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Solution-Phase Parallel Synthesis with Oligoethylene Glycol Sorting Tags. Preparation of All Four Stereoisomers of the Hydroxybutenolide Fragment of Murisolin and Related Acetogenins

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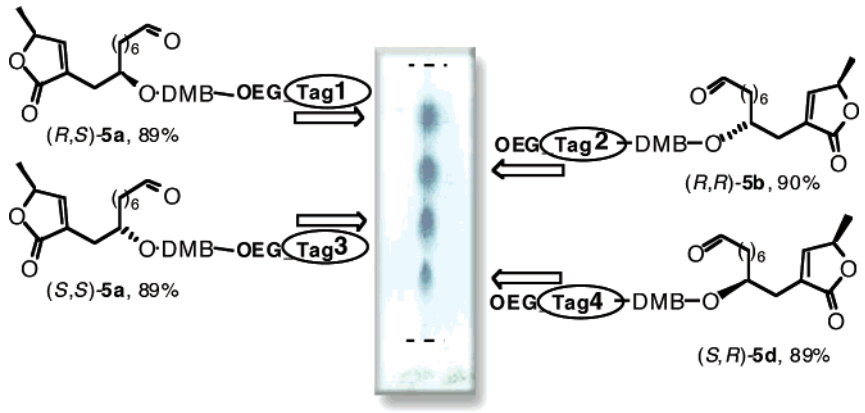

The principles of the oligoethylene glycol (OEG) mixture synthesis are illustrated with the synthesis of all four possible stereoisomers of a hydroxybutenolide fragment common to murisolin and many other acetogenins. Modified dimethoxybenzyl groups with varying numbers of OEG units ($-CH_2CH_2O-$) are used to protect alcohols and serve as codes for configurations at two stereocenters. The encoded isomers are carried through several steps in a sequence of mixing prior to the reaction and then demixing during the separation to give individual pure products. A new tagging scheme is introduced in which a stereocenter bearing a hydroxy group is given two different tags. These initially redundant tags then serve to encode the configuration of another (untagged) stereocenter by appropriate pairwise reactions of the tagged precursors. The experimental features (reaction, analysis, separation, and characterization) of OEG mixture synthesis are detailed and are compared to and contrasted with those of fluorous mixture synthesis.

Introduction

The traditional "one at a time" synthesis of stereoisomers has recently been supplemented by both solid-phase and solution-phase mixture synthesis techniques.[1] Mixture syntheses can be divided into two broad classes on the basis of whether the final target products are isolated as mixtures or as individual pure products. The first solution-phase technique to provide for the orchestrated preparation of individual pure products by way of intermediate mixtures was a fluorous-mixture synthesis.[2] Analogues or isomers are "coded" by the attachment of fluorous tags that differ in fluorine content.[3] The tagged compounds are mixed and carried through a synthesis as if they were a single compound. The last mixture is ultimately sorted into its individual components just prior to detagging to give the final products.

We recognized that sorting tags applicable to predictable chromatographic separations should feature an incremental change that can be targeted by a complementary chromatographic separation technique. In a fluorous mixture synthesis, the incremental change is homologation of the tags by the addition of CF_2 groups, and the complementary separation

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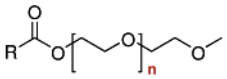


1, n = 1, 2, 3, 4

R = Ph, 2-PhC$_6$H$_4$, 2-naphthyl, etc.

The variation of OEG increments (n) has a much larger effect on silica gel retention than the variation of R

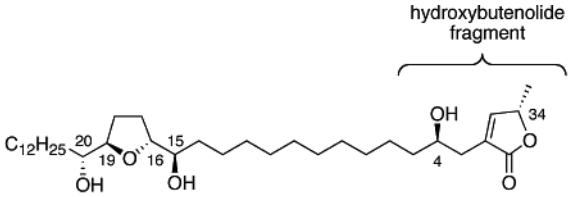
FIGURE 1. Mixtures of esters can be sorted by their differing OEG tags.

technique that sorts mixtures on the basis of this increment is specially prepared fluorous chromatography media.

In an effort to further empower the concept of chromatographic tagging strategies and to extend the concept of mixture synthesis, we conceived the idea that the oligoethylene glycol (OEG) unit (−OCH_2CH_2−) might be a suitable component for sorting tagged molecules and that the separation of OEG tags could be accomplished by standard silica gel chromatography without recourse to special fluorous media.[4] We prepared a series of 18 OEG esters **1** (Figure 1) with assorted substituents (R) and bearing incremented tags consisting of 1−4 OEG units (n = 1−4). TLC and HPLC experiments demonstrated that the retention effects on standard silica gel induced by changing the OEG increment (n) were much larger than the effects of changing the ester substituents (R). These results suggest that OEG tags can be useful for mixture synthesis, but the idea has not been tested before this time. Herein we describe the first example of OEG mixture synthesis.

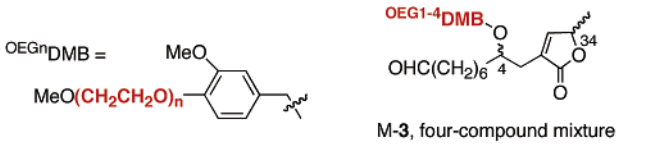
This first OEG mixture synthesis was undertaken to support the synthesis of new diasteromers of the murisolin class of acetogenins (Figure 2).[5−7] Curran and co-workers have substantial experience in the fluorous mixture synthesis of these molecules,[3c] and we recognized the opportunity to leverage the planned OEG mixture synthesis by using the products of this work in a double mixture synthesis.[5]

Making multiple stereoisomers of the hydroxyl butenolide fragment (the right portion) of murisolin is important because structure assignments of murisolin and related acetogenins are complicated by similarities of the spectra of diastereomers that arise in combinations between the dihydroxy THF ring (the left portion of murisolin) and the hydroxyl butenolide fragment (the right portion). Experience shows that it is difficult to assign the configurations of the dihydroxy THF fragment relative to



murisolin, **2** (4*R*,15*R*,16*R*,19*R*,20*R*,34*S*)

Four diastereomeric building blocks to be made by OEG mixture synthesis



M-**3**, four-compound mixture

3a 4*R*,34*S*; n=1 **3c** 4*S*,34*S*; n=3
3b 4*R*,34*R*; n=2 **3d** 4*S*,34*R*; n=4

FIGURE 2. Structure of murisolin and target diastereomers.

the hydroxyl butenolide fragment and to assign which side chain is on which end (C15 or C20) of the dihydroxy THF fragment.[8] To create unambiguous stereoisomers of the complete molecule, one must create each diastereomer of the hydroxyl butenolide entity and attach each isomer to uniquely identified isomers of the tetrahydrofuran moiety.

Curran and co-workers prepared 16 stereoisomers of the dihydroxy THF fragment of murisolin **2**, (the left half) all of which have the 4*R*,34*S* configuration in the hydroxyl butenolide fragment, and found that these exhibit only six different sets of ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectra.[3c,9] We envisioned that our OEG approach would allow the synthesis of four new diastereomers of the right half of this natural product, each diastereomer encoded by a chosen OEG tag, and that the synthesis of these isomers might be accomplished in parallel. When connected to four of Curran's isomers, we would have in hand four known isomers and 12 new isomers of murisolin.

The OEG-tagged hydroxybutenolide mixture M-**3** (Figure 2, the prefix "M" denotes a quasi-isomeric mixture) represents the entire set of stereoisomers possible for the right half of murisolin, an unexplored domain of stereoisomer space. These four diastereomers were chosen as our target, because any of these isomers might be attached to known intermediates of the murisolin synthesis by a Kocienski−Julia reaction, followed by hydrogenation, and would thereby lead to new examples of the family of murisolin stereoisomers.

