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# Synthesis of the Proposed Structure of Mucoxin via Regio- and Stereoselective Tetrahydrofuran Ring-Forming Strategies

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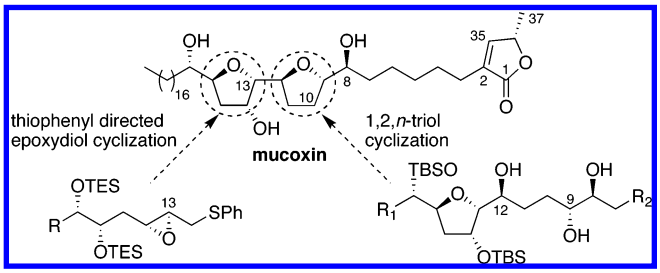


An enantioselective total synthesis of the proposed structure of mucoxin (**1**) is described. Mucoxin, an annonaceous acetogenin isolated from bioactive leaf extracts of *Rollinia mucosa*, is the first acetogenin containing a hydroxylated trisubstituted tetrahydrofuran (THF) ring. This natural product is a highly potent and specific antitumor agent against MCF-7 (breast carcinoma) cell lines ($ED_{50} = 3.7 \times 10^{-3}$ $\mu$g/mL compared to adriamycin, $ED_{50} = 1.0 \times 10^{-2}$ $\mu$g/mL). The total synthesis described herein features two regio- and stereoselective THF ring-forming reactions. The 2,3,5-trisubstituted THF portion (C13−C17) was accessed using a highly regioselective cyclization of a methylene-interrupted epoxydiol, and the 2,5-disubstituted THF ring (C8−C12) was conveniently assembled via a 1,2-*n*-triol cyclization strategy. The spectral data of the synthetic material and two of its diastereomers did not match the reported data for the natural product. On the basis of detailed spectroscopic analysis of the synthesized molecule, we reason that the spectral discrepancies are due to stereochemical misassignment of the natural product.

## Introduction

Although plant extracts of the *annonaceae* family have been historically used in folk medicines, modern bioactivity guided isolation techniques have identified fatty-acid-derived polyketides, now known as annonaceous acetogenins, as the likely active ingredients of these extracts.[1−4] Annonaceous acetogenins are known to be highly potent and selective antitumor agents. More interestingly, some members of this family have been shown to possess the ability to combat resistance in multi drug-resistant cancerous cells.[5,6] The origin of the selective cytotoxicity of acetogenins is believed to result from their complexation with ubiquinone-linked NADH oxidase present in the plasma membrane of tumor cells. Acetogenins also bind NADH-ubiquinone oxidoreductase (complex I), which is a membrane protein present in the mitochondrial electron-transport system.[7−11] Complex I has been implicated in several diseases including idiopathic Parkinson's disease, maturity onset diabetes, stroke-like episodes, and Huntington's disease.[12] However, the precise

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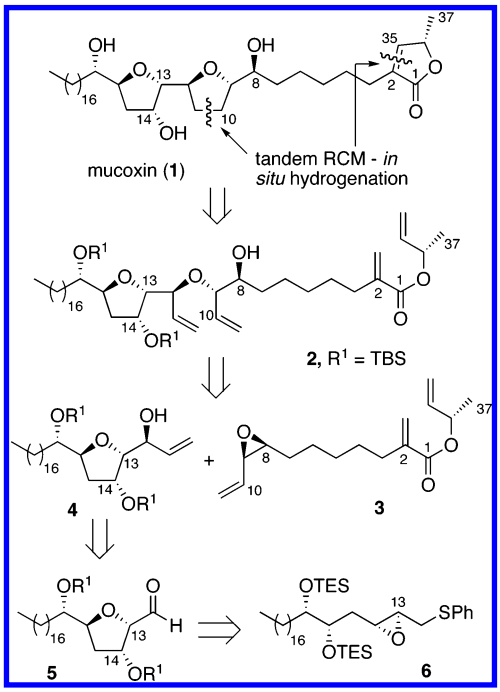


**FIGURE 1.** Retrosynthetic analysis for preparation of mucoxin.

mode of complexation of acetogenins with the target proteins has not been delineated. In view of the promising bioactivity profiles of acetogenins, it would be interesting to investigate their interaction with the relevant proteins at the molecular level.

Structurally, classical acetogenins contain an array of 2,5-disubstituted tetrahydrofuran (THF) rings. More recently, new nonclassical acetogenins containing more complex tetrahydropyran (THP) rings and/or THF rings as the core have been isolated; examples of such are mucocin, muconin, pyragonicin, and Jimenezin, all of which are THP-containing acetongenins and have recently succumbed to total synthesis.[13−18] Mucoxin, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated THF ring (**1**, Figure 1).[19] In vitro cytotoxicity assays against a panel of six human tumor cell lines have shown mucoxin to be more potent and selective against MCF-7 (breast carcinoma) cell lines than adriamycin. Prompted by its novel hydroxy THF core as well as by the biological activity (although limited information is available because of lack of material), we undertook the total synthesis of mucoxin. Because only the relative configuration of the bistetrahydrofuran core (C8−C17) of mucoxin had been established, we chose the enantiomer represented in Figure 1 as the synthetic target. The absolute configuration at C36 was, however, assigned as *S* by McLaughlin and co-workers on the basis of the observation that over 400 acetogenins isolated to date possess the same stereochemistry. Herein, we describe the details of our studies on the first total synthesis of the proposed structure of mucoxin featuring a neighboring-group-directed regioselective cyclization of a methylene-interrupted epoxydiol[20,21] and a 1,2,-*n*-triol cyclization to afford the bistetrahydrofuran core of the natural product.[22−25] However, spectral mismatches between the natural product and the synthesized material, along with rigorous stereochemical assignment of the final product, suggest that the structure of mucoxin has been misidentified.

**Synthetic Strategy.** The initial retrosynthesis is outlined in Figure 1. We planned to construct both the C2−C35 and C10−C11 bonds simultaneously using a tandem Grubbs' ring-closing metathesis (RCM) of intermediate **2**, followed by an in situ hydrogenation.[26] The RCM precursor **2** would be synthesized via a regioselective ring opening of vinyl epoxide **3** with allylic alcohol **4**. The vinyl group in **3** was placed to serve a dual function: first, to direct the epoxide ring opening to C9 with the C12−OH in **4** as the nucleophilic moiety, and later, to serve as a participant in the RCM reaction. Intermolecular epoxide ring opening by alcohols often requires forcing conditions and a large excess of the nucleophile.[27−33] In light of this, the proposed union of densely functionalized reactants **3** and **4** was deemed rather challenging in our synthetic design. Nonetheless, if successful, this approach would provide a strategically novel and expeditious route to this class of natural products. Synthesis of allylic alcohol **4** would be accomplished via a 1,2-chelation-controlled addition of vinylmagnesium bromide to THF aldehyde **5**. The trisubstituted THF **5** would be accessed using a Lewis-acid-catalyzed, thiophenyl-directed, intramolecular ring opening of bis-protected epoxydiol **6** under our previously optimized conditions.[20,21] The thiophenyl directing group would channel the cyclization via intermediacy of the episulfonium ion (see Scheme 2 for the general structure of the episulfonium intermediate), thus leading to a net retention of the requisite configuration at C13. In addition, the choice of this directing group allows for the use of the corresponding *trans*-allylic alcohol as the Sharpless asymmetric epoxidation (SAE) precursor, a class of olefins known to exhibit optimal enantioselectivity in the SAE reaction.[34]

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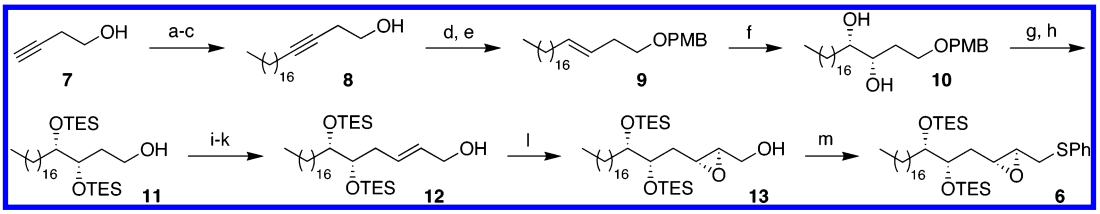
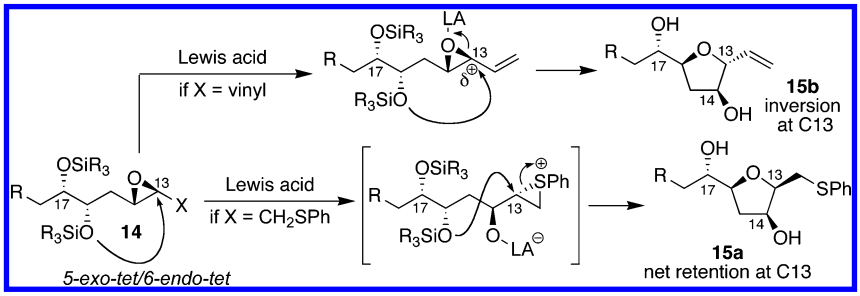
**SCHEME 1. Synthesis of Epoxysulfide 6**[a]




[a] (a) TBSCl, imid., DMF, room temperature (73%); (b) *n*-BuLi, $CH_3(CH_2)_{16}I$, THF/HMPA (3:1), 0 °C (80%); (c) TBAF, THF, −10 °C (90%); (d) LAH, diglyme, 125 °C (87%); (e) NaH, PMBCl, TBAI, THF, 60 °C (91%); (f) AD-mix-α, $MeSO_2NH_2$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH/$H_2O$ (1:1), 0 °C (92%); (g) TESCl, $Et_3N$, DMAP, THF, room temperature, (quantitative); (h) DDQ, $CH_2Cl_2$/pH 7 phosphate buffer (10:1), 0 °C (78%); (i) $PhI(OAc)_2$, TEMPO, $CH_2Cl_2$, room temperature (96%); (j) $Ph_3P{=}CHCO_2Et$, THF, reflux (91%); (k) DIBALH, $Et_2O$, 0 °C (89%); (l) (D)-DIPT/$Ti(O^iPr)_4$ (1.2:1.0), *t*-BuOOH, MS 4 Å, $CH_2Cl_2$, −20 °C (73%); (m) $(PhS)_2$, $Bu_3P$, TEA, 0 °C to room temperature (94%).

**SCHEME 2. 5-*Exo-tet*/6-*Endo-tet* Ring Closure through Activation of C13 by Either a Pendant Vinyl Group or a *β*-Thiophenyl Ether**




## Results and Discussion

**Synthesis of Epoxydiol 6.** Synthesis of bis-protected epoxydiol **6** was accomplished starting with commercially available 3-butynol (**7**), as outlined in Scheme 1. Alkylation of lithium acetylide derived from TBS-protected **7** with 1-iodoheptadecane in THF/HMPA (3:1) afforded the homopropargylic TBS ether. TBAF-mediated silyl deprotection furnished homopropargylic alcohol **8**, which was transformed to the corresponding *E*-homoallylic alcohol in a completely stereoselective manner by LAH reduction, and the alcohol was protected as a PMB ether to afford **9**. Sharpless asymmetric dihydroxylation reaction (AD-mix-α)[35] of **9** provided diol **10** in excellent yield and enantioselectivity (>98% ee as determined by Mosher's ester analysis),[36] which was subsequently protected with TESCl. After some experimentation, we found that the use of phosphate buffer (pH 7) was crucial to achieve deprotection of the PMB group with minimal loss of the TES groups. The resultant free alcohol **11** was transformed into the allylic alcohol **12** via $PhI(OAc)_2$/TEMPO-mediated oxidation to aldehyde,[37] Wittig olefination with (carbethoxymethylene)triphenyl phosphorane, and subsequent reduction with DIBAL−H. Sharpless asymmetric epoxidation of allylic alcohol **12** required significant optimization. Ultimately, we were able to obtain the desired epoxy alcohol in excellent diastereoselectivity (>98:2, by $^1H$ NMR) and good yields (73%) only under stoichiometric conditions using (D)-DIPT/$Ti(O^iPr)_4$ (mol ratio = 1.2:1.0). Finally, epoxy alcohol **13** was converted to the requisite thiophenyl derivative **6** using Hata conditions.[38]

**Synthesis of the Left-Hand Fragment (C12−C34) 5.** We next turned our attention to the neighboring-group-assisted cyclization of bis-protected epoxydiol **6**. Intramolecular ring opening of an epoxydiol system of the general structure **14** (Scheme 2) can potentially lead to several different cyclic ethers depending upon which of the two hydroxyl groups participates, which epoxidic carbon is the site of ring opening, and the stereochemical outcome (retention vs inversion) at the point of cyclization. In our earlier investigations, we had demonstrated that by the appropriate choice of directing group X, the acid promoter, and reaction conditions, cyclization of an epoxydiol such as **14** could be directed along one of the many available avenues in a stereo- and regiocontrolled manner.[20,21] To construct the C12−C17 hydroxylated THF ring of mucoxin, we would need to accomplish a disfavored 5-*exo-tet*/6-*endo-tet* ring closure (see Scheme 2, structure **14**), which could be achieved by utilizing either a vinyl group (resultant product **15b** with inversion of stereochemistry at C13) or a thiophenyl group (resultant product **15a** with retention of stereochemistry at C13) as the X-directing moiety (Scheme 2).[39−45] The vinyl group adjacent to the epoxide would stabilize the incipient carbocation, thus favoring attack at C13 (Scheme 2, X = vinyl). In a complimentary fashion, positioning of a thiophenyl ether *β* to an epoxide would lead to the product with the same regiochem-

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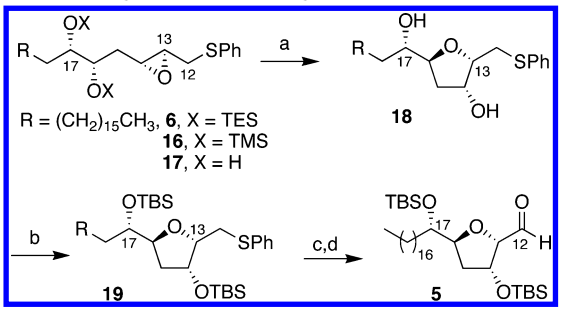
**SCHEME 3. Synthesis of Aldehyde 5**[a]




[a] (a) $BF_3{\cdot}OEt_2$ (6 equiv), $Et_2O$ (0.04 M), 0 °C to room temperature (56%); (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C (91%); (c) *m*-CPBA, $CH_2Cl_2$, 0 °C (quantitative); (d) (i) TFAA, 2,6-lutidine, $CH_2Cl_2$, 0 °C; (ii) $NaHCO_3$ (solid), $CH_3CN$ (63% over two steps).

