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Development of an Enantioselective Synthesis of (−)-Euonyminol

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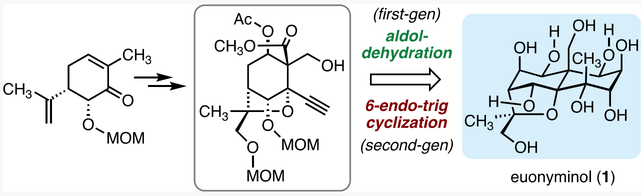

ABSTRACT: We detail the development of the first enantioselective synthetic route to euonyminol (**1**), the most heavily oxidized member of the dihydro-*β*-agarofuran sesquiterpenes and the nucleus of the macrocyclic alkaloids known as the cathedulins. Key steps in the synthetic sequence include a novel, formal oxyalkylation reaction of an allylic alcohol by [3 + 2] cycloaddition; a tandem lactonization−epoxide opening reaction to form the *trans*-C2−C3 vicinal diol residue; and a late-stage diastereoselective trimethylaluminum-mediated *α*-ketol rearrangement. We report an improved synthesis of the advanced unsaturated ketone intermediate **64** by means of a 6-*endo*-dig radical cyclization of the enyne **42**. This strategy nearly doubled the yield through the intermediate steps in the synthesis and avoided a problematic inversion of stereochemistry required in the first-generation approach. Computational studies suggest that the mechanism of this transformation proceeds via a direct 6-*endo*-trig cyclization, although a competing 5-*exo*-trig cyclization, followed by a rearrangement, is also energetically viable. We also detail the challenges associated with manipulating the oxidation state of late-stage intermediates, which may inform efforts to access other derivatives such as 9-*epi*-euonyminol or 8-*epi*-euonyminol. Our successful synthetic strategy provides a foundation to synthesize the more complex cathedulins.

■ INTRODUCTION

Euonyminol (**1**, Figure 1a) is the most heavily oxidized member of the dihydro-*β*-agarofuran metabolites isolated from Celastraceae.[1] The Celastraceae genera are native to tropical and subtropical areas of the world. The crude extracts of these plants have been extensively used in traditional agriculture and medicine due to their insecticidal,[2] anti-inflammatory,[3] anticancer,[4] and antiviral[5] properties. Collectively, this family of natural products is characterized by the presence of a *trans*-decalin (A- and B-ring) fused to a tetrahydrofuran ring (C-ring) and a high degree of oxidation leading to a large structural diversity (e.g., **2**−**4**).

The nonahydroxylated metabolite euonyminol (**1**) was first described in 1953 by Beroza as a ″polyhydroxy substance without a definite melting point and having a molecular formula $C_{15}H_{26}O_{10}$″.[6] Nearly 20 years later, Wada and co-workers determined the structure of euonyminol as **1**.[7] They performed a series of spectroscopic studies on the related alkaloid evonine (**5**, Figure 1b) to arrive at the correct structure of **1**. Though **5** possesses a ketone oxidation state at the C8 position, a direct link between the two natural products was found upon treatment of **5** with excess lithium aluminum hydride. This reduction proceeded to give euonyminol (**1**, 30%) as the major product along with small amounts of its C8 epimer (15%), thereby confirming its structural and stereochemical assignment. However, to the best of our knowledge, NMR spectroscopic data of natural **1** have not been reported in the literature. The octaacetate (**2**) has been isolated and fully characterized.[8] It can also be prepared in semisynthetic form by exhaustive acetylation of **1**.[9]

Euonyminol (**1**) itself constitutes the core of the macrocyclic isolates known as the cathedulins (**6**−**7**, Figure 1c). These complex terpenoid alkaloids were isolated from the shrub *Catha edulis* (Khat). The structures of over 20 cathedulins were elucidated by the Crombie group in the 1980s via a series of spectroscopic and crystallographic efforts.[10] The cathedulins are characterized by the presence of one macrocyclic bridge, as exemplified by cathedulin K-2 (**6**), or two dilactone bridges, as in cathedulin K-19 (**7**), which is perhaps the most complex member of this family. Despite the remarkable structures of the cathedulins, there has been no completed total synthesis of any member of this family.

The first synthesis of (±)-euonyminol was reported by White and co-workers.[11] A key step in their synthesis was a twofold epoxide opening cyclization cascade (**9** → **10**, Scheme 1a) to construct the tricyclic core of the target. Unfortunately, late-stage dihydroxylation of a C3−C4 alkene intermediate proceeded with 8:1 diastereoselectivity in favor of the undesired isomer. Spivey and co-workers reported a tandem Ireland ester−

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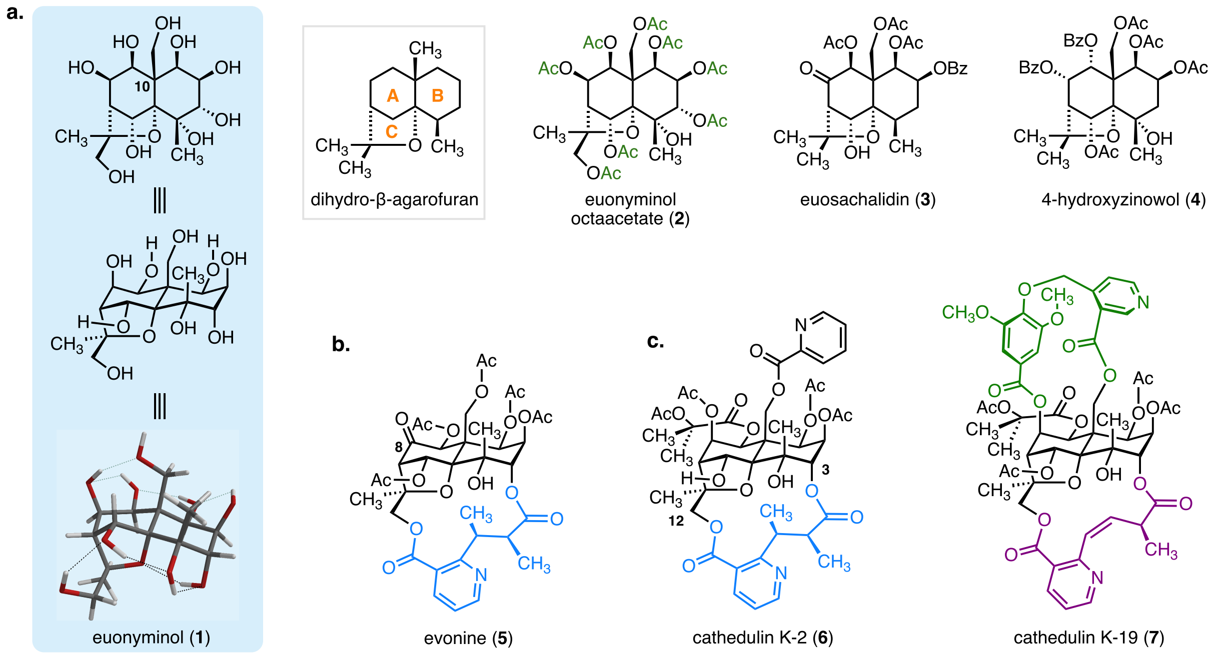
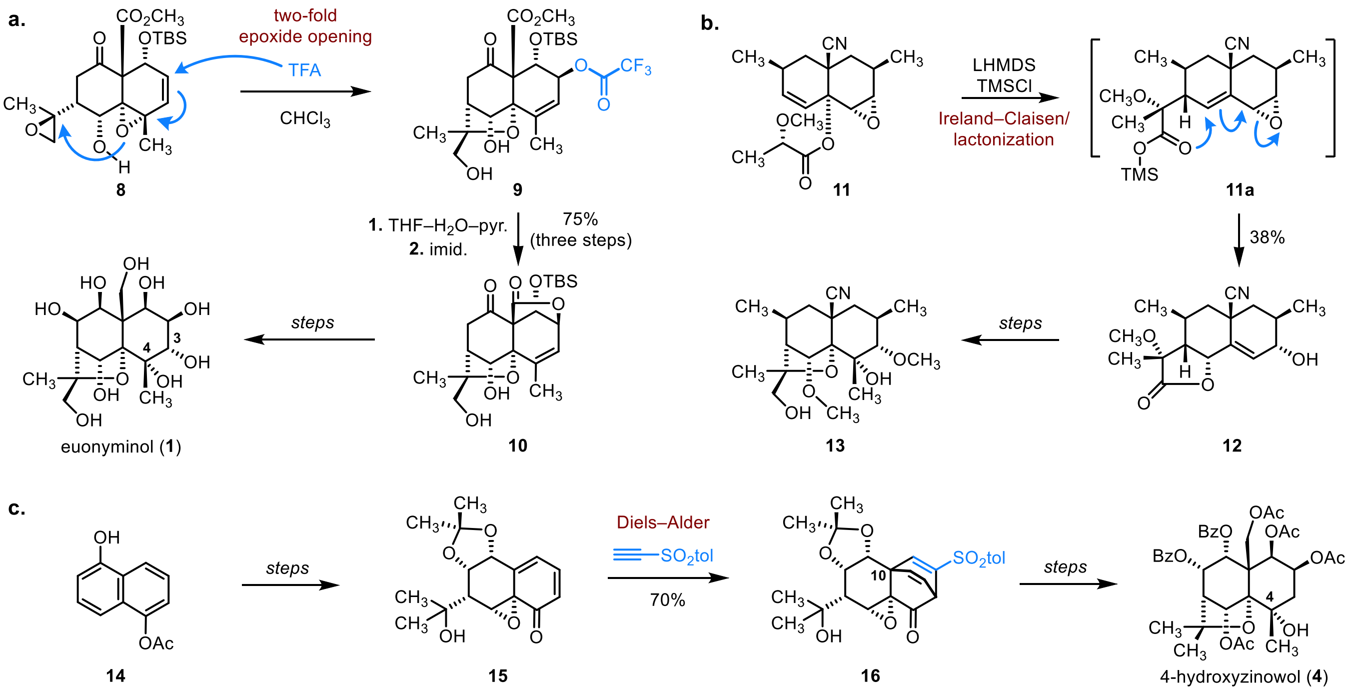


Figure 1. (a) Structures of euonyminol (**1**), euonyminol octaacetate (**2**), and selected dihydro-*β*-agarofuran isolates (**3**−**4**). (b) Structure of evonine (**5**). (c) Structures of cathedulins K-2 and K-19 (**6**−**7**).

Scheme 1. (a) Overview of Approach to Euonyminol (1) by White and Co-workers. (b) Overview of the Synthesis of the Tricycle 13 Possessing the *trans*-Decalin of Euonyminol (1) by Spivey and Co-workers. (c) Overview of the Synthesis of (−)-4-Hydroxyzinowol (4) by Inoue and Co-workers

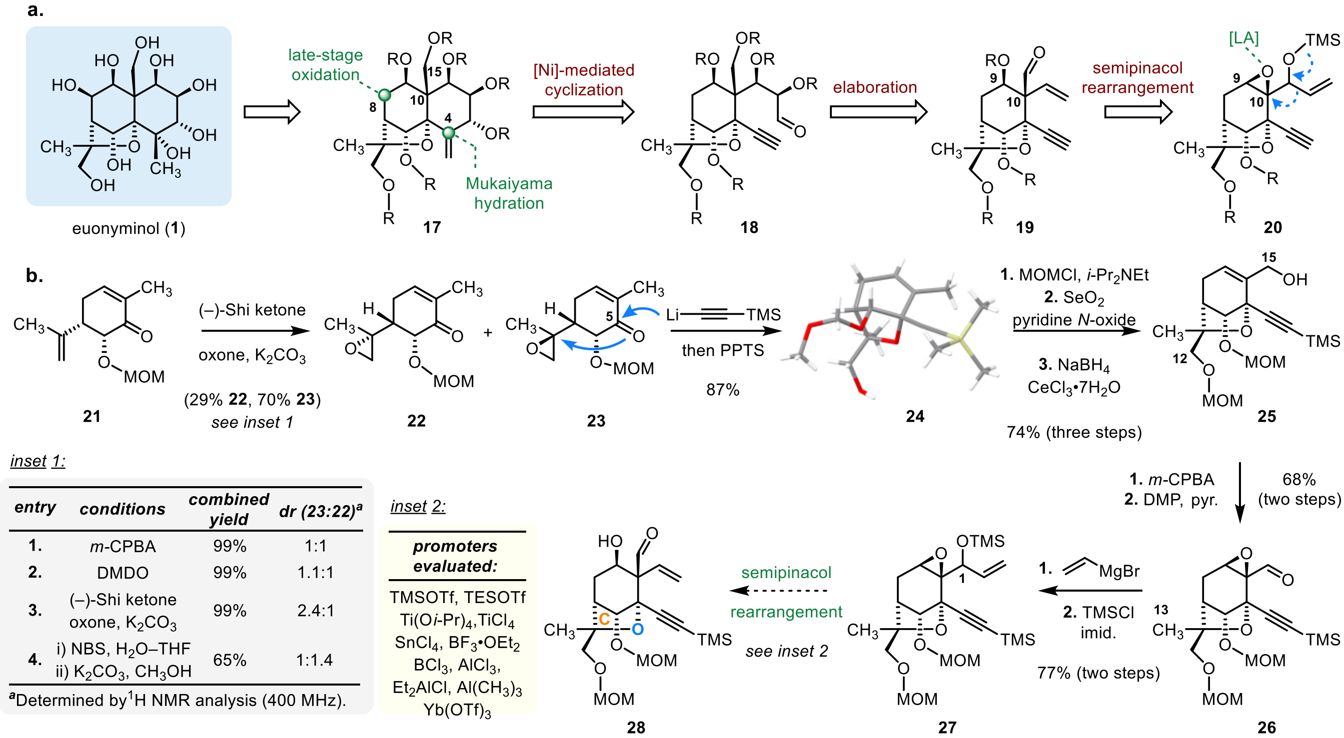


Claisen rearrangement−epoxide opening approach to euonyminol (Scheme 1b).[12] Thus, a [3,3] rearrangement of the trimethylsilyl ketene acetal derived from **11**, followed by an S_N2' opening of the allylic epoxide by the resulting silyl ester **11a**, provided the lactone **12** (38%). The lactone **12** was then elaborated to the advanced intermediate **13**. In 2014, Inoue and co-workers reported the synthesis of the highly oxygenated (−)-4-hydroxyzinowol (**4**) (Scheme 1c).[13b] Their strategy utilized a stereoselective Diels−Alder cycloaddition between the complex diene **15** and ethynyl *p*-tolyl sulfone to construct the C10 quaternary stereocenter (70%). Additional synthetic studies toward related dihydro-*β*-agarofuran isolates have also been described.[13]

■ RESULTS AND DISCUSSION

We recently disclosed a synthetic route to (−)-euonyminol (**1**) from (*R*)-carvone.[14] We envision that, with further refinement, this route may serve as an entry to the cathedulins. Here we

Scheme 2. (a) Initial Retrosynthetic Analysis of Euonyminol (**1**). (b) Approach to the 2,3-Epoxyether **27**



inset 1:

entry	*conditions*	*combined yield*	*dr (23:22)*[a]
1.	*m*-CPBA	99%	1:1
2.	DMDO	99%	1.1:1
3.	(−)-Shi ketone oxone, K_2CO_3	99%	2.4:1
4.	i) NBS, H_2O–THF ii) K_2CO_3, CH_3OH	65%	1:1.4

[a] Determined by ^{1}H NMR analysis (400 MHz).

inset 2:

promoters evaluated:

TMSOTf, TESOTf
Ti(O*i*-Pr)$_4$,$TiCl_4$
$SnCl_4$, BF_3•OEt_2
BCl_3, $AlCl_3$,
Et_2AlCl, $Al(CH_3)_3$
$Yb(OTf)_3$

describe in full the development of our successful synthetic strategy including several alternative approaches to the target and new improvements in streamlining the synthesis including a shorter, higher-yielding strategy to construct the *trans*-decalin ring of **1**.

Several distinct challenges are conflated within the structure of euonyminol (**1**). The stereocontrolled construction of the C10 quaternary center bearing an axial hydroxymethyl group was envisioned to be one of the primary difficulties in the synthesis. White derived this center from a [4 + 2] cycloaddition, while Spivey accessed this center by the addition of cyanide to a 1,6-epoxydecalin. Second, given its degree of oxygenation, we anticipated that formation of β-hydroxycarbonyl intermediates en route to euonyminol (**1**) would be unavoidable. As detailed below, we found these to be susceptible to ring-opening retro-aldol additions, which constrained the pathways and reagents suitable for late-stage intermediates. Additionally, achieving high levels of stereocontrol in the functionalization of advanced intermediates was challenging, observations that we also attributed to the extensive oxygenation of the target, which makes anticipating the preferred mode of interaction of reagents (especially Lewis acids) challenging.

■ RESULTS

Our initial retrosynthetic analysis is shown in Scheme 2a. We envisioned accessing euonyminol (**1**) by late-stage oxidation at C8 in the decalin **17**. We anticipated that a variety of strategies could be employed, including directed oxidation of the corresponding C15 carboxylic acid,[15] functionalization via 1,5-hydrogen atom transfer (HAT) to a C15 alkoxy radical,[16] or intermolecular approaches such as hydrogen atom abstraction[17] or dioxirane insertion.[18] The allylic alcohol residue within **17** was anticipated to derive from a nickel-catalyzed reductive cyclization[19] of the ynal **18**. The latter could be prepared from the alkenyl aldehyde **19**, which itself was anticipated to be accessible via a semipinacol rearrangement of the 2,3-epoxyether **20**.[20,13h]

Lee and Floreancig[21] have published an efficient and scalable route to the carvone derivative **21**, and this served as the starting point for our studies (Scheme 2b). Epoxidation with the Shi ketone[22] proceeded with 2.4:1 diastereoselectivity in favor of **23** (70%).[23] Oxidation of **21** with *m*-chloroperbenzoic acid (*m*-CPBA) or dimethyldioxirane (DMDO) proceeded in quantitative yield, but the selectivity was reduced (∼1:1). The epoxide could be formed by a two-step sequence comprising bromohydrin formation followed by base-catalyzed cyclization, but the undesired isomer predominated (1:1.4 dr). Nonetheless, samples of **23** free of the minor diastereomer could be readily obtained by flash-column chromatography on 10 g scale. We also developed a three-step protocol comprising acid-mediated hydrolysis of the epoxide, mesylation, and displacement to interconvert the undesired isomer **22** to **23** (40% overall, see Experimental Section). The relative configuration of the major diastereomer was determined by X-ray analysis (vide infra).

