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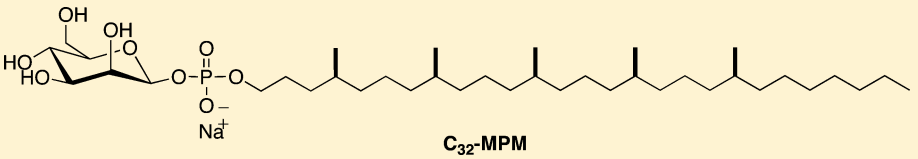
Highly Stereocontrolled Total Synthesis of β-D-Mannosyl Phosphomycoketide: A Natural Product from *Mycobacterium tuberculosis*

Nan-Sheng Li,*[,†] Louise Scharf,[†,§] Erin J. Adams,[†] and Joseph A. Piccirilli*[,†,‡]

[†]Department of Biochemistry and Molecular Biology and [‡]Department of Chemistry, University of Chicago, 929 East 57th Street, Chicago, Illinois 60637, United States

Supporting Information



C_{32}-MPM

ABSTRACT: β-D-Mannosyl phosphomycoketide (**C_{32}-MPM**), a naturally occurring glycolipid found in the cell walls of *Mycobacterium tuberculosis*, acts as a potent antigen to activate T-cells upon presentation by CD1c protein. The lipid portion of **C_{32}-MPM** contains a **C_{32}-mycoketide**, consisting of a saturated oligoisoprenoid chain with five chiral methyl branches. Here we develop several stereocontrolled approaches to assemble the oligoisoprenoid chain with high stereopurity (>96%) using Julia−Kocienski olefinations followed by diimide reduction. By careful choice of olefination sites, we could derive all chirality from a single commercial compound, methyl (2*S*)-3-hydroxy-2-methylpropionate (>99% ee). Our approach is the first highly stereocontrolled method to prepare **C_{32}-MPM** molecule with >96% stereopurity from a single >99% ee starting material. We anticipate that our methods will facilitate the highly stereocontrolled synthesis of a variety of other natural products containing chiral oligoisoprenoid-like chains, including vitamins, phytol, insect pheromones, and archaeal lipids.

INTRODUCTION

Major histocompatibility complex (MHC) class I, MHC class II, and CD1 are three important antigen-presenting systems that function to display structurally diverse antigens. Whereas classical MHC proteins bind peptides and glycopeptides, CD1 proteins bind lipids specifically.[1−6] Five homologous isoforms, CD1a, CD1b, CD1c, CD1d, and CD1e, comprise the human CD1 family.[7] Among the lipids presented by CD1c are β-D-mannosyl phosphomycoketides (**C_{30-34}-MPMs**), which were isolated in 2000 from the cell walls of *M. tuberculosis* and *M. avium*.[8] Biosynthesized via the action of polyketide synthase 12,[9] these **MPMs** contain single alkyl chains that have five methyl branches with (*S*)-configuration.[10] T cells reactive to CD1c presenting MPM secrete IFN-γ, an important cytokine in the immunological response against *M. tuberculosis*.[8,9] We were interested in obtaining a sizable amount of **C_{32}-MPM** (Figure 1) in stereopure form for use in co-crystallization with CD1c. When we initiated this work, CD1c was the only member of the human CD1 family for which no crystal structure was available.

Isolation from natural sources has produced exceedingly low yields of **C_{32}-MPM**, but total chemical synthesis has provided useful quantities of these antigenic lipids and several derivatives thereof, enabling analysis of structural features that confer a T-cell response.[8,10] Two previous reports on the synthesis of **MPM** compounds have appeared in literature.[11,12] In 2002, Crich and Dudkin reported a stereorandom synthesis of **C_{20-30}-MPMs**, starting from geranyl acetate, via coupling of planar alkene precursors and subsequent Adams (PtO_2) catalytic hydrogenation.[11] In 2006, van Summeren et al. reported the synthesis of **C_{32}-MPM** in enantiomerically enriched form via Julia−Kocienski couplings of chiral building blocks containing one or two methyl branches and palladium-catalyzed hydrogenations.[12] The chiral building blocks derive from conjugate addition of methylmagnesium bromide to α,β-unsaturated carbonyl thioester[12] and from conjugate addition of dimethylzinc to cycloocta-2,7-dienone[13] in the presence of chiral phosphorus ligands. This synthetic approach reportedly gave **C_{32}-mycoketide** containing only trace amounts of diastereomeric impurities, attributed to the relatively low enantioselectivity (93% ee) of the conjugate addition of methylmagnesium bromide to α,β-unsaturated carbonyl thioester that was carried through the synthesis.[12,14] However, Curran and coworkers recently demonstrated that the stereopurity of **C_{32}-mycoketide** prepared in this manner has only modest stereopurity (~70%).[15] This low stereopurity of the mycoketide is possiblly due to both stereochemical heterogenity of the building blocks and epimerization that likely occurred during palladium catalyzed hydrogenation.[16] Analogous hydrogenation reactions described here underscore the latter concern.

We report several new synthetic strategies to prepare **C_{32}-mycoketide** with significantly higher stereopurity than reported previously. In contrast to the existing approaches,[12] which required multiple conjugate addition reactions involving

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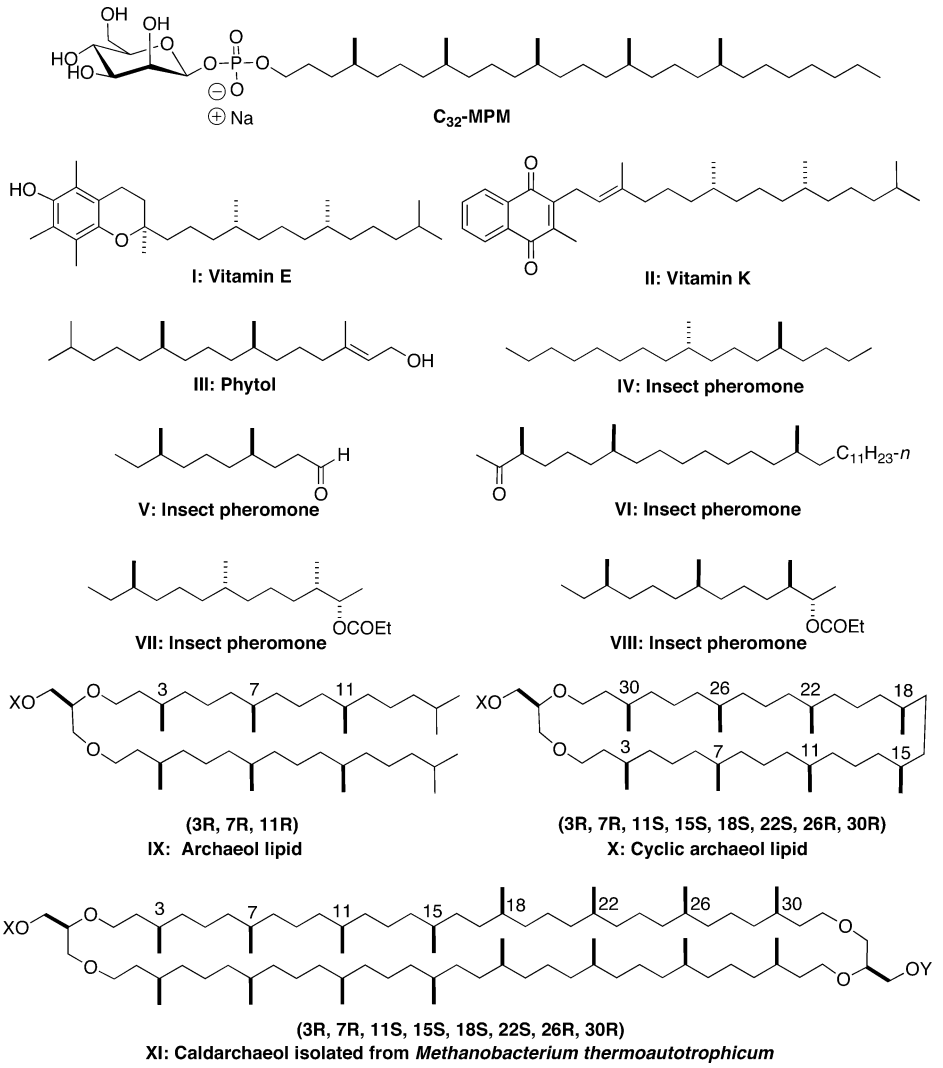

Figure 1. Examples of natural products containing saturated 1,5-dimethyl alkyl subunits.

different starting materials, all chiral fragments used in this work derive from a single commercially available chiral substrate, methyl (2*S*)-3-hydroxy-2-methylpropionate (**1**) (>99.0% ee). In addition, our synthetic approach circumvents the formation of diastereomeric impurities. Crystallization of CD1c loaded with our synthetic **C_{32}-MPM** ligand yielded a 2.5 Å crystal structure of the complex.[17] In addition to enabling facile synthesis of other MPM derivatives and stereoisomers, we anticipate that our synthetic strategies will facilitate the synthesis of other natural products containing 1,5-dimethyl alkyl subunits (Figure 1), such as vitamins (**I**, **II**),[18,19] phytol (**III**),[20] insect pheromones (**IV**–**VIII**),[21−29] and archaeal lipids (**IX**–**XI**).[30−35]

Retrosynthetic Analysis. Previous work[12] has shown that Julia–Kocienski olefinations[36,37] followed by hydrogenation enabled access to the **C_{32}-mycoketide** from three appropriately derivatized fragments corresponding to C_{1-6}, C_{7-14}, and C_{15-20+} (see top of Figure 2 for carbon numbering scheme), each containing one or two chiral methyl groups.[12] With this overall strategy in mind, we envisioned that shifting the bond disconnections by one unit would allow access to the **C_{32}-mycoketide** via three fragments (corresponding to C_{1-5}, C_{6-13}, and C_{14-20+}), which could be derived from the same commercially available chiral source, methyl (2*S*)-3-hydroxy-2-methylpropionate (**1**). Additionally, this adjustment would circumvent the conjugate addition reaction that putatively limited the overall stereopurity in the previous approach.[12] We evaluated three different strategies for the synthesis of **C_{32}-mycoketide** using *N*-phenyltetrazolyl sulfone (**9**) as the C_{1-5} fragment, an unsaturated aldehyde (**17** or **32**) as the C_{6-13} fragment, and an *N*-phenyltetrazolyl sulfone (**22** or **39**) or aldehyde **32** as the C_{14-20+} fragment (Figure 2, Methods A, B and C).

RESULTS AND DISCUSSION

Method A: Synthesis of C_{32}-Mycoketide (83% Stereopurity) by the Coupling of Fragments 9, 17, and 22 Followed by Pt/Pd-Catalyzed Hydrogenations (Schemes 1−4). *1. Synthesis of the C_{1-5} Fragment: β-Methylalkyl N-Phenyltetrazolyl Sulfone **9** (Scheme 1).* Nicolaou et al.[38] have prepared **7** in seven steps from methyl (2*S*)-3-hydroxy-2-methylpropionate (**1**) in 52% overall yield. Using the same starting material **1**, we developed an alternative synthetic approach to alcohol **7** in nine steps (57% overall yield) (Scheme 1). Compound **1** allowed access to enantiomerically pure (3*R*)-4-(*tert*-butyldiphenylsiloxy)-3-methylbutanal (**3**)[39,40] in five steps (81% yield). Wittig reaction or Julia–Kocienski olefination of aldehyde **3** gave terminal alkene **4** in 81% yield.

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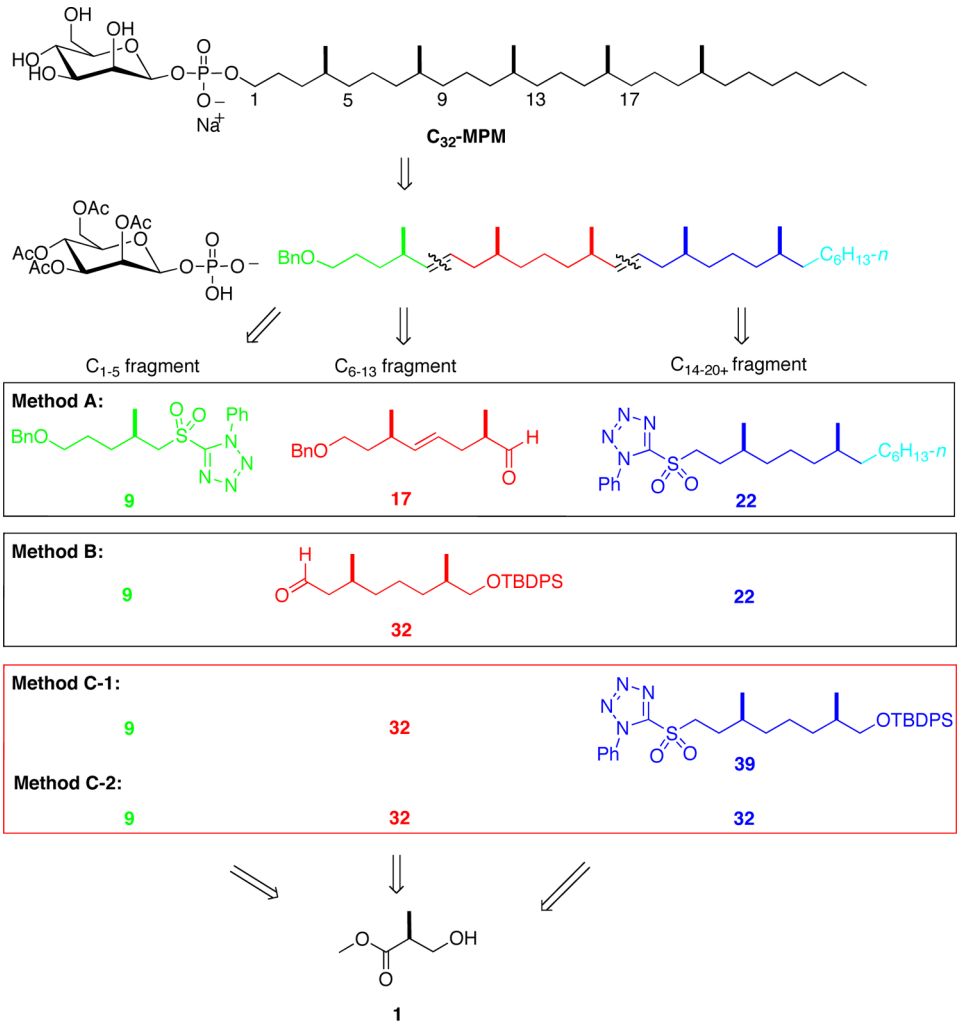
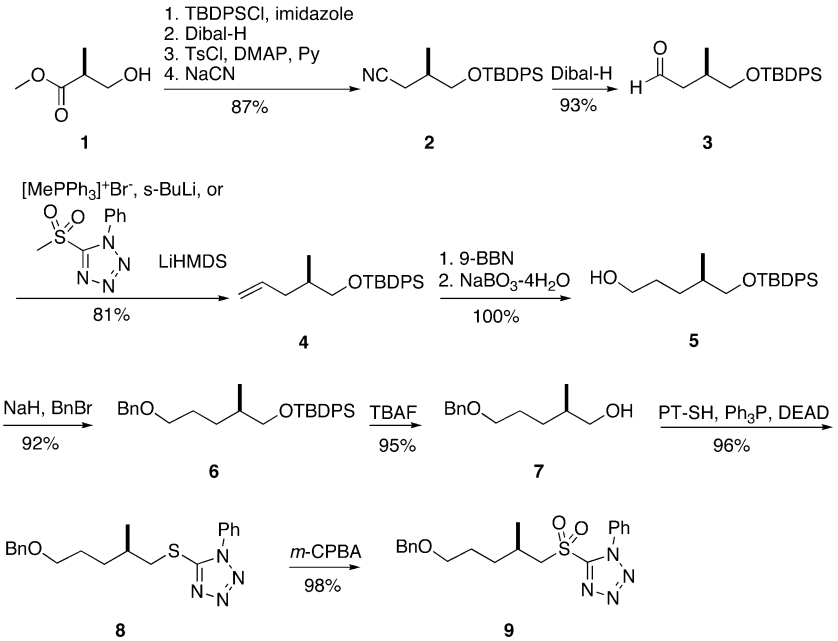


Figure 2. Retrosynthetic analysis of C_{32}-**MPM**.