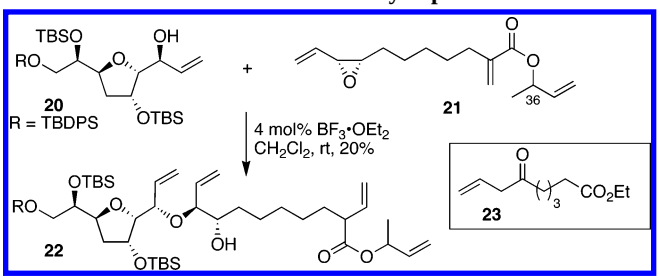
istry, however, with the opposite stereochemistry at the site of ring closure (Scheme 2, X = $CH_2SPh$). In this case, activation of the epoxide with a Lewis acid yields an intermediate episulfonium ion, which upon subsequent intramolecular ring opening (consequently, a double inversion at C13) yields the product. The desire to use a *trans*-olefin for the asymmetric epoxidation necessitated the use of the thiophenyl directing group to retain the stereochemistry at C13, which was obtained in high ee from the SAE reaction.

We were pleased to find that exposure of **6** to $BF_3{\cdot}OEt_2$ under our standard conditions (Scheme 3) led to formation of the desired THF diol **18** in 56% yield, which could be cleanly separated from a 20% yield of an inseparable mixture of other isomeric cyclic diols.[20] Treatment of bis-TMS-protected epoxydiol **16** as well as free diol **17** with $BF_3{\cdot}OEt_2$ resulted in a similar mixture of products indicating that the relative rates of silyl deprotection and episulfonium ion capture may not be a factor in determining the regioselectivity. Attempts to improve the regioselectivity in the cyclization of **6** by changing solvents, concentration, temperature, and acid promoters were unsuccessful. Utilization of modified conditions reported previously[21] (PPTS in $CH_2Cl_2$) did result in a higher yield of **18** (75%), but the side products produced under these conditions could not be separated efficiently; thus, for scaleup, it proved advantageous to utilize the lower yielding Lewis acid conditions.

The hydroxyl groups in **18** were protected as TBS ethers (**19**), and in preparation for the Pummerer rearrangement,[46,47] the thiophenyl group was oxidized to the corresponding sulfoxide in quantitative yield using *m*-CPBA. The sulfoxide was then reacted with trifluoroacetic anhydride in the presence of 2,6-lutidine to afford the anticipated α-trifluoroacetoxy sulfide intermediate. Treatment of this intermediate with a variety of hydrolyzing agents including saturated aqueous $NaHCO_3$, aqueous $CuCl_2$, aqueous $HgCl_2$, wet $SiO_2$, 5% HCl, and $Na_2CO_3$ in MeOH either led to incomplete hydrolysis or decomposition.[48,49] Ultimately, we found that treatment with solid $NaHCO_3$ in a solution of $CH_3CN$ for 18 h followed by slow elution of the product on a wet silica gel (10% $H_2O$) column provided aldehyde **5** in good yield.

**Attempted Intermolecular Epoxide Ring Opening Using Model Systems.** As mentioned previously, the intermolecular union of **3** and **4** (Figure 1) was deemed challenging for a variety

**SCHEME 4. Model Study of the Regioselective Intermolecular Etherification of Vinyl Epoxide 21**




of factors. For the purposes of initial exploration and optimization of the proposed coupling, we decided to employ model allylic alcohol **20** and vinyl epoxide **21**. Compound **20** was obtained through the 1,2-chelation control addition of vinylmagnesium bromide to the appropriate aldehyde precursor (not shown). This aldehyde precursor, which served as a model for **5**, was accessible from 2-deoxy-D-ribose via a much shorter reaction sequence.[20] Vinyl epoxide **21** is akin to **3** except in that the former is a racemate at C36 (see Supporting Information for synthesis of **21**). After extensive screening of a variety of acid promoters, transition-metal activators, solvents, and temperatures, the best result obtained for the coupling reaction is shown in Scheme 4. Exposure of a mixture of **20** and **21** to a catalytic amount of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at 1.0 M concentration afforded the desired coupled product (**22**) in 20% yield.[50] In most cases, unreacted allylic alcohol was recovered unharmed, whereas the vinyl epoxide component was rapidly consumed. In retrospect, this is not surprising because Jung and co-workers and others have demonstrated that vinyl epoxides undergo a facile 1,2-hydride shift to yield the corresponding nonconjugated enone.[51−57] In fact, we were able to isolate $\beta,\gamma$-unsaturated ketone **23** on many occasions.

At this juncture, we decided to pursue a revised synthetic plan in which the left-hand portion was conserved as aldehyde **5**, whereas the right-hand THF ring would be built via manipulations of the bishomoallylic alcohol **26** (Figure 2). More specifically, the triol derived from the asymmetric dihydroxylation of olefin **26** would serve as the precursor for our newly disclosed 1,2-*n*-triol cyclization strategy.[25] The one-pot cyclization of 1,2-*n*-triols is achieved through the in situ formation of an ortho ester (Scheme 5), which upon treatment with a Lewis acid yields a reactive acetoxonium intermediate.[22−25] Intramolecular attack by the free hydroxyl group yields the cyclic ether ring with inversion of stereochemistry at the site of ring formation. The latter methodology can be thought of as equating

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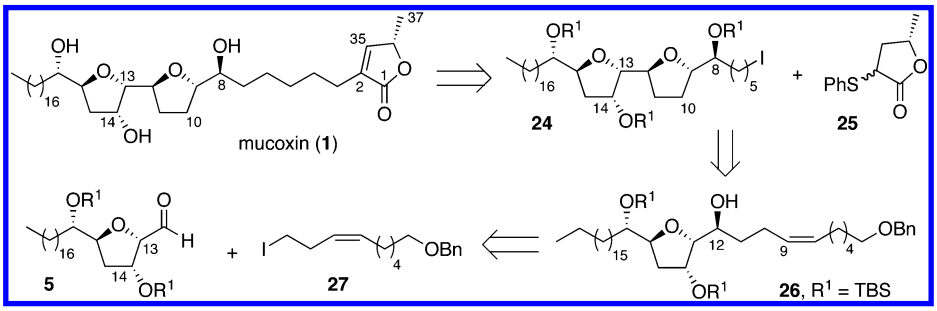
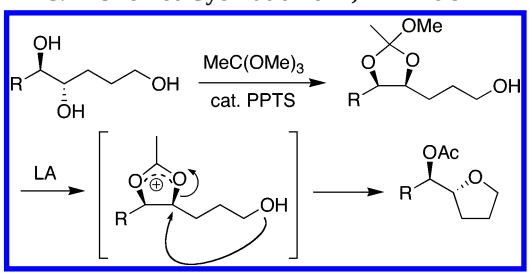
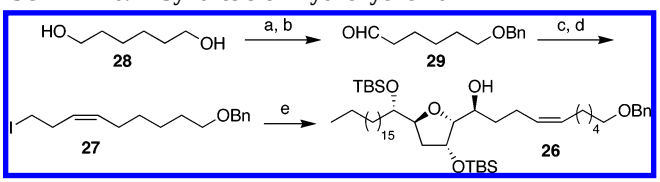



**FIGURE 2.** Revised retrosynthesis for construction of the disubstituted THF ring.

**SCHEME 5. One-Pot Cyclization of 1,2-*n*-Triols**




**SCHEME 6. Synthesis of Hydroxyene 26[a]**




[a] (a) NaH, BnBr, TBAI, THF, 60 °C (78%); (b) PCC, $CH_2Cl_2$, room temperature (82%); (c) $Ph_3P(CH_2)_3OHBr$, KHMDS, TMSCl, then AcOH/THF/$H_2O$ (6:3:1), 0 °C (83%); (d) (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (ii) NaI, acetone, reflux, 77%; (e) *t*-BuLi, −100 °C, $MgBr_2{\cdot}OEt_2$, $Et_2O$, −95 °C then **5**, $MgBr_2{\cdot}OEt_2$, −40 °C (88%).

the reactivity of a 1,2-diol functionality to an epoxide. This can be advantageous in many cases where utilizing the SAD reaction simplifies the synthetic scheme as compared to using the SAE reaction, which requires more stringent structural prerequisites for high enantioselectivity. This methodology compliments the use of cyclic sulfates and sulfites in transforming 1,2-diols into reactive species.[58,59] However, as was the case in our studies, formation of the cyclic sulfates and sulfites can at times be difficult and substrate dependent.

The development of the 1,2-*n*-triol cyclization was necessitated as a result of unsuccessfully exploring other options to stereoselectively install a homoallylic epoxide in **26**. An example of such, found in the acetogenin literature, is the hydroxy-directed, $VO(acac)_2$/$^t$BuOOH-mediated epoxidation−cyclization method pioneered by Kishi.[60] A limitation of this methodology, however, is that depending upon the structure of the parent hydroxy olefin the epoxidation may occur with low facial selectivity. In addition, because stereocontrol is substrate derived, this method lacks versatility that would allow access to other unnatural stereoisomers of the natural product. Other potential options for stereoselective epoxidation include the Jacobsen and Shi epoxidation reactions; however, olefin **26** lacks the specific structural features required for optimal stereoselectivity under the two protocols.[34,61−63] In view of the above limitations, the one-pot 1,2-*n*-triol cyclization method offered a promising alternative that would alleviate the difficulties posed by traditional methods.

In the new synthetic scheme, the terminal butenolide ring would be installed by displacement of bistetrahydrofuran iodide **24** by known α-thiophenyl γ-methyl lactone **25**[64] and subsequent oxidation/syn elimination of the thiophenyl group (Figure 2). The olefinic precursor **26** for the AD and triol cyclization would be assembled via 1,2-chelation-controlled addition of an organometallic reagent derived from iodide **27** and aldehyde **5**.

**Synthesis of Bishomoallylic Alcohol 26.** The synthetic strategy now required elaboration of aldehyde **5** to alcohol **26** by chelation control addition of a suitable organometallic reagent derived from iodide **27** (Figure 2). Synthesis of **27** could be accomplished in a concise manner, as shown in Scheme 6. Commercially available 1,6-hexane diol **28** was monoprotected and oxidized to provide aldehyde **29**. The *Z*-selective Wittig olefination of **29** with 3-hydroxypropyltriphenylphosphonium bromide was achieved by in situ protection of the ylide's hydroxy group as a TMS ether, which was cleaved during workup using aqueous acetic acid.[65,66] The desired homoallylic alcohol was obtained in >10:1 diastereoselectivity. Finally, mesylation of the alcohol and ensuing displacement by sodium iodide furnished target iodide **27**.

Derivatization of **27** as a Grignard reagent for the chelation control addition required some optimization. Upon reacting **27** (or its bromide counterpart) with metallic magnesium under reflux, only the corresponding homodimer and diene from elimination of the iodide (not shown) were detected.[67,68] Successful preparation of the Grignard reagent entailed, first, a low-temperature lithium−halogen exchange followed by transmetalation with freshly prepared $MgBr_2{\cdot}OEt_2$ at −95 °C.[69,70]

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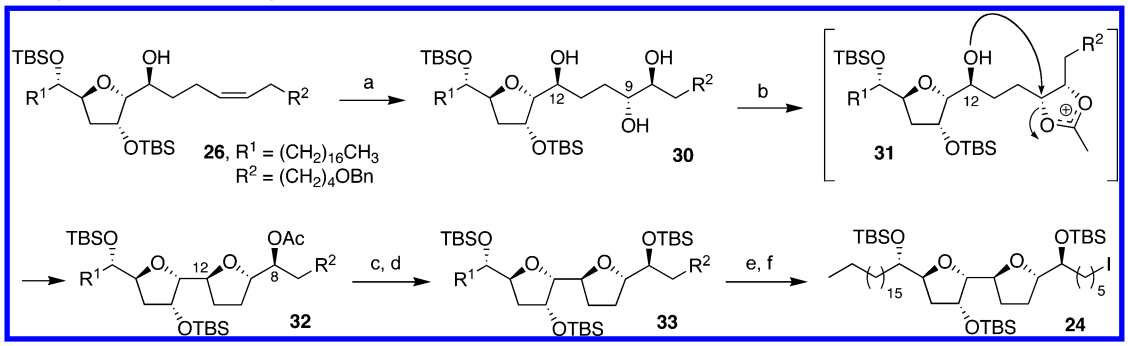
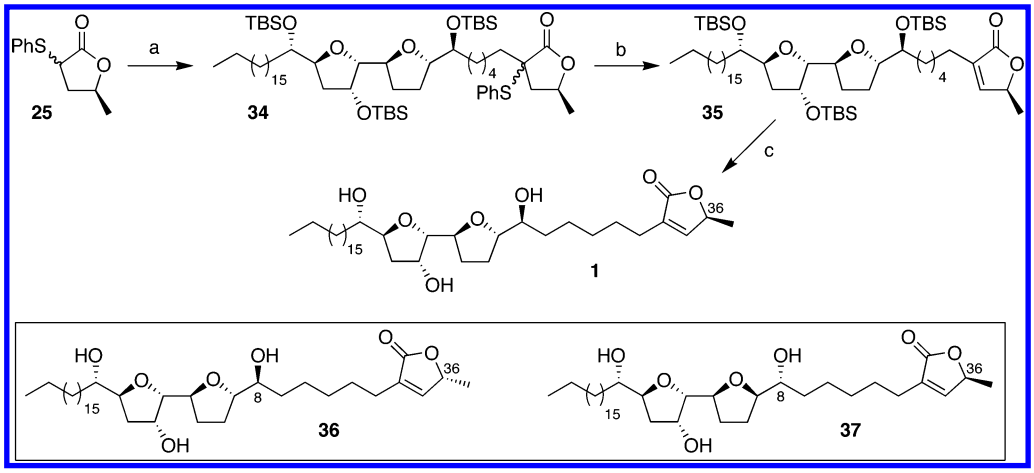
**SCHEME 7. Synthesis of Bistetrahydrofuran 24**[a]




[a] (a) AD-mix-α, $MeSO_2NH_2$, $K_2OsO_4 \cdot 2H_2O$, 0 °C (88% yield, dr = 5:1); (b) $MeC(OMe)_3$, PPTS (10 mol %), $CH_2Cl_2$, room temperature, then $BF_3 \cdot OEt_2$ (25 mol %); (c) $K_2CO_3$, MeOH, room temperature; (d) TBSOTf, 2,6-lutidine, 0 °C (90%, 3 steps); (e) $H_2$, Pd/C, EtOAc/*i*-PrOH (1:1), room temperature (92%); (f) $PPh_3$, imid., $I_2$, toluene, room temperature (87%).

