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# Total Synthesis of (−)-Goniotrionin

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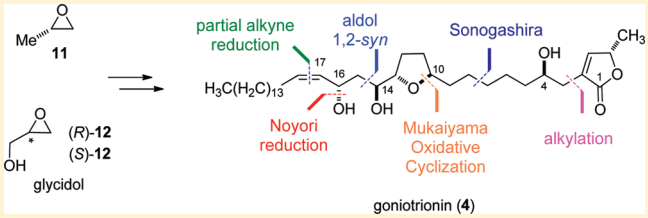
Supporting Information

**ABSTRACT:** A stereoselective total synthesis of the reported structure of goniotrionin (**4**) has been accomplished. The key steps involved the opening of a chiral epoxide, a highly diastereoselective Mukaiyama aerobic oxidative cyclization, a selective 1,2-*syn* Mukaiyama aldol reaction, and a Noyori reduction.




## 1. INTRODUCTION

Natural products derived from terrestrial plants play a significant role in the search for new molecules with potential pharmacological activity, particularly in the battle against cancer.[1] Plants of the *Annonaceous* family have been investigated over the last two decades due to a number of antifungal and cytotoxic constituents found in their leaves and bark.[2] Annonaceous acetogenins (AGEs) are a series of polyketides that were initially isolated from various Annonaceous plant species.[3] They are typically constituted as long-chain fatty acids derivatives (32 or 34 carbons) containing hydroxyl groups, one or more tetrahydrofuran (THF) or tetrahydropyran units, and a γ-lactone (Scheme 1). Since the antitumor activity of uvaricin (**1**) was first described in 1982,[4] there has been a great deal of interest in this family of natural products. Further interest was generated by the discovery of other biological activities, such as immunosuppressive, pesticidal and antimalarial effects. More than 500 AGEs have been isolated, and more than 60 total syntheses have been published.[2] Some examples of AGEs are shown in Scheme 1.[5]

Acetogenins have emerged as excellent leads for the development of the next generation of antitumor drugs. Their mechanism of action is attributed to the blocking of oxidative pathways in the mitochondrial complex I (CMI) and the inhibition of NADH oxidases, inducing the apoptosis of tumor cells even in multidrug-resistant (MDR) tumors.[6,7]

Although Annonaceae species are relatively abundant, the AGEs within these plants are present in very small amounts and are found as complex mixtures of similar isomers. Due to the difficulty of crystallizing aliphatic AGEs, the assignment of their absolute stereochemistries remains a major challenge. The use of Mosher ester or acetonide derivatives and the total synthesis of analogs are currently the most suitable methods for the determination of AGE configurations.[8]

Goniotrionin (**4**) was isolated in 1998 by Alali, McLaughlin and co-workers in small quantities (1.5 mg as a whitish wax) from *Goniothalamus giganteus*, a tree native to Thailand (Scheme 1).[5j] Goniotrionin (**4**) exhibited a high cytotoxicity against the A-549, MCF-7, A-498 and PACA-2 cancer cell lines, resulting in ED50 values of 7.7, $5.3 \times 10^{-3}$, 2.0 and 5.4 ng/mL, respectively. In particular, goniotrionin was found to be $10^5$ times more potent than adriamycin against the breast cancer cell line MCF-7. The skeletal structure of goniotrionin (**4**) was assigned based on NMR, 2D-NMR and EIMS analysis, and the relative stereochemistry of the C10−C16 fragment was established by comparing the $^1$H and $^{13}$C NMR spectra to the corresponding Fujimoto's[9] model and 1,3-diol[10] systems.

We describe herein our efforts toward the total synthesis of the assigned enantiomer of goniotrionin (**4**) for the purposes of checking McLaughlin's structural assignment, obtaining material for further biological evaluation and gaining access to novel analogues.

## 2. RETROSYNTHETIC ANALYSIS OF GONIOTRIONIN (4)

Goniotrionin (**4**) has a number of unique structural features that make it a challenging synthetic target (Scheme 2). Our disconnection approach began with the installation of the C14 stereogenic center through a late-stage chelation-controlled 1,2-*syn* Mukaiyama aldol reaction between aldehyde **6** and either alkynyl silyl enol ether **5** or the *Z*-alkenyl silyl enol ether **5′**.[11] The subsequent steps required to construct the *Z*-allylic alcohol unit of goniotrionin (**4**) will depend on the choice of enol silyl ether. If **5** is used, the obvious path forward would involve a selective carbonyl reduction followed by a partial alkyne reduction, whereas if **5′** is used, a selective carbonyl reduction would be sufficient because the *Z*-alkene would already be installed. The terminal butenolide portion of aldehyde **6** would be assembled by an alkylation reaction involving the lithium enolate of White's lactone **8** and the proper electrophile, which could be obtained from intermediate **7** following the removal of the PMB group. To access the THF unit of intermediate **7**, a Sonogashira cross-coupling reaction between fragments **9** and **10** was considered. We planned to establish the *trans*-THF configuration in vinyl iodide **10** by a Mukaiyama oxidative cyclization catalyzed by **13**.[12] This convergent synthetic plan therefore divided goniotrionin (**4**) into the chiral fragments **8**, **9** and **10**, which could all be easily prepared from commercially available enantiomerically pure

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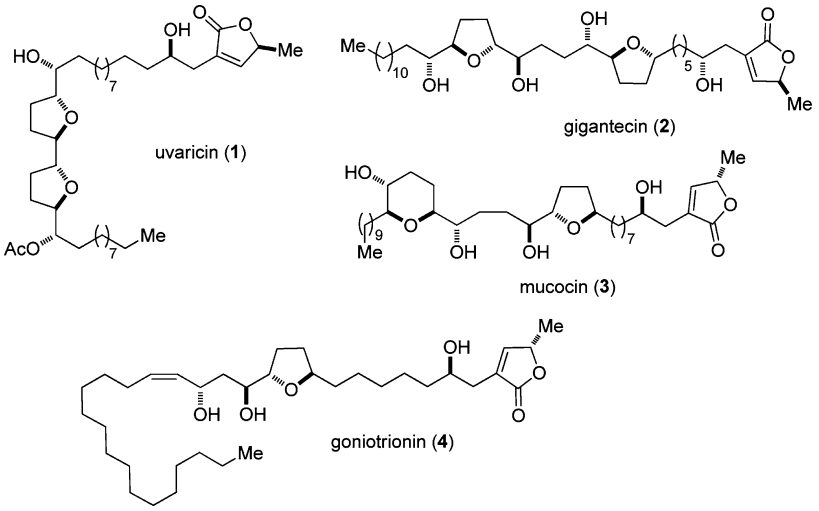
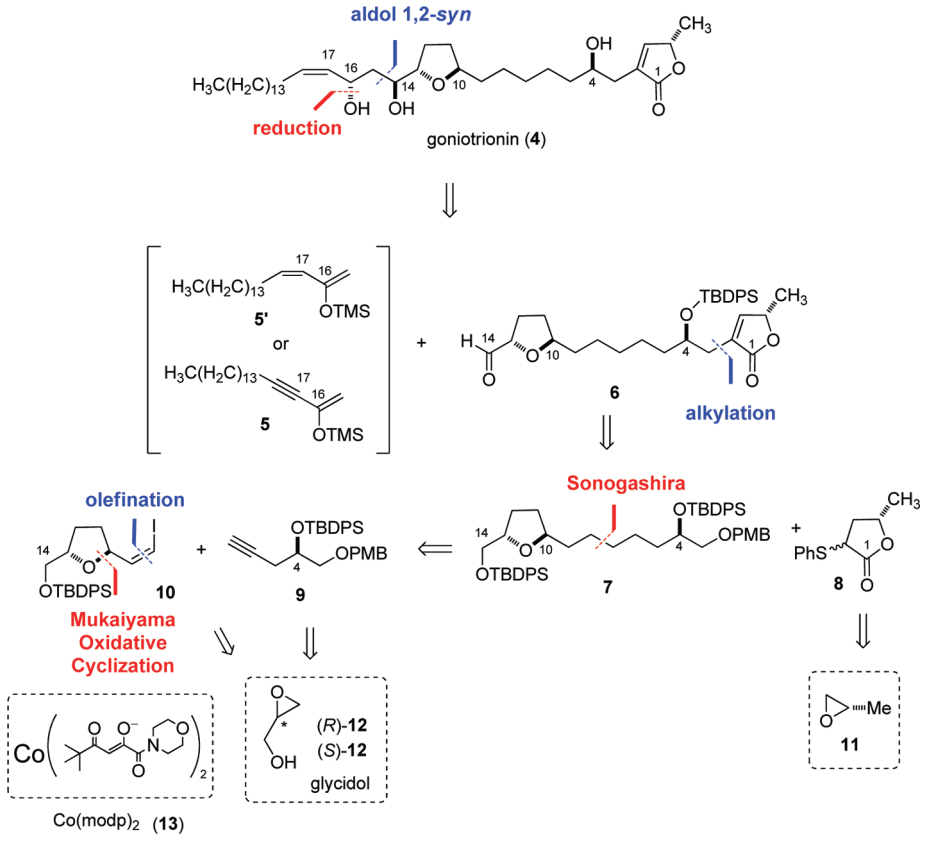
**Scheme 1. Representative Examples of AGEs**




**Scheme 2. Synthetic Route to Goniotrionin (4)**




epoxides **11** and **12**. Alternatively, epoxides **11** and **12** can be obtained by hydrolytic kinetic resolution using Jacobsen's methodology.[13]

## 3. RESULTS AND DISCUSSION

**3.1. Preparation of Aldehyde 6.** Our synthesis began with the preparation of vinyl iodide **10** (Scheme 3). The protection of the primary hydroxyl group of glycidol (*R*)-**12** with the TBDPS group (62%) followed by the opening of epoxide **14** with allylmagnesium bromide (**15**) led to hydroxyalkene **16** in 90% yield.[14] The subsequent aerobic oxidative cyclization of **16** was mediated by a Co(modp)$_2$ (**13**) catalyst according to Mukaiyama's protocol,[12] providing 2,5-*trans*-THF **17** as a single diastereoisomer in 73% yield (*dr* > 95:05) on a multigram scale. This methodology has proven to be a very useful synthetic tool for accessing 2,5-*trans*-THF rings in natural product syntheses.[12b,5g,h,15] The $^1$H NMR, $^{13}$C NMR and $[\alpha]_D$ of *trans*-THF **17** matched the reported values for this compound, which was obtained previously by a different synthetic route.[16] Next, a Swern oxidation of primary alcohol **17** followed by a Wittig olefination using phosphonium salt **19**[17] afforded *Z*-vinyl iodide **10** as the only isolated product (77% yield for the 2-step sequence).

Our efforts to prepare the Co(modp)$_2$ (**13**) catalyst were based on the previously reported procedure by Pagenkopf and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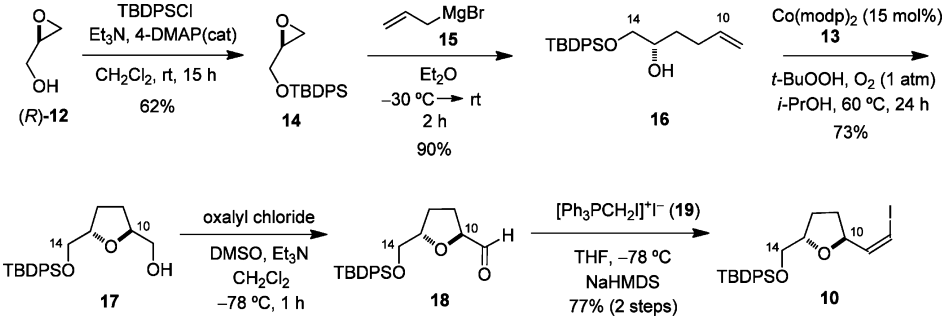
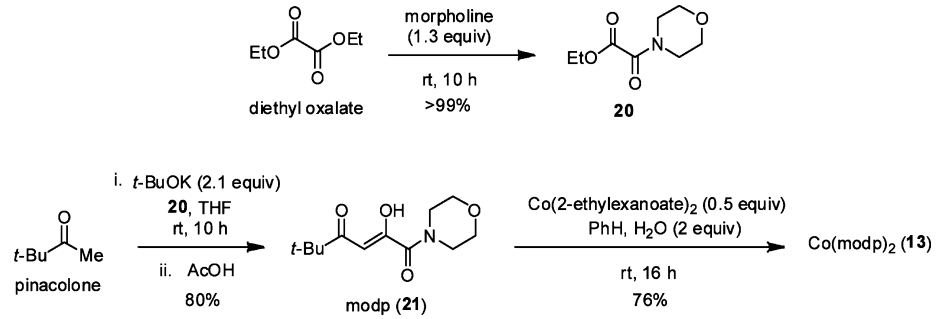
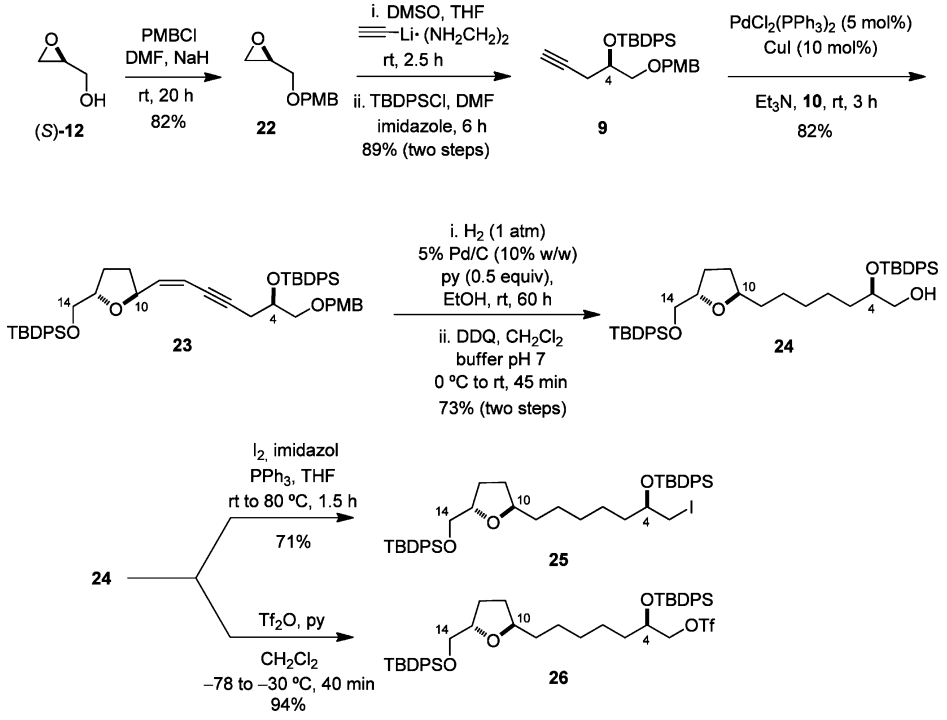
**Scheme 3. Preparation of Vinyl Iodide 10**




**Scheme 4. Preparation of the Co(modp)$_2$ Catalyst (13)**




**Scheme 5. Preparation of Alcohol 24 and Electrophiles 25 and 26**




co-workers[18] but with a slight modification in the preparation of intermediate **20**, in which we used solvent-free conditions (Scheme 4).

The next step involved the protection of glycidol (*S*)-**12** with a PMB group (Scheme 5).[19] The subsequent opening of epoxide **22** with a lithium acetylide ethylenediamine complex followed by protection of the resulting hydroxyl group with TBDPS led to alkyne **9** (89% yield for two steps). Sonogashira cross-coupling between **9** and **10** led to compound **23** in 82% yield.[20] A two-step enyne reduction and PMB deprotection was performed on **23** under neutral conditions to prevent silyl migration in diol **24**.[21] Enyne reduction with $H_2$/Pd−C followed by the removal of the PMB protecting group with DDQ in a phosphate buffer (pH 7) led to primary alcohol **24** in 73% yield for the two-step sequence. With alcohol **24** in hand, we turned our attention to the alkylation step in which the butenolide portion of goniotrionin would be installed by alkylating White's lactone **8**.[22] For this purpose, we investigated


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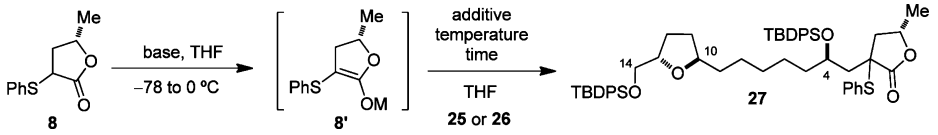
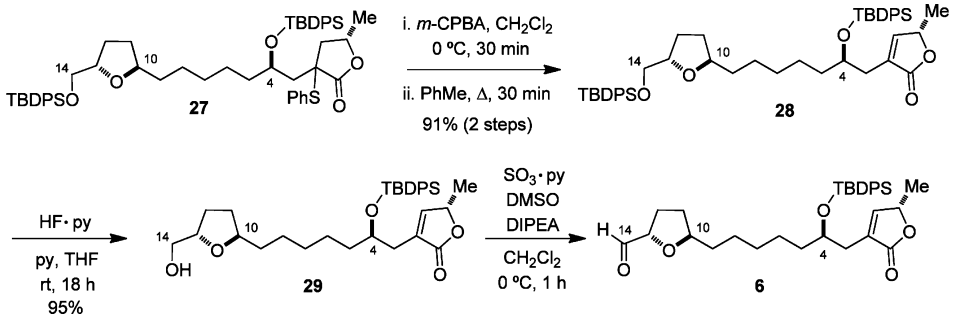
**Table 1. Alkylation Reaction Involving White's Lactone 8 and Electrophiles 25 and 26**



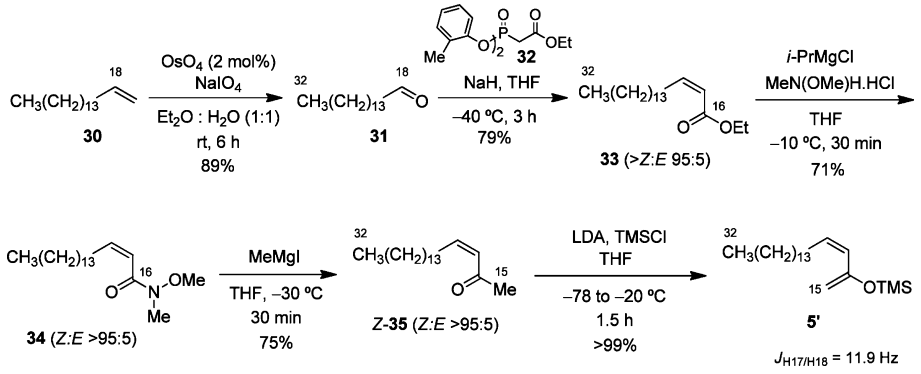

| entry | electrophile | base[a] | equiv of 8[b] | additive (equiv) | $T$ (°C) | time (h) | yield[c] |
|---|---|---|---|---|---|---|---|
| 1 | **25** | LDA | 1.3 | | rt | 16 | NR[d] |
| 2 | **25** | LDA | 4 | HMPA (4) | rt | 16 | NR[d] |
| 3 | **25** | LiHMDS | 4 | HMPA (4) | 50 | 16 | ND[e] |
| 4 | **25** | NaHMDS | 4 | HMPA (4) | rt | 16 | NR[d] |
| 5 | **26** | LiHMDS | 3 | | rt | 16 | NR[d] |
| 6 | **26** | LiHMDS | 3 | HMPA (2) | rt | 16 | trace |
| 7 | **26** | LiHMDS | 3 | HMPA (10) | 0 to rt | 2 | 62% |

[a]Base:**8** (1:1.4), 1.0 M solution of the base. [b]Excess **8** was recovered by silica gel column chromatography. [c]Yield of the isolated product. [d]Only starting material was recovered. [e]Complex mixture by TLC.