The addition of lithium trimethylsilylacetylide to the ketone of **23** proceeded with 13:1 diastereoselectivity. The tertiary alcohol intermediate (not shown) underwent partial cyclization to the tetrahydrofuran **24** upon purification. Thus, to simplify isolation, the unpurified product was treated directly with pyridinium *para*-toluenesulfonate (PPTS) in dichloromethane. Following purification, the tricyclic product **24** was obtained (87% overall). Attempted additions of alternative nucleophiles were less efficient. For example, the addition of (1-ethoxyvinyl)lithium proceeded in 67% yield and with 8:1 diastereoselectivity. The addition of ethynylmagnesium bromide proceeded in 63% yield and with 6:1 diastereoselectivity. The C12 alcohol formed in the ring opening was protected (methoxymethyl chloride (MOMCl), Hünig's base), and the resulting product was subjected to allylic oxidation (selenium dioxide, pyridine *N*-oxide) to provide a C15 aldehyde (not shown). 1,2-Reduction

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(sodium borohydride) proceeded smoothly to furnish the allylic alcohol **25** (74%, three steps). Directed epoxidation of **25** (*m*-CPBA) followed by oxidation of the C15 alcohol generated the α,β-epoxyaldehyde **26** (68%, two steps). The epoxide was formed with >20:1 diastereoselectivity (^{1}H NMR analysis), a result that we attributed to the shielding of the α-face of the alkene by the C13 methyl substituent. The addition of vinyl magnesium bromide to the aldehyde **26** formed the corresponding allylic alcohol (not shown) as a 3.4:1 mixture of inseparable diastereomers. Protection of the alcohol (trimethylsilyl chloride, imidazole) then provided the rearrangement substrate **27** (77%, two steps).

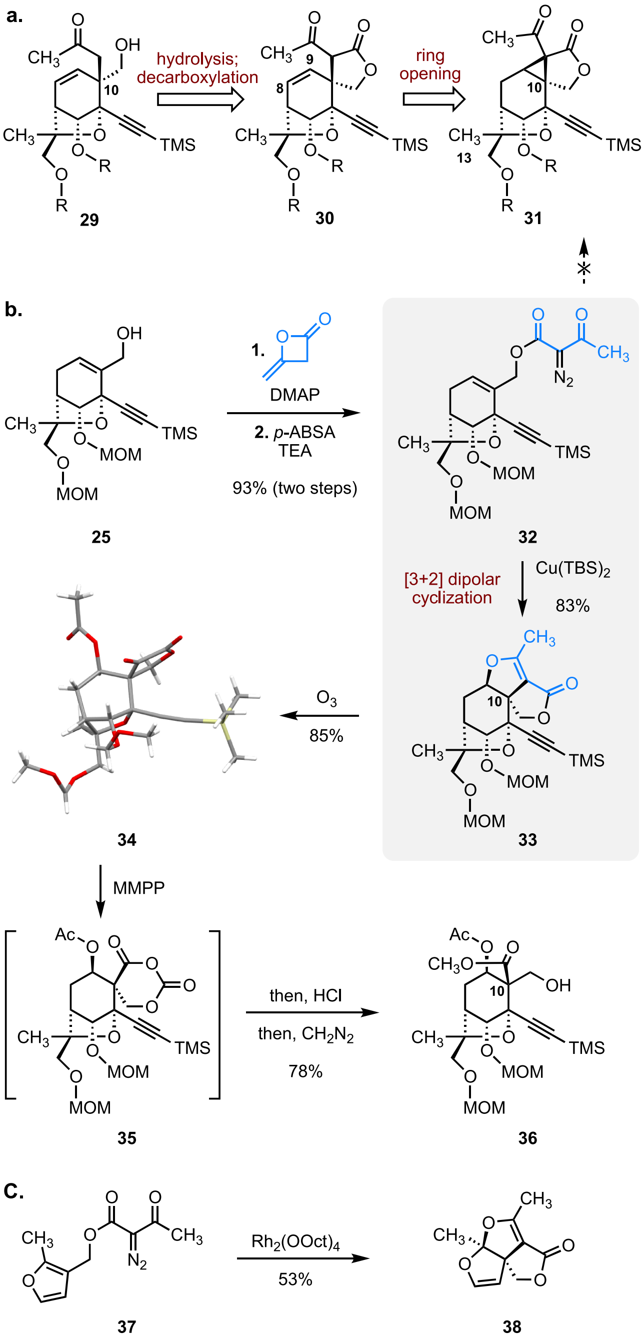
We then proceeded to evaluate the rearrangement. We anticipated that the alkene would migrate preferentially owing to the higher energy of the π-system. However, in spite of a large number of exploratory experiments, we were unable to obtain the desired product **28** (Scheme 2, inset 2). In most instances, we observed the decomposition of the starting material via an opening of the tetrahydrofuran (C-) ring. We speculate that the two methoxymethyl ethers create a binding pocket that positions the Lewis acid promoters in proximity to the tetrahydrofuranal oxygen (highlighted in blue), thereby activating it for ring opening.

The failure of the 2,3-epoxyether **27** to rearrange underscored the challenges in constructing the C10 quaternary center of the target. Accordingly, we refocused our synthetic planning around alternative methods to reliably construct this center. In one embodiment, we envisioned that this center could be constructed by ring opening of the electrophilic cyclopropane **31** at C9 (see **31**, Scheme 3a). This transformation would also provide a C8−C9 alkene for further functionalization. The cyclopropane **31** could be derived from the allylic alcohol **29** via the intramolecular addition of a metal carbenoid to the alkene. The β-cyclopropane was expected to predominate owing to the steric shielding of the α-face of the alkene by the C13 methyl substituent.

Synthesis of the cyclopropanation precursor began with a base-catalyzed addition of the allylic alcohol **25** to diketene followed by diazo transfer (*p*-acetamidobenzenesulfonyl azide (*p*-ABSA)) to form the α-diazo β-ketoester **32** (93% over two steps, Scheme 3b). We then evaluated a number of catalysts to achieve the desired cyclopropanation (Table 1).[14] Treatment with dirhodium tetraacetate, copper triflate, or $Rh_2(esp_2)$[24] led to the recovery of the hydrodediazotization product (entries 1−3). However, when copper bis(*tert*-butylacetoacetate) ($CuTBS_2$) was used as the catalyst, the formal [3 + 2] cycloaddition product **33** was obtained in 40% yield (entry 4) as a single detectable diastereomer (^{1}H NMR analysis). While unanticipated, we recognized **33** as a potentially valuable product as it contained the C10 quaternary center. Following further optimization of this reaction (dilution to 20 mM and deoxygenation, entries 5 and 6), the cycloaddition product **33** was isolated in 83% yield (2 g scale).

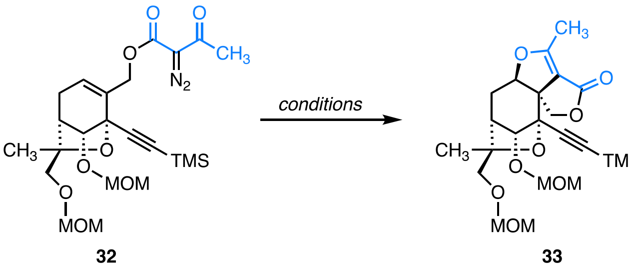
The formation of [3 + 2] cycloaddition products has been observed in the reactions of donor-substituted alkenes with rhodium carbenoids. For example, Davies and Calvo obtained the vinylogous carbonate **38** (53%, Scheme 3c) upon treatment of the furan derivative **37** with dirhodium tetraoctanoate.[25] The [3 + 2] addition of metal carbenoids to acyclic vinyl ethers has also been reported.[26a] To the best of our knowledge, however, the generation of [3 + 2] addition products derived from unactivated alkenes has not been disclosed. A plausible mechanism for this transformation may involve an asynchronous dipolar addition or a cyclopropanation followed by a Cloke−Wilson-type rearrangement pathway to generate **33**.[26b] Efforts to delineate the mechanism and scope of this transformation are underway and will be reported in due course.

Scheme 3. (a) Approach to the C10 Quaternary Center by Cyclopropane Opening. (b) Synthesis of the B-Hydroxyester 36. (c) Prior Report by Davies and Co-workers Describing the Formal [3 + 2] Addition of Donor-Substituted Alkenes to Electron-Deficient Carbenoids



The cycloaddition product **33** was advanced via oxidative cleavage (ozone) to the α-ketolactone **34**, the structure of which was confirmed by X-ray analysis (85%, Scheme 3b). Baeyer−Villiger oxidation using magnesium monoperoxyphthalate (MMPP) proceeded smoothly to form the acylcarbonate intermediate **35**, which upon exposure to aqueous hydrochloric acid underwent hydrolysis and decarboxylation to the

Table 1. Optimization of the Intramolecular [3 + 2] cycloaddition[a]



entry	catalyst	solvent	T	yield of 33[b]
1	$Cu(OTf)_2$	DCE	50 °C	nd[c]
2	$Rh_2(OAc)_4$	CH_2Cl_2	23 °C	nd
3	$Rh_2(esp)_4$	CH_2Cl_2	23 °C	nd
4	$Cu(TBS)_2$	$PhCH_3$	110 °C	40%
5	$Cu(TBS)_2$	$PhCH_3$[d]	100 °C	67%
6	$Cu(TBS)_2$	$PhCH_3$[d,e]	100 °C	83%

[a] Conditions: 30 mol % catalyst, [**32**] = 0.10 M. [b] Isolated yields following purification by flash-column chromatography. [c] None detected. [d] [**32**] = 0.02 M. [e] Solvent was deoxygenated by sparging with argon for 1 h.

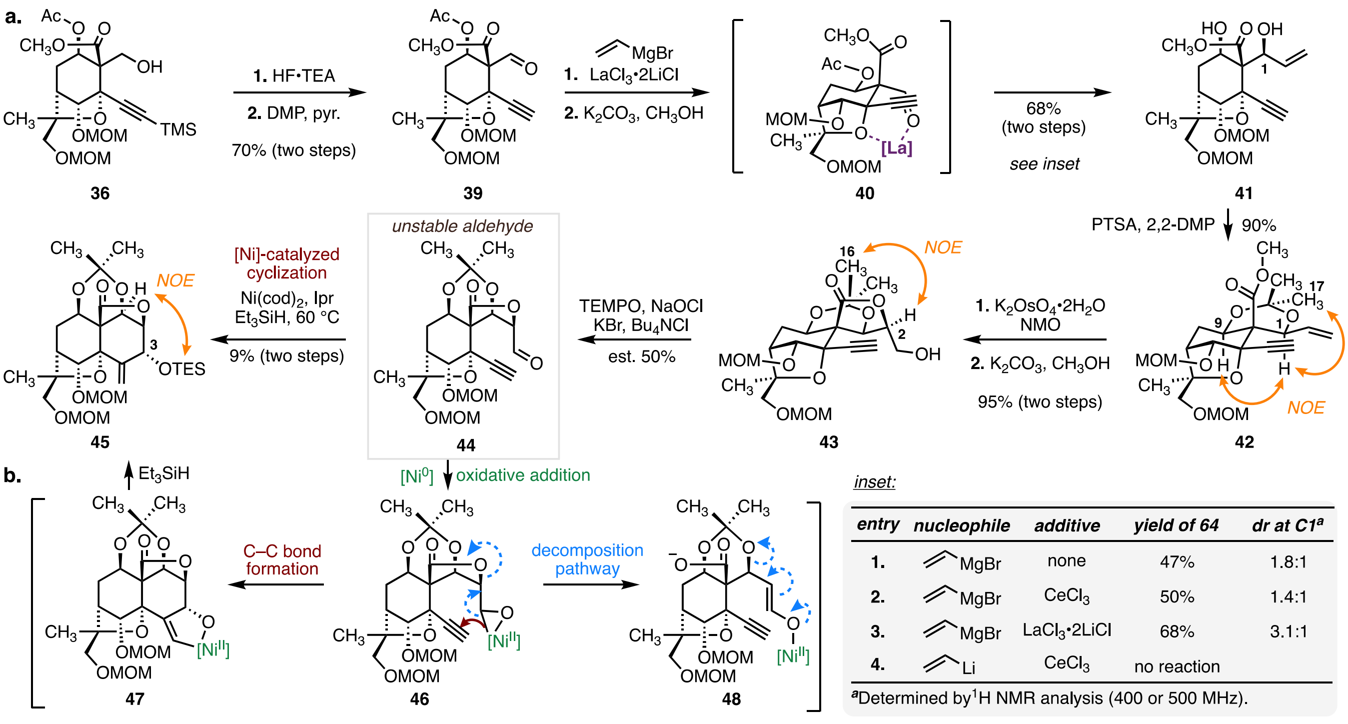
corresponding carboxylic acid (not shown). Esterification (diazomethane) provided the β-hydroxy ester **36**, which contains the C10 stereocenter of the target (78% overall).

The alkyne **36** was elaborated to the reductive cyclization precursor **44** by the pathway shown in Scheme 4a. Cleavage of the silylalkyne (hydrogen fluoride−triethylamine) followed by oxidation with the Dess−Martin periodinane (DMP)[27] provided the aldehyde **39** (70%, two steps). We then evaluated the addition of various vinyl nucleophiles to **39** (see inset, Scheme 4). We found that the addition of vinyl magnesium bromide proceeded to form the product **41** as a 1.8:1 mixture of C1 diastereomers (determined by ^{1}H NMR analysis). The addition of cerium chloride[28] eroded the diastereoselectivity (1.4:1), while the lanthanum chloride−lithium chloride complex[29] increased the selectivity to 3.1:1. In practice, the unpurified mixture of addition products was treated with potassium carbonate and methanol to cleave the acetate ester and provide the diol **41** (68% yield over two steps following the chromatographic separation of diastereomers). When vinyllithium was used as the nucleophile, we observed no productive addition to the aldehyde, potentially due to a competitive deprotonation of the alkyne moiety.

Ketalization of the 1,3-diol (p-toluenesulfonic acid (PTSA), 2,2-dimethoxypropane) provided the acetonide **42** (90%). An NOE interaction between H1 and H9, as well as H1 and the C17 methyl group of the acetonide, established the C1 stereocenter of the major diastereomer as that shown in structure **42**. A heuristic model that accounts for the stereoselectivity in the addition is shown in Scheme 4a. Formation of the bidentate complex **40** by binding of the aldehyde and tetrahydrofuranyl oxygen to the lanthanum center would result in preferential addition to the α-face of the aldehyde due to shielding of the β-face by the adjacent alkyne. This mode of binding and addition would lead to the major addition diastereomer observed.

Dihydroxylation of the alkene (osmium tetroxide, N-methylmorpholine N-oxide (NMO)) followed by treatment with potassium carbonate in methanol provided the lactone **43** in 95% yield as a single detectable diastereomer (^{1}H NMR analysis). Oxidation of the primary alcohol then generated the aldehyde **44**. We estimated the yield of the oxidation product **44** as ∼50% based on ^{1}H NMR analysis of the unpurified product mixture. Unfortunately, however, the aldehyde **44** was unstable toward purification on silica gel and was found to decompose appreciably within 2 h at room temperature in neat form.

Scheme 4. (a) Synthesis of the Reductive Cyclization Precursor 44 and Its Transformation to the Allylic Silyl Ether 45. (B) Potential Pathway for the Decomposition of the Aldehyde 44



entry	nucleophile	additive	yield of 64	dr at C1[a]
1.	MgBr	none	47%	1.8:1
2.	MgBr	$CeCl_3$	50%	1.4:1
3.	MgBr	$LaCl_3$•2LiCl	68%	3.1:1
4.	Li	$CeCl_3$	no reaction	

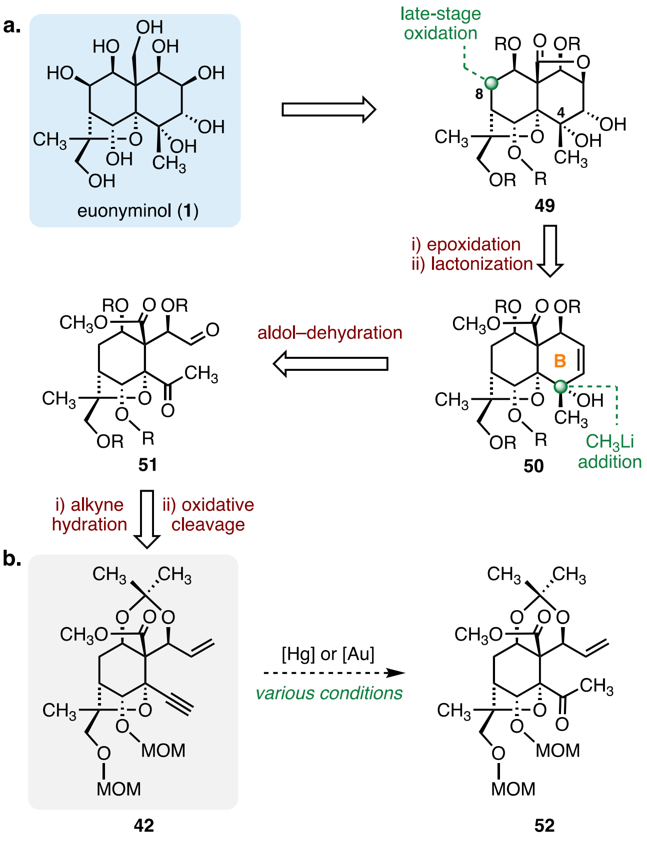
[a] Determined by ^{1}H NMR analysis (400 or 500 MHz).