**SCHEME 8. Completion of the Synthesis of the Proposed Structure of Mucoxin (1)**[a]




[a] (a) LDA, **24**, THF/HMPA (4:1), 0 °C−room temperature (87%); (b) (i) *m*-CPBA, $CH_2Cl_2$, 0 °C; (ii) toluene, reflux (84% over two steps); (c) HF·Py, THF, room temperature (80%).

The organometallic reagent was then treated with aldehyde **5**, also precomplexed with $MgBr_2 \cdot OEt_2$ at −40 °C. Following this optimized procedure, the desired alcohol **26** was isolated as a single diastereomer. The absolute configuration of the newly formed stereocenter was confirmed as *S* by standard Mosher's ester analysis.

**Synthesis of Bistetrahydrofuran Iodide 24.** We now focused our efforts on constructing the C8−C12 THF ring. The hydroxy olefin **26** was transformed to triol **30** by Sharpless asymmetric dihydroxylation using AD-mix-α (Scheme 7). While positioning olefin **26** according to the stereochemical model of the AD reaction, we reasoned that the unbranched alkyl substituent might preferentially occupy the SW quadrant as compared to the highly oxygenated THF portion.[35,71] In this orientation, AD-mix-α would attack the olefin from the *si* face to afford the 8*S*,9*R* isomer **30**. Stereoselectivity in the AD reaction of *Z*-disubstituted olefins is generally less than optimal,[72] but to our satisfaction, we obtained the desired triol **30** in a 5:1 diastereomeric ratio and 88% yield. Absolute configuration of the newly formed 8,9-diol was established only after the cyclization reaction.

Treatment of **30** with trimethyl orthoacetate and 10 mol % PPTS followed by addition of catalytic $BF_3 \cdot OEt_2$ led to cyclization of the triol to provide **32** in excellent yield. The reaction was accompanied by TBS cleavage to a small extent (8%). However, the free hydroxy groups could be easily reprotected using TBSOTf/2,6-lutidine, which resulted in isolation of **32** in overall 99% yield. The reaction proceeds via exo cyclization of the reactive acetoxonium intermediate **31**, thereby inverting the configuration at C9. After deacetylation of the hydroxyl group, the absolute configuration at C8 in **32** was confirmed as *S* by Mosher's ester analysis. The trans relationship across the C9−C12 THF ring was confirmed by nuclear Overhauser effect (nOe) experiments. Under the optimized conditions, the three-step conversion of triol **30** to tris-TBS ether **33** could be achieved without purification of the intermediates in excellent overall yield (Scheme 7).

**Completion of the Synthesis.** With the bistetrahydrofuran core in place, the final task was installation of the terminal butenolide ring. Debenzylation of **33** with $H_2$ over Pd/C afforded the corresponding free alcohol. Subsequently, iodination of the alcohol was accomplished by treatment with $PPh_3$ and $I_2$ to secure iodide **24** (Scheme 7).

The final stages of the synthesis are outlined in Scheme 8. α-Phenylthio-γ-lactone **25** was synthesized by White's procedure from commercially available thiophenyl acetic acid.[64] Optimized conditions for coupling of lactone **25** with iodide

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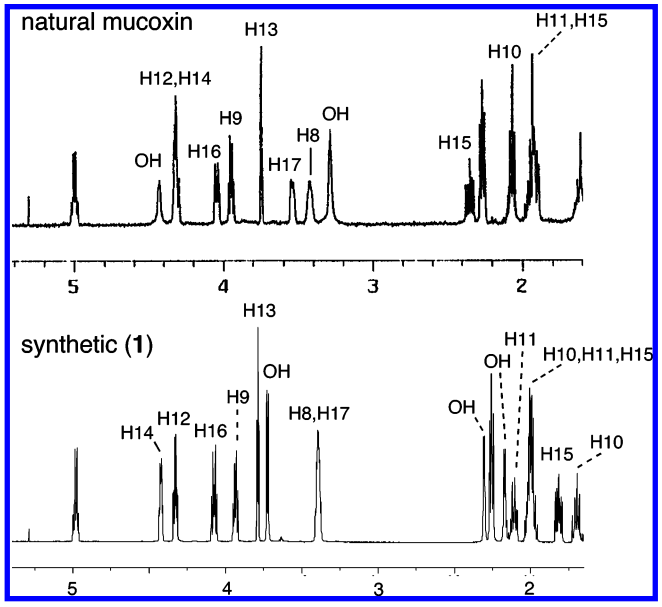
(72) Johnson, R. A.; Sharpless, K. B. Catalytic asymmetric dihydroxylation-discovery and development. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 357−398.

**TABLE 1. $^1$H NMR Comparison of the Natural and Synthetic Mucoxin**




| proton | **1** | natural mucoxin | Δδ (**1**-natural) |
|---|---|---|---|
| $H_8$ | 3.41 | 3.42 | −0.01 |
| $H_9$ | 3.96 | 3.95 | +0.01 |
| $H_{10}$ | 1.84, 2.02 | 1.91, 2.05 | −0.07, −0.03 |
| $H_{11}$ | 2.02, 2.13 | 1.91, 2.05 | 0.11, 0.08 |
| $H_{12}$ | 4.35 | 4.31 | 0.04 |
| $H_{13}$ | 3.80 | 3.71 | 0.09 |
| $H_{14}$ | 4.44 | 4.32 | 0.12 |
| $H_{15}$ | 1.84, 2.02 | 1.91, 2.35 | −0.07, −0.33 |
| $H_{16}$ | 4.09 | 4.04 | 0.05 |
| $H_{17}$ | 3.41 | 3.53 | −0.12 |

**24** involved LDA-mediated α-deprotonation of **25**, which was then reacted with **24** in THF/HMPA (4:1) to afford adduct **34**. Treatment with *m*-CPBA in $CH_2Cl_2$ led to the syn elimination of the sulfoxide in refluxing toluene to afford exclusively the internal α,*β*-unsaturated lactone **35**. Finally, global deprotection of **35** using HF·Py occurred uneventfully to furnish target molecule **1**, which was isolated in high purity after HPLC. The structure of **1** was confirmed by $^1$H, $^{13}$C, COSY, and nOe NMR experiments.

**Comparison of Spectral Data of the Synthetic and Natural Mucoxin.** Both $^1$H and $^{13}$C NMR spectra of the synthetic sample (**1**) differed from the published spectra of the natural compound.[19] Major differences in the $^1$H NMR spectra resided within the bistetrahydrofuran (C8−C17) region (Table 1). In particular, H11, H14, H15, and H17 in **1** exhibited differences of greater than 0.1 ppm as compared to the reported spectrum of the natural mucoxin. In an attempt to trace the sources of the discrepancies, we synthesized two stereoisomers of **1** (Scheme 8). Isomer **36** is the C36 epimer, and **37** is the C8,C9 epimer of **1**. Starting from hydroxy olefin **26**, **37** was obtained by following the same reaction sequence as that outlined in Schemes 7 and 8, with the exception that AD-mix-*β* was used in the Sharpless asymmetric dihydroxylation reaction of **26** (Scheme 7). As a result, the C9−C12 THF in **37** bears a cis instead of the proposed trans relationship across the ring. $^1$H and $^{13}$C NMR spectra of diastereomer **36** were found to be identical with those of **1** indicating that configuration at C36 is inconsequential. On the other hand, spectral mismatches between **37** and the natural compound were even greater. We therefore

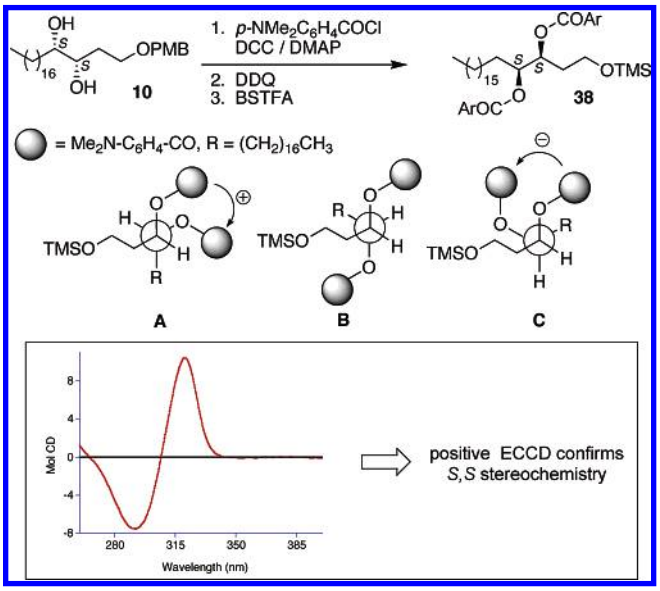



**FIGURE 3.** ECCD of the C16,C17 diol confirms the desired *S*,*S* stereochemistry.

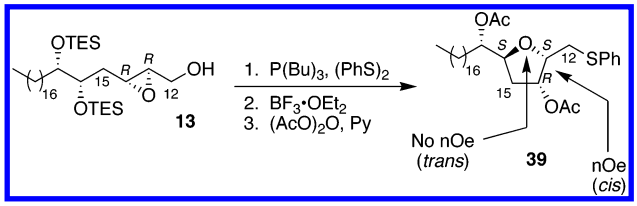



**FIGURE 4.** Lack of nOe correlation between H13 and H16 corroborates the trans stereochemistry, which is possible only if the SAE reaction proceeded with the predicted stereochemistry (*cis*-H13/H16 does exhibit nOe; data not shown).

refocused our attention on the original synthetic material (**1**) for further analysis.

Asymmetric reactions employed for installation of each of the stereogenic centers in the C8−C17 portion of **1** and the analytical experiments used for assignment of their relative and absolute configurations are described below.

The C16 and C17 stereocenters were set using the Sharpless asymmetric dihydroxylation (AD) reaction of olefin **9** (Scheme 1). On the basis of the mnemonic device for the AD reaction, **9** was positioned so that the long hydrocarbon chain occupied the SW quadrant.[35] In this orientation, AD-mix-α would react from the *si* face to afford the *S*,*S*-diol **10** as the major enantiomer. The enantioselectivity of the AD reaction was determined to be >99:1 on the basis of $^1$H NMR of the chiral bis-Mosher ester derivative of **10**. The absolute configuration of the diol, on the other hand, was established independently by exciton coupled circular dichroism (ECCD) spectroscopy.[73] Bis-4-dimethylamino benzoate derivative **38** proved most suitable for the ECCD analysis (Figure 3).[74,75] Out of the three possible staggered conformations (**A**, **B**, and **C**) of **38**, **B** is ECCD inactive because the angle between the transition dipoles

(73) Berova, N.; Nakanishi, K.; Woody, R. *Circular dichroism: principles and applications*, 2nd ed.; Wiley-VCH: New York, 2000; p xix, p 877.

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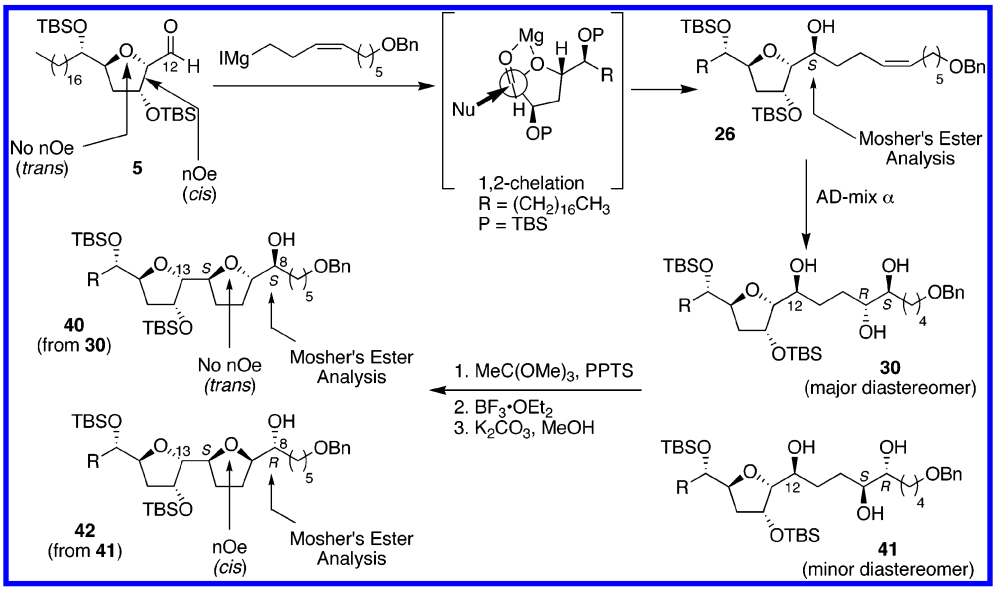


**FIGURE 5.** Stereochemical assignment of C12, obtained through the anticipated chelation with the THF ring oxygen, was confirmed by Mosher ester analysis of the ester derived from **26**. The stereochemistry of the dihydroxylation reaction was verified after cyclization in two independent manners. The stereochemistry of C8−OH was analyzed by Mosher ester analysis of both the major and the minor diastereomer. Also, lack of nOe correlation between H12 and H9 in the diastereomer **40** obtained from the major product **30**, in conjuction with observable nOe's for the same protons in the diastereomer **42** obtained from the minor product **41**, verified the assignment of the dihydroxylation reaction.

of the two chromophores is 180°. Conformer **A**, which bears two gauche interactions is expected to be lower in energy and hence preferred over conformer **C**, which suffers from three gauche interactions. The clockwise orientation of the transition dipole moments of the coupling chromophores in conformer **A** should lead to a positive ECCD. Thus, if the absolute configuration of diol **10** is *S*,*S*, its dibenzoate derivative **38** is expected to produce a positive ECCD spectrum. We indeed observed positive ECCD for **38** in various solvents ranging from cyclohexane to methanol. A representative spectrum of **38** in MeCN is shown in Figure 3, which confirms the assigned configuration of diol **10**.

