(ε)的一种极性非质子有机溶剂中、在范围从约-25℃至约100℃的温度下,与或者a)相对于或者所述FDM或者bHMTHF的羟基的pKa具有≥15的pKa差(ΔpKa)的不受阻的布朗斯特碱,或者b)受阻的布朗斯特碱和亲核体接触。

2.根据权利要求1所述的方法,其中所述FDM和bHMTHF是衍生自5-(羟甲基)糠醛(HMF)的还原产物。

3.根据权利要求1所述的方法,其中所述不受阻的布朗斯特碱是一种金属氢化物。

4.根据权利要求3所述的方法,其中所述不受阻的布朗斯特碱是氢化锂、氢化钠、或氢化钾中的至少一种。

5.根据权利要求1所述的方法,其中所述不受阻的布朗斯特碱是一种有机金属碱。

6.根据权利要求5所述的方法,其中所述不受阻的布朗斯特碱是烷基锂、烷基镁、或烷基铜酸盐化合物中的至少一种。

7.根据权利要求1所述的方法,其中所述不受阻的布朗斯特碱是一种金属酰胺或格氏试剂。

8.根据权利要求1所述的方法,其中所述受阻的布朗斯特碱是叔丁醇钠或叔丁醇钾、或二异丙氨基锂中的至少一种。

9.根据权利要求1所述的方法,其中所述受阻的布朗斯特碱具有至少16的pKa。

10.根据权利要求9所述的方法,其中所述受阻的布朗斯特碱具有≥20的pKa。

11.根据权利要求1所述的方法,其中所述极性的、非质子有机溶剂具有≥30的电容率(ε)。

12.根据权利要求1所述的方法,其中所述极性的、非质子有机溶剂是以下项中的至少一种:二甲基甲酰胺(DMF)、二甲亚砜(DMSO)、二甲基乙酰胺(DMA)、N-甲基吡咯烷酮(NMP)、六甲基磷酰胺(HMPA)、丙酮、乙腈(ACN)、硝基甲烷、环丁砜、四氢呋喃(THF)、1,4-二噁烷、以及乙酸乙酯。

13.根据权利要求1所述的方法,其中所述亲核体是以下项中的至少一种:具有在C_5-C_{25}之间的烷基链长度的烷基卤化物或磺酸酯。

14.根据权利要求13所述的方法,其中所述烷基卤化物或磺酸酯具有在C_8-C_{18}之间的烷基链长度。

15.根据权利要求13所述的方法,其中所述卤化物是Cl、Br、或I中的至少一种。

16.根据权利要求13所述的方法,其中所述磺酸酯是以下项中的至少一种:-OTf(三氟甲磺酸酯)、-OMs(甲磺酸酯)、-OTs(甲苯磺酸酯)、-OBs(对溴苯磺酸酯)、或-OEs(乙磺酸酯)。

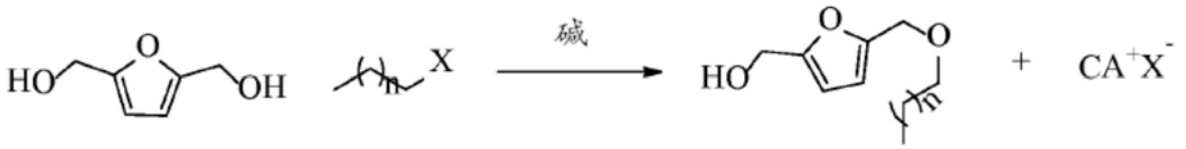
17.根据权利要求1所述的方法,其中所述温度是在从约-10℃至约70℃的范围内。

18.根据权利要求1所述的方法,其中所述温度是在从约-5℃至约35℃的范围内。

19.根据权利要求1所述的方法,其中所述FDM和bHMTHF的单-和二醚具有C_5-C_{25}的直链烃链长度。

20.根据权利要求19所述的方法,其中所述bHMTHF和FDM的单-和二醚具有C_6-C_{18}的直链烃链长度。

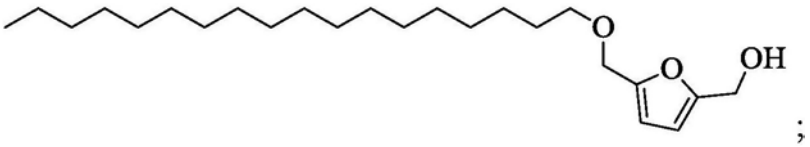
21.一种用于制备单醚的方法，该方法包括：使FDM与布朗斯特碱和1摩尔当量或更少的烷基-X物种根据以下式进行接触：



其中："X"是离去基团，"n"是从5至25的整数，并且"CA"是该碱的一种共轭酸。

22.根据权利要求21制备的FDM的单醚，其中所述FDM的单醚是以下化合物中的至少一种：

a.(5-((十八烷氧基)甲基)呋喃-2-基)甲醇



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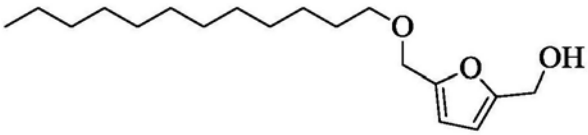
b.(5-((十二烷氧基)甲基)呋喃-2-基)甲醇



以及

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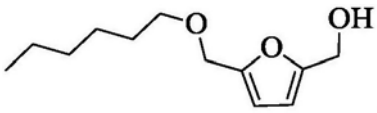
c.(5-((己氧基)甲基)呋喃-2-基)甲醇



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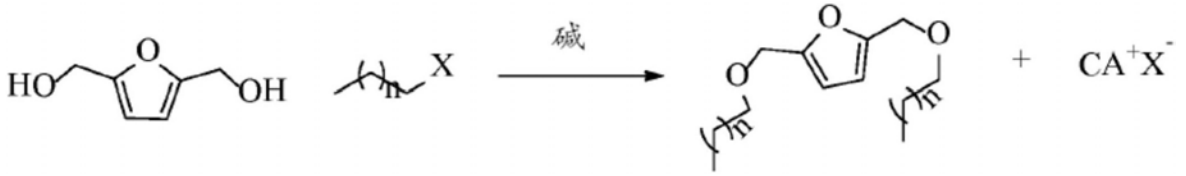
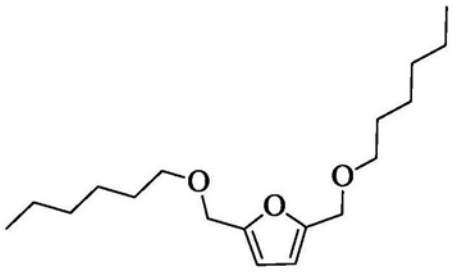
23.一种用于制备二醚的方法，该方法包括：使FDM与布朗斯特碱和最少2摩尔当量的烷基-X物种根据以下式进行接触：



其中："X"是离去基团，"n"是从5至25的整数，并且"CA"是该碱的一种共轭酸。

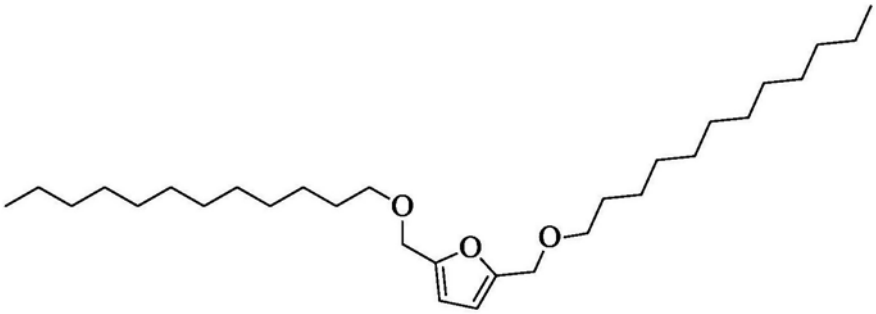
24.根据权利要求23制备的FDM的二醚，其中所述FDM的二醚是以下化合物中的至少一种：

a.2,5-双((己氧基)甲基)呋喃



；

b.2,5-双((十二烷氧基)甲基)呋喃



以及

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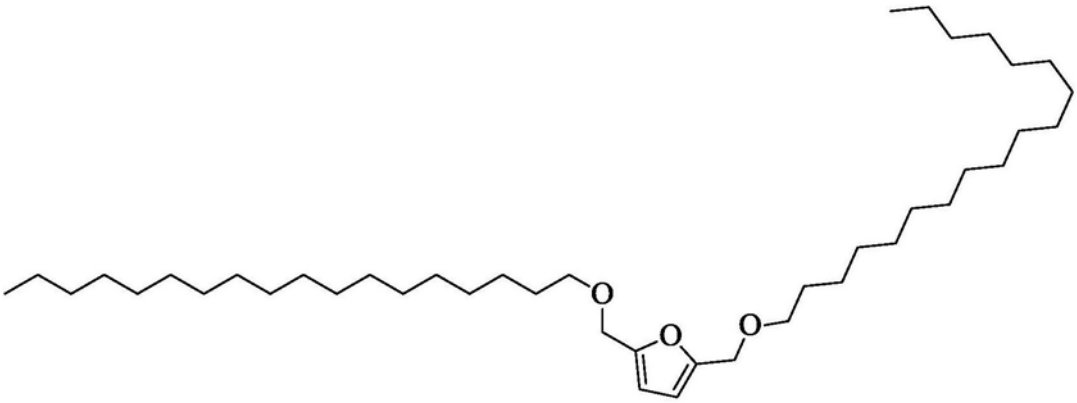
c.2,5-双((十八烷氧基)甲基)呋喃



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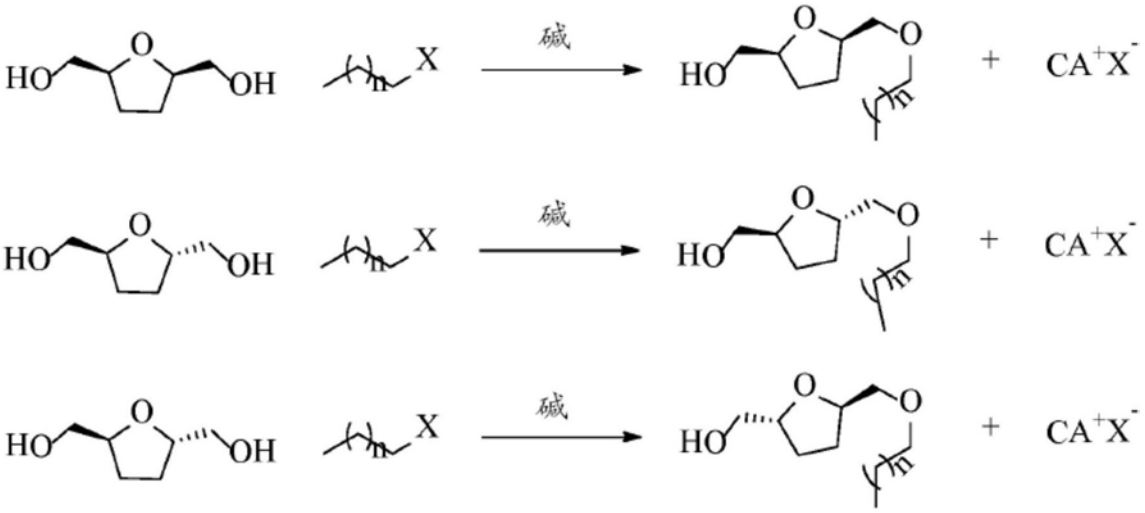
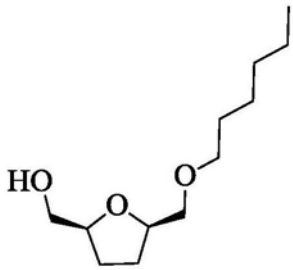
25.一种用于制备单醚的方法,该方法包括:使bHMTHF与布朗斯特碱和1摩尔当量或更少的烷基-X物种根据以下式中的至少一种进行接触:



其中:"X"是离去基团,"n"是从5至25的整数,并且"CA"是一种共轭酸。

26.根据权利要求25制备的bHMTHF的单醚,其中所述bHMTHF的单醚是以下化合物中的至少一种:

a.((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇



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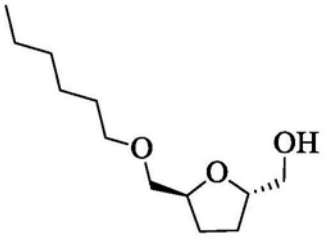
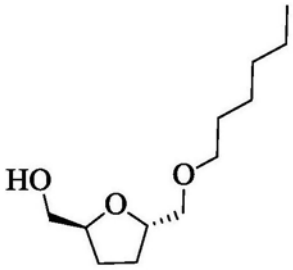
b.((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇



;

c.((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇



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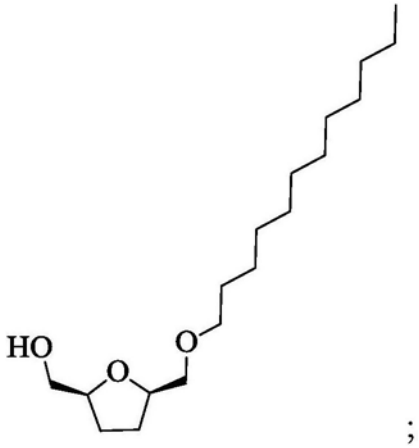
d.((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇



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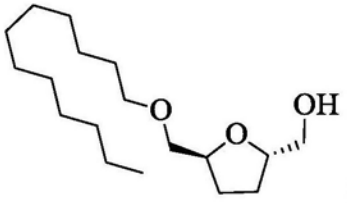
e.((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇



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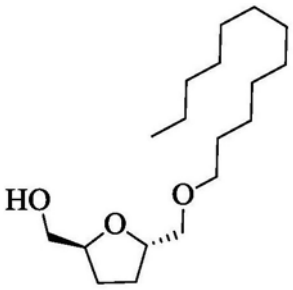
f.((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇



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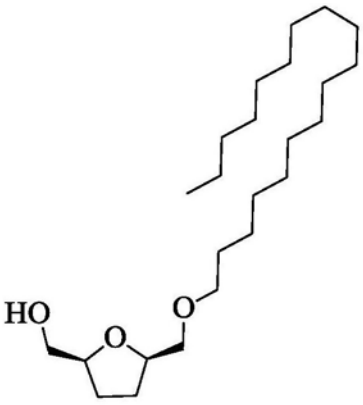
g.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇



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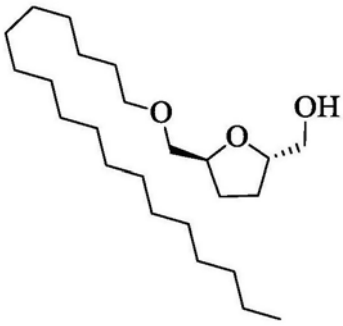
h.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇



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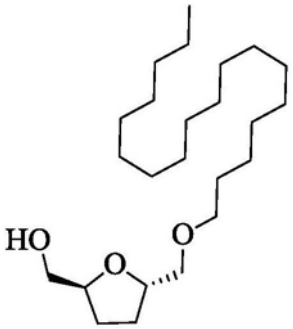
i.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇



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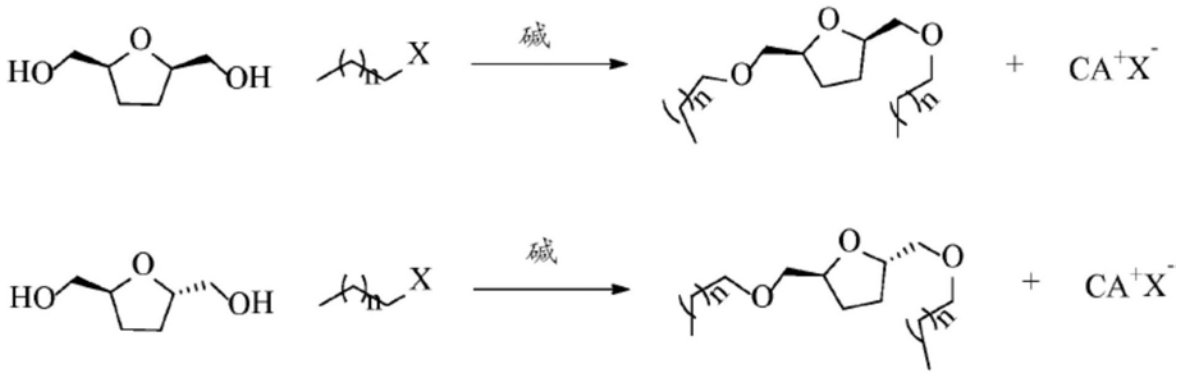
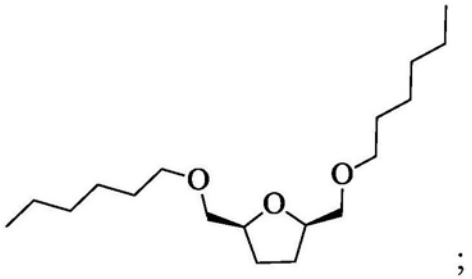
27.一种用于制备二醚的方法,该方法包括:使bHMTHF与布朗斯特碱和最少2摩尔当量的烷基-X物种根据以下式进行接触:



其中:“X”是离去基团,“n”是从5至25的整数,并且“CA”是一种共轭酸。

28.根据权利要求27制备的bHMTHF的二醚,其中所述bHMTHF的二醚是以下化合物中的至少一种:

a.(2R,5S)-2,5-双((己氧基)甲基)四氢呋喃



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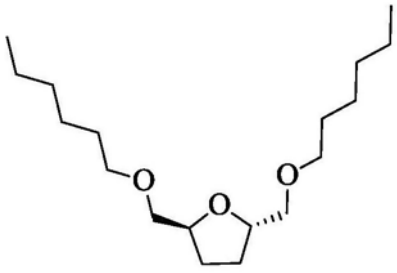
b.(2S,5S)-2,5-双((己氧基)甲基)四氢呋喃



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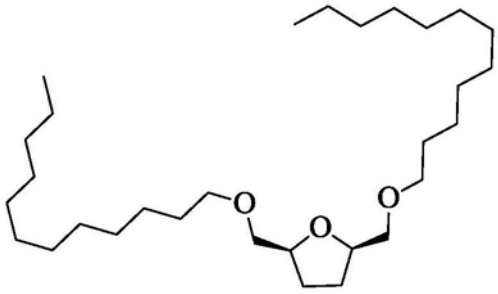
c.(2R,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃



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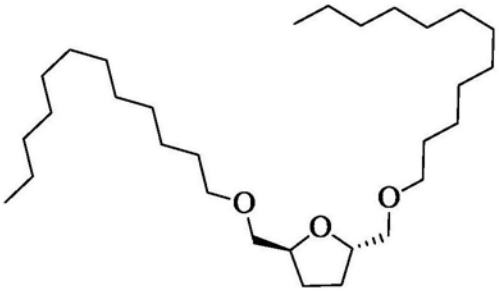
d.(2S,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃



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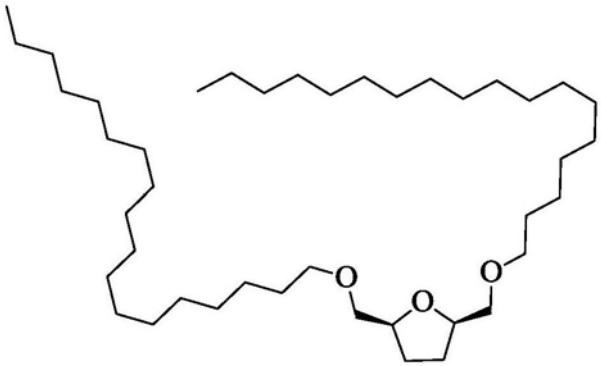
e.(2R,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃



以及

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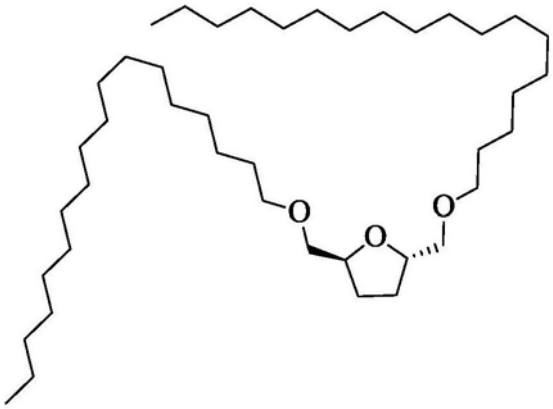
f.(2S,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃



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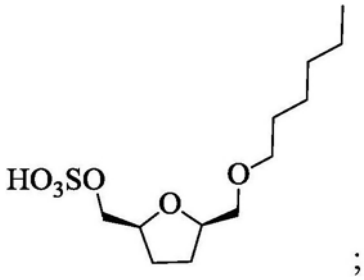
29.一种用于由单醚制备衍生化合物的方法,该方法包括使bHMTHF的单醚与a)氯磺酸接触以产生硫酸酯,或与b)三氟甲烷磺酸酐接触以产生三氟甲烷磺酸酯。

30.根据权利要求29制备的硫酸酯,其中所述硫酸酯是以下化合物中的至少一种:

a.硫酸氢((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯



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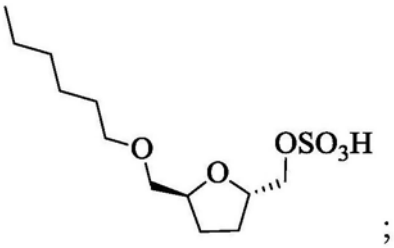
b.硫酸氢((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯



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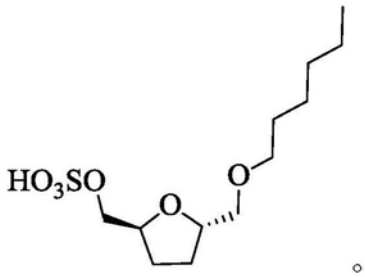
c.硫酸氢((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯



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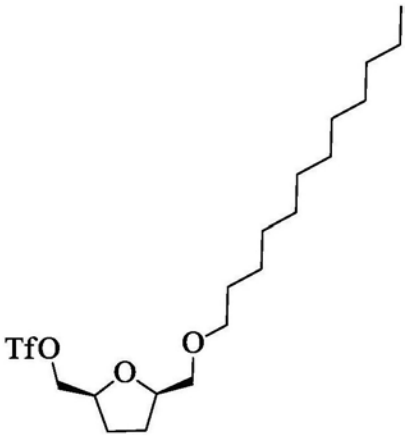
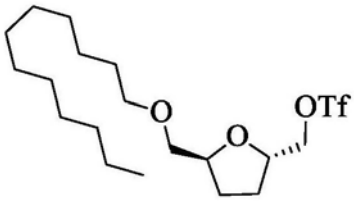
31.根据权利要求29产生的三氟甲烷磺化的单醚,其中所述三氟甲烷磺化的单醚是以下化合物中的至少一种:

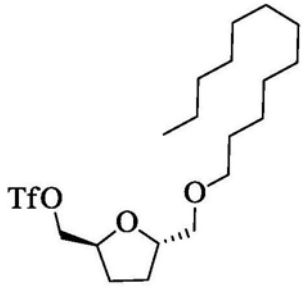
a.三氟甲烷磺酸((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯



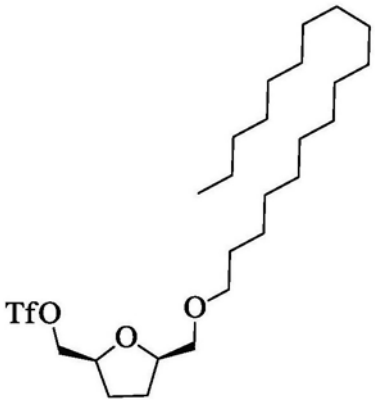
b.三氟甲烷磺酸((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯



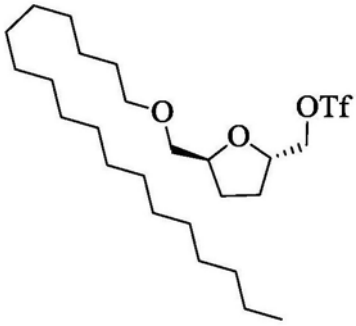
c.三氟甲烷磺酸((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯



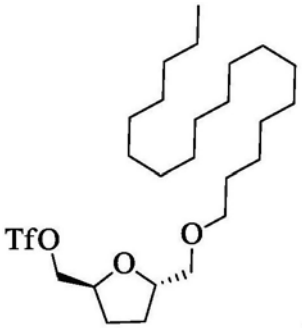
d.三氟甲烷磺酸((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯



e.三氟甲烷磺酸((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯



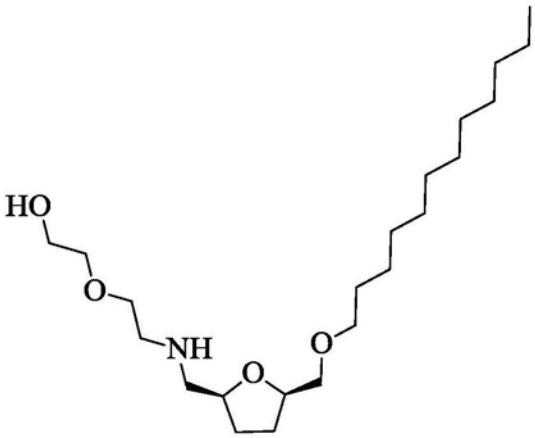
f.三氟甲烷磺酸((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯



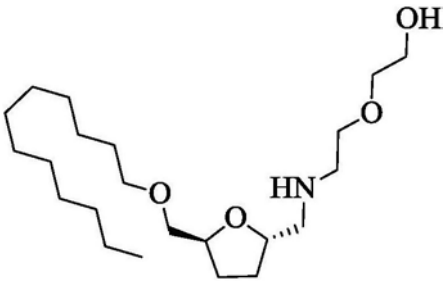
32.根据权利要求29所述的方法,进一步包括通过用乙醇胺取代磺酸酯基团产生bHMTHF单醚磺酸酯化合物的乙氧基乙醇胺衍生物。

33.根据权利要求32制备的乙氧基乙醇胺,其中所述乙氧基乙醇胺是以下化合物中的至少一种:

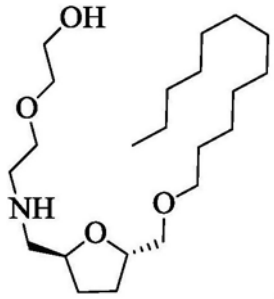
a.2-(2-((((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇



b.2-(2-((((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇



c.2-(2-((((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇

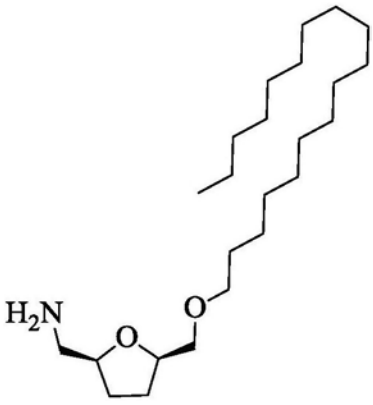


。

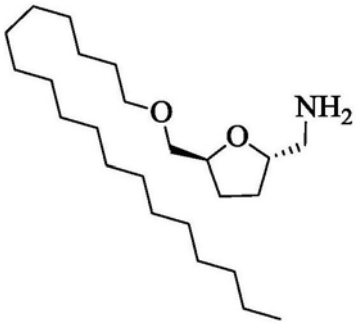
34.根据权利要求29所述的方法,进一步包括通过取代三氟甲烷磺酸酯基团接着催化脱苄基作用来产生bHMTHF单醚的伯胺。

35.根据权利要求34制备的伯胺,其中所述伯胺是以下化合物中的至少一种:

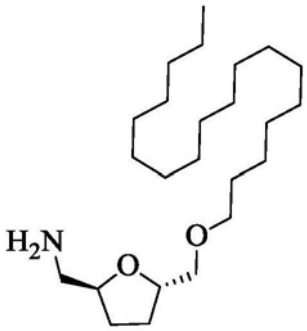
a.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺



b.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺



c.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

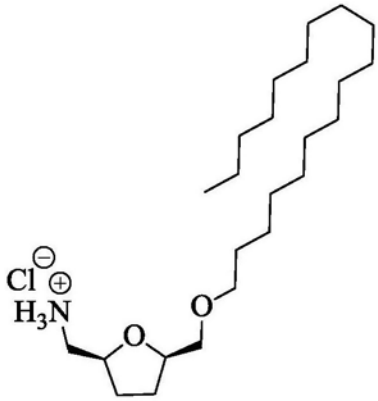


。

36.根据权利要求29所述的方法,进一步包括通过取代三氟甲烷磺酸酯基团接着催化脱苄基作用以及通过具有pKa≤0的布朗斯特酸的质子化来制备所述bHMTHF单醚的伯铵盐。

37.根据权利要求36所述的伯铵盐,其中所述伯铵盐是以下化合物中的至少一种:

a.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物



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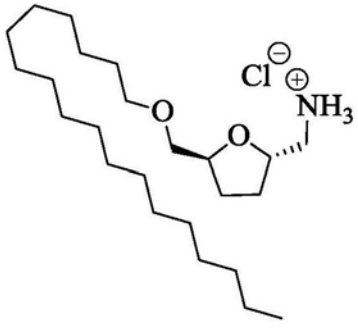
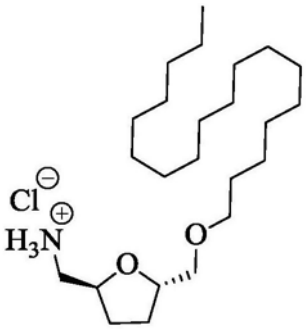
b.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物



;

c.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物



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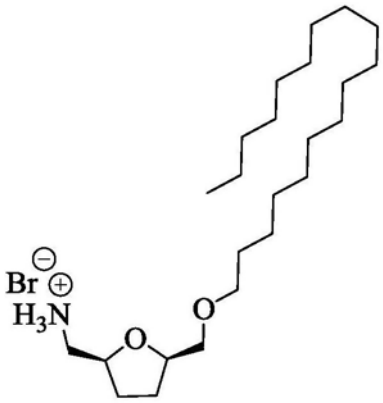
d.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物



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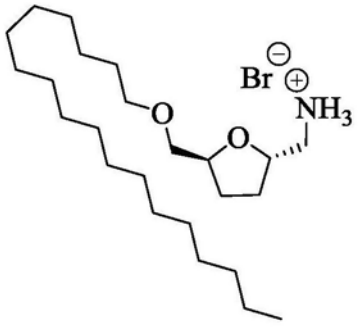
e.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物



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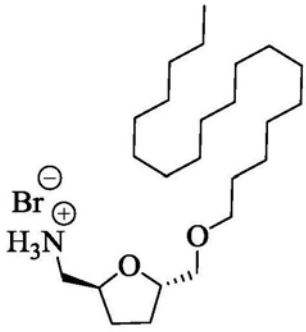
f.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物



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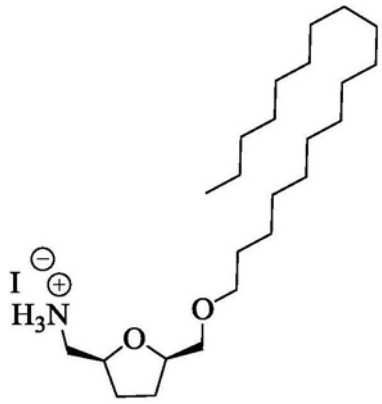
g.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物



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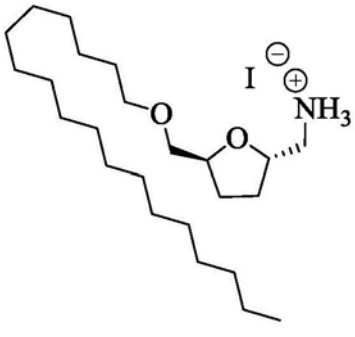
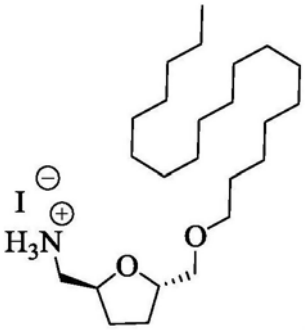
h.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物



;

i.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物



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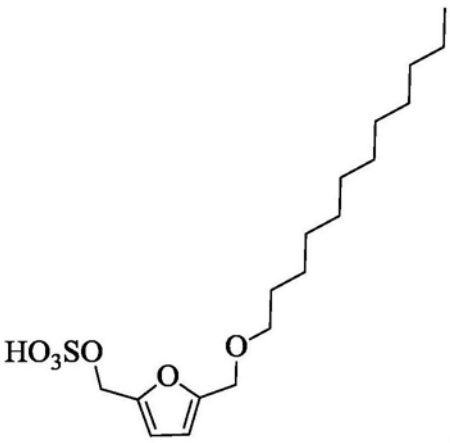
38.一种用于由单醚制备衍生化合物的方法,该方法包括使FDM的单醚与a)氯磺酸接触以产生硫酸酯,或与b)三氟甲烷磺酸酐接触以产生三氟甲烷磺酸酯。

39.根据权利要求38制成的硫酸酯,其中所述硫酸酯是以下化合物:

硫酸氢(5-((十二烷氧基)甲基)呋喃-2-基)甲酯



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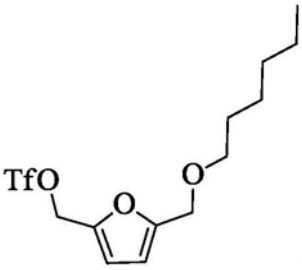
40.根据权利要求38制成的三氟甲烷磺酸酯，其中所述三氟甲烷磺酸酯是以下结构中的至少一种：

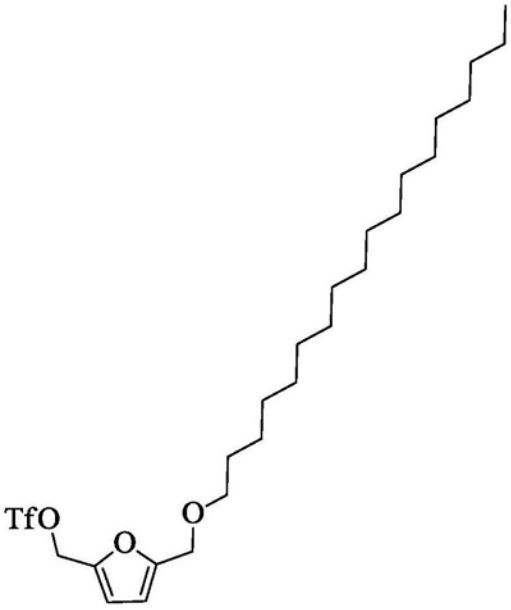
a.三氟甲烷磺酸(5-((己氧基)甲基)呋喃-2-基)甲酯



以及

;

b.三氟甲烷磺酸(5-((十八烷氧基)甲基)呋喃-2-基)甲酯

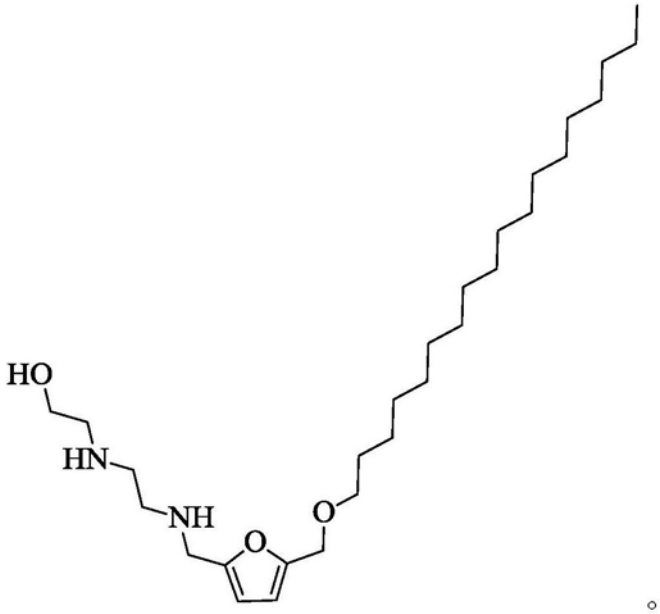


。

41.根据权利要求38所述的方法，进一步包括通过取代三氟甲烷磺酸酯基团接着催化脱苄基作用以及通过具有pKa≤0的布朗斯特酸的质子化来制备所述FDM单醚的伯铵衍生物。

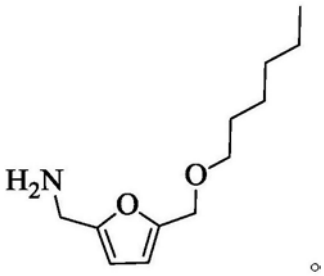
42.一种氨乙基乙醇胺，其中所述氨乙基乙醇胺是以下项：

2-((2-(((5-((十八烷氧基)甲基)呋喃-2-基)甲基)氨基)乙基)氨基)-乙醇



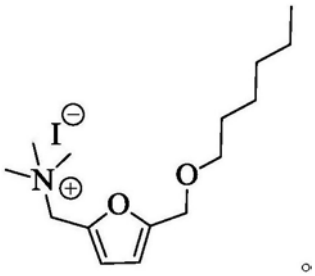
43.一种伯胺,其中所述伯胺是以下项:

(5-((己氧基)甲基)呋喃-2-基)甲胺



44.一种三甲基季铵盐,其中所述三甲基季铵盐是以下项:

1-(5-((己氧基)甲基)呋喃-2-基)-N,N,N-三甲基甲铵碘化物



呋喃-2,5-二甲醇和(四氢呋喃-2,5-二基)二甲醇的单-和二烷基醚以及其两亲衍生物

[0001] 优先权权益

[0002] 本申请要求2013年12月19日提交的美国临时申请号:61/918,239的优先权权益，该临时申请的内容通过引用结合在此。

发明领域

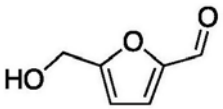
[0003] 本披露涉及作为聚合物合成中的单体、以及中间体化合物有用的某些环状双官能材料。具体地，本发明涉及呋喃-2,5-二甲醇(FDM)和/或(四氢呋喃-2,5-二基)二甲醇(bHMTHF)的醚、其制备方法、以及其衍生化合物。

[0004] 背景

[0005] 鉴于对化石燃料的气候变化的影响和逐渐耗竭的越来越多的关注，对于用于石油基平台化学品的可再生的、生物基替代物的研究正在增长。糖普遍存在于农业材料中，并且因此是“绿色”材料领域中用于实证创新的合理前体。容易地衍生自糖的有机化合物除了其他工业成分之外包括呋喃，具有可用于制造某些聚合物、药物、或溶剂的结构特征的稳健环醚。

[0006] 近来已经受到相当大的关注的一种相关化合物是5-(羟甲基)糠醛(HMF)，(图1)，丰富的、廉价的单糖，果糖的突出的脱水产物。

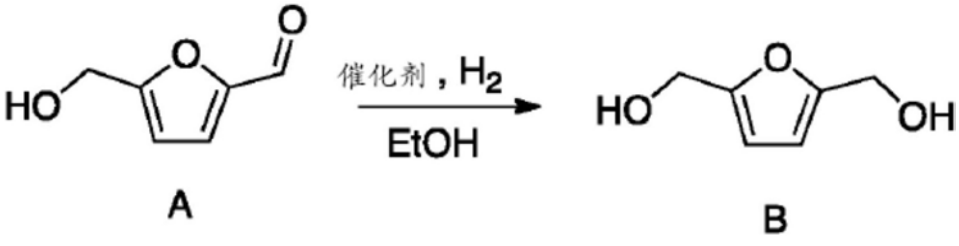
[0007] 图1.HMF的化学结构

[0008] 