Consequently, the aldehyde **44** was used in the following step immediately upon preparation. Other oxidation conditions, such as IBX, DMP, Swern, sulfur trioxide−pyridine, or TEMPO/PIDA, failed to provide any of the desired aldehyde **44**.

We proceeded to evaluate the reductive cyclization of unpurified **44** using a variety of nickel-based catalysts and reductants. After some experimentation, we found that the product **45** could be obtained in 9% yield when the reductive cyclization of **44** was carried out using nickel bis(1,4-cyclooctadiene) ($Ni(COD)_2$) as catalyst, 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IPr) as ligand, and triethylsilane as reductant. A large number of decomposition products were also formed (TLC and ^1H NMR analysis); the characterization of these products was not possible because we could not procure large amounts of the aldehyde **44**. A survey of the literature reveals an absence of *α*-heteroatom-substituted aldehydes in these transformations. Accordingly, we hypothesize that the η^2-metallaepoxide **46** formed en route to the desired product **45** might be unstable toward elimination of the lactone substituent, to generate a nickel enolate such as **48** (Scheme 4b). Further elimination pathways, such as loss of the acetonide, are also easily envisioned.

Given the instability of the aldehyde and the failure of the reductive cyclization to provide workable yields of the product, we adapted our synthetic strategy, as shown in Scheme 5a. We sought to retain the vinylogous carbonate **33** in the synthetic sequence as the [3 + 2] cycloaddition (Scheme 3b) remained the only viable method to construct the C10 quaternary stereocenter that we had identified. In this modified approach, we envisioned preparing the B-ring by an aldol−dehydration reaction of the keto aldehyde **51**. Such an intermediate was expected to be readily accessible from the enyne **42** by a Markovnikov-selective hydration of the alkyne and oxidative cleavage of the alkene.

Scheme 5. (a) Revised Retrosynthetic Analysis Incorporating an Aldol−Dehydration Reaction to Construct the B-Ring. (b) Attempted Alkyne Hydration of the Enyne 42



Surprisingly, the alkyne function within **42** was recalcitrant to hydration when exposed to a broad range of catalysts and promoters (Scheme 5b). The attempted hydration using mercury-[30] or gold-based[31] catalysts under acidic conditions resulted in only the cleavage of the methoxymethyl or acetonide protecting groups without any productive alkyne hydration. We reasoned that the approach of reagents to the alkyne, which is fixed in an equatorial position by the bicyclic skeleton, was shielded by the adjacent equatorial substituent at C6 and the protruding alkene. We surmised that use of an intramolecular nucleophile might overcome this, and the alkynyl alcohol **36a** emerged as a logical substrate to test this hypothesis (Scheme 6). Consistent with this analysis, we found that the desired methyl ketone **54** was obtained in 83% yield by treatment of **36a** with mercury triflate in the presence of tetramethylurea (TMU). We presume that this hydration proceeds via formation of the enol ether **53** followed by in situ hydrolysis. Oxidation of the primary alcohol (DMP) then generated the neopentyl aldehyde **55** (90%).

Unfortunately, while the 1,2-addition to the alkynyl aldehyde **39** proceeded to form the desired configuration at C1 (see **39** → **41**, Scheme 4a), the 1,2-addition to the ketoaldehyde **55** was more challenging (Table 2).[14] Treatment of **55** with a variety of nucleophiles, including vinyllithium, vinylmagnesium bromide, and ethynylmagnesium bromide, resulted in the recovery of the starting material (entries 1−5). Fortunately, when ethynylmagnesium bromide was used as nucleophile and lanthanum chloride was used as additive, the 1,2-addition product **56** was obtained in 94% yield and with >20:1 diastereoselectivity at C1 (^1H NMR analysis; entry 6). To establish the configuration at C1, the propargyl alcohol **56** was converted to the cyclic carbonate **57** via a two-step sequence comprising acetate cleavage (potassium carbonate, methanol) followed by treatment with triphosgene and pyridine (63%, two steps). Conclusive NOE correlations within **57** (see orange arrows) supported the stereochemical assignment shown in Scheme 6. We also attempted to form a silylcyanohydrin at C1. However, the yield of the product was only 60% and the silyl ether protecting group could not be removed under acidic or basic conditions without the elimination of cyanide (entry 7).

A variety of attempts to invert the C1 stereocenter using exogenous nucleophiles were unsuccessful. Drawing inspiration from our earlier successful hydration of the alkynyl alcohol **36**, wherein the pendant alcohol behaved as the nucleophile, we envisioned that conversion of the C1 hydroxyl to a sufficiently activated leaving group might allow for engagement of the methyl ketone as an intramolecular nucleophile. After much experimentation, we found that triflation of the propargylic alcohol (triflic anhydride) at 0 °C followed by warming to 23 °C provided the cyclic enol ether **58**, in which the C1 stereochemistry was cleanly inverted (50%; no other diastereomers were detectable by ^1H NMR analysis of the unpurified product mixture). Acid-catalyzed hydrolysis of the enol ether (hydrochloric acid) followed by removal of the C9 acetate (potassium carbonate, methanol) generated the hemiketal **59**. The hemiketal **59** existed exclusively as the ring isomer. Prolonged (10 day) exposure of the hemiketal to di-*tert*-butylsilyl ditriflate

Scheme 6. Synthesis of the *α*,*β*-Unsaturated Ketone 64

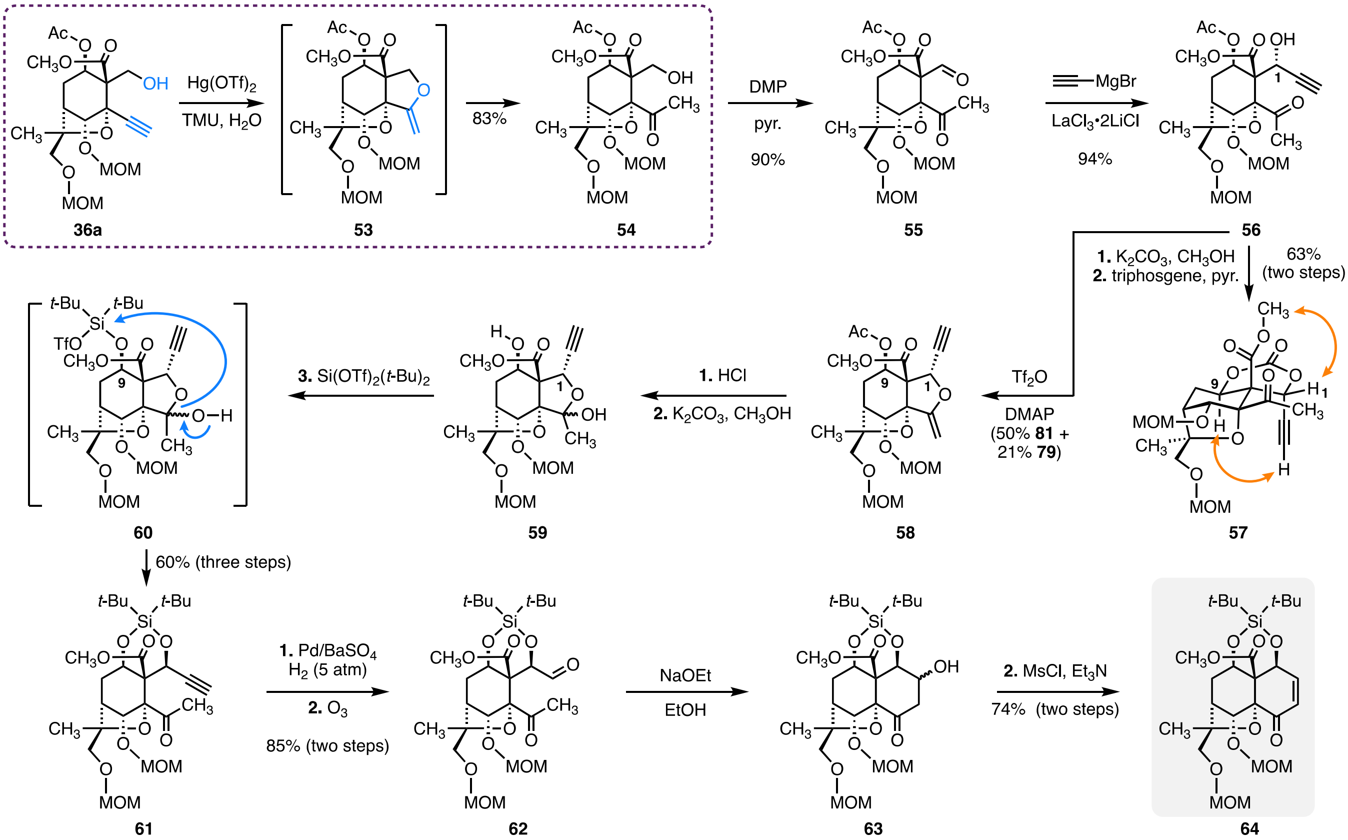
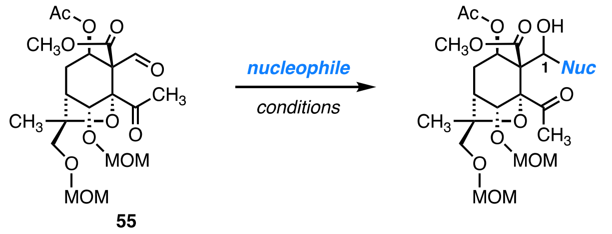


Table 2. Evaluation of Nucleophiles in the Addition to the Aldehyde 55[a]



entry	nucleophile	additive	result
1	⫽╲MgBr	none	no reaction
2	⫽╲MgBr	$LaCl_3 \cdot 2LiCl$	no reaction
3	⫽╲Li	none	no reaction
4	⫽╲Li	$CeCl_3$	no reaction
5	≡—MgBr	none	no reaction
6	≡—MgBr	$LaCl_3 \cdot 2LiCl$	94%,[b] >20:1 dr[c]
7	TMSCN, Et_3N	none	60%,[d] 3:1 dr[c,d]

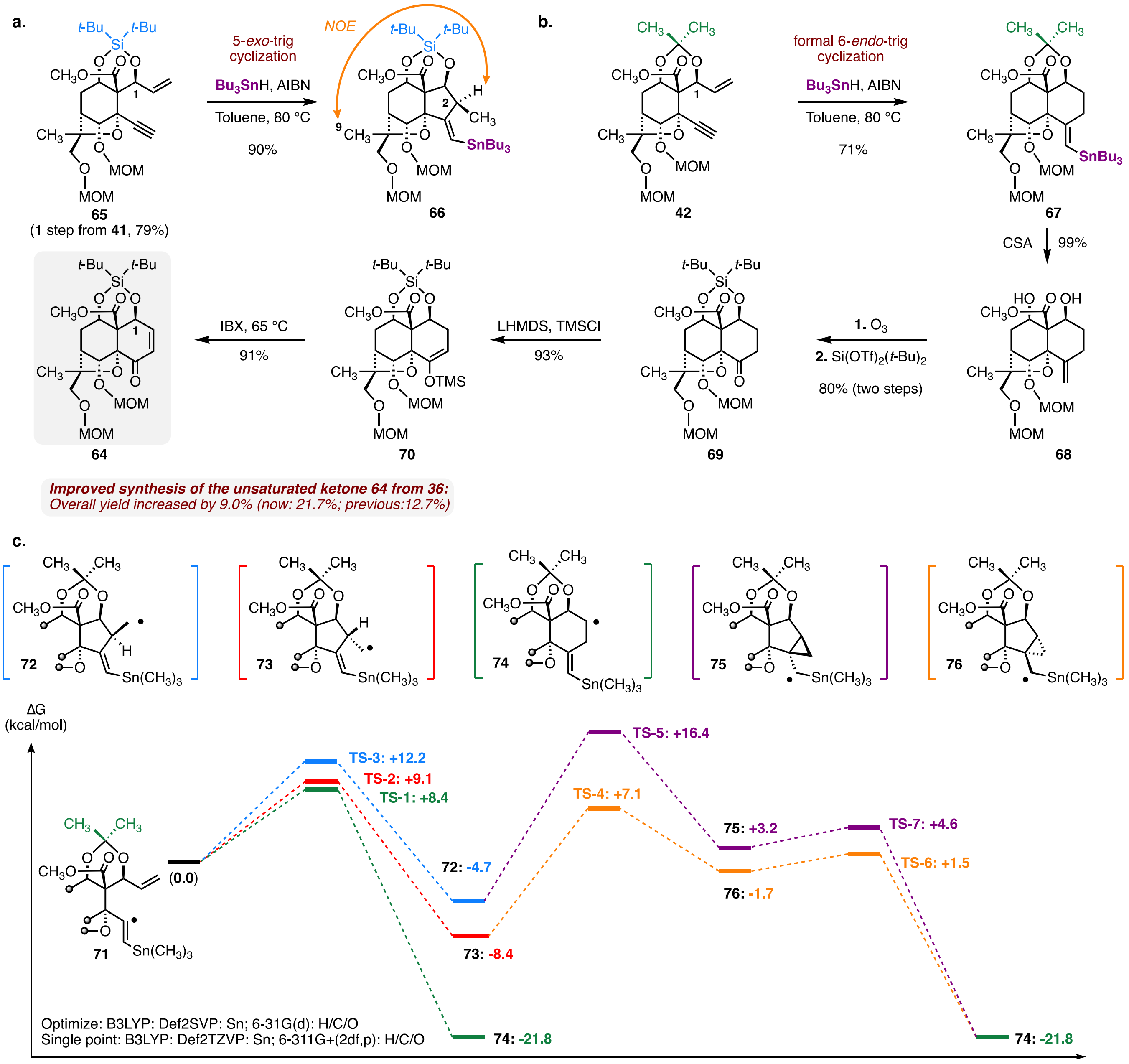
[a] Conditions: 3 equiv of nucleophile and 3 equiv of additive were employed. [b] Isolated yield of **56** following purification by flash-column chromatography. [c] Determined by ^1H NMR analysis of an unpurified product mixture (500 MHz). [d] Diastereomers were not separable; yield refers to the isolated yield of the diastereomeric mixture of products.

provided the silylene acetal **61** in 60% yield from **58**. Monitoring of this reaction by LC/MS revealed a rapid conversion to a silyl ether (presumably at C9, **60**) followed by a slower conversion to the product. We believe that this pendant C9 silyl ether serves to trap small amounts of the chain isomer, thereby driving the equilibrium for ring opening forward.

A sequence comprising semireduction of the alkene (dihydrogen, palladium on barium sulfate) followed by oxidative cleavage (ozone) generated the ketoaldehyde **62** (82% overall). A two-step aldol addition (sodium ethoxide, ethanol)−dehydration (methanesulfonyl chloride, triethylamine) then provided the unsaturated ketone **64** (74%, two steps). While the route to the unsaturated ketone **64** outlined in Scheme 6 was sufficient to complete the synthesis of euonyminol (**1**), we sought a faster pathway to facilitate access to the cathedulins. In the course of examining other pathways for the ring closure, we discovered that the silylene acetal **65** underwent a 5-*exo*-trig cyclization when treated with tributyltin hydride and azobis(*iso*-butyrylnitrile) (AIBN, 90%, Scheme 7a). Surprisingly, however, the related acetonide **42** (Scheme 7b) underwent a formal 6-*endo*-trig cyclization to provide the *trans*-decalin **67** (71%). We speculate that the basis for the difference in reaction outcomes arises from the change in bond lengths between the C1 oxygens and the protecting group (silicon or carbon) resulting in an alteration of the preferred geometry of the vinyl acceptor.

While radical cyclization mechanisms have been extensively studied, we sought to determine if the formation of **67** had occurred via a kinetically favored 5-*exo*-trig addition followed by the formation of a cyclopropane and its rearrangement or via a direct 6-*endo*-trig addition pathway.[32] We carried out DFT calculations to probe these mechanisms. A trimethyl stannyl substituent was employed to reduce the computational cost (Scheme 7c). The results show that the direct 6-*endo*-trig addition pathway proceeds via the lowest energy transition state

Scheme 7. (a) Cyclization of the Silylene Ether 65 by a 5-*exo*-Trig Pathway. (b) Cyclization of the Acetonide 42 and Elaboration to the Enone 64. (c) Calculated Pathway for the Radical Cyclization of the Acetonide 71

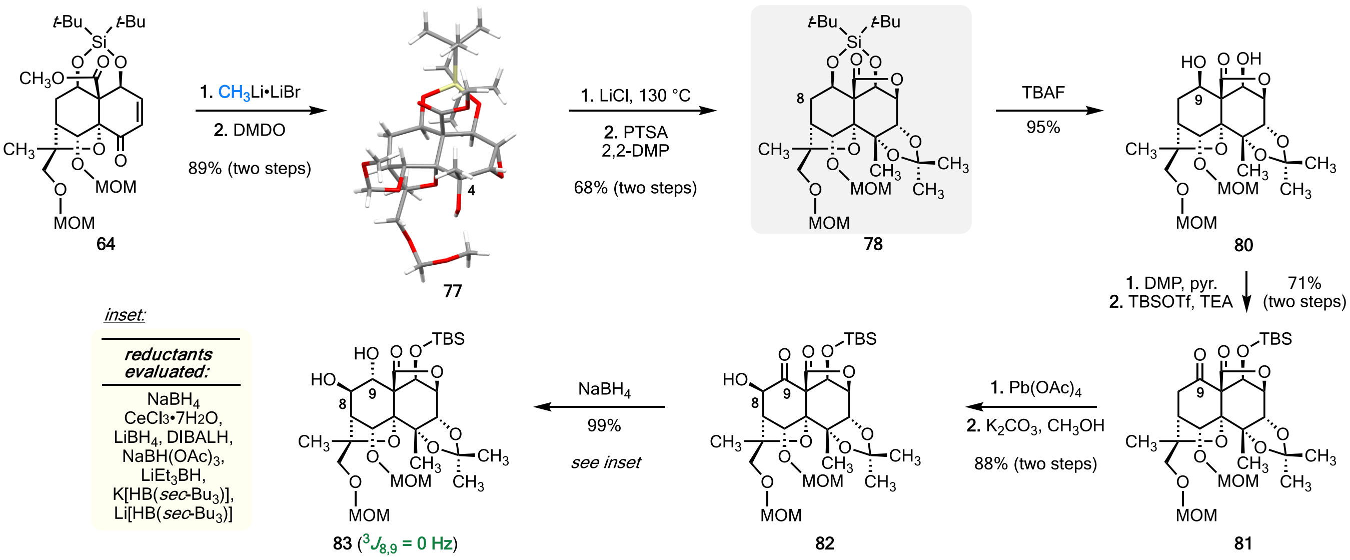


(TS-1, green series) but that an alternative 5-*exo*-trig addition followed by cyclopropane rearrangement is accessible (red and orange series). The 5-*exo*-trig that results in the α-methyl configuration (TS-2) is only 0.7 kcal/mol higher in energy than TS-1.