**Scheme 6. Preparation of the Aldehyde 6**




**Scheme 7. Preparation of Enol Silane 5′**




both iodide **25** and triflate **26** as electrophiles. First, alcohol **24** was subjected to the Appel reaction conditions,[23a,b] providing iodide **25** in 71% yield (Scheme 5). The triflate **26** was formed in 94% yield by employing $Tf_2O$[23c] and pyridine.

Table 1 summarizes the conditions that we investigated for the alkylation reaction. We were unable to obtain satisfactory results with iodide **25** and metal enolate **8′** (Table 1, entries 1−4), probably due to the close proximity of the bulky OTBDPS group to the electrophilic carbon C3. In contrast, we were pleased to find that the more reactive triflate **26** is a competent substrate for the alkylation of **8′**, leading to intermediate **27** as a mixture of diastereoisomers, and in an acceptable yield (62% yield), although 10 equivalents of HMPA are required (Table 1, entry 7). We were unable to devise conditions that provided higher yields.[24]

Next, *m*-CPBA oxidation of sulfide **27** to the sulfoxide derivative and thermal elimination led to intermediate **28** in 91% yield over 2 steps (Scheme 6). Selective removal of the primary TBDPS group using an HF·py complex provided alcohol **29** in 95% yield.[25] Alcohol **29** was then subjected to the Parikh-Doering oxidation procedure to prepare the desired aldehyde **6**.

**3.2. Preparation of Enol Silanes 5 and 5′.** Silyl enol ether **5′** was prepared as outlined in Scheme 7. Oxidative cleavage of terminal alkene **30** with $NaIO_4$ in the presence of catalytic amounts of $OsO_4$ lead to aldehyde **31** in 89% yield. Next, HWE coupling using Ando's phosphonate reagent **32**[26] and aldehyde **31** provided the *Z*-ester **33** (79% yield, *Z*:*E* > 95:5). The conversion of ester **33** to the Weinreb amide **34**[27] followed by reaction with methyl magnesium iodide gave exclusively the *Z*-α,β-unsaturated methyl ketone *Z*-**35** in 75% yield. Next, the treatment of methyl ketone *Z*-**35** with LDA and TMSCl gave the silyl enol ether **5′** in quantitative yield.[28] We assigned the Z configuration to silyl enol ether **5′**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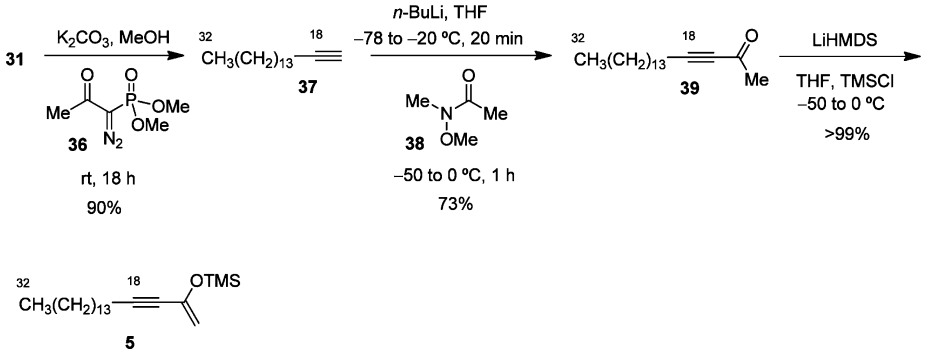
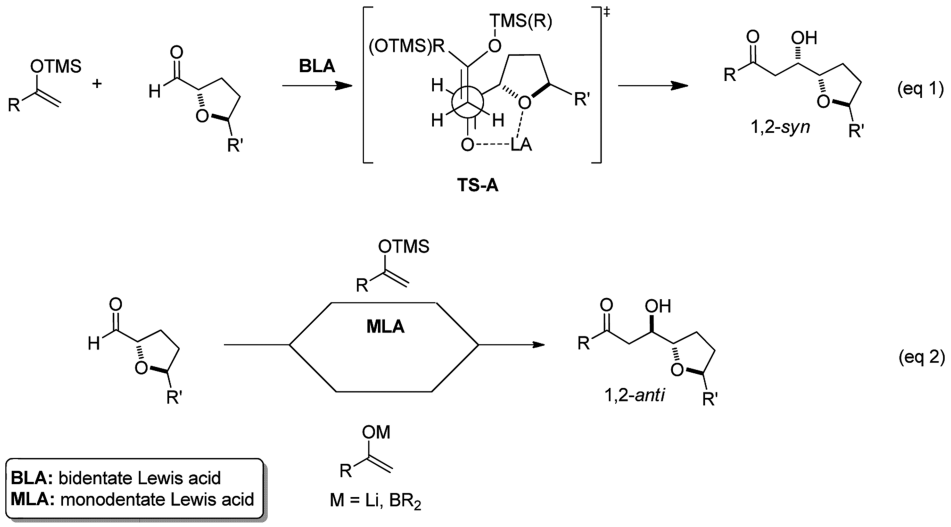
**Scheme 8. Preparation of Enol Silane 5**




**Scheme 9. Expected Stereochemical Outcome for a Chelation-controlled Mukaiyama Aldol Reaction**




by examining the coupling constant in the $^1$H NMR spectrum ($J_{H17/H18}$ = 11.9 Hz).

The construction of enol silane **5** started with a Seyferth-Gilbert homologation from aldehyde **31** using the Ohira-Bestmann reagent **36**.[29] Further treatment with *n*-BuLi and Weinreb amide **38** produced methyl ketone **39** in 73% yield (Scheme 8). Finally, treatment of methyl ketone **39** with LiHMDS and TMSCl gave enol silane **5** in quantitative yield.

**3.3.1. Installation of the C14 Stereocenter and Completion of the Synthesis of Goniotrionin (4).** *Studies on the Mukaiyama Aldol Reaction and the 1,3-Carbonyl Reduction.* Our goal at this point was to develop conditions favoring the nucleophilic attack of an enol silane from the *si* face of α–alkoxy aldehyde **6** to produce the required C14 stereocenter of goniotrionin (**4**). We hypothesized that a chelation-controlled Mukaiyama aldol reaction might achieve the desired C14 stereocenter as depicted in Scheme 9 (eq 1).[30] The coordination between the Lewis acid and the THF oxygen atom keeps the substrate in a rigid conformation, allowing the enol silane to attack from the less sterically hindered side of the aldehyde through a Cram-chelate transition state (**TS-A**), thus leading to the 1,2-*syn* aldol adducts.[31] A Mukaiyama aldol reaction involving activation of the α–alkoxy aldehyde by a monodentate Lewis acid or an aldol reaction involving a preformed metal enolate cannot be used in this case because they would produce the undesired 1,2-*anti* aldol adduct (eq 2).[32]

The diastereoselectivity of the key Mukaiyama aldol reaction was first investigated using the simpler aldehydes **18** and **41** as model substrates before exposing the advanced aldehyde **6** to the aldol coupling (Table 2). Our first choice was to use silyl enol ether **5′** because the aldol adduct would already contain the necessary *Z* double bond geometry. Previous reports have shown that B- and Li-enolates of *Z*-unsaturated ketones can be used without losing the *Z* double bond geometry.[27,33] However, we were unable to obtain acceptable results with enol silane **5′**. The exposure of aldehyde **41** to enol silane **5′** in the presence of $MgBr_2{\cdot}Et_2O$ at −30 °C led to aldol adduct *Z*-**42**, but the presence of *E*-**42** confirmed that some double bond isomerization had occurred (Table 2, entry 2). An increase in the temperature led to exclusive formation of the *E*-**43** aldol adduct (Table 2, entry 4). $SnCl_4$ and $TiCl_4$ have been found to be the best Lewis acids for many chelation-controlled Mukaiyama aldol reactions,[30] but the use of these catalysts on our system showed only decomposition of the enol silane, leading to the double-bond isomerization product, methyl ketone *E*-**34** (Table 2, entries 5–6). The same behavior was observed for $Sn(OTf)_2$ and $Me_2AlCl$ (Table 6, entries 7–8). $LiClO_4$ has also been used as a Lewis acid in chelation-controlled Mukaiyama aldol reactions, either at high concentrations (homogeneous system in ethyl ether, entry 9)[34a] or in catalytic amounts (heterogeneous system in $CH_2Cl_2$, entry 10).[34b] However, even under these conditions, we did not observe any formation of the desired aldol adduct.


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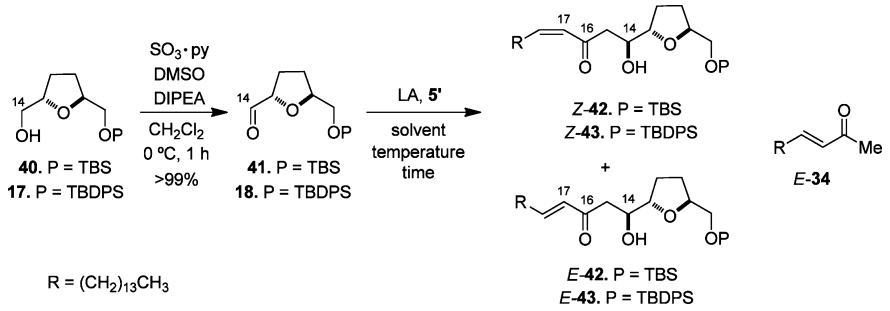
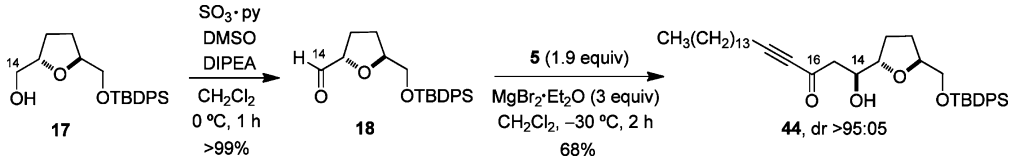
**Table 2. Model Studies of the Mukaiyama Aldol Reaction between Enol Silane 5′ and Aldehyde 18 or 41**[a]




| entry | P | solvent | T (°C) | LA (equiv) | time (h) | yield |
|---|---|---|---|---|---|---|
| 1 | TBS | $CH_2Cl_2$ | −78 | $MgBr_2{\cdot}OEt_2$ (3) | 4.5 | 6.3% [*Z*-42], 55% [*E*-34] |
| 2 | TBS | $CH_2Cl_2$ | −30 | $MgBr_2{\cdot}OEt_2$ (3) | 4.5 | 38% [*Z*-42], 22% [*E*-42], 28% [*E*-34] |
| 3 | TBS | PhMe | −30 | $MgBr_2{\cdot}OEt_2$ (3) | 4.5 | only *E*-34[b] |
| 4 | TBDPS | $CH_2Cl_2$ | 0 | $MgBr_2{\cdot}OEt_2$ (3) | 4.5 | 20% [*E*-43], 21% [*E*-34] |
| 5 | TBDPS | $CH_2Cl_2$ | −78 | $SnCl_4$ (1) | 1 | only *E*-34[b] |
| 6 | TBDPS | $CH_2Cl_2$ | −78 | $TiCl_4$ (1) | 1 | only *E*-34[b] |
| 7 | TBDPS | $CH_2Cl_2$ | −78 | $Sn(OTf)_2$ (1) | 1 | only *E*-34[b] |
| 8 | TBDPS | $CH_2Cl_2$ | −78 | $Me_2AlCl$ (1) | 1 | only *E*-34[b] |
| 9 | TBDPS | $Et_2O$ | rt | $LiClO_4$ (5 M) | 18 | only *E*-34[b] |
| 10 | TBDPS | $CH_2Cl_2$ | rt | $LiClO_4$ (3 mol %) | 4 | only *E*-34[b] |

[a]Conditions: A 0.2 M solution of **5′** (1.5 equiv) was added to a 0.2 M solution of aldehyde (1 equiv) that had been preactivated with the Lewis acid for 5 min. [b]Yield not determined.

**Scheme 10. Model Study of the Mukaiyama Aldol Reaction between Aldehyde 18 and Enol Silane 5**




In contrast, to our delight, we found that the chelation-controlled Mukaiyama aldol reaction between aldehyde **18** and silyl enol ether **5** using $MgBr_2{\cdot}OEt_2$ provided the aldol adduct **44** in 68% yield as the only diastereoisomer measured by NMR spectra (Scheme 10).

With the aldol adduct **44** in hand, we continued our model studies, investigating the best way to establish the *anti*-diol relationship between the C14 and C16 stereocenters present in goniotrionin (**4**). Using $Me_4NBH(OAc)_3$ in AcOH and MeCN produced the inseparable diols **45** and **46** in excellent yields but with low diastereoselectivity (7:3) in favor of *anti*-diol **45** (Scheme 11). Previous reports have also shown low 1,3-*anti* selectivity for alkynyl ketone substrates.[35] In general, a large preference for 1,3-*anti* reduction is observed when employing this methodology, but we strongly believe that the presence of the triple bond in ketone **44** attenuates the 1,3-diaxial repulsions in the cyclic transition state **TS-B′** that are responsible for the diastereoselectivity of this transformation.[36] Acetonide formation permitted the confirmation of the stereochemistry in diols **45** and **46** via Rychnovsky acetonide $^{13}C$ NMR analysis of compounds **47** and **48** (which were separable by chromatography).[37] Acetonides **47** and **48** matched with the *anti* class 3 and *syn* class acetonides proposed by Rychnovsky,[37] respectively.

In light of these disappointing results, we envisaged the possibility of using the asymmetric Noyori carbonyl reduction of $\alpha,\beta$-acetylenic ketones[38] to construct the 1,3-*anti* diol relationship found in goniotrionin (**4**).

*3.3.2. Mukaiyama Aldol Reaction between Silyl Enol Ether 5 and Aldehyde 6 and the Conclusion of the Synthesis of Goniotrionin (4).* At this point, the advanced fragments **5** (C15−C32) and **6** (C1−C14) were coupled by a chelation-controlled Mukaiyama aldol reaction using the optimized conditions, which employ $MgBr_2{\cdot}OEt_2$ as a Lewis acid, providing aldol adduct **49** in 59% yield (for two steps) as a single diastereoisomer (Scheme 12). With the desired aldol adduct **49** available, construction of the stereogenic center at C16 was performed using Noyori hydrogenation.[38] When **49** was exposed to (*S*,*S*)-Noyori's catalyst (**50**) (5 mol %), a clean reduction of the carbonyl occurred, providing diol **51** as a single diastereoisomer in 71% isolated yield.

Again, the preparation of acetonide **52** allowed us to confirm the relative stereochemistry for diol **51** via Rychnovsky acetonide $^{13}C$ NMR analysis (Scheme 13).[37] At this point, we attempted to determine the absolute stereochemistry of the newly created stereogenic centers at C14 and C16. Efforts to reach the Mosher ester derivatives **53a−b** from aldol adduct **49** proved to be unfruitful because the decomposition of the starting material was observed under the various conditions tested. Furthermore, the modified Mosher's method using di-MTPA is not useful in the case of acyclic *anti*-1,3-diols because the $\Delta\delta$ values are irregularly arranged.[39] As an alternative to the direct use of Mosher's method, the aldol adduct **49** was protected with a TBS group, and a subsequent Noyori reduction produced the monoprotected diol **55**,[40] as depicted in Scheme 13. The monodesilylation[41] of 1,3-diol **55** produced compound **51** (Scheme 13), which had identical spectroscopic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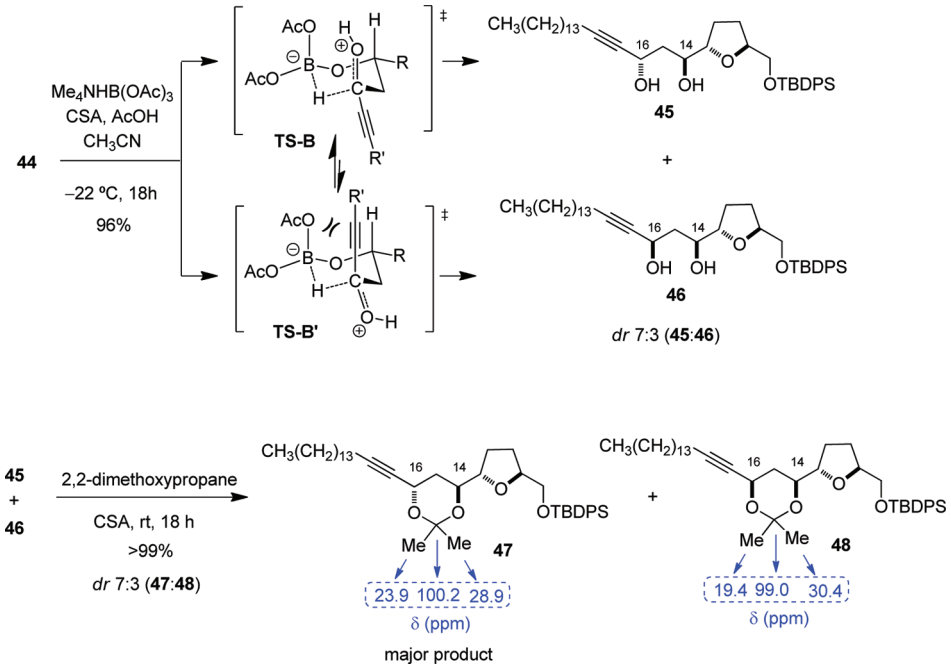
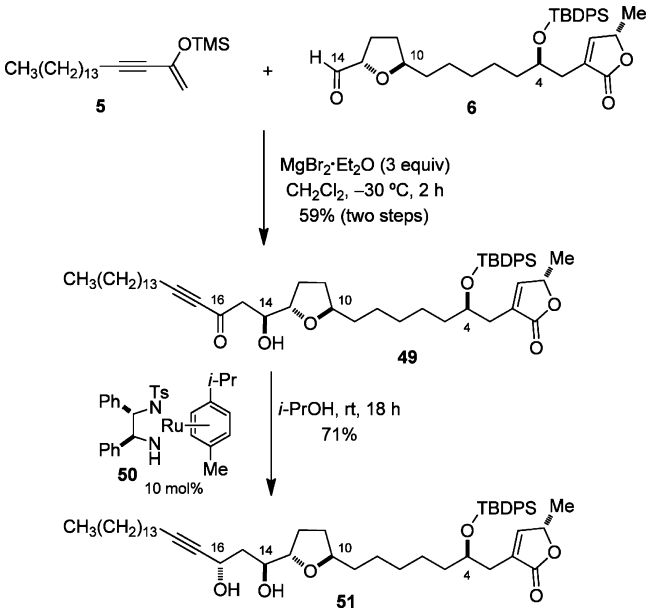
**Scheme 11. 1,3-Reduction of Aldol Adduct 44**




**Scheme 12. Synthesis of Intermediate 51 (C1–C32)**




data and physical properties when compared to the same compound prepared directly from aldol adduct **49** (Scheme 12; in the Supporting Information, see Figures S80, S81, S97, and S98), ensuring that both diols had the same absolute stereochemistry. Finally, the preparation of Mosher ester derivatives **56a–b** and the subsequent NMR analysis ($\delta S - \delta R$)[42] directly confirmed the absolute configuration at C16 and indirectly confirmed the configuration at C14 (from acetonide **52**).