[0009] HMF是多种呋喃环基衍生物的一种通用化学前体，这些衍生物是用于众多化学合成的已知中间体并且作为衍生自石油资源的芳香烃的似然替代物。由于HMF的多种多样的功能性，一些已建议将HMF用于生产各式各样的商品例如聚合物、溶剂、表面活性剂、药物、以及植物保护剂。作为替代物，HMF的衍生物与苯基芳香族化合物或含有呋喃或四氢呋喃(THF)的其他化合物是可比较的。因此，HMF和2,5-二取代的呋喃和THF类似物在来自可再生农业资源的中间体化学品领域中具有很大的潜力。

[0010] 然而，HMF本身相当不适合作为化学中间体底物，考虑到它在热氧化条件下分解的倾向。因此，人们应当寻找用于实际商业应用的HMF衍生物。一种衍生物是呋喃-2,5-二甲醇(缩写为FDM)(方案1)，它是从HMF的部分氢化(醛还原)产生的。

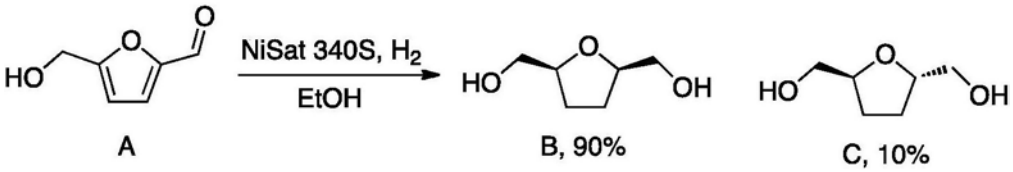
[0011] 方案1.-来自HMF A的部分氢化的FDM B

[0012] 

A B

[0013] 另一种衍生物是2,5-双(羟甲基)四氢呋喃(缩写为bHMTHF),当HMF的环和醛部分两者完全还原时以9:1顺式(B):反式(C)非对映异构体比产生的饱和的类似物(方案2)。

[0014] 方案2.-来自HMF的彻底还原的bHMTHF

[0015] 

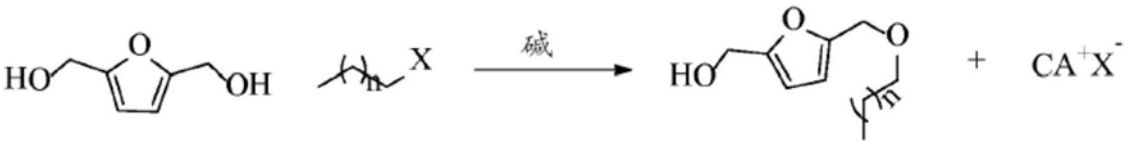
[0016] 这些材料作为分子前体,例如,对于聚酯、聚氨酯泡沫、FDCA、增塑剂、添加剂、润滑剂、以及两亲物可能是有价值的。

[0017] 然而,为了变得与石油产品有市场竞争性,从标准农业原料(如糖)制备HMF衍生物需要就成本而言变得经济上可行。迄今为止,对于使用FDM和/或bHMTHF的化学衍生物的研究部分地由于这些化合物的很大的成本和相对缺乏(例如,商业上每克约$200)受到有限的关注。最近,对于发掘FDM和bHMTHF以及它们的衍生化合物的潜能的方式出现一种需要,因为这些化学实体作为用于制备聚合物、溶剂、添加剂、润滑剂、以及增塑剂等的有价值的乙醇酸前体已经受到关注。此外,bHMTHF的固有的、不变的手性使得这些化合物作为用于药物应用的潜在物种或在不对称有机合成的新兴手性助剂领域中的候选物是有用的。鉴于这些潜在用途,可以从FDM和/或bHMTHF合成衍生物的一种有成本效益的且简单的方法作为更好地利用生物质衍生的碳资源的方式同样将受到工业和专用化学品两者的制造商欢迎。

[0018] 发明概述

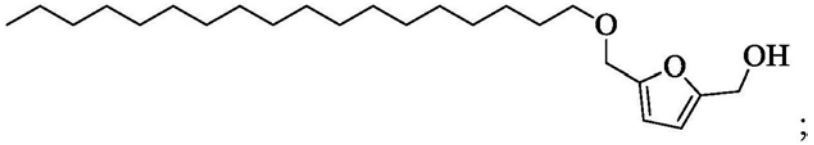
[0019] 本披露部分地描述了呋喃-2,5-二甲醇(FDM)和/或2,5-双(羟甲基)四氢呋喃(bHMTHF)的直链单-和二-烷基醚、以及其合成方法。总体上,该方法包括:使或者FDM或者bHMTHF在一种具有>8的电容率(ε)的极性非质子有机溶剂中、在范围从约-25℃至约100℃的温度下,与或者a)相对于或者FDM或者bHMTHF的羟基的pKa具有≥15的pKa差(ΔpKa)的不受阻的布朗斯特碱(Brønsted base)、或者b)受阻的布朗斯特碱和亲核体接触。

[0020] 在一个具体的实施例中,本披露提供了一种用于制备单醚的方法,该方法涉及:使FDM与布朗斯特碱和一摩尔当量或更少的烷基-X物种根据以下式进行接触:

[0021] 

[0022] 其中:“X”是离去基团(离核体),“n”是从5至25的整数,并且“CA”是一种共轭酸。所产生的FDM的单醚可以是,例如,以下化合物中的至少一种:

[0023] a.(5-((十八烷氧基)甲基)呋喃-2-基)甲醇

[0024] 

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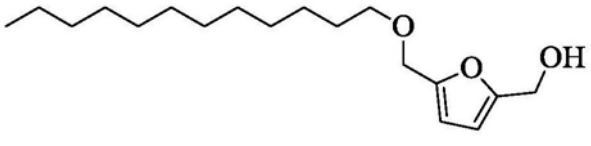
[0025] b.(5-((十二烷氧基)甲基)呋喃-2-基)甲醇

[0026] 

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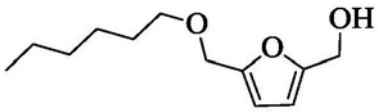
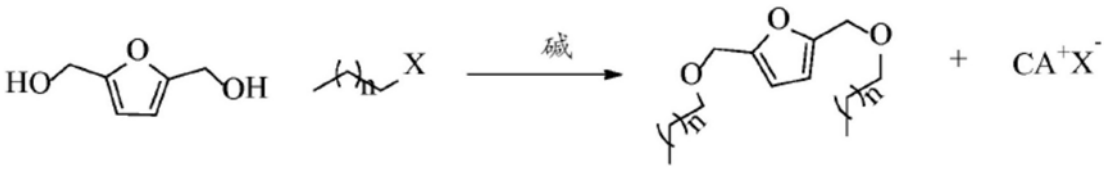
[0027] c.(5-((己氧基)甲基)呋喃-2-基)甲醇

[0028] 

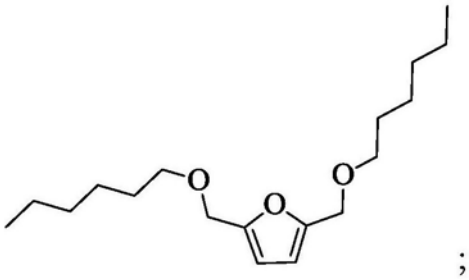
。

[0029] 在用于制备二醚的一个实施例中，该方法涉及：使FDM与布朗斯特碱和最少2摩尔当量的烷基-X物种根据以下式进行接触：

[0030] 

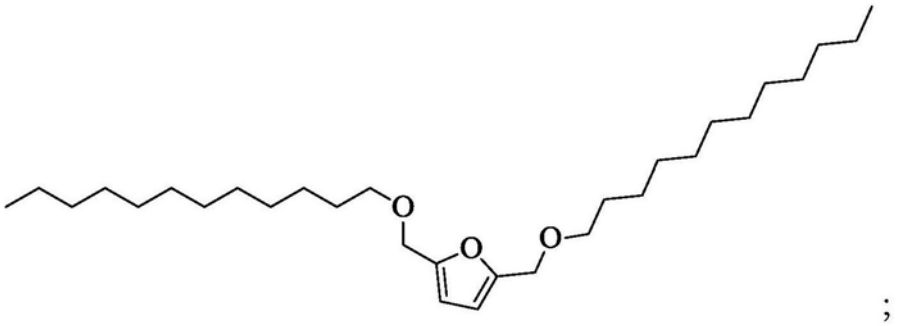
[0031] 其中："X"是离核体，"n"是从5至25的整数，并且"CA"是一种共轭酸。所产生的FDM的二醚可以是，例如，以下化合物中的至少一种：

[0032] a.2,5-双((己氧基)甲基)呋喃

[0033] 

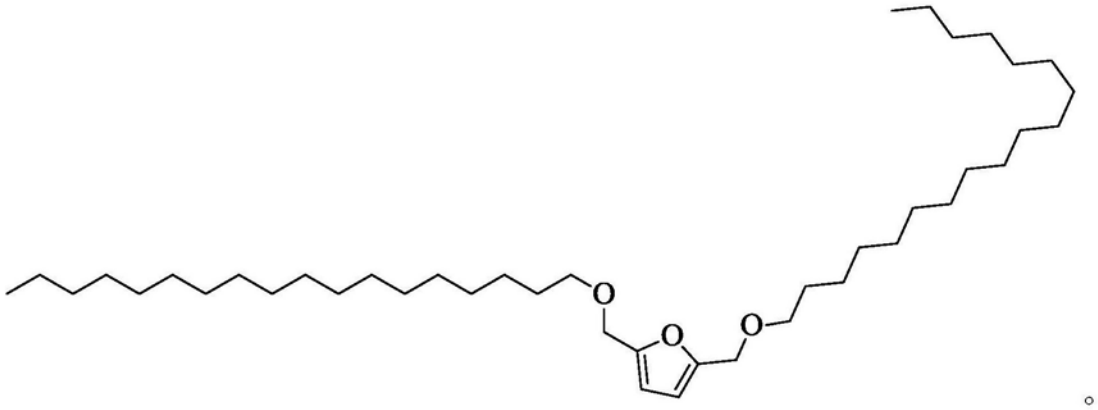
;

[0034] b.2,5-双((十二烷氧基)甲基)呋喃

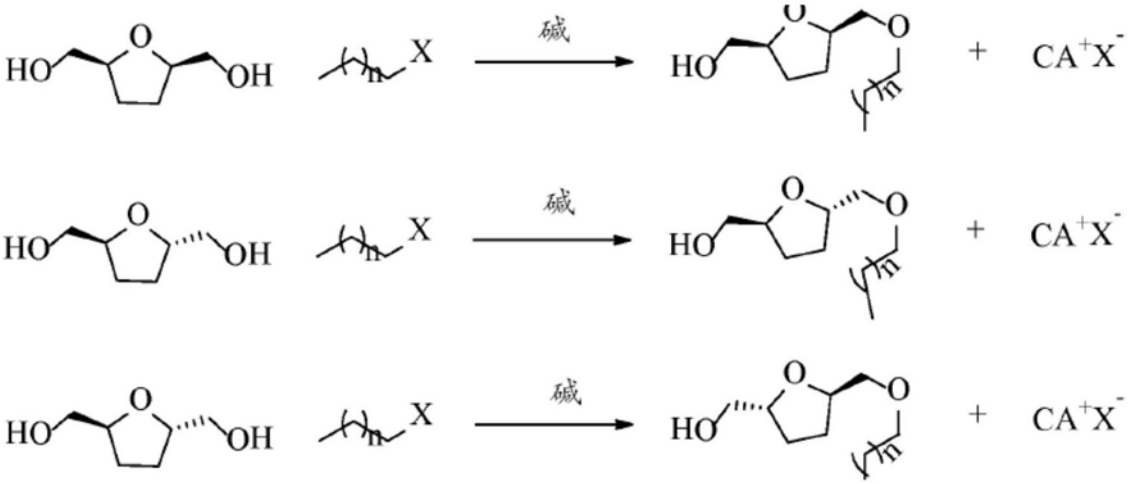
[0035] 

;

[0036] c.2,5-双((十八烷氧基)甲基)呋喃

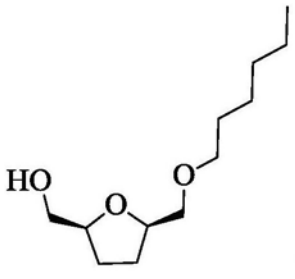
[0037] 

[0038] 在又另一个实施例中，本披露提供了一种用于制备单醚的方法，该方法涉及：使bHMTHF与布朗斯特碱和1摩尔当量或更少的烷基-X物种根据以下式进行接触：

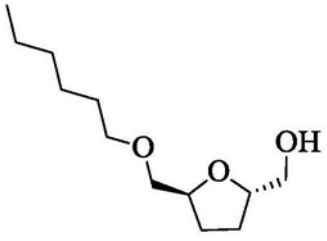
[0039] 

[0040] 其中："X"是离核体，"n"是从5至25的整数，并且"CA"是一种共轭酸。所产生的bHMTHF的单醚可以是，例如，以下化合物中的至少一种：

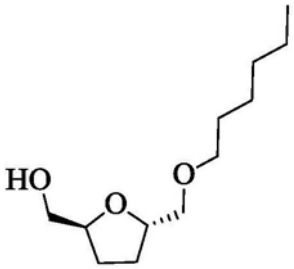
[0041] a.((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇

[0042] 
；

[0043] b.((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇

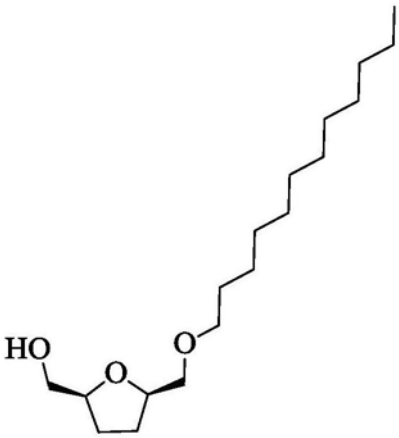
[0044] 
；

[0045] c.((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇

[0046] 

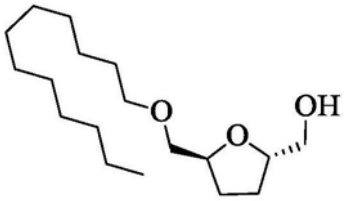
;

[0047] d.((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇

[0048] 

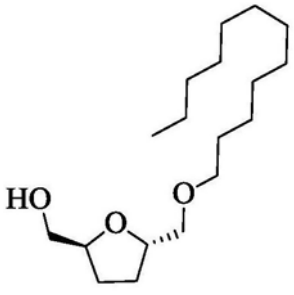
;

[0049] e.((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇

[0050] 

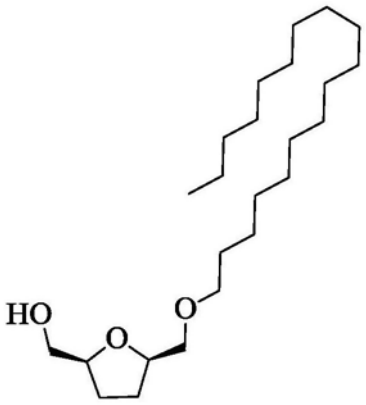
;

[0051] f.((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇

[0052] 

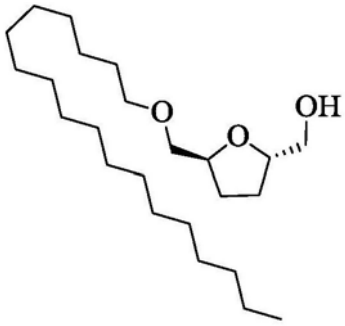
;

[0053] g.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇

[0054] 

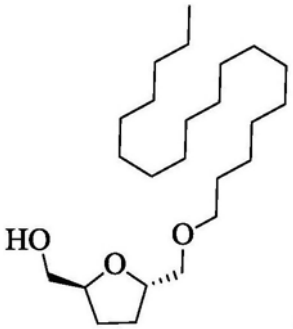
;

[0055] h.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇

[0056] 

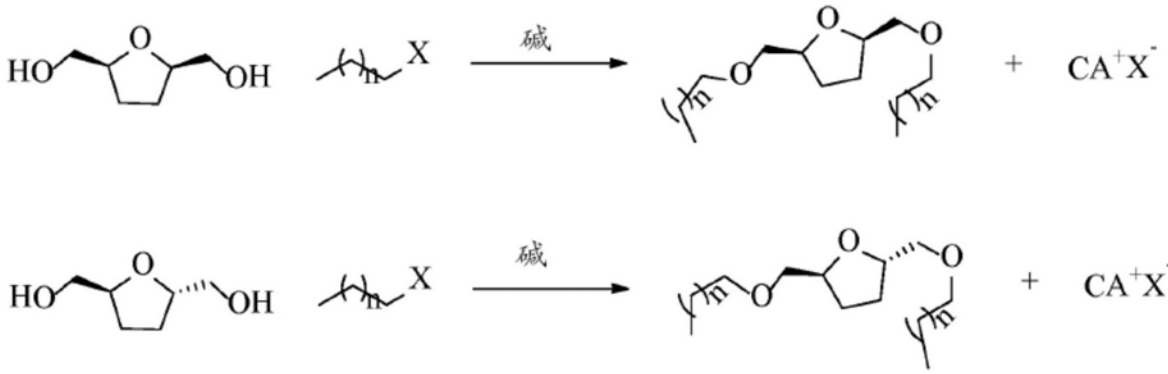
;

[0057] i.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇

[0058] 

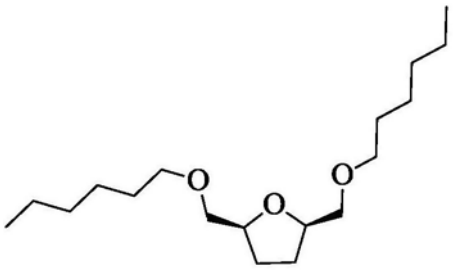
。

[0059] 在用于制备二醚的一个实施例中，该方法涉及：使bHMTHF与布朗斯特碱和最少两摩尔当量的烷基-X物种根据以下式进行接触：

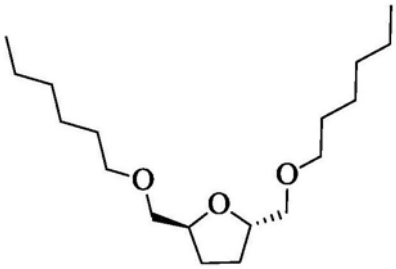
[0060] 

[0061] 其中：“X”是离核体，“n”是从5至25的整数，并且“CA”是一种共轭酸。所产生的bHMTHF的二醚可以是，例如，以下化合物中的至少一种：

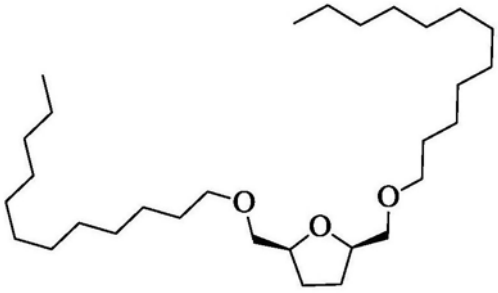
[0062] a.(2R,5S)-2,5-双((己氧基)甲基)四氢呋喃

[0063]  ;

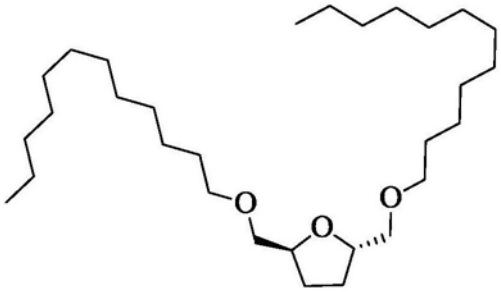
[0064] b.(2S,5S)-2,5-双((己氧基)甲基)四氢呋喃

[0065]  ;