The object of this paper is to report the full details of the OEG mixture synthesis of M-**3**.[5b] We will also present the details of the use of OEG tags and compare OEG tags to the use of fluorous tags. To accomplish the synthesis of four diastereomers, each encoded by a separate identifiable tag, we needed to create

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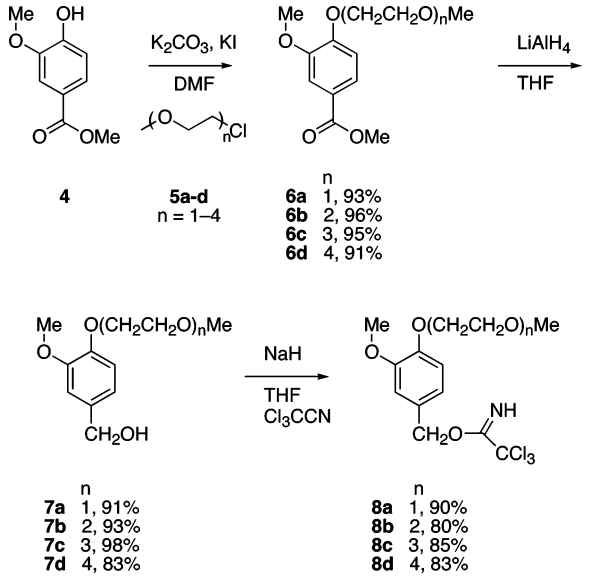
SCHEME 1. Synthesis of OEG DMB Imidate Protecting Reagents 8a−d



the tagging reagents and incorporate them at the right time to arrange for a unique relationship between the tag and the stereoconfiguration of the tagged molecules.

Results and Discussion

To succeed in our goal of preparing four diastereomers in a one-pot parallel synthesis, we were required to prepare four different stereoisomers and to end with a mixture in which each steroisomer bore a unique tagged OEG protecting group. The goal is well-represented by the concept of a code; each tagged isomer, when decoded based on the tag, reports the identity of the stereocenters. Furthermore, and of great practical importance, each encoding protecting group, differing in the OEG attachment, functions as a means of separation of these stereoisomers. The physical basis of separation was to be based on the OEG choice, but the means of attachment was an open question. We chose the link between the OEG tag and the stereoisomer to be through a well-known protecting group entity, the dimethoxybenzyl ether (DMB) structure, because the successful removal of the OEG tag can be confidently predicted based on organic chemists' experience with DMB protecting groups.

The needed OEG-tagged DMB protecting reagents were readily prepared, as summarized in Scheme 1. The synthesis of the smallest and least-polar analogue **8a** ($n = 1$) is representative of the series. *O*-Alkylation of methyl vanillate **4** with commercial 1-chloro-2-methoxyethane **5a**, employing K_2CO_3 and KI in DMF, provided ester **6a**, which was reduced to the alcohol **7a** with $LiAlH_4$. In turn, this was converted to the imidate **8a** by treatment with NaH in THF followed by the addition of trichloroacetonitrile.[10] The other chlorides, **5b−d**, were prepared by treating the commercially available alcohols with thionyl chloride and were then taken through the same series of steps. Yields were uniformly high, and each of the imidate reagents, **8a−d**, was isolated as a clear oil in good purity.

Following previous syntheses of molecules such as M-**3**,[3c] the key step in the OEG mixture-synthesis plan is the alkylation of thiophenyl butenolide enantiomers **10** with quasiracemates

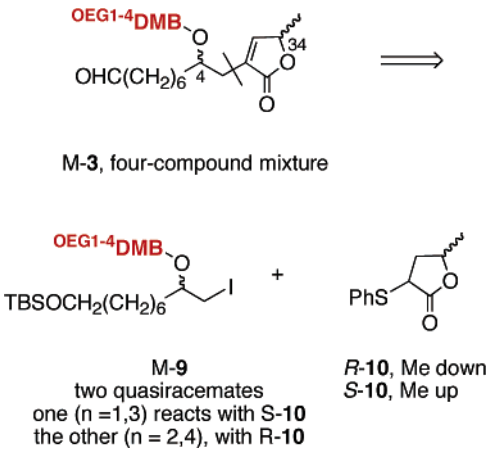


FIGURE 3. Strategy and tagging plan for the OEG mixture synthesis.

M-**9** (Figure 3). To make all isomers, we need to code configurations of the stereocenters on both the butenolide (C34) and the side chain (C4) of **3** with OEG tags. We opted to code both stereocenters through the side-chain protecting group by making two different quasiracemates of M-**9**, reacting each quasiracemate with a different enantiomer of **10**, and then mixing the resulting pairs of quasidiastereomers. In this way, the stereocenter of the butenolide (C34) is coded unambiguously even though the tags are all located on the hydroxy group at C4.

Tosylates **16a−d** are the immediate precursors of the required iodides M-**9**, and the syntheses of these molecules are summarized in Scheme 2. In the previous synthesis of murisolin,[3c] a Sharpless asymmetric dihydroxylation was employed to install the stereocenter at C4. However, the enantiomer ratios of the products of these reactions were only about 90/10. When carried through the synthesis, the minor enantiomers ultimately resulted in minor diastereomeric impurities in the final murisolin isomers. To avoid the careful chromatographic effort that was required to isolate pure isomers in the earlier work, we decided in this work to modify the synthesis to make enantiopure precursors. After briefly exploring other options, we settled on an approach based on the Jacobsen hydrolytic kinetic resolution.[11]

Silylation of 8-nonen-1-ol **11** with TBSCl and exposure of the resulting silyl ether to *m*CPBA provided *rac*-**12** in 97% overall yield. Hydrolytic kinetic resolution of *rac*-**12** with (*R*,*R*)-**13** under standard conditions provided 43% of alcohol (*S*)-**14** along with 56% of epoxide **12**, now enriched in the other enantiomer. Resolution of this epoxide sample with (*S*,*S*)-**13** then provided (*R*)-**14** in 45% overall yield from the racemate. Both samples exhibited ee's >98%, according to a Mosher ester analysis. Selective monotosylation of (*R*)- and (*S*)-**14** was accomplished by the treatment with TsCl, Et_3N, and 2 mol % dibutyltin oxide,[12] to provide the enantiomeric tosylates **15**. In the last steps prior to the mixture synthesis, tosylate (*R*)-**15** was alkylated with each of the shorter OEG imidates **8a** and **8b**, and (*S*)-**15** was alkylated with the two longer OEG imidates **8c** and **8d**. This establishes a "short/long" code in which the (*S*) configuration at C4 is indicated by two shorter OEG increments ($n = 1$ or 2) and the (*R*) configuration is indicated by the two

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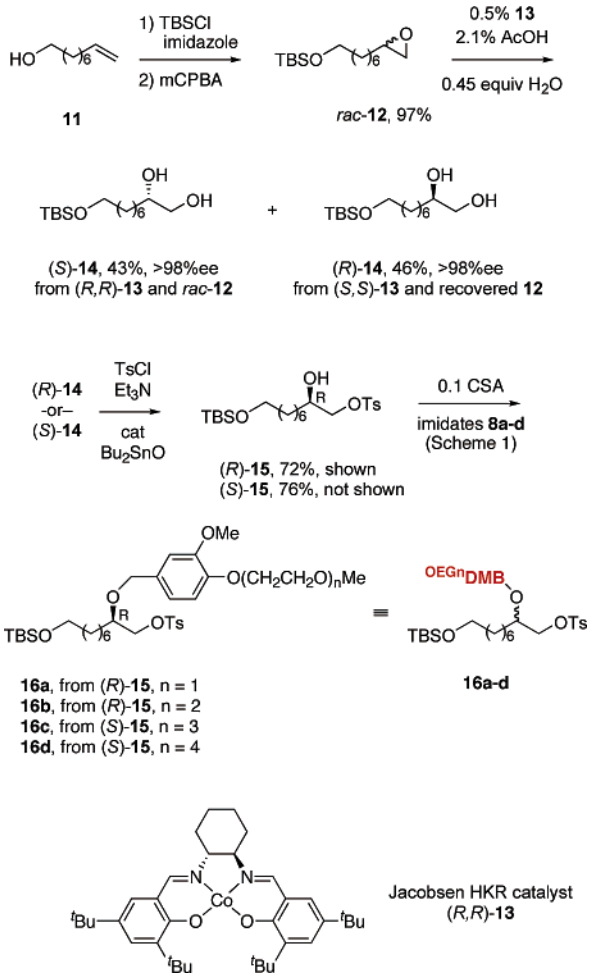
SCHEME 2. Premix Stage: Synthesis of the OEG-Tagged Tosylates 16