Next, assignment of the C13 and C14 stereocenters, which were established via the SAE reaction, were examined (Figure 4). The configuration at the two oxirane carbons was assigned as *R*,*R* on the basis of the mnemonic for the SAE reaction.[76] This assignment was confirmed after cyclization of **13**. The THF diol generated after thiophenyl-directed epoxydiol cyclization (**6** to **18**, Scheme 3) was derivatized as its corresponding bisacetate **39** for ease of characterization (Figure 4). A 2,5-trans relationship across the THF ring was established by the absence of a nOe signal between H13 and H16, where a strong positive nOe signal between H13 and H14 was indicative of the cis relation.[77] Lack of nOe's, especially in five-membered rings, must be examined carefully because of pseudoaxial−axial disposition of hydrogens in a 1,3-relationship. To confirm the nOe result, the corresponding 2,3,5-trisubstituted THF ring with cis 2,5-appendages was synthesized and positive nOe results were obtained (data not shown). Because the absolute configuration at C16 was confirmed as *S* (vide supra), in combination with the nOe experiments discussed above, the stereochemistries of C13 and C14 after cyclization were confirmed as *S* and *R*, respectively. Extrapolation back to the parent epoxide **13** supports the *R*,*R*-epoxide stereochemistry predicted by the mnemonic.

Next, we examined the Pummerer rearrangement depicted in Scheme 3 (conversion of **18** to **5**). The 2,3-cis-5-trans relative configuration about the THF ring in **5** was reconfirmed by nOe experiments, which conclusively established that the C13 stereocenter was not epimerized under the Pummerer conditions (Figure 5). 1,2-Chelation-controlled addition of a Grignard reagent derived from iodide **27** to aldehyde **5** set the C12 stereocenter. The stereochemistry of the newly formed secondary alcohol was confirmed as *S* with Mosher's ester analysis using both *R* and *S* Mosher's ester derivatives.

Olefin **26** was transformed to triol **30** by the AD reaction. Dihydroxylation of a 1,2-disubstituted *cis*-olefin can lead to either a *S*,*R*- or *R*,*S*-diol. In our case, the *S*,*R* isomer **30** was the desired diastereomer. Triol **30** was isolated as a single diastereomer in 74% yield (14% of the other diastereomer (**41**) could be separated by column chromatography). The absolute configuration of **30** was established after cyclization that afforded the hydroxy THF **40**. The C8 hydroxyl group in **40** was derivatized as *R* and *S* Mosher's esters and based on standard $^1$H NMR analysis of both derivatives; the configuration at C8 was assigned as *S*. This also established the *R* configuration at C9 for triol **30**. Moreover, 1D-NOESY experiments showed no nOe correlation between H9 and H12 in **40**, suggesting a trans relationship between the two hydrogens.

(76) Johnson, R. A.; Sharpless, K. B. Catalytic asymmetric epoxidation of allylic alcohols. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 231−280.

(77) Vicinal protons on substituted THF rings often do give rise to nOe's regardless of their relative geometries. Therefore, the presence of a strong nOe between H13 and H14 does not conclusively establish the cis configuration of substituents at C13 and C14. However, stereochemistry at C13/C14 arises from the SAD reaction of a *trans*-olefin, which must yield a *trans*-epoxide. Although it is very unlikely that the undesired diastereomer is obtained during the asymmetric epoxidation, to allow for that possibility, the relationship between H16 and H13 would have to be necessarily cis after cyclization to the tetrahydrofuran ring (note that the retention of stereochemistry during the cyclization reaction has been clearly demonstrated in ref 20). Because the trans stereochemistry is clearly established between H13 and H16, the assigned and expected cis relationship between H13 and H14 is further supported.

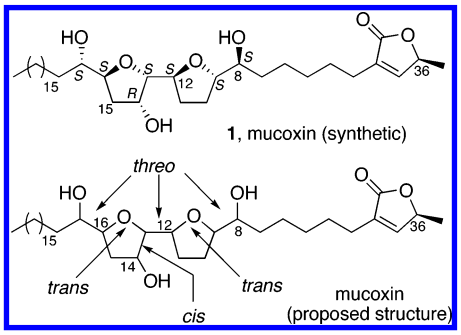


**FIGURE 6.** Structure of synthetic mucoxin (**1**) and proposed mucoxin.

Conversely, cyclization of the minor isomer from the AD reaction (**41**) did yield a *cis*-THF ring product (**42**) that exhibited nOe correlation, further confirming the relative and absolute stereochemical assignments.

On the basis of the extensive spectroscopic analysis, we reason that the configuration of the C8−C17 portion of synthetic mucoxin (**1**) is as shown in Figure 6 and that it is identical to the proposed relative stereostructure for natural mucoxin.[19] In addition, from the published 2D-COSY and HRMS fragmentation of the tri-TMS derivative of natural mucoxin, we believe that the proposed structure for natural mucoxin is constitutionally correct. It is therefore likely that the spectral discrepancies are due to stereochemical misassignment(s) of the natural sample. Our synthetic scheme has been so devised that several diastereomers of the C8−C17 core can be prepared by reagent control and/or by way of minor changes in substrate structure.

## Summary

We have synthesized the proposed structure of mucoxin (**1**) in 32 steps (26 steps along the longest linear sequence). The synthesis features two regio- and stereoselective THF ring-forming methods developed in our laboratory. The trisubstituted hydroxy THF ring (C13−C17) was constructed using neighboring-group-directed epoxydiol cyclization,[20] and the disubstituted THF (C8−C12) was synthesized by a one-pot 1,2-*n*-triol cyclization strategy.[25] Because the epoxydiol and polyol precursors for the cyclization reactions were assembled via Sharpless asymmetric epoxidation and dihydroxylation reactions, other diastereomers of the C8−C17 core can be easily built simply by using the appropriate choice of olefin geometry and ligands for the asymmetric reactions. This is particularly advantageous in light of the fact that spectral data for the synthetic and natural materials did not match. On the basis of the spectroscopic evidence, we believe that the structural mismatch is likely due to misassignment of the relative stereochemistry in the C8−C17 core. Further investigations to determine the real structure of mucoxin are currently underway.

## Experimental Section

**Homopropargylic Alcohol 8.** To a 0 °C solution of 3-butyn-1-ol (27 mL, 29.16 g, 0.416 mmol) and imidazole (61 g, 0.896 mmol) in DMF (100 mL) was added a solution of *t*-butyldimethylchlorosilane (64.5 g, 0.428 mmol) in DMF (125 mL), and the mixture was stirred at the same temperature for 40 min under $N_2$. The reaction was then warmed to ambient temperature and stirred for 3 h after which $H_2O$ (500 mL) was added. The aqueous layer was extracted with 4:1 hexanes/EtOAc (4 × 400 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated. After flash column chromatography, the silyl ether was obtained as a colorless oil (62 g, 73%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.74 (t, $J$ = 7.1 Hz, 2 H), 2.40 (dt, $J$ = 7.2, 2.7 Hz, 2 H), 1.95 (d, $J$ = 2.7 Hz, 1 H), 0.90 (s, 9 H), 0.07 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 81.7, 69.5, 69.4, 62.0, 26.1, 23.1, 18.5, −5.1. IR (thin film): 3330, 2954, 2860, 2753, 2711, 2123, 1839, 1590, 1471, 1388, 1255, 1106, 1006, 916, 837, 777, 643 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{10}H_{20}OSi$, 185.1362 *m*/*z* [M + H]$^+$; observed, 185.1361 *m*/*z*.

A solution of this TBS-protected butynol (13.63 g, 74.08 mmol) in THF (113 mL) was cooled to −30 °C. To this, *n*-BuLi (7.8 mL of 9.97 M solution in hexanes, 77.8 mmol) was added dropwise, and the solution was warmed to −10 °C over 1 h. After cooling the lithium acetylide back to −78 °C, 1-iodoheptadecane in 3:1 THF/HMPA (147 mL) was added and the solution was stirred for 10 min at the same temperature. The reaction was allowed to warm to 0 °C over 1 h and then was quenched by adding $H_2O$ (300 mL). The aqueous layer was extracted with $Et_2O$ (3 × 400 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated to afford a crude oil, which was purified by flash column chromatography (hexanes, 19:1 hexanes/EtOAc) to yield the silyl-protected homopropargylic alcohol (26.7 g, 85%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.69 (t, $J$ = 7.06 Hz, 2 H), 2.36 (dt, $J$ = 7.3, 2.4 Hz, 2 H), 2.12 (dt, $J$ = 7.2, 2.4 Hz, 2 H), 1.45 (q, $J$ = 7.1 Hz, 2 H), 1.39−1.23 (m, 30 H), 0.90 (s, 9 H), 0.88 (t, $J$ = 7.01 Hz, 3 H), 0.07 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 81.5, 76.8, 62.5, 31.9, 29.7, 29.6, 29.4, 29.2, 29.1, 28.9, 25.9, 23.2, 22.7, 18.2, 183, 14.1, −5.3. IR (thin film): 2923, 2854, 1466, 1383, 1362, 1253, 1105, 1059, 1007, 916, 837, 777, 721 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{27}H_{54}OSi$, 421.3866 *m*/*z* [M − H]$^+$; observed, 421.3874 *m*/*z*.

To a solution of this silyl-protected homopropargylic alcohol (35.9 g, 0.085 mol) in THF (100 mL) was added TBAF (130 mL of 1 M solution in THF, 0.13 mol) at −20 °C under $N_2$. After stirring for 30 min at the same temperature, $H_2O$ (200 mL) was added. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 400 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (4:1 hexanes/EtOAc) to furnish the homopropargylic alcohol **8** as a white solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.67 (t, $J$ = 6.2 Hz, 2 H), 2.43 (dt, $J$ = 6.2, 2.4 Hz, 2 H), 2.15 (dt, $J$ = 7.2, 2.4 Hz, 2 H), 1.76 (s, br, 1 H), 1.48 (q, $J$ = 7.1 Hz, 2 H), 1.37−1.25 (m, 28 H), 0.88 (t, $J$ = 6.6 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 82.9, 76.2, 61.4, 31.9, 29.8, 29.7, 29.6, 29.4, 29.2, 29.0, 28.9, 23.2, 22.7, 18.8, 14,1. IR (thin film): 2953, 2914, 2848, 1470, 1049, 1018, 874, 752 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{21}H_{40}O$, 307.3001 *m*/*z* [M − H]$^+$; observed, 307.3003 *m*/*z*. Mp = 61−62 °C.

***E*-Homoallylic Alcohol 9.** A 1 L two-necked round-bottom flask fitted with a stir bar and a reflux condenser was charged with LAH (7.7 g, 0.203 mol). To this, a solution of homopropargylic alcohol **8** (35 g, 0.113 mol) in diglyme (350 mL) was carefully added dropwise at 0 °C. While stirring vigorously, the mixture was heated to 125 °C. After 17 h, the reaction was cooled to room temperature, upon which 7.7 mL of $H_2O$ was added dropwise. 15% NaOH (7.7 mL) was then added followed by $H_2O$ (22 mL). The resultant mixture was heated at 50 °C for 45 min and filtered after cooling to ambient temperature. The filtrate was diluted with EtOAc (500 mL) and washed with 1.5 N HCl (5 × 100 mL) to remove diglyme from the organic layer. The organic layer was dried ($Na_2SO_4$) and concentrated. Chromatographic purification of the crude product (19:1 hexanes/EtOAc, 2.3:1 hexanes/EtOAc) yielded the corresponding *E*-homoallylic alcohol (30.5 g, 87%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.58−5.52 (m, 1 H), 5.40−5.34 (m, 1 H), 3.62 (t, $J$ = 6.3 Hz, 2 H), 2.26 (dt, $J$ = 12.5, 6.08, 2 H), 2.00 (dt, $J$ = 14.3, 7.3 Hz, 2 H), 1.48 (s, br, 1 H), 1.36−1.25 (m, 30 H), 0.88 (t, $J$ = 6.8 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 134.4, 125.7, 62.1, 36.1, 32.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 22.7, 14.1. IR (thin film): 3448, 3136, 2914, 2848, 1637, 1470, 1047, 1020,

926, 890, 715 $cm^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{21}H_{42}O$, 309.3157 *m*/*z* $[M - H]^+$; observed, 309.3142 *m*/*z*. Mp = 55−56 °C.