Scheme 1. Synthesis of *β*-Methylalkyl *N*-Phenyltetrazolyl Sulfone 9



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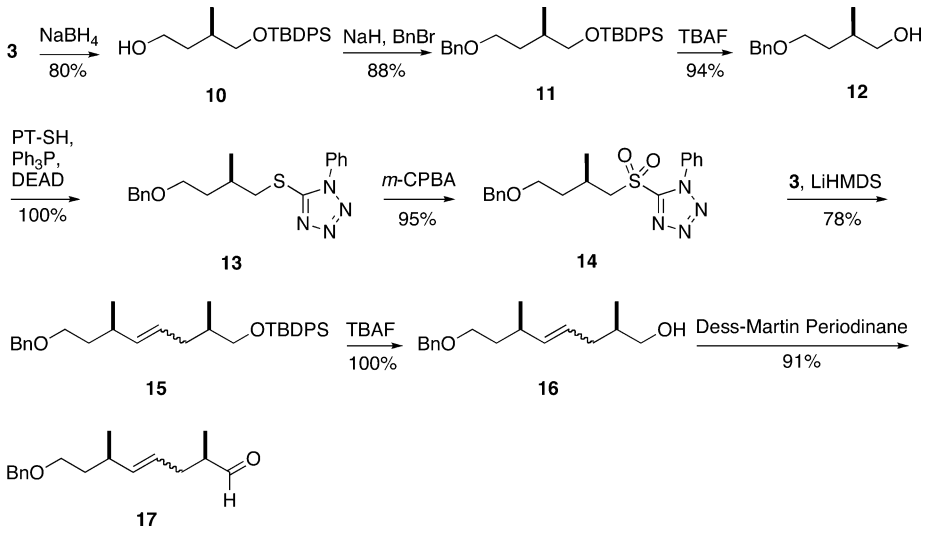
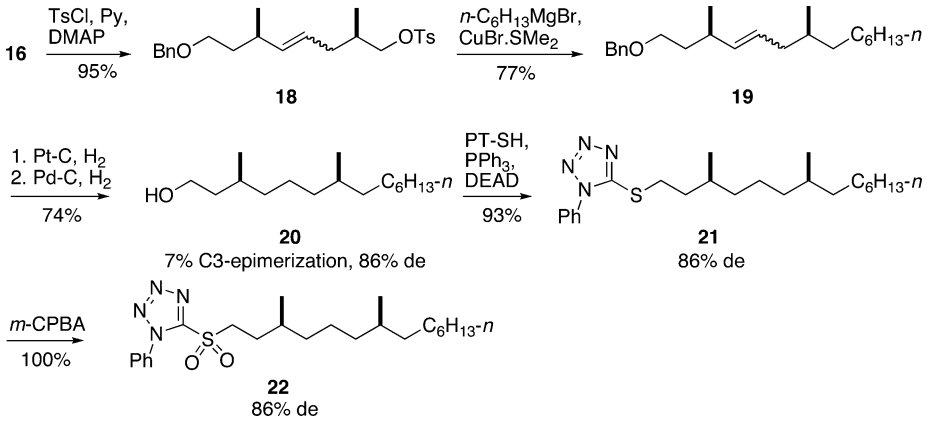
Scheme 2. Synthesis of 4,5-Unsaturated Aldehyde 17



Scheme 3. Synthesis of 3,7-Dimethylalkyl *N*-Phenyltetrazolyl Sulfone 22 (86% de)



Successive hydroboration of **4** with 9-BBN followed by oxidation with sodium perborate[41] gave alcohol **5** in quantitative yield. Subsequent benzyl protection and desilylation converted alcohol **5** into monobenzyl protected alcohol **7** in 92% and 95% yields, respectively. To convert compound **7** to **9**, a two-step substitution−oxidation sequence was employed. Compound **7** was first reacted with 1-phenyl-1*H*-tetrazole-5-thiol (PT-SH) under Mitsunobu conditions, followed by oxidation with 3-chloroperoxybenzoic acid (*m*-CPBA)[42] to generate the *N*-phenyltetrazolyl sulfone **9** in 94% yield (two steps).

*2. Synthesis of the C_{6-13} Fragment: (2R,6R)-2,6-Dimethyl-4,5-unsaturated Aldehyde **17** (Scheme 2).* Similar to the synthesis of sulfone **9**, we prepared sulfone **14** from the corresponding monobenzyl protected alcohol **12**. Substituting TBDPS for TBS to protect the hydroxyl group in **1**, the procedure outlined by Dandapani et al.[43] was used to form the monobenzyl protected alcohol **12** in slightly higher overall yield than what was previously reported (i.e., 54% yield versus 46%; Scheme 2). PT-SH substitution followed by *m*-CPBA oxidation converted **12** into the *N*-phenyltetrazolyl sulfone **14** in 95% yield. Julia−Kocienski olefination of aldehyde **3** with sulfone **14** in the presence of lithium hexamethyldisilazide yielded alkene **15** in 78% yield as a mixture of (*E*/*Z* 3:1)-isomers. The olefination yield improved in the presence of excess sulfone **14**, which could be recovered by silica gel chromatography during product purification. Desilylation of **14** with TBAF followed by oxidation with Dess−Martin periodinane (1.2 mol equiv, 3 h) gave the α-methyl-4,5-unsaturated aldehyde **17** in 91% yield.[44]

*3. Synthesis of the C_{13-20+} Fragment: (3S,7S)-3,7-Dimethyltetradecyl N-Phenyltetrazolyl Sulfone **22** (86% de) (Scheme 3).* Reaction of alcohol **16** with TsCl in pyridine yielded the corresponding tosylate **18** in 95% yield. Chain elongation of **18** with hexylmagnesium bromide in the presence of copper(I) bromide-dimethyl sulfide yielded **19** in 77% yield. Catalytic hydrogenation of **19** with 10% palladium on active carbon reduced the double bond and removed the benzyl group to give 3,7-dimethyltetradecanol (**20**). Analysis of ^{13}C NMR data for the hydrogenation product indicated that during the reduction reaction, 30% α-epimerization occurred at C-3. Metal-catalyzed hydrogenations of alkenes are known to cause α-epimerization through reversible hydrometalation.[43,45,46] Catalytic hydrogenation with platinum reportedly gave products with less isomerization than catalytic hydrogenation with palladium.[16] Using 10% platinum on active carbon, hydrogenation of **19** reduced the double bond as expected, but access to the alcohol **20** required a second, palladium-catalyzed hydrogenation to remove the benzyl group. This two-step procedure gave compound **20** in 74% yield with only 7% epimerization. The PT-SH substitution/*m*-CPBA oxidation

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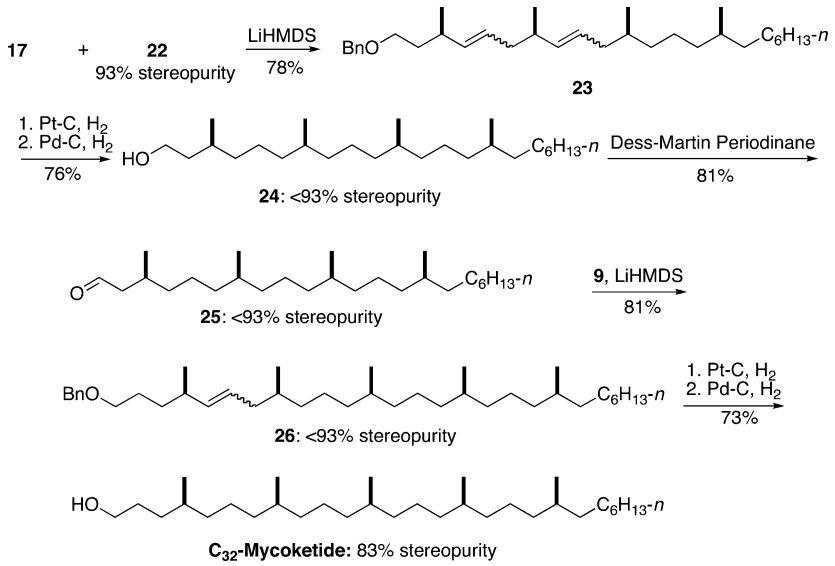
Scheme 4. Method A: Synthesis of C_{32}-Mycoketide (83% Stereopurity)



sequence converted alcohol **20** into (3*S*,7*S*)-3,7-dimethyltetradecyl *N*-phenyltetrazolyl sulfone **22** (86% de) in 93% yield (Scheme 3).

4. Synthesis of ***C_{32}-Mycoketide*** *(83% Stereopurity) by the Coupling of Fragments* ***9***, ***17***, *and* ***22*** *(86% de) Followed by Pt/Pd-Catalyzed Hydrogenation (Scheme 4).* Julia–Kocienski coupling of α-methyl-aldehyde **17** with sulfone **22** (86% de) gave diene **23** in 78% yield, corresponding to a C_{6-20+} segment. Using the two-step platinum- and, later, palladium-mediated hydrogenation procedure developed for the synthesis of **20**, we converted diene **23** to the saturated alcohol **24** in 76% yield. Oxidation of **24** with Dess–Martin periodinane generated aldehyde **25** in 81% yield. Julia–Kocienski coupling of aldehyde **25** with sulfone **9** yielded alkene **26** in 81% yield. Hydrogenation of **26**, first using platinum and then using palladium as catalysts, gave **C_{32}-mycoketide** in 73% yield and 83% stereopurity, which was estimated by a recently published ^{13}C NMR method (Figure 3A).[15] The complicated ^{13}C NMR spectrum suggested that further epimerization might have occurred in the platinum-catalyzed hydrogenation reactions of **23** and **26** (Scheme 4). Accordingly, we sought to eliminate epimerization by developing an approach that avoids the metal-catalyzed hydrogenation steps.

Method B: Total Synthesis of C_{32}-Mycoketide (>96% Stereopurity) by Coupling of Sulfone 9, Saturated Aldehyde 32, and Stereopure Sulfone 22 Followed by Diimide Reduction (Scheme 5). *1. Synthesis of the Stereopure C_{13-20+} Fragment: (3S,7S)-3,7-Dimethyltetradecyl N-Phenyltetrazolyl Sulfone* ***22*** *via Diimide Reduction.* Diimide (HN=NH), a widely investigated reagent in organic synthesis, offered an attractive alternative for alkene reduction, as the proposed reaction mechanism involves a cyclic transition state that precludes epimerization.[47,48] We carried out reduction reactions with alkene **15** under a variety of conditions and obtained the best results with 100 equiv of hydrazine and 10% copper(II) sulfate in ethanol at 70 °C for 15 h. These conditions converted **15** into the stereopure **27** in 97% yield with no detectable epimerization (Scheme 5). Desilylation followed by tosylation converted **27** to tosylate **29** in high yield (89%). Extension of the alkyl chain by coupling with hexylmagnesium bromide in the presence of copper(I) bromide-dimethyl sulfide complex gave the benzyl ether **30** in 84% yield. Following debenzylation with palladium-catalyzed hydrogenation, we converted the stereopure *syn,syn*-3,7-dimethyl-1-tetradecanol **20** into stereopure *N*-phenyltetrazolyl sulfone **22** according to the method described in Scheme 3 (93% yield, two steps).

2. Synthesis of the C_{6-13} Fragment: Saturated Aldehyde ***32***. We prepared aldehyde **32** from the stereopure chiral substrate **27** in two steps (Scheme 5). Debenzylation of **27** by palladium-catalyzed hydrogenation gave stereopure alcohol **31** in 93% yield. Attempts to obtain **31** directly from **15** by palladium-catalyzed hydrogenation and debenzylation gave only 64% yield of product with only 87% stereopurity (74% de). Clearly, the diimide reduction procedure circumvented the epimerization issue. Oxidation of **31** with either NMO-oxide/TPAP[49] or Dess–Martin periodinane gave the corresponding aldehyde **32** in 69% and 97% yield, respectively.

3. Synthesis of ***C_{32}-Mycoketide*** *(>96% Stereopurity) by Coupling of Fragments* ***9***, ***22***, *and* ***32*** *(Scheme 5).* Julia–Kocienski coupling of aldehyde **32** with sulfone **9** gave alkene **33** in 70% yield. Desilylation of **33** with TBAF followed by oxidation with NMO-oxide/TPAP or Dess–Martin periodinane gave the corresponding aldehyde **35** in 72% and 90% yield, respectively. A second Julia–Kocienski coupling of aldehyde **35** to stereopure sulfone **22** produced the pentamethyl substituted diene **36** in 80% yield. Subsequent reduction of **36** with diimide generated the benzyl alkyl ether **37** in 86% yield. Finally, debenzylation of **37** by palladium-catalyzed hydrogenation gave 93% yield of **C_{32}-mycoketide** (>96% stereopurity) (Figure 3B).

Method C: Synthesis of C_{32}-Mycoketide (~96% Stereopurity) by Coupling of Fragments 9, 32, and 39 (C-1) or 9, 32, and 32 (C-2) (Scheme 6). *1. Method C-1: Synthesis by the Coupling of Fragments* ***9***, ***32***, *and* ***39***. We converted the dimethyl-substituted alcohol **31** to the corresponding *N*-phenyltetrazolyl sulfone **39** in two steps (86% yield) (Scheme 6). Julia–Kocienski coupling of **39** to the trimethyl substituted unsaturated aldehyde **35** in the presence of LiHMDS gave the pentamethyl substituted diene **40** in 65% yield.