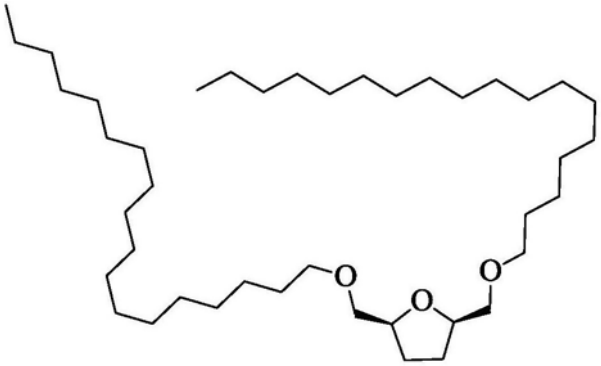
[0066] c.(2R,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃

[0067]  ;

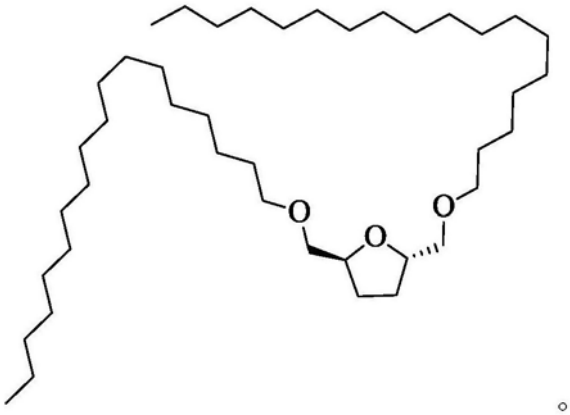
[0068] d.(2S,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃

[0069]  ;

[0070] e.(2R,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃

[0071]  ;

[0072] f.(2S,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃

[0073] 

[0074] 此外,在另一个方面中,本披露涉及来自以上描述的FDM和bHMTHF的直链单醚的衍生化合物以及用于制造这些衍生物的方法。这些衍生化合物是这些单醚的两亲变体并且作为前体或似然生物基表面活性剂、分散剂、和/或亲水物是有价值的。

[0075] 本发明方法的另外的特征和优点将披露于以下详细说明中。应理解的是上述概述以及以下详细说明和实例都仅代表本发明,并且旨在提供用于理解如所要求保护的本发明的综述。

[0076] 发明详述

[0077] 部分I.-说明

[0078] 本发明的合成方法打开了用于由二醇FDM和/或bHMTHF(由果糖衍生的5-(羟甲基)糠醛(HMF)在温和条件下的还原产生的分子)直接制备直链烷基醚、以及它们的衍生化合物的一种途径。(尽管不必要,在某些实施例中,根据在此描述的本发明的反应过程,该方法还可以包括在选择性醚化之前的氢化步骤中或者首先将HMF部分还原为FDM或将HMF完全还原为bHMTHF。)这些烷基醚,进而,是具有生物基两亲特性的有价值的前体,这些前体可以在表面活性剂、分散剂、和增塑剂中使用。

[0079] 总体上,用于产生烷基醚的方法可以在单一反应步骤中实施,其中使该FDM或bHMTHF二醇与或者一当量或两当量的卤化的或磺化的(离去基团)烷烃反应,对应地取决于所希望的是单醚产物还是二醚产物。一种具有约10、优选约16的最小pKa的受阻的布朗斯特碱、或相对于或者FDM或者bHMTHF的羟基的pKa具有≥15的pKa差(ΔpKa)的不受阻的布朗斯特碱用于使这些二醇的-OH部分去质子化,将其对于离核体取代的亲核性增强了若干个数量级。(据信,在布朗斯特碱与FDM和/或bHMTHF二醇的-OH部分之间的pKa的显著差异的情况下,该布朗斯特碱应该在亲核取代和/或消去反应中具有与烷基卤化物或磺酸酯反应的有限的倾向。)一种具有≥10、优选≥30的介电常数的极性非质子有机溶剂用于经由电荷分离能力来增大布朗斯特碱的碱度。典型地,该反应在从约-20℃至约100℃的范围内的温度下、在约2或3小时的时段内进行。在一些其他重复中,如条件可能要求的,时间可以涉及约4或8小时直到约12或24小时。

[0080] A.布朗斯特碱

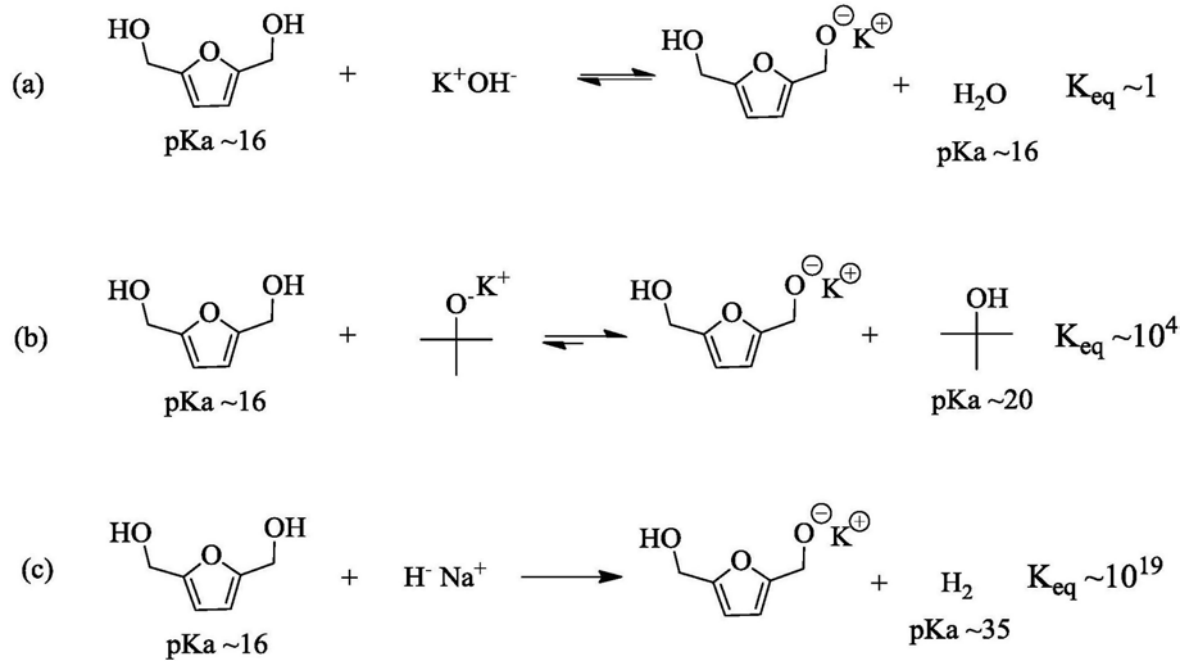
[0081] 如所述,在反应中的布朗斯特碱用来使二醇的-OH部分去质子化。这有助于将二醇FDM和bHMTHF的相应的亲核性增强约至少6或更多的数量级(例如,8-10-12),并且推动在烷基试剂上的卤化物/磺酸酯取代。在反应中使用的布朗斯特碱的相对强度对于提供二醇至

特别地单烷基醚的高转化率是重要的。

[0082] 对于具有至少10至约15的pKa的一些布朗斯特碱，该合成反应通常需要添加热量来进行；因此，反应温度是约45℃-50℃或更高。然而，这可能增加产生副产物(例如，用该烷基卤化物/磺酸酯的布朗斯特碱-亲和取代的产物和/或由布朗斯特碱介导的烷基卤化物/磺酸酯的消去反应形成的烯烃)并且降低所希望的合成的总产率的风险。为了最小化副产物的生成并且抵消这种现象，根据本发明方法的某些实施例，具有至少约16、典型≥20的pKa的布朗斯特碱是有利的。具有更大pKa的布朗斯特碱更容易地与二醇的-OH部分反应。这是帮助人们在约环境室温(例如，约18℃-22℃)或更低的温度下有效地运行该反应的优点。一些合适的布朗斯特碱可以包括，例如，氢氧化物(例如，甲醇盐、乙醇盐，叔丁醇盐、以及苄醚)。优选地，当去质子化平衡有助于产生所希望的产物时，使用具有≥30的pKa的布朗斯特碱，如在实例中在方案3中说明的。这种类型的某些有利的布朗斯特碱可以包括例如金属氢化物(例如，氢化锂、氢化钾、或氢化钠)；金属酰胺(例如，氨基钾或氨基钠)；二异丙基氨基锂(LDA)；有机金属化合物(例如，烷基锂(例如，甲基锂、正丁基锂、或苯基锂)、烷基镁、或烷基铜酸盐)和格氏试剂(例如，溴化乙基镁、溴化苯基镁)。相比之下，某些不利的布朗斯特碱可以包括，例如，以氮为中心的碱(例如，叔胺、芳基胺)，因为偏好低pKa的反应物和亲核倾向。

[0083] 方案3.-用于FDM的不同布朗斯特碱去质子化的平衡常数：a)用氢氧化钾；b)用叔丁醇钾；c)用氢化钠。

[0084]

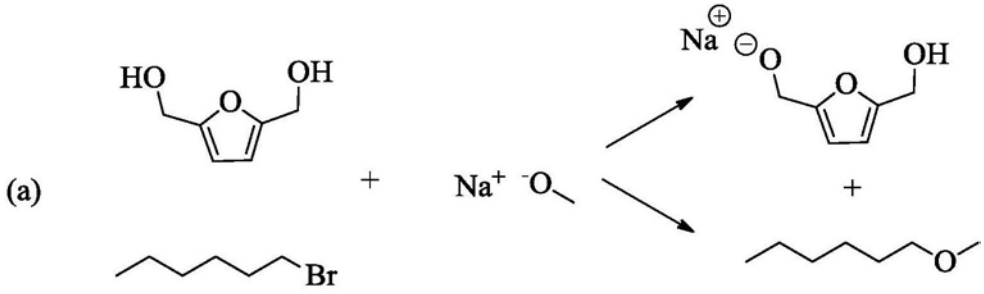


[0085] 反应(a)示出了当使用具有约16的pKa的布朗斯特碱时，该反应趋向于在产物与反应物之间平衡。在反应(b)中，当使用具有约20的pKa的布朗斯特碱时，该反应倾向于更有利于产物，而在反应(c)中，当使用具有pKa≥30的布朗斯特碱时，该反应完全被推动朝向产物形成。

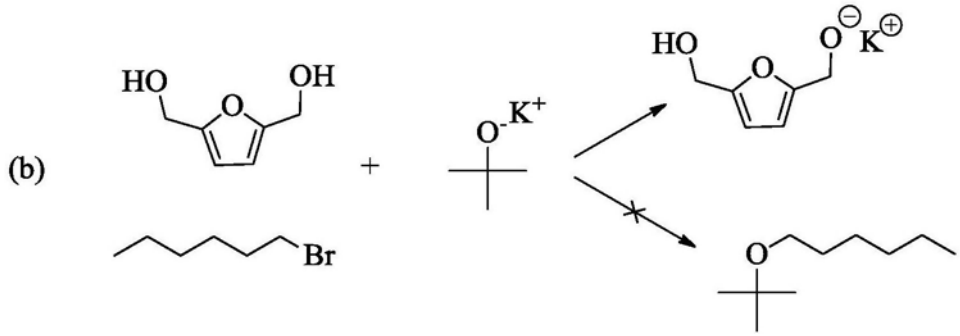
[0086] 根据本发明的一个实施例的另一个因素是采用具有分子体积的布朗斯特碱。有利地，该庞大的布朗斯特碱阻止该布朗斯特碱与该烷基卤化物/磺酸酯的不希望的亲核取代。

因此，更空间受阻的布朗斯特碱更有效地增强了该反应以便主要产生醚产物。方案4展示了这种特征。作为一个实例，使用不受阻的布朗斯特碱的反应(a)倾向于制造直链的和FDM醚二者的混合的产物。相比之下，使用更庞大的、受阻的布朗斯特碱的反应(b)产生单独的FDM醚。

[0087] 方案4.-布朗斯特碱的实例：a)不受阻的、亲核的碱，用甲醇钠；b)受阻的、非亲核的碱，用叔丁醇钾。

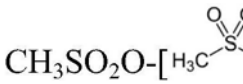
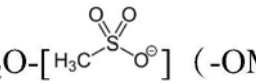
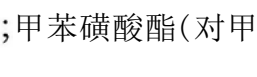
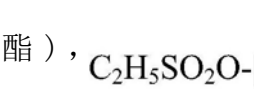


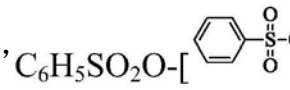
[0088]



[0089] B.烷基卤化物和磺酸酯

[0090] 本说明书的醚化反应可以以在二醇与活化的烷烃之间的碱-介导的、二级取代反应为特征。为了在极性非质子有机溶剂中最迅速地实现希望的醚的令人满意的产率，接至烷烃上的离去基团应该呈现有利的离核特性。在此上下文中，一些物种可以是例如卤化物(例如，Cl、Br、I)和磺酸酯(例如-OTf、-OTs、-OMs)。典型地，人们可以使用具有5至25个碳长度的直链的烷基卤化物或磺酸酯进行该反应。在一些反应中，例如，该烷基链长度可以范围从约5或8至约16或18个碳、或约6或10至约20或22个碳(例如，C_8-C_{18}、C_5-C_{15}、C_6-C_{12})、或在其之间的任何重复。

[0091] 人们可以使用多种磺酸酯，包括但不限于甲磺酸酯(甲烷磺酸酯)，  (-OMs)；三氟甲磺酸酯(三氟甲烷磺酸酯)，  (-OTfs)；甲苯磺酸酯(对甲苯磺酸酯)，  (-OTs)；乙磺酸酯(乙烷磺酸酯)，  (-OEs)；苯磺酸酯(besylate)(苯磺酸酯

(benzenesulfonate)),  以及其他烷基和芳基磺酸酯而没有限制。

[0092] 由于卤化物(如溴化物)和醇是更经济上可获得的商业烷烃来源,根据一些实施例,它们可以有利地用于更大规模的、工业用途。在其中烷基卤化物是不可获得或过分昂贵、但相应的醇可获得的情况下,人们可以通过简单的磺化反应取代该醇用于相应的磺酸酯。

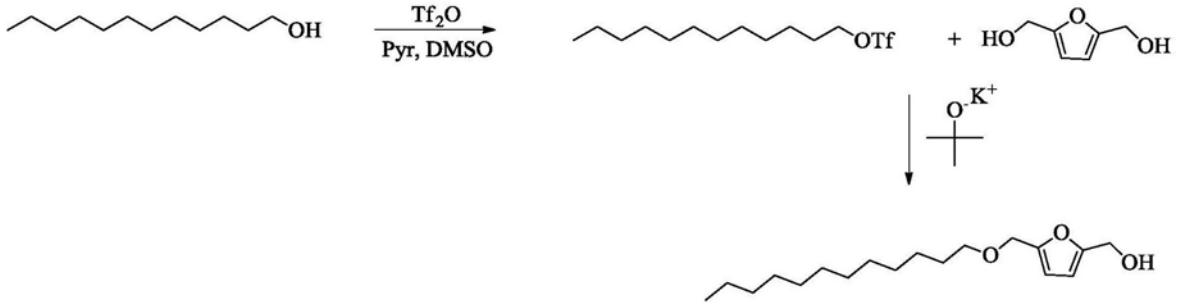
[0093] 在某些实施例中,该磺酸酯优选地是三氟甲磺酸酯,因为它是一种强大的离去基团。这种反应呈现了比较快的动力学并且产生一种活化的三氟甲磺酸络合物。通常在小于0℃(例如,典型地约-10℃或-12℃至约-20℃或-25℃)的低温下进行该反应,以便更容易地控制反应动力学。这种反应基本上是不可逆的,因为所释放的三氟甲磺酸酯完全是不亲核的。然后该三氟甲磺酸络合物与FDM或bHMTHF容易地反应,对应地形成FDM或bHMTHF-三氟甲磺酸酯,同时伴随亲核碱(例如,嘧啶、二甲基-氨基吡啶、咪唑、吡咯烷、和吗啉)的释放和质子化。

[0094] 甲苯磺酸酯、甲磺酸酯、对溴苯磺酸酯、苯磺酸酯、乙基磺酸酯或其他磺酸酯物种可以与三氟甲磺酸酯一样有效给予离去基团,并且显示出与使用三氟甲磺酸酯所实现的总产率同量的总产率。但是,这些其他磺酸酯与三氟甲磺酸酯相比趋向于更缓慢地反应。为了对此进行补偿,当使用这些其他物种时,更好的产率典型地需要在更高的温度下的操作。

[0095] 经常,在进行与二醇的取代反应之前,该转化可以在一个单一反应容器内顺序进行,如方案5中展示的。

[0096] 方案5.-在FDM与十二烷醇之间的单一容器顺序磺化、取代反应。

[0097]

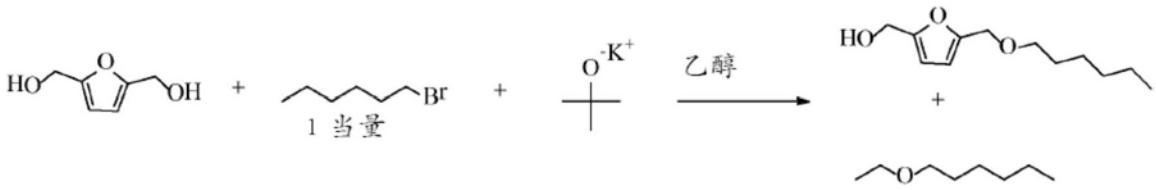


[0098] C.有机溶剂

[0099] 在本发明的合成方法中,使用非质子溶剂,因为它们不含有对于标题反应的用二醇、烷基卤化物/磺酸酯和布朗斯特碱的共价改性不稳定的官能团,并且因此不干扰该Sn2-驱动的过程。此外,极性非质子溶剂(即,具有永久偶极矩但没有充当氢键供体的能力的溶剂)在本发明的醚化反应中是有利的。极性非质子溶剂充分溶解这些二醇和该烷基卤化物/磺酸酯,一种有效的反应发生的特征。该功能不同于非极性溶剂像己烷或苯,这些非极性溶剂缺乏进行将该阴离子布朗斯特碱与其阳离子对应物电荷分离的能力,致使其是非活性的。另外,极性非质子溶剂不倾向于与该烷基卤化物/磺酸酯反应(参见,方案6,可能产生不希望的副产物的乙醇(极性质子溶剂))。

[0100] 方案6.-用乙醇(极性质子溶剂)的溶剂醚化可能性。

[0101]



[0102] 在非质子溶剂中，较大的介电常数可以帮助防止该溶剂与主要试剂反应，因此最小化副产物的形成。本发明的合成方法的反应在具有≥ ε_r 25、典型地约30或35的相对电容率的溶剂中进行。例如，DMSO和DMF显示出相对高的介电常数(例如，约30或32)。其他具有高的沸点和介电常数的溶剂，如NMP和DMA，在用于磺酸酯取代反应的氰化物中是有效的。在一种具有≥110℃的沸点的溶剂的溶液中进行用磺酸酯衍生化FDM或bHMTHF的反应。

[0103] 适合此方法的一些常见的极性非质子溶剂是：二甲基甲酰胺(DMF)、二甲亚砜(DMSO)、二甲基乙酰胺(DMA)、N-甲基吡咯烷酮(NMP)、六甲基磷酰胺(HMPA)、丙酮、乙腈(ACN)、硝基甲烷、环丁砜、四氢呋喃(THF)、1,4-二噁烷、以及乙酸乙酯。