A 1 L round-bottom flask fitted with a reflux condenser was charged with a stir bar and NaH (14 g of 60 wt % dispersion in oil, 0.36 mol). A solution of the above *E*-homoallylic alcohol (37 g, 0.12 mol) in THF (400 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for an additional 1 h. *p*-Methoxybenzyl chloride (25 g, 0.16 mmol) and TBAI (16.5 g, 0.045 mol) were added, and the reaction mixture was heated to 60 °C for 18 h. The reaction was cooled to ambient temperature and carefully quenched by adding saturated $NH_4Cl$ solution. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 300 mL). Combined organic layers were dried ($MgSO_4$) and concentrated to furnish a crude solid, which upon purification by flash column chromatography (49:1 hexanes/EtOAc) afforded the PMB-protected homoallylic alcohol **9** (47 g, 91%, crude yield containing an inseparable impurity, 81% pure yield based on NMR) as a white solid. The PMB-containing impurity observable in the $^1H$ NMR spectrum could not be removed through chromatography; however, it proved inconsequential because it did not retard the next reaction. The product of the next reaction did not contain the impurity after purification and thus was removed at that stage. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.27 (d, $J$ = 8.7 Hz, 2 H), 6.88 (d, $J$ = 8.7 Hz, 2 H), 5.54−5.48 (m, 1 H), 5.45−5.39 (m, 1 H), 4.46 (s, 2 H), 3.81 (s, 3 H), 3.47 (t, $J$ = 7.0 Hz, 2 H), 2.31 (dt, $J$ = 13.5, 6.6 Hz, 2 H), 2.0 (dt, $J$ = 13.9, 6.9 Hz, 2 H), 1.37−1.28 (m, 30 H), 0.9 (t, $J$ = 6.9, 3 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.2, 132.7, 130.7, 129.4, 129.3, 126.2, 113.8, 113.7, 72.5, 70.1, 55.3, 33.1, 32.7, 32.2, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 14.2. IR (thin film): 2954, 2918, 2848, 1969, 1896, 1614, 1522, 1462, 1361, 1246, 1176, 1097, 1030, 964, 822 $cm^{-1}$. HRMS (EI) calcd for $C_{29}H_{50}O_2$, 430.3811 *m*/*z* $[M]^+$; observed, 430.3799 *m*/*z*. Mp = 38−39 °C.

**Diol 10.** A 2 L two-necked round-bottom flask fitted with a mechanical stirrer was charged with AD-mix-α (97.8 g). *t*-BuOH (330 mL) and $H_2O$ (330 mL) were added followed by methanesulfonamide (6.6 g) and $K_2OsO_4 \cdot 2H_2O$ (144 mg). This mixture was stirred until a clear solution was obtained which was cooled to 0 °C. To this was added the olefin **9** (30 g, 0.07 mol) in one portion. The reaction was vigorously stirred at 0 °C for 20 h, after which sodium sulfite (100 g) was added at the same temperature. The mixture was then warmed to room temperature, stirred for 45 min, and then diluted with EtOAc (500 mL) and washed with $H_2O$ (200 mL). The aqueous layer was extracted with EtOAc (3 × 300 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated to yield a crude solid which was purified by flash column chromatography (9:1 hexanes/EtOAc, 2:3 hexanes/EtOAc) to yield diol **10** (32.5 g, 92% yield, >98% ee as determined after derivatization of diol with (*R*)-Mosher acids). $[\alpha]^{20}_D$ −2.0 (*c* 1.0, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.24 (d, $J$ = 8.4 Hz, 2 H), 6.88 (d, $J$ = 8.4 Hz, 2 H), 4.45 (s, 2 H), 3.80 (s, 3 H), 3.72−3.62 (m, 3 H), 3.42−3.39 (m, 1 H), 1.89−1.74 (m, 2 H), 1.44−1.50 (m, 3 H), 1.33−1.21 (m, 31 H), 0.88 (t, $J$ = 6.8 Hz, 3 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.4, 129.8, 129.4, 113.9, 74.3, 73.7, 73.1, 68.3, 55.3, 33.6, 33.2, 32.0, 29.7, 29.6, 29.5, 29.4, 25.8, 22.7, 14.1. IR (thin film): 3354, 2916, 2848, 1612, 1514, 1467, 1369, 1248, 1178, 1114, 1035, 814 $cm^{-1}$. HRMS (EI) calcd for $C_{29}H_{52}O_4$, 464.3866 *m*/*z* $[M]^+$; observed, 464.3875 *m*/*z*. Mp = 75−77 °C.

**Alcohol 11.** To a solution of the diol **10** (29 g, 0.062 mol) in THF (600 mL) was added triethylamine (202 mL) followed by triethylsilyl chloride (63 mL, 0.374 mol) and DMAP (2.9 g, 0.024 mol) at ambient temperature. The reaction was stirred under $N_2$ for 3 h, after which it was quenched by adding a saturated $NaHCO_3$ solution (400 mL). The aqueous layer was extracted with 1:5 EtOAc/hexanes (3 × 500 mL) to afford crude oil, which was purified by column chromatography (35:1 hexanes/EtOAc) providing the fully protected triol (43 g, quantitative). $[\alpha]^{20}_D$ −17.5 (*c* 3.0, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.26 (d, $J$ = 8.6 Hz, 2 H), 6.87 (d, $J$ = 8.6 Hz, 2 H), 4.43 (s, 2 H), 3.81 (s, 3 H), 3.78−3.74 (m, 1 H), 3.58−3.51 (m, 3 H), 2.04−2.00 (m, 1 H), 1.63−1.43 (m, 3 H), 1.35−1.19 (m, 30 H), 1.00−0.88 (m, 21 H), 0.63−0.51 (m, 12 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 159.0, 131.0, 129.1, 113.6, 75.3, 72.3, 72.1, 67.5, 55.3, 31.9, 30.6, 30.2, 29.9, 29.7, 29.6, 29.4, 26.7, 22.7, 14.1, 7.0, 6.9, 6.6, 6.4, 5.8, 5.2, 5.1. IR (thin film): 3324, 2924, 2856, 2071, 2003, 1876, 1614, 1587, 1513, 1461, 1414, 1379, 1301, 1247, 1172, 1099, 1014, 825, 738 $cm^{-1}$. HRMS (EI) calcd for $C_{41}H_{80}O_4Si_2$, 692.5595 *m*/*z* $[M - H]^+$; observed, 692.5567 *m*/*z*.

To a 0 °C solution of the protected triol (15 g, 0.02 mol) in 460 mL of $CH_2Cl_2$/phosphate buffer (10:1) was added DDQ (5.7 g, 0.03 mol) in one portion. After stirring the reaction under $N_2$ at the same temperature for 90 min, saturated $NaHCO_3$ solution (200 mL) was added. The mixture was warmed to ambient temperature and carefully extracted with $CH_2Cl_2$ (3 × 200 mL) to avoid emulsions. The combined organic layers were dried ($Na_2SO_4$) and concentrated, and the crude oil was purified by flash column chromatography (3% EtOAc in hexanes) to afford 12.6 g (78%) of the primary alcohol **11**. $[\alpha]^{20}_D$ −24.3 (*c* 2.34, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 3.78−3.58 (m, 4 H), 2.88 (t, $J$ = 5.7 Hz, 1 H), 1.95−1.90 (m, 1 H), 1.67−1.57 (m, 2 H), 1.40−1.46 (m, 1 H), 1.37−1.17 (m, 30 H), 0.99−0.90 (m, 18 H), 0.87 (t, $J$ = 7.0 Hz, 3 H), 0.63−0.52 (m, 12 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 75.9, 75.1, 61.1, 34.7, 32.1, 30.6, 30.0, 29.9, 29.8, 29.5, 26.8, 22.9, 14.2, 7.0, 5.3, 5.2. IR (thin film): 3471, 2928, 2851, 1468, 1411, 1374, 1242, 1080, 1023, 723 $cm^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{33}H_{72}O_3Si_2$, 571.4942 *m*/*z* $[M - H]^+$; observed, 571.4927 *m*/*z*.

**Allylic Alcohol 12.** To a solution of alcohol **11** (15.5 g, 0.03 mol) in $CH_2Cl_2$ (50 mL) at room temperature was added bis-acetoxyiodobenzene (9.61 g, 0.03 mol). After addition of TEMPO (437 mg, 3.0 mmol), the clear orange solution was stirred at room temperature for 2 h. The reaction was then diluted with $CH_2Cl_2$ (150 mL) and treated with saturated sodium sulfite solution until it became colorless. Upon separation of the layers, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by column chromatography (2% EtOAc in hexanes) to furnish the corresponding aldehyde as a colorless oil (14.8 g, 96%). $[\alpha]_D^{20}$ −21.6 (*c* 1.95, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 9.67 (t, $J$ = 2.22 Hz, 1 H), 4.20−4.17 (m, 1 H), 3.62−3.59 (m, 1 H), 2.65 (ddd, $J$ = 1.8, 4.0, 15.9 Hz, 1 H), 2.43 (ddd, $J$ = 2.9, 8.2, 15.7 Hz, 1 H), 1.66−1.60 (m, 1 H), 1.47−1.31 (m, 1 H), 1.30−1.12 (m, 30 H), 0.92−0.88 (m, 18 H), 0.86 (t, $J$ = 7.1 Hz, 3 H), 0.62−0.48 (m, 12 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 201.9, 75.1, 70.8, 46.1, 32.1, 30.6, 30.0, 29.9, 29.8, 29.5, 26.7, 22.9, 14.2, 7.0, 5.3, 5.1. IR (thin film): 2930, 2978, 2855, 2716, 1732, 1640, 1414, 1381, 1327, 1240, 1103, 1007, 976, 833, 743, 673 $cm^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{33}H_{70}O_3Si_2$, 569.4785 *m*/*z* $[M - H]^+$; observed, 569.4775 *m*/*z*.

A solution of this aldehyde (15.1 g, 0.02 mol) and (carbethoxymethylene)triphenylphosphorane (13.9, 0.05 mol) in THF (245 mL) was heated to reflux for 16 h. After cooling the solution to room temperature, the solvent was evaporated and the crude product was purified by column chromatography (EtOAc/hexanes 1:99) to afford the trans α,β-unsaturated ester as a yellow oil (15.1 g, 91%). $[\delta]_D^{20}$ −30.1 (*c* 1.99, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.37−6.98 (m, 1 H), 5.85 (d, $J$ = 15.5, 1 H), 4.19 (q, $J$ = 7.1 Hz, 2 H), 3.71−3.61 (m, 1 H), 3.60−3.58 (m, 1 H), 2.57−2.52 (m, 1 H), 2.23−2.17 (m, 1 H), 1.67−1.20 (m, 30 H), 1.02−0.92 (m, 18 H), 0.90 (t, $J$ = 7.0 Hz, 3 H), 0.65−0.55 (m, 12 H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 166.6, 147.9, 123.0, 75.6, 75.0, 60.2, 60.1, 34.2, 34.1, 32.1, 30.3, 30.0, 29.9, 29.6, 26.8, 22.9, 14.5, 14.4, 14.3, 7.1, 7.0, 5.4, 5.2. IR (thin film): 2926, 2878, 2855, 1729, 1657, 1464, 1414, 1379, 1368, 1318, 1264, 1238, 1167, 1100, 1047, 1005, 984, 849, 743, 673 $cm^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{37}H_{76}O_2Si_2$, 639.5204 *m*/*z* $[M - H]^+$; observed, 639.5213 *m*/*z*.

To a cold (0 °C) solution of the ester (15.2 g, 23.8 mmol) in diethyl ether (245 mL) was added DIBAL-H (75 mmol, 50 mL of 1.5 M solution in toluene) under $N_2$. After stirring for 30 min at the same temperature, saturated potassium−sodium tartrate solution

(240 mL) was added and the mixture was brought to room temperature. $Et_2O$ (250 mL), $H_2O$ (50 mL), and glycerol (12 mL) were added, and the resultant heterogeneous mixture was stirred overnight. The two layers were then separated, and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product after chromatographic purification (5% EtOAc in hexanes) afforded allylic alcohol **12** as a colorless oil (14.2 g, 89%). $[\delta]_D^{20}$ −27.1 (*c* 2.22, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.74−5.64 (m, 2 H), 4.10−4.07 (m, 2 H), 3.62−3.55 (m, 2 H), 2.43−2.39 (m, 1 H), 2.07−2.00 (m, 1 H), 1.64−1.24 (m, 32 H), 0.99−0.93 (m, 18 H), 0.88 (t, $J$ = 7.0 Hz, 3 H), 0.63−0.51 (m, 12 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 131.6, 130.9, 75.7, 64.1, 33.9, 32.1, 30.4, 29.9, 29.8, 29.6, 26.8, 22.9, 14.3, 7.1, 7.0, 5.4. IR (thin film): 3333, 2928, 2978, 2853, 1460, 1414, 1379, 1329, 1238, 1098, 1007, 972, 909, 743, 673 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{35}H_{74}O_3Si_2$, 597.5098 *m*/*z* [M − H]$^+$; observed, 597.5090 *m*/*z*.