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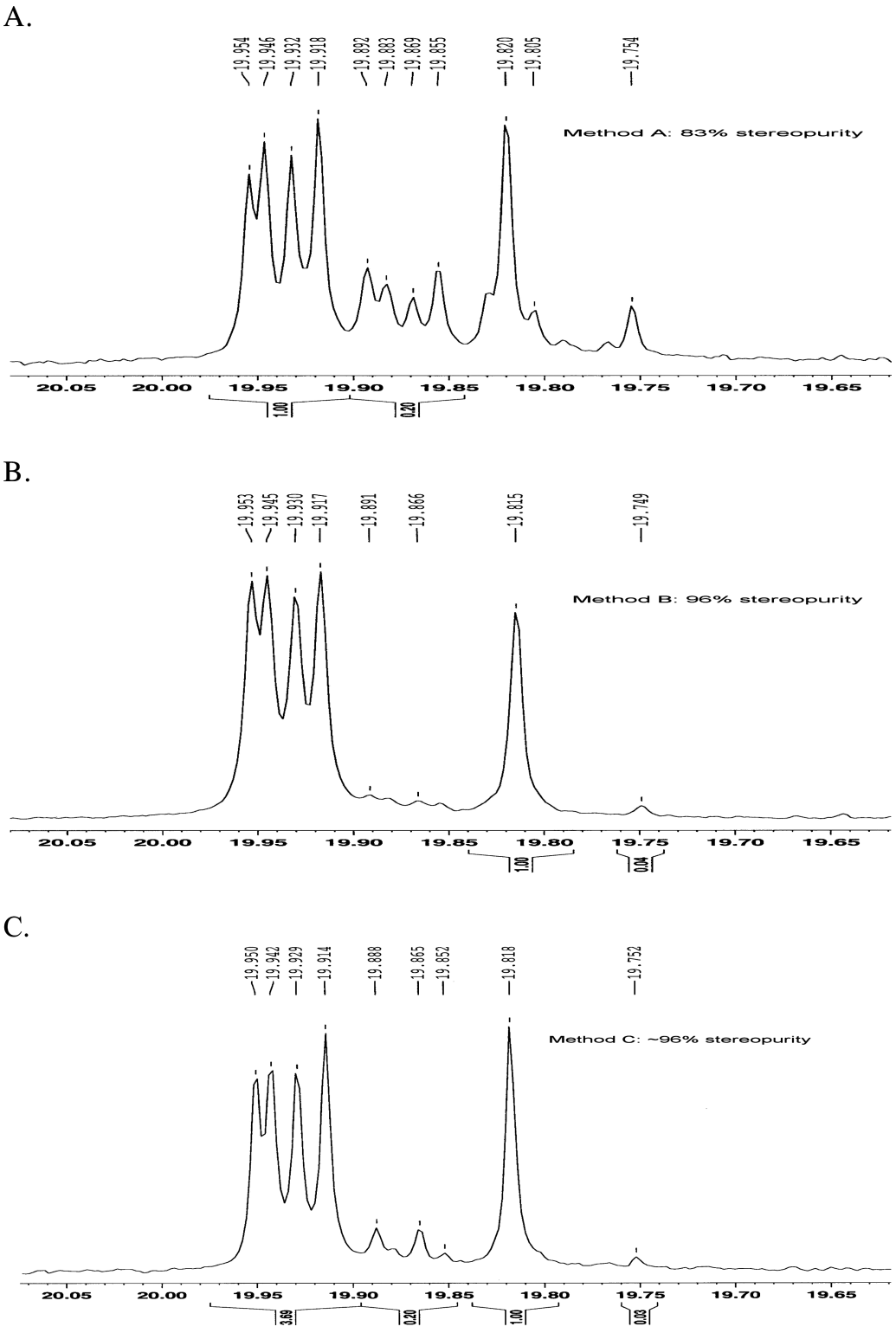

Figure 3. Mycoketide purities were estimated by integration of the ^{13}C NMR peaks. (A) Method A: 83% stereopurity, (B) Method B: 96% stereopurity, and (C) Method C: 95−97% stereopurity.

*2. Method C-2: Synthesis by Coupling of Fragments **9**, **32**, and **32**.* We also converted unsaturated alcohol **34** to the trimethyl substituted *N*-phenyltetrazolyl sulfone **43** in three steps (61% yield, Scheme 6). Julia−Kocienski coupling of **43** with dimethyl-substituted aldehyde **32** gave the pentamethyl substituted alkene **44** in 56% yield.

*3. Synthesis of **C_{32}-Mycoketide** (~96% Stereopurity) from Pentamethyl-Substituted Alkenes **40** and **44**.* Reduction of **40** and **44** with diimide gave **45** in 96% and 78% yield, respectively. Removal of the TBDPS group of **45** with TBAF followed by tosylation and coupling with Grignard reagent (hexylmagnesium bromide or butylmagnesium chloride) gave the stereopure benzyl alkyl ethers **37** and **37a** in 85% and 91%

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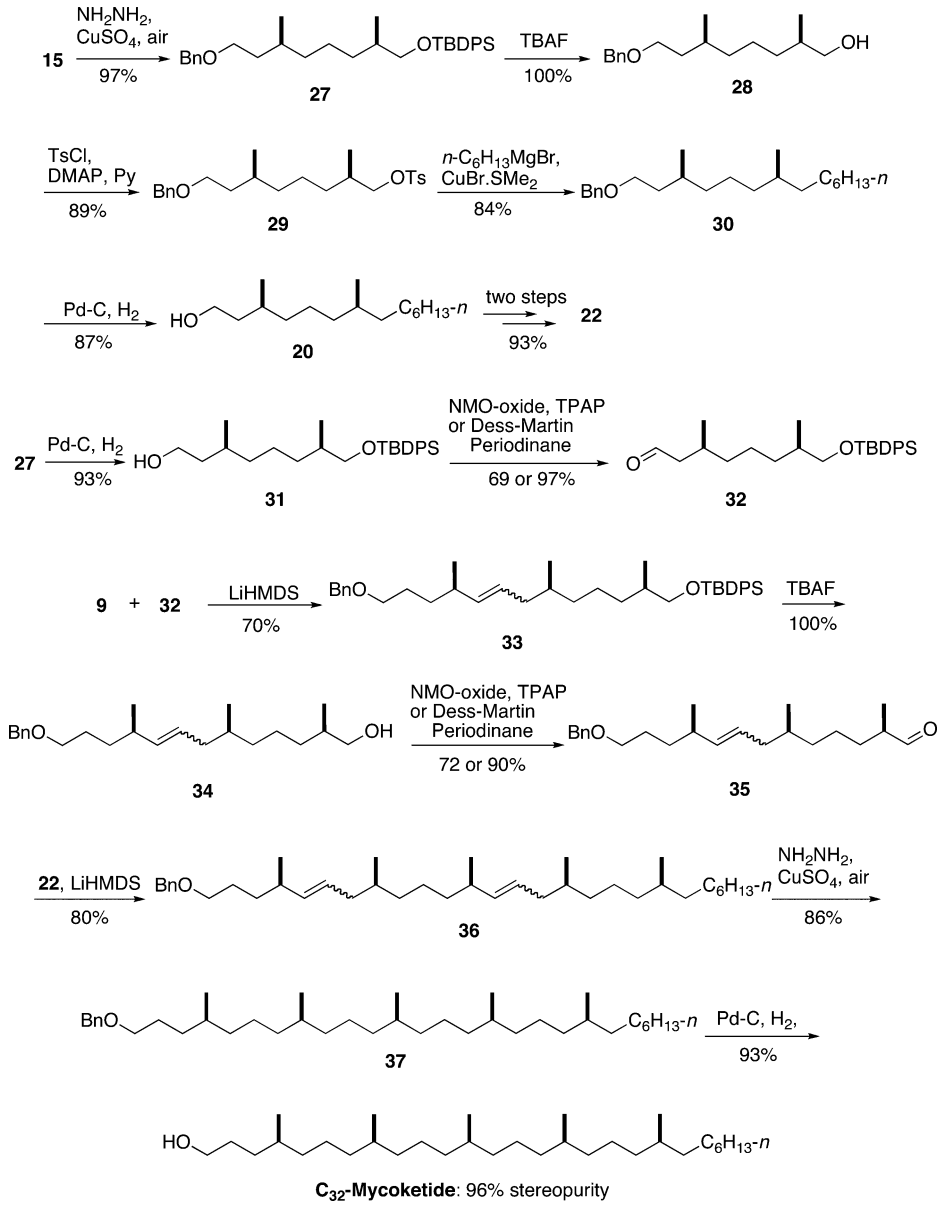
Scheme 5. Method B: Synthesis of Stereopure C_{32}-Mycoketide (>96% Stereopurity)



yield, respectively (Scheme 6). Finally, debenzylation of compound **37** afforded the **C_{32}-mycoketide** in 93% yield and ~96% stereopurity (Figure 3C). Installation of the terminal alkyl tail at the last stage renders this approach attractive for accessing other mycoketides. For example, copper-catalyzed coupling of the tosylate **47** with butylmagnesium chloride would generate the **C_{30}-mycoketide**.

Synthesis of C_{32}-MPM from C_{32}-Mycoketide (Scheme 7). We converted the **C_{32}-mycoketide** prepared from Methods B or C to the **C_{32}-MPM** molecule in two steps (83% yield) according to literature procedures[12] with some modifications. In the first step, we added DMAP to accelerate the reaction and decreased the reaction time from 4 days to 2 days. The procedure to prepare the final product **C_{32}-MPM** is described in detail in the Experimental Section.

Analysis of the Stereopurity of C_{32}-Mycoketide, Key Precursor to C_{32}-MPM. To analyze the stereoisomer impurities of our **C_{32}-mycoketides** derived from Methods A, B, and C, we used a recently published ^{13}C NMR method of Curran and co-workers.[13] As shown in Figure 3, we observed five large peaks corresponding to the five chiral methyl groups of the mycoketide and five small peaks corresponding to the methyl groups of its stereoisomer. By integration of those peaks we estimated that Method A gave **C_{32}-mycoketide** with 83% stereopurity, while Methods B and C gave **C_{32}-mycoketide** with 96% stereopurity. Most likely the measurement of 4% stereoimpurities derives partially from the method errors and the <0.5% stereoimpurity of the starting material, which would be enriched after total synthesis.

CONCLUSIONS

We have described several strategies to obtain **C_{32}-MPM** with up to 96% stereopurity. Using methyl (2*S*)-3-hydroxy-2-methylpropionate (**1**) (>99.0% ee) as the sole source of chirality, we constructed chiral building blocks corresponding to three separate fragments and connected them via Julia–Kocienski olefinations. Subsequent reduction of the double bonds with diimide allowed access to the target molecules while

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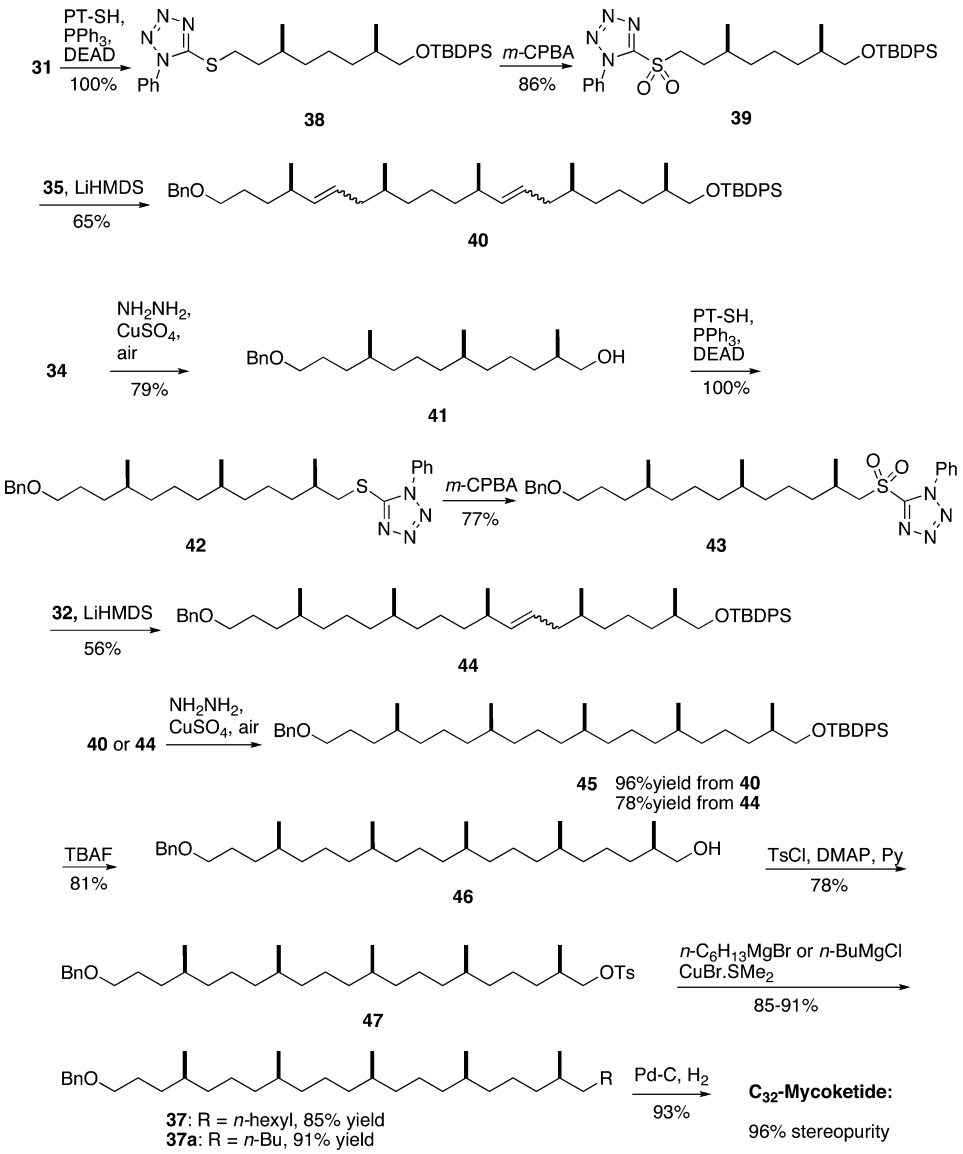
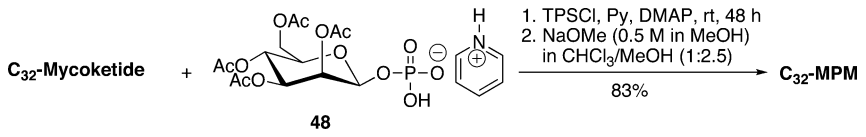
Scheme 6. Method C: Synthesis of Stereopure C_{32}-Mycoketide (~96% Stereopurity)



Scheme 7. Synthesis of C_{32}-MPM from C_{32}-Mycoketide



preserving the stereochemical integrity of the chiral centers. Although the approach bears some similarities to the approach of van Summeren et al.[12] and requires a similar number of steps, several relatively simple changes described in this work allow access to **C_{32}-mycoketide** in higher yield (Method B) and with greater stereopurity than reported previously. First, by shifting bond disconnections by one unit we are able to use a single, commercially available chiral source. In the previous synthesis of **C_{32}-mycoketide**, access to the chiral building blocks alone required substantial effort and included multiple conjugate addition reactions in the presence of chiral ligands.[12,13] One of those reactions proceeded with relatively low stereoselectivity (93% ee). Second, our use of diimide instead of catalytic hydrogenation to accomplish the reductions following olefination has completely eliminated the epimerization problem that likely corrupted stereochemical integrity in the previous synthesis. Our approach represents the only highly stereocontrolled approach to prepare the C_{32}-MPM molecule with up to 96% stereopurity from >99% ee starting material.