Treatment of the cyclization product **67** with camphorsulfonic acid (CSA) resulted in clean protodestannylation with concomitant removal of the acetonide to form the 1,3-diol **68** (>99%). Ozonolysis of the alkene followed by silylene ether formation generated the ketone **69** (80%, two steps). Finally, a two-step procedure comprising enoxysilane formation (lithium hexamethyldisilazane, trimethylsilyl chloride) followed by oxidation (IBX) generated the enone **64**. This improved sequence nearly doubled the overall yield from **36** to **64** and reduced the number of steps in the overall synthesis.

The unsaturated ketone **64** was advanced by the pathway shown in Scheme 8. The addition of methyllithium—lithium bromide proceeded with 9:1 selectivity (^{1}H NMR analysis) to establish the C4 tertiary alcohol of the target (not shown). Directed oxidation of the alkene (DMDO) formed the 2,3-epoxyalcohol 77as a single detectable diastereomer (^{1}H NMR analysis, 89%, two steps). The complete relative stereochemistry of the epoxidation product was determined by single crystal X-ray analysis. Nucleophilic cleavage of the methyl ester (lithium chloride, 130 °C) proceeded with in situ opening of the epoxide by the intermediate carboxylate. Protection of the resulting vicinal diol (PTSA, 2,2-DMP) generated the acetonide **78** (68% overall). The acetonide intermediate **78** contains all of the carbon atoms present in the natural product and is missing only a single oxidation at the C8 position.

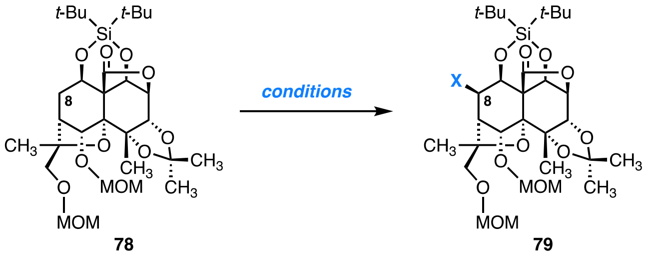
Scheme 8. Elaboration of the Enone 64 to the α-Hydroxy Ketone 82 via the Lactone 80

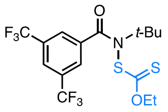
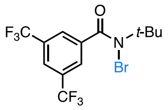


We envisioned introducing this hydroxyl substituent via intermolecular hydrogen abstraction/insertion or directed oxidation methodologies. However, despite extensive efforts aimed at achieving this transformation, we were unsuccessful (Table 3).[14] For example, when the iron-based catalyst (Fe-PDP) developed by Chen and White was employed,[33] we observed only the selective oxidation of the primary methoxymethyl ether group without any oxidation at C8 (entries 1−2). Similarly, the use of small dioxiranes oxidants (DMDO or TFDO)[34] did not result in any productive C−H oxidation. We also examined light-mediated functionalization approaches such as radical xanthylation (entry 5) or bromination (entry 6) developed by the Alexanian lab.[17] However, these conditions only delivered unreacted starting material, suggesting that the C8 position may be sterically inaccessible.

Consequently, we turned our attention to a reduction of the lactone moiety to examine a directed oxidation via 1,5-HAT to an oxygen-centered radical. However, **78** proved to be completely unreactive toward a large number of reductants. For example, heating **78** in the presence of excess lithium aluminum hydride (LAH) only returned unreacted starting material. We were also unable to hydrolyze the lactone to the corresponding carboxylic acid under acidic or basic conditions. In light of these difficulties, we developed an alternative sequence aimed at introducing the C8 oxygen.

Table 3. Attempted Conditions Aimed at C8 Oxidation of Acetonide 78[a]

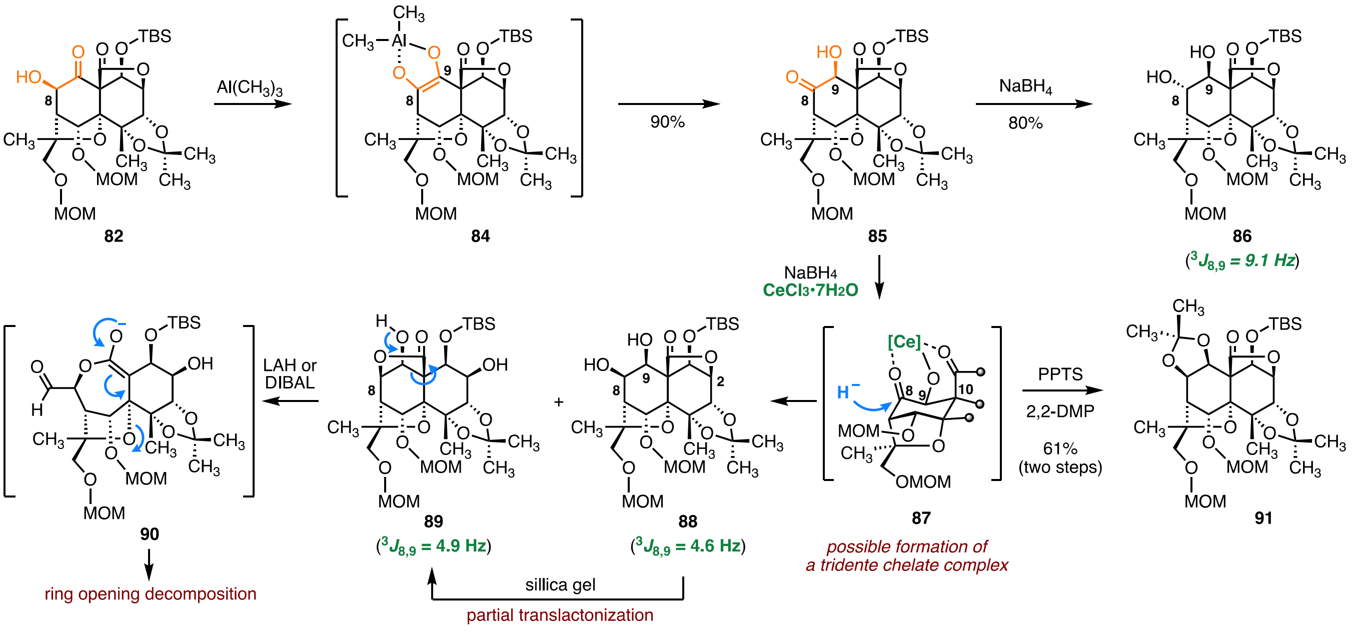


entry	conditions	result
1	Fe(*S,S*-PDP), H_2O_2[a]	oxidation of the methoxymethyl ether group
2	Fe(*R,R*-PDP), H_2O_2[a]	oxidation of the methoxymethyl ether group
3	DMDO[b]	no reaction
4	TFDO[b]	complex mixture
5	 blue LED[c]	no reaction
6	 visible light[d]	no reaction

[a]Conditions: 25 mol % catalyst and 5.0 equiv of H_2O_2 added via slow addition to a solution of **78** in CH_3CN and AcOH. [b]Oxidant (2.5 equiv) added via slow addition at −78 °C followed by gradual warming. [c]Xanthylamide (1.1 equiv), $PhCF_3$, and Kessil Blue LED light. [d]Bromoamide (1.1 equiv), benzene, and 100 W tungsten lightbulb. See the Supporting Information for a complete description of the reaction conditions.

To this end, the silylene acetal was removed (tetra-*n*-butylammonium fluoride, TBAF) to provide the 1,3-diol **80** (95%). Site-selective oxidation of the less-hindered C9 hydroxyl group followed by protection of the remaining alcohol (*tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), triethylamine) formed the silyloxy ketone **81** (71% overall). Diastereoselective α-acetoxylation (lead tetraacetate) followed by cleavage of the acetate (potassium carbonate, methanol) formed the α-hydroxy ketone **82** (88%, two steps). We envisioned that the reduction of the C9 ketone by pseudoaxial approach of hydride to the α-face would provide a means to access the C8,C9 *cis*-diol of the target. However, a large survey of reducing agents, solvents, and temperatures provided only the undesired *trans*-vicinal diol as the single diastereomer (see inset, Scheme 8). The relative stereochemistry of the reduction product was readily determined by analysis of $^3J_{H,H}$ coupling constants.

Scheme 9. Elaboration of the α-Hydroxyketone 82 to the Bis(acetonide) 91



We were cognizant of an α-ketol rearrangement successfully employed by White and co-workers en route to euonyminol.[11b,c] These conditions (trimethylaluminum) worked well when applied to the substrate **82** to provide the rearranged ketone **85** as a single diastereomer (^{1}H NMR analysis) and in 90% yield (Scheme 10). Reduction of **85** with sodium borohydride provided predominantly the *trans*-vicinal diol **86**, a C8/C9 diastereomer of the diol obtained above, in 80% yield and in 8:1 dr. The $^3J_{H8,H9}$ coupling constant was 9.1 Hz, which is consistent with a diaxial orientation of the hydrogen substituents. Inspired by Inoue and co-workers, we found that the addition of cerium chloride resulted in a reversal of selectivity to 4.2:1 dr favoring diastereomer **88**.[13c] We speculate that the stereochemical outcome is driven by a formation of a tridentate chelate **87** between the C8 ketone, C9 hydroxyl, and lactone carbonyl (Scheme 9). This complexation drives the position of the C8 ketone in the upward direction, thereby allowing for a preferential reduction via the pro-equatorial mode of attack. The desired reduction product was obtained as a mixture of the *cis*-C8,C9 diol **88** and its corresponding translactonized product **89**. The product mixture was difficult to purify due to the nearly co-polar nature of the two compounds and the fact that silica gel acted as a vehicle for driving the partial conversion of **88** to **89** (see the Supporting Information). We were able to obtain small amounts of the pure translactonized product via preparative thin layer chromatography; however, in practice the unpurified product mixture containing both compounds was used in the subsequent steps.

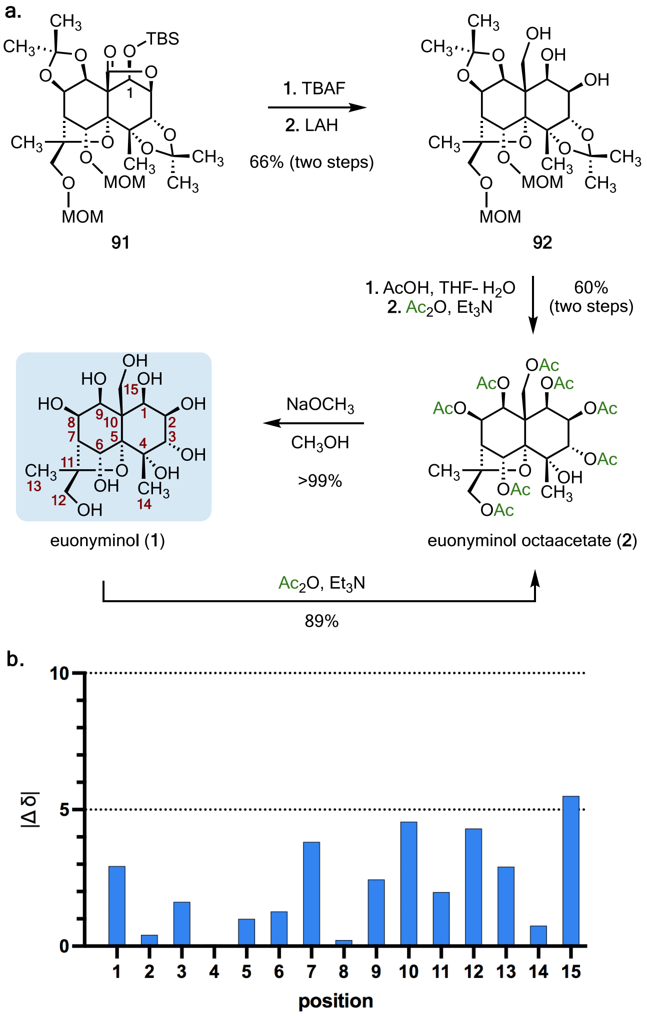
Unfortunately, the attempted reduction of **88** to the corresponding tetraol was unsuccessful. In all cases, we observed slow decomposition of our starting material, presumably via a ring opening and β-elimination, as shown in Scheme 9. Analysis of these reactions was also further complicated by the presence of mixtures of compounds arising from the two isomeric lactones. In light of these difficulties, we protected the C8,C9 diol (*p*-toluenesulfonic acid, 2,2-dimethoxypropane) to provide the stable bis(acetonide) **91** (61% from **85**). Removal of the C1 silyl ether (tetra-*n*-butylammonium fluoride) was followed by exhaustive reduction of the lactone (lithium aluminum hydride) to form the triol **92** (66%, two steps, Scheme 10a). The protecting groups were removed by heating in aqueous acetic acid at 85 °C for 42 h. Because of the unusually high polarity of **1**, the unpurified product mixture was exhaustively acylated (acetic anhydride, triethylamine) to provide euonyminol octaacetate (**2**, 60% two steps). Spectroscopic data for the octaacetate **2** were in complete agreement with those reported in the literature by Shizuri and co-workers[9] as well as Bazzochi and co-workers.[8]

The only spectroscopic data for euonyminol (**1**) itself of which we are aware are ^{1}H NMR shifts reported by White and co-workers. We observed some discrepancies between the ^{1}H NMR shifts of our sample and those of White (see Table S2). Accordingly, we calculated the expected ^{13}C chemical shifts of euonyminol (**1**) using the method of Hehre et al.[35] We found the theoretical ^{13}C chemical shifts to be in good agreement with the experimental values (Scheme 10b; root-mean-square deviation = 2.79). We also carried out the identical purification procedure reported by White involving a filtration of synthetic euonyminol (**1**) through a small pad of Amberlite-120 resin; however, the ^{1}H NMR spectrum remained unchanged. As an additional measure, we reacetylated synthetic euonyminol (**1**) (acetic anhydride, pyridine, 89%). Spectroscopic data for euonyminol octaacetate (**2**) obtained in this way were indistinguishable from the literature and those obtained by the deprotection and acetylation of **91**.

■ CONCLUSIONS

In conclusion, we presented the development of our enantioselective synthetic strategy to access the most heavily oxidized dihydro-β-agarofuran, euonyminol (**1**). This densely oxidized metabolite contains 9 free hydroxyl groups and 11 contiguous stereocenters. Ultimately, our synthetic efforts were enabled by the efficient construction of the bicyclic framework from the readily available (−)-carvone derivative **21**, the discovery of a highly diastereoselective formal oxyalkylation reaction, a tandem lactonization−epoxide opening sequence, and a late-stage α-ketol rearrangement to introduce the C8−C9 oxidation. We also developed a new approach to the essential unsaturated ketone intermediate **64** via a radical cyclization of

Scheme 10. (a) Completion of the Synthesis of Euonyminol (1). (b) Graphical Representation of the Difference between Experimental and Theoretical ^{13}C NMR shifts of 1



the enyne **42**. DFT calculations suggest that this reaction may proceed via a direct 6-*endo*-trig cyclization or 5-*exo*-trig cyclization followed by rearrangement. This new sequence significantly improved material throughput and the overall yield from **36** to **64**. Importantly, it also avoided a low-yielding C1 stereochemical inversion present in the first-generation synthesis. The results presented establish the foundation for synthetic efforts toward the macrocyclic cathedulin terpenoid alkaloids.

■ EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level < 10 ppm). Organic solutions were concentrated by rotary evaporation at 28−32 °C. Flash-column chromatography was performed as described by Still et al.[36] employing silica gel ("SiliaFlash P60", 60 Å, 40−63 μm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates precoated with silica gel (250 μm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM) or *para*-anisaldehyde (PAA) followed by brief heating on a hot plate (120 °C, 10−15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), *N,N*-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.[37] Pyridine was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use. Toluene was deoxygenated by sparging with argon for 1 h. Triethylamine was distilled from calcium hydride immediately prior to use. The molarities of *n*-butyllithium, ethynylmagnesium bromide, vinylmagnesium bromide, vinyllithium, phenyllithium, methyllithium, and methyllithium lithium bromide solutions were determined by titration against a standard solution of menthol and 1,10-phenanthroline in tetrahydrofuran (average of three determinations).[38] Bis(*N*-*tert*-butylsalicylaldiminato) copper (II) was prepared according to the method of Beenakker et al.[39] Dimethyldioxirane was prepared according to the procedure of Taber et al.[40] Methyl(trifluoromethyl)dioxirane was prepared according to the Baran open-flask synthetic protocol.[41] *tert*-Butyldimethylsilyl trifluoromethanesulfonate and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) were purified by vacuum transfer distillation and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon at −20 °C. The compounds **1−2**, **24−25**, **32−34**, **36**, **36a**, **54−58**, **61−62**, **64**, **77−82**, **85**, and **91−92** were prepared according to published procedures.[14] The methoxymethyl ether **21**,[21] the Shi ketone **S1**,[22] the *N*-xanthylamide **S11**,[17a] and the *N*-bromoamide **S12**[17b] were prepared according to published procedures.