**Epoxy Alcohol 13.** A two-necked round-bottom flask charged with 4 Å molecular sieves (1.17 g) and $CH_2Cl_2$ (47 mL) was cooled to −20 °C. To this, Ti(O$^i$Pr)$_4$ (3.04 mL, 10.0 mmol) and a $CH_2Cl_2$ solution of D-(−)-DET (2.91 g, 12.4 mmol in 41 mL of $CH_2Cl_2$) were added in that order and stirred at the same temperature under $N_2$ for 30 min. After cooling the complex to −30 °C, *t*-BuOOH (13 mL of 3.1 M solution in toluene, 40 mmol) was added dropwise and the mixture was stirred for another 45 min. A solution of allylic alcohol **12** (6.21 g, 10.4 mmol) in $CH_2Cl_2$ (31 mL) was added via a syringe pump over 45 min. The reaction was warmed to −20 °C, stirred for 2 h, and then quenched by adding saturated $Na_2SO_4$ and $Na_2SO_3$ solutions (6.8 mL each). $Et_2O$ (25 mL) was added, and the resultant yellow mixture was vigorously stirred at room temperature for 4 h. The yellow gelatinous mass was further diluted with $Et_2O$ (200 mL). Celite was added, and the mixture was filtered through a pad of Celite. The filter cake was washed with $Et_2O$ (ca. 600 mL) until it turned dry and granular. The filtrate was concentrated, and epoxy alcohol **13** was isolated in 73% yield after purification by column chromatography (7% EtOAc in hexanes). $[\delta]_D^{20}$ −16.7 (*c* 1.06, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.05−4.03 (m, 1 H), 3.93 (dt, $J$ = 4.3, 8.4 Hz, 1 H), 3.76−3.72 (m, 2 H), 3.23 (dt, $J$ = 2.3, 7.2 Hz, 1 H), 3.04 (m, 1 H), 2.09 (s, br, 1 H), 1.98−1.76 (m, 4 H), 1.63−1.37 (m, 30 H), 1.15−1.05 (m, 18 H), 1.03 (t, $J$ = 7.0 Hz, 3 H), 0.77−0.67 (m, 12 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 75.6, 73.6, 62.2, 58.8, 54.9, 33.7, 32.2, 30.4, 30.0, 29.9, 29.8, 29.6, 26.8, 22.9, 14.4, 7.2, 7.1, 5.3, 5.2. IR (thin film): 3438, 2932, 2878, 2855, 1462, 1414, 1379, 1329, 1238, 1098, 1009, 976, 903, 874, 743, 673 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{35}H_{74}O_4Si_2$, 613.5047 *m*/*z* [M − H]$^+$; observed, 613.5052 *m*/*z*.

**Phenylthiomethyl Epoxide 6.** To a solution of diphenyl disulfide (6.4 g, 29.3 mmol) in triethylamine (20 mL) was added tributylphosphine (7.1 mL, 29.3 mmol) at ambient temperature under $N_2$. This solution was cooled to 0 °C, and to it was cannulated a precooled solution of epoxy alcohol **13** (5.96 g, 9.67 mmol) in $Et_3N$. The reaction was warmed to ambient temperature over 6 h. After quenching the reaction mixture with water (50 mL), the aqueous solution was extracted with EtOAc (3 × 150 mL). The combined EtOAc extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes to 2% EtOAc in hexanes) to afford **6** as a colorless oil (6.43 g, 94%). $[\delta]_D^{20}$ −26.2 (*c* 1.62, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.41 (d, $J$ = 1.3 Hz, 2 H), 7.40−7.18 (m, 3 H), 3.75 (dt, $J$ = 4.2, 8.2 Hz, 1 H), 3.57−3.55 (m, 1 H), 3.13 (dd, $J$ = 5.1, 13.9 Hz, 1 H), 2.97−2.87 (m, 3 H), 1.69−1.31 (m, 4 H), 1.30−1.15 (m, 30 H), 0.98−0.91 (m, 18 H), 0.88 (t, $J$ = 7.1 Hz, 3 H), 0.62−0.53 (m, 12 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 135.9, 130.0, 129.2, 126.7, 75.4, 73.5, 58.2, 57.3, 36.5, 33.9, 32.2, 30.4, 30.1, 30.0, 29.9, 29.8, 29.6, 26.8, 23.0, 14.4, 7.2, 5.3. IR (thin film): 3077, 3061, 2853, 1806, 1586, 1482, 1439, 1416, 1379, 1327, 1302, 1238, 1184, 1092, 1007, 970, 943, 916, 747, 699 cm$^{-1}$. HRMS (EI) calcd for $C_{41}H_{78}O_3SSi_2$, 706.5210 *m*/*z* [M]$^+$; observed, 706.5223 *m*/*z*.

**THF Diol 18.** To a solution of **6** (4.0 g, 5.66 mmol) in $Et_2O$ (150 mL) at 0 °C was added dropwise $BF_3{\cdot}OEt_2$ (4.3 mL, 33.8 mmol). After addition was complete, the mixture was slowly warmed to room temperature over 5 h. The reaction mixture was quenched with $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford a mixture of regio- and stereoisomeric products. Flash column chromatography provided the desired THF diol **18** (1.52 g, 56%) cleanly as a single diastereomer along with an inseparable mixture of isomers (543 mg) (data for **18** is shown). $[\delta]_D^{20}$ −36.2 (*c* 0.32, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.41−7.20 (m, 5 H), 4.45−4.44 (m, 1 H), 4.10 (dt, $J$ = 6.2, 9.5 Hz, 1 H), 4.00 (ddd, $J$ = 3.1, 5.4, 8.8 Hz, 1 H), 3.81−3.34 (m, 1 H), 3.27 (dd, $J$ = 5.3, 13.0 Hz, 1 H), 3.14 (dd, $J$ = 9.1, 13.3 Hz, 1 H), 2.17−2.12 (s, br, 1 H), 2.04−1.80 (m, 2 H), 1.58−1.25 (m, 32 H), 0.88 (t, $J$ = 7.0 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 195.1, 135.6, 129.9, 129.3, 126.8, 100.9, 91.5, 81.5, 74.2, 73.0, 37.7, 33.7, 32.7, 32.2, 29.9, 29.8, 29.6, 25.8, 22.9, 14.3. IR (thin film): 3440, 3400, 2918, 2841, 1585, 1464, 1414, 1325, 1173, 1092, 1026, 964, 949, 879, 810, 729, 683 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{29}H_{50}O_3S$, 477.3402 *m*/*z* [M − H]$^+$; observed, 477.3398 *m*/*z*.

**Sulfoxide 19.** 2,6-Lutidine (1.3 mL, 11.2 mmol) was added to a 0 °C solution of THF diol **18** (1.72 g, 3.59 mmol) in $CH_2Cl_2$ (18 mL). A solution of TBSOTf (1.9 mL, 8.25 mmol) in $CH_2Cl_2$ (10 mL) was then added, and the reaction mixture was stirred at 0 °C for 30 min. When TLC indicated completion of the reaction, water (50 mL) was added and the aqueous solution was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford the crude product as a colorless oil. After purification by flash column chromatography, 2.26 g of the bis-TBS ether was obtained in 87% yield. $[\delta]_D^{20}$ −71.0 (*c* 0.57, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.37−7.14 (m, 5 H), 4.40 (m, 1 H), 4.21 (dt, $J$ = 5.3, 10.4, 1 H), 3.96 (dt, $J$ = 3.1, 6.8, 1 H), 3.59 (m, 1 H), 3.15 (m, 2 H), 1.88−1.79 (m, 2 H), 1.38−1.22 (m, 32 H), 0.91 (s, 9 H), 0.89 (t, $J$ = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 137.0, 129.1, 128.7, 125.8, 81.7, 80.7, 74.6, 73.0, 37.3, 32.7, 32.2, 30.1, 29.9, 29.8, 29.6, 26.2, 26.0, 22.9, 18.5, 18.3, 14.4, −4.0, −4.2, −4.3, −4.6. IR (thin film): 2926, 2856, 1585, 1470, 1439, 1389, 1362, 1254, 1194, 1078, 1057, 1007, 960, 835, 775, 737, 690 cm$^{-1}$. HRMS (ES) calcd for $C_{41}H_{78}O_3Ssi_2$, 707.5289 *m*/*z* [M + H]$^+$; observed, 707.5269 *m*/*z*.

To a 0 °C solution of the above bis-TBS ether (1 g, 1.4 mmol) in $CH_2Cl_2$ (16 mL) was added a solution of *m*-CPBA (350 mg, 1.4 mmol) in $CH_2Cl_2$ (16 mL). After 30 min at 0 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution (30 mL) and the aqueous mixture was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford sulfoxide **19** as a mixture of diastereomers, which was used without further purification.

**THF Aldehyde 5.** The crude sulfoxide (**19**) was dissolved in $CH_2Cl_2$ (11.3 mL) and cooled to 0 °C, and 2,6-lutidine (0.56 mL) was added. TFAA (0.69 mL, 4.95 mmol) in $CH_2Cl_2$ (11.3 mL) was then added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford a clear oil. This material was taken up in 1:1 acetonitrile/water (50 mL), and solid $NaHCO_3$ (2.5 g) was added. The reaction mixture was stirred at ambient temperature for 16 h, upon which the solution was diluted with water (25 mL). The aqueous solution was extracted with $CH_2Cl_2$ (3 × 25 mL), and the combined extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. Slow chromatography on wet silica gel containing 10% water (3% EtOAc in hexanes) afforded aldehyde **5** (532 mg) in 63% yield over the three steps. $[\delta]_D^{20}$ −33.0 (*c* 0.91, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.58 (d, $J$ = 2.2 Hz, 1 H), 4.73−4.72 (m, 1 H), 4.46−4.44 (m, 1 H), 4.28−4.16 (m, 1 H), 3.68−3.66 (m, 1 H), 1.87−

1.84 (m, 2 H), 1.40−1.22 (m, 32 H), 0.93−0.84 (m, 21 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 203.1, 87.2, 82.8, 76.0, 74.4, 38.0, 33.2, 32.2, 30.0, 29.9, 29.8, 29.6, 26.2, 26.0, 25.9, 25.8, 22.9, 18.4, 18.1, 14.3, −4.1, −4.3, −4.5, −5.1. IR (thin film): 2928, 2855, 1738, 1475, 1464, 1441, 1389, 1362, 1256, 1186, 1076, 1065, 998, 939, 837, 808, 777, 737, 691, 664 cm$^{-1}$. HRMS (CI, $CH_4$) calcd for $C_{35}H_{72}O_4Si_2$, 611.4891 *m*/*z* $[M - H]^+$; observed, 611.4898 *m*/*z*.

**Aldehyde 29.** To a slurry of NaH (7 g, 0.18 mol) in THF (300 mL) was added 1,6-hexanediol (20 g, 0.17 mol) at 0 °C, and the mixture was stirred for 1 h while warming to room temperature. Benzyl bromide (20 mL, 0.17 mmol) was added dropwise followed by TBAI (2.6 g). The reaction was heated to 60 °C for 15 h. After cooling to room temperature, $H_2O$ (150 mL) was carefully added. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 300 mL). The combined organic layers (dried with $MgSO_4$) were concentrated. The corresponding monobenzyl-protected alcohol was obtained as clear oil (35.4 g, 78%) after chromatographic purification (30% EtOAc in hexanes). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.35−7.25 (m, 5 H), 4.50 (s, 2 H), 3.56 (t, $J$ = 6.6 Hz, 2 H), 3.47 (t, $J$ = 6.6 Hz, 2 H), 1.63 (quint, $J$ = 6.6 Hz, 2 H), 1.54 (quint, $J$ = 7.0 Hz, 2 H), 1.38−1.32 (m, 4 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 138.8, 128.6, 127.9, 127.8, 73.1, 70.6, 62.8, 32.9, 29.9, 26.2, 25.9. IR (thin film): 3393, 3063, 2933, 2859, 1951, 1874, 1810, 1603, 1454, 1363, 1309, 1251, 1205, 1099, 1028, 909, 735, 675 cm$^{-1}$. HRMS (EI) calcd for $C_{13}H_{20}O_2$, 208.1458 *m*/*z* $[M]^+$; observed, 208.1463 *m*/*z*.

To a slurry of PCC (31.6 g, 0.15 mol) in $CH_2Cl_2$ (300 mL) was added a solution of the above alcohol (20.4 g, 98.1 mmol) in $CH_2Cl_2$ (100 mL) at room temperature under $N_2$ with vigorous stirring. After 2 h, anhydrous $Et_2O$ (400 mL) was added and the reaction mixture was filtered through a Celite pad. The filtrate was concentrated, and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde **29** as a clear liquid (16.6 g, 82%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.75 (t, $J$ = 2.2 Hz, 1 H), 7.39−7.20 (m, 5 H), 4.49 (s, 2 H), 3.47 (t, $J$ = 6.4, 2 H), 2.40−2.48 (m, 2 H), 1.72−1.61 (m, 4 H), 1.46−1.38 (m, 2 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 202.8, 138.8, 128.6, 127.8, 127.7, 73.1, 70.2, 44.0, 29.7, 26.0, 22.1. IR (thin film): 3031, 2936, 2860, 2720, 1954, 1875, 1724, 1453, 1409, 1363, 1391, 1101, 1026, 906, 737, 703 cm$^{-1}$. HRMS (EI) calcd for $C_{13}H_{18}O_2$, 206.1307 *m*/*z* $[M]^+$; observed, 206.1309 *m*/*z*.

***Z*-Homoallylic Iodide 27.** KHMDS (175 mL of 0.5 M solution in toluene, 87.5 mmol) was added to a −20 °C slurry of 3-hydroxypropyltriphenylphosphonium bromide (17.6 g, 43.7 mmol) in THF (55 mL). The mixture was brought to room temperature and stirred for 1 h. After cooling back to 0 °C, TMSCl (5.8 mL, 43.7 mmol) was added and stirring was continued at the same temperature for 15 min. The reaction was then cooled to −78 °C upon which a THF solution of aldehyde **29** (5 g, 24.3 mmol in 40 mL) was added. The reaction was warmed to −10 °C over 1 h and then treated with AcOH/$H_2O$/THF (6:3:1, 250 mL). After 15 h of stirring at room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 400 mL), and the combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by column chromatography (10% EtOAc in hexanes) to secure the homoallylic alcohol (9 g, 83%, *Z*/*E* > 10:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.37−7.25 (m, 5 H), 5.55−5.51 (m, 1 H), 5.39−5.34 (m, 1 H), 4.50 (s, 2 H), 3.60 (t, $J$ = 6.9 Hz, 2 H), 3.47 (t, $J$ = 6.9 Hz, 2 H), 2.32−2.28 (m, 2 H), 2.08−2.04 (m, 3 H), 1.66−1.60 (m, 2 H), 1.42−1.37 (m, 4 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 175.5, 138.8, 133.0, 128.6, 127.9, 127.7, 125.5, 73.1, 70.6, 62.4, 30.9, 29.8, 29.7, 27.5, 26.0, 20.9. IR (thin film): 3386, 3028, 2861, 2063, 1950, 1872, 1809, 1714, 1654, 1605, 1453, 1366, 1250, 1204, 1050, 872, 735, 695 cm$^{-1}$. HRMS (EI) calcd for $C_{16}H_{24}O_2$, 248.1776 *m*/*z* $[M]^+$; observed, 248.1769 *m*/*z*.