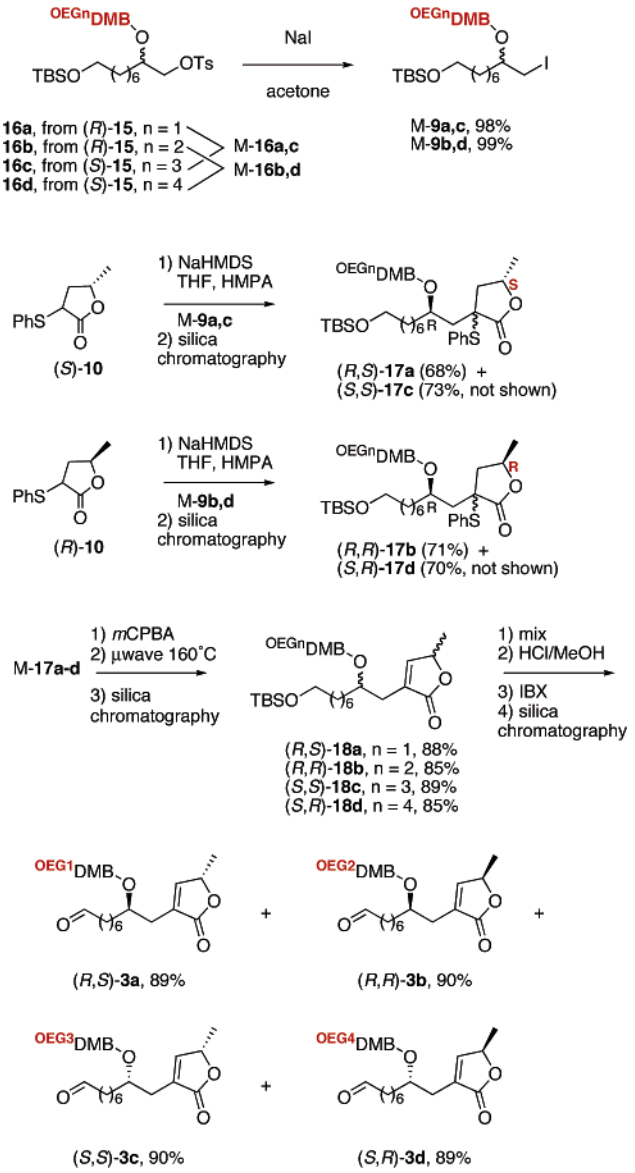


longer ones (n = 3 or 4). The double coding is initially redundant but will presently permit the coding of the C34 butenolide stereocenter without bringing in additional tags.

Mixture Synthesis Stage. The mixture synthesis stage of the work is summarized in Scheme 3. Quasiracemate tosylates M-**16a**,**c** and M-**16b**,**d** were separately converted to the corresponding iodides M-**9** by treatment with sodium iodide in refluxing acetone. After 20 h, the reactions were complete by TLC analysis (see below), and each mixture exhibited only two spots for the corresponding iodides (**9a** and **9c**, or **9b** and **9d**), with no detectable spots for starting tosylates. Accordingly, the reactions were worked up, and the crude iodide mixtures were used directly in the next step.

Quasiracemate M-**9a**,**c** was alkylated with the enolate derived from butenolide (*S*)-**10** under standard conditions (NaHDMS, THF/HMPA, reflux). After workup, the crude product of this reaction was subjected to standard silica flash chromatography. As expected, this resulted in demixing and provided the less-polar quasidiastereomer (*R*,*S*)-**17a** (66%, n = 1), followed by the more-polar (*S*,*S*)-**17c** (73%, n = 3). In turn, quasiracemate M-**9b**,**d** was reacted with enantiomeric butenolide (*R*)-**10** to give (*S*,*S*)-**17b** (71%, n = 2) and (*S*,*R*)-**17d** (70%, n = 4) after flash chromatography. Each of the four isolated quasidiastereomers was characterized by the usual battery of spectroscopic techniques (see below and Supporting Information). The use of the two different quasiracemates of **11** establishes an "odd/even" coding of the butenolide stereocenter (C34), with an odd number

SCHEME 3. OEG Mixture Synthesis of Target Aldehydes 3



of OEG increments (1,3) encoding the (*S*) configuration and an even number of increments (2,4) encoding the (*R*) configuration. Each of the four quasi-isomers of **17** now has a unique OEG tag.

Remixing to make the four component mixture M-**17a**−**d** was followed by *m*CPBA-mediated oxidation to the sulfoxide and direct elimination at 160 °C (microwave) to provide a mixture of four butenolides, M-**18a**−**d**.[13] Standard silica chromatography then provided the four pure butenolides, **18a**−**d**, in yields ranging from 85 to 89%. Finally, the four butenolides were remixed, and the mixture M-**18a**−**d** was desilylated with a catalytic amount of HCl in MeOH.[14] Without purification, the resulting mixture of crude alcohols was oxidized with *o*-iodoxybenzoic acid (IBX),[15] and the crude product was purified by flash chromatography with concomitant demixing to provide the target aldehydes (*R*,*S*)-**3a**, (*R*,*R*)-**3b**, (*S*,*S*)-**3c**, and

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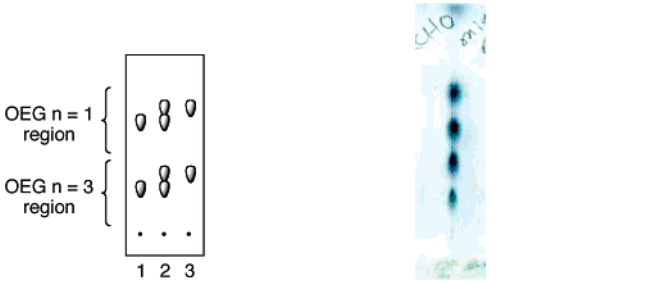

(a) Reaction progress in conversion of tosylate M-**16a,c** to iodide M-**9a,c**
solvent, 50% EtOAc in hexane
Lane 1, starting tosylate mixture
Lane 2, reaction mixture after 8 h
Lane 3, reaction mixture after 20 h

(b) Photograph of the TLC of crude aldehydes M-**3a-d** prior to flash chromatography
solvent, 100% EtOAc

FIGURE 4. Typical TLC analyses of OEG-tagged product mixtures.

(*S*,*R*)-**3d**. In work not reported here but communicated separately, these aldehydes were mixed and applied to the synthesis of 12 new isomers of murisolin.[5]

Analysis, Separation, and Identification Features of an OEG Mixture Synthesis. Any solution-phase mixture-synthesis technique based on separation tagging must provide for methods for the characterization of intermediates during a synthesis. In short, it must be possible to analyze, separate, and identify components of a mixture. In an OEG mixture synthesis, tag-based separation is accomplished by silica gel chromatography, and we used standard techniques in this work both to follow reactions of mixtures and to purify products.

Figure 4 shows two representative TLC analyses of reaction products from this work. On the left is a diagram of the TLC analysis (50% EtOAc in hexane) of the reaction mixture from the Finkelstein reaction of quasiracemic tosylates M-**16a**,**c** after treatment to provide iodides M-**9a**,**c**. The starting material (Lane 1) shows an upper spot corresponding to (*R*)-**16a** with the smaller OEG tag ($n = 1$) and a lower spot corresponding to (*S*)-**16c** with the larger tag ($n = 3$). After heating M-**16a**,**c** at reflux in acetone in the presence of sodium iodide for 8 h, the two starting spots remain, but there are two new spots that indicate partial conversion to the products **9**. After heating for 20 h, both tosylate spots disappear, and only the spots corresponding to iodides (*R*)-**9a** and (*S*)-**9c** are visible. In effect, the TLC analyses of the mixtures behave like two (or four) standard TLCs stacked on top of each other, with the larger (primary) separation dictated by the OEG increment and the smaller (secondary) separation dictated by the structural change in the molecule.