Additional benefits of our approach include relatively straightforward access to ***β*-C_{32}-MPM** stereoisomers and other mycoketide derivatives. Both methyl (2*R*)- and (2*S*)-3-hydroxy-2-methylpropionate are commercially available (>99.0% ee) and can serve as chiral precursors to prepare stereopure forms of any of the 32 **C_{32}-MPM** stereoisomers via Methods B and C. Method C installs the straight-chain alkyl group at a late stage, allowing convenient preparation of other mycoketide derivatives from intermediate **47** (Scheme 6). The

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facile synthesis of other MPM molecules such as **C_{30}-MPM** and the MPM stereoisomers may allow detailed functional analysis of how CD1c protein binds to various natural and unnatural **MPMs** that may activate, partially activate, or deactivate T-cells. The ability to produce highly stereopure methyl branched isoprenoid chains may also be applied to the total synthesis of other natural products containing 1,5-dimethyl alkyl subunits (Figure 1) including archaeal lipids, which have garnered great attention recently for biotechnology applications.[50−58]

EXPERIMENTAL SECTION

(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutanenitrile (2). (62.0 g, 87% yield) Prepared from methyl (2*S*)-3-hydroxy-2-methylpropionate (**1**) (25.0 g, 212 mmol) in four steps according to literature procedure.[39,40] ^{1}H NMR ($CDCl_3$/TMS) δ 7.68−7.60 (m, 4H), 7.48−7.36 (m, 6H), 3.63 (dd, 1H, J = 4.4, 10.0 Hz), 3.47 (dd, 1H, J = 7.2, 10.0 Hz), 2.56 (dd, 1H, J = 5.6, 16.8 Hz), 2.38 (dd, 1H, J = 7.6, 16.8 Hz), 2.08 (m, 1H), 1.06 (s, 9H), 1.03 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 135.67, 135.64, 133.32, 133.26, 130.0, 127.9, 119.0, 67.0, 33.4, 27.0, 21.2, 19.4, 16.0.

(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutanal (3). (12.0 g, 93% yield) Prepared from (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanenitrile (**2**) (12.8 g, 37.9 mmol) according to literature procedure.[39,40] ^{1}H NMR ($CDCl_3$/TMS) δ 9.78 (dd, 1H, J = 2.0, 2.4 Hz), 7.70−7.60 (m, 4H), 7.48−7.30 (m, 6H), 3.58 (dd, 1H, J = 5.2, 10.0 Hz), 3.43 (dd, 1H, J = 7.2, 10.0 Hz), 2.60 (ddd, 1H, J = 2.0, 5.6, 15.8 Hz), 2.40−2.20 (m, 2H), 1.05 (s, 9H), 0.94 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 202.8, 135.70, 135.68, 133.58, 133.56, 129.8, 127.8, 68.5, 48.3, 31.4, 26.9, 19.4, 16.9.

(4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methyl-1-petene (4). *A. Via Wittig Reaction.* Under argon, *s*-BuLi (1.4 M in cyclohexane) (21.4 mL, 30.0 mmol) was added slowly to a suspension of triphenylmethylphosphonium bromide (10.7 g, 30.0 mmol) in anhydrous THF (60 mL) at −78 °C. After the mixture was stirred at −78 °C for 1 h, a solution of (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanal (**3**) (4.09 g, 12.0 mmol) in anhydrous THF (30 mL) was transferred to the mixture under argon. The mixture was warmed to rt and stirred overnight. The solid was filtered off and rinsed with Et_2O. The filtrate was washed with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with hexane to give **4** as an oil:[59] 3.24 g (80% yield).

B. Via Julia−Kocienski Olefination. Under argon, LiHMDS (0.50 M in THF, 17.0 mL, 8.50 mmol) was added in a dropwise fashion over 30 min to a solution of 5-(methanesulfonyl)-1-phenyl-1*H*-tetrazole (1.80 g, 8.01 mmol) and (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanal (**3**) (2.72 g, 7.99 mmol) in anhydrous THF (70 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 3 h and then allowed to warm to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with Et_2O (3 × 35 mL). The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with hexane to give **4** as an oil:[59] 2.19 g (81% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.64 (m, 4H), 7.43−7.32 (m, 6H), 5.82−5.68 (m, 1H), 5.04−4.92 (m, 2H), 3.49 (m, 2H), 2.26 (m, 1H), 1.91 (m, 1H), 1.76 (m, 1H), 1.06 (s, 9H), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 137.3, 135.7, 134.1, 129.6, 127.7, 115.8, 68.4, 37.7, 35.8, 27.0, 19.4, 16.5.

(4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methyl-1-petanol (5). Under argon, 9-BBN (2.27 g, 9.30 mmol) was added to a solution of (4*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-methyl-1-petene (**4**) (2.11 g, 6.23 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred at rt overnight. Water (15 mL) and $NaBO_3{\cdot}4H_2O$ (8.59 g, 55.8 mmol) were added, and the mixture was stirred at rt for 2 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined and washed with brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give **5** as an oil:[38,60] 2.22 g, (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.64 (m, 4H), 7.43−7.32 (m, 6H), 5.82−5.68 (m, 1H), 5.04−4.92 (m, 2H), 3.49 (m, 2H), 2.26 (m, 1H), 1.91 (m, 1H), 1.76 (m, 1H), 1.06 (s, 9H), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 135.6, 134.0, 129.5, 127.6, 68.7, 63.3, 35.5, 30.2, 29.1, 26.9, 19.3, 16.8.

(2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-methyl-5-benzoxypentane (6). Under argon to a solution of (4*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-methyl-1-petanol (**5**) (0.235 g, 0.659 mmol) in anhydrous THF (5 mL) at 0 °C was added NaH (50.0 mg, 95%, 1.98 mmol). After the mixture was stirred at 0 °C for 10 min, benzyl bromide (339 mg, 1.98 mmol) was added, and the reaction mixture was stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **6** as an oil:[6] 0.270 g (92% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.63 (m, 4H), 7.44−7.22 (m, 11H), 4.49 (s, 2H), 3.52 (dd, 1H, J = 6.0, 9.6 Hz), 3.47−3.40 (m, 3H), 1.72−1.59 (m, 2H), 1.59−1.45 (m, 2H), 1.19 (m, 1H), 1.05 (s, 9H), 0.93 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.8, 134.2, 129.6, 128.5, 127.72, 127.70, 127.6, 73.0, 70.9, 69.0, 35.8, 29.8, 27.4, 27.0, 19.5, 17.0.

(2*R*)-2-Methyl-5-benzoxy-1-pentanol (7). TBAF (1.0 M in THF, 3.4 mL, 3.4 mmol) was added to a solution of (2*R*)-1-(*tert*-butyldiphenylsilyloxy)-2-methyl-5-benzoxypentane (**6**) (1.01 g, 2.26 mmol) in THF (5 mL). After the mixture was stirred at rt overnight, the solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 20% ethyl acetate in hexane to give **7** as an oil:[38] 0.445 g (95% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.50 (s, 2H), 3.49−3.40 (m, 4H), 1.81 (brs, 1H), 1.76−1.42 (m, 4H), 1.21 (m, 1H), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 138.6, 128.5, 127.8, 127.7, 73.1, 70.8, 68.2, 35.7, 29.7, 27.2, 16.7.

5-[(2*R*)-5-Benzoxy-2-methylpentylsulfanyl]-1-phenyl-1*H*-tetrazole (8). Under argon to a solution of (2*R*)-2-methyl-5-benzoxy-1-pentanol (**7**) (922 mg, 4.43 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (947 mg, 5.31 mmol) in anhydrous THF (15 mL) at 0 °C were added PPh_3 (1.39 g, 5.31 mmol) and DEAD (0.85 mL, 5.3 mmol). After the mixture was stirred at rt for 1 h, the reaction was quenched with water. The aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed under vacuum. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **8** as an oil: 1.57 g (96% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.60−7.50 (m, 5H), 7.36−7.23 (m, 5H), 4.49 (s, 2H), 3.50−3.43 (m, 3H), 3.27 (dd, 1H, J = 12.4, 7.2 Hz), 1.97 (m, 1H), 1.78−1.54 (m, 3H), 1.41−1.25 (m, 1H), 1.05 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 154.8, 138.6, 133.8, 130.1, 129.8, 128.4, 127.7, 127.6 123.9, 73.0, 70.3, 40.5, 32.9, 32.5, 27.2, 19.1; HRMS (ESI/APCl) calcd for $C_{20}H_{25}N_4OS$ [MH^+] 369.1744, found 369.1749.

5-[(2*R*)-5-Benzoxy-2-methylpentane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (9). To a solution of 5-[(2*R*)-5-benzoxy-2-methylpentylsulfanyl]-1-phenyl-1*H*-tetrazole (**8**) (1.54 g, 4.18 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *m*-CPBA (77% purity, 4.69 g, 20.9 mmol). After the reaction mixture was stirred at rt overnight, 10% aqueous $Na_2S_2O_3$ (8.0 mL) and saturated aqueous $NaHCO_3$ (12 mL) were added and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and subsequently washed with 10% aqueous $Na_2S_2O_3$ (2 × 8 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **9** as semisolid: 1.64 g (98% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.61 (m, 2H), 7.51 (m, 3H), 7.35−7.20 (m, 5H), 4.46 (s, 2H), 3.77 (dd, 1H, J = 14.5, 4.5 Hz), 3.54 (dd, 1H, J = 14.5, 7.5 Hz), 3.44 (m, 2H), 2.32 (m, 1H), 1.70−1.55 (m, 1H), 1.43 (m, 1H), 1.12 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 153.9, 138.2, 132.9, 131.2, 129.4, 128.2, 127.43, 127.37, 125.0, 72.7, 69.7, 61.5, 32.9, 28.0, 26.4, 19.4; HRMS (ESI/APCl) calcd for $C_{20}H_{25}N_4O_3S$ [MH^+] 401.1642, found 401.1641.

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(3*R*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methyl-1-butanol (10). To a solution of (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanal (**3**) (11.5 g, 33.7 mmol) in a mixed solvent of methanol/water (10:1, v/v) (150 mL) at 0 °C was added slowly sodium borohydride (3.19 g, 84.3 mmol). After the mixture was stirred at 0 °C for 1 h, the reaction was quenched with 1 N HCl. The aqueous layer was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give **10** as an oil:[61,62] 9.23 g (80% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.60 (m, 4H), 7.48−7.30 (m, 6H), 3.69 (m, 2H), 3.52 (m, 2H), 2.50 (brs, 1H), 1.82 (m, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 1.06 (s, 9H), 0.90 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 135.60, 135.59, 133.5, 129.7, 127.7, 69.2, 61.2, 37.4, 33.3, 26.8, 19.2, 17.2.

(2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-methyl-4-benzoxybutane (11). Under argon, NaH (95% purity, 440 mg, 17.4 mmol) was added to a solution of (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanol (**10**) (4.57 g, 13.4 mmol) in anhydrous THF (25 mL) at 0 °C. After the mixture was stirred at 0 °C for 20 min, benzyl bromide (3.14 g, 2.18 mL) was added, and the mixture was stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 2% ethyl acetate in hexane to give **11** as an oil:[62] 5.10 g (88% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.68−7.62 (m, 4H), 7.45−7.22 (m, 11H), 4.46 (m, 2H), 3.55−3.43 (m, 4H), 1.90−1.75 (m, 2H), 1.45 (m, 1H), 1.05 (s, 9H), 0.94 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 138.80, 135.76, 134.1, 129.6, 128.5, 127.73, 127.72, 127.6, 73.0, 68.9, 68.8, 33.3, 33.1, 27.0, 19.5, 17.1.

(2*R*)-2-Methyl-4-benzoxy-1-butanol (12). (2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-methyl-4-benzoxybutane (**11**) (9.55 g, 22.1 mmol) was dissolved into THF (50 mL) and treated with TBAF (1.0 M, 33.0 mL, 33.0 mmol) at rt overnight. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 20% ethyl acetate in hexane to give **12** as an oil:[43] 4.04 g (94% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.52 (s, 2H), 3.60−3.40 (m, 4H), 2.68 (brs, 1H), 1.80 (m, 1H), 1.69 (m, 1H), 1.57 (m, 1H), 0.92 (d, 3H, J = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 138.1, 128.5, 127.9, 127.8, 73.2, 68.8, 68.2, 34.2, 34.1, 17.3.

5-[(2*R*)-4-Benzoxy-2-methylbutylsulfanyl]-1-phenyl-1*H*-tetrazole (13). Under argon, PPh_3 (6.53 g, 24.9 mmol) and DEAD (4.0 mL, 25 mmol) were added to a solution of (2*R*)-2-methyl-4-benzoxy-1-butanol (**12**) (4.03 g, 20.7 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (4.44 g, 24.9 mmol) in anhydrous THF (70 mL) at 0 °C. After the mixture was stirred at rt for 1 h, the reaction was quenched with water, and the aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **13** as an oil: 7.34 g (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.60−7.50 (m, 5H), 7.35−7.24 (m, 5H), 4.52−4.46 (m, 2H), 3.60−3.52 (m, 2H), 3.49 (dd, 1H, J = 12.5, 6.0 Hz), 3.33 (dd, 1H, J = 12.5, 7.5 Hz), 2.16 (m, 1H), 1.84 (m, 1H), 1.58 (m, 1H), 1.06 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 154.8, 138.4, 133.8, 130.1, 129.8, 128.4, 127.7, 127.6 124.0, 73.1, 68.0, 40.5, 35.6, 30.5, 19.2; HRMS (ESI/APCl) calcd for $C_{19}H_{23}N_4OS$ [MH^+] 355.1587, found 355.1592.

5-[(2*R*)-4-Benzoxy-2-methylbutane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (14). To a solution of 5-[(2*R*)-4-benzoxy-2-methylbutylsulfanyl]-1-phenyl-1*H*-tetrazole (**13**) (7.30 g, 20.6 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added *m*-CPBA (77% purity, 23.1 g, 103 mmol). After the reaction mixture was stirred at rt overnight, 10% aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous $NaHCO_3$ (60 mL) were added and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The organic layers were combined and subsequently washed with 10% aqueous $Na_2S_2O_3$ (2 × 40 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **14** as semisolid: 7.59 g (95% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.55 (m, 5H), 7.36−7.24 (m, 5H), 4.48 (s, 2H), 4.00 (dd, 1H, J = 14.8, 4.4 Hz), 3.61 (dd, 1H, J = 14.8, 8.4 Hz), 3.59−3.51 (m, 2H), 2.54 (m, 1H), 1.83 (m, 1H), 1.71 (m, 1H), 1.18 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 154.1, 138.2, 133.2, 131.5, 129.8, 128.5, 127.8, 125.3, 73.2, 67.4, 61.9, 36.1, 26.4, 19.9; HRMS (ESI/APCl) calcd for $C_{19}H_{23}N_4O_3S$ [MH^+] 387.1485, found 387.1490.