A solution of the latter homoallylic alcohol (9.1 g, 36.7 mmol) in $CH_2Cl_2$ (140 mL) was cooled to 0 °C. To this, mesyl chloride (8.55 mL, 0.11 mol) and triethylamine (17 mL) were added and stirring was continued at the same temperature for 30 min. The reaction was quenched with $H_2O$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL), and combined organic layers were concentrated. The residue and sodium iodide (25 g, 0.17 mol) were taken up in acetone (150 mL) and refluxed for 2 h. Upon cooling to room temperature, the reaction was treated with saturated sodium sulfite until it became colorless. The aqueous layer was extracted with EtOAc (3 × 200 mL). Chromatographic purification (3% EtOAc in hexanes) of the crude product obtained by concentration of the organic portion afforded iodide **27** (10.1 g, 77%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.36−7.28 (m, 5 H), 5.55−5.52 (m, 1 H), 5.35−5.32 (m, 1 H), 4.52 (s, 2 H), 3.48 (t, $J$ = 6.6 Hz, 2 H), 3.14 (t, $J$ = 7.3 Hz, 2 H), 2.66−2.61 (m, 2 H), 2.06−2.04 (m, 2 H), 1.66−1.63 (m, 2 H), 1.42−1.39 (m, 4 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 138.9, 132.7, 128.6, 128.2, 127.9, 127.7, 73.1, 70.6, 31.8, 29.9, 29.6, 27.7, 26.1, 5.7. IR (thin film): 3028, 3009, 2932, 2855, 2791, 1920, 1850, 1790, 1495, 1454, 1361, 1242, 1169, 1105, 1028, 734, 698 cm$^{-1}$. HRMS (EI) calcd for $C_{16}H_{23}IO$, 358.0794 *m*/*z* $[M]^+$; observed, 358.0800 *m*/*z*.

***Z*-Bishomoallylic Alcohol 26.** *t*-BuLi (7.6 mL of 1.3 M solution in pentane, 9.94 mmol) was added dropwise to precooled (−100 °C) $Et_2O$ (18 mL). To this was added a solution of iodide **27** (1.78 g, 4.97 mmol) in $Et_2O$ (14 mL) over 10 min. After stirring for 5 min at −100 to −90 °C, $MgBr_2$·$OEt_2$ in $Et_2O$ (12.4 mL of 1.0 M solution (freshly prepared)),[78,79] was added and the mixture was warmed to 0 °C over 1 h. Meanwhile, a solution of aldehyde **5** (1 g, 1.63 mmol) in $Et_2O$ (18 mL) was cooled to −40 °C. $MgBr_2$·$OEt_2$ in $Et_2O$ (5.0 mL of 1.0 M solution, 5.0 mmol) was added to the solution of aldehyde and stirred for 10 min. To this precomplexed aldehyde, a solution of the above-mentioned Grignard reagent was cannulated at −40 °C and the reaction mixture was stirred overnight at the same temperature. The reaction was then quenched by slow addition of saturated $NH_4Cl$ solution (20 mL) and $H_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (3 × 100 mL). Combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography (2% EtOAc in hexanes) furnished the adduct **26** (1.17 g, 85%) as a single diastereomer. $[\alpha]^{20}_D$ −17.1 (*c* 0.97, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.33−7.25 (m, 5 H), 5.39−5.33 (m, 2 H), 4.52 (s, 2 H), 4.50−4.39 (m, 1 H), 4.25−4.21 (m, 1 H), 3.8 (dt, $J$ = 4.3, 8.8 Hz, 1 H), 3.68−3.62 (m, 2 H), 3.46 (t, $J$ = 6.6 Hz, 2 H), 2.96 (s, br, 1 H), 2.29−2.05 (m, 4 H), 1.88−1.86 (m, 2 H), 1.65−1.47 (m, 4 H), 1.38−1.23 (m, 36 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, $J$ = 7.0 Hz, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 139.0, 130.3, 129.7, 128.5, 127.8, 127.6, 85.0, 80.5, 75.0, 74.6, 73.1, 70.7, 38.2, 33.4, 32.9, 30.1, 29.9, 29.8, 29.6, 27.4, 26.2, 26.1, 26.0, 25.8, 23.7, 22.9, 18.4, 18.1, 14.3, −4.0, −4.1, −4.3, −4.8. IR (thin film): 3596, 3521, 3031, 3004, 2928, 2856, 1464, 1406, 1389, 1362, 1256, 1190, 1076, 1005, 955, 939, 835, 808, 775, 733, 696, 662 cm$^{-1}$. HRMS (EI) calcd for $C_{51}H_{96}O_5Si_2$, 844.6796 *m*/*z* $[M]^+$; observed, 844.6789 *m*/*z*.

**Triol 30.** AD-mix-α (1.26 g) was dissolved in a 1:1 *t*-BuOH/$H_2O$ (13 mL) mixture. To this clear, orange solution were added methane sulfonamide (86 mg, 0.9 mmol) and potassium osmate (19 mg), and the mixture was stirred until all the solids dissolved. The solution was then cooled to 0 °C upon which hydroxy olefin **26** (760 mg, 0.90 mmol) was added in one portion. The reaction was vigorously stirred for 16 h, after which solid sodium sulfite (1.35 g) was added at the same temperature. The mixture was warmed to room temperature, and stirring was continued for 45 min. EtOAc (50 mL) and $H_2O$ (20 mL) were added, and the layers

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(79) Black, T. H.; Mcdermott, T. S.; Brown, G. A. *Tetrahedron Lett.* **1991**, *32*, 6501−6502.

were separated. The aqueous layer was extracted with EtOAc (4 × 50 mL), and combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography (8% EtOAc in hexanes). The desired diastereomer **30** was isolated in 73% (577 mg) yield as a colorless oil. $[\alpha]^{20}_D$ −16.2 (*c* 0.87, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.33−7.24 (m, 5 H), 4.49 (s, 2 H), 4.42−4.41 (m, 1 H), 4.22−4.20 (m, 1 H), 3.88−3.87 (m, 1 H), 3.71−3.69 (m, 1 H), 3.64−3.58 (m, 3 H), 3.47 (t, $J$ = 6.6 Hz, 2 H), 3.23 (s, br, 1 H), 3.03 (s, br, 1 H), 1.88−0.186 (m, 2 H), 1.68−1.22 (m, 44 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.88 (t, $J$ = 7.0, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 138.9, 128.5, 127.8, 127.7, 85.0, 80.6, 74.9, 74.8, 74.5, 74.4, 73.1, 71.3, 70.6, 38.3, 32.9, 32.1, 31.9, 30.1, 29.9, 29.8, 29.6, 27.7, 26.5, 26.1, 25.9, 25.8, 22.9, 18.4, 18.1, 14.3, −4.0, −4.2, −4.3, −4.9. IR (thin film): 3596, 3521, 3031, 3004, 2928, 2856, 1464, 1406, 1389, 1362, 1256, 1190, 1076, 1005, 955, 939, 835, 808, 775, 733, 696, 662 cm$^{-1}$. HRMS (ES) calcd for $C_{51}H_{98}O_7Si_2$, 879.6929 *m*/*z* [M + H]$^+$; observed, 879.6931 *m*/*z*.

**Bistetrahydrofuran Acetate 32.** PPTS (6 mg, 0.02 mmol) was added to a solution of triol **30** (200 mg, 0.22 mmol) and trimethylortho acetate (36 $\mu$L, 0.23 mmol) in $CH_2Cl_2$ (3 mL) at room temperature. After complete consumption of the triol (ca. 5 min, as judged by TLC), a solution of $BF_3{\cdot}OEt_2$ (8 $\mu$L, 0.06 mmol) in $CH_2Cl_2$ (1 mL) was rapidly added to the reaction. After 10 min, the reaction was slowly poured into saturated $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). Combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure, and the crude product was purified by flash column chromatography (2% EtOAc in hexanes) to furnish bistetrahydrofuran acetate **32** (187 mg, 91%) as a clear oil. $[\alpha]^{20}_D$ −29.3 (*c* 0.47, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.35−7.25 (m, 5 H), 4.91−4.87 (m, 1 H), 4.48 (s, 2 H), 4.29−4.18 (m, 3 H), 4.05−4.01 (m, 1 H), 3.74−3.71 (m, 1 H), 3.63 (dd, $J$ = 3.6, 7.7 Hz, 1 H), 3.44 (t, $J$ = 6.4 Hz, 2 H), 2.08−2.00 (m, 1 H), 2.04 (s, 3 H), 1.96−1.80 (m, 4 H), 1.66−1.51 (m, 6 H), 1.48−1.18 (m, 34 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.86 (t, $J$ = 7.0 Hz, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 171.1, 138.9, 128.5, 127.8, 127.6, 85.5, 81.0, 79.3, 79.2, 75.8, 75.4, 73.7, 73.1, 70.6, 36.8, 32.1, 32.0, 31.0, 30.1, 29.9, 29.6, 28.6, 27.9, 26.4, 26.2, 25.9, 25.6, 22.9, 21.4, 18.4, 18.1, −3.9, −4.0, −4.5, −4.8. IR (thin film): 2926, 2854, 1739, 1463, 1354, 1244, 1100, 1056, 940, 833, 775 cm$^{-1}$. HRMS (ES) calcd for $C_{53}H_{98}O_7Si_2$, 903.6929 *m*/*z* [M + H]$^+$; observed, 903.6913 *m*/*z*.

**Bistetrahydrofuran 33.** Acetate **32** (440 mg, 0.49 mmol) was dissolved in MeOH (7 mL). Solid $K_2CO_3$ was added to this solution, and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with $CH_2Cl_2$ (20 mL) and washed with $NaHCO_3$ (5 mL) and $H_2O$ (10 mL). The aqueous layers were mixed and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layer was dried with $Na_2SO_4$. The solvent was evaporated, and the alcohol was used without further purification. To a 0 °C solution of this alcohol (172 mg, 0.20 mmol) in $CH_2Cl_2$ (5 mL) were added 2,6-lutidine (0.15 mL, 1.2 mmol) and TBSOTf (0.14 mL, 0.6 mmol) in that order. After 30 min at the same temperature, saturated $NaHCO_3$ solution (2 mL) was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL), and combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford a crude oil. Upon purification of the oil by column chromatography (1% EtOAc in hexanes), bistetrahydrofuran benzyl ether **33** was obtained in 97% yield (189 mg). $[\alpha]^{20}_D$ −30.5 (*c* 0.83, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.34−7.26 (m, 5 H), 4.50 (s, 2 H), 4.31−4.27 (m, 2 H), 4.19−4.15 (m, 1 H), 3.97−3.93 (m, 1 H), 3.78−3.76 (m, 1 H), 3.75−3.71 (dd, $J$ = 3.5, 7.7, 1 H), 3.46 (t, $J$ = 6.6, 2 H), 2.00−1.16 (m, 4 H), 1.57−1.2 (m, 42 H), 0.90 (t, $J$ = 7.0, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.87 (s, 9 H) 0.08 (s, 3 H), 0.06 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 139.0, 128.5, 127.8, 127.6, 85.9, 81.7, 80.5, 79.2, 74.4, 74.0, 73.7, 73.1, 70.7, 36.3, 32.1, 31.9, 31.5, 30.1, 30.0, 29.9, 29.6, 28.7, 26.7, 26.6, 26.4, 26.2, 26.1, 25.9, 22.9, 18.4, 18.3, 18.1, 14.3, −3.9, −4.1, −4.4, −4.8. IR (thin film): 2904, 2855, 1990, 1871, 1463, 1366, 1254, 1098 cm$^{-1}$. HRMS (ES) calcd for $C_{57}H_{110}O_6Si_3$, 975.7689 *m*/*z* [M + H]$^+$; observed, 975.7697 *m*/*z*.

**Iodide 24.** Benzyl ether **33** (390 mg, 0.40 mmol) was dissolved in 1:1 EtOAc/*i*-PrOH (20 mL). To this solution was added 10% Pd−C (111 mg), and the mixture was stirred vigorously under $H_2$ (1 atm). The hydrogenolysis was complete in 1 h, after which the reaction was filtered through a Celite pad. The filtrate was concentrated, and the crude product was purified by flash column chromatography (5% EtOAc in hexanes) to furnish the free alcohol in 92% yield (326 mg). $[\alpha]^{20}_D$ −29.4 (*c* 0.83, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.30−4.26 (m, 2 H), 4.17−4.13 (m, 1 H), 3.97−3.93 (m, 1 H), 3.76−3.72 (m, 2 H), 3.65−3.63 (m, 1 H), 3.62 (t, $J$ = 6.6 Hz, 2 H), 2.00−1.64 (m, 4 H), 1.59−1.12 (m, 44 H), 0.89 (t, $J$ = 7.0, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 6 H), 0.04 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 85.9, 81.6, 80.5, 79.2, 74.3, 74.0, 73.6, 63.2, 36.3, 33.0, 32.1, 31.9, 31.5, 29.9, 29.8, 29.7, 29.6, 28.7, 26.5, 26.4, 26.2, 26.1, 26.0, 25.9, 22.9, 18.4, 18.3, 18.1, 14.3, 1.2, −3.9, −4.0, −4.1, −4.4, −4.8. IR (thin film): 3385, 2926, 2855, 1600, 1463, 1360, 1255, 1079, 835, 774 cm$^{-1}$. HRMS (ES) calcd for $C_{50}H_{104}O_6Si_3$, 885.7219 *m*/*z* [M + H]$^+$; observed, 885.7217 *m*/*z*.