[0104] 当在该醚化方法中使用极性非质子溶剂时，进一步的考虑是充分地电荷分离布朗斯特碱，这样使得可以使这些二醇-OH部分去质子化。电荷分离能力的一种反映是介电常数的电容率，由ε(无单位)表示，其中更大的数字代表螯合离子的更大的能力。总体上，e>20有利于有效的电荷分离，其中例外是THF(ε＝7.58)以及1,4-二噁烷(ε＝2.21)，其氧原子可以与阳离子推拉地(captodatively)配位。优选的ε是>30。具有有利的的极性非质子溶剂的实例是DMSO(ε＝46.7)、环丁砜(ε＝43.3)、DMA(ε＝37.8)、乙腈(ε＝37.5)、DMF(ε＝36.7)、硝基甲烷(ε＝35.9)、NMP(ε＝32.0)、HMPA(ε＝30.0)、丙酮(ε＝20.0)。

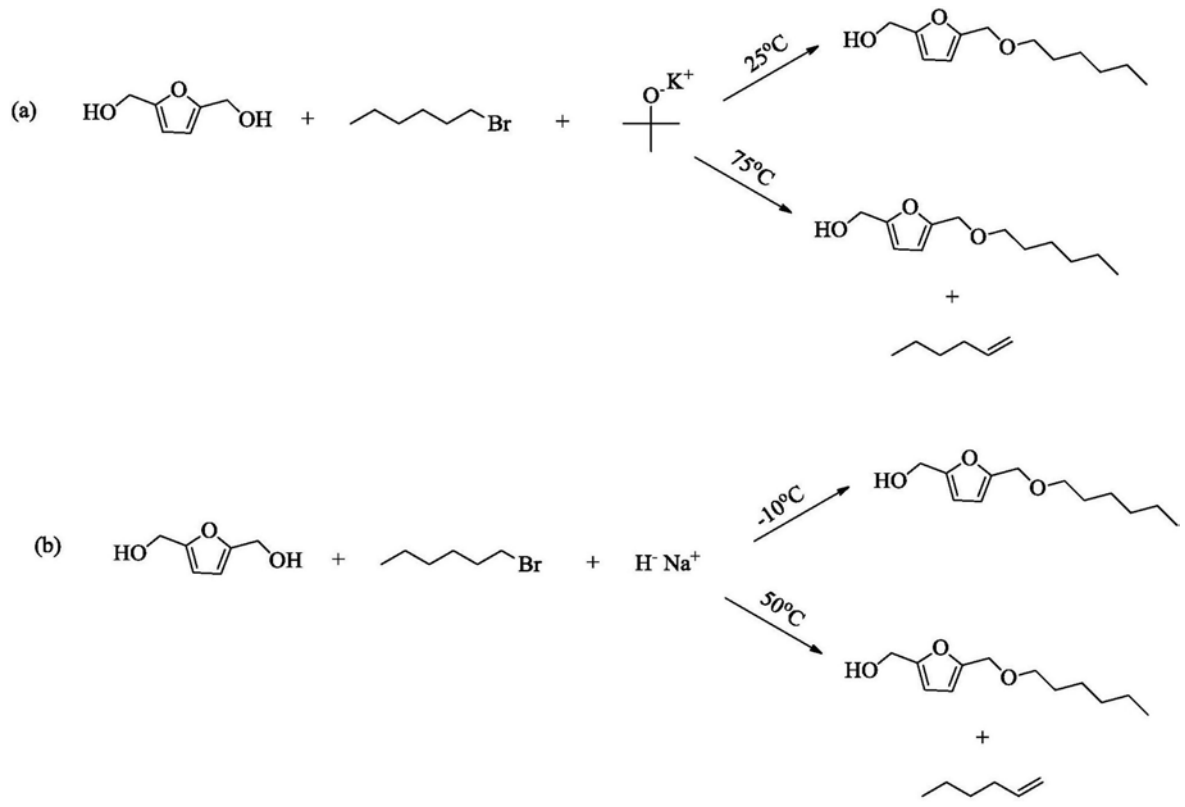
[0105] D.反应温度

[0106] 本发明的合成方法的优点之一是该合成方法可以在相对温和的温度范围内并且在比一些其他常规反应方法较不恶劣的条件下操作。依赖于具体的布朗斯特碱，反应温度可以在约-25℃或-20℃至约80℃或100℃之间的范围内。典型地，该反应温度是在从约-12℃或-7℃至约65℃或70℃、更典型地从约-10℃或-5℃至约40℃或50℃的范围内。在某些实施例中，优选的温度可以范围从约-10℃或-8℃至约25℃或30℃、或约-3℃或0℃至约32℃或35℃(包含)。优选地，该反应可以在处于或低于环境室温(例如，≤约22℃或25℃)下进行。因为由碱介导的烷基卤化物/磺酸酯在高温下的消去反应产生烯烃的可能性或倾向、以及当使用某些布朗斯特碱时潜在的缓慢的反应动力学(方案7)，用于本发明的选择性醚化的温度控制是一个重要的因素。(如上述的，一种具有低于16的pKa的布朗斯特碱，这指定了FDM和bHMTHF的-OH部分的pKa，在平衡时趋向于有利于反应物；因此，该反应在高温(例如>25℃、35℃、或40℃)下进行以推动醚化，尽管伴随形成副产物(烯烃)的更大的风险。)

[0107] 方案7.-使用a)叔丁醇钾，以及

[0108] b)氢化钠作为布朗斯特碱的反应温度分布(profile)。

[0109]



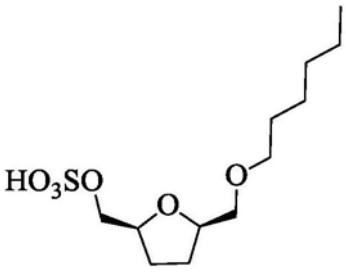
[0110] E.衍生物

[0111] 在另一方面,多种两亲化合物可以由FDM或bHMTHF醚作为起始或前体材料合成。此类衍生材料可以是作为表面活性剂、分散剂、增塑剂中的现有化合物的替代物或新的化学结构单元、或其他应用中的一种组分有用的。这些衍生两亲化合物可以根据可供用于有机合成的各种化学反应制备。一些代表性的衍生化合物的制备在以下所附实例中进一步描述。

[0112] 这些方法可以包括:使bHMTHF或FDM的单醚分别与:a)氯磺酸反应以产生每种二醇物种的硫酸酯,或b)三氟甲烷磺酸酐反应以产生每种二醇物种的三氟甲烷磺酸酯。对于bHMTHF单醚的衍生物,硫酸酯产物可以是,例如,以下化合物中的至少一种:

[0113] a.硫酸氢((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯

[0114]



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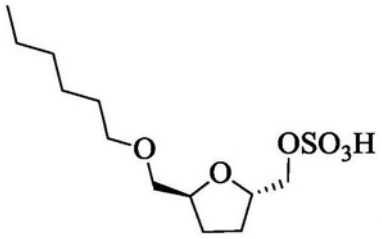
[0115] b.硫酸氢((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯

[0116] 

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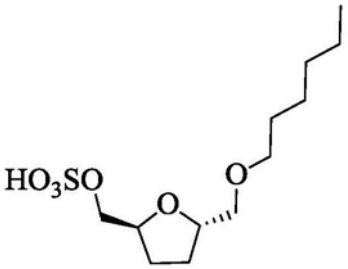
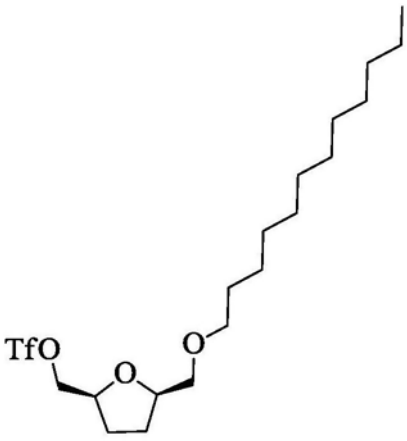
[0117] c.硫酸氢((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲酯

[0118] 

。

[0119] 可替代地,由该bHMTHF单醚所产生三氟甲烷磺酸化的单醚可以是,例如,以下化合物中的至少一种:

[0120] a.三氟甲烷磺酸((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯

[0121] 

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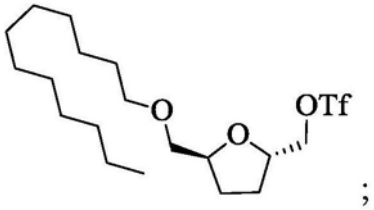
[0122] b.三氟甲烷磺酸((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯

[0123] 

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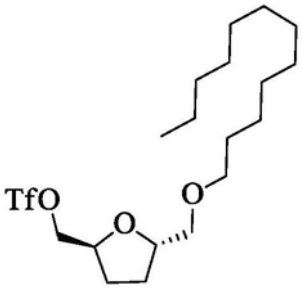
[0124] c.三氟甲烷磺酸((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲酯

[0125] 

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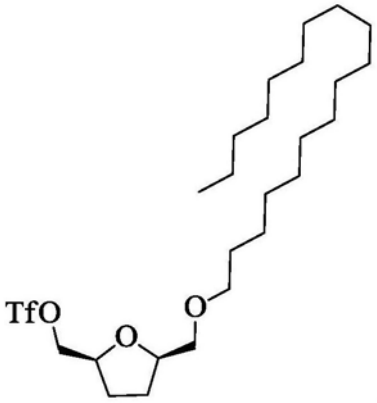
[0126] d.三氟甲烷磺酸((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯

[0127] 

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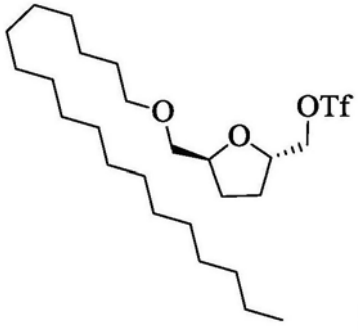
[0128] e.三氟甲烷磺酸((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯

[0129] 

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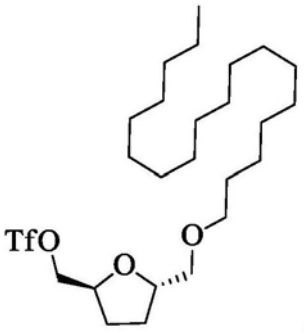
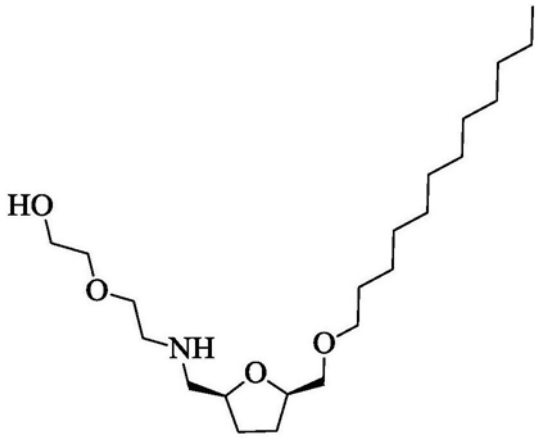
[0130] f.三氟甲烷磺酸((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲酯

[0131] 

。

[0132] 该方法可以进一步涉及通过用乙醇胺取代磺酸酯基团产生bHMTHF单醚磺酸酯化合物的乙氧基乙醇胺衍生物。所制备的生成的乙氧基乙醇胺可以是,例如,以下化合物中的至少一种:

[0133] a.2-(2-((((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇

[0134] 

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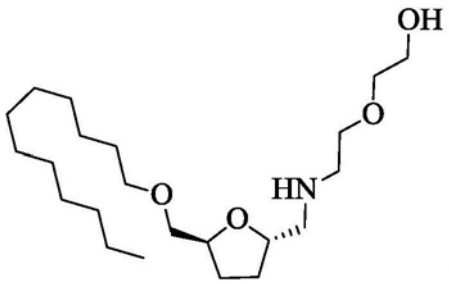
[0135] b.2-(2-((((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇

[0136] 

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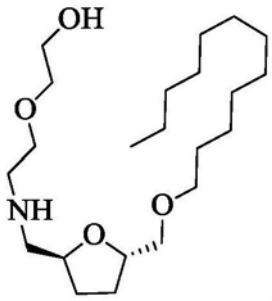
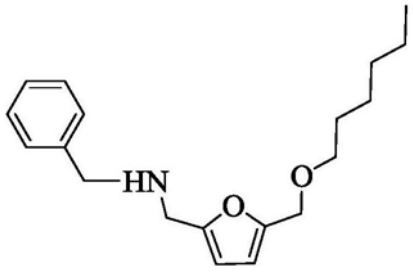
[0137] c.2-(2-((((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲基)氨基)乙氧基)-乙醇

[0138] 

。

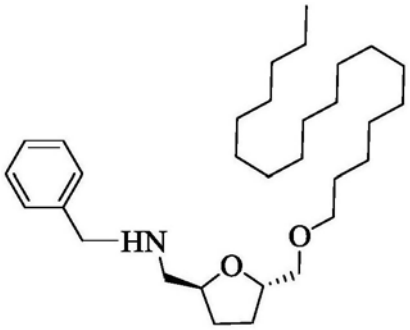
[0139] 在一个替代实施例中,该方法可以进一步包括通过以下方式产生bHMTHF单醚的伯胺:取代三氟甲烷磺酸酯基团以形成一种苄基胺,如以下项中的一种:

[0140] a)N-苄基-1-(5-((己氧基)甲基)呋喃-2-基)甲胺

[0141] 

;

[0142] b)N-苄基-1-((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0143] 

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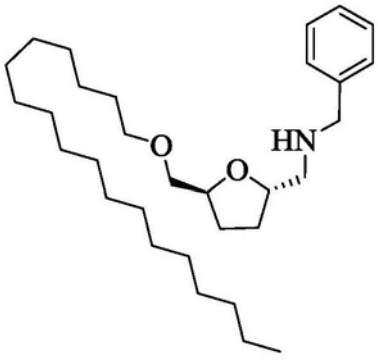
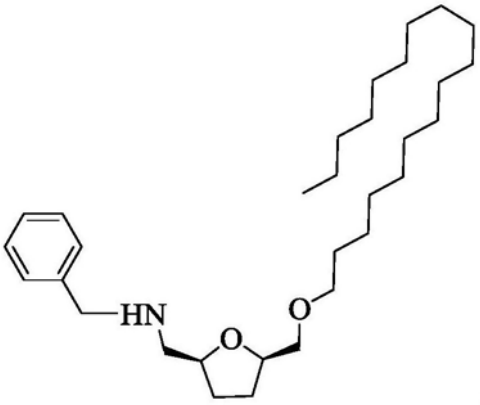
[0144] c)N-苄基-1-((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0145] 

以及
;

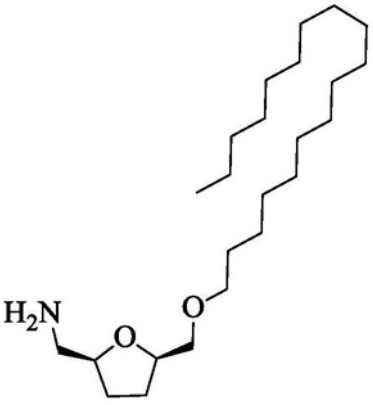
[0146] d)N-苄基-1-((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0147] 

。

[0148] 随后,人们通过用例如一种钯催化剂在碳上的催化脱苄基作用产生该伯胺。所生成的伯胺可以是,例如,以下化合物中的至少一种:

[0149] a.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0150] 

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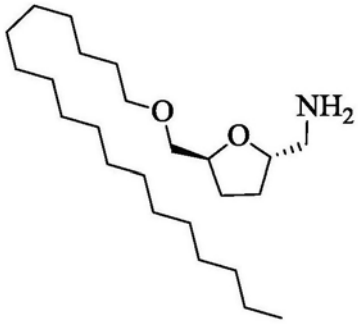
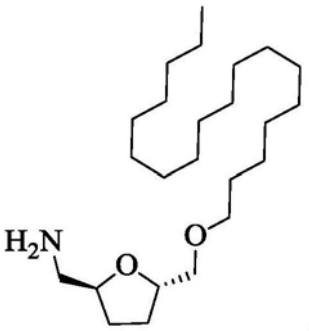
[0151] b.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0152] 

;

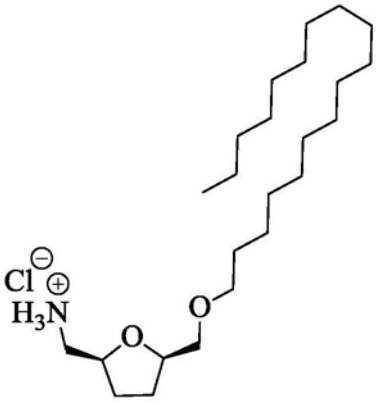
[0153] c.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲胺

[0154] 

。

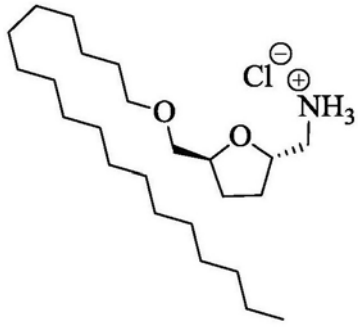
[0155] 在另一个替代实施例中,该方法可以进一步包括通过以下方式制备该bHMTHF单醚的伯铵盐:取代三氟甲烷磺酸酯基团、随后催化脱苄基作用以及通过具有pKa≤0的布朗斯特酸(例如,HCl、HBr、HI)的质子化作用。所生成的伯铵基团可以是,例如,以下化合物中的至少一种:

[0156] a.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵(methanaminium)氯化物

[0157] 

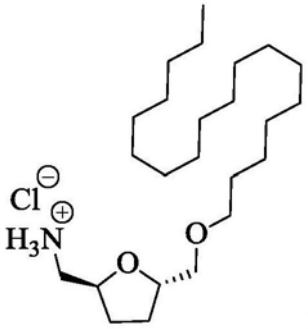
;

[0158] b.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物

[0159] 

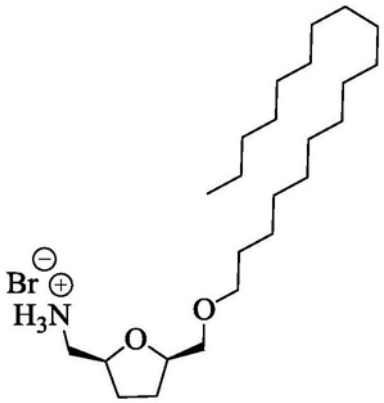
;

[0160] c.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物

[0161] 

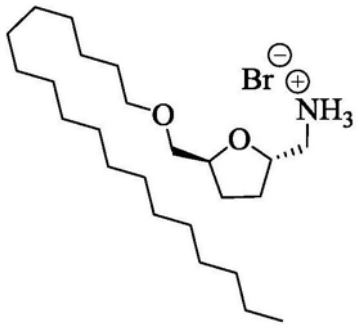
;

[0162] d.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物

[0163] 

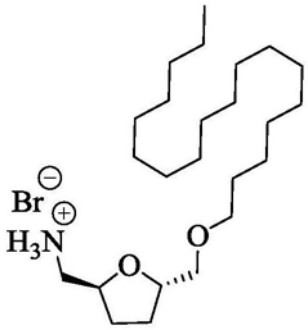
;

[0164] e.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物

[0165] 

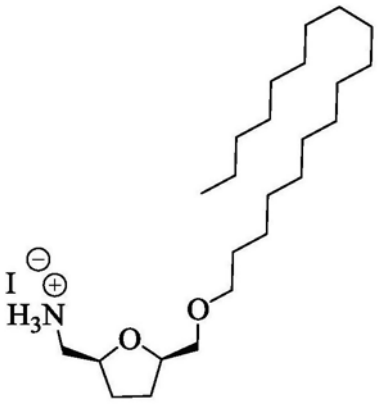
;

[0166] f.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵溴化物

[0167] 