Finally, a highly *cis*-selective zinc-mediated partial reduction of alkyne **51** was performed, producing *Z*-allylic alcohol **57** in 86% yield (Scheme 14).[43] Deprotection of the silyl group at C4 provided goniotrionin (**4**) in 95% yield.

Spectral data ($^1$H and $^{13}$C NMR, IR, and HRMS) from the synthetic sample were in complete agreement with those reported in the literature for the natural product (Table 3).[5j] However, the optical rotation value for natural goniotrionin (**4**) was not reported, and because a sample of the authentic natural product was not available for comparison, the absolute stereochemistry of goniotrionin (**4**) is still subject to conjecture. Our synthetic sample showed low specific rotation values that were dependent on the concentration: $[\alpha]_D^{23} = -7$ ($c$ = 1.2/$CHCl_3$), $[\alpha]_D^{23} = -3$ ($c$ = 0.12/$CHCl_3$), $[\alpha]_D^{23} = 0$ ($c$ = 0.012/$CHCl_3$). In a discussion with Prof. Alali,[5j] he suggested that the originally isolated goniotrionin (**4**) may not have exhibited an optical rotation due to the very low isolated mass (1.5 mg). The optical rotation values for our synthetic sample corroborate this hypothesis. We believe that this result might represent a complex equilibrium of self-aggregating species. It is known that the formation of dimers or trimers can result in a nonlinear concentration dependence for self-aggregating species in solution. This may help to explain the differences in optical rotation at different concentrations of goniotrionin (**4**) because the positive and negative contributions from equilibrating species to $[\alpha]_D$ may cancel out at low concentrations.[44] In this case, the solution becomes cryptochiral despite the presence of a single diastereoisomer.[45]

However, the not reported specific rotation data for the natural sample of goniotrionin prevented the assignment of the absolute configuration, and the diastereomeric relationship between the remote C4/C34 and *trans*-THF associated stereocenters. Consequently, it is possible that the $^1$H and $^{13}$C NMR chemical shifts of the proposed structure for goniotrionin (**4**) and one of the diastereoisomers are nearly identical simply by coincidence.

## CONCLUSION

In conclusion, we have accomplished the first total synthesis of the reported structure of goniotrionin (**4**) in 4% overall yield over a longest-linear sequence of 17 steps from comercial epoxide (*R*)-**12**. Our synthetic route employed an epoxide-opening strategy, using chiral epoxides as building blocks. Key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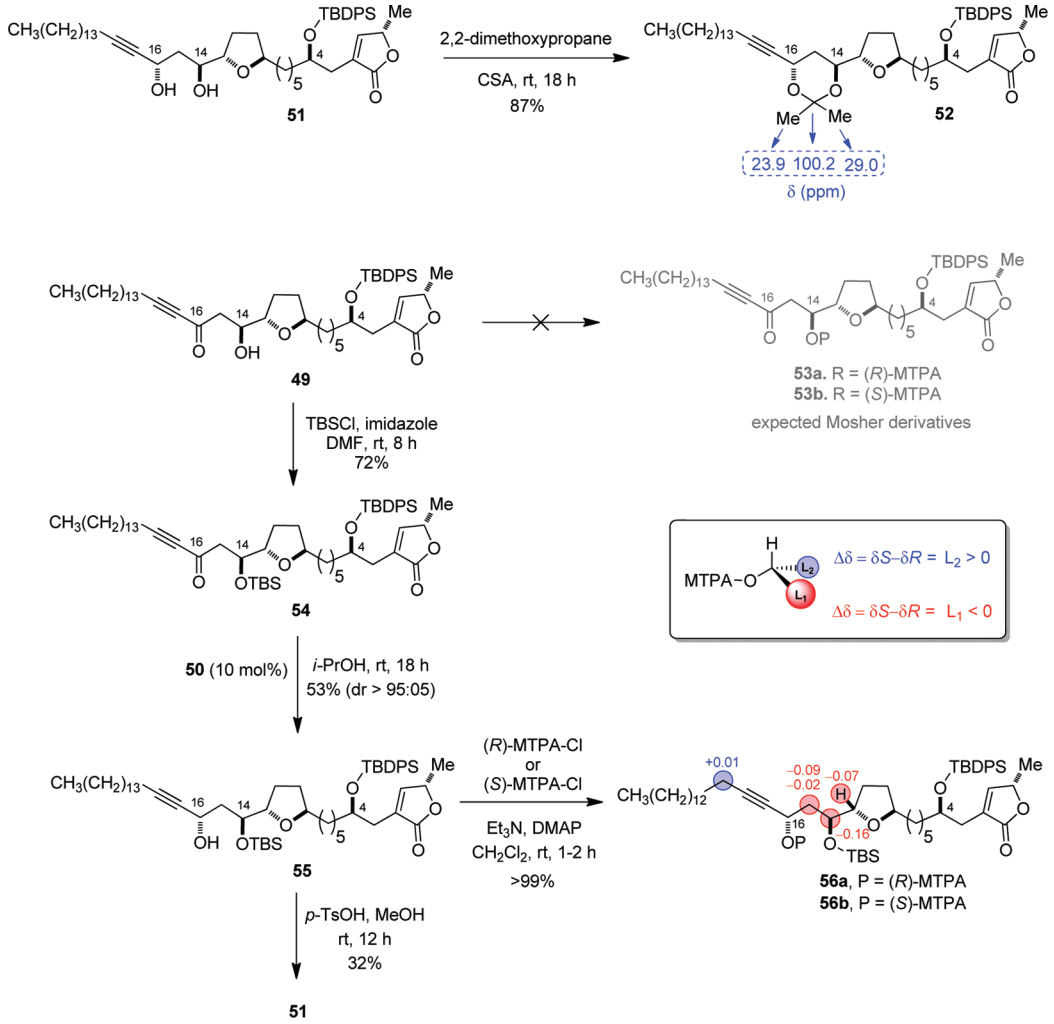
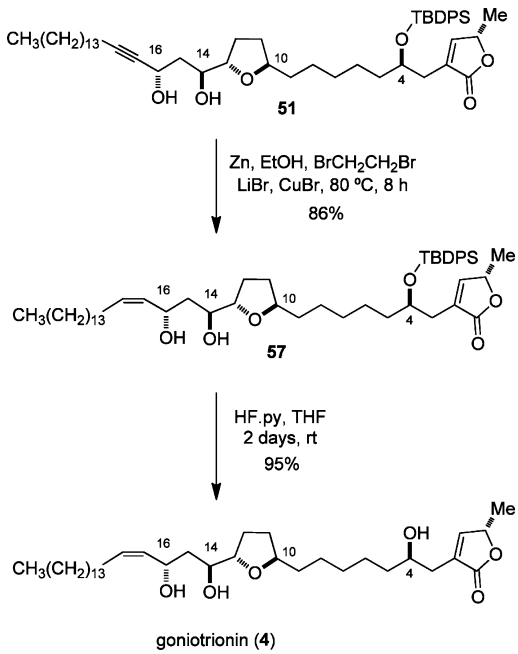
**Scheme 13. Confirming the Stereochemistry at C14 and C16**




**Scheme 14. Completion of the Synthesis of Goniotrionin (4)**




steps included a Mukaiyama aerobic oxidative cyclization and a 1,2-*syn* selective Mukaiyama aldol reaction. This synthesis employs highly flexible key couplings that allow for the preparation of analogs, including other diastereoisomers of goniotrionin (**4**). To get more insights about the remote relative configuration of natural goniotrionin (**4**), efforts to synthesize others diastereoisomers are currently in progress and will be reported in due course.

## EXPERIMENTAL SECTION

**Materials and Methods.** Unless otherwise noted, all reactions were performed under an argon atmosphere in flame-dried glassware with magnetic stirring. Dichloromethane ($CH_2Cl_2$), triethylamine ($Et_3N$), 2,6-lutidine, diisopropylethylamine (DIPEA), dimethylformamide (DMF), benzene, pyridine (py), and diisopropylamine (DIPA) were distilled from $CaH_2$. Dimethyl sulfoxide (DMSO) and HMPA were distilled under reduced pressure from $CaH_2$ and stored over molecular sieves. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled from sodium/benzophenone. $SnCl_4$ and $TiCl_4$ were distilled over $CaH_2$ before use. $LiClO_4$ was activated under high vacuum at 120 °C for 24 h before use. Oxalyl chloride was distilled immediately prior to use. The reaction products were purified by flash column chromatography using silica gel (230−400 mesh). Analytical thin-layer chromatography was performed on silica-gel 60 and GF (5−40 $\mu$m thickness) plates. The TLC plates were visualized with UV light and phosphomolybdic acid followed by heating. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{\circ C}$ (c = g/100 mL, solvent). For the infrared spectra, wavelengths of maximum absorbance (max) are quoted in wavenumbers ($cm^{-1}$). $^1H$ and proton-decoupled $^{13}C$ NMR spectra were taken in $C_6D_6$, $CDCl_3$ or DMSO-$d_6$


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Table 3. $^{1}H$ and $^{13}C$ NMR Chemical Shifts for Natural and Synthetic Goniotrionin (4)

| | isolated natural product | | | synthetic product | | |
|---|---|---|---|---|---|---|
| position | δ (H) | δ (C) | multiplicity H (J in Hz) | δ (H)[a] | δ (C)[a] | multiplicity H (J in Hz) |
| 1 | | 174.6 | | | 174.6 | |
| 2 | | 131.1 | | | 131.1 | |
| 3a | 2.54 | 33.4 | ddt (15.5, 3.5, and 1.0) | 2.52 | 33.4 | ddt (15.1, 3.2, and 1.5) |
| 3b | 2.40 | | ddt (15.0, 8.0, and 1.0) | 2.38 | | ddt (15.1, 8.3, and 1.2) |
| 4 | 3.85 | 69.9 | m | 3.85 | 69.9 | m |
| 5 | 1.48 | 37.2 | m | 1.48 | 37.3 | m |
| 6–8 | 1.18–1.65 | 25.5–37.2[b] | m | 1.18–1.65 | 25.5–29.7 | m |
| 9 | 1.53–1.64 | 35.4 | m | 1.57–1.69 | 35.4 | m |
| 10 | 3.89 | 79.3 | m | 3.89 | 79.3 | m |
| 11 | 2.03 and 1.54 | 32.4 | m | 2.03 and 1.54 | 32.4 | m |
| 12 | 1.96 and 1.60 | 28.2 | m | 1.95 and 1.60 | 28.2 | m |
| 13 | 3.85 | 81.8 | m | 3.85 | 81.8 | m |
| 14 | 3.73 | 71.5 | dt (11.5 and 3.5) | 3.73 | 71.5 | td (7.8 and 3.9) |
| 15 | 1.58 | 39.6 | m | 1.59 | 39.7 | m |
| 16 | 4.78 | 65.0 | dt (8.0 and 4.0) | 4.77 | 65.0 | dt (7.81 and 4.15) |
| 17 | 5.48 | 131.6 | m | 5.47 | 131.6 | m |
| 18 | 5.44 | 132.2 | m | 5.46 | 132.2 | m |
| 19 | 2.10 and 2.05 | 25.5–37.2[b] | m | 2.10 and 2.05 | 27.7 | m |
| 20–29 | 1.18–1.65 | 25.5–37.2[b] | m | 1.18–1.65 | 25.5–29.7 | m |
| 30 | 1.18–1.65 | 31.9 | m | 1.18–1.65 | 31.9 | m |
| 31 | 1.30 | 22.7 | m | 1.18–1.65 | 22.7 | m |
| 32 | 0.88 | 14.1 | t (7.0) | 0.87 | 14.1 | t (6.8) |
| 33 | 7.19 | 151.9 | q (1.5) | 7.18 | 151.8 | m |
| 34 | 5.07 | 78.0 | qq (7.0 and 1.5) | 5.05 | 78.0 | qq (6.8 and 1.5) |
| 35 | 1.44 | 19.1 | d (7.0) | 1.43 | 19.1 | d (6.7) |
| OH | nr[c] | | nr[c] | 2.80, 2.63, and 2.36 | | bs |

[a]Assignment based on COSY, HMBC and HMQC experiments. [b]The value 37.2 is a typo because this value was attributed to the C5 carbon. [c]Not reported.

at 250 MHz ($^{1}H$) and 62.9 MHz ($^{13}C$), 400 MHz ($^{1}H$) and 100 MHz ($^{13}C$) or 500 MHz ($^{1}H$) and 125 MHz ($^{13}C$). The chemical shifts (δ) are reported in ppm using the solvent peak as an internal standard ($C_6D_6$ at 7.16 ppm, $CDCl_3$ at 7.26 ppm and DMSO-$d_6$ at 2.49 ppm for $^{1}H$ NMR spectra and $C_6D_6$ at 128.0 ppm, $CDCl_3$ at 77.0 ppm and DMSO-$d_6$ at 39.50 ppm for $^{13}C$ NMR spectra). Data are reported as the following: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, td = triplet of doublets, tt = triplet of triplets, qd = quartet of doublets, m = multiplet, ad = apparent doublet, aquint = apparent quintuplet; coupling constant(s) in Hz; integration. The signals from the minor isomers are listed in brackets. High-resolution mass spectrometry (HRMS) was performed using either electrospray ionization (ESI) or electron ionization (EI). The parent ions ($[M + H]^+$, $[M + Na]^+$, $[M + K]^+$, $[M - OH]^+$, and $[M - C_6H_5]^+$) are listed.

**Preparation of Aldehyde 6: (2*S*)-1-(tert-Butyldiphenylsilyloxy)-prop-2-enoxide (14).**[14] $R_f$ 0.58 (10% EtOAc in hexane). $[\alpha]_D^{23}$ = −2.3 (*c* = 10.0/$CH_2Cl_2$). Lit.[13]: $[\alpha]_D^{29}$ = −2.1 (*c* = 1.8/$CH_2Cl_2$). $^{1}H$ NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.63 (dd, *J* = 5.2 and 2.7 Hz, 1H), 2.66 (dd, *J* = 5.2 and 4.1 Hz, 1H), 3.10–3.19 (m, 1H), 3.72 (dd, *J* = 11.8 and 4.8 Hz, 1H), 3.88 (dd, *J* = 11.8 and 3.2 Hz, 1H), 7.33–7.50 (m, 6H), 7.65–7.77 (m, 4H). $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 19.3 (C), 26.7 ($CH_3$), 44.4 ($CH_2$), 52.3 (CH), 64.3 ($CH_2$), 127.7 (CH), 129.7 (CH), 133.2 (CH), 135.54 (C), 135.59 (CH).

**(*S*)-1-((tert-Butyldiphenylsilyl)oxy)hex-5-en-2-ol (16).**[14] Allyl magnesium bromide (2.1 equiv, 80.0 mL, 80.0 mmol, 1.0 M in $Et_2O$) was added to a flame-dried flask under an Ar atmosphere at −20 °C, and a solution of **14** (12.0 g, 38.4 mmol) in anhydrous $Et_2O$ (10 mL) was added dropwise while stirring the reaction vigorously. After 10 min at −20 °C and 1 h at rt, a saturated aqueous solution of ammonium chloride (60 mL) and $H_2O$ (7 mL) were added. The suspension was warmed to rt, and the reaction mixture was extracted with $Et_2O$ (2 × 50 mL). The combined organic phases were dried ($Na_2SO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography using $Et_2O$/hexane (1:4) as the eluent gave the known secondary alcohol **16** (12.3 g, 34.6 mmol) in 90% yield as a colorless oil. $R_f$ 0.58 (20% $Et_2O$ in hexane). $[\alpha]_D^{23}$ = −7.2 (*c* = 2.1/$CH_2Cl_2$). Lit.[13]: $[\alpha]_D^{29}$ = −7.8 (*c* = 1.8/$CH_2Cl_2$). $^{1}H$ NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.38–1.66 (m, 2H), 2.00–2.30 (m, 2H), 2.38 (s, 1H), 3.51 (dd, *J* = 9.9 and 7.5 Hz, 1H), 3.68 (dd, *J* = 9.9 and 3.5 Hz, 1H), 3.71–3.81 (m, 1H), 4.90–5.08 (m, 2H), 5.81 (ddt, *J* = 17.1, 10.3, and 5.8 Hz, 1H), 7.33–7.50 (m, 6H), 7.60–7.76 (m, 4H). $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 19.2 (C), 26.8 ($CH_3$), 29.7 ($CH_2$), 31.9 ($CH_2$), 67.9 ($CH_2$), 71.3 (CH), 114.74 ($CH_2$), 127.76 (CH), 129.8 (CH), 133.1 (C), 135.5 (CH), 138.3 (CH). IR $\nu_{max}$ (film) 3577, 3436, 3072, 2929, 2858, 1959, 1890, 1824, 1739, 1641, 1589, 1473, 1427, 1261, 1112, 912, 823, 740, 702.

**((2*S*,5*S*)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)methanol (17).** $Co(modp)_2$ (**13**) (2.71 g, 5.03 mmol) was added to a solution of *i*-PrOH (500 mL), **16** (11.3 g, 33.4 mmol) and *t*-BuOOH (6.1 mL, 33.4 mmol, 5–6 M in nonane). The mixture was kept under an $O_2$ atmosphere (1 atm) and stirred vigorously at 60 °C. After stirring for 24 h, the reaction mixture was cooled to rt. A saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was then added, the organic solvent was removed *in vacuo* and the residual dark green oil was partitioned between EtOAc (150 mL) and a saturated aqueous solution of $NH_4Cl$ (50 mL). The aqueous phase was then extracted with EtOAc (3 × 70 mL), the organic solvent was removed *in vacuo* and the residue was purified by flash column chromatography using $Et_2O$/hexane (1:9 to 3:7) as an eluent to afford the known compound **17** as a light green oil (8.98 g, 24.2 mmol) in 73% yield. $R_f$ 0.46 (30% EtOAc in hexane). $[\alpha]_D^{23}$ = +9.0 (*c* = 1.4/$CHCl_3$). Lit.[15]: $[\alpha]_D^{20}$ = +5.9 (*c* = 1.7/$CHCl_3$). $^{1}H$ NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.61–2.10 (m, 4H), 2.23 (bs, 1H), 3.49 (dd, *J* = 11.5 and 6.1 Hz, 1H), 3.60–3.76 (m, 3H), 4.05–4.21 (m, 2H), 7.32–7.49 (m, 6H), 7.64–7.75 (m, 4H).