8-Benzoxy-1-(*tert*-butyldiphenylsilyloxy)-(2*R*,6*R*)-2,6-dimethyl-4-(*Z*/*E*)-4-octene (15). Under argon, LiHMDS (0.50 M in THF, 20.0 mL, 10.0 mmol) was added in a dropwise fashion over 30 min to a solution of 5-[(2*R*)-4-benzoxy-2-methyl-butane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (**14**) (3.89 g, 10.1 mmol) and (3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutanal (**3**) (2.76 g, 8.11 mmol) in anhydrous THF (100 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 3 h and then allowed to warm to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **15** as an oil: 3.16 g (78% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.22 (m, 15H), 5.35−5.10 (m, 2H), 4.44 (m, 2H), 3.54−3.37 (m, 4H), 2.30−2.10 (m, 2H), 1.88−1.78 (m, 1H), 1.73−1.47 (m, 3H), 1.06 (s, 9H), 0.97−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 138.8, 137.3, 136.6, 135.8, 134.20, 134.18, 129.6, 128.4, 127.8, 127.7, 127.6, 127.3, 127.2, 73.1, 73.0, 69.0, 68.8, 68.7, 68.5, 37.4, 37.0, 36.7, 36.3, 36.2, 33.8, 31.1, 28.8, 27.0, 21.5, 21.2, 19.5, 16.9, 16.6; HRMS (ESI/APCl) calcd for $C_{33}H_{44}O_2NaSi$ [MNa^+] 523.3003, found 523.3003.

8-Benzoxy-(2*R*,6*R*)-2,6-dimethyl-4-(*Z*/*E*)-4-octenol-1 (16). TBAF (1.0 M in THF, 15 mL, 15 mmol) was added to a solution of 8-benzoxy-1-(*tert*-butyldiphenylsilyloxy)-(2*R*,6*R*)-2,6-dimethyl-4-(*Z*/*E*)-4-octene (**15**) (5.05 g, 10.1 mmol) in THF (20 mL). After the mixture was stirred at rt overnight, the solvent was removed, and the residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give **16** as an oil: 2.65 g (100% yield). ^{1}H NMR showed the ratio of two isomers ~78:22. ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.23 (m, 5H), 5.40−5.15 (m, 2H), 4.47 (m, 2H), 3.50−3.32 (m, 4H), 2.35−1.40 (m, 6H), 0.98 (d, 2.35H, J = 7.0 Hz), 0.95 (d, 0.65H, J = 6.5 Hz), 0.90 (d, 0.65H, J = 6.5 Hz), 0.88 (d, 2.35H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 138.7, 137.6, 137.0, 128.8, 128.4, 128.2, 127.7, 127.6, 127.5, 126.8, 126.7, 73.0, 68.7, 68.6, 67.9, 67.8, 37.2, 36.8, 36.5, 36.2, 36.0, 33.8, 31.0, 28.6, 21.4, 21.1, 16.6, 16.4; HRMS (ESI/APCl) calcd for $C_{17}H_{27}O_2$ [MH^+] 263.2006, found 263.2003.

8-Benzoxy-(2*R*,6*R*)-2,6-dimethyl-4-(*Z*/*E*)-4-octenal (17). Under argon, Dess−Martin periodinane (522 mg, 1.23 mmol) was added to a solution of 8-benzoxy-(2*R*,6*R*)-2,6-dimethyl-(*Z*/*E*)-4-octenol-1 (**16**) (0.269 g, 1.03 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. After stirring at rt for 3 h, the reaction mixture was diluted with Et_2O (20 mL). The resulting solid was filtered off and rinsed with Et_2O. The filtrate was subsequently washed with 10% $Na_2S_2O_3$ (5 mL), $NaHCO_3$ (5 mL), and brine (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **17** as an oil: 0.242 g (91% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 9.61 (m, 1H), 7.40−7.20 (m, 5H), 5.40−5.20 (m, 2H), 4.51−4.44 (m, 2H), 3.50−3.35 (m, 2H), 2.70−2.03 (m, 4H), 1.75−1.40 (m, 2H), 1.08−0.93 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 205.0, 204.9, 138.8, 138.7, 138.0, 128.4, 127.8, 127.7, 127.6, 125.0, 124.8, 73.04, 73.00, 68.6, 68.5, 46.6, 46.3, 37.1, 36.7, 33.8, 33.7, 28.7, 28.5, 21.3, 21.0, 13.2, 13.1; HRMS (ESI/APCl) calcd for $C_{17}H_{25}O_3$ [$M + OH]^+$ 277.1804, found 277.1805. The MS result indicated the aldehyde was oxidized to the corresponding carboxylic acid.

8-Benzoxy-(2*R*,6*R*)-2,6-dimethyl-4-(*E*/*Z*)-4-octenyl *p*-Toluenesulfonate (18). Under argon, *p*-TsCl (1.41 g, 7.40 mmol) was added to a solution of 8-benzoxy-(2*R*,6*R*)-2,6-dimethyl-(*Z*/*E*)-4-octenol-1 (**16**) (1.52 g, 5.79 mmol) and DMAP (5 mg) in pyridine (10 mL) at 0 °C. After the mixture was stirred at rt overnight, TLC showed the reaction was complete. Water (10 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The organic layers were combined and subsequently washed with 1 N HCl (20 mL), water (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **18**

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as an oil: 2.29 g (95% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.78 (d, 2H, J = 7.5 Hz), 7.37−7.23 (m, 8H), 5.25−5.13 (m, 2H), 4.53−4.40 (m, 2H), 3.92−3.82 (m, 1H), 3.82−3.75 (m, 1H), 3.47−3.30 (m, 2H), 2.55 (m, 0.45H), 2.431 (s) and 2.427 (s, 3H), 2.23 (m, 0.55H), 2.12−1.95 (m, 1H), 1.90−1.75 (m, 2H), 1.69−1.39 (m, 2H), 0.93 (d, 1.65H, J = 7.0 Hz), 0.91 (d, 1.35H, J = 7.0 Hz), 0.87 (d, 1.35H, J = 6.5 Hz), 0.85 (d, 1.65H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 144.7, 138.7, 138.6, 137.8, 133.2, 129.88, 129.87, 128.4, 128.0, 127.74, 127.68, 127.56, 127.55, 125.4, 125.3, 74.6, 74.5, 73.01, 72.99, 68.6, 68.5, 37.2, 36.8, 35.7, 33.7, 33.5, 33.1, 30.6, 28.7, 21.69, 21.68, 21.3, 20.9, 16.5, 16.2; HRMS (ESI/APCl) calcd for $C_{24}H_{33}O_4S$ [MH^+] 417.2094, found 417.2101.

1-Benzoxy-(3*R*,7*S*)-3,7-dimethyl-4-(*E*/*Z*)-4-tetradecene (19). Under argon, hexylmagnesium bromide (2.0 M in Et_2O, 7.10 mL, 14.2 mmol) was added over 40 min to a solution of 8-benzoxy-(2*R*,6*R*)-dimethyl-4-(*E*/*Z*)-4-octenyl *p*-toluenesulfonate (**18**) (0.736 g, 1.77 mmol) and CuBr-SMe_2 (91 mg, 0.44 mmol) in dry THF (20 mL) at −78 °C. After stirring at −78 °C for 2 h, the solution was allowed to warm to 0 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O, and the organic layers were combined and washed with brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **19** as an oil: 453 mg (77% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.35−7.23 (m, 5H), 5.40−5.10 (m, 2H), 4.50 (m, 2H), 3.50−3.35 (m, 2H), 2.62 (m, 0.40 H), 2.27 (m, 0.60H), 2.06 (m, 0.40H), 1.95 (m, 0.6H), 1.81 (m, 1H), 1.72−1.35 (m, 3H), 1.35−1.18 (m, 11H), 1.08 (m, 1H), 1.00−0.80 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 138.84, 138.80, 137.0, 136.3, 128.5, 127.9, 127.79, 127.77, 127.6, 73.10, 73.08, 69.0, 68.9, 40.2, 37.4, 37.0, 36.8, 36.7, 34.9, 33.9, 33.6, 33.3, 32.1, 30.1, 29.5, 28.8, 27.3, 27.2, 22.8, 21.5, 21.3, 19.8, 19.6, 14.3; HRMS (ESI/APCl) calcd for $C_{23}H_{39}O$ [MH^+] 331.2995, found 331.3003.

(3*S*,7*S*)-3,7-Dimethyl-1-tetradecanol (20). *A. Method A (Product 93% Stereopurity): From 1-Benzoxy-(3R,7S)-3,7-dimethyl-4-(E/Z)-4-tetradecene (**19**) via the Two-Step Metal-Catalyzed Hydrogenation.* A suspension of 10% Pt on carbon (267 mg, 0.137 mmol) in a solvent mixture of benzene/ethanol (1:1, v/v) (15.0 mL) was pretreated with hydrogen by 5 vacuum-hydrogen cycles. Under hydrogen, a solution of **19** (453 mg, 1.37 mmol) in the same solvent mixture of benzene/ethanol (1:1, v/v) (5.0 mL) was very slowly added. After the mixture was stirred under a hydrogen balloon at rt for 16 h, the catalyst was filtered off, and the solvent was removed under vacuum. The crude intermediate was dissolved in ethyl acetate (15 mL), and 10% Pd on carbon (146 mg, 0.137 mmol) was added. The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring overnight under a hydrogen balloon, TLC showed reaction was complete. The catalyst was then filtered off, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give **20** (with 93% stereopurity) as an oil: 246 mg (74% yield). ^{13}C NMR indicated the product containing ∼7% of its isomer.

*B. Method B (Product Stereopure): From 1-Benzoxy-(3S,7S)-3,7-dimethyltetradecane (**30**).* 10% Pd on carbon (132 mg, 0.124 mmol) was added to a solution of **30** (412 mg, 1.24 mmol) in ethyl acetate (30 mL). The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring overnight under a hydrogen balloon, TLC showed reaction was complete. The catalyst was then filtered off, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give pure **20** as an oil: 262 mg (87% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 3.67 (m, 2H), 1.73 (brs, 1H), 1.59 (m, 2H), 1.42−1.00 (m, 20H), 0.92−0.82 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 61.3, 40.1, 37.6, 37.5, 37.2, 32.9, 32.1, 30.1, 29.7, 29.5, 27.2, 24.5, 22.8, 19.84, 19.78, 14.2. HRMS (EI-GCMS) calcd for $C_{16}H_{33}O$ [$M - H]^+$ 241.2531, found 241.2534.

5-[(3*S*,7*S*)-3,7-Dimethyltetradecylsulfanyl]-1-phenyl-1*H*-tetrazole (21). Under argon to a solution of (3*S*,7*S*)-3,7-dimethyl-1-tetradecanol (**20**) (947 mg, 3.91 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (837 mg, 5.31 mmol) in anhydrous THF (15 mL) at 0 °C were added PPh_3 (1.23 g, 4.69 mmol) and DEAD (0.75 mL, 4.7 mmol). After the mixture was stirred at rt for 1 h. the reaction was quenched with water. The aqueous layer was extracted with Et_2O, and the organic layers were combined. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **21** as an oil: 1.46 g (93% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.63−7.50 (m, 5H), 3.50−3.32 (m, 2H), 1.81 (m, 1H), 1.68−1.52 (m, 2H), 1.40−1.00 (m, 19H), 0.94 (d, 3H, J = 6.4 Hz), 0.88 (t, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 154.6, 133.9, 130.2, 129.9, 123.9, 37.4, 37.1, 37.0, 36.1, 32.9, 32.4, 32.0, 31.5, 30.1, 29.5, 27.2, 24.4, 22.8, 19.8, 19.3, 14.2; HRMS (ESI/APCl) calcd for $C_{23}H_{39}N_4S$ [MH^+] 403.2890, found 403.2896.

5-[(3*S*,7*S*)-3,7-Dimethyltetradecanesulfonyl]-1-phenyl-1*H*-tetrazole (22). To a solution of 5-[(3*S*,7*S*)-dimethyltetradecylsulfanyl]-1-phenyl-1*H*-tetrazole (**21**) (1.45 g, 3.61 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added *m*-CPBA (77% purity, 4.05 g, 18.1 mmol). After the reaction mixture was stirred at rt overnight, 10% aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, and subsequently washed with 10% aqueous $Na_2S_2O_3$ (10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **22** as an oil: 1.57 g (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.75−7.55 (m, 5H), 3.73 (m, 2H), 1.96 (m, 1H), 1.77 (m, 1H), 1.64 (m, 1H), 1.40−1.00 (m, 19H), 0.97 (d, 3H, J = 6.4 Hz), 0.88 (t, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 153.5, 133.1, 131.4, 129.7, 125.1, 54.3, 37.2, 37.1, 36.7, 32.7, 32.00, 31.96, 30.0, 29.4, 28.3, 27.1, 24.2, 22.7, 19.7, 19.2, 14.2; HRMS (ESI/APCl) calcd for $C_{23}H_{39}N_4O_2S$ [MH^+] 435.2788, found 435.2786.

1-Benzoxy-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethyl-4-(*E*/*Z*)-8-(*E*/*Z*)-decosa-4,8-diene (23) (≤93% Stereopurity). Under argon, LiHMDS solution (0.5 M in THF, 7.2 mL, 3.6 mmol) was added in a dropwise fashion over 30 min to a solution of 5-[(3*S*,7*S*)-3,7-dimethyltetradecanesulfonyl]-1-phenyl-1*H*-tetrazole (**22**) (93% stereopurity, 1.56 g, 3.59 mmol) and 8-benzoxy-(2*R*,6*R*)-2,6-dimethyl-(*Z*/*E*)-4-octenal (**17**) (658 mg, 2.53 mmol) in anhydrous THF (36 mL) at −78 °C. The reaction mixture was stirred at −78 °C for additional 3 h and then allowed to warm to rt overnight. The reaction was then quenched with saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 2% ethyl acetate in hexane to give product **23** (≤93% stereopurity) as an oil: 925 mg (78% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 5.38−5.10 (m, 4H), 4.48 (m, 2H), 3.50−3.35 (m, 2H), 2.68−1.00 (m, 28H), 1.00−0.80 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 138.85, 138.80, 137.3, 137.1, 137.02, 136.97, 136.55, 136.46, 136.3, 136.2, 128.4, 127.8, 127.74, 127.73, 127.6, 127.5, 127.41, 127.38, 127.35, 127.29, 127.2, 127.1, 73.10, 73.05, 73.03, 68.95, 68.94, 68.85, 68.82, 40.6, 40.4, 40.20, 40.18, 37.52, 37.51, 37.47, 37.4, 37.3, 37.21, 37.17, 37.15, 37.13, 37.06, 37.01, 36.98, 35.2, 35.0, 34.94, 34.93, 33.9, 33.6, 33.33, 33.31, 32.92, 32.91, 32.90, 32.4, 32.3, 32.1, 30.1, 29.5, 28.80, 28.79, 27.2, 24.7, 24.6, 22.8, 21.54, 21.48, 21.20, 21.16, 21.0, 20.8, 20.6, 20.3, 19.9, 19.8, 19.7, 19.6, 14.3; HRMS (ESI/APCl) calcd for $C_{33}H_{57}O$ [MH^+] 469.4404, found 469.4407.