The right side of Figure 4 shows a photograph of the TLC analysis of the final crude reaction product, aldehyde M-**3a**−**d**, following the IBX oxidation. This is representative of the TLC analyses of the four-product mixture reactions and shows four spots, implying clean conversion of the precursors to the products. Because of the wide range of R_f values for the spots, preparative flash chromatography under standard isocratic conditions was not practical—either the products with shorter OEG tags came off too fast to separate, or the products with longer tags never eluted. This problem was readily solved by conducting preparative separations with step gradients. The solvent compositions of the steps were selected by standard TLC experiments that determined the amount of the more-polar solvent (EtOAc) needed to move each successive product off the baseline to an R_{xc4} of about 0.15−0.3. For example, flash chromatography of M-**3a**−**d**, shown in Figure 4b, with 25% EtOAc in hexanes initially provided (*R*,*S*)-**3a**. The eluent composition was then changed in three subsequent stages to 35, 50, and finally 70% EtOAc to elute in sequence (*R*,*R*)-**3b**, (*S*,*S*)-**3c**, and (*S*,*R*)-**3d**. Each step gradient was treated like a standard flash chromatography—fractions were analyzed by TLC and those containing impurities were not combined with the pure fractions. The impurities were generally small and did not arise from the late elution of the preceding OEG tag or the early elution of the subsequent one. Instead, they were minor compounds bearing the same tag as the target compound.

In practice, OEG mixture synthesis is an iterative process of mixing to conduct a reaction, followed by demixing during a subsequent separation. The demixing can be avoided when crude reaction products are taken directly to the next step without purification. This is very different from fluorous mixture synthesis, where demixing is typically used for analysis but not for preparative purification of intermediates. Fluorous techniques such as LCMS or LC NMR over fluorous silica gel allow the individual analysis and identification of mixture components;[2b] however, the components can often be purified without demixing by flash chromatography over standard silica gel.

The question of whether the iterative "mix/demix" feature of an OEG mixture synthesis is an advantage or a disadvantage depends on your point of view. On one hand, it is a disadvantage because a little additional work is generated each time a mixture is separated into its components. For example, preparative purification of a four-compound fluorous mixture[3] might entail the collection of a single spot, while the same purification of an OEG mixture requires the collection of four spots in the successive step gradient. The four compounds must briefly be handled individually prior to remixing for the next reaction. On the other hand, the enforced demixing by OEG tags is an advantage because the individual products can be analyzed and characterized by traditional means. For example, in fluorous mixture synthesis, "average yields" are usually calculated based on the weight of a mixture and the mol % of its underlying components. And the individual components of mixtures are only occasionally characterized by ^{1}H NMR spectroscopy and even less frequently by ^{13}C NMR spectroscopy. In contrast, we have recorded, herein, accurate weight yields of all the purified components of several mixtures. (These yields are identical to standard yields of individual reactions.) All of the demixed products from the mixture synthesis stage of this work have been characterized by the usual spectroscopic means (see Supporting Information).

Copies of the ^{1}H NMR and ^{13}C NMR spectra from representative quasi-isomers are shown in the Supporting Information. These spectra are readily interpretable, and as expected, the quasienantiomeric pairs exhibit essentially identical spectra, except for the region with the OEG peaks. The quasidiastereomers exhibit very similar spectra, but there are small differences.

Polyethylene glycol (PEG) tags have been used by Janda and Gravert and others for the synthesis of individual small molecules,[16] and the spectra of OEG-tagged molecules resemble these, except that the integration of the ethylene glycol resonances is much smaller with respect to the rest of the resonances. Entities bearing PEG-tags are heterogeneous materials, because PEG is a mixture consisting of a range of macromolecules of differing molecular weights. In contrast,

(16) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509.

OEG-tagged compounds are single molecular entities, because each molecule of a precursor is tagged with a single OEG tag.

Conclusions

The first multistep OEG mixture synthesis has been successfully completed, and the features of the new method are beginning to emerge. The components of the quasi-isomeric mixtures of this work all showed similar reactivity during the reaction stages, but they showed very different separation properties on standard silica gel. As projected, the nature of the OEG-tag dominated in all cases over the molecule that was tagged, with mixture components reliably eluting in order of the increasing size of the OEG group. This dominance may be expected in other applications as well, provided that the structures of the tagged components are reasonably analogous.

While only four OEG tags have been used in this work, it is easy to envision lower homologation to a null tag ($n = 0$, that is, a bare methoxy group) as well as higher homologation into the range of n ≈ 10. Beyond this point, the highly polar tagged molecules will probably exhibit significant water solubility as their properties begin to converge on those of PEG-tagged molecules.

This report also introduces a pro-tagging method used to encode the configuration of a stereocenter in a portion of the molecule (the butenolide ring) that has no convenient functionality for the attachment of a tag. Instead, two pairs of (apparently) redundant tags were introduced to encode the hydroxy-bearing stereocenter, and then an appropriate pairwise combination of these tagged compounds with the untagged butenolide enantiomers provided an unambiguous coding scheme. Ultimately, the final aldehyde mixture M-**3a**−**d** in this work was used as a key component in a double mixture synthesis that yielded sixteen stereoisomers of the acetogenin murisolin.[5] Four of these 16 stereoisomers were identical to existing samples,[3c] thereby confirming the success of the reaction sequence and the encoding scheme in both this single OEG mixture synthesis and the subsequent OEG-fluorous double mixture synthesis.

At this early stage, OEG mixture synthesis shares features of mixture synthesis by separation tagging and with features of traditional synthesis of individual pure compounds. This hybrid nature originates because of the "mix/demix" feature, with mixing occurring prior to every reaction and demixing occurring in the subsequent separation. The demixing has the disadvantage that a bit more work is needed, but a dividend of much more information (accurate yields, characterization data) is paid back in return. In practice, OEG mixture synthesis has considerable flexibility, because the automatic demixing can be avoided either by taking the crude mixtures ahead into the next step or by changing the fraction collection criteria in the flash chromatography.

Despite the shared conceptual basis for separation tagging in solution-phase mixture synthesis, the techniques of fluorous mixture synthesis and OEG mixture synthesis are proving to be quite different in practice. Taken separately, the techniques are complementary, with different strengths and weakness that may dictate which is preferred for a given problem. Taken together, they allow for a double mixture synthesis in which the number of encoded products in the mixture is the multiple of the number of each class of tags rather than the sum.

Experimental Section

General Procedure 1. Synthesis of Alkyl Chlorides (5): A solution of thionyl chloride (92 mmol) in $CHCl_3$ (15 mL) was added slowly over 15 min to a stirred solution of OEG monomethyl ether (72 mmol) and pyridine (72 mmol) in $CHCl_3$ (60 mL) under argon, followed by refluxing the above reaction mixture for 3 h. The above reaction mixture was washed with 300 mL of water, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product (yellow to brown colored) was spectroscopically pure and can be used in the next step without further purification. However, bulb-to-bulb (kugelrohr distillation) distillation into a cold receiving flask (−78 °C) under reduced pressure gave the desired alkyl chloride as colorless to pale yellow oils.

1-Chloro-2-(2-methoxyethoxy)ethane (5b): Performing the general procedure 1 with 2-(2-methoxyethoxy)ethanol (**15b**; 8.7 g, 72 mmol) gave 1-chloro-2-(2-methoxyethoxy)ethane (**5b**; 9.2 g, 92%) as a colorless oil. See Supporting Information for **5c**,**d**.