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$^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 19.2 (C), 26.8 ($CH_3$), 27.4 ($CH_2$), 28.1 ($CH_2$), 64.9 ($CH_2$), 66.4 ($CH_2$), 79.6 (CH), 79.7 (CH), 127.6 (CH), 129.6 (CH), 133.54 (C), 135.59 (CH). IR $\nu_{max}$ (film) 3456, 3070, 3049, 2948, 2856, 1961, 1892, 1824, 1739, 1589, 1473, 1427, 1242, 1109, 823, 740, 700.

**tert-Butyl(((2*S*,5*S*)-5-((*Z*)-2-iodovinyl)tetrahydrofuran-2-yl)-methoxy)diphenylsilane (10).** A solution of oxalyl chloride (5.84 mL, 68.0 mmol) in anhydrous $CH_2Cl_2$ (390 mL) was stirred vigorously under an argon atmosphere at −78 °C, and DMSO was added dropwise (6.90 mL, 97.1 mmol). After 30 min, a solution of alcohol **17** (7.20 g, 19.4 mmol) in anhydrous $CH_2Cl_2$ (52 mL) was added, and the solution was stirred for an additional 30 min. Then, $Et_3N$ (17.7 mL, 126 mmol) was added dropwise, and the resulting suspension was vigorously stirred for another 30 min. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (30 mL) followed by $H_2O$ (20 mL). The aqueous phase was then extracted with EtOAc (3 × 70 mL). The combined organic phases were washed with $H_2O$ (2 × 70 mL) and a saturated aqueous solution of NaCl (70 mL) and then dried with $Na_2SO_4$. The organic solvent was removed *in vacuo* to afford the crude aldehyde **18** (7.2 g), which was used in the next step without further purification. $R_f$ 0.65 (30% EtOAc in hexane).

A flame-dried round-bottomed flask was charged with a suspension of the phosphonium salt **19** (1.6 equiv, 7.0 g, 13.0 mmol) in anhydrous THF (240 mL) at 0 °C, and NaHMDS (1.5 equiv, 6.1 mL, 12.2 mmol, 2.0 M in THF) was added dropwise. The solution was stirred vigorously for 10 min at rt and then cooled to −78 °C. A solution of crude aldehyde **18** (3.01 g, 8.12 mmol) in anhydrous THF (60 mL) was added dropwise, and the reaction mixture was stirred for an additional 30 min. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (50 mL), and the aqueous phase was extracted with $Et_2O$ (2 × 30 mL). The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was then purified by flash column chromatography, eluting with EtOAc/hexane (1:9) to produce vinyl iodide **10** (3.10 g, 6.29 mmol) as a colorless oil in 77% yield over two steps. $[\alpha]_D^{23}$ = +60 ($c$ = 0.33/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.09 (s, 9H), 1.54−2.36 (m, 4H), 3.62−3.76 (m, 2H), 4.14−4.27 (m, 1H), 4.69 (dt, $J$ = 8.2 and 6.0 Hz, 1H), 6.27−6.39 (m, 2H), 7.32−7.49 (m, 6H), 7.64−7.75 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 19.3, 26.9, 28.0, 31.7, 66.4, 79.8, 81.4, 81.8, 127.7, 129.6, 133.54, 133.57, 135.63, 142.3. IR $\nu_{max}$ (film) 3070, 3051, 2958, 2931, 2858, 1471, 1427, 1265, 1112, 1072, 1006, 999, 738, 703. HRMS (ESI-TOF) $m/z$ $[M + K]^+$ for $C_{23}H_{29}O_2SiKI$ calcd 531.0619, found 531.0645.

**(Iodomethyl)triphenylphosphonium Iodide (19).**[17] A solution of $PPh_3$ (12.02 g, 45.8 mmol) and $CH_2I_2$ (4.92 mL, 61.1 mmol) in toluene (40 mL) was made under an argon atmosphere in a flask equipped with a reflux condenser and protected from the light by aluminum foil. The solution was heated at 100 °C for 20 h and then cooled to 0 °C. The resulting white crystals were filtered, washed with cold toluene, and dried under vacuum, giving the known phosphonium salt **19** (22.1 g, 41.7 mmol) as a white solid in 91% yield. $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 4.93−5.10 (m, 2H), 7.65−8.00 (m, 15H). $^{13}$C NMR (62.9 MHz, DMSO-$d_6$) $\delta$ −15.2 (d, $^1J_{P/C}$ = 52 Hz, $CH_2$), 118.4 (d, $^1J_{P/C}$ = 88 Hz, C), 130.2 (d, $^2J_{P/C}$ = 13 Hz, CH), 133.8 (d, $^3J_{P/C}$ = 10 Hz, CH), 135.1 (CH).

**Ethyl 2-Morpholino-2-oxoethaneperoxoate (20).** A 100 mL round-bottomed flask was charged with diethyl oxalate (6.33 g, 43.3 mmol), and morpholine (1.3 equiv, 5.0 mL, 65 mmol) was added over 5 min. The reaction was stirred for 10 h at rt. The organic solvent was then removed under vacuum to give the known compound **20** (8.11 g, 43.3 mmol) in >99% yield as a colorless oil, which was used without further purification. $R_f$ 0.39 (50% $Et_2O$ in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.1 Hz, 3H), 2.82−3.23 (m, 8H), 3.90 (q, $J$ = 7.1 Hz).

**(Z)-2-Hydroxy-5,5-dimethyl-1-morpholinohex-2-ene-1,4-dione (21).**[18a] A solution of *t*-BuOK (2.1 equiv, 2.50 g, 22.5 mmol) in THF (19.6 mL) was added via cannula over 40 min to a solution of pinacolone (1 equiv, 1.07 g, 1.34 mL, 10.7 mmol) and **20** (1 equiv, 2.00 g, 10.7 mmol) in THF (4.5 mL) at rt. After 3 h, AcOH (3.6 equiv, 2.20 mL, 38.5 mmol) was added over 5 min, the resulting mixture was filtered, and the solids were washed with $CH_2Cl_2$. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with $Na_2SO_4$, and filtered, and the organic solvent was removed under vacuum to give the known compound **21** (2.07 g, 8.58 mmol) as an orange solid in 80% yield, which was used without further purification. $R_f$ 0.51 (50% $Et_2O$ in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.12 (s, 9H), 3.50−3.72 (m, 8H), 5.95 (s, 1H). $^{13}$C NMR (125.7 MHz, $CDCl_3$) $\delta$ 27.0, 42.04, 42.07, 46.5, 66.4, 66.7, 95.3, 163.7, 184.5, 201.0.

**Co(modp)$_2$ (13).** To a solution of ligand **21** (1 equiv, 14.7 g, 60.9 mmol) in benzene (30 mL) was added Co(ethylhexanoate)$_2$ (0.5 equiv, 16.2 mL, 30.4 mmol, 1.88 M in mineral spirits). After 15 min, water (2 equiv, 2.2 mL, 120 mmol) was added, and stirring was continued for 16 h. Hexanes (1200 mL) were added, and the brown solids were separated by filtration, washed with hexane, and dried to afford the known Co(modp)$_2$ catalyst (**13**) (12.5 g, 23.1 mmol) as a beige solid in 76% yield.

**(R)-2-(((4-Methoxybenzyl)oxy)methyl)oxirane (22).**[19] $R_f$ 0.55 (30% EtOAc in hexane). $[\alpha]_D^{23}$ = +3.9 ($c$ = 1.6/$CHCl_3$). Lit.[19]: $[\alpha]_D^{19}$ = +3.5 ($c$ = 1.0/$CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.60 (dd, $J$ = 5.0 and 2.9 Hz, 1H), 2.79 (dd, $J$ = 5.0 and 4.2 Hz, 1H), 3.17 (ddt, $J$ = 5.8, 4.1, and 2.9 Hz, 1H), 3.40 (dd, $J$ = 11.4 and 5.8 Hz, 1H), 3.73 (dd, $J$ = 11.4 and 2.9 Hz, 1H), 3.80 (s, 3H), 4.48 (d, $J$ = 11.5 Hz, 1H), 4.54 (d, $J$ = 11.5 Hz, 1H), 6.88 (d, $J$ = 8.7 Hz, 2H), 7.27 (d, $J$ = 8.7 Hz, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 44.2 ($CH_2$), 50.9 (CH), 55.2 ($CH_3$), 70.4 ($CH_2$), 72.9 ($CH_2$), 113.7 (CH), 129.4 (CH), 129.9 (C), 159.2 (C).

**(*R*)-tert-Butyl((1-((4-methoxybenzyl)oxy)pent-4-yn-2-yl)-oxy)diphenylsilane (9).** A solution of lithium acetylide ethylenediamine complex (2 equiv, 1.70 g, 15.8 mmol) was stirred in anhydrous DMSO (9 mL) under an argon atmosphere at rt. A solution of glycidol **22** (1.5 g, 7.9 mmol) in THF (2.6 mL) was then added slowly over 30 min. The reaction mixture was stirred for 2 h and then cooled to 0 °C. The reaction was cautiously quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (6 mL) followed by $H_2O$ (2 mL). The THF was removed under vacuum, and the aqueous phase was extracted with $Et_2O$ (3 × 10 mL). The combined organic phases were washed with brine, dried with $Na_2SO_4$, and filtered, and the organic solvent was removed under vacuum to give a known homopropargylic alcohol[19] (1.78 g), which was used in the next step without further purification. An analytically pure sample was obtained by flash column chromatography using EtOAc/hexane (1:1) as the eluent. $R_f$ 0.73 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = +4.5 ($c$ = 1.94/$CHCl_3$). Lit.[19]: *ent*-compound $[\alpha]_D$ = −4.4 ($c$ = 1.0/$CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.02 (t, $J$ = 2.7 Hz, 1H), 2.43 (dd, $J$ = 6.3 and 2.7 Hz, 2H), 2.51 (s, 1H), 3.47 (dd, $J$ = 9.6 and 6.6 Hz, 1H), 3.58 (dd, $J$ = 9.6 and 4.0 Hz, 1H), 3.80 (s, 3H), 3.95 (m, 1H), 4.49 (s, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 7.26 (d, $J$ = 8.5 Hz, 2H).

The previously obtained homopropargylic alcohol (1.78 g) was dissolved in anhydrous DMF (3 mL) under an argon atmosphere at rt. Imidazole (2.64 g, 38.7 mmol) and TBDPSCl (2.11 mL, 8.13 mmol) were then added to this solution, and the reaction was stirred for 18 h. The reaction mixture was then diluted with EtOAc (60 mL), and the organic phase was washed with $H_2O$ (3 × 10 mL), a saturated aqueous solution of $NH_4Cl$ (10 mL), and brine (10 mL). The organic phase was dried with $Na_2SO_4$ and filtered, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography using EtOAc/hexane (1:4) as the eluent, affording **9** (2.68 g, 5.85 mmol) as a colorless oil in 74% yield. $R_f$ 0.50 (10% EtOAc in hexane). $[\alpha]_D^{23}$ = +6 ($c$ = 1.2/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.06 (s, 9H), 1.92 (t, $J$ = 2.6 Hz, 1H), 2.24−2.50 (m, 2H), 3.46 (dd, $J$ = 9.7 and 5.2 Hz, 1H), 3.52 (dd, $J$ = 9.7 and 5.4 Hz, 1H), 3.78 (s, 3H), 3.98 (aquint, $J$ = 5.3 Hz, 1H), 4.27−4.39 (m, 2H), 6.82 (d, $J$ = 8.7 Hz, 2H), 7.14 (d, $J$ = 8.7 Hz, 2H), 7.28−7.45 (m, 6H), 7.64−7.73 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 19.3 (C), 24.1 ($CH_2$), 26.9 ($CH_3$), 55.2 ($CH_3$), 70.0 (C), 70.36 (CH), 72.43 ($CH_2$), 72.8 ($CH_2$), 81.0 (C), 113.6 (CH), 127.46 (CH), 127.53 (CH), 129.1 (CH), 129.6 (C), 129.7 (C), 130.4 (C), 133.7 (C), 133.9 (C), 135.8 (CH), 135.9 (CH), 159.0 (C). IR $\nu_{max}$ (film) 3306, 3072, 3051, 2958, 2931, 2858, 1612, 1514, 1463, 1427, 1265, 1248, 1111, 1036, 821, 739,


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704. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ for $C_{29}H_{34}O_3SiNa$ calcd 481.2175, found 481.2161.

**tert-Butyl(((2*S*,5*S*)-5-((*R*,*Z*)-6-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl) oxy)hept-1-en-3-yn-1-yl)tetrahydrofuran-2-yl)methoxy)diphenylsilane (23).**[20] To a solution of vinyl iodide **10** (3.01 g, 6.11 mmol) in $Et_3N$ (50 mL), CuI (0.11 g, 0.61 mmol) and $PdCl_2(PPh_3)_2$ (0.21 g, 0.31 mmol) were added in one portion under an argon atmosphere. The resulting suspension was stirred at rt for 30 min. To this solution was added alkyne **9** (2.80 g, 6.11 mmol) in $Et_3N$ (30 mL), and stirring was continued for an additional 2 h. The reaction was quenched by adding a saturated aqueous solution of $NH_4Cl$ (50 mL). The $Et_3N$ was removed under vacuum, the aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine and dried with $Na_2SO_4$. The organic solvent was removed under vacuum and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:5) to give **23** (4.12 g, 5.00 mmol) as a colorless oil in 82% yield. $R_f$ 0.52 (15% EtOAc in hexane). $[\alpha]_D^{23}$ = +34 ($c$ = 0.25/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.08 (s, 9H), 1.09 (s, 9H), 1.52−2.31 (m, 4H), 2.44−2.67 (m, 2H), 3.42−3.57 (m, 2H), 3.64 (dd, $J$ = 10.4 and 5.4 Hz, 1H), 3.74 (dd, $J$ = 10.4 and 4.7 Hz, 1H), 3.81 (s, 3H), 4.00 (aquint, $J$ = 5.5 Hz, 1H), 4.14−4.26 (m, 1H), 4.28−4.41 (m, 2H), 4.87−4.99 (m, 1H), 5.44−5.53 (m, 1H), 5.88 (dd, $J$ = 10.9 and 8.1 Hz, 1H), 6.84 (d, $J$ = 8.7 Hz, 1H), 7.15 (d, $J$ = 8.7 Hz, 1H), 7.30−7.50 (m, 12H), 7.65−7.79 (m, 8H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 19.2 (C), 19.3 (C), 25.3 ($CH_2$), 26.8 ($CH_3$), 26.9 ($CH_3$), 28.7 ($CH_2$), 32.5 ($CH_2$), 55.2 ($CH_3$), 66.5 ($CH_2$), 70.68 (CH), 72.72 ($CH_2$), 72.8 ($CH_2$), 77.20 (C), 77.25 (CH), 78.2 (C), 79.5 (CH), 92.3 (C), 110.2 (CH), 113.6 (CH), 127.47 (CH), 127.53 (CH), 127.6 (CH), 129.1 (CH), 129.56 (CH), 129.63 (CH), 130.4 (C), 133.6 (C), 133.7 (C), 134.0 (C), 135.6 (CH), 135.8 (CH), 135.9 (CH), 142.8 (CH), 159.0 (CH). IR $\nu_{max}$ (film) 3583, 3070, 3049, 2957, 2932, 2858, 1612, 1587, 1514, 1472, 1463, 1427, 1390, 1361, 1302, 1248, 1173, 1113, 1038, 1007, 824, 739, 702. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{52}H_{63}O_5Si_2$ calcd 823.4214, found 823.4245.

**(*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)heptan-1-ol (24).** To a solution of enyne **23** (2.91 g, 3.53 mmol) in EtOH (60 mL) (compound **23** was dissolved in EtOH by heating with a heat-gun under continuous shaking) was added 5% Pd/C (0.30 g, 10% w/w). The resulting suspension was vigorously stirred at rt under a $H_2$ atmosphere (1 atm) after three vacuum/$H_2$ cycles were performed to remove any air from the reaction flask. The reaction mixture was stirred for 60 h before it was filtered (silica flash), and the filtrate was concentrated to give 2.41 g of a reduced compound that was used in the next step without further purification. $R_f$ 0.50 (10% EtOAc in hexane).

To a solution of the previously obtained reduced compound (2.41 g) in a mixture of $CH_2Cl_2$ (32 mL) and pH 7 phosphate buffer (4 mL), DDQ (1.29 g, 5.42 mmol) was added at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and stirred for an additional 35 min before it was diluted with $Et_2O$ (100 mL) and quenched with water (30 mL). The resulting heterogeneous mixture was filtered, and the organic phase was separated, washed with saturated aqueous $NaHCO_3$ (20 mL), dried with $Na_2SO_4$, and filtered. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to afford the pure alcohol **24** (1.82 g, 2.57 mmol) as a colorless oil in 73% yield over two steps. $R_f$ 0.59 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = −14 ($c$ = 0.55/$CH_2Cl_2$). $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 1.17 (s, 9H), 1.20 (s, 9H), 1.08−1.79 (m, 14H), 3.45 (dd, $J$ = 11.0 and 5.2 Hz, 1H), 3.50 (dd, $J$ = 11.0 and 3.8 Hz, 1H), 3.68 (dd, $J$ = 10.5 and 4.8 Hz, 1H), 3.72 (dd, $J$ = 10.5 and 4.5 Hz, 1H), 3.79−3.88 (m, 2H), 4.14 (dt, $J$ = 7.0 and 4.7 Hz, 1H), 7.19−7.30 (m, 12H), 7.76−7.91 (m, 8H). $^{13}$C NMR (125.7 MHz, $C_6D_6$) $\delta$ 19.5 (C), 19.6 (C), 25.4 ($CH_2$), 26.7 ($CH_2$), 27.1 ($CH_3$), 27.3 ($CH_3$), 28.4 ($CH_2$), 30.1 ($CH_2$), 32.4 ($CH_2$), 34.0 ($CH_2$), 36.3 ($CH_2$), 66.2 ($CH_2$), 67.2 ($CH_2$), 74.7 (CH), 79.1 (CH), 79.5 (CH), 128.3 (C), 129.9 (CH), 130.0 (CH), 134.2 (C), 134.3 (C), 134.5 (C), 134.7 (C), 136.10 (CH), 136.14 (CH), 136.31 (CH). IR $\nu_{max}$ (film) 3584, 3053, 2934, 2860, 1474, 1427, 1265, 1111, 897, 824, 739, 706. HRMS (ESI-TOF) $m/z$ [M + K]$^+$ for $C_{44}H_{60}O_4Si_2K$ calcd 747.3667, found 747.3649.