(3*S*,7*S*,11*S*,15*S*)-3,7,11,15-Tetramethyl-1-decosanol (24) (≤93% Stereopurity). A suspension of 10% Pt on carbon (103 mg, 0.0528 mmol) in a solvent mixture of benzene/ethanol (1:1, v/v) (8.0 mL) was pretreated with hydrogen by 5 vacuum-hydrogen cycles. Under hydrogen, a solution of 1-benzoxy-(3*R*,7*R*,11*S*,15*S*)-3,7,11,15-tetramethyl-4-(*E*/*Z*)-8-(*E*/*Z*)-decosa-4,8-diene (**23**) (≤93% stereopurity, 249 mg, 0.531 mmol) in the same solvent mixture of benzene/ethanol (1:1, v/v) (2.0 mL) was very slowly added. After the mixture was stirred under a hydrogen balloon overnight, the catalyst was filtered off, and the solvent was removed. The crude intermediate was dissolved in ethyl acetate (10 mL), and 10% Pd on carbon (140 mg, 0.132 mmol) was added. The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring under a hydrogen balloon overnight, the catalyst was filtered off, and the

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solvent was removed. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **24** (≤93% stereopurity) as an oil: 155 mg, (76% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 3.65 (m, 2H), 1.90 (brs, 1H), 1.68−1.50 (m, 2H), 1.45−1.00 (m, 34H), 0.93−0.80 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 61.2, 40.1, 37.7, 37.6, 37.54, 37.47, 37.2, 32.93, 32.90, 32.1, 30.1, 29.7, 29.6, 27.2, 24.6, 24.5, 22.8, 19.90, 19.88, 19.8, 14.2; HRMS (ESI/APCl) calcd for $C_{26}H_{55}O_2$ [M + H_2O − H] 399.4197, found 399.4198.

(3*S*,7*S*,11*S*,15*S*)-3,7,11,15-Tetramethyl-decosanal (25) (≤93% Stereopurity). Under argon, Dess−Martin periodinane (206 mg, 0.486 mmol) was added to a solution of (3*S*,7*S*,11*S*,15*S*)-3,7,11,15-tetramethyl-1-decosanol (**24**) (≤93% stereopurity, 155 mg, 0.405 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. After stirring at rt for 3 h, the reaction mixture was diluted with Et_2O (50 mL). The resulting solid was removed by filtration and rinsed with Et_2O. The filtrate was subsequently washed with 10% $Na_2S_2O_3$ (10 mL), $NaHCO_3$ (10 mL), and brine (10 mL) and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **25** (≤93% stereopurity) as an oil: 0.125 g (81% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 9.76 (dd, 1H, J = 2.8, 2.0 Hz), 2.40 (ddd, 1H, J = 2.0, 3.6, 16.0 Hz), 2.22 (ddd, 1H, J = 2.4, 7.6, 16.0 Hz) 2.05 (m, 1H), 1.44−1.00 (m, 33H), 0.96 (d, 3H, J = 6.8 Hz), 0.93−0.80 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 203.2, 51.2, 37.6, 37.53, 37.50, 37.4, 37.2, 32.93, 32.91, 32.87, 32.1, 30.1, 29.6, 28.3, 27.2, 24.6, 24.5, 22.8, 20.2, 19.92, 19.89, 19.85, 14.3; HRMS (ESI/APCl) calcd for $C_{26}H_{52}O_2$ [M + O]$^+$ 396.3967, found 396.3970. The MS result indicated the aldehyde was oxidized to the corresponding carboxylic acid.

1-Benzoxy-(4*R*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethyl-5-(*E*/*Z*)-5-heptacosene (26) (≤93% Stereopurity). Under argon, LiHMDS solution (0.5 M in THF, 0.80 mL, 0.40 mmol) was added in a dropwise fashion over 3 min to a solution of 5-[(2*R*)-5-benzoxy-2-methyl-pentane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (**9**) (0.154 g, 0.385 mmol) and (3*S*,7*S*,11*S*,15*S*)-3,7,11,15-tetramethyl-decosanal (**25**) (≤93% stereopurity, 0.125 g, 0.328 mmol) in anhydrous THF (4 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to rt overnight, the reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give product **26** (≤93% stereopurity) as an oil: 149 mg (81% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 5.40−5.10 (m, 2H), 4.49 (s, 2H), 3.50−3.40 (m, 2H), 2.50−1.00 (m, 41H), 1.00−0.80 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.4, 136.8, 128.4, 127.73, 127.71, 127.57, 127.56, 127.51, 127.46, 72.99, 72.97, 70.8, 51.2, 40.2, 37.61, 37.58, 37.55, 37.53, 37.51, 37.4, 37.3, 37.2, 37.12, 37.08, 36.9, 34.9, 34.1, 33.7, 33.6, 33.4, 32.96, 32.95, 32.94, 32.91, 32.90, 32.1, 31.7, 30.2, 29.6, 28.4, 27.9, 27.8, 27.3, 24.7, 24.6, 22.9, 21.2, 20.2, 19.95, 19.93, 19.92, 19.87, 19.86, 19.7, 14.3; HRMS (ESI/APCl) calcd for $C_{39}H_{71}O$ [MH$^+$] 555.5499, found 555.5502.

8-Benzoxy-1-(*tert*-butyldiphenylsilyloxy)-(2*R*,6*S*)-2,6-dimethyl-octane (27). $CuSO_4$ (62 mg, 0.39 mmol) was added to a solution of 8-benzoxy-1-(*tert*-butyldiphenylsilyloxy)-(2*R*,6*R*)-2,6-dimethyl-(*Z*/*E*)-4-octene (**15**) (1.96 g, 3.91 mmol) and hydrazine (12.3 mL, 391 mmol) in ethanol (200 mL). The mixture was bubbled with air and stirred at 70 °C for 15 h. The solution was filtered, and the filtrate was evaporated. The resulting residue was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **27** as an oil: 1.91 g (97% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.64 (m, 4H), 7.45−7.23 (m, 11H), 4.49 (s, 2H), 3.55−3.39 (m, 4H), 1.70−1.00 (m, 10H), 1.05 (s, 9H), 0.91 (d, 3H, J = 6.4 Hz), 0.85 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.8, 134.3, 129.6, 128.5, 127.72, 127.68, 127.6, 73.0, 69.0, 68.9, 37.5, 36.9, 35.8, 33.6, 30.0, 27.0, 24.4, 19.8, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{33}H_{46}O_2NaSi$ [MNa$^+$] 525.3159, found 525.3157.

8-Benzoxy-(2*R*,6*S*)-2,6-dimethyl-1-octanol (28). TBAF (1.0 M, 8.0 mL, 4.0 mmol) was added to a solution of **27** (846 mg, 1.68 mmol) in THF (8 mL). After the mixture was stirred at rt overnight, the solvent was removed, and the residue was purified by silica gel chromatograph, eluting with 15% ethyl acetate in hexane to give product **28** as an oil: 444 mg (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.49 (s, 2H), 3.55−3.34 (m, 4H), 1.72−1.00 (m, 10H), 0.90 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 138.8, 128.4, 127.7, 127.6, 73.0, 68.8, 68.4, 37.5, 36.8, 35.8, 33.5, 30.0, 24.4, 19.8, 16.7; HRMS (ESI/APCl) calcd for $C_{17}H_{29}O_2$ [MH$^+$] 265.2162, found 265.2167.

8-Benzoxy-(2*R*,6*S*)-2,6-dimethyl-octyl *p*-Toluenesulfonate (29). Under argon, *p*-TsCl (411 mg, 2.15 mmol) was added to a solution of 8-benzoxy-(2*R*,6*S*)-2,6-dimethyl-1-octanol (**28**) (444 mg, 1.68 mmol) and DMAP (2 mg) in pyridine (5 mL) at 0 °C. After the mixture was stirred at rt overnight, water (5 mL) was added, and the mixture was extracted with Et_2O. The organic layers were combined, subsequently washed with 1 N HCl (10 mL), water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), and then dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **29** as an oil: 629 mg (89% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.78 (dt, 2H, J = 2.0, 8.4 Hz), 7.42−7.23 (m, 7H), 4.49 (s, 2H), 3.87 (dd, 1H, J = 5.6, 9.6 Hz), 3.79 (dd, 1H, J = 6.4, 9.6 Hz), 3.48 (m, 2H), 2.43 (s, 3H), 1.80−1.00 (m, 10H), 0.87 (d, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 144.7, 138.7, 133.2, 129.9, 128.4, 128.0, 127.7, 127.6, 75.2, 73.0, 68.7, 37.2, 36.8, 33.0, 32.9, 29.8, 24.0, 21.7, 19.7, 16.6; HRMS (ESI/APCl) calcd for $C_{24}H_{34}O_4NaS$ [MNa$^+$] 441.2070, found 441.2081.

1-Benzoxy-(3*S*,7*S*)-3,7-dimethyl-tetradecane (30). Under argon, hexylmagnesium bromide (2.0 M in Et_2O, 5.92 mL, 11.8 mmol) was added to a solution of **29** (620 mg, 1.48 mmol) along with CuBr-SMe_2 (76 mg, 0.37 mmol) in dry THF (20 mL) at −78 °C. After stirring at −78 °C for 2 h, the mixture was allowed to warm to 0 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the reaction mixture was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **30** as an oil: 412 mg (84% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.50 (m, 2H), 3.50 (m, 2H), 1.72−1.50 (m, 2H), 1.47−1.00 (m, 20H), 0.92−0.81 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 138.9, 128.5, 127.7, 127.6, 73.0, 68.9, 37.6, 37.5, 37.2, 36.9, 32.9, 32.1, 30.2, 30.0, 29.6, 27.2, 24.5, 22.8, 19.89, 19.86, 14.3; HRMS (ESI/APCl) calcd for $C_{23}H_{39}O$ [M − H]$^+$ 331.2995, found 331.2990.

8-(*tert*-Butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-1-octanol (31). 10% Pd on carbon (807 mg, 0.758 mmol) was added to a solution of 8-benzoxy-1-(*tert*-butyldiphenylsilyloxy)-(2*R*,6*S*)-2,6-dimethyl-octane (**27**) (1.91 g, 3.79 mmol) in ethyl acetate (50 mL). The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring overnight under a hydrogen balloon, the catalyst was filtered off, and the solvent was removed under vacuum. The resulting residue was purified by silica gel chromatography, eluting with 15% ethyl acetate in hexane to give stereopure **31** as an oil: 1.45 g (93% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.69−7.64 (m, 4H), 7.45−7.34 (m, 6H), 3.66 (m, 2H), 3.51 (dd, 1H, J = 6.0, 10.0 Hz), 3.44 (dd, 1H, J = 6.4, 10.0 Hz), 1.70−1.08 (m, 11H), 1.06 (s, 9H), 0.92 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 135.8, 134.3, 129.6, 127.7, 69.0, 61.4, 40.1, 37.6, 35.9, 33.6, 29.6, 27.0, 24.4, 19.8, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{26}H_{40}O_2NaSi$ [MNa$^+$] 435.2690, found 435.2691.

8-(*tert*-Butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-octanal (32). *A. Oxidation with NMO.* To a solution of 8-(*tert*-butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-1-octanol (**31**) (771 mg, 1.87 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added powdered 3 Å molecular sieves (1.0 g), 4-methylmorpholine *N*-oxide (NMO) (329 mg, 2.81 mmol), and TPAP (32 mg, 0.091 mmol). The resulting mixture was stirred at 0 °C for 30 min, then warmed to rt, and stirred for additional 2 h. The mixture was filtered through a pad of silica gel and then washed with 50% ethyl acetate in hexane. The solvent was removed under vacuum, and the residue was purified by silica gel

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chromatography, eluting with 5% ethyl acetate in hexane to give **32** as an oil: 0.529 g (69% yield).

B. Oxidation with Dess–Martin Periodinane. Under argon, Dess–Martin periodinane (2.67 g, 6.30 mmol) was added to a solution of **31** (2.167 g, 5.25 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring at 0 °C for 3 h, the mixture was diluted with Et_2O. The resulting solid was filtered off and rinsed with Et_2O. The filtrate was subsequently washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **32** as an oil: 2.09 g (97% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 9.73 (m, 1H), 7.69–7.64 (m, 4H), 7.45–7.34 (m, 6H), 3.55–3.40 (m, 2H), 2.34 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.65 (m, 1H), 1.50–1.00 (m, 7H), 1.06 (s, 9H), 0.95–0.89 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 203.2, 135.7, 134.2, 129.6, 127.7, 68.9, 51.1, 37.3, 35.8, 33.3, 28.3, 27.0, 24.4, 20.1, 19.4, 17.0; HRMS (ESI/APCl) calcd for $C_{26}H_{39}O_3Si$ [M + OH] 427.2663, found 427.2671. The MS result indicated the aldehyde was easily oxidized to the corresponding carboxylic acid.

1-Benzoxy-13-(*tert*-butyldiphenylsilyloxy)-(4*R*,8*S*,12*R*)-4,8,12-trimethyl-5-(*Z*/*E*)-5-tridecene (33). Under argon, LiHMDS (0.50 M in THF, 10.0 mL, 5.0 mmol) was added in a dropwise fashion over 20 min to a solution of 5-[(2*R*)-5-benzoxy-2-methyl-pentane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (**9**) (1.93 g, 4.82 mmol) and 8-(*tert*-butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-octanal (**32**) (1.794 g, 4.37 mmol) in anhydrous THF (50 mL) at −78 °C. The resulting yellow solution was stirred at −78 °C for 3 h and then allowed to warm to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **33** as an oil: 1.79 g (70% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70–7.20 (m, 15H), 5.40–5.10 (m, 2H), 4.48 (s, 2H), 3.60–3.40 (m, 4H), 2.50–1.00 (m, 15H), 1.06 (s, 9H), 1.00–0.80 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 138.8, 137.5, 136.8, 135.8, 134.3, 129.6, 128.4, 127.70, 127.68, 127.6, 127.5, 127.4, 73.1, 73.0, 70.7, 69.0, 40.1, 37.04, 36.98, 36.9, 35.9, 34.9, 34.1, 33.7, 33.6, 33.3, 31.7, 27.9, 27.8, 27.0, 24.6, 24.5, 21.5, 21.2, 19.9, 19.6, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{39}H_{60}NO_2Si$ [M + NH_4^+] 602.4388, found 602.4393.

13-Benzoxy-(2*R*,6*S*,10*R*)-2,6,10-trimethyl-8-(*Z*/*E*)-8-tridecenol-1 (34). TBAF (1.0 M in THF, 6.0 mL, 6.0 mmol) was added to a solution of 1-benzoxy-13-(*tert*-butyldiphenylsilyloxy)-(4*R*,8*S*,12*R*)-4,8,12-trimethyl-5-(*Z*/*E*)-5-tridecene (**33**) (1.79 g, 3.06 mmol) in anhydrous THF (10 mL). After the reaction mixture was stirred at rt overnight, the solvent was removed under vacuum, and the resulting residue was purified by silica gel chromatography, eluting with 10–15% ethyl acetate in hexane to give **34** as an oil: 1.06 g (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.33 (m, 5H), 5.40–5.10 (m, 2H), 4.49 (s, 2H), 3.50–3.30 (m, 4H), 2.50–1.00 (m, 15H), 1.00–0.80 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 138.7, 137.4, 136.8, 128.4, 127.7, 127.5, 127.34, 127.29, 72.9, 70.7, 68.5, 68.4, 40.2, 40.1, 36.9, 36.8, 35.9, 35.8, 34.8, 34.0, 33.6, 33.5, 33.2, 31.7, 27.9, 27.7, 24.6, 24.5, 21.5, 21.2, 19.9, 19.7, 16.73, 16.65; HRMS (ESI/APCl) calcd for $C_{23}H_{39}O_2$ [MH^+] 347.2945, found 347.2947.