3-Methoxy-4-(2-methoxyethoxy)benzoic Acid Methyl Ester (6a): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate (**4**; 5.0 g, 27 mmol) and 1-chloro-2-methoxyethane (**5a**; 3.4 g, 36 mmol) in dry DMF, and the reaction mixture was stirred for 24 h under argon. The DMF was removed by concentrating the reaction mixture with a rotovap equipped with a dry ice/acetone bath (−78 °C condenser). Dichloromethane (15 mL) was added to the above crude product, and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated, and the traces of solvents (CH_2Cl_2 and DMF) present in it were removed in vacuo (0.08 mmHg, 45 °C) into a cold receiving flask (−78 °C) by bulb-to-bulb (kugelrohr) distillation. The resulting residue was distilled bulb-to-bulb (0.08 mmHg, 55−60 °C) into a cold receiving flask (−78 °C) to yield 3-methoxy-4-(2-methoxyethoxy)benzoic acid methyl ester (**6a**; 6.1 g, 93%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 3.77−3.80 (m, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.19−4.22 (m, 2H), 6.89 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.63 (dd, J = 8.5, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 55.7, 58.9, 67.9, 70.5, 111.6, 112.0, 122.6, 123.1, 148.7, 152.0, 166.5; IR (neat) 1720, 1600, 1513; EIMS m/z 240 (M^+); HRMS calcd for $C_{12}H_{16}O_5$, 240.0998; found, 240.0985.

3-Methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzoic Acid Methyl Ester (6b): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate (**4**; 5.0 g, 27 mmol) and 1-(2-chloroethoxy)-2-methoxyethane (**5a**; 4.9 g, 36 mmol) in dry DMF (125 mL), and the reaction mixture was stirred at 60 °C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry ice/acetone bath (−78 °C condenser). Dichloromethane (15 mL) was added to the above crude product, and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated, and the traces of solvents (CH_2Cl_2, DMF) and the excess of alkyl halide present in it were removed in vacuo (0.08 mmHg, 50−55 °C) into a cold receiving flask (−78 °C) by bulb-to-bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mmHg, 68−72 °C) into a cold (−78 °C) receiving flask to yield 3-methoxy-4-[2-(2-methoxyethoxy)ethoxy] benzoic acid methyl ester (**6b**; 7.5 g, 96%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.56−3.59 (m, 2H), 3.72−3.75 (m, 2H), 3.90−3.94 (m, 8H), 4.94 (t, J = 5.0 Hz, 2H), 6.93 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.5, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.8, 58.9, 68.2, 69.3, 70.7, 71.8, 111.8, 112.2, 122.7, 123.3, 148.8, 152.1, 166.7; IR (neat) 2928, 2888, 1714, 1599; EIMS m/z 284 (M^+); HRMS calcd for $C_{14}H_{20}O_6$, 284.1260; found, 284.1265.

3-Methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzoic Acid Methyl Ester (6c): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate (**4**; 5.0 g, 27 mmol) and 1-[2-(2-chloroethoxy)-ethoxy]-2-methoxyethane (**5c**; 6.6 g, 36 mmol) in dry DMF (125

mL), and the reaction mixture was stirred at 60 °C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry ice/acetone bath (−78 °C condenser). Dichloromethane (15 mL) was added to the above crude product, and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated, and the traces of solvents (CH_2Cl_2, DMF) and excess of alkyl halide present in it were removed in vacuo (0.08 mmHg, 65 °C) into a cold receiving flask (−78 °C) by bulb-to-bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mmHg, 85−90 °C) to yield 3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzoic acid methyl ester (**6c**; 8.5 g, 95%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.39−3.42 (m, 2H), 3.48−3.56 (m, 4H), 3.60−3.63 (m, 2H), 3.76−3.80 (m, 8H), 4.11 (t, J = 5.0 Hz, 2H), 6.80 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 8.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 55.5, 58.6, 68.0, 69.0, 70.1, 70.2, 70.5, 71.5, 111.6, 111.9, 122.4, 123.0, 148.6, 152.0, 166.4; IR (neat) 3085, 2870, 1716, 1508; EIMS *m*/*z* 328 (M^+); HRMS calcd for $C_{16}H_{24}O_7$, 328.1522; found, 328.1523.

3-Methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)-benzoic Acid Methyl Ester (6d): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate (**4**; 5.0 g, 27 mmol) and 1-[2-(2-chloroethoxy)ethoxy]-2-(2-methoxyethoxy)ethane (**5d**; 8.1 g, 36 mmol) in dry DMF (125 mL), and the reaction mixture was stirred at 60 °C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry ice/acetone bath. Dichloromethane (15 mL) was added to the above crude product, and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated, and the traces of solvents (CH_2Cl_2, DMF) and excess alkyl halide present in it were removed in vacuo (0.08 mmHg, 65 °C) into a cold receiving flask (−78 °C) by bulb-to-bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mmHg, 85−90 °C) into a cold receiving flask (−78 °C) to yield 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzoic acid methyl ester (**6d**; 9.3 g, 91%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.35−3.38 (m, 2H), 3.46−3.51 (m, 8H), 3.55−3.59 (m, 2H), 3.71−3.75 (m, 8H), 4.06 (t, J = 5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 1.5 Hz, 1H), 7.46 (dd, J = 8.5, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.4, 55.5, 58.5, 67.9, 69.0, 70.0, 70.1, 70.4, 71.4, 111.6, 111.9, 122.4, 122.9, 148.5, 151.9, 166.24; IR (neat) 2941, 2873, 1716, 1598, 1509; EIMS *m*/*z* 373 (M + H), 372 (M^+); HRMS calcd for $C_{18}H_{28}O_8$, 372.1784; found, 372.1796.

General Procedure 2. Reduction of Esters 6a−d to Alcohols 7a−d with $LiAlH_4$: A solution of ester **6** (1.0 equiv) in THF was added slowly to a suspension of $LiAlH_4$ (0.55 equiv) in THF at 0 °C, and the resulting reaction mixture was stirred at 0 °C for 15 min, followed by 30 min at room temperature. The reaction mixture was quenched with methanol and diluted with ethyl acetate and saturated sodium potassium tartarate (1:1), followed by vigorous stirring for 3.5 h. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to yield the alcohol **7** as an oil.

[3-Methoxy-4-(2-methoxyethoxy)phenyl]methanol (7a): Performing the general procedure 2 with 3-methoxy-4-(2-methoxyethoxy)benzoic acid methyl ester (**6a**; 5.9 g, 24 mmol) gave [3-methoxy-4-(2-methoxyethoxy)phenyl]methanol (**7a**; 4.7 g, 91%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.78 (t, J = 5.1 Hz, 2H), 3.87 (s, 3H), 4.15 (t, J = 3.1 Hz, 2H), 4.62 (s, 2H), 6.87−6.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 59.2, 65.1, 68.5, 71.1, 110.8, 113.6, 119.2, 134.3, 147.7; IR (neat) 3400, 2940, 2868, 1588, 1516. See Supporting Information for **7b−d**.

General Procedure 3. 2,2,2-Trichloroacetimidic Acid 3-Methoxy-4-(2-methoxyethoxy)benzyl Ester (8a): [3-Methoxy-4-(2-methoxyethoxy)phenyl]methanol (**7a**; 4.5 g, 21 mmol) was added slowly to a suspension of sodium hydride (51 mg, 2.1 mmol) in THF (25 mL) under argon. The reaction mixture was stirred at room temperature for 20 min and then cooled to 0 °C, followed by the slow addition of trichloroacetonitrile (2.1 mL, 21 mmol) over 15 min. The reaction mixture was allowed to warm to room temperature over 1 h, followed by concentration under reduced pressure. To the concentrate was added a mixture of pentane/methanol (49:1, 50 mL), followed by vigorous shaking, filtration, and concentration of filtrate and pentane washings[17] (3 × 30 mL), resulting in 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)-benzyl ester (**8a**; 6.8 g, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.79 (t, J = 4.9 Hz, 2H), 3.87 (s, 3H), 4.18 (t, J = 4.9 Hz, 2H), 5.29 (s, 2H), 6.90−6.98 (m, 3H), 8.38 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 59.0, 68.3, 70.6, 70.8, 91.3, 111.5, 113.3, 120.4, 128.4, 148.2, 149.4, 162.3; IR (neat) 3320, 2939, 1665, 1594, 1513; EIMS *m*/*z* 355 (M^+); HRMS calcd for $C_{13}H_{16}NO_4Cl_3$, 355.0145; found, 355.0127. See Supporting Information for **8b−d**.