**tert-Butyl(((2*S*,5*R*)-5-((*R*)-6-((tert-butyldiphenylsilyl)oxy)-7-iodoheptyl) tetrahydrofuran-2-yl)methoxy)diphenylsilane (25).** To a solution of alcohol **24** (0.133 g, 0.192 mmol) in THF (7 mL) were added $I_2$ (0.17 g, 0.653 mmol) and $PPh_3$ (0.076 g, 0.288 mmol). The reaction mixture was stirred for 1 h at rt. Additional equivalents of $I_2$ (0.17 g, 0.653 mmol) and $PPh_3$ (0.076 g, 0.288 mmol) were added, and the reaction mixture was stirred for another 1 h at 80 °C for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and stirred for 5 min before it was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $Na_2SO_4$ and filtered, and the organic solvent was removed under vacuum. The residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:9) to give the desired iodide **25** (0.111 g, 0.136 mmol) as a colorless oil in 71% yield. $R_f$ 0.63 (10% EtOAc in hexane). $[\alpha]_D^{23}$ = +2 ($c$ = 0.69/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.07 (s, 9H), 1.09 (s, 9H), 1.14−2.10 (m, 14H), 3.10−3.18 (m, 2H), 3.39−3.50 (m, 1H), 3.63 (dd, $J$ = 10.4 and 5.2 Hz, 1H), 3.69 (dd, $J$ = 10.4 and 4.8 Hz, 1H), 3.82−3.97 (m, 1H), 4.07−4.20 (m, 1H), 7.30−7.56 (m, 12H), 7.62−7.86 (m, 8H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.5 ($CH_2$), 19.3 (C), 19.4 (C), 24.6 ($CH_2$), 26.2 ($CH_2$), 26.9 ($CH_3$), 27.0 ($CH_3$), 28.2 ($CH_2$), 29.5 ($CH_2$), 32.0 ($CH_2$), 35.8 ($CH_2$), 36.7 ($CH_2$), 66.6 ($CH_2$), 71.4 (CH), 78.8 (CH), 79.5 (CH), 127.6 (CH), 129.5 (CH), 129.7 (CH), 129.8 (CH), 133.8 (C), 133.9 (C), 135.6 (CH), 135.85 (CH), 135.89 (CH). IR $\nu_{max}$ (film) 3072, 3051, 2959, 2932, 2858, 1962, 1902, 1827, 1776, 1589, 1472, 1463, 1427, 1391, 1361, 1265, 1188, 1113, 1084, 1007, 939, 895, 824, 739, 704. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ for $C_{44}H_{59}IO_3Si_2Na$ calcd 841.2945, found 841.2958.

**(2*RS*,5*S*)-5-Methyl-3-(phenylthio)dihydrofuran-2(3H)-one (8).**[22] $R_f$ 0.34 (20% EtOAc in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.29−1.39 (m, 6H), 1.75−1.90 (m, 1H), 2.17−2.42 (m, 2H), 2.66−2.79 (m, 1H), 3.86−4.02 (m, 2H), 4.44−4.61 (m, 2H), 7.27−7.37 (m, 6H), 7.48−7.57 (m, 4H).

**(3*RS*,5*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-heptyl)-5-methyl-3-(phenylthio) dihydrofuran-2(3H)-one (27).** To a solution of anhydrous pyridine (0.20 mL) and $CH_2Cl_2$ (7 mL), $Tf_2O$[23] (0.36 mL, 2.14 mmol) was added dropwise at −78 °C under an argon atmosphere. The reaction mixture was stirred for 15 min. Next, a solution of alcohol **24** (0.68 g, 0.96 mmol) in $CH_2Cl_2$ (7 mL) was added dropwise to the reaction mixture and stirred for 20 min at −78 °C. The reaction mixture was warmed to −30 °C and stirred for an additional 20 min. The reaction was then diluted with $CH_2Cl_2$ (25 mL) and washed with a 0.1 M aqueous solution of HCl (2 × 10 mL). The organic solvent was removed under vacuum, providing triflate **26** (0.76 g, 0.90 mmol) as a light brown oil in 94% yield, which was used in the next step without further purification.

To a solution of lactone **8** (0.540 g, 2.88 mmol) in THF (5 mL), a solution of LiHMDS (2.11 mL, 2.11 mmol, 1 M in THF) was added dropwise at −78 °C. The resulting mixture was stirred for 5 min and warmed to 0 °C. After an additional 30 min at 0 °C, HMPA (1.7 mL) was added dropwise. Next, a solution of triflate **26** (0.76 g, 0.90 mmol) in THF (7 mL) was added dropwise, and the resulting solution was stirred for 30 min at 0 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (15 mL) and diluted with EtOAc (25 mL), and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried with $Na_2SO_4$ and filtered, and the organic solvents were removed under vacuum. The residue was purified by flash column chromatography, eluting with EtOAc/hexane (1.5:8.5) to afford **27** (0.49 g, 0.55 mmol) as a colorless oil in 62% yield, and as a mixture of diastereoisomers. Some lactone **8** was also recovered (0.33 g). $R_f$ 0.55 (15% EtOAc and hexane). Major diastereoisomer: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.05 (s, 9H), 1.06 (s, 9H), 1.16 (d, $J$ = 6.1 Hz, 3H), 0.33−1.53 (m, 12H), 1.69−2.18 (m, 5H), 2.93 (dd, $J$ = 13.7 and 7.2 Hz, 1H), 3.56−3.72 (m, 2H), 3.74−3.91 (m, 1H), 4.03−4.19 (m, 1H), 4.20−4.33 (m, 1H), 4.40 (sext, $J$ = 6.8 Hz, 1H), 7.21−7.54 (m, 17H), 7.60−7.83 (m, 8H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 19.25 (C), 19.31 (C), 21.1 ($CH_3$), 24.7 ($CH_2$), 26.1 ($CH_2$), 26.8 ($CH_3$), 27.0 ($CH_3$), 28.2 ($CH_2$),


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29.3 ($CH_2$), 31.9 ($CH_2$), 35.6 ($CH_2$), 38.1 ($CH_2$), 39.5 ($CH_2$), 41.4 ($CH_2$), 55.5 (C), 66.6 ($CH_2$), 71.3 (CH), 73.2 (CH), 78.8 (CH), 79.5 (CH), 127.5 (CH), 127.7 (CH), 129.0 (CH), 129.5 (C), 135.6 (CH), 135.86 (CH), 135.88 (CH), 136.6 (CH), 177.5 (C).

**(*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (28).** To a solution of **27** (0.300 g, 0.355 mmol) in $CH_2Cl_2$ (8 mL) at 0 °C was added *m*-CPBA (0.090 g, 0.37 mmol, 77% w/w), and the reaction was stirred for 30 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$/$Na_2S_2O_3$ (1:1, 10 mL), warmed to room temperature and stirred for an additional 30 min. The aqueous phase was extracted with $CH_2Cl_2$ (20 mL), the combined organic phases were dried with $Na_2SO_4$, and the organic solvents were removed under vacuum. The residue was then dissolved in benzene (20 mL), and the solution was refluxed for 30 min. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to provide the desired $\alpha,\beta$-unsaturated lactone **28** (0.254 g, 0.322 mmol) as a colorless oil in 91% yield over two steps. $R_f$ 0.54 (20% EtOAc in hexane). $[\alpha]_D^{23} = -7$ ($c$ = 1.7/$CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.03 (s, 9H), 1.05 (s, 9H), 1.30 (d, $J$ = 6.8 Hz, 3H), 1.03−1.52 (m, 11H), 1.74−2.06 (m, 3H), 2.37−2.48 (m, 2H), 3.61 (dd, $J$ = 10.5 and 5.2 Hz, 1H), 3.66 (dd, $J$ = 10.5 and 4.6 Hz, 1H), 3.81−3.90 (m, 1H), 4.02 (quint, $J$ = 5.6 Hz, 1H), 4.11 (tt, $J$ = 6.9 and 4.9 Hz, 1H), 4.82−4.90 (m, 1H), 6.90 (d, $J$ = 1.3 Hz, 1H), 7.32−7.45 (m, 12H), 7.61−7.73 (m, 8H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) 18.9 ($CH_3$), 19.3 (C), 19.4 (C), 24.9 ($CH_2$), 26.2 ($CH_2$), 26.8 ($CH_3$), 27.0 ($CH_3$), 28.2 ($CH_2$), 29.6 ($CH_2$), 31.8 ($CH_2$), 32.0 ($CH_2$), 35.8 ($CH_2$), 36.3 ($CH_2$), 66.6 ($CH_2$), 71.7 (CH), 77.4 (CH), 78.8 (CH), 79.5 (CH), 127.55 (CH), 127.58 (CH), 129.5 (CH), 129.6 (CH), 130.6 (C), 133.74 (C), 133.76 (C), 134.05 (C), 134.09 (C), 135.6 (CH), 135.8 (CH), 135.9 (CH), 151.2 (CH), 174.0 (C). IR $\nu_{max}$ (film) 3071, 3049, 2932, 2858, 1757, 1589, 1472, 1461, 1427, 1388, 1362, 1319, 1265, 1194, 1113, 1080, 1029, 1007, 824, 739, 702, 613. HRMS (ESI-TOF) $m/z$ [M + K]$^+$ for $C_{49}H_{64}O_5Si_2K$ calcd 827.3929, found 827.3940.

**(*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (29):.[25]** To a solution of silyl ether **28** (0.124 g, 0.157 mmol) in anhydrous THF (4 mL) and pyridine (4 mL), HF·py complex (1 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), and solid $NaHCO_3$ was added until gas evolution ceased. The aqueous phase was extracted with $Et_2O$ (3 × 30 mL), the combined organic solvents were removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to give the desired primary alcohol **29** (0.0818 g, 0.149 mmol) in 95% yield as a colorless oil. $R_f$ 0.73 (15% EtOAc in hexane). $[\alpha]_D^{23} = -8$ ($c$ = 2.0/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.03 (s, 9H), 1.31 (d, $J$ = 6.8 Hz, 3H), 1.10−1.80 (m, 11H), 1.85−2.13 (m, 3H), 2.36−2.50 (m, 2H), 3.40−3.54 (m, 1H), 3.56−3.68 (m, 1H), 3.78−3.93 (m, 1H), 3.94−4.17 (m, 2H), 4.82−4.94 (m, 1H), 6.91 (s, 1H), 7.29−7.48 (m, 6H), 7.58−7.75 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) 18.9 ($CH_3$), 19.3 (C), 24.8 ($CH_2$), 26.0 ($CH_2$), 27.0 ($CH_3$), 27.5 ($CH_2$), 29.5 ($CH_2$), 31.7 ($CH_2$), 32.0 ($CH_2$), 35.5 ($CH_2$), 36.3 ($CH_2$), 65.0 ($CH_2$), 71.7 (CH), 77.4 (CH), 78.8 (CH), 79.3 (CH), 127.5 (CH), 129.6 (CH), 130.6 (C), 134.0 (C), 134.1 (C), 135.8 (CH), 135.8 (CH), 151.3 (CH), 174.0 (C). IR $\nu_{max}$ (film) 3447, 3071, 3051, 2932, 2858, 1755, 1463, 1427, 1375, 1319, 1267, 1198, 1105, 1078, 1027, 822, 739, 704, 611. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{33}H_{47}O_5Si$ calcd 551.3193, found 551.3176.

**Preparation of Enol Silanes 5 and 5′: Pentadecanal (31).** To a vigorously stirred solution of hexadec-1-ene (**30**) (4.35 g, 19.3 mmol) in 1:1 $H_2O$/$Et_2O$ (90 mL) was added a solution of $OsO_4$ (2 mol %, 2.00 mL, 0.400 mmol, 0.2 M in *t*-BuOH) at room temperature. After 30 min, $NaIO_4$ (16.0 g, 75.3 mmol) was added in small portions, and the reaction mixture was stirred for 6 h. The phases were separated, and the aqueous phase was extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were dried with $MgSO_4$ and filtered, and the organic solvents were removed under vacuum. The residue was then loaded onto a silica gel flash plug and eluted with EtOAc/hexane (0.5:9.5) to give the known compound pentadecanal (**31**)[46] (3.92 g, 17.2 mmol) as a brown oil in 89% yield, which was used in the next step without further purification. An analytical sample was purified by flash column chromatography, eluting with EtOAc/hexane (0.5:9.5). $R_f$ 0.50 (5% EtOAc in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 6.8 Hz, 3H), 1.17−1.36 (m, 22H), 1.61 (q, $J$ = 7.2 Hz, 2H), 2.40 (dt, $J$ = 7.2 and 1.7 Hz, 2H), 9.74 (t, $J$ = 1.7 Hz, 1H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1, 22.1, 22.7, 29.2, 29.3, 29.4, 29.57, 29.63, 29.66, 203.0.

**(Z)-Ethyl heptadec-2-enoate (33).** To a suspension of NaH (0.960 g, 24.1 mmol, 60% in mineral oil) in THF (51 mL), a solution of phosphonate **32**[26] (6.00 g, 17.2 mmol) in THF (20 mL) was added dropwise at 0 °C under an argon atmosphere. After 15 min, the reaction mixture was cooled to −40 °C, and a solution of **31** (3.90 g) in THF (18 mL) was added dropwise. The reaction mixture was vigorously stirred at −40 °C for 3 h. The reaction was quenched with a saturated aqueous solution of $NH_4Cl$ (5 mL), the organic phase was dried with $MgSO_4$, and the organic solvent was removed under vacuum. The residue was then purified by flash column chromatography, eluting with EtOAc/hexane (5:95) to afford the *Z*-$\alpha,\beta$-unsaturated ester **33** (4.03 g, 13.6 mmol) in 79% yield as a colorless oil (*Z*:*E* > 95:5). $R_f$ 0.62 (5% EtOAc in hexane). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 0.97 (t, $J$ = 7.1 Hz, 3H), 1.21−1.43 (m, 24H), 2.79 (q, $J$ = 7.0 Hz, 2H), 4.00 (q, $J$ = 7.1 Hz, 2H), 5.83 (d, $J$ = 11.7 Hz, 1H), 5.92 (dt, $J$ = 11.7 and 7.0 Hz, 1H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.26, 14.34, 23.1, 29.2, 29.4, 29.7, 29.81, 29.84, 30.0, 30.08, 30.11, 30.14, 32.3, 59.6, 120.1, 150.6, 166.0. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{19}H_{37}O_2$ calcd 297.2794, found 297.2776.

**(Z)-*N*-Methoxy-*N*-methylheptadec-2-enamide (34).** To a solution of *Z*-$\alpha,\beta$-unsaturated ester **33** (1.00 g, 3.37 mL) and N,O-dimethylhydroxylamine hydrochloride (0.654 g, 6.74 mmol) in THF (7.5 mL), a solution of *i*-PrMgCl (8.70 mL, 14.8 mmol, 1.7 M in THF) was slowly added at −10 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and quenched with a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous phase was then extracted with $Et_2O$ (3 × 15 mL), and the combined organic phases were dried with $MgSO_4$. The organic solvents were removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:9) to give the *Z*-Weinreb amide **34** (0.745 g, 2.39 mmol) in 71% yield (*Z*:*E* > 95:5). $R_f$ 0.19 (5% EtOAc in hexane). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.20−1.52 (m, 24H), 2.91 (qd, $J$ = 7.7 and 1.6 Hz, 2H), 2.91 (s, 3H), 3.08 (s, 3H), 5.99 (dt, $J$ = 11.5 and 7.7 Hz, 1H), 6.30 (dt, $J$ = 11.5 and 1.6 Hz, 1H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3, 23.1, 29.4, 29.75, 29.77, 29.79, 29.92, 30.05, 30.10, 30.14, 31.9, 32.3, 60.8, 118.7, 147.6, 167.5. IR $\nu_{max}$ (film) 2957, 2926, 2854, 1659, 1634, 1464, 1441, 1348, 1265, 1178, 1097, 1001, 795, 739, 704. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{19}H_{38}NO_2$ calcd 312.2903, found 312.2928.

**(Z)-Octadec-3-en-2-one (Z-35).** To a solution of the *Z*-Weinreb amide **34** (0.500 g, 1.61 mmol) in THF (7 mL) was added a solution of MeMgI (3.22 mL, 3.22 mmol, 1 M in $Et_2O$) at −30 °C. The reaction mixture was warmed to 0 °C and stirred for 30 min. The reaction was then quenched with a saturated aqueous solution of $NH_4Cl$ (2 mL), and the aqueous phase was extracted with $Et_2O$/EtOAc (1:1, 3 × 8 mL). The combined organic phases were dried with $MgSO_4$, the solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:9) to give methyl ketone *Z*-**35** (0.320 g, 1.20 mmol) in 75% yield as a colorless oil (*Z*:*E* > 95:5). $R_f$ 0.71 (10% EtOAc in hexane). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.21−1.42 (m, 24H), 1.80 (s, 3H), 2.71 (q, $J$ = 6.3 Hz, 2H), 5.68−5.83 (m, 2H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3, 23.1, 29.6, 29.7, 29.8, 29.9, 30.0, 30.10, 30.14, 31.18, 32.3, 127.2, 147.8, 197.5. IR $\nu_{max}$ (film) 2926, 2854, 1691, 1612, 1465, 1421, 1356, 1265, 1180, 741, 706. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{18}H_{35}O$ calcd 267.2688, found 267.2666.

**(Z)-Trimethyl(octadeca-1,3-dien-2-yloxy)silane (5′).** To a solution of diisopropylamine (2.0 equiv, 0.32 mL, 2.2 mmol) in THF (5.7 mL), *n*-BuLi (2.5 equiv, 2.0 mL, 2.8 mmol, 1.4 M in hexane) was added dropwise at −78 °C under an argon atmosphere. The reaction


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mixture was stirred for 10 min at −78 °C, and a solution of methyl ketone *Z*-**35** (0.300 g, 1.12 mmol) in THF (4 mL) was then added. After 20 min, TMSCl (3.0 equiv, 0.43 mL, 3.4 mmol) was added dropwise, and the reaction mixture was stirred for another 5 min and warmed to −20 °C. After 1 h, the reaction was diluted with hexane (5 mL), and the organic phase was washed with saturated aqueous solutions of $NaHCO_3$ (3 × 5 mL) and NaCl (5 mL). The combined organic phases were dried with $MgSO_4$, and the organic solvent was removed under vacuum, producing enol silyl ether **5′** (0.39 g) in >99% yield as a slightly yellow oil that was used in the next step without further purification. $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.21 (s, 9H), 0.92 (t, $J$ = 6.8 Hz, 3H), 1.26−1.35 (m, 24H), 2.58 (dt, $J$ = 7.5 and 1.6 Hz, 2H), 4.34 (s, 1H), 4.37 (s, 1H), 5.44 (dt, $J$ = 11.9 and 7.5 Hz, 1H), 5.84 (dt, $J$ = 11.9 and 1.6 Hz, 1H).