13-Benzoxy-(2*R*,6*S*,10*R*)-2,6,10-trimethyl-8-(*Z*/*E*)-8-tridecenal (35). *A. Oxidation with NMO.* To a solution of 13-benzoxy-(2R,6S,10R)-2,6,10-trimethyl-8-(*Z*/*E*)-8-tridecenol-1 (**34**) (170 mg, 0.491 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added powdered 3 Å molecular sieves (0.25 g), NMO (86 mg, 0.73 mmol), and TPAP (8.6 mg, 0.024 mmol). After the mixture was stirred at rt for 2 h, TLC showed the reaction was not complete. Additional molecular sieves (750 mg), NMO (86 mg, 0.73 mmol), and TPAP (8.6 mg, 0.024 mmol) were added. The reaction was stirred at 0 °C for an additional 30 min until TLC showed the reaction was complete. The mixture was passed through a pad of silica gel, eluting with 5% ethyl acetate to give **35** as an oil: 121 mg (72% yield).

B. Oxidation with Dess–Martin Periodinane. Under argon, Dess–Martin periodinane (1.56 g, 3.67 mmol) was added to a solution of **34** (1.06 g, 3.06 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was allowed to warm to rt for 3 h until TLC showed the reaction was complete. The mixture was diluted with Et_2O, and the resulting solid was filtered off and rinsed with Et_2O. The filtrate was subsequently washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **35** as an oil: 949 mg (90% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 9.60 (m, 1H), 7.40–7.20 (m, 5H), 5.40–5.10 (m, 2H), 4.49 (s, 2H), 3.50–3.40 (m, 2H), 2.50–1.10 (m, 15H), 1.10–0.80 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 205.5, 138.8, 137.7, 137.0, 128.5, 127.8, 127.7, 127.6, 127.2, 127.1, 73.0, 70.7, 46.4, 40.0, 36.9, 36.6, 36.5, 34.8, 34.0, 33.7, 33.4, 33.1, 31.7, 30.9, 27.9, 27.8, 24.6, 24.5, 21.5, 21.2, 19.8, 19.6, 13.49, 13.46; HRMS (ESI/APCl) calcd for $C_{23}H_{37}O_3$ [M + O − H] 361.2737, found 361.2743. The MS result indicated the aldehyde was easily oxidized to the corresponding carboxylic acid.

1-Benzoxy-(4*R*,8*S*,12*R*,16*S*,20*S*)-4,8,12,16,20-pentamethyl-5-(*E*/*Z*)-13-(*E*/*Z*)-heptacos-5,13-diene (36). Under argon, LiHMDS solution (0.5 M in THF, 2.50 mL, 1.25 mmol) was added in a dropwise fashion over 10 min to a solution of pure 5-[(3*S*,7*S*)-3,7-dimethyltetradecanesulfonyl]-1-phenyl-1*H*-tetrazole (**22**) (489 mg, 1.13 mmol) and 13-benzoxy-(2*R*,6*S*,10*R*)-2,6,10-trimethyl-8-(*Z*/*E*)-tridecenal (**35**) (284 mg, 0.824 mmol) in anhydrous THF (10 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to rt overnight, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O, and the organic layers were combined. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **36** as an oil: 365 mg (80% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40–7.20 (m, 5H), 5.40–5.10 (m, 4H), 4.49 (s, 2H), 3.50–3.35 (m, 2H), 2.50–1.00 (m, 37H), 1.00–0.80 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.9, 137.8, 137.4, 137.2, 136.8, 128.5, 127.8, 127.6, 127.53, 127.46, 127.43, 127.12, 127.06, 73.0, 70.8, 40.23, 40.19, 38.0, 37.62, 37.55, 37.2, 37.1, 37.01, 36.97, 36.9, 36.8, 35.0, 34.9, 34.1, 33.71, 33.66, 33.6, 33.4, 33.3, 32.9, 32.1, 31.8, 31.7, 30.2, 29.6, 27.9, 27.8, 27.2, 25.1, 25.0, 24.9, 24.7, 24.6, 22.9, 21.5, 21.24, 21.19, 19.90, 19.85, 19.7, 19.6, 14.3; HRMS (ESI/APCl) calcd for $C_{39}H_{69}O$ [MH^+] 553.5343, found 553.5358.

1-Benzoxy-(4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethylheptacosane (37). *A. From 1-Benzoxy-(4R,8S,12R,16S,20S)-4,8,12,16,20-pentamethyl-5-(E/Z)-13-(E/Z)-heptacos-5,13-diene (36).* $CuSO_4$ (10 mg, 0.0653 mmol) was added to a solution of **36** (361 mg, 0.653 mmol) and hydrazine (2.05 mL, 65.2 mmol) in anhydrous ethanol (35 mL). After the mixture was bubbled with air and stirred at 70 °C for 15 h, the solution was filtered, and the filtrate was evaporated in vacuum. The resulting residue was then extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was evaporated under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **37** as an oil: 0.311 g (86% yield).

B. From 21-Benzoxy-(2R,6R,10R,14S,18S)-2,6,10,14,18-Pentamethylheneicosyl p-Toluenesulfonate (47). Under argon, hexylmagnesium bromide (2.0 M in Et_2O, 1.40 mL, 2.80 mmol) was added to a solution of **47** (178 mg, 0.277 mmol) along with CuBr-SMe_2 (14 mg, 0.069 mmol) in dry THF (5 mL) at −78 °C. After stirring at −78 °C for 2 h, the mixture was allowed to warm to 0 °C and then stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **37** as an oil: 131 mg (85% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 7.40–7.20 (m, 5H), 4.51 (s, 2H), 3.45 (t, 2H, J = 6.8 Hz), 1.75–1.50 (m, 2H), 1.45–0.98 (m, 43H), 0.95–0.82 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 138.9, 128.5, 127.8, 127.6, 73.0, 71.1, 37.6, 37.5, 37.2, 33.5, 33.0, 32.9, 32.8, 32.1, 30.2, 29.6, 27.5, 27.3, 24.6, 22.9, 20.0, 19.9, 19.8, 14.3; HRMS (ESI/APCl) calcd for $C_{39}H_{71}O$ [M − H]$^+$ 555.5499, found 555.5487.

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1-Benzoxy-(4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethylpentacosane (37a). Following the procedure described for the synthesis of **37** from **47**, compound **37a** was prepared from butylmagnesium chloride (2.0 M in THF, 1.0 mL, 2.0 mmol) and **47** (115 mg, 0.179 mmol) in the presence of CuBr-SMe_2 (9.2 mg, 0.045 mmol) in dry THF (5 mL). The reaction gave **37a** as an oil: 86 mg (91% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.50 (s, 2H), 3.45 (t, 2H, J = 6.8 Hz), 1.75−1.50 (m, 2H), 1.45−0.98 (m, 39H), 0.93−0.82 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 138.9, 128.5, 127.7, 127.6, 73.0, 71.1, 37.6, 37.5, 37.2, 33.5, 33.0, 32.9, 32.8, 32.4, 27.5, 26.9, 24.6, 22.9, 20.0, 19.94, 19.92, 19.8, 14.3; HRMS (ESI/APCl) calcd for $C_{37}H_{67}O$ [M − H]$^+$ 527.5186, found 527.5169.

5-[8-*tert*-Butyldiphenylsilyloxy-(3*S*,7*R*)-3,7-dimethyloctylsulfanyl]-1-phenyl-1*H*-tetrazole (38). To a solution of 8-(*tert*-butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-1-octanol (**31**) (1.215 g, 2.94 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (629 mg, 3.53 mmol) in anhydrous THF (10 mL) at 0 °C under argon were added PPh_3 (926 mg, 3.53 mmol) and DEAD (0.56 mL, 3.5 mmol). The mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with water, and the aqueous layer was then extracted with Et_2O. The organic layers were combined, and the solvent was removed under vacuum. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **38** as an oil: 1.68 g (100% yield). ^{1}H NMR ($CDCl_3$/TMS): δ 7.70−7.30 (m, 15H), 3.55−3.30 (m, 4H), 1.90−1.00 (m, 10H), 1.05 (s, 9H), 0.95−0.82 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 154.6, 135.7, 134.2, 133.9, 130.2, 129.9, 129.6, 127.7, 124.0, 69.0, 37.0, 36.1, 35.8, 33.5, 32.3, 31.5, 27.0, 24.3, 19.4, 19.3, 17.1; HRMS (ESI/APCl) calcd for $C_{33}H_{44}N_4ONaSiS$ [MNa^+] 595.2897, found 595.2907.

5-[8-*tert*-Butyldiphenylsilyloxy-(3*S*,7*R*)-3,7-dimethyl-octanesulfonyl]-1-phenyl-1*H*-tetrazole (39). To a solution of 5-[8-*tert*-butyldiphenylsilyloxy-(3*S*,7*R*)-3,7-dimethyl-octane-sulfanyl]-1-phenyl-1*H*-tetrazole (**38**) (1.68 g, 2.93 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added *m*-CPBA (77% purity, 3.28 g, 14.7 mmol). After the reaction mixture was stirred at rt overnight, 10% aqueous $Na_2S_2O_3$ (6 mL) and saturated aqueous $NaHCO_3$ (9 mL) were added and stirred for an additional 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed subsequently with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **39** as an oil: 1.523 g (86% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.74−7.33 (m, 15H), 3.81−3.62 (m, 2H), 3.50 (dd, 1H, J = 5.6, 9.6 Hz), 3.44 (dd, 1H, J = 6.0, 9.6 Hz), 2.00−1.02 (m, 10H), 1.05 (s, 9H), 0.93 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 153.6, 135.7, 134.2, 133.2, 131.6, 129.8, 129.6, 127.7, 125.2, 68.9, 54.4, 36.7, 35.8, 33.4, 32.1, 28.5, 27.0, 24.2, 19.4, 19.2, 17.0; HRMS (ESI/APCl) calcd for $C_{33}H_{44}N_4O_3NaSiS$ [MNa^+] 627.2796, found 627.2810.

1-Benzoxy-21-*tert*-butyldiphenylsilyloxy-(4*R*,8*S*,12*R*,16*S*,20*S*)-4,8,12,16,20-pentamethyl-5-(*E*/*Z*)-13-(*E*/*Z*)-heneicos-5,13-diene (40). Under argon, LiHMDS solution (0.50 M in THF, 4.80 mL, 2.40 mmol) was added in a dropwise fashion over 20 min to a solution of 5-[8-*tert*-butyldiphenylsilyloxy-(3*S*,7*R*)-3,7-dimethyl-octane-sulfonyl]-1-phenyl-1*H*-tetrazole (**39**) (1.432 mg, 2.37 mmol) and 13-benzoxy-(2*R*,6*S*,10*R*)-2,6,10-trimethyl-8-(*Z*/*E*)-tridecenal (**35**) (612 mg, 1.78 mmol) in anhydrous THF (25 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to rt overnight, the reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give product **40** as an oil: 837 mg (65% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.22 (m, 15H), 5.40−5.10 (m, 4H), 4.49 (s, 2H), 3.55−3.40 (m, 4H), 2.50−1.00 (m, 25H), 1.06 (s, 9H), 0.98−0.80 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 138.8, 137.93, 137.88, 137.4, 137.2, 136.8, 135.8, 134.3, 129.6, 128.5, 127.71, 127.68, 127.6, 127.5, 127.4, 127.1, 127.04, 126.98, 73.0, 70.8, 69.0, 40.2, 40.1, 38.0, 37.66, 37.59, 37.1, 37.00, 36.96, 36.9, 36.8, 35.9, 35.0, 34.9, 34.1, 33.7, 33.6, 33.32, 33.30, 31.8, 31.7, 27.9, 27.8, 27.0, 25.10, 25.05, 25.0, 24.9, 24.6, 24.5, 21.5, 21.2, 19.89, 19.86, 19.6, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{49}H_{74}O_2SiK$ [MK^+] 761.5090, found 761.5086.

13-Benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyl-1-tridecanol (41). $CuSO_4$ (6.8 mg, 0.043 mmol) was added to a solution of 13-benzoxy-(2*R*,6*S*,10*R*)-2,6,10-trimethyl-8-(*Z*/*E*)-tridecenol-1 (**34**) (149 mg, 0.430 mmol) and hydrazine (1.34 mL, 42.7 mmol) in anhydrous ethanol (22 mL). After the mixture was bubbled with air and stirred at 70 °C for 15 h, the solution was filtered, and the filtrate was evaporated under vacuum. The resulting residue was extracted with Et_2O. The organic layers were combined and washed with brine. The solvent was evaporated, and the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **41** as an oil: 118 mg (79% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.50 (s, 2H), 3.52−3.35 (m, 4H), 1.70−1.10 (m, 19H), 0.93−0.82 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 138.8, 128.4, 127.7, 127.6, 73.0, 71.0, 68.4, 37.42, 37.40, 35.9, 33.6, 33.4, 32.84, 32.76, 27.4, 24.5, 19.9, 19.8, 16.8; HRMS (ESI/APCl) calcd for $C_{23}H_{41}O_2$ [MH^+] 349.3101, found 349.3110.

5-[13-Benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyl-1-tridecylsulfanyl]-1-phenyl-1*H*-tetrazole (42). Under argon, PPh_3 (131 mg, 0.50 mmol) and DEAD (0.10 mL, 0.60 mmol) were added to a solution of 13-benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyl-1-tridecanol (**41**) (116 mg, 0.332 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (89 mg, 0.50 mmol) in anhydrous THF (2 mL) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction was quenched with water. The aqueous layer was extracted with Et_2O, and the organic layers were combined and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **42** as an oil: 169 mg (100% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.62−7.24 (m, 10H), 4.50 (s, 2H), 3.50−3.42 (m, 3H), 3.26 (dd, 1H, J = 7.6, 12.4 Hz), 1.93 (m, 1H), 1.70−1.00 (m, 18H), 1.04 (d, 3H, J = 6.4 Hz), 0.86 (d, 3H, J = 6.4 Hz), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 154.9, 138.8, 133.9, 130.2, 129.9, 128.4, 127.7, 127.6, 124.0, 73.0, 71.0, 40.7, 37.4, 37.2, 36.4, 33.4, 33.1, 32.84, 32.78, 27.4, 24.5, 24.4, 19.84, 19.78, 19.3; HRMS (ESI/APCl) calcd for $C_{30}H_{45}N_4OS$ [MH^+] 509.3309, found 509.3316.

5-[13-Benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyltridecanesulfonyl]-1-phenyl-1*H*-tetrazole (43). *m*-CPBA (77% purity, 3.72 mg, 1.66 mmol) was added to a solution of 5-[13-benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyl-1-tridecylsulfanyl]-1-phenyl-1*H*-tetrazole (**42**) (169 mg, 0.332 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. After the reaction mixture was stirred at rt overnight, 10% aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (3 mL) were added and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were subsequently washed with 10% aqueous $Na_2S_2O_3$ (5 mL), saturated aqueous $NaHCO_3$ (3 × 5 mL), and brine. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 8% ethyl acetate in hexane to give **43** as an oil: 139 mg (77% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.23 (m, 10H), 4.50 (s, 2H), 3.80 (dd, 1H, J = 4.8, 14.8 Hz), 3.58 (dd, 1H, J = 8.0, 14.4 Hz), 3.45 (t, 2H, 1H, J = 6.8 Hz), 2.33 (m, 1H), 1.70−1.00 (m, 18H), 1.15 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 154.2, 138.8, 133.2, 131.5, 129.8, 128.4, 127.7, 127.5, 125.2, 72.9, 71.0, 60.9, 37.4, 37.0, 36.9, 33.4, 32.8, 32.7, 28.4, 27.4, 24.5, 23.9, 19.83, 19.77, 19.76; HRMS (ESI/APCl) calcd for $C_{30}H_{45}N_4O_3S$ [MH^+] 541.3207, found 541.3219.