***tert*-Butyldimethyl-non-8-enyloxysilane:** *tert*-Butyldimethylsilyl chloride (19 g, 0.13 mol) was added to a stirred solution of non-8-en-1-ol (**11**; 14 g, 0.1mol) and imidazole (9.3 g, 0.14 mol) in dichloromethane at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then for 1 h at room temperature. The reaction mixture was diluted with water, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated to give *tert*-butyldimethyl-non-8-enyloxy-silane (25 g, 99%) as a colorless oil. The crude reaction mixture was taken to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.32 (s, 8H), 1.40−1.55 (m, 2H), 2.05 (q, J = 7.0 Hz, 2H), 3.61 (t, J = 6.3 Hz, 2H), 4.92−5.02 (m, 1H), 5.74−5.88 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ −5.2, 18.4, 25.9, 26.1, 29.0, 29.2, 29.4, 33.0, 33.9, 63.3, 114.2, 139.2; IR (neat, cm^{-1}) 2933, 2858, 1471; EIMS *m*/*z* 241 (M − CH_3), 199 (M − C_4H_9); HRMS calcd for (M − CH_3)$^+$ $C_{14}H_{29}$-OSi, 241.1987; found, 241.1984.

(7*R*,7*S*)-*tert*-Butyldimethyl-(7-oxiranylheptyloxy)silane (*rac*-12): *m*-Chloroperbenzoic acid (25 g, 0.11 mol, 75% w/w in H_2O) was added to a solution of *tert*-butyldimethyl-non-8-enyloxysilane (25 g, 98 mmol) in dichloromethane (325 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 1 h and treated with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography (SiO_2, 20% ethyl acetate/hexanes) to give *tert*-butyldimethyl-(7-oxiranylheptyloxy)silane (***rac*-12**; 26 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.30−1.51 (m, 12H), 2.43 (dd, J = 4.9, 2.7 Hz, 1H), 2.69−2.73 (m, 1H), 2.84−2.90 (m, 1H), 3.57 (t, J = 6.59 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.4, 25.7, 26.0, 29.4, 29.5, 32.5, 32.8, 47.1, 52.3, 63.2; IR (neat) 2933, 2856, 1464; EIMS *m*/*z* 215 (M − C_4H_9)$^+$; HRMS calcd for (M − C_4H_9)$^+$ $C_{11}H_{23}O_2Si$, 215.1467; found, 215.1471.

9-(*tert*-Butyldimethylsilanyloxy)nonane-1,2-diol (14): The (*R*,*R*)-Jacobson catalyst (0.28 g, 0.46 mmol) was dissolved in *tert*-butyldimethyl-(7-oxiranylheptyloxy)silane (***rac*-12**; 25 g, 92 mmol), AcOH (110 μL, 1.8 mmol), and 0.3 mL THF. The solution was cooled to 0 °C, treated with H_2O (0.74 mL, 41 mmol), and stirred for 12 h at room temperature. The reaction mixture was distilled bulb-to-bulb (kugelrohr) under reduced pressure (0.08 mmHg, 120−130 °C) to remove the residual epoxide (14 g, 52 mmol), followed by a second distillation (0.08 mmHg, 180−190 °C) to yield (*S*)-9-(*tert*-butyldimethylsilanyloxy)nonane-1,2-diol ((*S*)-**14**; 12 g, 43%, >99% enantiomeric excess based on a Mosher ester analysis) as a colorless oil. Similar procedure with the above recovered epoxide (14 g, 51.3 mmol) and (*S*,*S*)-Jacobson catalyst (0.28 g, 0.46 mmol)

(17) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin. Trans. 1*, **1985**, 2247.

resulted in (*R*)-9-(*tert*-butyl-dimethylsilanyloxy) nonane-1,2-diol ((*R*)-**14**; 12 g, 45%, >99% ee by a Mosher ester analysis) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.28−1.50 (m, 12H), 3.38−3.44 (m, 1H), 3.57 (t, J = 6.6 Hz, 2H), 3.65−3.78 (br m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.4, 25.6, 25.8, 26.0, 29.4, 29.7, 32.9, 33.1, 63.3, 66.8, 72.4. EIMS *m*/*z* 259 $(M - CH_3O)^+$; HRMS calcd for $(M - CH_3O)^+$ $C_{14}H_{31}O_2Si$, 259.2093; found, 259.2091.

Toluene-4-sulfonic Acid 9-(*tert*-Butyldimethylsilanyloxy)-2-hydroxynonyl Ester (15): To a solution of (*R*)-9-(*tert*-butyldimethylsilanyloxy)nonane-1,2-diol ((*R*)-**14**; 12 g, 41 mmol) in CH_2Cl_2 (80 mL) were added Bu_2SnO (2.0 g, 8.1 mmol), *p*-TsCl (7.7 g, 41 mmol), and Et_3N (5.6 mL, 41 mmol), followed by stirring the above reaction mixture for 3 h. The reaction mixture was concentrated and purified by flash chromatography (SiO_2, EtOAc/hexanes = 1:3) to yield toluene-4-sulfonic acid (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester ((*R*)-**15**; 14 g, 76%) as white waxy solid; similar procedure with (*S*)-diol (11 g, 38 mmol) yielded (*S*)-sulfonyl ester ((*S*)-**15**; 12 g, 72%) as a white waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.20−1.48 (m, 12H), 2.41 (s, 3H), 2.54 (br s, 1H), 3.56 (t, J = 6.4 Hz, 2H), 3.74−3.89 (m, 2H), 3.98 (dd, J = 9.9, 3.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 21.5, 25.1, 25.6, 25.9, 29.2, 29.4, 32.6, 32.7, 63.2, 69.2, 73.9, 127.9, 129.9, 132.7, 144.9; HRMS calcd for $C_{22}H_{40}O_5SSiNa$, 467.2263; found, 467.2287.

General Procedure 4. Toluene-4-sulfonic Acid (*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)-benzyloxy]nonyl Ester (16a): A solution of (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester ((*R*)-**15**; 2.3 g, 5.2 mmol), 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)-benzyl ester (**8a**; 3.7 g, 10 mmol), and 10-camphorsulfonic acid (0.12 g, 0.52 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 24 h and then diluted with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (SiO_2, EtOAc/hexanes = 3:7) to yield **16a** (2.0 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.18−1.46 (m, 12 H), 2.43 (s, 3H), 3.44 (s, 3H), 3.55−3.60 (m, 3H), 3.76−3.79 (m, 2H), 3.86 (s, 3H), 4.00 (t, J = 4.39 Hz, 2H), 4.14 (t, J = 4.39 Hz, 2H), 4.41 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 6.74−6.86 (m, 3H), 7.31 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.4, 21.6, 25.1, 25.7, 26.0, 29.3, 29.5, 31.3, 32.8, 55.8, 59.1, 63.2, 68.2, 70.9, 71.7, 72.0, 76.1, 111.6, 113.1, 120.3, 127.9, 129.9, 131.3, 132.8, 144.9, 147.8, 149.4; IR (neat) 2927, 2856, 1597, 1514, 1461; HRMS $(M + Na)^+$ calcd for $C_{33}H_{54}O_8SiS$, 661.3206; found, 661.3209. See Supporting Information for **16b**−**d**.