**Hexadec-1-yne (37).** To a solution of aldehyde **31** (1.71 g, 7.57 mmol) and the Bestmann-Ohira phosphonate **36**[29] (1.89 g, 9.84 mmol) in MeOH (177 mL) was added $K_2CO_3$ (1.77 g) in one portion. The reaction mixture was vigorously stirred at room temperature for 18 h before it was quenched with a saturated aqueous solution of $NH_4Cl$ (20 mL). The organic solvent was removed under vacuum, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried with $Na_2SO_4$, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:19) to give the known alkyne **37**[47] (1.52 g, 6.83 mmol) in 90% yield. $R_f$ 0.93 (5% EtOAc in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.8 Hz, 3H), 1.18−1.44 (m, 22H), 1.45−1.60 (m, 2H), 1.91 (t, $J$ = 2.7 Hz, 1H), 2.17 (td, $J$ = 7.1 and 2.7 Hz, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1 ($CH_3$), 18.4 ($CH_2$), 22.7 ($CH_2$), 28.5 ($CH_2$), 28.8 ($CH_2$), 29.1 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.7 ($CH_2$), 68.0 (CH), 84.8 (CH).

**Octadec-3-yn-2-one (39).** To a solution of alkyne **37** (1.4 g, 6.3 mmol) in THF (46 mL), *n*-BuLi (3.9 mL, 6.3 mmol, 1.6 M in hexane) was added dropwise at −78 °C. The solution was stirred for 20 min, warmed to −20 °C and stirred for an additional 10 min. Next, the solution was cooled to −50 °C, and amide **38** (0.61 mL, 6.3 mmol) was added dropwise. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The reaction was quenched with a saturated aqueous solution of $NH_4Cl$ (10 mL), the aqueous phase was extracted with $Et_2O$ (3 × 40 mL), and the combined organic phases were dried with $Na_2SO_4$. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:19) to give $\alpha,\beta$-unsaturated alkynyl ketone **39** (1.20 g, 4.61 mmol) in 73% yield as a colorless oil. $R_f$ 0.44 (5% EtOAc in hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 7.0 Hz, 3H), 1.19−1.45 (m, 22H), 1.48−1.61 (m, 2H), 2.29 (s, 3H), 2.33 (t, $J$ = 7.0 Hz, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1, 18.9, 22.7, 27.7, 28.8, 29.0, 29.3, 29.4, 29.55, 29.62, 31.9, 32.7, 81.4, 94.1, 184.9. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ for $C_{18}H_{33}O$ calcd 265.2531, found 265.2508.

**Trimethyl(octadec-1-en-3-yn-2-yloxy)silane (5).** To a solution of alkynyl ketone **39** (0.40 g, 1.51 mmol) in anhydrous THF (13.3 mL), a solution of LiHMDS (1.6 equiv, 2.4 mL, 2.4 mmol, 1 M solution in THF) was added dropwise under an argon atmosphere at −50 °C. After 20 min, TMSCl (0.23 mL) was added dropwise, and the resulting suspension was warmed to 0 °C and stirred for 30 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), the organic volatiles were removed under vacuum, and the aqueous phase was extracted with pentane (60 mL). The organic phase was washed with $H_2O$ (20 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL), and the combined organic phases were dried with $Na_2SO_4$. The organic solvent was removed under vacuum, yielding enol silyl ether **5** (0.50 g, 1.50 mmol) as a slightly yellow oil that was used in the next step without further purification. $R_f$ 0.95 (hexane). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.27 (s, 9H), 0.92 (t, $J$ = 6.8 Hz, 3H), 1.12−1.45 (m, 24H), 2.08 (t, $J$ = 7.0 Hz, 2H), 4.77 (s, 1H), 4.79 (s, 1H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 0.3 ($CH_3$), 14.3 ($CH_3$), 19.2 ($CH_2$), 23.1 ($CH_2$), 28.7 ($CH_2$), 29.2 ($CH_2$), 29.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 30.0 ($CH_2$), 30.10 ($CH_2$), 30.14 ($CH_2$), 32.3 ($CH_2$), 79.2 (C), 89.0 (C), 101.2 ($CH_2$), 140.3 (C).

**Studies on the Mukaiyama Aldol Reaction and the 1,3-Carbonyl Reduction.** *General Procedure for the Preparation of Aldehydes **41** and **18**.* To a solution of alcohol **40** or **17** (1 equiv, 0.895 mmol) in $CH_2Cl_2$ (11 mL) were added DMSO (10 equiv, 0.63 mL, 8.95 mmol) and DIPEA (5 equiv, 0.73 mL, 4.5 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 5 min, $SO_3$·py (3 equiv, 0.43 g, 2.7 mmol) was added in one portion, and the reaction mixture was then stirred for 1 h at 0 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), warmed to rt and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were washed with $H_2O$ (10 mL) and a saturated aqueous solution of NaCl (10 mL) and dried with $Na_2SO_4$. The organic solvent was then removed under vacuum to produce the corresponding aldehyde (quantitative yield) as a slightly yellow oil that was submitted to azeotropic distillation with benzene (2 × 3 mL) and used in the next step without further purification.

*General Procedure for the Chelated Mukaiyama Aldol Reaction between Enol Silane 5′ and Aldehyde **41** or **18**.* To a solution of aldehyde **41** or **18** (1 equiv, 0.409 mmol) in $CH_2Cl_2$ (2 mL), a solution of enol silane **5′** (2 equiv) in $CH_2Cl_2$ (2 mL) was added dropwise under an argon atmosphere at the temperature and with the Lewis acid indicated in Table 2. The reaction mixture was monitored by TLC and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) after the length of time indicated in Table 2. The reaction mixture was then warmed to rt, the aqueous phase was extracted with $Et_2O$ (3 × 5 mL), and the combined organic phases were dried with $Na_2SO_4$. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:9).

*(S,Z)-1-((2S,5S)-5-(((tert-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-1-hydroxynonadec-4-en-3-one (Z-**42**):* $R_f$ 0.36 (15% EtOAc in hexane). $[\alpha]_D^{23}$ = −8 ($c$ = 1.1/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.07 (s, 6H), 0.92 (t, $J$ = 6.8 Hz, 3H), 0.98 (s, 9H), 1.22−1.43 (m, 24H), 1.51−1.80 (m, 4H), 2.36 (dd, $J$ = 16.3 and 4.0 Hz, 1H), 2.68 (dd, $J$ = 16.3 and 8.4 Hz, 1H), 2.68−2.85 (m, 3H), 3.41−3.53 (m, 2H), 3.81 (td, $J$ = 6.8 and 4.4 Hz, 1H), 3.91−4.06 (m, 2H), 5.79 (dt, $J$ = 11.4 and 7.3 Hz, 1H), 5.95 (dt, $J$ = 11.4 and 1.4 Hz, 1H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ −5.2, 14.3, 18.5, 23.1, 26.1, 27.8, 28.5, 29.5, 29.7, 29.8, 29.9, 30.0, 30.10, 30.14, 32.3, 48.1, 66.1, 70.4, 80.3, 82.1, 127.4, 148.6, 200.1. IR $\nu_{max}$ (film) 3449, 3053, 2955, 2928, 2856, 1734, 1688, 1614, 1464, 1444, 1420, 1388, 1362, 1265, 1082, 1005, 939, 837, 777, 740, 704. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ for $C_{30}H_{59}O_4Si$ calcd 511.4183, found 511.4159.

*(S,E)-1-((2S,5S)-5-(((tert-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-1-hydroxynonadec-4-en-3-one (E-**42**):* $[\alpha]_D^{23}$ = −25 ($c$ = 1.5/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.07 (s, 6H), 0.94 (t, $J$ = 6.2 Hz, 3H), 0.98 (s, 9H), 1.10−1.38 (m, 24H), 1.60−1.91 (m, 6H), 2.48 (dd, $J$ = 16.3 and 3.8 Hz, 1H), 2.85 (dd, $J$ = 16.3 and 8.5 Hz, 1H), 2.96 (d, $J$ = 3.0 Hz, 1H), 3.50−3.55 (m, 2H), 3.96 (td, $J$ = 6.3 and 4.3 Hz, 1H), 4.04−4.14 (m, 2H), 6.06 (dt, $J$ = 16.0 and 1.4 Hz, 1H), 6.70 (dt, $J$ = 16.0 and 6.8 Hz, 1H). HRMS (ESI-TOF) $m/z$ $[M + H]^+$ for $C_{30}H_{59}O_4Si$ calcd 511.4183, found 511.4171.

*(S,E)-1-((2S,5S)-5-(((tert-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-1-hydroxynonadec-4-en-3-one (E-**43**).* $R_f$ 0.44 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = −3 ($c$ = 1.8/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 7.0 Hz, 3H), 1.18 (s, 9H), 1.22−1.40 (m, 24H), 1.49−1.91 (m, 6H), 2.47 (dd, $J$ = 16.0 and 3.9 Hz, 1H), 2.84 (dd, $J$ = 16.0 and 8.6 Hz, 1H), 2.86 (d, $J$ = 4.3 Hz, 1H), 3.56−3.70 (m, 2H), 3.85 (td, $J$ = 6.6 and 4.3 Hz, 1H), 4.00−4.14 (m, 2H), 6.07 (ad, $J$ = 16.0 Hz, 1H), 6.72 (dt, $J$ = 16.0 and 6.6 Hz, 1H), 7.20−7.30 (m, 6H), 7.73−7.89 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3 ($CH_3$), 19.5 (C), 23.1 ($CH_2$), 27.1 ($CH_3$), 27.9 ($CH_2$), 28.3 ($CH_2$), 28.5 ($CH_2$), 29.5 ($CH_2$), 29.8 ($CH_2$), 30.0 ($CH_2$), 30.10 ($CH_2$), 30.14 ($CH_2$), 32.3 ($CH_2$), 32.6 ($CH_2$), 44.2 ($CH_2$), 67.0 ($CH_2$), 70.3 (CH), 80.3 (CH), 82.1 (CH), 129.9 (CH), 131.2 (CH), 134.1 (C), 134.2 (C), 136.04 (CH), 136.08 (CH), 147.4 (CH), 198.9 (C). IR $\nu_{max}$ (film) 3470, 3071, 3049, 2955, 2926, 2854, 1697, 1668, 1626, 1464, 1427, 1361, 1113, 1082, 1007, 1001, 824, 741, 702, 613. HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ for $C_{40}H_{62}O_4SiNa$ calcd 657.4315, found 657.4329.

*(E)-Octadec-3-en-2-one (E-**34**).* $R_f$ 0.69 (10% EtOAc in hexane). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.10−1.41 (m, 24H), 1.84 (qd, $J$ = 6.6 and 1.6 Hz, 2H), 1.89 (s, 3H), 5.96 (dt, $J$ = 16.0 and 1.6 Hz, 1H), 6.47 (dt, $J$ = 16.0 and 6.8 Hz, 1H). $^{13}$C NMR


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(62.9 MHz, $C_6D_6$) $\delta$ 14.3, 23.1, 26.7, 28.4, 29.5, 29.8, 30.0, 30.1, 30.2, 32.3, 32.5, 131.6, 146.9, 196.4. IR $\nu_{max}$ (film) 2955, 2926, 2854, 1697, 1676, 1628, 1466, 1362, 1265, 1256, 980, 741, 704. HRMS (EI-TOF) $m/z$ $[M]^+$ for $C_{18}H_{34}O$ calcd 266.2610, found 266.2636.

**(*S*)-1-((2*S*,5*S*)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-1-hydroxynonadec-4-yn-3-one (44).** To a solution of aldehyde **18** (1 equiv, 0.29 g, 0.79 mmol) in $CH_2Cl_2$ (3.6 mL), $MgBr_2{\cdot}Et_2O$ (3 equiv, 0.66 g, 2.37 mmol) was added quickly in one portion under an argon atmosphere at −30 °C. The heterogeneous mixture was vigorously stirred for 5 min. Next, a solution of enol silane **5** (1.9 equiv, 0.501 g, 1.50 mmol) in $CH_2Cl_2$ (3.6 mL) was added dropwise. The reaction mixture was stirred for 1.5 h at −30 °C and was quenched with a 10% aqueous solution of $NaHCO_3$ (5 mL). The reaction mixture was warmed to rt, the aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic phases were dried with $Na_2SO_4$. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (5:95) to afford the desired aldol adduct **44** (0.34 g, 54 mmol) in 68% yield as a colorless oil. $R_f$ 0.53 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = +1 ($c$ = 0.84/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.16 (s, 9H), 1.16−1.37 (m, 24H), 1.45−1.75 (m, 4H), 1.93 (t, $J$ = 6.8 Hz, 2H), 2.48 (d, $J$ = 5.7 Hz, 1H), 2.54 (dd, $J$ = 16.3 and 4.1 Hz, 1H), 2.89 (dd, $J$ = 16.3 and 8.7 Hz, 1H), 3.50−3.66 (m, 2H), 3.67−3.80 (m, 1H), 3.90−4.03 (m, 1H), 4.05−4.19 (m, 1H), 7.20−7.34 (m, 6H), 7.72−7.88 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3 ($CH_3$), 18.9 ($CH_2$), 19.5 (C), 23.1 ($CH_2$), 27.1 ($CH_2$), 27.9 ($CH_2$), 28.0 ($CH_2$), 28.4 ($CH_2$), 29.1 ($CH_2$), 29.4 ($CH_2$), 29.79 ($CH_2$), 29.81 ($CH_2$), 30.02 ($CH_2$), 30.08 ($CH_2$), 30.13 ($CH_2$), 32.3 ($CH_2$), 50.3 ($CH_2$), 66.8 ($CH_2$), 69.9 (CH), 80.2 (CH), 81.9 (CH), 82.0 (C), 93.8 (C), 128.0 (CH), 128.5 (CH), 130.0 (CH), 134.05 (C), 134.10 (C), 136.0 (CH), 136.1 (CH), 185.5 (C). IR $\nu_{max}$ (film) 3483, 3070, 3049, 2926, 2854, 2212, 1672, 1466, 1427, 1389, 1362, 1240, 1157, 1113, 1072, 1007, 999, 824, 741, 702, 613. HRMS (ESI-TOF) $m/z$ $[M - C_6H_5]^+$ for $C_{34}H_{55}O_4Si$ calcd 555.3870, found 555.3836.

**(1*S*,3*S*)-1-((2*S*,5*S*)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-tetrahydrofuran-2-yl)nonadec-4-yne-1,3-diol (45) and (1*S*,3*R*)-1-((2*S*,5*S*)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)nonadec-4-yne-1,3-diol (46).** To a suspension of $Me_4NBH(OAc)_3$ (0.29 g, 1.1 mmol) in $CH_3CN$ (1 mL) was added anhydrous acetic acid (1 mL). The reaction mixture was stirred for 30 min at rt before being cooled to −40 °C, at which point a solution of aldol adduct **44** (0.068 g, 0.107 mmol) in $CH_3CN$ (1 mL) was added dropwise to the reaction mixture. CSA (2 mg) was added, and the reaction mixture was stirred for 36 h at −20 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and poured into an Erlenmeyer flask containing a saturated aqueous solution of Na/K tartrate (10 mL) and $Et_2O$ (50 mL). The heterogeneous mixture was vigorously stirred for 8 h. The organic phase was dried with $Na_2SO_4$, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (5:95) to produce an inseparable mixture of diols **45** and **46** (0.065 g, 0.102 mmol) in 96% yield with a diastereoselectivity of 7:3 (**45**:**46**). $R_f$ 0.34 (20% EtOAc in hexane).

*(1S,3S)-1-((2S,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)nonadec-4-yne-1,3-diol (**45**).* $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.8 Hz, 3H), 1.05 (s, 9H), 1.18−1.58 (m, 24H), 1.58−2.09 (m, 6H), 2.13−2.26 (m, 2H), 2.75 (bs, 1H), 3.31 (bs, 1H), 3.59−3.72 (m, 2H), 3.78−3.99 (m, 2H), 4.06−4.21 (m, 1H), 4.60−4.74 (m, 1H), 7.32−7.47 (m, 6H), 7.63−7.74 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1 ($CH_3$), 18.7 ($CH_2$), 19.2 (C), 22.7 ($CH_2$), 26.8 ($CH_3$), 28.1 ($CH_2$), 28.2 ($CH_2$), 28.7 ($CH_2$), 28.9 ($CH_2$), 29.1 ($CH_2$), 29.3 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.7 ($CH_2$), 31.9 ($CH_2$), 40.2 ($CH_2$), 60.6 (CH), 66.3 ($CH_2$), 71.7 (CH), 79.7 (CH), 80.8 (C), 82.30 (CH), 85.6 (C), 127.6 (CH), 129.6 (CH), 133.5 (C), 133.6 (C), 135.57 (CH), 135.62 (CH).

*(1S,3R)-1-((2S,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)nonadec-4-yne-1,3-diol (**46**).* $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.8 Hz, 3H), 1.05 (s, 9H), 1.18−1.58 (m, 24H), 1.58−2.09 (m, 6H), 2.13−2.26 (m, 2H), 2.78 (bs, 1H), 3.11 (bs, 1H), 3.59−3.72 (m, 2H), 3.78−3.99 (m, 2H), 4.06−4.21 (m, 1H), 4.60−4.74 (m, 1H), 7.32−7.47 (m, 6H), 7.63−7.74 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1 ($CH_3$), 18.7 ($CH_2$), 19.2 (C), 22.7 ($CH_2$), 26.8 ($CH_3$), 28.0 ($CH_2$), 28.2 ($CH_2$), 28.6 ($CH_2$), 28.9 ($CH_2$), 29.1 ($CH_2$), 29.3 ($CH_2$), 29.5 ($CH_2$), 29.64 ($CH_2$), 29.66 ($CH_2$), 31.9 ($CH_2$), 41.4 ($CH_2$), 61.8 (CH), 66.3 ($CH_2$), 73.4 (CH), 79.7 (CH), 80.7 (C), 82.28 (CH), 85.5 (C), 127.6 (CH), 129.6 (CH), 133.5 (C), 133.6 (C), 135.57 (CH), 135.62 (CH).

**tert-Butyl(((2*S*,5*S*)-5-((4*S*,6*S*)-6-(hexadec-1-yn-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)tetrahydrofuran-2-yl)methoxy)diphenylsilane (47) and tert-Butyl(((2*S*,5*S*)-5-((4*S*,6*R*)-6-(hexadec-1-yn-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)tetrahydrofuran-2-yl)methoxy) diphenylsilane (48).** To a solution of diols **45** and **46** (0.053 g, 0.083 mmol) in 2,2-dimethoxypropane (5 mL), CSA (5 mg) was added. The solution was stirred overnight at rt, and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and diluted with $Et_2O$ (15 mL). The organic phase was dried with $Na_2SO_4$, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (5:95) to produce acetonides **47** (0.037 g, 0.055 mmol) and **48** (0.020 g, 0.029 mmol) in >99% yield.