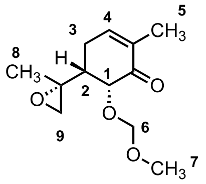
Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400, 500, or 600 megahertz (MHz) at 23 °C unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.16; CD_2HOD, δ 3.31; and DHO, δ 4.79). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, and app = apparent), coupling constant in hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100, 125, or 150 MHz at 23 °C unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.1; and CD_3OD, δ 49.0). Distortionless enhancement by polarization transfer [DEPT (135)], heteronuclear single quantum coherence (HSQC), and hetereonuclear multiple bond correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C unless otherwise noted. ^{13}C NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift and carbon type [obtained from DEPT (135) or HSQC experiments]. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra-high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C_{18} column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile−water containing 0.1% formic acid → 100% acetonitrile containing 0.1% formic acid over 0.75 min followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min at a flow rate of 800 μL/min. High-resolution mass spectrometry (HRMS) was obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C_{18} column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile−water containing 0.1% formic acid → 95% acetonitrile−water containing 0.1% formic acid for 1 min at a flow rate of 600 μL/min. Optical rotations were measured on a Rudolph Research

https://doi.org/10.1021/acs.joc.1c02167

Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ($[\alpha]_{\lambda}^{\mathrm{T}}$), concentration (g/mL), and solvent.

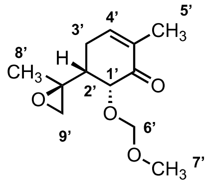
Synthetic Procedures. Note: Synthetic intermediates not shown in the manuscript are numbered below beginning with **S1**.

*Synthesis of the Epoxides **22** and **23**.*



22

+



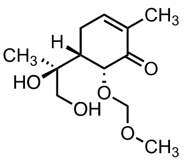
23

The (−)-Shi ketone (**S1**, 12.3 g, 47.6 mmol, 1.00 equiv), a solution of sodium tetraborate decahydrate and ethylenediamine tetraacetic acid disodium salt dihydrate (EDTA−Na_2) in water (50 mM in sodium tetraborate decahydrate, 400 μM in EDTA−Na_2, 1.24 L), and tetrabutylammonium hydrogensulfate (3.23 g, 9.51 mmol, 0.200 equiv) were added in sequence to a solution of the unsaturated ketone **21** (10.0 g, 47.6 mmol, 1 equiv) in acetonitrile−dimethoxymethane (1:2 v/v, 950 mL) at 23 °C. The reaction mixture was then cooled to 0 °C. A solution of oxone and EDTA−Na_2 in water (212 mM in oxone, 400 μM in EDTA−Na_2, 448 mL, 95.1 mmol, 2.00 equiv oxone) and aqueous potassium carbonate solution (890 mM, 428 mL, 380 mmol, 8.00 equiv) were then added dropwise simultaneously using two addition funnels over 1 h. Upon completion of the addition, the reaction mixture was stirred for 1 h at 0 °C. The product mixture was warmed to 23 °C over 1 h. The warmed product mixture was diluted sequentially with water (1.0 L) and ethyl acetate (1.0 L). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 L). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate−hexanes) to provide the epoxide **22** as a yellow oil (3.12 g, 29%) and **23** as a yellow oil (7.50 g, 70%). ^{1}H NMR analysis of the unpurified product mixture indicated the presence of a 1:2.4 mixture of diastereomers. The relative stereochemistry of **23** was established by X-ray analysis of the cyclic ether **24** (vide infra).

22: R_f = 0.44 (25% ethyl acetate−hexanes; UV, PAA). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (ddq, J = 5.5, 2.7, 1.4 Hz, H_4, 1H), 4.72 (d, J = 6.7 Hz, H_{6a}, 1H), 4.60 (d, J = 6.7 Hz, H_{6b}, 1H), 4.15 (d, J = 2.4 Hz, H_1, 1H), 3.32 (s, H_7, 3H), 2.84 (d, J = 4.6 Hz, H_{9a}, 1H), 2.57 (d, J = 4.6 Hz, H_{9b}, 1H), 2.38−2.23 (m, $H_{2,3}$, 3H), 1.77 (d, J = 1.7 Hz, H_5, 3H), 1.40 (s, H_8, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.3 (C), 144.0 (CH), 133.4 (C), 95.8 (CH_2), 95.2 (CH), 76.3 (CH), 56.4 (C), 55.8 (CH_3), 52.0 (CH_2), 44.8 (CH), 23.7 (CH_2), 21.0 (CH_3), 15.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2975 (m), 2958 (m), 1675 (m). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{12}H_{18}NaO_4$ 249.1103; found 249.1103. $[\alpha]_D^{20}$ = +30.2 (c = 0.88, $CHCl_3$).

23: R_f = 0.40 (25% ethyl acetate−hexanes; UV, PAA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.70 (td, J = 3.4 Hz, $H_{4'}$, 1H), 4.75 (d, J = 6.7 Hz, $H_{6a'}$, 1H), 4.68 (d, J = 6.7 Hz, $H_{6b'}$, 1H), 4.20 (d, J = 3.7 Hz, $H_{1'}$, 1H), 3.36 (s, $H_{7'}$, 3H), 2.75 (d, J = 4.8 Hz, $H_{9a'}$, 1H), 2.73−2.65 (m, $H_{3a'}$, 1H), 2.62 (d, J = 4.7 Hz, $H_{9b'}$, 1H), 2.49−2.40 (m, $H_{3b'}$, 1H), 2.11 (ddd, J = 7.4, 5.5, 3.7 Hz, $H_{2'}$, 1H), 1.80 (q, J = 1.9 Hz, $H_{5'}$, 3H), 1.33 (s, $H_{8'}$, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 197.2 (C), 143.6 (CH), 134.1 (C), 95.8 (CH_2), 77.0 (CH), 57.4 (C), 56.2 (CH_3), 53.9 (CH_2), 46.2 (CH), 25.6 (CH_2), 20.2 (CH_3), 15.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2984 (m), 2975 (m), 1683 (m). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{12}H_{18}NaO_4$ 249.1103; found 249.1110. $[\alpha]_D^{20}$ = +18.6 (c = 0.06, $CHCl_3$).

*Synthesis of the Epoxide **23** from **22**. Part 1: Synthesis of the Diols **S2** and **S3**.*



S2

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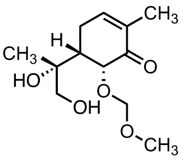
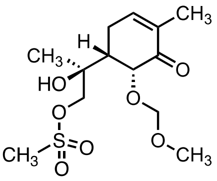


S3

Aqueous sulfuric acid solution (2.0 M, 44.2 mmol, 22.1 mL, 2.00 equiv) was added in one portion to a solution of the epoxide **22** (5.00 g, 22.1 mmol, 1 equiv) in tetrahydrofuran (110 mL) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C. The reaction mixture was then allowed to warm to 23 °C over 30 min. The warmed reaction mixture was then immersed in an oil bath that had been preheated to 45 °C. The reaction mixture was stirred and heated for 5 h at 45 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (200 mL), saturated aqueous sodium bicarbonate solution (100 mL), and water (100 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was used directly in the next step.

*Part 2: Synthesis of the Mesylates **S4** and **S5**.*



S4

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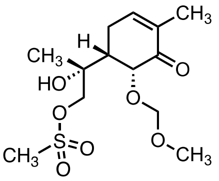
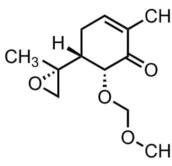


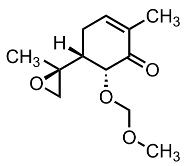
S5

Triethylamine (15.4 mL, 110 mmol, 5.00 equiv) and methanesulfonyl chloride (1.48 mL, 44.2 mmol, 2.00 equiv) were added in sequence to a solution of the residue obtained in the preceding step (nominally 22.1 mmol, 1 equiv) in dichloromethane (140 mL) at 0 °C. The resulting solution was stirred for 90 min at 0 °C. The cold product mixture was diluted sequentially with dichloromethane (200 mL), saturated aqueous ammonium chloride solution (100 mL), and water (100 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was used directly in the next step.

*Part 3: Synthesis of the Epoxides **22** and **23**.*



+

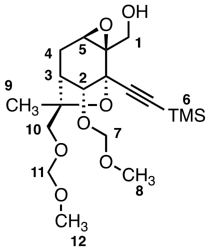


22 **23**

1,8-Diazabicyclo[5.4.0]undec-7-ene (9.90 mL, 66.3 mmol, 3.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 22.1 mmol, 1 equiv) in tetrahydrofuran (150 mL) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C. The reaction mixture was then allowed to warm to 23 °C. The warmed reaction mixture was stirred for 3 h at 23 °C. The product mixture was then diluted sequentially with ethyl acetate (200 mL), saturated aqueous ammonium chloride solution (100 mL), and water (100 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate−hexanes) to provide the epoxide **22** as a yellow oil (660 mg, 13%) and the epoxide **23** as a yellow oil (2.00 g, 40%).

^{1}H NMR analysis of the unpurified product mixture indicated the presence of a 1:3 mixture of diastereomers. NMR spectroscopic data for the epoxides **22** and **23** obtained in this way were in agreement with spectroscopic data obtained via epoxidation.

*Synthesis of the Aldehyde **26**. Part 1: Synthesis of the Epoxide **S6**.*

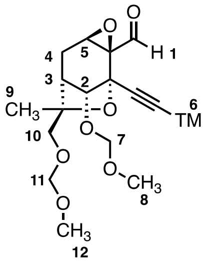


S6

meta-Chloroperoxybenzoic acid (923 mg, 3.75 mmol, 1.80 equiv) was added in one portion to a solution of the allylic alcohol **25** (800 mg, 2.08 mmol, 1 equiv) in dichloromethane (10 mL) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 10 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and dichloromethane (100 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate−hexanes) to provide the epoxide **S6** as a yellow oil (750 mg, 90%). Within the limits of detection, the epoxide **S6** was formed as a single diastereomer (^{1}H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the epoxide **S6** was established via conversion to the aldehyde **26**.

R_f = 0.40 (50% ethyl acetate−hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (d, J = 6.8 Hz, H_{7a}, 1H), 4.69 (d, J = 6.8 Hz, H_{7b}, 1H), 4.66−4.59 (m, H_{11}, 2H), 4.26 (s, H_2, 1H), 4.10 (d, J = 2.7 Hz, H_1, 2H), 3.80 (d, J = 9.0 Hz, H_{10a}, 1H), 3.55 (d, J = 9.0 Hz, H_{10b}, 1H), 3.39 (s, H_8, 3H), 3.34 (s, H_5, H_{12}, 4H), 2.33 (d, J = 1.7 Hz, H_3, 1H), 2.12 (t, J = 3.3 Hz, H_4, 2H), 1.33 (s, H_9, 3H), 0.17 (s, H_6, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 99.3 (C), 96.8 (CH_2), 95.8 (CH_2), 94.4 (C), 85.1 (C), 82.1 (CH), 81.0 (C), 74.0 (CH_2), 66.0 (C), 59.9 (CH_2), 55.6 (CH_3), 55.4 (CH_3), 54.8 (CH), 44.2 (CH), 27.3 (CH_2), 22.6 (CH_3), −0.2 (3× CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (m), 2975 (s), 1412 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{32}NaO_7Si$ 423.1815; found 423.1810. $[\alpha]_D^{20}$ = +5.77 (c = 0.17, CHCl3).

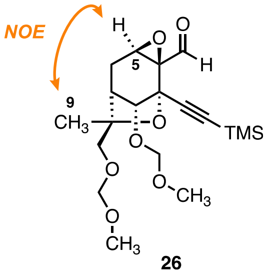
*Part 2: Synthesis of the Aldehyde **26**.*



26

The Dess−Martin periodinane (826 mg, 1.95 mmol, 1.50 equiv) was added in five equal portions (∼165 mg/addition) over 1 h to a solution of the epoxide **S6** (520 mg, 1.30 mmol, 1 equiv) and pyridine (731 μL, 9.09 mmol, 7.00 equiv) in dichloromethane (13 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (50 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium thiosulfate solution (20 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate−hexanes) to provide the aldehyde **26** as a colorless oil (750 mg, 76%).

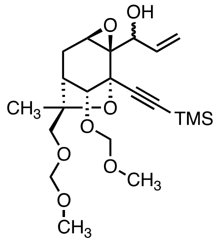
NOE correlations between the C5 hydrogen atom and the C9 methyl substituent support the relative configuration depicted.



26

R_f = 0.30 (25% ethyl acetate−hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, H_1, 1H), 4.83 (d, H_{7a}, J = 6.8 Hz, 1H), 4.71 (d, H_{7b}, J = 6.8 Hz, 1H), 4.67−4.58 (m, H_{11}, 2H), 4.25 (s, H_2, 1H), 3.85 (d, H_{10a}, J = 9.1 Hz, 1H), 3.59 (d, H_{10b}, J = 9.0 Hz, 1H), 3.40 (s, H_{12}, 3H), 3.35 (s, H_8, 3H), 3.32 (s, H_5, 1H), 2.39 (s, H_3, 1H), 2.18 (t, J = 3.0 Hz, H_4, 2H), 1.32 (s, H_9, 3H), 0.15 (s, H_6, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.4 (CH), 98.8 (C), 96.7 (CH_2), 95.7 (CH_2), 95.0 (C), 85.6 (C), 81.5 (CH), 78.5 (C), 73.6 (CH_2), 66.6 (C), 58.4 (CH), 55.6 (CH_3), 55.3 (CH_3), 44.1 (CH), 27.5 (CH_2), 22.7 (CH_3), −0.4 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 3734 (s), 3628 (m), 2932 (s), 1733 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{30}NaO_7Si$ 421.1658; found 421.1653. $[\alpha]_D^{20}$ = +21.1 (c = 0.30, CHCl3).

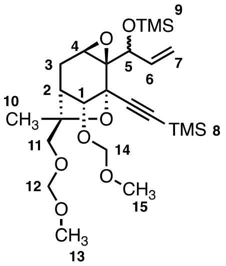
*Synthesis of the Trimethylsilyl Protected Allylic Alcohol **27**. Part1: Synthesis of the Allylic Alcohol **S7**.*



S7

A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 2.84 mL, 1.98 mmol, 2.00 equiv) was added dropwise via a syringe over 30 min to a solution of the aldehyde **26** (395 mg, 991 μmol, 1 equiv) in tetrahydrofuran (8.0 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. The product mixture was then warmed to 0 °C over 30 min. The warmed product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL), water (20 mL), and ethyl acetate (50 mL). The diluted product mixture was warmed to 23 °C over 30 min. The warmed mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was used directly in the following step. Within the limits of detection, the product **S7** was formed as a 3.4:1 mixture of diastereomers (^{1}H NMR analysis, 400 MHz).

*Part 2: Synthesis of the Silyl Ether **27**.*

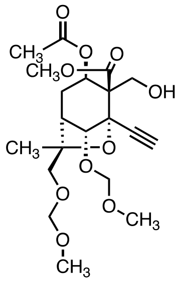


27

Trimethylsilyl chloride (252 μL, 1.98 mmol, 2.00 equiv) was added dropwise via a syringe to a solution of the residue obtained in the preceding step (nominally, 991 μmol, 1 equiv) and imidazole (270 mg, 3.96 mmol, 4.00 equiv) in dichloromethane (6.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 8 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and dichloromethane (50 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate−hexanes) to provide the silyl ether **27** as a colorless oil (370 mg, 77% over two steps).

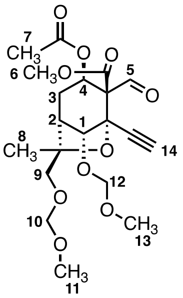
R_f = 0.50 (40% ethyl acetate−hexanes; PAA). *Denotes second diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (ddd, H_6, J = 16.8, 10.4, 4.6 Hz, 1H), 6.13−5.97 (m, H_{6*}, 1H), 5.34−5.22 (m, $H_{7a,7a*}$, 2H), 5.20−5.08 (m, $H_{7b,7b*}$, 2H), 4.98 (d, H_{5*}, J = 5.0 Hz, 1H), 4.85 (d, H_5, J = 4.7 Hz, 1H), 4.80 (dd, $H_{12a,12a*}$, J = 14.6, 6.7 Hz, 2H), 4.68 (d, $H_{12b,12b*}$, J = 6.8 Hz, 2H), 4.63−4.55 (m, $H_{14,14*}$, 4H), 4.34 (s, H_1,1H), 4.22 (s, H_{1*}, 1H), 3.84 (t, $H_{11a,11a*}$, J = 9.5 Hz, 2H), 3.51 (d, H_{11b*}, J = 8.9 Hz, 1H), 3.46 (d, H_{11b}, J = 8.9 Hz, 1H), 3.38 (s, H_{13}, 3H), 3.37 (s, H_{13*}, 3H), 3.34 (s, H_{15*}, 3H), 3.32 (s, H_{15}, 3H), 3.29−3.24 (m, $H_{4,4*}$, 2H), 2.31 (s, $H_{2,2*}$, 2H), 2.13−1.89 (m, $H_{3,3*}$, 4H), 1.33 (s, H_{10}, 3H), 1.22 (s, H_{10*}, 3H), 0.18 (s, H_9, 9H), 0.17 (s, H_{9*}, 9H), 0.13 (s, H_{8*}, 9H), 0.10 (s, H_8, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 138.0 (CH), 136.9 (CH)*, 115.6 (CH_2)*, 113.8 (CH_2), 100.5 (C)*, 99.9 (C), 96.69 (CH_2)*, 96.67 (CH_2), 95.76 (CH_2), 95.76 (CH_2)*, 93.9 (C)*, 93.6 (C), 84.9 (C)*, 84.7 (C), 82.9 (CH), 82.6 (CH)*, 81.8 (C)*, 80.9 (C), 74.2. (CH_2), 74.2 (CH_2)*, 70.4 (CH)*, 69.6 (CH), 68.7 (C)*, 66.9 (C), 55.42 (CH_3), 55.39 (CH_3)*, 55.2 (CH_3), 54.8 (CH_3)*, 52.5 (CH), 52.5 (CH)*, 43.9 (CH), 43.7 (CH)*, 27.2 (CH_2)*, 26.8 (CH_2), 22.6 (CH_3)*, 22.4 (CH_3), 0.45 (3 × CH_3)*. 0.041 (3 × CH_3), 0.3 (3 × CH_3), −0.4 (3 × CH_3)*. IR (ATR-FTIR), cm^{-1}: 3734 (m), 3646 (m), 2956 (m), 1683 (m). HRMS (ESI-TOF) *m/z*: calcd for $C_{24}H_{42}NaO_7Si_2$ 521.2367; found 521.2376. $[\alpha]_D^{20}$ = +25.2 (c = 0.08, CHCl3).