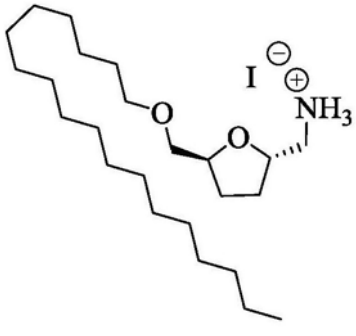
;

[0168] g.((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物

[0169] 

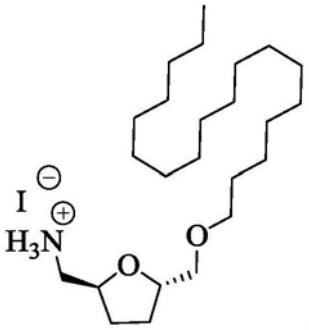
;

[0170] h.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物

[0171] 

;

[0172] i.((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵碘化物

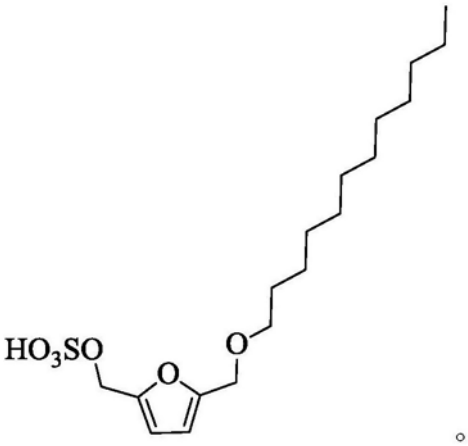
[0173] 

。

[0174] 该伯胺的盐变体使分子与阳离子表面活性剂的极性头更两亲。

[0175] 对于由与FDM的单醚的反应制成的衍生化合物,所生成的硫酸酯产物可以是例如:

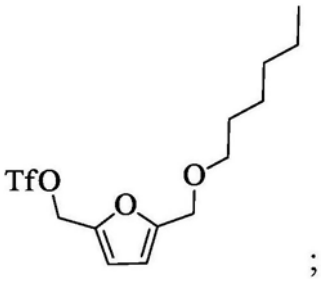
[0176] a.硫酸氢(5-((十二烷氧基)甲基)呋喃-2-基)甲酯

[0177] 

。

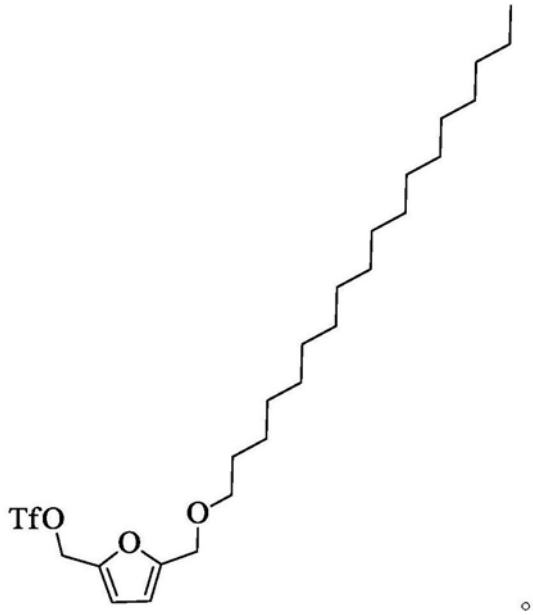
[0178] 并且,由FDM单醚所产生的三氟甲烷磺酸酯可以是,例如,以下结构中的至少一种:

[0179] a.三氟甲烷磺酸(5-((己氧基)甲基)呋喃-2-基)甲酯

[0180] 

;

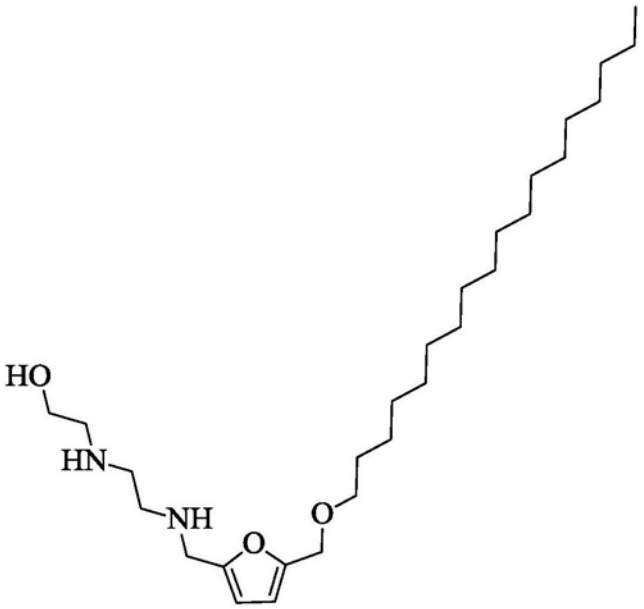
[0181] b.三氟甲烷磺酸(5-((十八烷氧基)甲基)呋喃-2-基)甲酯

[0182] 

。

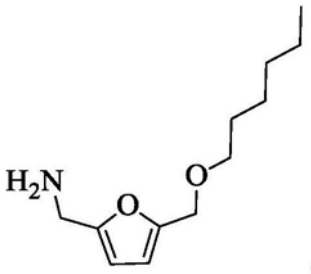
[0183] 类似于用bHMTHF单醚的方法,用于使用FDM单醚制备伯铵基团的方法还涉及取代三氟甲烷磺酸酯基团、随后是催化脱苄基作用以及通过具有pKa≤0的布朗斯特酸的质子化作用。所产生的氨乙基乙醇胺可以是,例如以下项:

[0184] a.2-((2-(((5-((十八烷氧基)甲基)呋喃-2-基)甲基)氨基)乙基)氨基)-乙醇

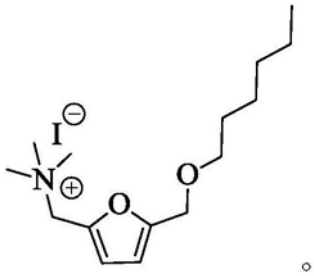
[0185] 

[0186] 根据另一个实施例,使用FDM单醚作为起始材料制备的一种伯胺衍生物可以是,例

如,以下项:(5-((己氧基)甲基)呋喃-2-基)甲胺

[0187] 

[0188] 可替代地,人们还可以制备一种三甲基季铵盐,如:1-(5-((己氧基)甲基)呋喃-2-基)-N,N,N-三甲基甲铵碘化物

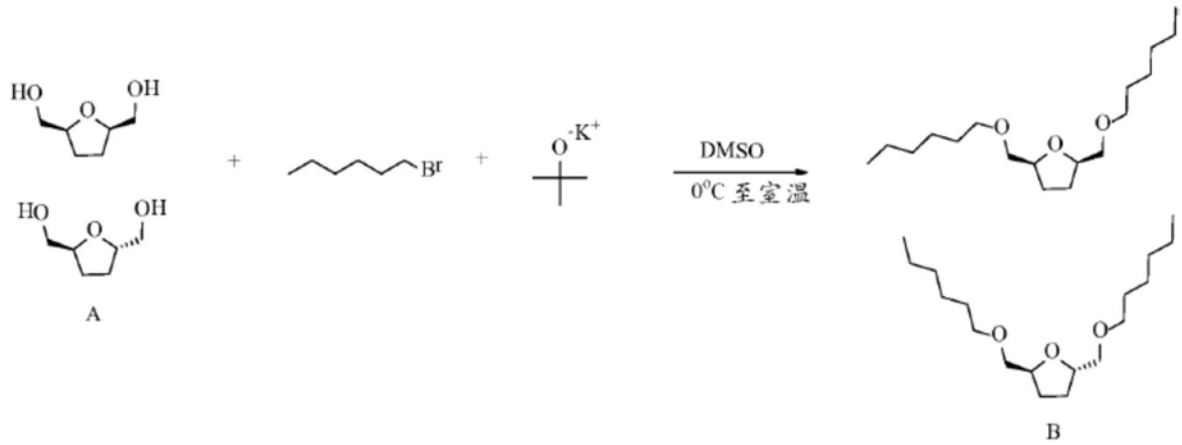
[0189] 

[0190] 部分II.-实例

[0191] 本发明的合成体系在用于制造以下各项的以下实例中进一步说明:A)bHMTHF二醚;B)bHMTHF单醚;C)bHMTHF单醚的衍生物;D)FDM二醚;E)FDM单醚;以及F)FDM单醚的两亲衍生物。

[0192] A.bHMTHF二醚

[0193] 实例1:(2R,5S)-2,5-双((己氧基)甲基)四氢呋喃和(2S,5S)-2,5-双((己氧基)甲基)四氢呋喃,B的合成。

[0194] 

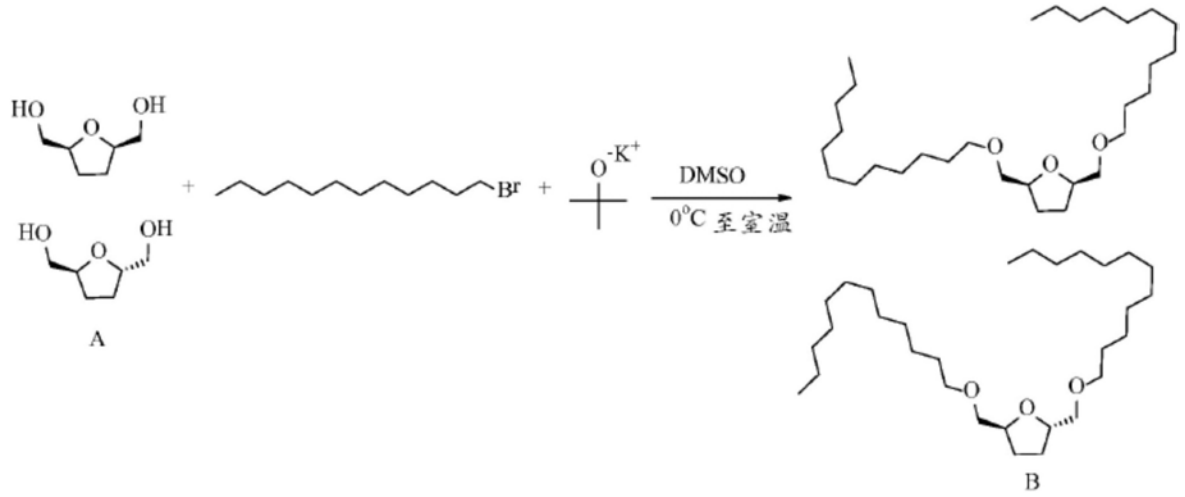
A B

[0195] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将106mg的叔丁醇钾(0.946mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将117μL的1-溴己烷(0.832mmol)经由注射器加入。然

后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在9:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。A的特征条带(基线)明显是不存在的，表明了这种试剂已经完全转化。在此，将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中，然后将其在真空下干燥，提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中，其中用己烷至己烷中10％的乙酸乙酯的快速色谱法提供在浓缩后呈淡黄色油状物的64mg的B(理论值的56％)。^{1}H NMR(400MHz,$CDCl_3$,对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)4.21(m,2H),3.64(m,2H),3.40-3.36(m,4H),2.11(m,2H),1.61(m,2H),1.47(t,J＝6.2Hz,4H),1.40(m,4H),1.35-1.30(m,10H),0.94(t,J＝7.0Hz,6H);^{13}C NMR(100MHz,$CDCl_3$对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)87.1,78.3,68.9,33.2,31.2,29.8,25.4,23.1,13.3。

[0196] 实例2:(2R,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃和(2S,5S)-2,5-双((十二烷氧基)甲基)四氢呋喃,B的合成

[0197]

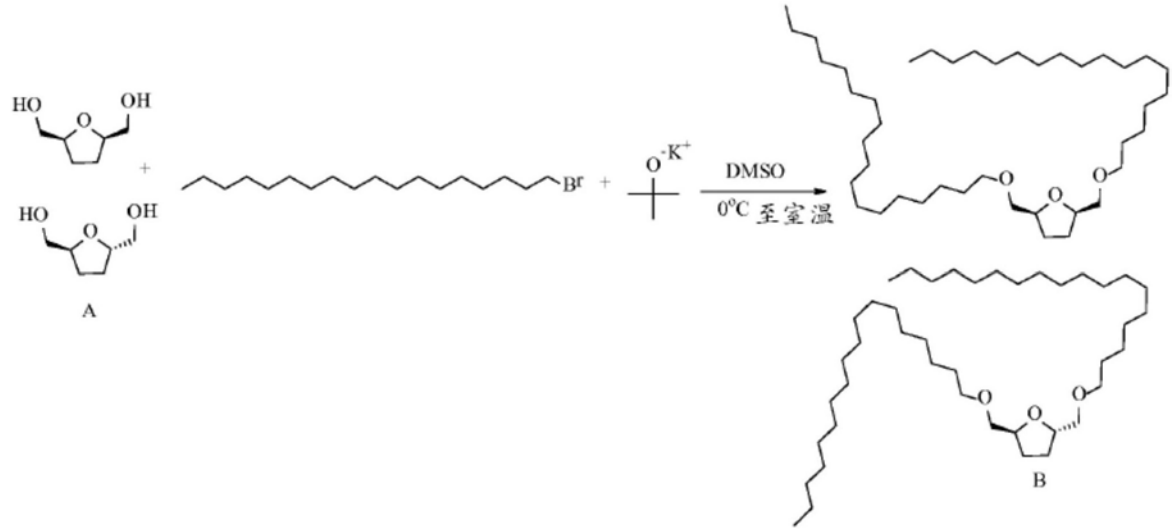


[0198] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时，将106mg的叔丁醇钾(0.946mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时，将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下，将200μL的1-溴十二烷(0.832mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在10:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。A的特征条带(基线)明显是不存在的，表明了这种试剂已经完全转化。在此，将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中，然后将其在真空下干燥，提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中，其中用己烷至己烷中7％的乙酸乙酯的快

速色谱法提供在浓缩后呈米色固体的118mg的B(理论值的65%)。^{1}H NMR(400MHz,$CDCl_3$,对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)4.20(m,2H),3.63(m,2H),3.41-3.38(m,4H),2.09(m,2H),1.59(m,2H),1.49(t,J=6.2Hz,4H),1.42(m,4H),1.38-1.30(m,34H),0.92(t,J=6.8Hz,6H);^{13}C NMR(100MHz,$CDCl_3$对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)87.4,78.1,69.1,33.0,31.2,30.9,29.8,28.7,26.2,25.4,24.9,24.1,23.3,22.1,13.3。

[0199] 实例3:(2R,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃和(2S,5S)-2,5-双((十八烷氧基)甲基)四氢呋喃,B的合成

[0200]

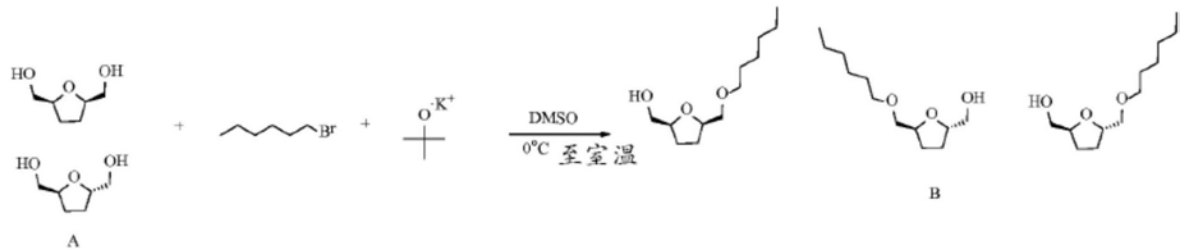


[0201] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将106mg的叔丁醇钾(0.946mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14"针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将277μL的1-溴十八烷(0.832mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后,移出一个等分试样并且将其点样到硅胶TLC板上,在11:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。A的特征条带(基线)明显是不存在的,表明了这种试剂已经完全转化。在此,将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中,然后将其在真空下干燥,提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中,其中用己烷至己烷中5%的乙酸乙酯的快速色谱法提供在浓缩后呈灰白色固体的132mg的B(理论值的55%)。^{1}H NMR(400MHz,$CDCl_3$,对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)4.20(m,2H),3.63(m,2H),3.41-3.38(m,4H),2.08(m,2H),1.65(m,2H),1.48(t,J=6.2Hz,4H),1.41(m,4H),1.40-1.28(m,58H),0.89(t,J=6.8Hz,6H);^{13}C NMR(100MHz,$CDCl_3$对应于大量过量的顺式(内消旋)衍生物的显著的峰)δ(ppm)87.4,78.1,69.1,33.0,31.2,30.9,29.8,28.7,26.2,25.4,24.9,24.1,23.8,23.3,22.9,22.7,22.5,22.1,21.7,21.3,13.3。

[0202] B.bHMTHF单醚

[0203] 实例4:((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇、((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇、和((2S,5S)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇,B的合成

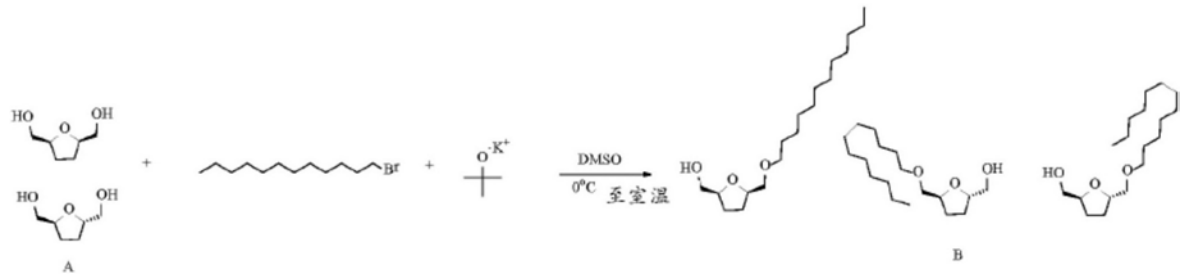
[0204]



[0205] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将42mg的叔丁醇钾(0.378mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将53μL的1-溴己烷(0.378mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后,移出一个等分试样并且将其点样到硅胶TLC板上,在3:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出两个显著的条带(钼酸铈染色),Rf_1=0.54(目标B),Rf_2=基线(未反应的THF-二醇A)。通过GC/MS的分析(EI,初始70℃,坡度5℃/分钟至350℃,保持60min.)显示出具有如下保留时间的三个显著的信号:a)12.4min.,m/z 132.1(M+,未反应的THF-二醇),b)18.7min.,m/z 216.1(M+,一种或多种目标单醚),19.2min.m/z 216.1(M+,一种或多种目标单醚)。

[0206] 实例5:((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇、((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇、((2S,5S)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇,B的合成

[0207]

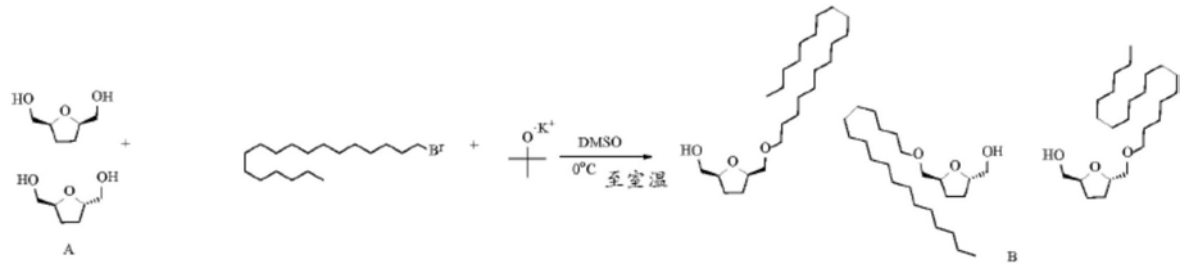


[0208] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将42mg的叔丁醇钾(0.378mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将91μL的1-溴十二烷(0.378mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后,移出一个等分试样并且将其点样