*tert-Butyl(((2S,5S)-5-((4S,6S)-6-(hexadec-1-yn-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)tetrahydrofuran-2-yl)methoxy)diphenylsilane (**47**):* $R_f$ 0.46 (5% EtOAc in hexanes). $[\alpha]_D^{23}$ = +2 ($c$ = 0.93/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.18 (s, 9H), 1.19−1.45 (m, 24H), 1.45 (s, 3H), 1.59−1.83 (m, 5H), 1.69 (s, 3H), 2.05−2.21 (m, 3H), 3.60−3.73 (m, 2H), 3.87−3.98 (m, 1H), 4.06−4.22 (m, 2H), 4.83−4.92 (m, 1H), 7.20−7.32 (m, 6H), 7.77−7.89 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3 ($CH_3$), 19.1 ($CH_2$), 19.5 (C), 23.1 ($CH_2$), 23.9 ($CH_3$), 27.1 ($CH_3$), 27.5 ($CH_2$), 28.3 ($CH_2$), 28.93 ($CH_3$), 28.94 ($CH_2$), 29.2 ($CH_2$), 29.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 30.04 ($CH_2$), 30.08 ($CH_2$), 30.12 ($CH_2$), 32.3 ($CH_2$), 33.9 ($CH_2$), 60.1 (CH), 67.0 ($CH_2$), 68.8 (CH), 80.2 (CH), 81.1 (CH), 81.7 (C), 85.9 (CH), 100.2 (C), 128.0 (CH), 128.3 (CH), 129.9 (CH), 134.2 (C), 134.2 (C), 136.1 (CH). IR $\nu_{max}$ (film) 3070, 3049, 2955, 2928, 2854, 1464, 1427, 1379, 1362, 1263, 1246, 1223, 1200, 1178, 1161, 1138, 1113, 1086, 999, 978, 947, 874, 824, 739, 702, 613. HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ for $C_{43}H_{66}O_4SiNa$ calcd 697.4628, found 697.4624.

*tert-Butyl(((2S,5S)-5-((4S,6R)-6-(hexadec-1-yn-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)tetrahydrofuran-2-yl)methoxy)diphenylsilane (**48**):* $R_f$ 0.31 (5% EtOAc in hexane). $[\alpha]_D^{23}$ = +8 ($c$ = 0.92/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.92 (t, $J$ = 6.8 Hz, 3H), 1.18 (s, 9H), 1.16−1.37 (m, 21H), 1.21 (s, 3H), 1.37−1.81 (m, 8H), 1.51 (s, 3H), 1.97−2.18 (m, 3H), 3.52−3.72 (m, 3H), 3.84−3.96 (m, 1H), 4.07−4.19 (m, 1H), 4.54−4.64 (m, 1H), 7.20−7.32 (m, 6H), 7.77−7.89 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ 14.3 ($CH_3$), 19.0 ($CH_2$), 19.4 ($CH_3$), 19.5 (C), 23.1 ($CH_2$), 27.1 ($CH_3$), 27.3 ($CH_2$), 28.2 ($CH_2$), 29.1 ($CH_2$), 29.2 ($CH_2$), 29.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 30.07 ($CH_2$), 30.10 ($CH_2$), 30.14 ($CH_2$), 30.4 ($CH_3$), 32.3 ($CH_2$), 34.0 ($CH_2$), 60.9 (CH), 67.0 ($CH_2$), 71.5 (CH), 80.1 (CH), 80.4 (C), 81.1 (CH), 84.8 (C), 99.0 (C), 128.0 (CH), 128.3 (CH), 129.9 (CH), 134.2 (C), 136.1 (CH). IR $\nu_{max}$ (film) 3070, 3049, 2955, 2926, 2854, 1464, 1427, 1379, 1362, 1258, 1199, 1178, 1163, 1113, 1090, 1065, 999, 968, 866, 824, 740, 702, 613. HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ for $C_{43}H_{66}O_4SiNa$ calcd 697.4628, found 697.4648.

**Mukaiyama Aldol Reaction between Enol Silane 5 and Aldehyde 6 and the Conclusion of the Synthesis of Goniotrionin (4). (*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-((*S*)-1-hydroxy-3-oxononadec-4-yn-1-yl)-tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (49).** To a solution of alcohol **29** (0.0387 g, 0.0703 mmol) in $CH_2Cl_2$ (2 mL) were added DMSO (0.05 mL, 0.70 mmol) and DIPEA (0.06 mL, 0.34 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 5 min. $SO_3{\cdot}py$ (0.033 g, 0.21 mmol) was then added in one portion, and the reaction mixture was stirred for an additional 1 h at 0 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), diluted with $CH_2Cl_2$ (10 mL), warmed to rt and extracted with $CH_2Cl_2$ (1 × 10 mL). The combined organic phases were washed with $H_2O$ (5 mL) and a saturated aqueous solution of NaCl (5 mL) and dried with $Na_2SO_4$. The organic solvent was then removed under vacuum, yielding aldehyde **6** (0.038 g) as a slightly


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yellow oil that was submitted to azeotropic distillation with benzene (2 × 3 mL) and used in the next step without further purification.

To a solution of aldehyde **6** (0.038 g) in $CH_2Cl_2$ (1 mL), $MgBr_2{\cdot}Et_2O$ (3 equiv, 0.054 g, 0.21 mmol) was added quickly in one portion under an argon atmosphere at −30 °C. The heterogeneous mixture was vigorously stirred for 5 min. Next, a solution of enol silane **5** (4 equiv, 0.094 g, 0.28 mmol) in $CH_2Cl_2$ (1 mL) was added. The reaction mixture was stirred for 1.5 h at −30 °C before being quenched with a 10% aqueous solution of $NaHCO_3$ (5 mL). The reaction mixture was warmed to rt, the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic phases were dried with $Na_2SO_4$. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (5:95) to produce the desired aldol adduct **49** (0.034 g, 0.041 mmol) in 59% yield as a colorless oil. $R_f$ 0.43 (25% EtOAc in hexane). $[\alpha]_D^{23} = -8$ ($c$ = 0.30/$CH_2Cl_2$). $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.83 (d, $J$ = 6.9 Hz, 3H), 0.92 (t, $J$ = 7.0 Hz, 3H), 1.04−1.40 (m, 32H), 1.17 (s, 9H), 1.14−1.79 (m, 6H), 1.92 (t, $J$ = 7.0 Hz, 2H), 2.48−2.53 (m, 2H), 2.55 (dd, $J$ = 16.1 and 4.0 Hz, 1H), 2.61 (d, $J$ = 4.8 Hz, 1H), 2.90 (dd, $J$ = 16.1 and 8.8 Hz, 1H), 3.67−3.76 (m, 2H), 4.14 (dq, $J$ = 8.3 and 4.0 Hz, 1H), 4.20 (quint, $J$ = 5.8 Hz, 1H), 4.24−4.31 (m, 1H), 6.31 (ad, $J$ = 1.3 Hz, 1H), 7.20−7.33 (m, 6H), 7.74−7.86 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.3 ($CH_3$), 18.8 ($CH_3$), 18.9 ($CH_2$), 19.6 (C), 23.1 ($CH_2$), 25.1 ($CH_2$), 26.4 ($CH_2$), 27.3 ($CH_3$), 28.0 ($CH_2$), 29.1 ($CH_2$), 29.4 ($CH_2$), 29.8 ($CH_2$), 30.01 ($CH_2$), 30.08 ($CH_2$), 30.13 ($CH_2$), 32.3 ($CH_2$), 32.6 ($CH_2$), 36.0 ($CH_2$), 36.7 ($CH_2$), 50.1 ($CH_2$), 70.4 (CH), 72.1 (CH), 76.8 (CH), 79.8 (CH), 81.1 (CH), 82.1 (C), 93.8 (C), 128.3 (CH), 130.1 (CH), 131.0 (C), 134.5 (C), 134.7 (C), 136.2 (CH), 150.8 (CH), 173.2 (C), 185.5 (C). HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ for $C_{51}H_{76}O_6SiNa$ calcd 835.5309, found 835.5320.

**(*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-((1*S*,3*S*)-1,3-dihydroxynonadec-4-yn-1-yl)tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (51).** To a solution of aldol adduct **49** (0.137 g, 0.170 mmol) in *i*-PrOH (4 mL) was added (*S*,*S*)-Noyori's catalyst (**50**)[38] (10 mol %, 10 mg, 0.085 mmol). The reaction mixture was stirred for 18 h, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to afford the desired diol **51** (0.10 g, 0.12 mmol) in 71% yield as a brown oil. $R_f$ 0.68 (40% EtOAc in hexane). $[\alpha]_D^{23}$ = −17 ($c$ = 0.97/$CH_2Cl_2$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 6.8 Hz, 3H), 1.03 (s, 9H), 1.32 (d, $J$ = 6.9 Hz, 3H), 1.07−1.57 (m, 36H), 1.72 (ddd, $J$ = 14.5, 6.3, and 2.3 Hz, 1H), 1.84 (ddd, $J$ = 14.5, 9.3, and 3.5 Hz, 1H), 1.90−2.07 (m, 2H), 2.21 (td, $J$ = 6.9 and 1.6 Hz, 2H), 2.39−2.50 (m, 2H), 2.79 (d, $J$ = 3.3 Hz, 1H), 3.32 (d, $J$ = 7.2 Hz), 3.75−3.96 (m, 3H), 4.01 (quint, $J$ = 5.6 Hz, 1H), 4.59−4.73 (m, 1H), 4.82−4.96 (m, 1H), 6.91 (bs, 1H), 7.32−7.48 (m, 6H), 7.58−7.71 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1 ($CH_3$), 18.7 ($CH_2$), 18.9 ($CH_3$), 19.3 (C), 22.7 ($CH_2$), 24.8 ($CH_2$), 26.0 ($CH_2$), 27.0 ($CH_3$), 28.2 ($CH_2$), 28.7 ($CH_2$), 28.9 ($CH_2$), 29.1 ($CH_2$), 29.3 ($CH_2$), 29.45 ($CH_2$), 29.53 ($CH_2$), 29.63 ($CH_2$), 29.66 ($CH_2$), 31.8 ($CH_2$), 31.9 ($CH_2$), 32.3 ($CH_2$), 35.4 ($CH_2$), 36.3 ($CH_2$), 39.8 ($CH_2$), 60.6 (CH), 71.7 (CH), 71.9 (CH), 77.4 (CH), 79.4 (CH), 80.9 (C), 81.5 (CH), 85.6 (C), 127.6 (CH), 129.7 (CH), 130.6 (C), 134.0 (C), 134.1 (C), 135.80 (CH), 135.84 (CH), 151.3 (CH), 173.9 (C). IR $\nu_{max}$ (film) 3427, 2928, 2854, 1759, 1464, 1427, 1375, 1319, 1198, 1111, 1072, 1028, 822, 739, 704, 611. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ for $C_{51}H_{79}O_6Si$ calcd 815.5646, found 815.5667.

**(*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-((4*S*,6*S*)-6-(hexadec-1-yn-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (52).** To a solution of diol **51** (0.011 g, 0.014 mmol) in 2,2-dimethoxypropane (1.5 mL), CSA (1 mg) was addeed, and the solution was stirred for 3 h at rt. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and diluted with $Et_2O$ (15 mL). The organic phase was dried with $Na_2SO_4$, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to give acetonide **52** (0.010 g, 0.012 mmol) in 87% yield. $R_f$ 0.48 (20% EtOAc in hexane). $[\alpha]_D^{23} = -5$ ($c$ = 0.9/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.82 (d, $J$ = 6.9 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H), 1.16 (s, 9H), 1.25−2.75 (m, 40H), 1.45 (s, 3H), 1.70 (s, 3H), 2.09 (td, $J$ = 6.8 and 1.9 Hz, 2H), 2.38−2.59 (m, 2H), 3.83−4.03 (m, 2H), 4.08−4.33 (m, 3H), 4.83−4.94 (m, 1H), 6.29 (s, 1H), 7.19−7.33 (m, 6H), 7.70−7.85 (m, 4H). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.3 ($CH_3$), 18.8 ($CH_3$), 19.1 ($CH_2$), 19.6 (C), 23.1 ($CH_2$), 23.9 ($CH_3$), 25.1 ($CH_2$), 26.4 ($CH_2$), 27.3 ($CH_3$), 27.5 ($CH_2$), 28.96 ($CH_2$), 29.00 ($CH_3$), 29.2 ($CH_2$), 29.5 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 30.05 ($CH_2$), 30.10 ($CH_2$), 30.14 ($CH_2$), 32.3 ($CH_2$), 32.6 ($CH_2$), 33.9 ($CH_2$), 36.2 ($CH_2$), 36.8 ($CH_2$), 60.1 (CH), 68.9 (CH), 72.1 (CH), 76.7 (CH), 79.8 (CH), 80.2 (CH), 81.8 (C), 85.9 (C), 100.2 (C), 128.3 (CH), 130.0 (CH), 131.1 (C), 134.5 (C), 134.7 (C), 136.3 (CH), 150.5 (CH), 173.1 (C). IR $\nu_{max}$ (film) 2928, 2854, 1759, 1462, 1427, 1379, 1317, 1200, 1111, 1094, 1078, 1028, 822, 741, 704, 611. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ for $C_{54}H_{82}O_6SiNa$ calcd 877.5778, found 877.5747.

**(*S*)-3-((*R*)-7-((2*R*,5*S*)-5-((*S*)-1-((tert-Butyldimethylsilyl)oxy)-3-oxononadec-4-yn-1-yl)tetrahydrofuran-2-yl)-2-((tert-butyldiphenylsilyl)oxy)heptyl)-5-methylfuran-2(5H)-one (54).** To a solution of aldol adduct **49** (0.035 g, 0.043 mmol) in anhydrous DMF (0.5 mL), imidazole (0.020 g, 0.32 mmol) and TBSCl (0.020 g, 0.073 mmol) were added under an argon atmosphere at rt. The reaction mixture was stirred for 18 h, at which point the reaction was diluted with EtOAc (10 mL), and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic phase was dried with $Na_2SO_4$ and filtered, and the organic solvent was removed under vacuum. The residue was then purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to afford **54** (0.029 g, 0.031 mmol) as a colorless oil in 72% yield. $R_f$ 0.65 (20% EtOAc in hexane). $[\alpha]_D^{23} = -9$ ($c$ = 2.9/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.26 (bs, 6H), 0.83 (d, $J$ = 7.1 Hz, 3H), 0.88−0.97 (m, 3H), 1.05 (s, 9H), 1.18 (s, 9H), 1.10−1.74 (m, 38H), 1.96 (t, $J$ = 6.8 Hz, 2H), 2.41−2.60 (m, 2H), 2.69 (dd, $J$ = 15.3 and 4.4 Hz, 1H), 2.79 (dd, $J$ = 15.3 and 7.9 Hz, 1H), 3.68−3.82 (m, 1H), 3.92−4.04 (m, 1H), 4.14−4.39 (m, 2H), 4.50 (ddd, $J$ = 7.7, 6.0, and 4.4 Hz, 1H), 6.31 (s, 1H), 7.20−7.31 (m, 6H), 7.73−7.87 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ −4.6, −4.1, 14.3, 18.5, 18.8, 18.9, 19.6, 23.1, 25.1, 26.3, 26.5, 27.3, 27.9, 28.0, 29.1, 29.4, 29.80, 29.84, 29.95, 30.03, 30.10, 30.14, 32.3, 32.5, 32.6, 36.2, 36.8, 49.8, 72.1, 72.2, 76.8, 79.7, 81.4, 82.4, 93.4, 130.0, 131.0, 134.5, 134.7, 136.3, 150.6, 173.1, 184.9. HRMS (ESI-TOF) $m/z$ [M+H]$^+$ for $C_{57}H_{91}O_6Si_2$ calcd 927.6354, found 927.6360.

**(S)-3-((R)-7-((2R,5S)-5-((1S,3S)-1-((tert-Butyldimethylsilyl)-oxy)-3-hydroxynonadec-4-yn-1-yl)tetrahydrofuran-2-yl)-2-((tert-butyldiphenylsilyl)oxy)heptyl)-5-methylfuran-2(5H)-one (55).** To a solution of compound **54** (0.020 g, 0.022 mmol) in *i*-PrOH (3 mL) was added (*S*,*S*)-Noyori's catalyst (**50**)[38] (10 mol %, 0.0013 g, 0.011 mmol). The reaction mixture was stirred for 18 h, the organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (1:4) to produce the desired alcohol **55** (0.012 g, 0.011 mmol) in 53% yield as a brown oil. $R_f$ 0.68 (40% EtOAc in hexane). $[\alpha]_D^{23} = -6$ ($c$ = 0.5/$CH_2Cl_2$). $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 0.24 (s, 3H), 0.27 (s, 3H), 0.82 (d, $J$ = 6.8 Hz, 3H), 0.92 (t, $J$ = 6.9 Hz, 3H), 1.05 (s, 9H), 1.18 (s, 9H), 1.20−1.72 (m, 38H), 1.88 (ddd, $J$ = 14.0, 8.6, and 3.6 Hz, 1H), 2.00 (ddd, $J$ = 14.0, 9.2, and 3.6 Hz, 1H), 2.14 (td, $J$ = 6.9 and 1.7 Hz, 2H), 2.40−2.61 (m, 2H), 3.64−3.78 (m, 1H), 3.85−3.98 (m, 1H), 3.99−4.11 (m, 1H), 4.14−4.32 (m, 2H), 4.80−4.91 (m, 1H), 6.30 (bs, 1H), 7.19−7.32 (m, 6H), 7.71−7.86 (m, 4H). $^{13}$C NMR (62.9 MHz, $C_6D_6$) $\delta$ −4.6, −3.8, 14.3, 18.6, 18.8, 19.1, 19.6, 23.1, 25.2, 26.4, 26.6, 27.3, 28.4, 29.2, 29.3, 29.6, 29.8, 30.0, 30.11, 30.14, 32.3, 32.6, 36.2, 36.8, 41.8, 59.6, 72.1, 73.2, 76.8, 79.4, 81.9, 82.9, 84.7, 130.0, 131.0, 134.5, 134.7, 136.3, 150.6, 173.1. HRMS (ESI-TOF) $m/z$ [M − OH]$^+$ for $C_{57}H_{91}O_5Si_2$ calcd 911.6405, found 911.6433.