*Synthesis of the Aldehyde **39**.*



36a

Compound **36a** was prepared according to the procedure reported by Tomanik and co-workers.[14]

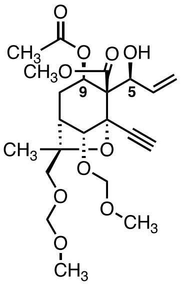


39

The Dess–Martin periodinane (3.70 g, 8.71 mmol, 1.50 equiv) was added in five equal portions (~740 mg/addition) over 1 h to a solution of the alcohol **36a** (2.50 g, 5.81 mmol, 1 equiv) and pyridine (3.30 mL, 40.7 mmol, 7.00 equiv) in dichloromethane (40 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with dichloromethane (100 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium thiosulfate solution (40 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the aldehyde **39** as a colorless oil (1.85 g, 74%).

R_f = 0.50 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, H_5, 1H), 5.78 (dd, J = 10.6, 7.1 Hz, H_4, 1H), 5.28 (s, H_1, 1H), 4.84 (d, J = 6.7 Hz, H_{12a}, 1H), 4.76 (d, J = 6.7 Hz, H_{12b}, 1H), 4.60 (s, H_{10}, 2H), 3.92 (d, J = 9.2 Hz, H_{9a}, 1H), 3.82 (s, H_6, 3H), 3.52 (d, J = 9.1 Hz, H_{9b}, 1H), 3.42 (s, H_{11}, 3H), 3.34 (s, H_{13}, 3H), 2.81 (s, H_{14}, 1H), 2.54–2.52 (m, H_{3a}, 1H), 2.53 (s, H_2, 1H), 1.97 (s, H_7, 3H), 1.89–1.87 (m, H_{3b}, 1H), 1.46 (s, H_8, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 193.8 (C), 169.3 (C), 167.1 (C), 96.7 (CH_2), 96.0 (CH_2), 87.1 (C), 82.3 (CH), 81.7 (C), 79.2 (CH), 77.4 (C), 73.5 (CH_2), 68.6 (C), 65.9 (CH), 55.7 (CH_3), 55.3 (CH_3), 52.8 (CH_3), 42.5 (CH), 31.2 (CH_2), 20.8 (CH_3), 20.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3734 (s), 2953 (s), 2119 (m), 1748 (s), 1728 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{28}NaO_{10}$ 451.1580; found 451.1574. $[\alpha]_D^{20}$ = +36.3 (c = 0.17, CHCl3).

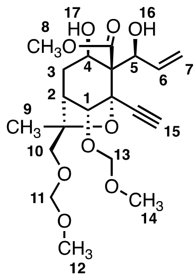
*Synthesis of the Diol **41**. Part 1: Synthesis of the Allylic Alcohol **S8**.*



S8

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (600 mM, 14.0 mL, 8.40 mmol, 3.00 equiv) was added to a solution of the aldehyde **39** (1.20 g, 2.80 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 23 °C. The resulting solution was stirred for 1 h at 23 °C and then cooled to 0 °C. A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 12.0 mL, 8.40 mmol, 3.00 equiv) was then added dropwise via a syringe over 30 min at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (50 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (100 mL). The resulting mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred vigorously for 45 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was used directly in the following step. Due to the partial cleavage of the C9 acetate group, the diastereomeric ratio at the C5 position was obtained in the subsequent step.

*Part 2: Synthesis of the Diol **41**.*

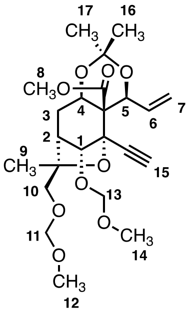


41

Potassium carbonate (774 mg, 5.60 mmol, 2.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally, 2.80 mmol, 1 equiv) in methanol (20 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (30 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to provide the diol **41** as a yellow oil (789 mg, 68% over two steps). Within the limits of detection, the product **41** was obtained as a 3.1:1 mixture of diastereomers (^{1}H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the allylic alcohol **S8** was established via conversion to the acetonide **42**.

R_f = 0.20 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (ddd, J = 17.4, 10.4, 7.2 Hz, H_6, 1H), 5.27 (d, J = 17.1 Hz, H_{7a}, 1H), 5.21 (d, J = 7.2 Hz, H_5, 1H), 5.12 (d, J = 9.5 Hz, H_{7b}, 1H), 4.72 (d, J = 6.8 Hz, H_{13a}, 1H), 4.69 (d, J = 6.8 Hz, H_{13b}, 1H), 4.67–4.65 (m, H_4, 1H), 4.61 (s, H_{11}, 2H), 4.17 (s, H_1, 1H), 3.97 (d, J = 9.3 Hz, H_{10a}, 1H), 3.74 (s, H_8, 3H), 3.54 (d, J = 9.2 Hz, H_{10b}, 1H), 3.37 (s, H_{12}, 3H), 3.35 (s, H_{14}, 3H), 2.77 (s, H_{15}, 1H), 2.49–2.47 (m, H_2, 1H), 2.33 (ddd, J = 13.9, 7.0, 3.7 Hz, H_{3a}, 1H), 1.92 (ddd, J = 14.1, 11.2, 3.0 Hz, H_{3b}, 1H), 1.47 (s, H_9, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.2 (C), 137.5 (CH), 116.4 (CH_2), 96.6 (CH_2), 95.3 (CH_2), 87.8 (C), 86.2 (C), 83.3 (CH), 78.6 (CH), 77.2 (C), 75.9 (CH), 73.3 (CH_2), 64.7 (CH), 63.2 (C), 55.5 (CH_3), 55.3 (CH_3), 52.2 (CH_3), 43.2 (CH), 35.1 (CH_2), 19.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 3735 (s), 3628 (s), 2950 (m), 1717 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{30}NaO_9$ 437.1788; found 437.1783. $[\alpha]_D^{20}$ = −6.27 (c = 0.17, CHCl3).

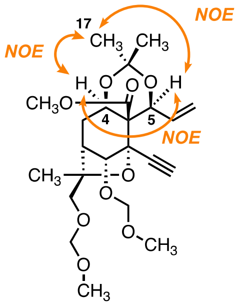
*Synthesis of the Acetonide **42**.*



42

para-Toluenesulfonic acid monohydrate (46.6 mg, 241 μmol, 0.20 equiv) was added in one portion to a solution of the diol **41** (500 mg, 121 mmol, 1 equiv) in acetone (4.0 mL) and 2,2-dimethoxypropane (4.0 mL) at 23 °C. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (40 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (10 mL). The diluted product mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate−hexanes) to provide the acetonide **42** as a colorless oil (490 mg, 90%).

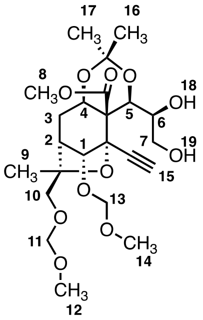
NOE correlations between the C4 hydrogen atom and the C17 methyl substituent, the C5 hydrogen and the C17 methyl substituent, and the C4 hydrogen atom and the C5 hydrogen support the relative configuration depicted.



42

R_f = 0.50 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.59 (ddd, J = 16.9, 10.5, 6.2 Hz, H_6, 1H), 5.36 (d, J = 17.0 Hz, H_{7a}, 1H), 5.21 (d, J = 10.5 Hz, H_{7b}, 1H), 4.74 (d, J = 6.8 Hz, H_{13a}, 1H), 4.67 (d, J = 7.0 Hz, $H_{13b,\ 5}$ 2H), 4.62 (s, H_{11}, 2H), 4.46 (dd, J = 12.1, 5.9 Hz, H_4, 1H), 4.12 (s, H_1, 1H), 4.02 (d, J = 9.2 Hz, H_{10a}, 1H), 3.77 (s, H_8, 3H), 3.60 (d, J = 9.2 Hz, H_{10b}, 1H), 3.36 (s, H_{12}, 3H), 3.35 (s, H_{14}, 3H), 2.64 (s, H_{15}, 1H), 2.54 (t, J = 3.4 Hz, H_2, 1H), 2.13 (td, J = 12.5, 2.8 Hz, H_{3a}, 1H), 1.99 (ddd, J = 13.3, 5.9, 3.9 Hz, H_{3b}, 1H), 1.53 (s, H_{16}, 3H), 1.51 (s, H_9, 3H), 1.43 (s, H_{17}, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.6 (C), 135.0 (CH), 118.1 (CH_2), 100.2 (C), 96.7 (CH_2), 95.3 (CH_2), 87.6 (C), 84.5 (CH), 82.6 (C), 79.8 (C), 78.5 (CH), 76.3 (CH), 73.8 (CH_2), 69.8 (CH), 59.0 (C), 55.5 (CH_3), 55.3 (CH_3), 51.5 (CH_3), 43.1 (CH), 30.6 (CH_2), 29.5 (CH_3), 19.7 (CH_3), 19.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 3735 (s), 3648 (m), 2948 (m), 1735 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{34}NaO_9$ 477.2101; found 477.2100. $[\alpha]_D^{20}$ = +8.00 (c = 0.15, CHCl3).

*Synthesis of the Lactone **43**. Part 1: Synthesis of the Diol **S9**.*



S9

Potassium osmate(VI) dihydrate (12.2 mg, 33.0 μmol, 10.0 mol %) was added to a solution of the acetonide **42** (150 mg, 330 μmol, 1 equiv) and *N*-methyl-morpholine *N*-oxide (NMO, 116 mg, 990 μmol, 3.00 equiv) in 66% acetone−water (v/v, 3.0 mL) at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was poured into a stirring mixture of ethyl acetate (15 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The diluted product mixture was stirred for 10 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash column chromatography (eluting with 50% ethyl acetate−hexanes) to provide the diol **S9** as a colorless oil (159 mg, 99%). Within the limits of detection, the diol **S9** was formed as a >20:1 mixture of diastereomers (^{1}H NMR analysis, 400 MHz). The relative stereochemistry at the C6 position of the diol **S9** was established via conversion to the lactone **43**.

R_f = 0.10 (50% ethyl acetate−hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6): δ 5.35 (t, J = 5.2 Hz, H_4, 1H), 4.62 (d, J = 6.8 Hz, H_{13a}, 1H), 4.56−4.40 (m, H_1, H_5, H_6, H_{11}, H_{13b}, 6H), 4.22 (d, J = 9.3 Hz, H_{10a}, 1H), 4.08−4.01 (m, H_{7a}, 1H), 3.97−3.90 (m, H_{7b}, 1H), 3.70 (d, J = 5.1 Hz, H_{18}, 1H), 3.62 (d, J = 9.3 Hz, H_{10b}, 1H), 3.43 (s, H_8, 3H), 3.16 (s, H_{12}, 3H), 3.12 (s, H_{14}, 3H), 2.48 (s, H_{19}, 1H), 2.38 (t, J = 3.4 Hz, H_2, 1H), 2.30 (td, J = 12.6, 2.8 Hz, H_{3a}, 1H), 2.14 (s, H_{15}, 1H), 1.93−1.80 (m, H_{3b}, 1H), 1.44 (s, H_9, 3H), 1.32 (s, H_{16}, 3H), 1.28 (s, H_{17}, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 170.3 (C), 100.5 (CH_2), 96.9 (CH_2), 95.6 (C), 88.1 (CH), 84.7 (C), 82.5 (CH), 81.8 (C), 81.1 (CH), 78.2 (CH_2), 74.2 (CH_2), 71.8 (CH), 70.2 (CH), 64.1 (CH_2), 59.9 (C), 55.4 (CH_3), 55.0 (CH_3), 51.2 (CH_2), 43.3(CH), 31.3 (CH_3), 29.5 (CH_3), 19.4 (CH_3), 19.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 3733 (s), 3260 (s), 2990 (s), 2950 (m), 1733 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{36}NaO_{11}$ 511.2155; found 511.2146. $[\alpha]_D^{20}$ = +1.35 (c = 0.27, CHCl3).

https://doi.org/10.1021/acs.joc.1c02167
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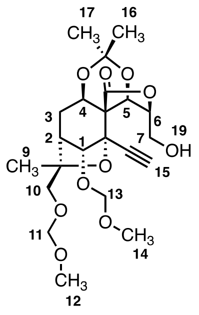
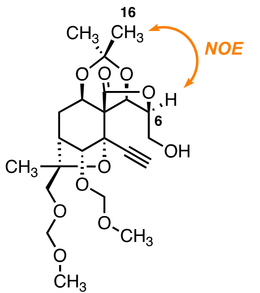
Part 2: Synthesis of the Lactone ***43****.*



43

Potassium carbonate (56.6 mg, 409 μmol, 2.00 equiv) was added in one portion to a solution of the diol **S9** (100 mg, 205 μmol, 1 equiv) in methanol (2.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and ethyl acetate (20 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate−hexanes) to provide the lactone **43** as a yellow oil (90.0 mg, 96%).

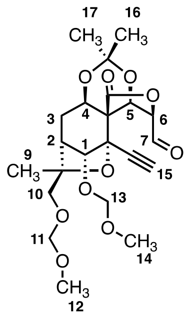
NOE correlations between the C6 hydrogen atom and the C16 methyl substituent support the relative configuration depicted.



43

R_f = 0.40 (50% ethyl acetate−hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6): δ 5.96 (s, H_1, 1H), 4.84 (d, J = 1.5 Hz, H_5, 1H), 4.72 (d, J = 6.5 Hz, H_{13a}, 1H), 4.68−4.65 (m, H_4, 1H), 4.65−4.63 (m, H_6, 1H), 4.60 (d, J = 6.5 Hz, H_{13b}, 1H), 4.56−4.47 (m, H_{11}, 2H), 4.26 (d, J = 9.3 Hz, H_{10a}, 1H), 3.83 (ddd, J = 11.8, 8.0, 3.7 Hz, H_{7a}, 1H), 3.67 (d, J = 9.3 Hz, H_{10b}, 1H), 3.60 (dt, J = 12.3, 6.8 Hz, H_{7b}, 1H), 3.22 (s, H_{12}, 3H), 3.17 (s, H_{14}, 3H), 2.49 (t, J = 3.4 Hz, H_2, 1H), 2.41 (td, J = 13.0, 2.5 Hz, H_{3a}, 1H), 1.92 (s, H_{19}, 1H), 1.79 (ddd, J = 13.2, 6.1, 4.2 Hz, H_{3b}, 1H), 1.48 (s, H_9, 3H), 1.32 (s, H_{16}, 3H), 1.26 (s, H_{17}, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 174.3 (C), 104.1 (C), 96.8 (CH_2), 96.3 (CH_2), 87.7 (C), 84.6 (CH), 82.6 (C), 82.0 (CH), 80.2 (C), 78.5 (CH), 77.3 (CH), 74.4 (CH_2), 66.0 (CH), 63.4 (CH_2), 59.1 (C), 55.5 (CH_3), 55.0 (CH_3), 43.1 (CH), 28.4 (CH_3), 28.1 (CH_2), 27.7 (CH_3), 19.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 3736 (s), 3260 (s), 2949 (s), 2159 (m), 1762 (s). HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{32}NaO_{10}$ 479.1893; found 479.1891. $[\alpha]_D^{20}$ = +17.2 (c = 0.33, CHCl3).

Synthesis of the Olefin ***45****. Part 1: Synthesis of the Aldehyde* ***44****.*



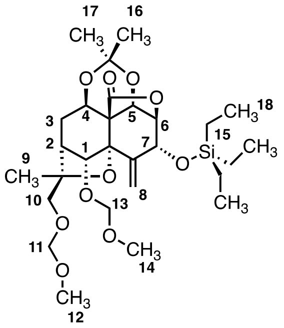
44

A solution of potassium bromide (29.0 mg, 244 μmol) and tetrabutylammonium chloride (30.0 mg, 108 μmol) in saturated aqueous sodium bicarbonate solution (4.0 mL) was prepared. A second solution of aqueous sodium hypochlorite (10−15% chlorine, 2.75 mL), saturated aqueous sodium bicarbonate solution (4.0 mL), and saturated aqueous sodium chloride solution (11.0 mL) was prepared separately. The potassium bromide solution (274 μL) and the aqueous sodium hypochlorite solution (183 μL) were added in sequence to a stirring solution of the lactone **43** (25.0 mg, 55.0 μmol, 1 equiv) and TEMPO (1.0 mg, 6.0 μmol, 0.10 eq) in dichloromethane (200 μL) at 0 °C. The biphasic reaction mixture was stirred vigorously for 90 min at 0 °C. The product mixture was diluted sequentially with dichloromethane (5.0 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and saturated aqueous sodium thiosulfate solution (5.0 mL). The diluted product mixture was stirred for 30 min at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was used directly in the following step.