到硅胶TLC板上，在5:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出两个显著的条带(钼酸铈染色)，Rf_1＝0.57(目标B)，Rf_2＝基线(残余THF-二醇A)。通过GC/MS的分析(EI，初始70℃，坡度5℃/分钟至350℃，保持60min)显示出具有如下保留时间的三个显著的信号：a)12.3min.，m/z 132.1(M+，未反应的THF-二醇A)，b)25.1min.，m/z 300.2(M+，一种或多种目标单醚)，25.9min.m/z 300.2(M+，一种或多种目标单醚)。

[0209] 实例6：((2S,5R)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇、((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲醇、((2S,5S)-5((十八烷氧基)甲基)四氢呋喃-2-基)甲醇，B的合成

[0210]

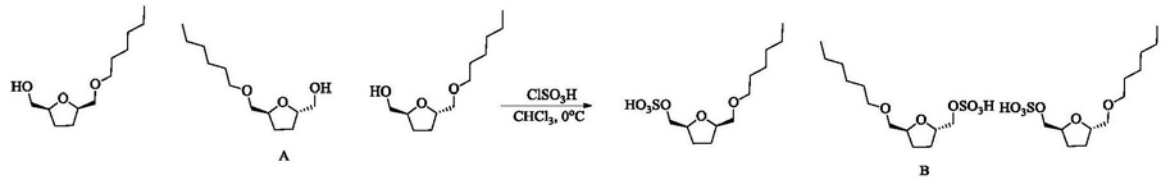


[0211] 实验：向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2R,5S)-四氢呋喃-2,5-二基)二甲醇和((2S,5S)-四氢呋喃-2,5-二基)二甲醇的9:1的混合物(0.378mmol)以及5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时，将42mg的叔丁醇钾(0.378mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时，将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下，将126μL的1-溴十二烷(0.378mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在6:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)，Rf_1＝0.62(目标B)和Rf_2＝基线(未反应的THF-二醇A)。A的特征条带明显是不存在的，表明了这种试剂已经完全转化。通过LC/MS的分析(APCI-，RP 1.7μm，2.1×50mm，流动相-梯度50％至0％的水在CH_3CN中，流速0.5mL/min.，M-1)m/z 383.4。

[0212] C.bHMTHF单醚的衍生物

[0213] 实例7：((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲基硫酸钾以及非对映异构体，B的合成

[0214]

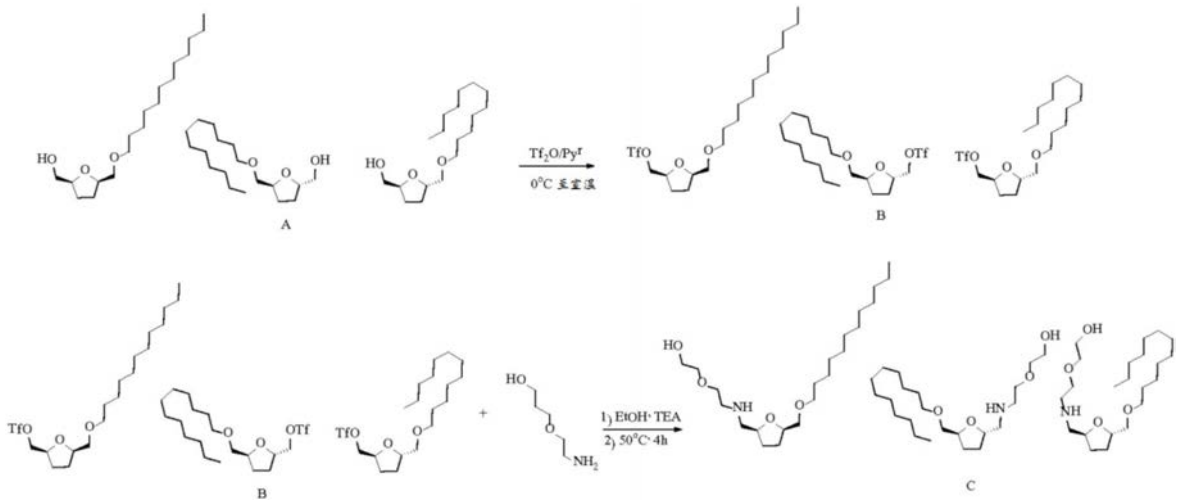


[0215] 实验：向配备有0.5”PTFE涂覆的锥形的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入50mg的((2S,5R)-5-((己氧基)甲基)四氢呋喃-2-基)甲醇和非对映异构体的9:1的混合物A(0.231mmol)以及5mL的无水$CHCl_3$。然后将该烧瓶浸入到冰-盐水浴(约-10℃)中并且在搅拌的同时，经15分钟逐滴加入15.4μL的氯磺酸(26.9mg，0.231mmol)。然后将该混合物加热至室温并继续反应1小时。在这段时间后，经由旋转蒸发和高真空去除

该溶剂和生成的HCl。将淡黄色油状残余物溶解在最小量的异丙醇中并且置于冷冻机中。在约3天之后，观察到悬浮的晶体，将其过滤并干燥，提供16mg(理论值的24％)的B。元素分析(C、H)：对于$C_{12}H_{24}O_6S$预测的(C，48.63；H，8.16)；发现的(C，48.66；H，8.23)。

[0216] 实例8：2-(2-((((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃2基)甲基)氨基)-乙氧基)乙醇和非对映异构体C(似然非离子表面活性剂)的合成

[0217]



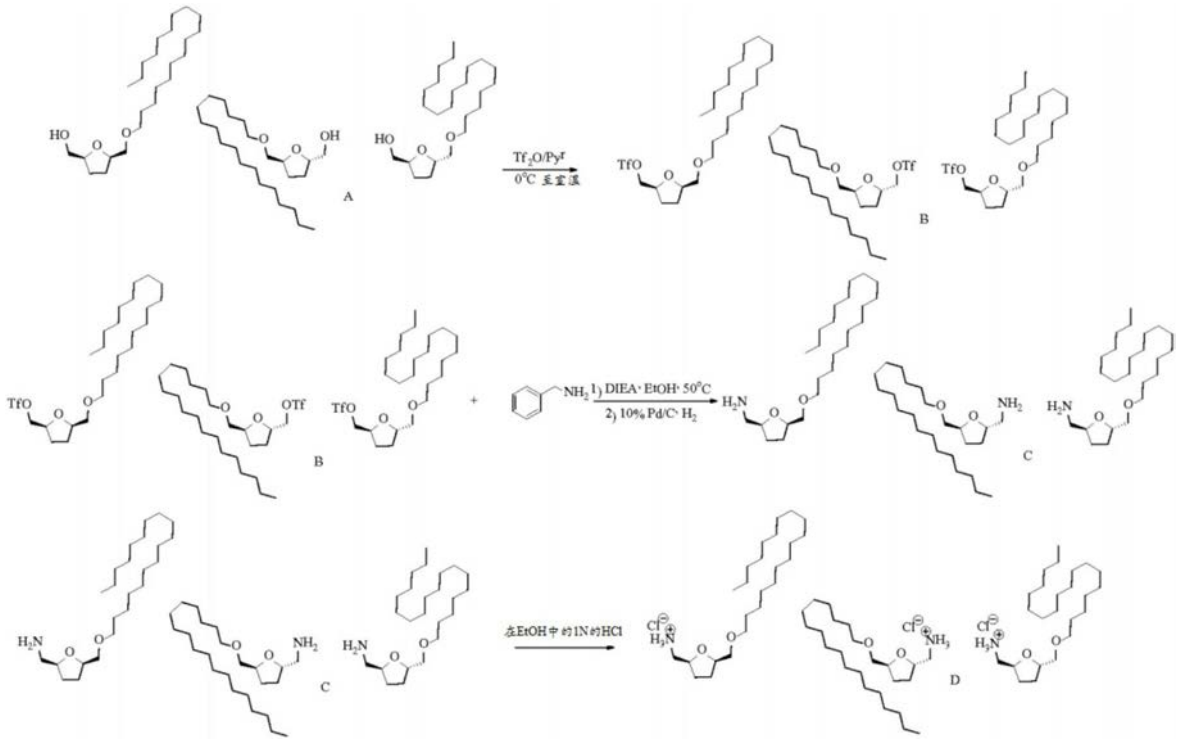
[0218] 实验：向配备有0.5”PTFE涂覆的八角形的磁力搅拌棒的一个烘箱干燥的、单颈的25mL的圆底烧瓶中装入200mg的((2S,5R)-5-((十二烷氧基)甲基)四氢呋喃-2-基)甲醇和非对映异构体的9:1的混合物A(0.666mmol)、107μL的吡啶(1.33mmol)以及5mL的无水二氯甲烷。然后将该烧瓶浸入到冰-盐水浴(约-10℃)中并且在搅拌的同时，经15分钟逐滴加入112μL的三氟甲磺酸酐(0.666mmol)。然后将该混合物加热至室温并继续反应2小时。在这段时间之后，移出一个等分试样并且将其点样在硅胶TLC板上，该硅胶TLC板用25％乙酸乙酯洗脱液展开。一个点出现在该板上(钼酸铈可视化)，其中Rf＝0.57。不存在对应于起始醇的条带，Rf＝0.44，表明完全转化。然后蒸发过量的溶剂，提供指定为B的261mg的淡黄色油状物(90％)。将这种材料在后续步骤中使用而没有进一步纯化。

[0219] 向配备有5/8”八角形的PTFE涂覆的磁力搅拌棒的一个单颈的50mL圆底烧瓶中装入250mg的B(0.578mmol)、69mg的3-(2-氨基乙氧基)丙-1-醇、81μL的三乙胺(0.578mmol)和10mL的无水乙醇。将一个回流冷凝器装配到该烧瓶上，并且在搅拌的同时，将该溶液加热到50℃，4个小时。在这段时间之后，将一个等分试样提取出来并且通过TLC(钼酸铈可视化)分析，展示B已经完全消失。直接将该混合物倾倒到一个短路径的、预先制造的包括中性氧化铝的柱上，其中用无水乙醇的快速色谱法提供呈粘性的浅黄色油状物的96mg的C(43％)。^1H NMR(400MHz，$CDCl_3$，对应于顺式(内消旋)物种的显著的峰)δ(ppm)4.12(m,1H)，4.03(m,1H)，3.64-3.62(m,4H)，3.53(t,J＝5.4Hz,2H)，3.41(t,J＝6.0Hz,2H)，3.30(t,J＝5.4Hz)，2.75-2.72(m,3H)，2.59(m,1H)，2.01(m,2H)，1.71(m,2H)，1.47(t,J＝5.6Hz,2H)，1.38(m,2H)，1.33-1.27(m,16H)，0.93(t,J＝6.8Hz,3H)；^{13}C NMR(100MHz，$CDCl_3$，显著的峰(顺式，内消旋))δ(ppm)84.1，82.2，77.8，73.6，69.0，68.4，63.2，55.9，50.0，32.4，31.9，31.4，30.8，30.6，30.5，30.2，29.9，29.7，29.6，29.3，29.1，16.0。

[0220] 实例9：((2S,5S)-5-((十八烷氧基)甲基)四氢呋喃-2-基)甲铵氯化物和非对映异

构体D(似然阳离子表面活性剂)的合成

[0221]



[0222] 实验:向配备有锥形的1cm的PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、25mL单颈圆底烧瓶中装入150mg的A(0.390mmol)、94μL的吡啶(1.17mmol)和10mL的无水二氯甲烷。然后将该烧瓶浸入到盐水/冰浴(约-10℃)中并且在剧烈搅拌的同时,经10分钟逐滴加入66μL的三氟甲磺酸酐(0.390mmol)。然后移除该冰浴并且使反应在室温下继续持续2h。在这段时间之后,移出一个等分试样,将其点样在硅胶TLC板上并用在己烷中20%的乙酸乙酯展开,表明了具有R_f=0.52的单一条带(钼酸铈可视化)。A的特征条带(R_f=0.39)明显是不存在的,表明了这种试剂已经完全转化。然后过滤固体并且将滤液在真空中浓缩过夜,提供呈浅棕色油状物的173g的B(88%)。将这种产物在接下来的步骤中使用而没有进一步纯化。

[0223] 向配备有1cm的PTFE涂覆的磁力搅拌棒的一个单颈50mL的圆底烧瓶中装入175mg的B(0.339mmol)、65μL的Hunig碱(0.373mmol)、37μL的苄胺、以及10mL的乙醇。该颈用一个回流冷凝器加盖,并且在剧烈搅拌的同时,将该混合物加热到50℃持续2小时。在这段时间之后,TLC(UV和钼酸铈可视化)表明单一的条带以及两种试剂的全部消耗。然后用10mL的水和10mL的二氯甲烷稀释该混合物并且通过液液萃取分层。水层用5mL体积的二氯甲烷(x2)萃取,有机层合并并且干燥,提供浅黄色蜡状固体。将这种材料与100mg的10%的Pd/C和10mL的无水乙醇一起装入一个配备有0.5”的PTFE涂覆的磁力搅拌棒的25mL的圆底烧瓶中。该颈用一个橡胶隔片加盖并且充满H_2的气球经由9英寸、16”针插入;剧烈搅拌该混合物并且通过TLC(UV-vis可视化)监控。2h后,该反应被认为完成;通过硅藻土的衬垫过滤催化剂并且滤液在真空下浓缩过夜,提供呈淡黄色松散油状物的74mg的C(52%)。这种材料在随后的步骤中使用而没有进一步纯化。

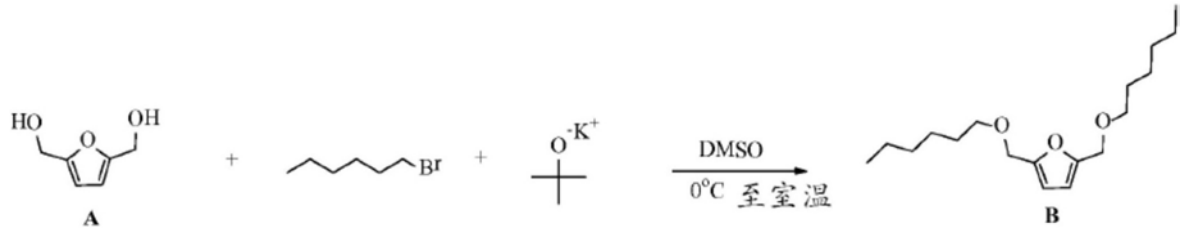
[0224] 向配备有0.5”八角形的PTFE涂覆的磁力搅拌棒的一个单颈的10mL的圆底烧瓶中装入50mg的C(0.130mmol)以及2mL的1N的乙醇HCl溶液。将该混合物搅拌15分钟,在此时间

后，首先用旋转蒸发器(50℃，30mmHg)，然后在高真空(<1托)下持续1周移除过量溶剂。这段时间之后，观察到对应于D的黄色半固体，称重为49mg(88％)。^{1}H NMR(400MHz，d^{6}-DMSO/D_2O，对应于顺式(内消旋)衍生物的显著的信号)δ(ppm)4.52(m,1H),4.13(m,1H),3.62-3.60(m,2H),3.32-3.28(m,4H),2.03(m,2H),1.75(m,2H),1.59(m,2H),1.48(m,2H),1.30-1.25(m,28H),0.95(t,J＝6.2Hz,3H)。13C NMR(100MHz，d^{6}-DMSO/D_2O对应于顺式(内消旋)衍生物的显著的信号)δ(ppm)85.1,81.2,77.3,72.2,49.2,32.6,32.2,31.9,31.5,31.2,30.5,30.3,30.0,29.8,29.6,29.3,29.1,28.9,28.8,28.6,28.3,28.0,27.9,13.1。

[0225] D.FDM二醚

[0226] 实例10:2,5-双((己氧基)甲基)呋喃，B的合成

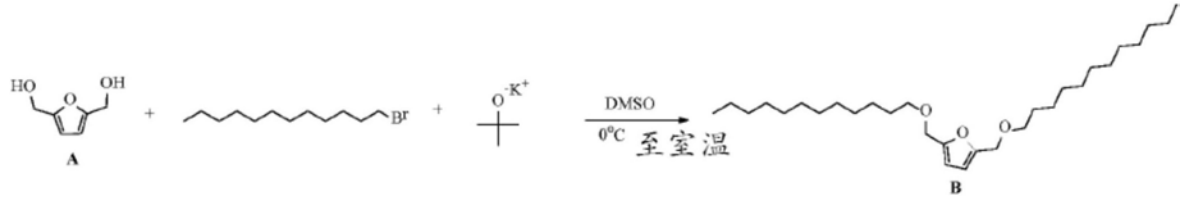
[0227]



[0228] 实验：向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时，将219mg的叔丁醇钾(1.95mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时，将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下，将240μL的1-溴己烷(1.72mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在9:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。FDM A的特征条带(基线)明显是不存在的，表明了这种试剂已经完全转化。在此，将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中，然后将其在真空下干燥，提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中，其中用己烷至己烷中13％的乙酸乙酯的快速色谱法提供在真空中浓缩后呈淡黄色油状物的124mg的B(理论值的53％)。^{1}H NMR(400MHz，$CDCl_3$)δ(ppm)6.32(s,2H),4.63(s,4H),3.40-3.36(m,4H),2.10(m,2H),1.59(m,2H),1.48(t,J＝6.0Hz,4H),1.42(m,4H),1.35-1.30(m,10H),0.91(t,J＝7.4Hz,6H)；^{13}C NMR(100MHz，$CDCl_3$)δ(ppm)152.23,108.3,71.6,68.1,32.6,31.4,29.8,25.4,13.3。

[0229] 实例11:2,5-双((十二烷氧基)甲基)呋喃，B的合成

[0230]

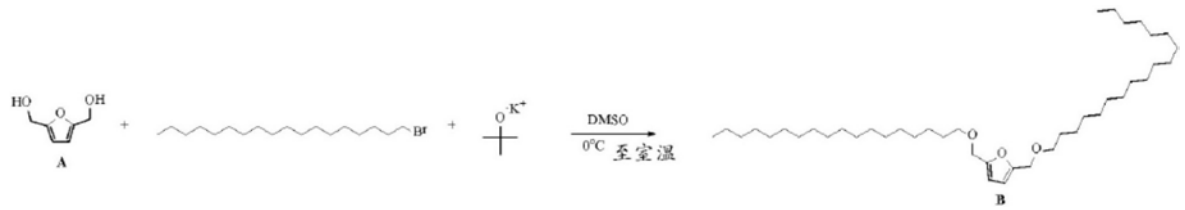


[0231] 实验：向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)

中并且在搅拌的同时，将219mg的叔丁醇钾(1.95mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时，将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下，将412μL的1-溴十二烷(1.72mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在10:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。FDM A的特征条带(基线)明显是不存在的，表明了这种试剂已经完全转化。在此，将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中，然后将其在真空下干燥，提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中，其中用己烷至己烷中9％的乙酸乙酯的快速色谱法提供在浓缩后呈米色固体的139mg的B(理论值的39％)。^{1}H NMR(400MHz,$CDCl_3$)δ(ppm)6.42(2,2H),4.67(s,4H),3.42-3.39(m,4H),2.06(m,2H),1.58(m,2H),1.47(t,J＝6.4Hz,4H),1.40(m,4H),1.38-1.30(m,34H),0.91(t,J＝7.0Hz,6H);^{13}C NMR(100MHz,$CDCl_3$)δ(ppm)152.4,108.5,73.4,69.9,33.0,31.2,30.9,29.8,28.7,26.2,25.4,24.9,24.1,23.3,22.1,13.3。

[0232] 实例12:2,5-双((十八烷氧基)甲基)呋喃,B的合成

[0233]