21-Benzoxy-1-*tert*-butyldiphenylsilyloxy-(2*R*,6*S*,10*R*,14*R*,18*S*)-2,6,10,14,18-pentamethyl-8-(*E*/*Z*)-8-heneicosene (44). Under argon, LiHMDS solution (0.5 M in THF, 0.55 mL, 0.28 mmol) was added in a dropwise fashion over 5 min to a solution of 5-[13-benzoxy-(2*R*,6*R*,10*S*)-2,6,10-trimethyltridecanesulfonyl]-1-phenyl-1*H*-tetrazole (**43**) (139 mg, 0.257 mmol) and 8-(*tert*-butyldiphenylsilyloxy)-(3*S*,7*R*)-3,7-dimethyl-octanal (**32**) (106 mg, 0.257 mmol) in anhydrous THF (3 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to rt overnight, the reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried

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over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give product **44** as an oil: 105 mg (56% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.22 (m, 15H), 5.40−5.10 (m, 2H), 4.50 (s, 2H), 3.55−3.40 (m, 4H), 2.50−1.00 (m, 29H), 1.04 (s, 9H), 0.98−0.80 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 138.9, 137.9, 137.3, 135.8, 134.3, 129.6, 128.5, 127.8, 127.7, 127.6, 127.1, 127.0, 73.0, 71.1, 69.1, 40.1, 38.1, 37.7, 37.6, 37.5, 37.4, 37.3, 37.1, 36.97, 36.95, 35.9, 34.9, 33.63, 33.59, 33.5, 33.3, 32.9, 32.8, 31.8, 27.5, 27.0, 25.1, 24.9, 24.6, 24.5, 21.5, 21.2, 19.9, 19.8, 19.6, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{49}H_{76}O_2SiK$ [MK^+] 763.5246, found 763.5236.

21-Benzoxy-1-*tert*-butyldiphenylsilyloxy-(2*R*,6*R*,10*R*,14*S*,18*S*)-2,6,10,14,18-pentamethyl-heneicosane (45). *A. From 1-Benzoxy-21-tert-butyldiphenylsilyloxy-(4R,8S,12R,16S,20S)-4,8,12,16,20-Pentamethyl-5-(E/Z)-13-(E/Z)-heneicos-5,13-diene (**40**).* $CuSO_4$ (7.6 mg, 0.048 mmol) was added to a solution of **40** (346 mg, 0.478 mmol) and hydrazine (1.50 mL, 47.7 mmol) in ethanol (25 mL). After the mixture was bubbled with air and stirred at 70 °C for 15 h, the solution was filtered, and the filtrate was evaporated under vacuum. The resulting residue was extracted with Et_2O and washed with brine. The combined organic layers were evaporated, and the residue was purified by silica gel chromatography, eluting with 1% ethyl acetate in hexane to give **45** as an oil: 807 mg (96% yield).

*B. From 21-Benzoxy-1-tert-butyldiphenylsilyloxy-(2R,6S,10R,14R,18S)-2,6,10,14,18-pentamethyl-8-(E/Z)-8-heneicosene (**44**).* Following to the above-described procedure, compound **44** (103 mg, 0.142 mmol) was reacted with hydrazine (0.45 mL, 14 mmol) in the presence of $CuSO_4$ (2.3 mg, 0.014 mmol) in ethanol (10 mL) at 70 °C for 15 h to give **45** as an oil: 81 mg (78% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 7.70−7.22 (m, 15H), 4.50 (s, 2H), 3.55−3.40 (m, 4H), 1.70−1.00 (m, 33H), 1.05 (s, 9H), 0.92 (d, 3H, J = 6.8 Hz), 0.88−0.81 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 138.8, 135.8, 134.3, 129.6, 128.5, 127.72, 127.67, 127.6, 73.0, 71.0, 69.0, 37.6, 37.52, 37.49, 37.46, 35.9, 33.6, 33.5, 33.0, 32.94, 32.90, 32.8, 27.5, 27.0, 24.62, 24.59, 24.5, 19.93, 19.91, 19.8, 19.5, 17.1; HRMS (ESI/APCl) calcd for $C_{49}H_{78}O_2SiK$ [MK^+] 765.5403, found 765.5414.

21-Benzoxy-(2*R*,6*R*,10*R*,14*S*,18*S*)-2,6,10,14,18-pentamethyl-1-heneicosanol (46). TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) was added to a solution of 21-benzoxy-1-*tert*-butyldiphenylsilyloxy-(2*R*,6*R*,10*R*,14*S*,18*S*)-2,6,10,14,18-pentamethylheneicosane (**45**) (729 mg, 1.00 mmol) in dry THF (8 mL). After the reaction mixture was stirred at rt overnight, the solvent was removed under vacuum, and the residue was purified by silica gel chromatography, eluting with 10−15% ethyl acetate in hexane to give **46** as an oil: 394 mg (81% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.40−7.20 (m, 5H), 4.50 (s, 2H), 3.55−3.30 (m, 4H), 1.70−1.00 (m, 33H), 0.91 (d, 3H, J = 6.4 Hz), 0.88−0.81 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 138.8, 128.4, 127.7, 127.6, 73.0, 71.0, 68.4, 37.52, 37.50, 37.44, 35.9, 33.6, 33.4, 32.91, 32.88, 32.8, 27.4, 24.6, 24.5, 19.91, 19.90, 19.8, 16.8; HRMS (ESI/APCl) calcd for $C_{33}H_{61}O_2$ [MH^+] 489.4666, found 489.4670.

21-Benzoxy-(2*R*,6*R*,10*R*,14*S*,18*S*)-2,6,10,14,18-pentamethyl-heneicosyl *p*-Toluenesulfonate (47). Under argon, *p*-TsCl (228 mg, 1.20 mmol) was added to a solution of 21-benzoxy-(2*R*,6*R*,10*R*,14*S*,18*S*)-2,6,10,14,18-pentamethyl-1-heneicosanol (**46**) (390 mg, 0.798 mmol) and DMAP (1.0 mg) in anhydrous pyridine (5 mL) at 0 °C. After the mixture was stirred at rt overnight, water (2.5 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, subsequently washed with 1 N HCl (5 mL), water (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The solvent was removed, and the residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in hexane to give **47** as an oil: 398 mg (78% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.81−7.76 (m, 2H), 7.37−7.23 (m, 7H), 4.50 (s, 2H), 3.88 (dd, 1H, J = 5.6, 9.2 Hz), 3.80 (dd, 1H, J = 6.4, 9.2 Hz), 3.45 (t, 2H, J = 6.8), 2.44 (s, 3H), 1.82−0.90 (m, 33H), 0.90−0.78 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 144.7, 138.8, 133.3, 129.9, 128.4, 128.0, 127.7, 127.6, 75.2, 73.0, 71.0, 37.53, 37.50, 37.46, 37.44, 37.2, 33.4, 33.1, 32.92, 32.80, 32.78, 27.4, 24.58, 24.56, 24.1, 21.7, 19.9, 19.8, 16.6; HRMS (ESI/APCl) calcd for $C_{40}H_{67}O_4S$ [MH^+] 643.4755, found 643.4770.

C_{32}-Mycoketide: (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-Pentamethyl-1-heptacosanol. *A. Method A (Product 83% Stereopurity): From 1-Benzoxy-(4R,8S,12S,16S,20S)-4,8,12,16,20-pentamethyl-5-(E/Z)-5-heptacosene (**26**).* A suspension of 10% Pt on carbon (48 mg, 0.025 mmol) in a solvent mixture of benzene/ethanol (1:1, v/v) (4 mL) was pretreated with hydrogen by 5 vacuum-hydrogen cycles. Under H_2, a solution of **26** (≤*93% stereopurity*, 136 mg, 0.245 mmol) in the same solvent mixture of benzene/ethanol (1:1, v/v) (1.0 mL) was slowly added. After the combined mixture was stirred under a hydrogen balloon overnight, the catalyst was filtered off, and the solvent was removed. The resulting residue was dissolved in ethyl acetate (5 mL), and 10% Pd on carbon (65 mg, 0.061 mmol) was added. The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring overnight under hydrogen atmosphere, TLC showed reaction was complete. The catalyst was filtered off, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **C_{32}-mycoketide** (83% stereopurity) as an oil:[12] 83 mg, (73% yield).

*B. Methods B and C (Product up to 96% Stereopurity): From 1-Benzoxy-(4S,8S,12S,16S,20S)-4,8,12,16,20-pentamethyl-heptacosane (**37**).* 10% Pd on carbon (57 mg, 54 μmol) was added to a solution of **37** (296 mg, 0.531 mmol) in ethyl acetate (25 mL). The resulting suspension was saturated with hydrogen by 5 vacuum-hydrogen cycles. After stirring overnight under a hydrogen balloon, TLC showed reaction was complete. The catalyst was then filtered off, and the solvent was removed. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give **C_{32}-mycoketide** (up to 96% stereopurity) as an oil:[12] 0.230 g (93% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 3.60 (t, 2H, J = 6.6 Hz), 2.15 (brs, 1H), 1.67−1.47 (m, 2H), 1.45−0.98 (m, 43H), 0.92−0.82 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 63.4, 37.6, 37.5, 37.2, 33.1, 32.94, 32.91, 32.8, 32.1, 30.5, 30.2, 29.6, 27.2, 24.6, 22.8, 19.92, 19.90, 19.8, 14.3.

Pyridinium (2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl)-phosphate (48). Compound **48** was prepared according to a procedure in the literature.[12] ^{1}H NMR (D_2O) δ 8.67 (d, 2H, J = 5.6 Hz), 8.52 (t, 1H, J = 7.8 Hz), 7.97 (t, 2H, J = 6.8 Hz), 5.42 (d, 1H, J = 3.2 Hz), 5.35 (dd, 1H, J = 0.8, 8.8 Hz), 5.23 (dd, 1H, J = 3.2, 10.0 Hz), 5.11 (t, 1H, J = 10.0 Hz) 4.33 (dd, 1H, J = 3.6, 12.8 Hz), 4.09 (dd, 1H, J = 1.6, 12.8 Hz), 3.96 (ddd, 1H, J = 2.0, 3.2, 10.0 Hz), 2.13 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (D_2O) δ 173.9, 173.3, 173.2, 172.7, 147.3, 141.2, 127.5, 93.4 (d), 71.9, 71.3, 70.1(d), 65.5, 61.9, 20.23, 20.18, 20.1.

Sodium (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-Pentamethylheptacosylphosphoryl-β-D-mannopyranoside (C_{32}-MPM). Pyridinium (2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-phosphate (**48**) (84.0 mg, 0.163 mmol), (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethyl-1-heptacosanol (**C_{32}-mycoketide**) (38 mg, 0.081 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) (74.0 mg, 0.244 mmol) were coevaporated with dry pyridine (2 mL) and then dry toluene (2 × 2 mL). Under argon, the resulting white foam was redissolved in dry pyridine (2 mL), and DMAP (5.0 mg, 0.041 mmol) was added. After stirring at rt for 48 h, the reaction was quenched with methanol (3 mL), and the mixture was stirred at rt for additional 2 h. After the evaporation of the solvent, the resulting residue was dissolved in chloroform and washed with water and brine. After drying over anhydrous $MgSO_4$ and removal of the solvent, the residue was purified by silica gel chromatography, eluting with 10% methanol in chloroform, to give (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethylheptacosylphosphoryl-2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside:[12] 58 mg, 83% yield. ^{1}H NMR (D_2O) δ 5.48 (m, 1H), 5.42 (d, 1H, J = 7.6 Hz), 5.25−5.17 (m, 2H), 4.28 (dd, 1H, J = 4.4, 12.0 Hz), 4.16 (dd, 1H, J = 2.4, 12.4 Hz), 3.86 (m, 3H), 2.16 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.95 (s, 3H), 1.70−1.00 (m, 45H), 0.95−0.85 (m, 18H); ^{13}C NMR (CD_3OD) δ 173.0, 172.8, 172.3, 172.1, 95.7, 74.6, 73.3, 72.0, 68.5, 67.7, 64.2, 39.4, 39.33, 39.29, 39.25, 39.0, 35.1, 34.9, 34.80, 34.76, 34.7, 33.9, 31.9, 31.6, 31.4, 29.0, 26.5, 26.4, 26.3, 24.6, 21.64, 21.59, 21.5, 21.4, 21.23, 21.21, 21.16, 21.0, 15.4; ^{31}P NMR (D_2O) δ −5.6.

To a solution of (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethylheptacosylphosphoryl-2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside (51

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mg, 0.058 mmol) in a chloroform/methanol solvent mixture (1:2.5, v/v) (3.5 mL) was added NaOMe solution (0.5 M in MeOH, 0.20 mL, 0.10 mmol). The mixture was stirred at rt for 30 min and then diluted with 1-butanol (15 mL). The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was separated, then washed with water (3 × 10 mL), and coevaporated with toluene. The resulting solid was washed with acetone (25 mL) and then dissolved into a chloroform−methanol mixture (1:1, v/v) (35 mL). The solution was filtered through a pad of Celite and concentrated to give sodium (4*S*,8*S*,12*S*,16*S*,20*S*)-4,8,12,16,20-pentamethylheptacosylphosphoryl-β-D-mannopyranoside (**C_{32}-MPM**):[12] 41 mg (100% yield). ^{1}H NMR ($CDCl_3/CD_3OD/D_2O$, 0.45:0.45:0.05) δ 5.31 (m,, 1H), 4.19−4.00 (m, 4H), 3.82 (m, 2H), 3.56 (*t*, 2H, J = 1.6 Hz), 1.84 (m, 2H), 1.70−1.25 (m, 43H), 1.15−1.05 (m, 18H); ^{13}C NMR ($CDCl_3/CD_3OD/D_2O$, 0.45:0.45:0.05) δ 95.2, 76.6, 72.9, 70.9, 66.5, 66.2, 60.8, 37.00, 36.97, 36.93, 36.89, 36.6, 32.7, 32.4, 32.34, 32.30, 32.28, 31.5, 29.5, 29.2, 28.9, 27.9, 26.6, 24.1, 24.03, 23.97, 23.95, 22.2, 19.3, 19.2, 19.1, 18.8, 13.4; ^{31}P NMR ($CDCl_3/CD_3OD/D_2O$, 0.45:0.45:0.05, v/v/v) δ −1.4; MS (API-ES) calcd for $C_{38}H_{79}O_9P^-$ ($M - Na^+$) 707.5, found 707.4.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nli@uchicago.edu; jpicciri@uchicago.edu.

Present Address

[§]Division of Biology, California Institute of Technology, Pasadena, CA 91125.

Notes

The authors declare no competing financial interest.

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