The aldehyde product **44** proved unstable toward silica gel purification and was found to decompose appreciably within 2 h at 23 °C in neat form. Accordingly, we were able to obtain only ^{1}H NMR spectroscopic data on the unpurified product, and the aldehyde was used directly in the subsequent step.

R_f = 0.50 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 9.29 (s, H_7, 1H), 5.70 (s, H_1, 1H), 5.25 (s, H_6, 1H), 4.62 (d, J = 6.6 Hz, H_{13a}, 1H), 4.54 (dd, J = 12.5, 6.3 Hz, H_4, 1H), 4.51−4.47 (m, $H_{11a,13b}$, 2H), 4.45 (d, J = 6.3 Hz, H_{11b}, 1H), 4.38 (d, J = 1.1 Hz, H_5, 1H), 4.18 (d, J = 9.3 Hz, H_{10a}, 1H), 3.58 (d, J = 9.3 Hz, H_{10b},1H), 3.16 (s, H_{12}, 3H), 3.14 (s, H_{14}, 3H), 2.44 (t, J = 3.3 Hz, H_2, 1H), 2.36 (td, J = 13.0, 2.5 Hz, H_{3a}, 1H), 1.83−1.72 (m, $H_{3b,15}$, 2H), 1.40 (s, H_9, 3H), 1.21 (s, H_{16}, 4H), 1.17 (s, H_{17}, 3H).

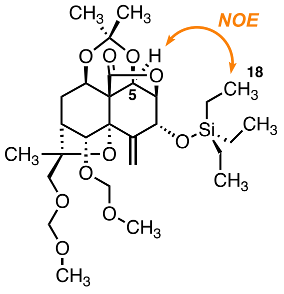
*Part 2: Reductive Cyclization of the Aldehyde **44** to Synthesize the Olefin **45**.*



45

A solution of the catalyst was prepared in a nitrogen-filled glovebox by stirring a solution of bis(1,5-cyclooctadiene)-nickel(0) (46.0 mg, 167 μmol, 1.00 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 65.4 mg, 167 μmol, 1.00 equiv) in tetrahydrofuran (1.0 mL) at 20 °C for 30 min. A portion of the catalyst stock solution (100 μL, 30 mol % nickel) was added to a 25 mL screw-capped pressure vessel containing a stirring solution of the aldehyde residue obtained in the preceding step (nominally 55.0 μmol, 1 equiv) and triethylsilane (26.0 μL, 165 μmol, 3.00 equiv) in tetrahydrofuran (1.8 mL) at 20 °C. The reaction vessel was sealed, and the sealed vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred and heated for 2 h at 60 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the olefin **45** as a colorless oil (2.9 mg, 9% over two steps).

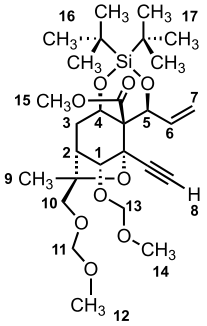
NOE correlations between the C5 hydrogen atom and the C18 methyl substituent support the relative configuration depicted.



45

R_f = 0.50 (33% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (s, H_{8a}, 1H), 5.70 (s, H_{8b}, 1H), 4.78 (s, H_5, 1H), 4.66 (s, H_1, 1H), 4.65–4.58 (m, $H_{4,\ 11a,\ 11b,\ 13a}$, 4H), 4.50 (d, J = 7.7 Hz, $H_{7,\ 13b}$, 2H), 4.25 (d, J = 3.6 Hz, H_6, 1H), 4.02 (d, J = 9.2 Hz, H_{10a}, 1H), 3.62 (d, J = 9.2 Hz, H_{10b}, 1H), 3.36 (s, H_{12}, 3H), 3.32 (s, H_{14}, 3H), 2.64 (s, H_2, 1H), 2.48 (t, J = 12.7 Hz, H_{3a}, 1H), 2.05–1.96 (m, H_{3b}, 1H), 1.56 (s, H_{16}, 3H), 1.51 (s, H_9, 3H), 1.43 (s, H_{17}, 3H), 0.97 (t, J = 7.9 Hz, H_{18}, 9H), 0.66 (q, J = 8.0 Hz, H_{15}, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 174.2 (C), 140.8 (C), 129.9 (CH_2), 101.2 (C), 96.7 (CH_2), 96.4 (CH_2), 85.6 (C), 84.0 (CH), 82.9 (C), 79.8 (CH), 74.1 (CH_2), 71.4 (CH), 71.4 (CH), 64.8 (CH), 55.9 (CH_3), 55.3 (CH_3), 54.0 (C), 44.5 (CH), 29.5 (CH_3), 28.7 (CH_2), 20.5 (CH_3), 19.3 (CH_3), 6.8 (3 × CH_3), 4.9 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 3734 (s), 3628 (s), 2975 (m), 1717 (m). HRMS (ESI-TOF) *m/z*: calcd for $C_{28}H_{46}NaO_{10}Si$ 593.2758; found 593.2752. $[\alpha]_D^{20}$ = −6.81 (c = 0.07, CHCl3).

*Synthesis of the Silylene Ether **65**.*

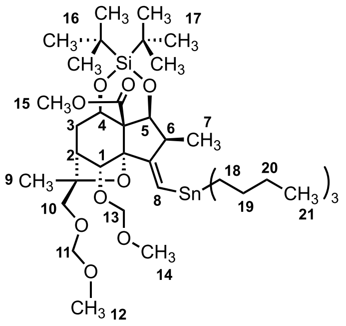


65

Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (118 μL, 362 μmol, 1.50 equiv) was added dropwise via a syringe to a solution of the diol **41** (100 mg, 241 μmol, 1 equiv) and pyridine (97.0 μL, 1.21 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 12 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and dichloromethane (15 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the silylene ether **65** as a yellow oil. The silylene ether **65** is inseparable from di-*tert*-butyl silenol byproduct, and the yield of this transformation was established by ^{1}H NMR of the unpurified product mixture (79%).

R_f = 0.30 (33% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (ddd, H_6, J = 16.9, 10.4, 5.1 Hz, 1H), 5.37 (d, H_{7a}, J = 18.6 Hz, 1H), 5.11 (d, H_{7b}, J = 10.4 Hz, 1H), 5.01 (d, H_5, J = 5.1 Hz, 1H), 4.72–4.57 (m, $H_{4,11,13}$, 5H), 4.41 (s, H_1, 1H), 3.98 (d, H_{10a}, J = 9.2 Hz, 1H), 3.69 (s, H_{15}, 3H), 3.57 (d, H_{10b}, J = 9.2 Hz, 1H), 3.35 (s, $H_{12,14}$, 6H), 2.67 (s, H_8, 1H), 2.50 (t, H_2, J = 2.9 Hz, 1H), 2.37–2.26 (m, H_{3a}, 1H), 2.19–2.08 (m, H_{3b}, 1H), 1.47 (s, H_9, 3H), 1.11 (s, H_{16}, 9H), 0.96 (s, H_{17}, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.7 (C), 138.6 (CH), 114.5 (CH_2), 96.7 (CH_2), 95.5 (CH_2), 87.6 (C), 83.4 (CH), 83.3 (C), 80.6 (CH), 79.9 (C), 79.2 (C), 73.8 (CH_2), 72.9 (CH), 63.9 (C), 55.5 (CH_3), 55.2 (CH_3), 51.4 (CH_3), 42.8 (CH), 33.3 (CH_2), 28.7 (3 × CH3), 27.2 (3 × CH3), 22.7 (C), 19.8 (C), 19.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2996 (m), 2975 (s), 2360 (m), 2003 (m), 1400 (s). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{46}NaO_9Si$ 577.2809; found 577.2819. $[\alpha]_D^{20}$ = +2.48 (c = 0.10, CHCl3).

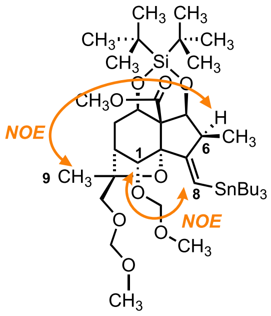
*Synthesis of the Vinyl Stannane **66**.*



66

A solution of azobis(isobutyronitrile) (AIBN, 1.0 mg, 5.0 μmol, 0.10 equiv) in degassed toluene (1.0 mL) and a solution of tributyltin hydride (29.0 μL, 108 μmol, 2.00 equiv) in degassed toluene (1.0 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the silylene ether **65** (25.0 mg, 54.0 μmol, 1 equiv) in degassed toluene (2.7 mL) at 80 °C. Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at 80 °C. The product mixture was then cooled to 23 °C over 1 h. The cooled product mixture was concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the vinyl stannane **66** as a yellow oil (41.0 mg, 90%).

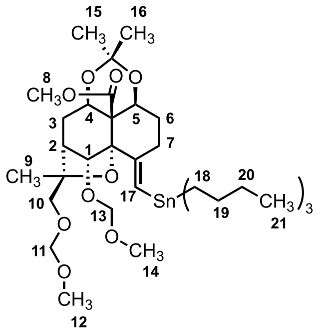
NOE correlations between the C6 hydrogen and the C9 methyl substituent, and the C8 vinyl hydrogen and the C1 hydrogen substituent support the shown stereochemical configuration.



66

R_f = 0.50 (25% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6): δ 7.02 (d, H$_{8}$, J = 2.4 Hz, 1H), 5.11 (dd, H$_{4}$, J = 11.8, 6.0 Hz, 1H), 4.74 (d, H$_{5}$, J = 9.2 Hz, 1H), 4.64–4.58 (m, H$_{1,13a}$, 2H), 4.56 (d, H$_{13b}$, J = 6.5 Hz, 1H), 4.51–4.42 (m, H$_{11}$, 2H), 4.27 (d, H$_{10a}$, J = 9.2 Hz, 1H), 3.78 (ddd, H$_{6}$, J = 9.3, 6.7, 2.5 Hz, 1H), 3.62 (d, H$_{10b}$, J = 9.1 Hz, 1H), 3.50 (s, H$_{15}$, 3H), 3.23 (s, H$_{12}$, 3H), 3.12 (s, H$_{14}$, 3H), 3.00–2.90 (m, H$_{3a}$, 1H), 2.54 (t, H$_{2}$, J = 3.3 Hz, 1H), 2.15 (ddd, H$_{3b}$, J = 13.1, 5.9, 3.6 Hz, 1H), 1.62 (dtd, H$_{18}$, J = 14.3, 7.6, 7.2, 3.2 Hz, 6H), 1.57–1.54 (m, H$_{9,7}$, 6H), 1.36 (q, H$_{20}$, J = 7.4 Hz, 6H), 1.31 (s, H$_{16}$, 9H), 1.15 (s, H$_{17}$, 9H), 1.07 (td, H$_{19}$, J = 7.4, 3.1 Hz, 6H), 0.93 (t, H$_{21}$, J = 7.3 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, C_6D_6): δ 171.2 (C), 162.1 (C), 127.8 (CH), 96.8 (CH$_2$), 94.9 (CH$_2$), 88.4 (C), 87.8 (CH), 83.9 (C), 83.5 (CH), 75.9 (CH), 75.1 (CH$_2$), 66.5 (C), 55.3 (CH$_3$), 54.9 (CH$_3$), 51.4 (CH$_3$), 45.6 (CH), 44.5 (CH), 32.4 (CH$_2$), 29.6 (3 × CH$_3$), 29.5 (3 × CH$_2$), 27.7 (3 × CH$_2$), 27.5 (3 × CH$_3$), 23.4 (C), 21.1 (CH$_3$), 20.1 (C), 19.8 (CH$_3$), 13.9 (3 × CH$_3$), 10.7 (3 × CH$_2$). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2996 (m), 2975 (s), 1400 (s). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{40}H_{74}NaO_9SiSn$ 869.4022; found 869.4031. $[\alpha]_D^{20}$ = −1.44 (c = 0.13, CHCl3).

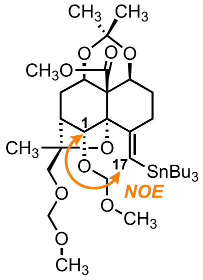
*Synthesis of the Vinyl Stannane **67**.*



67

A solution of azobis(isobutyronitrile) (AIBN, 2.0 mg, 11.0 μmol, 0.10 equiv) in degassed toluene (1.5 mL) and a solution of tributyltin hydride (36.0 μL, 132 μmol, 1.20 equiv) in degassed toluene (1.5 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the acetonide **42** (50.0 mg, 110 μmol, 1 equiv) in degassed toluene (5.5 mL) at 80 °C. Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at 80 °C. The product mixture was then cooled to 23 °C over 1 h. The cooled product mixture was directly concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the vinyl stannane **67** as a yellow oil (58.0 mg, 71%).

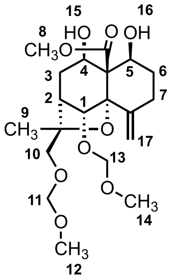
NOE correlations between the C17 hydrogen and the C1 hydrogen support the relative configuration depicted.



67

R_f = 0.50 (25% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.11 (s, H$_{17}$, 1H), 4.70 (d, H$_{13a}$, J = 6.7 Hz, 1H), 4.63–4.56 (m, H$_{13b,11}$, 3H), 4.53 (s, H$_{1}$, 1H), 4.48 (dd, H$_{4}$, J = 12.3, 6.1 Hz, 1H), 4.34 (dd, H$_{5}$, J = 12.0, 5.3 Hz, 1H), 3.90 (d, H$_{10a}$, J = 9.0 Hz, 1H), 3.67 (d, H$_{8}$, J = 1.6 Hz, 3H), 3.60 (d, H$_{10b}$, J = 9.1 Hz, 1H), 3.38 (s, H$_{12}$, 3H), 3.34 (s, H$_{14}$, 3H), 2.73–2.56 (m, H$_{7a,2}$, 2H), 2.55–2.38 (m, H$_{3a,6a}$, 2H), 2.13–2.03 (m, H$_{7b}$, 1H), 1.99 (dd, H$_{3b}$, J = 11.6, 6.1 Hz, 1H), 1.80–1.72 (m, H$_{6b}$, 1H), 1.58–1.44 (m, H$_{18,15,9}$, 12H), 1.41–1.20 (m, H$_{16,20}$, 9H), 0.98–0.82 (m, H$_{19,21}$, 15H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.1 (C),149.8 (C), 127.1 (CH), 101.7 (C), 96.7 (CH$_2$), 95.9 (CH$_2$), 87.3 (C), 84.4 (C), 83.2 (CH), 75.5 (CH), 74.9 (CH$_2$), 72.9 (CH), 60.1 (C), 56.5 (CH$_3$), 55.3 (CH$_3$), 51.1 (CH$_3$), 43.4 (CH), 34.5 (CH$_2$), 30.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_3$), 29.2 (3 × CH$_2$), 27.3 (3 × CH$_2$), 20.3 (CH$_3$), 19.8 (CH$_3$), 13.7 (3 × CH$_3$), 10.2 (3 × CH$_2$). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2996 (m), 2975 (s), 1401 (s). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{35}H_{62}NaO_9Sn$ 769.3313; found 769.3335. $[\alpha]_D^{20}$ = −63.3 (c = 0.17, CHCl3).

*Synthesis of the Olefin **68**.*

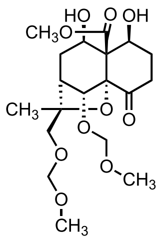


68

Camphorsulfonic acid (21.8 mg, 94.0 μmol, 1.40 equiv) was added in a single portion to a solution of the stannane **67** (50.0 mg, 67.0 μmol, 1 equiv) in dichloromethane (1.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with dichloromethane (10 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and water (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate−hexanes) to provide the olefin **68** as a colorless oil (27.8 mg, 99%).

R_f = 0.50 (25% ethyl acetate−hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (s, H_1,1H), 5.01 (s, H_{17a},1H), 4.97 (s, H_{17b},1H), 4.77 (d, H_{13a}, J = 6.6 Hz, 1H), 4.67 (d, H_{13b}, J = 6.8 Hz, 1H), 4.57 (s, H_{11}, 2H), 4.48 (dt, H_4, J = 12.0, 6.4 Hz, 1H), 4.36−4.24 (m, H_5, 1H), 3.89 (d, H_{10a}, J = 9.0 Hz, 1H), 3.74 (s, H_8, 3H), 3.48 (d, H_{10b}, J = 9.1 Hz, 1H), 3.43 (s, H_{12}, 3H), 3.33 (s, H_{14}, 3H), 3.30 (d, H_{16}, J = 9.4 Hz, 1H), 3.04 (d, H_{15}, J = 5.7 Hz, 1H), 2.63−2.47 (m, $H_{2,6a}$, 2H), 2.29 (ddd, H_{3a}, J = 13.8, 7.0, 4.1 Hz, 1H), 2.13 (ddd, H_{6b}, J = 13.1, 5.3, 2.1 Hz, 1H), 2.07−1.87 (m, $H_{3b,7}$, 3H), 1.49 (s, H_9, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.2 (C), 143.6 (C), 111.9 (CH_2), 96.7 (CH_2), 96.1 (CH_2), 88.5 (C), 83.7 (C), 82.8 (CH), 77.5 (CH), 74.6 (CH_2), 73.8 (CH), 65.7 (C), 56.6 (CH_3), 55.4 (CH_3), 51.8 (CH_3), 42.1 (CH), 33.9 (CH_2), 33.1 (CH_2), 31.4 (CH_2), 20.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 3499 (m), 3015 (s), 2996 (m), 2975 (s), 2957 (m), 2691 (m), 2265 (m), 2069 (m), 2003 (m), 1710 (s), 1458 (s). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{32}NaO_9$ 439.1944; found 439.1946. $[\alpha]_D^{20}$ = −48.1 (c = 0.10, CHCl3).