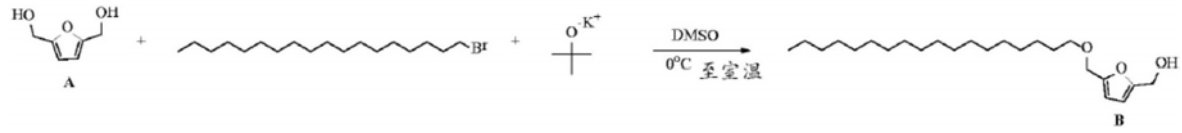


[0234] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时，将219mg的叔丁醇钾(1.95mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时，将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下，将586μL的1-溴十八烷(1.72mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在11:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出单一条带(钼酸铈染色)。FDM A的特征条带(基线)明显是不存在的，表明了这种试剂已经完全转化。在此，将该混合物用5mL的水和5mL的二氯甲烷稀释并且分区并且用3-5mL体积的二氯甲烷萃取该水层。将有机相合并、用无水硫酸镁干燥、过滤并且在真空下浓缩。将油状残余物溶解在最小量的二氯甲烷中并且加入到20g的硅胶中，然后将其在真空下干燥，提供吸附了产物的硅胶。将这种材料加入到一个预先制造的硅胶柱中，其中用己烷至己烷中6％的乙酸乙酯的快速色谱法提供在浓缩后呈灰白色固体的171mg的B(理论值的35％)。^{1}H NMR(400MHz,$CDCl_3$),δ(ppm)6.40(s,2H),4.52(s,4H),3.41-3.38(m,4H),2.08(m,2H),1.65(m,2H),1.48(t,J＝6.2Hz,4H),1.41(m,4H),1.40-1.28(m,58H),0.89(t,J＝6.8Hz,6H);^{13}C NMR(100MHz,$CDCl_3$)δ(ppm)152.7,108.6,73.6,69.0,33.0,31.2,30.9,29.8,28.7,26.2,25.4,24.9,24.1,23.8,23.3,22.9,22.5,22.1,21.7,21.3,13.3。

[0235] E.FDM单醚

[0236] 实例13:(5-((十八烷氧基)甲基)呋喃-2-基)甲醇,B的合成

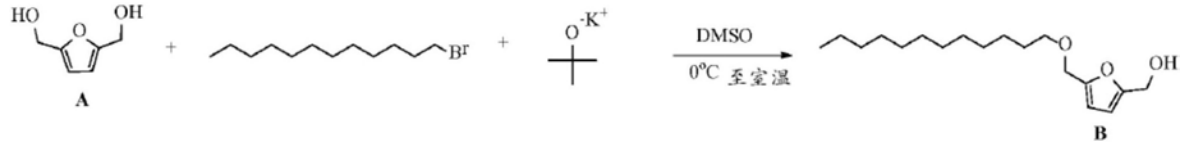
[0237]



[0238] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将87mg的叔丁醇钾(0.780mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将266μL的1-溴十八烷(0.780mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后,移出一个等分试样并且将其点样到硅胶TLC板上,在6:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出三个条带(钼酸铈染色),Rf_1=0.91(FDM二醚)和Rf_2=0.60,以及基线(未反应的FDM A)。A的特征条带明显是不存在的,表明了这种试剂已经完全转化。通过LC/MS的分析(APCI-,RP 1.7μm,2.150mm,流动相-梯度50%至0%的水在CH_3CN中,流速0.5mL/min.,M-1),泄露379.3的m/z。

[0239] 实例14:(5-((十二烷氧基)甲基)呋喃-2-基)甲醇,B的合成

[0240]



[0241] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将87mg的叔丁醇钾(0.780mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌的同时并且在氩气覆盖层下,将187μL的1-溴十二烷(0.780mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后,移出一个等分试样并且将其点样到硅胶TLC板上,在5:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出两个显著的条带(钼酸铈染色),Rf_1=0.91(FDM二醚),Rf_2=0.55(目标B),Rf_3=基线(FDM A)。通过GC/MS的分析(EI,初始70℃,坡度5℃/分钟至350℃,保持60min.)显示出具有如下保留时间的三个显著的信号:a)11.3min.,m/z 128.1(M+,FDM A),b)24.2min.,m/z 296.2(M+,FDM单醚B)。

[0242] 实例15:(5-((己氧基)甲基)呋喃-2-基)甲醇,B的合成

[0243]

[0244] 实验:向配备有PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、单颈10mL圆底烧瓶中装入100mg的FDM A(0.780mmol)和5mL的无水DMSO。然后将该烧瓶浸入冰-盐水浴(约-10℃)中并且在搅拌的同时,将87mg的叔丁醇钾(0.780mmol)分份地加入并且将该混合物在此温度下搅拌30分钟。在此时,将颈用橡胶垫片塞住并且经由14”针附接氩气进口。在剧烈搅拌

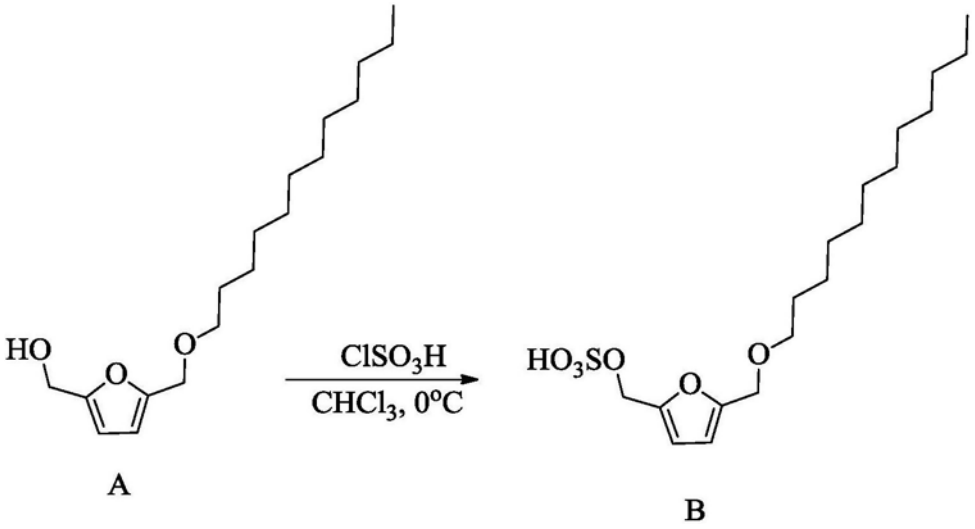
的同时并且在氩气覆盖层下，将109μL的1-溴己烷(0.780mmol)经由注射器加入。然后将该混合物加热至室温并继续反应过夜。在这段时间后，移出一个等分试样并且将其点样到硅胶TLC板上，在3:1的己烷/乙酸乙酯中展开后该硅胶TLC板显示出三个条带(钼酸铈染色)，Rf_1＝0.89(FDM二醚)，Rf_2＝0.57(目标B)，Rf_3＝基线(未反应的FDM A)。通过GC/MS的分析(EI，初始70℃，坡度5℃/分钟至350℃，保持60min.)显示出具有如下保留时间的三个显著的信号：a)11.3min.，m/z 128.1(M+，未反应的THF-二醇)，b)17.6min.，m/z 212.1(M+，FDM单醚，B)。

[0245] F.FDM单醚的两亲衍生物

[0246] 总体上，各种衍生物物种也可以由FDM单醚制成，并且这些FDM衍生物的制备采用与用于由bHMTHF作为起始材料合成衍生物的反应方案相同或相似的反应方案(加上必要的变更)，如在前述实例中描述的。因此，如普通技术人员将理解的，以下实例具有说明在合成中的某些变化的替代化合物，而不是重复整个系列的实例用于由FDM单醚合成衍生物。期望在这些变体实例中的每种化合物与衍生物bHMTHF单醚的每种化合物类似(例如，具有作为表面活性剂、分散剂、增塑剂等的潜在应用的不可水解的两亲物)。

[0247] 实例16：硫酸氢(5-((十二烷氧基)甲基)呋喃-2-基)甲酯，B的合成。

[0248]

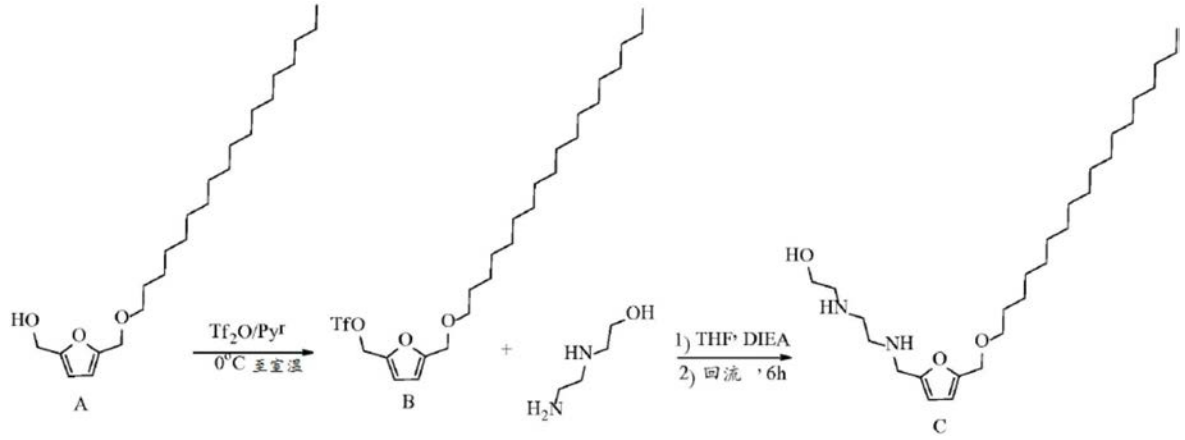


A B

[0249] 实验：向配备有0.5”PTFE涂覆的锥形的磁力搅拌棒的一个烘箱干燥的、单颈的10mL的圆底烧瓶中装入100mg的(5-((十二烷氧基)甲基)呋喃-2-基)甲醇A(0.337mmol)以及5mL的无水$CHCl_3$。然后将该烧瓶浸入到冰-盐水浴(约-10℃)中并且在搅拌的同时，经15分钟逐滴加入22.5μL的氯磺酸(39.2mg，0.231mmol)。然后将该混合物加热至室温并继续反应1小时。在这段时间后，经由旋转蒸发和高真空去除该溶剂和生成的HCl。将淡黄色油状残余物溶解在最小量的异丙醇中并且置于冷冻机中过夜。显示出大量的悬浮的晶体，将这些晶体过滤并且干燥，提供55mg(理论值的43％)的B。元素分析(C、H)：对于$C_{18}H_{32}O_6S$预测的(C，57.42；H，8.57)；发现的(C，57.51；H，8.60)。

[0250] 实例17：2-((2-(((5-((十八烷氧基)甲基)呋喃-2-基)甲基)氨基)乙基)氨基)-乙醇，C的合成

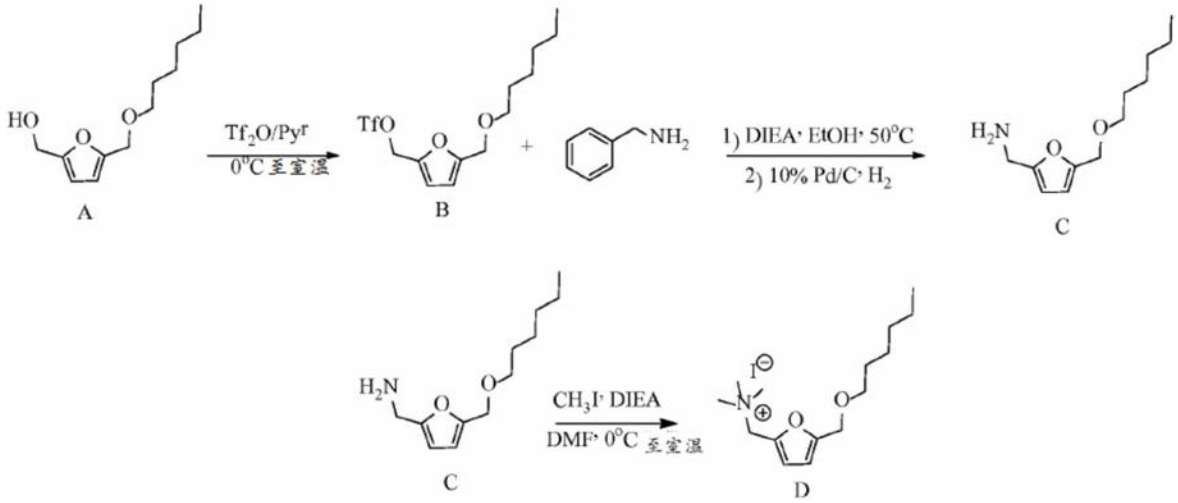
[0251]



[0252] 实验:向配备有0.5”PTFE涂覆的八角形的磁力搅拌棒的一个烘箱干燥的、单颈的25mL的圆底烧瓶中装入100mg的(5-((十八烷氧基)甲基)呋喃-2-基)甲醇A(0.263mmol)、42μL的吡啶(0.526mmol)以及5mL的无水二氯甲烷。然后将该烧瓶浸入到冰-盐水浴(约-10℃)中并且在搅拌的同时,经15分钟逐滴加入44.2μL的三氟甲磺酸酐(0.263mmol)。然后将该混合物加热至室温并继续反应2小时。在这段时间之后,移出一个等分试样并且将其点样在硅胶TLC板上,该硅胶TLC板用25%乙酸乙酯洗脱液展开。一个点出现在该板上(钼酸铈可视化),其中Rf=0.54。不存在对应于起始醇的条带,Rf=0.41,表明完全转化。然后蒸发过量的溶剂,提供指定为三氟甲烷磺酸(5-((十八烷氧基)甲基)呋喃-2-基)甲酯,B的110mg的淡黄色油状物(82%)。将这种材料在后续步骤中使用而没有进一步纯化。向配备有PTFE涂覆的磁力搅拌棒的一个单颈的50mL圆底烧瓶中装入100mg的三氟甲烷磺酸(5-((十八烷氧基)甲基)呋喃-2-基)甲酯B(0.195mmol)、20.3mg的2-((2-氨乙基)氨基)乙醇(0.195mmol)、67.9μL的二异丙基乙胺(0.390mmol)和10mL的无水THF。将一个回流冷凝器装配到该烧瓶上,并且在搅拌的同时,将该溶液加热至回流持续6个小时。在这段时间之后,将一个等分试样提取出来并且通过TLC(钼酸铈可视化)分析,展示B已经完全消失。直接将该混合物倾倒到一个短路径的、预先制造的包括中性氧化铝的柱上,其中用无水乙醇的快速色谱法提供呈松散的浅黄色油状物的31mg的2-((2-(((5-((十八烷氧基)甲基)呋喃-2-基)甲基)氨基)乙基)氨基)乙醇C(34%)。^{1}H NMR(400MHz,$CDCl_3$)δ(ppm)6.38(d,J=8.2Hz,1H),6.16(d,J=8.2Hz,1H),4.51(s,2H),3.62(m,3H),3.45(m,2H),3.32(t,J=6.0Hz,2H),2.94(m,2H),2.80(m,2H),2.61(m,4H),1.59(m,2H),1.42(m,2H),1.33-1.29(m,28H),0.91(t,J=6.8Hz,3H);^{13}C NMR(100MHz,$CDCl_3$)δ(ppm)149.9,149.1,108.2,107.0,73.5,68.2,62.1,51.6,50.9,47.8,46.6,30.3,30.0,29.6,29.5,29.4,29.3,29.2,29.0,28.9,28.8,28.7,28.6,28.4,28.2,28.0,21.8,13.8

[0253] 实例18:1-(5-((己氧基)甲基)呋喃-2-基)-N,N,N-三甲基甲铵碘化物,D的合成

[0254]



[0255] 实验:向配备有锥形的1cm的PTFE涂覆的磁力搅拌棒的一个烘箱干燥的、25mL单颈圆底烧瓶中装入125mg的(5-((己氧基)甲基)呋喃-2-基)甲醇A(0.589mmol)、94μL的吡啶(1.18mmol)和10mL的无水二氯甲烷。然后将该烧瓶浸入到盐水/冰浴(约-10℃)中并且在剧烈搅拌的同时,经10分钟逐滴加入99.1μL的三氟甲磺酸酐(0.589mmol)。然后移除该冰浴并且使反应在室温下继续持续2小时。在这段时间之后,移出一个等分试样,将其点样在硅胶TLC板上并用在己烷中20%的乙酸乙酯展开,表明了具有R_f=0.52的单一条带(钼酸铈可视化)。A的特征条带(R_f=0.39)明显是不存在的,表明了这种试剂已经完全转化。然后过滤固体并且将滤液在真空中浓缩过夜,提供呈米色油状物的183mg的三氟甲烷磺酸(5-((己氧基)甲基)呋喃-2-基)甲酯B(90%)。将这种产物在接下来的步骤中使用而没有进一步纯化。

[0256] 向配备有1cm的PTFE涂覆的磁力搅拌棒的一个单颈25mL的圆底烧瓶中装入150mg的三氟甲烷磺酸(5-((己氧基)甲基)呋喃-2-基)甲酯B(0.436mmol)、152μL的Hunig碱(0.871mmol)、48μL的苄胺(0.436mmol)以及10mL的乙醇。该颈用回流冷凝器加盖,并且在剧烈搅拌的同时,将该混合物加热到50℃持续2小时。在这段时间之后,TLC(UV和钼酸铈可视化)表明单一的条带以及两种试剂的全部消耗。然后用10mL的水和10mL的二氯甲烷稀释该混合物并且通过液液萃取分层。水层用5mL体积的二氯甲烷(x2)萃取,有机层合并并且干燥,提供浅黄色蜡状固体。将这种残余物与100mg的10%的Pd/C和10mL的无水乙醇一起装入一个配备有PTFE涂覆的磁力搅拌棒的25mL的圆底烧瓶中。该颈用一个橡胶隔片加盖并且充满H_2的气球经由9英寸、16”针插入;剧烈搅拌该混合物并且通过TLC(UV-vis可视化)监控。1.5h后,该反应被认为完成;通过硅藻土的衬垫过滤催化剂并且滤液在真空下浓缩过夜,提供呈无色松散油状物的71mg的(5-((己氧基)甲基)呋喃-2-基)甲胺C(77%)。将这种产物在接下来的步骤中使用而没有进一步纯化。

[0257] 向配备有PTFE涂覆的磁力搅拌棒的一个单颈的25mL的圆底烧瓶中装入50mg的(5-((己氧基)甲基)呋喃-2-基)甲胺C(0.237mmol)以及5mL的无水DMF。该烧瓶用一个附接到氩气进口上的橡胶隔片加盖,并且浸入饱和盐水/冰浴混合物(约0℃)中。在剧烈搅拌的同时并且在氩气下,将74μL的甲基碘(167mg,1.18mmol)在10分钟内逐滴加入该混合物。在完全加入时,撤去该冰浴并且在室温下搅拌该混合物过夜。在这段时间之后,加入15mL的二乙醚,这导致一种白色固体的沉淀。过滤该固体,用5mL的二乙醚(x3)洗涤并且高真空(<1托)

干燥持续1周。在这段时间之后，获得55mg(理论值的61％)的呈细白色粉末的1-(5-((己氧基)甲基)呋喃-2-基)-N,N,N-三甲基甲铵碘化物D。^{1}H NMR(400MHz,d^{6}-DMSO)δ(ppm)6.29(d,J＝8.2Hz,1H),6.10(d,J＝8.2Hz,1H),4.42(s,2H),4.30(s,2H),3.51(s,9H),3.40(t,J＝6.2Hz,2H),1.48-1.46(m,4H),1.33-1.31(m,4H),0.91(s,3H);^{13}C NMR(100MHz,d^{6}-DMSO)δ(ppm)152.7,151.4,109.0,108.2,73.6,70.0,68.8,50.6,30.8,30.1,23.4,22.5,15.8。

[0258] 已总体地并借助于实例详细地描述了本发明。本领域的普通技术人员应理解，本发明不必然限于特定披露的实施例，而是在不脱离如由以下权利要求书或其等效物(包括目前已知或有待开发的其他等效组分，它们可以在本发明的范围内使用)所定义的本发明的范围的情况下可以作出修改和变化。因此，除非变化另外脱离本发明的范围，否则这些变化应被解释为被包括在此。