General Procedure 5. *tert*-Butyl-{(*R*)-9-iodo-8-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyloxy}dimethylsilane (9a) and *tert*-Butyl-[(*S*)-9-iodo-8-(3-methoxy-4-{2-[2-(2-methoxyethoxy)-ethoxy]ethoxy}benzyloxy)nonyloxy]dimethylsilane (9c): A solution of **16a** (1.9 g, 3.0 mmol), **16c** (2.3 g, 3.2 mmol), and NaI (9.2 g, 61 mmol) in acetone (35 mL) was refluxed for 20 h, followed by concentration under reduced pressure. The concentrate was treated with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield a mixture of **9a** and **9c** as a light brown oil (3.9 g, 98%), which was used in the next step without further purification. However, for characterization purposes, a small sample (0.1 g) of the mixture M-**9a**,**c** was subjected to flash column chromatography (SiO_2) and gave **9a** (ethyl acetate/hexanes = 1:4), followed by **9c** (ethyl acetate/hexanes = 1:1), as colorless oils. For **9a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.30−1.64 (m, 12H), 3.21−3.33 (m, 3H), 3.46 (s, 3H), 3.60 (t, J = 6.6 Hz, 2H), 3.76−3.82 (m, 2H), 3.88 (s, 3H), 4.18 (t, J = 4.9 Hz, 2H), 4.47 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 6.84−6.89 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.2, 10.5, 18.5, 25.3, 25.8, 26.1, 29.4, 29.6, 32.9, 34.7, 56.0, 59.4, 63.3, 68.5, 71.0, 71.4, 77.7, 111.9, 113.6, 120.4, 131.7, 147.7, 149.7; IR (neat) 2929, 2857, 1593, 1514, 1463; HRMS [ESI, $(M + Na)^+$] calcd for $C_{26}H_{47}O_5SiI$, 617.2135; found, 617.2152. For **9c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.30−1.62 (m, 12H), 3.26−3.34 (m, 3H), 3.39 (s, 3H), 3.55−3.63 (m, 4H), 3.65−3.72 (m, 4H), 3.75 (dd, J = 6.2, 3.4 Hz, 2H), 3.88−3.90 (m, 5H), 4.17−4.22 (m, 2H), 4.44 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 6.87−6.89 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.2, 10.5, 18.4, 25.3, 25.8, 26.1, 29.4, 29.6, 32.9, 34.7, 56.0, 59.1, 63.3, 68.6, 69.6, 70.5, 70.6, 70.7, 71.3, 71.9, 77.6, 111.9, 113.5, 120.4, 131.4, 147.9, 149.6; IR (neat) 2929, 2857, 1593, 1515; HRMS $(M + Na)^+$ calcd for $C_{30}H_{55}O_7SiI$, 705.2660; found, 705.2686. See Supporting Information for **9b**,**d**.

General Procedure 6. (3*RS*,5*S*)-3-{(*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyl}-5-methyl-3-phenylsulfanyldihydrofuran-2-one (17a) and (3*RS*,5*S*)-3-[(*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyloxy)nonyl]-5-methyl-3-phenylsulfanyldihydrofuran-2-one (17c): A solution of NaHMDS (1.0 M in THF, 5.9 mL, 5.9 mmol) was added to a solution of (*S*)-5-methyl-3-phenylsulfanyldihydrofuran-2-one ((*S*)-**10**; 1.2 g, 5.9 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 30 min at this temperature, and then a solution of iodide M-**9a**,**c** (3.6 g, 5.6 mmol) in HMPA (3.5 mL) was added. The reaction mixture was allowed to warm to room temperature over 2 h, followed by refluxing it for 14 h. Then the reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2) to give **17a** (25% ethyl acetate/hexanes; 1.3 g, 69%), followed by **17c** (50% ethyl acetate/hexanes; 1.5 g, 71%) as oils. For **17a**: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.03 (d, J = 6.0 Hz, 6H), 1.21−1.37 (m, 10H), 1.48−1.56 (m, 2H), 1.90−2.15 (m, 3H), 2.69 (dd, J = 13.7, 7.1 Hz, 1H), 3.41 (s, 3H), 3.60 (t, J = 6.6 Hz, 2H), 3.66−3.75 (m, 3H), 3.84 (s, 3H), 4.10−4.14 (m, 2H), 4.22 (d, J = 10.4 Hz, 1H), 4.25−4.33 (m, 1H), 4.41 (d, J = 10.4 Hz, 1H), 6.78−6.88 (m, 2H), 6.92 (s, 1H), 7.29−7.40 (m, 3H), 7.55 (dd, J = 8.0, 1.4 Hz, 2H); IR (neat) 2929, 1763, 1516, 1458. For **17c**: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.14 (d, J = 6.4 Hz, 3H), 1.21−1.28 (m, 8H), 1.46−1.52 (m, 3H), 1.55−1.62 (m, 1H), 1.86 (dd, J = 14.2, 6.0 Hz, 1H), 1.92−2.09 (m, 2H), 2.81 (dd, J = 14.2, 7.8 Hz, 1H), 3.35 (s, 3H), 3.51−3.52 (m, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.62−3.66 (m, 4H), 3.71−3.72 (m, 2H), 3.84−3.94 (m, 6H), 4.15 (t, J = 5.3 Hz, 2H), 4.32−4.40 (m, 2H), 4.53 (d, J = 11.0 Hz, 1H), 6.78−6.91 (m, 3H), 7.30−7.38 (m, 3H), 7.54 (d, J = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.3, 18.3, 21.3, 24.5, 25.7, 25.9, 29.3, 29.7, 32.8, 33.4, 39.4, 40.1, 54.8, 55.9, 58.9, 63.2, 68.6, 69.5, 70.2, 70.4, 70.6, 70.7, 71.8, 73.0, 75.4, 76.8, 77.3, 111.7, 113.5, 119.8, 128.9, 129.6, 130.3, 131.4, 136.6, 147.6, 149.5, 177.3; IR (neat) 2929, 1763, 1515, 1463; MS *m*/*z* 785 (M + Na); HMRS (ESI) calcd for $C_{41}H_{66}O_9SSiNa$, 785.4095; found, 785.4124. See Supporting Information for **17b**,**d**.

Lactone Mixture (M-18a−d): *m*-Chloroperbenzoic acid (0.28 g, 1.6 mmol) was added to a mixture of **17a** (0.27 g, 0.4 mmol), **17b** (0.29 g, 0.4 mmol), **17c** (0.31 g, 0.4 mmol), and **17d** (0.32 g, 0.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 30 min and then quenched with saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2, followed by drying the combined organic layers with $MgSO_4$ and concentrating the organic layers. The concentrate, in 3.5 mL of DMF, was heated in a microwave (personal chemistry microwave, 150 W, ramped to 160 °C over 2 min and heated for 5 min at that temperature) for 5 min at 160 °C. Removal of DMF under reduced pressure, followed by purification by flash column chromatography on silica gel under gradient elution

gave **18a** (0.20 g, 88%; 25% ethyl acetate/hexanes), **18b** (0.21 g, 85%; 40% ethyl acetate/hexanes), **18c** (0.23 g, 89%; 60% ethyl acetate/hexanes), and **18d** (0.24 g, 85%; 80% ethyl acetate/hexanes) as pale yellow oils.

(*S*)-3-{(*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyl}-5-methyl-5*H*-furan-2-one (18a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 1.23−1.31 (m, 8H), 1.35 (d, J = 6.9 Hz, 3H), 1.42−1.49 (m, 2H), 1.53−1.58 (m, 2H), 2.48 (d, J = 6.0 Hz, 2H), 3.41 (s, 3H), 3.56 (t, J = 6.6 Hz, 2H), 3.62−3.67 (m, 1H), 3.72 (t, J = 4.6 Hz, 2H), 3.82 (s, 3H), 4.11−4.13 (m, 2H), 4.40 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.92 (q, J = 6.6 Hz, 1H), 6.78−6.84 (m, 3H), 7.05 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.3, 18.3, 19.1, 25.2, 25.7, 25.9, 29.3, 29.6, 32.7, 33.9, 55.8, 59.1, 63.2, 68.5, 70.9, 76.5, 77.5, 111.7, 113.6, 120.2, 130.5, 131.7, 147.7, 149.6, 151.4, 173.9; IR (neat) 2930, 2856, 1756, 1515, 1464. See Supporting Information for **18b**−**d**.