The alcohol (304 mg, 0.34 mmol), triphenylphosphine (223 mg, 0.85 mmol), and imidazole (61 mg, 0.90 mmol) were dissolved in toluene (12 mL). Upon addition of iodine (231 mg, 0.91 mmol), the clear, colorless solution turned yellowish brown and turbid. After 1 h of vigorous stirring at room temperature, saturated sodium sulfite solution was added to the reaction until the yellowish brown color disappeared. The layers were separated, and the aqueous layer was washed with EtOAc (3 × 15 mL). The combined organic layers were dried ($Na_2SO_4$), and the solvent was removed under reduced pressure to yield a gummy material. Purification of the crude material by column chromatography (3% EtOAc in hexanes) afforded iodide **24** (294 mg, 87%) as a colorless oil. $[\alpha]^{20}_D$ −27.7 (*c* 1.09, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.32−4.29 (m, 2 H), 4.19−4.15 (m, 1 H), 3.98−3.94 (m, 1 H), 3.78−3.72 (m, 2 H), 3.65 (dd, $J$ = 3.5, 7.7 Hz, 1 H), 3.18 (t, $J$ = 6.6 Hz, 2 H), 2.00−1.23 (m, 46 H), 0.90 (t, $J$ = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 85.9, 81.6, 80.6, 79.3, 77.5, 77.2, 77.0, 74.2, 74.0, 73.6, 36.3, 33.8, 32.1, 31.7, 31.5, 31.0, 30.1, 29.9, 29.8, 29.6, 28.7, 26.5, 26.4, 26.2, 26.1, 26.0, 25.2, 22.9, 18.4, 18.3, 18.1, 14.3, 7.3, −3.9, −4.0, −4.1, −4.3, −4.4, −4.8. IR (thin film): 2925, 2854, 1597, 1462, 1359, 1253, 1076, 835, 775 cm$^{-1}$. HRMS (ES) calcd for $C_{50}H_{103}IO_5Si_3$, 995.6236 *m*/*z* [M + H]$^+$; observed, 995.6259 *m*/*z*.

**Bistetrahydrofuran α-Phenylthiolactone 34.** A solution of diisopropylamine (5.8 $\mu$L, 0.06 mmol) in THF (0.5 mL) was cooled to −78 °C, and *n*-BuLi (24 $\mu$L of 2.5 M solution, 0.06 mmol) was added to it. After 15 min, lactone **25**[64] (12.6 mg, 0.06 mmol) in THF (0.4 mL) was added and stirring was continued for 30 min during which the solution was warmed to 0 °C. Iodide **24** (30 mg, 0.03 mmol) was then added as a solution in 1:1 THF/HMPA (0.5 mL). The reaction was warmed to room temperature. After 15 h, $H_2O$ (1 mL) and EtOAc (5 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude product was purified by column chromatography (1% − 3% EtOAc in hexanes) to afford the phenylthiolactone **34** as a mixture of diastereomers (28 mg, 87%). $[\alpha]^{20}_D$ −34.8 (*c* 0.78, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.56−7.52 (m, 2 H), 7.43−7.33 (m, 3 H), 4.53−4.46 (m, 1 H), 4.32−4.28 (m, 2 H), 4.19−4.15 (m, 1 H), 3.97−3.93 (m, 1 H), 3.78−3.72 (m, 2 H), 3.65 (dd, $J$ = 3.5, 7.7 Hz, 1 H), 2.52 (dd, $J$ = 3.5, 7.7 Hz, 1 H), 2.01−1.91 (m, 2 H), 1.90−1.21 (m, 50 H), 0.90 (t, $J$ = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 12 H). $^{13}$C NMR (125 MHz,

$CDCl_3$): $\delta$ 177.3, 137.3, 137.1, 130.8, 130.1, 129.9, 129.2, 129.1, 85.9, 81.6, 80.6, 79.3, 74.3, 74.0, 73.7, 73.6, 73.4, 56.4, 40.3, 36.7, 36.3, 32.1, 31.8, 31.5, 30.2, 30.1, 29.9, 29.6, 28.7, 26.5, 25.4, 26.2, 26.2, 26.0, 25.0, 22.9, 21.7, 18.4, 18.1, 14.3, −3.9, −4.0, −4.1, −4.3, −4.4, −4.8. IR (thin film): 2926, 2854, 1770, 1464, 1385, 1360, 1255, 1184, 1068, 968, 939, 835, 806, 775, 705, 692 $cm^{-1}$. HRMS (ES) calcd for $C_{62}H_{114}O_7SSi_3$, 1075.7671 *m/z* $[M + H]^+$; observed, 1075.7690 *m/z*.

**Bistetrahydrofuran γ-Methyl Butenolide 35.** To an ice cold solution of **34** (30 mg, 0.03 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise ca. 75% *m*-CPBA (6.8 mg, 0.03 mmol) in $CH_2Cl_2$ (1 mL). After 20 min, saturated $NaHCO_3$ solution (1 mL) was carefully added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried and concentrated to afford the corresponding sulfoxide. The crude sulfoxide was taken up in toluene (2 mL) and heated to reflux for 4 h. After cooling the solution to room temperature, the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (5% EtOAc in hexanes) to afford **35** (24 mg, 83%). $[\alpha]^{20}_D$ −17.9 (*c* 0.42, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.99 (d, *J* = 1.6 Hz, 1 H), 5.00−4.99 (m, 1 H), 4.31−4.28 (m, 2 H), 4.19−4.15 (m, 1 H), 3.98−3.94 (m, 1 H), 3.78−3.74 (m, 2 H), 3.65 (dd, *J* = 3.5, 7.7 Hz, 1 H), 2.27 (t, *J* = 7.3 Hz, 2 H), 2.02−1.12 (m, 49 H), 0.92−0.88 (m, 30 H), 0.08−0.05 (m, 18 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 174.0, 149.0, 134.5, 85.9, 81.6, 80.6, 79.3, 74.3, 74.0, 73.7, 36.3, 32.1, 31.7, 31.5, 30.1, 29.9, 29.8, 29.7, 29.6, 28.7, 27.6, 26.5, 26.4, 26.2, 26.1, 26.0, 25.4, 22.9, 19.4, 18.3, 18.1, 14.3, 1.2, −3.9, −4.0, −4.1, −4.4, −4.8. IR (thin film): 2954, 2927, 2854, 1761, 1463, 1361, 1319, 1257, 1081, 1026, 835, 802, 775 $cm^{-1}$. HRMS (ES) calcd for $C_{55}H_{108}O_7Si_3$, 965.7481 *m/z* $[M + H]^+$; observed, 965.7480 *m/z*.

**Proposed Mucoxin 1.** To a solution of **35** (9 mg, 9.31 μmol) in THF (0.5 mL) taken in a polyethylene vial was added HF·Py (32 μL) at room temperature. After stirring for 12 h, the reaction was neutralized by saturated $NaHCO_3$ solution. $H_2O$ (1 mL) and EtOAc (5 mL) were added, and the layers were separated. The organic layer was washed with saturated $CuSO_4$ (2 × 2 mL), and the combined aqueous layers were extracted with EtOAc (3 × 5 mL). The organic layers were mixed and dried over $Na_2SO_4$, and the solvent was evaporated to afford a waxy material. Sequential purification by column chromatography (EtOAc, 10% MeOH in EtOAc) and HPLC (10% *i*-PrOH in $Et_2O$) proposed that mucoxin **1** was isolated as a colorless wax (4.6 mg, 80%). $[\alpha]^{20}_D$ +3.2 (*c* 0.40, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.00 (d, *J* = 1.5 Hz, 1 H), 5.02−4.98 (m, 1 H), 4.46−4.43 (m, 1 H), 4.35 (dt, *J* = 3.4, 6.8 Hz, 1 H), 4.11−4.08 (m, 1 H), 3.97−3.94 (m, 1 H), 3.81 (t, *J* = 3.1 Hz, 1 H), 3.75 (d, *J* - 5.4 Hz, 1 H), 3.43−3.40 (m, 2 H), 2.32 (d, *J* = 4.4 Hz, 1 H), 2.28 (dt, *J* = 1.5, 7.8 Hz, 2 H), 2.19 (d, *J* = 5.4 Hz, 1 H), 2.15−2.11 (m, 1 H), 2.06−1.98 (m, 3 H), 1.84 (ddd, *J* = 4.4, 9.5, 13.4 Hz, 1 H), 1.75−1.69 (m, 1 H), 1.57−1.26 (m, 43 H), 0.89 (t, *J* = 6.9 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 174.0, 149.2, 134.4, 84.1, 83.3, 81.6, 79.3, 77.6, 74.7, 74.3, 73.6, 48.9, 39.0, 34.0, 33.6, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 28.0, 27.6, 25.8, 25.6, 25.3, 22.9, 19.4, 14.3. IR (thin film): 3404, 2917, 2850, 1749, 1590, 1465, 1319, 1072, 1045, 995, 873, 798, 719 $cm^{-1}$. HRMS (ES) calcd for $C_{37}H_{66}O_7$, 623.4887 *m/z* $[M + H]^+$; observed, 623.4879 *m/z*.

**Bis-4-dimethylamino Benzoate 38.** To a solution of diol **10** (54 mg, 0.11 mmol) in $CH_2Cl_2$ (1 mL) were added *p*-dimethylaminobenzoyl chloride (107 mg, 0.93 mmol) and DMAP (100 mg, 0.82 mmol), and the mixture was stirred for 15 h. The reaction was then quenched with $H_2O$ (3 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure, and the crude material was purified by flash column chromatography (30% EtOAc in hexanes) to afford the PMB-protected bisester (37 mg, 50%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.02−7.91 (m, 4 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6, 2 H), 6.62−6.71 (m, 4 H), 5.58−5.56 (m, 1 H), 5.37−5.35 (m, 1 H), 4.04 (s, 2 H), 3.78 (s, 3 H), 3.58−3.47 (m, 2 H), 3.04 (s, 6 H), 3.02 (s, 6 H), 2.02−1.98 (m, 2 H), 1.78−1.61 (m, 2 H), 1.56−1.20 (m, 30 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

DDQ (14 mg, 0.06 mmol) was added to a solution of the above PMB ether (37 mg, 0.05 mmol) in 9:1 $CH_2Cl_2/H_2O$ (1.1 mL) at 0 °C. After 30 min, the reaction mixture was carefully poured into saturated $NaHCO_3$ solution (2 mL). Extraction of the aqueous layer with $CH_2Cl_2$ (3 × 5 mL) followed by evaporation of the solvent and purification using column chromatography furnished the corresponding free alcohol in 50% yield (16 mg). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.96−7.94 (m, 4 H), 6.67−6.65 (m, 4 H), 5.41 (dt, *J* = 3.3, 10.6 Hz, 1 H), 5.36−5.32 (m, 1 H), 3.65 (s, br, 1 H), 3.56−3.52 (m, 1 H), 3.05 (s, 6 H), 3.04 (s, 6 H), 3.01−2.90 (m, 1 H), 1.97−1.69 (m, 3 H), 1.55−1.20 (m, 31 H), 0.86 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 168.1, 166.7, 153.8, 153.6, 131.9, 131.7, 116.3, 117.2, 74.4, 71.4, 58.4, 48.9, 40.3, 40.2, 34.1, 32.1, 31.4, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.4, 22.9, 14.3.

The alcohol (15 mg, 0.02 mmol) was dissolved in bis(trimethylsilyl)trifluoro acetamide (0.2 mL), and the solution was heated to 50 °C for 30 min. After cooling to room temperature, the volatiles were removed under reduced pressure and the TMS derivative **38** was used for ECCD analysis without further purification. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.00−7.94 (m, 4 H), 6.69−6.65 (m, 4 H), 5.47−5.44 (m, 1 H), 5.35−5.32 (m, 1 H), 3.68−3.65 (m, 2 H), 3.05 (s, 6 H), 3.04 (s, 6 H), 2.01−1.94 (s, 2 H), 1.73−1.69 (s, 2 H), 1.37−1.21 (m, 30 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 6 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 166.7, 166.5, 153.5, 131.7, 117.5, 117.4, 110.9, 74.2, 71.4, 59.2, 40.3, 34.5, 32.1, 31.3, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 25.5, 22.9, 14.3, 1.2, −0.4. HRMS (ES) calcd for $C_{42}H_{70}N_2O_5Si + Na^+$ (sodium adduct used for ionization), 733.4592 *m/z* $[M + Na]^+$; observed, 733.4920 *m/z*.

**THF Diol Bisacetate 39.** THF diol **18** (50 mg, 0.11 mmol) was preacetylated by treatment with acetic anhydride (43 mg, 0.42 mmol) and DMAP (52 mg, 0.42 mmol) in $CH_2Cl_2$ (1 mL) at room temperature to furnish **39** (61 mg, 99%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.39−7.18 (m, 5 H), 5.34 (m, 1 H), 4.83 (dt, *J* = 4.9, 8.4 Hz, 1 H), 4.21 (m, 1 H), 4.12 (m, 1 H), 3.19 (dd, *J* = 5.7, 13.5 Hz, 1 H), 3.06 (dd, *J* = 8.4, 13.4 Hz, 1 H), 2.09−1.86 (m, 2 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.58−1.49 (m, 2 H), 1.27−1.21 (m, 30 H), 0.87 (t, *J* = 6.6 Hz, 3 H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 171.1, 170.0, 135.8, 130.3, 129.2, 126.8, 80.2, 78.7, 75.1, 74.7, 35.6, 32.9, 32.2, 31.0, 29.9, 29.8, 29.7, 29.6, 25.6, 22.9, 21.4, 21.2, 14.4.

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**Supporting Information Available:** Synthesis of compounds **21** and Mosher's ester analysis of **26**, **40**, and **42** are provided. $^1$H and $^{13}$C spectra for new compounds **1**, **5**, **6**, **8**−**13**, **18**, **19**, **24**, **26**, **27**, **29**, **30**, and **32**−**39** (60 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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