**Monodesilylation Procedure: (*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-((1*S*,3*S*)-1,3-dihydroxynonadec-4-yn-1-yl)tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (51).** To a solution of alcohol **55** (0.020 g, 0.022 mmol) in MeOH (6 mL), *p*-toluenesulfonic acid monohydrate (0.004 g, 0.002 mmol) was added. The reaction mixture was stirred for 12 h and neutralized with a saturated aqueous solution of $NaHCO_3$ (1 mL). The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (2:3) to give the desired diol **21** (0.006 g, 0.007 mmol) in 32% yield.


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**(*R*)-(1*S*,3*S*)-1-((tert-Butyldimethylsilyl)oxy)-1-((2*S*,5*R*)-5-((*R*)-6-((tert-butyldiphenylsilyl)oxy)-7-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)heptyl) tetrahydrofuran-2-yl)nonadec-4-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (R-MTPA-56a).** To a solution of alcohol **55** (0.006 g, 0.007 mmol) in $CH_2Cl_2$ (0.3 mL) were added 1 crystal of DMAP, (*S*)-MTPA chloride (2.2 μL), and $Et_3N$ (10 μL). After 2 h, the reaction mixture was directly loaded onto a silica gel flash column, and elution with EtOAc/hexane (1:4) gave the desired Mosher derivative **56a** (0.007 g, 0.007 mmol) in >99% yield. $R_f$ 0.64 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = +8 (*c* = 0.45/$CH_2Cl_2$). $^1$H NMR (500 MHz, $C_6D_6$) δ 0.22 (s, 3H), 0.26 (s, 3H). 0.81 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 1.17 (s, 9H), 1.10−1.67 (m, 38H), 1.99 (m, 1H), 2.00 (td, *J* = 7.0 and 1.9 Hz, 2H), 2.28 (ddd, *J* = 13.7, 9.7, and 2.2 Hz, 1H), 2.47 (ddt, *J* = 14.6, 5.9, and 1.5 Hz, 1H), 2.53 (ddt, *J* = 14.6, 5.6, and 1.3 Hz, 1H), 3.56 (s, 3H), 3.70 (m, 1H), 3.86 (m, 2H), 4.20 (quint, *J* = 5.7 Hz, 1H), 4.25 (m, 1H), 6.17 (ddt, *J* = 9.8, 3.6, and 1.9 Hz, 1H), 6.29 (m, 1H), 7.00−7.28 (m, 11H), 7.72−7.83 (m, 4H). IR $\nu_{max}$ (film) 2928, 2856, 1757, 1655, 1572, 1464, 1452, 1362, 1258, 1188, 1170, 1110, 1080, 1018, 837, 779, 719, 704, 611. HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ for $C_{67}H_{99}F_3O_8Si_2Na$ calcd 1167.6729, found 1167.6713.

**(*S*)-(1*S*,3*S*)-1-((tert-Butyldimethylsilyl)oxy)-1-((2*S*,5*R*)-5-((*R*)-6-((tert-butyldiphenylsilyl)oxy)-7-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)heptyl)tetrahydrofuran-2-yl)nonadec-4-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (56b).** To a solution of alcohol **55** (0.005 g, 0.005 mmol) in $CH_2Cl_2$ (0.3 mL) were added 1 crystal of DMAP, (*R*)-MTPA chloride (2.2 μL), and $Et_3N$ (10 μL). After 1 h, the reaction mixture was directly loaded onto a silica gel flash column, and elution with EtOAc/hexane (1:4) gave the desired Mosher derivative **56b** (0.006 g, 0.005 mmol) in >99% yield. $R_f$ 0.65 (20% EtOAc in hexane). $[\alpha]_D^{23}$ = −17 (*c* = 0.55/$CH_2Cl_2$). $^1$H NMR (500 MHz, $C_6D_6$) δ 0.23 (s, 3H), 0.29 (s, 3H). 0.80 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.17 (s, 9H), 1.10−1.61 (m, 38H), 1.97 (ddd, *J* = 14.1, 9.1, and 3.2 Hz, 1H), 2.01 (td, *J* = 7.1 and 2.0 Hz, 2H), 2.19 (ddd, *J* = 14.1, 10.0, and 2.5 Hz, 1H), 2.47 (ddt, *J* = 14.5, 5.9, and 1.5 Hz, 1H), 2.53 (ddt, *J* = 14.5, 5.7, and 1.1 Hz, 1H), 3.60 (s, 3H), 3.66 (m, 1H), 3.70 (ddd, *J* = 9.2, 7.5, and 2.4 Hz, 1H), 3.79 (m, 1H), 4.19 (quint, *J* = 5.7 Hz, 1H), 4.25 (m, 1H), 6.20 (m, 1H), 6.29 (m, 1H), 6.95−7.30 (m, 11H), 7.73−7.89 (m, 4H). IR $\nu_{max}$ (film) 2928, 2856, 1759, 1471, 1464, 1452, 1427, 1373, 1254, 1232, 1186, 1171, 1111, 1080, 991, 837, 779, 739, 718, 702, 611. HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ for $C_{67}H_{99}F_3O_8Si_2Na$ calcd 1167.6729, found 1167.6731.

**(*S*)-3-((*R*)-2-((tert-Butyldiphenylsilyl)oxy)-7-((2*R*,5*S*)-5-((1*S*,3*S*,*Z*)-1,3-dihydroxynonadec-4-en-1-yl)tetrahydrofuran-2-yl)heptyl)-5-methylfuran-2(5H)-one (57).** To a suspension of Zn powder (0.40 g, 6.12 mmol) in EtOH (4 mL) at 80 °C, 1,2-dibromoethane (0.030 mL, 0.34 mmol) was added. After the evolution of gas ceased, an additional portion of 1,2-dibromoethane (0.030 mL, 0.34 mmol) was added. The reaction mixture was stirred at 80 °C for an additional 15 min and cooled to 50 °C, at which point a solution of LiBr (0.15 g, 1.73 mmol) and CuBr (0.10 g, 0.70 mmol) in THF (0.9 mL) was added dropwise with vigorous stirring. A solution of diol **51** (0.035 g, 0.043 mmol) in EtOH (1 mL) and THF (1 mL) was then added to the mixture. The resulting suspension was heated to 80 °C and stirred for an additional 8 h. The suspension was then filtered through a pad of silica gel, eluting with EtOAc. The organic solvent was removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane (2:3) to furnish the desired allylic alcohol **57** (0.030 g, 0.037 mmol) in 86% yield. $R_f$ 0.52 (40% EtOAc in hexane). $[\alpha]_D^{23}$ = −17 (*c* = 2.3/$CDCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.18−1.70 (m, 38H), 1.95−2.17 (m, 4H), 2.40−2.50 (m, 2H), 3.80−3.85 (m, 1H), 3.91−3.99 (m, 2H), 4.03 (quint, *J* = 5.6 Hz, 1H), 4.81−4.82 (m, 1H), 4.89−4.95 (m, 1H), 5.44−5.55 (m, 2H), 6.90−6.97 (m, 1H), 7.36−7.47 (m, 6H), 7.63−7.71 (m, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 18.9 ($CH_3$), 19.3 (C), 22.7 ($CH_2$), 24.7 ($CH_2$), 25.8 ($CH_2$), 27.0 ($CH_3$), 27.7 ($CH_2$), 28.1 ($CH_2$), 29.30 ($CH_2$), 29.33 ($CH_2$), 29.38 ($CH_2$), 29.5 ($CH_2$), 29.59 ($CH_2$), 29.61 ($CH_2$), 29.63 ($CH_2$), 29.64 ($CH_2$), 29.66 ($CH_2$), 29.67 ($CH_2$), 31.72 ($CH_2$), 31.9 ($CH_2$), 32.1 ($CH_2$), 35.2 ($CH_2$), 36.2 ($CH_2$), 39.0 ($CH_2$), 65.3 (CH), 71.7 (CH), 72.0 (CH), 77.5 (CH), 79.9 (CH), 81.7 (CH), 127.6 (CH), 129.65 (CH), 129.66 (CH), 130.5 (C), 131.6 (CH), 132.1 (CH), 134.0 (C), 134.19 (C), 135.77 (CH), 135.80 (CH), 135.82 (CH), 135.84 (CH), 151.4 (C), 174.1 (C). IR $\nu_{max}$ (film) 3447, 3015, 2928, 2856, 1751, 1464, 1427, 1375, 1319, 1215, 1111, 1076, 821, 758, 704, 667. HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ for $C_{51}H_{80}O_6SiNa$ calcd 839.5622, found 839.5616.

**Goniotrionin (4).** To a solution of HF·py complex (1.3 mL) in THF (1.9 mL), a solution of silyl ether **57** (0.023 g, 0.028 mmol) in THF (1.9 mL) and pyridine (0.5 mL) was added dropwise over 5 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 days. The reaction was then cooled to 0 °C and quenched carefully with MeOTMS (13 mL). The organic solvents were removed under vacuum, and the residue was purified by flash column chromatography, eluting with EtOAc/hexane/MeOH (1:1:0.05) to produce goniotrionin **4** (0.015 g, 0.027 mmol) in 95% yield as a whitish wax. $R_f$ 0.34 (EtOAc/hexane/MeOH 1:1:0.05). $[\alpha]_D^{23}$ = −7 (*c* = 1.2/$CHCl_3$). $[\alpha]_D^{23}$ = −3 (*c* = 0.12/$CHCl_3$). $[\alpha]_D^{23}$ = 0 (*c* = 0.012/$CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.18−1.39 (m, 30H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.48 (m, 2H), 1.54 (m, 1H), 1.59 (m, 2H), 1.60 (m, 1H), 1.57−1.69 (m, 2H), 1.95 (m, 1H), 2.03 (m, 1H), 2.05 (m, 1H), 2.10 (m, 1H), 2.36 (bs, 1H), 2.38 (ddt, *J* = 15.1, 8.3, and 1.2 Hz, 1H), 2.52 (ddt, *J* = 15.1, 3.2, and 1.5 Hz, 1H), 2.63 (bs, 1H), 3.73 (td, *J* = 7.8 and 3.9 Hz, 1H), 2.80 (bs, 1H), 3.85 (m, 2H), 3.89 (m, 1H), 4.77 (dt, *J* = 7.8 and 4.2 Hz, 1H), 5.05 (qq, *J* = 6.8 and 1.5 Hz, 1H), 5.46 (m, 1H), 5.47 (m, 1H), 7.18 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 14.1 ($CH_3$), 19.1 ($CH_3$), 22.7 ($CH_2$), 25.5 ($CH_2$), 26.1 ($CH_2$), 27.7 ($CH_2$), 28.2 ($CH_2$), 29.30 ($CH_2$), 29.34 ($CH_2$), 29.50 ($CH_2$), 29.51 ($CH_2$), 29.60 ($CH_2$), 29.64 ($CH_2$), 29.65 ($CH_2$), 29.66 ($CH_2$), 29.67 ($CH_2$), 29.68 ($CH_2$), 31.9 ($CH_2$), 32.4 ($CH_2$), 33.4 ($CH_2$), 35.4 ($CH_2$), 37.3 ($CH_2$), 39.7 ($CH_2$), 65.0 (CH), 69.9 (CH), 71.5 (CH), 78.0 (CH), 79.3 (CH), 81.8 (CH), 131.1 (C), 131.6 (CH), 132.2 (CH), 151.8 (CH), 174.6 (C). IR $\nu_{max}$ (film) 3531, 3371, 2955, 2918, 2874, 2851, 1740, 1722, 1499, 1468, 1329, 1205, 1121, 1086, 1059, 1030, 843, 719, 652. HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ for $C_{35}H_{62}O_6Na$ calcd 601.4444, found 601.4433.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H, $^{13}$C, IR and HRMS spectra for the prepared compounds are available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) Pettit, G. R.; Mukku, V. J. R. V.; Cragg, G.; Herald, D. L.; Knight, J. C.; Herald, C. L.; Chapuis, J.-C. *J. Nat. Prod.* **2008**, *71*, 130.

(2) (a) Leboeuf, M.; Cave, A.; Bhaumik, P. K.; Mukherjee, B.; Mukherjee, R. *Phytochemistry* **1982**, *21*, 2783. (b) Wu, Y. C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Biomedical: Amsterdam, 2006; Vol. *33*, p 957.

(3) Bermejo, A.; Figadère, B; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.

(4) Isolation: (a) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151. Total synthesis: (b) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org.*

*Chem.* **1998**, *63*, 5863. (c) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953.
(5) Gigantecin (**2**). Isolation: (a) Alkofahi, A.; Rupprecht, J. K.; Liu, Y. M.; Chang, C. J.; Smith, D. L.; McLaughlin, J. L. *Experientia* **1990**, *46*, 539. Total synthesis: (b) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (c) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383. Mucocin (**3**). Isolation: (d) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-m.; Zhao, G.-x.; He, K.; MacDougal, M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409. Total synthesis: (e) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (f) Baurle, S.; Hoppen, S.; Koert, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 1263. (g) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751. (h) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702. (i) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369. Goniotrionin (**4**). Isolation: (j) Alali, F. Q.; Rogers, L.; Zhang, Y; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833.
(6) (a) Chih, H. W.; Chiu, H. F.; Hsian, Y. M.; Tseng, C. H.; Wu, M. J.; Wu, Y. C. *Biochem. Pharmacol.* **2003**, *65*, 319. (b) Chih, H. W.; Chiu, H. F.; Tang, K. S.; Chang, F. R.; Wu, Y. C. *Life Sci.* **2001**, *69*, 1321.
(7) (a) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73. (b) Oberlies, N. H.; Chang, C.-J.; McLaughlin, J. L. *Med. Chem.* **1997**, *40*, 2102.
(8) Liaw, C.-C.; Wu, T.-Y.; Chang, F.-R.; Wu, Y.-C. *Plant. Med.* **2010**, *76*, 1390.
(9) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175.
(10) (a) Wu, F.-E.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; Zhang, Y.; Schwedler, J. T.; McLaughlin, J. L. *J. Nat. Prod.* **1995**, *58*, 902. (b) Wu, F.-E.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; Zhang, Y.; Schwedler, J. T.; McLaughlin, J. L. *J. Nat. Prod.* **1995**, *58*, 909. (c) Tam, V. T.; Chaboche, C.; Figadère, B.; Chappe, B.; Hieu, B. C.; Cave, A. *Tetrahedron Lett.* **1994**, *35*, 883.
(11) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.
(12) (a) Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 67. (b) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 667. (c) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Eur. J. Org. Chem.* **2000**, 349.
(13) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(14) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem.—Eur. J.* **2002**, *8*, 1621.
(15) (a) Wang, Z. M.; Tian, S. K.; Shi, M. *Tetrahedron Lett.* **1999**, *40*, 977. (b) Zhao, H. D.; Gorman, J. S. T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379. (c) Wang, J.; Pagenkopf, B. L. *Org. Lett.* **2007**, *9*, 3703.
(16) Koert, U.; Wagner, H.; Pidun, U. *Chem. Ber.* **1994**, *127*, 1447.
(17) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B. *J. Organomet. Chem.* **1966**, *5*, 267.
(18) (a) Wang, J.; Morra, N. A.; Zhao, H.; Gorman, J. S. T.; Lynch, V.; McDonald, R.; Reichwein, J. F.; Pagenkopf, B. L. *Can. J. Chem.* **2009**, *87*, 328. (b) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2009**, *11*, 5614.
(19) White, J. D.; Lincoln, C. M.; Yang, J.; Martin, W. H. C.; Chan, D. B. *J. Org. Chem.* **2008**, *73*, 4139.
(20) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 177.
(21) For silyl migration under acidic conditions see: (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (b) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945.
(22) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.
(23) (a) Downie, I.; Holmes, J.; Lee, J. *Chem. Ind.* **1966**, 900. (b) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300. (c) Stang, P. J.; Dueber, T. E. *Org. Synth.* **1988**, *Coll. Vol. 6*, 757.
(24) For similar alkylation involving OTBS group leading low yields see: (a) Quinn, K. J.; Isaacs, A. K.; De Christopher, B. A.; Szklarz, S. C.; Arvary, R. A. *Org. Lett.* **2005**, *7*, 1243. (b) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdinsuren, B.; Nakamori, S. *Chem.—Eur. J.* **2003**, *9*, 389.
(25) Pattenden, G.; Ashweek, N. J.; Baker-Glenn, C. A. G.; Walker, G. M.; Yee, J. G. K. *Angew. Chem., Int. Ed.* **2007**, *119*, 4437.
(26) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
(27) Dias, L. C.; Salles, A. G. Jr. *J. Org. Chem.* **2009**, *74*, 5584.
(28) Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784.
(29) (a) Müller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Roth, G.; Liepold, B.; Müller, S.; Bestmann, H. J. *Synthesis* **2004**, 59.
(30) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.
(31) For examples of Mukaiyama aldol reactions using bidented carbonyl activations involving $\alpha$–alkoxy aldehydes see: (a) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. (b) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1985**, *26*, 1001. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (d) Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5434.
(32) For examples of 1,2-anti aldol adducts involving $\alpha$-alkoxy aldehydes, see: (a) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920. (b) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761. (c) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433. (d) Borg, T.; Danielsson, J.; Somfai, P. *Chem. Commun.* **2010**, *46*, 1281. (e) Borg, T.; Danielsson, K.; Mohiti, M.; Restorp, P.; Somfai, P. *Adv. Synth. Catal.* **2011**, *353*, 2022.
(33) Paterson, I.; Delgado, O.; Florence, G. J.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150.
(34) (a) Reetz, M. T.; Raguse, B.; Marth, C. F.; Hügel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1992**, *48*, 5731. (b) Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119.
(35) Chauhan, K.; Bhatt, R. K.; Falck, J. R.; Capdevila, J. H. *Tetrahedron Lett.* **1994**, *35*, 1825.
(36) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(37) Rychnovsky, S. D.; Rogers, J. B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
(38) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(39) Konno, K.; Fujishima, T.; Liu, Z.; Takayama, H. *Chirality* **2000**, *13*, 72.
(40) Kouda, K.; Ooi, T.; Kusumi, T. *Tetrahedron Lett.* **1999**, *40*, 3005.
(41) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1987**, *52*, 3521.
(42) Seco, J. M.; Quiñoá, E.; Rigueira, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781.
(43) (a) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320. (b) Aerssens, M. H. P. J; van der Heiden, R.; Heus, M.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3421.
(44) (a) Sugeta, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3706. (b) Nakao, Y.; Sugeta, H.; Kyogoku, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1767.
(45) For a theoretical and experimental study of a cryptochiral solutions of self aggregation-species at low concentrations see: Goldsmith, M.-R.; Jayasuriya, N.; Beratan, D. N.; Wipf, P. *J. Am. Chem. Soc.* **2003**, *125*, 15696.
(46) Sbardella, G.; Castellano, S.; Vicidomini, C.; Rotili, D.; Nebbioso, A.; Miceli, M.; Altucci, L.; Mai, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2788.
(47) Mun, J.-Y.; Onorato, A; Nichols, F. C.; Morton, M. D.; Saleh, A. I.; Welzel, M.; Smith, M. B. *Org. Biomol. Chem.* **2007**, *5*, 3826.