Alcohol Mixture: Acetyl chloride[18] (11 μL) was added to a 1:1:1:1 mixture of **18a**, **18b**, **18c**, and **18d** (0.26 g, 0.39 mmol) in methanol at 0 °C and stirred for 15 min. Then the solution was concentrated to yield the alcohol. The resulting mixture of alcohols (0.20 g, 99%) was spectroscopically pure and was used in the next step without further purification. However, spectroscopic data for individual compounds was obtained by repeating the above experimental procedure with individual compounds.

General Procedure 11. (*S*)-3-{(*R*)-9-Hydroxy-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyl}-5-methyl-5*H*-furan-2-one: Acetyl chloride (11 μL) was added to a solution of **18a** (30 mg, 0.053 mmol) in methanol, and the mixture was stirred for 15 min. The concentration of the reaction mixture gave the alcohol (23 mg, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26−1.34 (m, 8H), 1.37 (d, J = 7.1 Hz, 3H), 1.40−1.56 (m, 4H), 1.85 (br s, 1H), 2.49 (d, J = 5.5 Hz, 2H), 3.42 (s, 3H), 3.59 (t, J = 6.6 Hz, 2H), 3.63−3.67 (m, 1H), 3.73−3.79 (m, 2H), 3.84 (s, 3H), 4.13 (t, J = 4.94 Hz, 2H), 4.43 (s, 2H), 4.94 (q, J = 6.59 Hz, 1H), 6.78−6.86 (m, 3H), 7.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 25.2, 25.6, 29.3, 29.5, 29.6, 32.7, 33.9, 55.8, 59.2, 62.8, 68.5, 70.9, 76.4, 111.8, 113.5, 120.4, 130.5, 131.7, 147.8, 149.6, 151.6, 174.0; IR (neat) 3406, 2928, 1751, 1515, 1456; EIMS m/z 450 (M^+); HRMS calcd for $C_{25}H_{38}O_7$, 450.2617; found, 467.2637. See Supporting Information for acylations of **18b**−**d**.

Aldehyde Mixture (M-3): IBX (0.40 g, 1.1 mmol) was added to a mixture of alcohols (0.18 g, 0.36 mmol) in ethyl acetate (10 mL). The resulting suspension was heated, open to the atmosphere, in an oil bath set to 80 °C until TLC indicated complete conversion (3 h). Then the reaction mixture was cooled to room temperature, filtered, and concentrated to yield a mixture of aldehyde that on column chromatography on silica gel by gradient elution (25−70% EtOAc/hexanes) gave the four aldehydes **3** (0.16 g, 0.32 mmol, 90%) as separate oils.

(*R*)-8-[3-Methoxy-4-(2-methoxyethoxy)benzyloxy]-9-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal (3a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25−1.35 (m, 8H), 1.38 (d, J = 7.1 Hz, 3H), 1.44−1.63 (m, 2H), 2.41 (td, J = 7.1, 1.6 Hz, 2H), 2.50 (d, J = 5.5 Hz, 2H), 3.43 (s, 3H), 3.61−3.72 (m, 1H), 3.75−3.78 (m, 2H), 3.85 (s, 3H), 4.11−4.16 (m, 2H), 4.44 (s, 2H), 4.95 (q, J = 6.6 Hz, 1H), 6.78−6.89 (m, 3H), 7.07 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 22.0, 25.1, 29.1, 29.4, 29.6, 33.9, 43.9, 55.9, 59.2, 68.5, 71.1, 76.5,111.8, 113.6, 120.4, 130.5, 131.7, 147.8, 149.6, 151.6, 174.0, 202.8; IR (neat) 2927, 1751, 1720, 1514, 1465; HRMS [ESI, $(M + Na)^+$] calcd for $C_{25}H_{36}O_7$, 471.2359; found, 471.2380.

(*R*)-8-{3-Methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyloxy}-9-((*R*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal (3b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27−1.32 (m, 8H), 1.35 (d, J = 6.9 Hz, 3H), 1.41−1.59 (m, 2H), 2.39 (t, J = 6.6 Hz, 2H), 2.49 (br s, 2H), 3.36 (s, 3H), 3.52−3.57 (m, 2H), 3.62−3.67 (m, 1H), 3.67−3.72 (m, 2H), 3.82 (s, 3H), 3.85 (t, J = 5.3 Hz, 2H), 4.15 (t, J = 5.3 Hz, 2H), 4.42 (s, 2H), 4.94−4.98 (m, 1H), 6.79−6.85 (m, 3H), 7.09 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.0, 21.9, 25.0, 29.0, 29.3, 29.6, 33.8, 43.8, 55.9, 59.0, 68.6, 69.6, 70.7, 71.0, 71.9, 76.5, 77.5, 111.9, 113.6, 120.3, 130.5, 131.6, 147.8, 149.5, 151.6, 173.9, 202.7; HRMS [ESI, $(M + Na)^+$] calcd for $C_{27}H_{40}O_8$, 515.2621; found, 515.2625.

(*S*)-8-(3-Methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-benzyloxy)-9-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24−1.28 (m, 8H), 1.35 (d, J = 6.6 Hz, 2H), 1.41−1.59 (m, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.49 (br s, 2H), 3.36 (s, 3H), 3.42−3.54 (m, 2H), 3.60−3.76 (m, 9H), 3.83−3.93 (m, 5H), 4.15 (t, J = 5.2 Hz, 2H), 4.33 (s, 2H), 4.97 (q, J = 6.2 Hz, 1H), 6.79−6.86 (m, 3H), 7.08 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 21.9, 25.1, 29.0, 29.3, 29.6, 33.8, 43.8, 55.9, 59.0, 68.6, 69.6, 70.5, 70.7, 71.0, 71.9, 76.5, 76.6, 77.5, 111.9, 113.6, 120.4, 130.5, 131.6, 147.8, 149.5, 151.6, 174.0, 202.8; IR (neat) 2927, 1751, 1515, 1457; EIMS m/z 537 (M + H), 536 (M^+); HRMS calcd for $C_{29}H_{44}O_9$, 536.2985; found, 536.2986.

(*S*)-8-[3-Methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-ethoxy)benzyloxy]-9-((*R*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)-nonanal (3d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26−1.37 (m, 8H), 1.39 (d, J = 6.6 Hz, 2H), 1.43−1.65 (m, 2H), 2.42 (td, J = 7.1, 1.6 Hz, 2H), 2.51 (d, J = 5.5 Hz, 2H), 3.38 (s, 3H), 3.53−3.56 (m, 2H), 3.61−3.76 (m, 13H), 3.82−3.92 (m, 5H), 4.17 (t, J = 5.2 Hz, 2H), 4.44 (s, 2H), 4.91−5.03 (m, 1H), 6.84 (m, 3H), 7.08 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 21.9, 25.1, 29.1, 29.4, 29.7, 33.9, 43.8, 55.9, 59.0, 68.6, 69.6, 70.6, 70.8, 71.0, 71.9, 76.5, 76.7, 77.5, 111.9, 113.6, 120.4, 130.5, 131.6, 147.8, 149.6, 151.6, 174.0, 202.8; IR (neat) 2926, 2855, 1751, 1719, 1515, 1457; HRMS [ESI, $(M + Na)^+$] calcd for $C_{31}H_{48}O_{10}$, 603.3145; found, 603.3154.

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Supporting Information Available: Contains additional experimental data and copies of spectra of all purified intermediates (90 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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