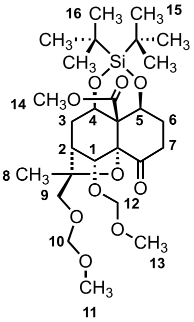
*Synthesis of the Silylene Ether Ketone **69**. Part 1: Synthesis of the Ketone **S10**.*



S10

Ozone was bubbled through a solution of the olefin **68** (30.0 mg, 72.0 μmol, 1 equiv) in a mixture of dichloromethane (1.3 mL) and methanol (500 μL) at −78 °C until a dark blue color persisted. Dioxygen was then passed through the solution to remove any unreacted ozone, resulting in a colorless solution. Triphenylphosphine (37.8 mg, 141 μmol, 2.00 equiv) was then added in one portion. The cooling bath was removed, and the mixture was allowed to warm to 23 °C over 1 h. The warmed product mixture was concentrated, and the residue obtained was partially purified by elution over a short plug of silica gel (2.0 × 1.0 cm, eluting with 50% ethyl acetate−hexanes). The filtrate was collected, and the residue obtained was used directly in the following step.

*Part 2: Synthesis of the Silylene Ether Ketone **69**.*



69

Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (25.0 μL, 79.2 μmol, 1.10 equiv) was added dropwise via a syringe to a solution of the residue obtained in the preceding step (nominally 72.0 μmol, 1 equiv) and pyridine (16.0 μL, 202 μmol, 2.80 equiv) in dichloromethane (500 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then the cooling bath was removed. The reaction mixture was warmed to 23 °C over 30 min. The mixture was stirred for 1 day at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (3.0 mL), water (3.0 mL), and dichloromethane (10 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate−hexanes) to provide the silylene ether ketone **69** as a colorless oil (32.0 mg, 80% over two steps).

R_f = 0.50 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.87 (dd, H_4, J = 11.8, 6.4 Hz, 1H), 4.85−4.79 (m, H_5, 1H), 4.69 (d, H_{12a}, J = 6.9 Hz, 1H), 4.63 (d, H_{12b}, J = 7.0 Hz, 1H), 4.59 (d, H_{10a}, J = 7.2 Hz, 1H), 4.56 (d, H_{10b}, J = 7.1 Hz, 1H), 4.25 (s, H_1, 1H), 3.91 (d, H_{9a}, J = 9.3 Hz, 1H), 3.67 (s, H_{14}, 3H), 3.54 (d, H_{9b}, J = 9.2 Hz, 1H), 3.36 (s, H_{11}, 3H), 3.33 (s, H_{13}, 3H), 2.97−2.83 (m, H_{7a}, 1H), 2.74−2.63 (m, H_{6a}, 1H), 2.47 (s, H_2, 1H), 2.44−2.30 (m, $H_{3a,7b}$, 2H), 2.22−2.03 (m, $H_{3b,6b}$, 2H), 1.54 (s, H_8, 3H), 1.14 (s, H_{16}, 9H), 0.93 (s, H_{15}, 9H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 202.9 (C), 170.2 (C), 97.1 (CH_2), 96.6 (CH_2), 87.5 (C), 86.6 (C), 81.4 (CH), 77.3 (CH), 74.8 (CH), 74.3 (CH_2), 63.7 (C), 55.5 (CH_3), 55.2 (CH_3), 51.7 (CH_3), 44.5 (CH), 37.7 (CH_2), 32.4 (CH_2), 31.6 (CH_2), 29.0 (3 × CH_3), 27.1 (3 × CH_3), 23.1 (C), 19.6 (C), 19.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 3014 (s), 2997 (m), 2975 (s), 2958 (m), 2808 (m), 2691 (m), 2262 (s), 2070 (m), 2004 (s), 1458 (s). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{46}NaO_{10}Si$ 581.2758; found 581.2769. $[\alpha]_D^{20}$ = +12.2 (c = 0.07, CHCl3).

https://doi.org/10.1021/acs.joc.1c02167
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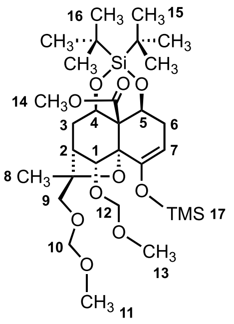
*Synthesis of the Enoxysilane **70**.*

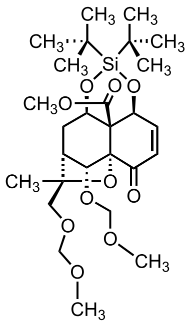


70

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.00 M, 179 μL, 179 μmol, 5.00 equiv) was added dropwise via a syringe to a solution of the ketone **69** (20.0 mg, 35.8 μmol, 1 equiv) in tetrahydrofuran (900 μL) at −78 °C. The resulting solution was stirred for 15 min at −78 °C. The reaction vessel was then placed in an ice bath. The reaction mixture was stirred for 1 h at 0 °C. The reaction vessel was then cooled to −78 °C over 15 min. Chlorotrimethylsilane (36.0 μL, 285 μmol, 8.00 equiv) was added dropwise via a syringe to the reaction mixture at −78 °C. The resulting solution was stirred for 15 min at −78 °C. The reaction vessel was then placed in an ice bath and stirred at 0 °C for 30 min. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (4.0 mL), and saturated aqueous sodium bicarbonate solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate−hexanes) to provide the enoxysilane **70** as a colorless oil (21.0 mg, 93%).

R_f = 0.30 (15% ethyl acetate−hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6): δ 5.13−5.00 (m, $H_{7,4}$, 2H), 4.92−4.84 (m, H_5, 1H), 4.72 (d, H_{12a}, J = 6.8 Hz, 1H), 4.66 (s, H_1, 1H), 4.63 (d, H_{10a}, J = 6.2 Hz, 1H), 4.59 (d, H_{10b}, J = 6.2 Hz, 1H), 4.42 (dd, $H_{12b,9a}$, J = 15.3, 8.0 Hz, 2H), 3.54−3.51 (m, $H_{9b,14}$, 4H), 3.22 (s, H_{11}, 3H), 3.16−3.02 (m, $H_{13,6a}$, 4H), 2.82−2.70 (m, H_{3a}, 1H), 2.57−2.46 (m, $H_{2,6b}$, 2H), 2.28−2.14 (m, H_{3b}, 1H), 1.57 (s, H_8, 3H), 1.19 (s, H_{16}, 9H), 1.14 (s, H_{15}, 9H), 0.22 (s, H_{17}, 9H). ^{13}C{^{1}H} NMR (125 MHz, C_6D_6): δ 170.6 (C), 146.9 (C), 107.7 (CH), 96.8 (CH_2), 95.8 (CH_2), 85.5 (C), 85.0 (C), 82.6 (CH), 74.8 (CH), 74.6 (CH_2), 74.6 (CH), 60.7 (C), 55.0 (CH_3), 54.7 (CH_3), 51.2 (CH_3), 45.7 (CH), 33.2 (CH_2), 31.6 (CH_2), 29.2 (3 × CH_3), 27.6 (3 × CH_3), 23.2 (C), 19.9 (C), 19.5 (CH_3), 0.35 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2996 (m), 2975 (s), 2808 (m), 2691 (m), 2067 (m), 2005 (m), 1400 (s). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{54}NaO_{10}Si_2$ 653.3153; found 653.3100. $[\alpha]_D^{20} = -5.92$ (c = 0.10, CHCl3).

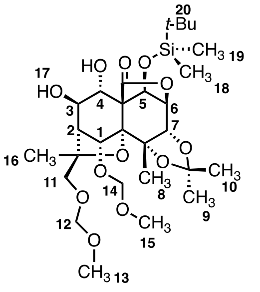
*Synthesis of the Unsaturated Ketone **64**.*



64

A solution of 2-iodoxybenzoic acid (4.3 mg, 15.2 μmol, 1.20 equiv) in dimethyl sulfoxide (150 μL) was prepared and stirred for 30 min at 23 °C before use. A solution of the enoxysilane **70** (8.0 mg, 12.7 μmol, 1 equiv) in dimethyl sulfoxide (150 μL) was then added dropwise via a syringe. The reaction vessel was then placed to an oil bath that had been preheated to 65 °C. The reaction mixture was stirred and heated for 5 h at 65 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (8.0 mL), water (3.0 mL), and saturated aqueous sodium bicarbonate solution (3.0 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 8.0 mL). The organic layers were combined, and the combined organic layers were washed sequentially with water (8.0 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate−hexanes) to provide the unsaturated ketone **64** as a colorless oil (6.4 mg, 91%). NMR spectroscopic data for the unsaturated ketone **64** obtained in this way were in agreement with those previously reported.[14]

*Synthesis of the Diol **83**.*



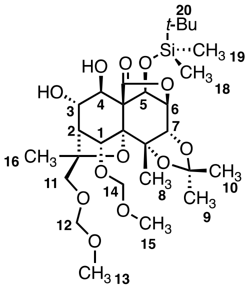
83

Sodium borohydride (2.0 mg, 50.0 μmol, 10.0 equiv) was added in one portion to a solution of the ketone **82** (3.0 mg, 5.00 μmol, 1 equiv) in methanol (500 μL) at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0

mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate−hexanes) to provide the diol **83** as a colorless oil (3.0 mg, 99%). Within the limits of detection, the diol **83** was formed as a single diastereomer (^{1}H NMR analysis, 600 MHz). $^3J_{H4,H3}$ = 0 Hz, supporting the *trans*-diequatorial configuration depicted.

R_f = 0.30 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.22 (s, H_5, 1H), 4.77 (d, J = 6.8 Hz, H_{12a}, 1H), 4.74 (d, J = 4.8 Hz, H_6, 1H), 4.69 (d, J = 6.7 Hz, H_{12b}, 1H), 4.61 (d, J = 6.3 Hz, H_{14a}, 1H), 4.58 (d, J = 6.3 Hz, H_{14b}, 1H), 4.47 (d, J = 1.6 Hz, H_{17}, 1H), 4.35 (s, H_4, 1H), 4.34 (s, H_1, 1H), 4.32 (d, J = 2.9 Hz, H_3, 1H), 4.22 (d, J = 4.8 Hz, H_7, 1H), 4.08 (d, J = 8.8 Hz, H_{11a}, 1H), 3.44 (d, J = 8.7 Hz, H_{11b}, 1H), 3.41 (s, H_{13}, 3H), 3.35 (s, H_{15}, 3H), 2.74 (d, J = 2.9 Hz, H_2, 1H), 1.64 (s, H_{16}, 3H), 1.59 (s, H_8, 3H), 1.58 (s, H_9, 3H), 1.40 (s, H_{10}, 3H), 0.91 (s, H_{20}, 9H), 0.21 (s, H_{18}, 3H), 0.20 (s, H_{19}, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 176.6 (C), 112.3 (C), 96.7 (CH_2), 96.6 (CH_2), 89.2 (C), 85.2 (C), 81.9 (CH), 80.7 (CH), 80.6 (C), 80.3 (CH), 76.5 (CH), 75.3 (CH), 75.0 (CH), 74.4 (CH_2), 63.1 (C), 57.0 (CH_3), 55.4 (CH_3), 49.1 (CH), 26.8 (CH_3), 25.8 (CH_3), 25.8 (3 × CH_3), 25.4 (CH_3), 21.9 (CH_3), 17.8 (C), −4.1 (CH_3), −5.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2975 (s), 2361 (s), 1784 (m), 1412 (s). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{48}NaO_{12}Si$ 627.2813; found 627.2820. $[\alpha]_D^{20}$ = +5.33 (c = 0.03, CHCl3).

*Synthesis of the Diol **86**.*



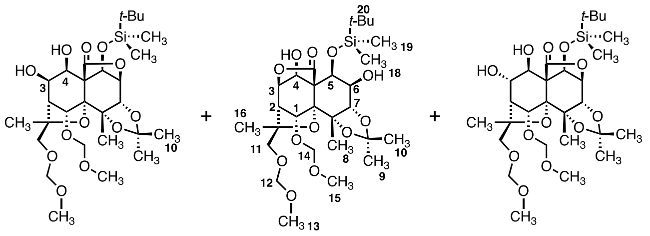
86

Sodium borohydride (1.5 mg, 40.0 μmol, 6.0 equiv) was added in one portion to a solution of the ketone **85** (4.0 mg, 7.00 μmol, 1 equiv) in methanol (500 μL) at 0 °C. The resulting mixture was stirred for 40 min at 0 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate−hexanes) to provide the diol **86** as a colorless oil (3.2 mg, 80%).

Within the limits of detection, the diol **86** was formed as an 8:1 mixture of diastereomers (^{1}H NMR analysis, 500 MHz). The $^3J_{H4,H3}$ = 9.1 Hz supports the *trans*-diaxial configuration depicted.

R_f = 0.20 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (s, H_5, 1H), 4.79 (d, J = 6.8 Hz, H_{14a}, 1H), 4.67 (m, $H_{6,\ 14b}$, 2H), 4.62−4.56 (m, H_{12}, 2H), 4.31 (d, J = 9.1 Hz, H_4, 1H), 4.22−4.19 (m, $H_{3,7}$, 2H), 4.15 (s, H_1, 1H), 4.09 (d, J = 9.0 Hz, H_{11a}, 1H), 3.40 (s, $H_{11b,\ 13}$, 4H), 3.34 (s, H_{15}, 3H), 2.86 (d, J = 3.4 Hz, H_2, 1H), 1.62 (s, H_{16}, 3H), 1.59 (s, H_8, 3H), 1.56 (s, H_{10}, 3H), 1.39 (s, H_9, 3H), 0.95 (s, H_{20}, 9H), 0.21 (s, H_{18}, 3H), 0.19 (s, H_{19}, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.2 (C), 112.5 (C), 96.8 (CH_2), 96.6 (CH_2), 89.9 (C), 86.1 (C), 82.9 (CH), 82.7 (CH), 80.7 (C), 80.0 (CH), 75.9 (CH), 74.3 (CH_2), 74.3 (CH), 71.9 (CH), 61.7 (C), 56.9 (CH_3), 55.4 (CH_3), 46.4 (CH), 26.9 (CH_3), 26.3 (CH_3), 25.8 (3 × CH_3), 25.7 (CH_3), 22.0 (C), 17.9 (C), −4.6 (CH_3), −4.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 3015 (s), 2995 (m), 2975 (s), 2956 (m), 2360 (s), 1785 (m), 1721 (m), 1412 (s). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{48}NaO_{12}Si$ 627.2813; found 627.2822. $[\alpha]_D^{20}$ = −0.20 (c = 0.10, CHCl3).

*Synthesis of Diols **88**, **89**, and **86**.*



88 **89** **86**

Cerium (III) chloride heptahydrate (30.9 mg, 83.0 μmol, 2.50 equiv) was added in one portion to a solution of the α-hydroxy ketone **85** (35.0 mg, 33.0 μmol, 1 equiv) in methanol (660 μL) at 23 °C. The resulting solution was cooled to −78 °C. Sodium borohydride (6.3 mg, 166 μmol, 5.00 equiv) was added in one portion, and the resulting mixture was stirred for 35 min at −78 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 20 min. The warmed biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate−hexanes) to provide the diol **86** as a colorless oil (3.5 mg, 17%). However, during the purification, we observed an incomplete conversion of the *cis*-C8,C9 diol **88** to the corresponding translactonized diol **89**. These two intermediates were nearly co-polar and were chromatographically inseparable. See the Supporting Information for the overlay of the ^{1}H NMR spectroscopic data. We were able to obtain a small amount (1.5 mg) of the translactonized diol **89** in analytically pure form as a colorless oil, and the spectrum is reported bellow. In practice, the product mixture was used in the subsequent steps without purification. The relative stereochemistry of the C3 hydroxyl substituent in **88** was established by the coupling constant $^3J_{H4,H3}$ = 4.6 Hz supporting the C8,C9 configuration depicted. The relative stereochemistry of the C3 hydroxyl substituent in the translactonized diol **89** was also established by the coupling constant $^3J_{H4,H3}$ = 4.9 Hz supporting the C8,C9 configuration depicted.

R_f = 0.25 (33% ethyl acetate−hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.99 (s, H_5, 1H), 4.81−4.76 (m, $H_{1,\ 14a}$, 2H), 4.71 (d, J = 6.6 Hz, H_{14b}, 1H), 4.66 (d, J = 4.7 Hz, H_6, 1H), 4.61 (d, J = 6.4 Hz, H_{12a}, 1H), 4.58 (d, J = 6.4 Hz, H_{12b}, 1H), 4.28 (t, J = 5.0 Hz, H_3, 1H), 4.21 (d, J = 5.0 Hz, $H_{4,\ 7}$, 2H), 4.12 (d, J = 8.9 Hz, H_{11a}, 1H), 3.43 (d, J = 8.8 Hz, H_{11b}, 1H), 3.43 (*s*, H_{13}, 3H), 3.35 (s, H_{15}, 3H), 2.88 (d, J = 4.3 Hz, H_2, 1H), 1.63 (s, H_8, 3H), 1.55 (s, H_9, 3H), 1.42 (s, H_{16}, 3H), 1.39 (s, H_{10}, 3H), 0.94 (s, H_{20}, 9H), 0.19 (s, H_{18}, 3H), 0.18 (s, H_{19}, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 172.9 (C), 112.5 (C), 97.0 (CH_2), 96.7 (CH_2), 88.6 (C), 84.9 (C), 82.6 (CH), 80.7 (C), 80.0 (CH), 79.9

(CH), 75.9 (CH), 74.1 (CH_2), 69.2 (CH), 66.4 (CH), 63.5 (C), 57.2 (CH_3), 55.5 (CH_3), 47.7 (CH), 26.9 (CH_3), 26.3 (CH_3), 25.8 (CH_3), 25.7 (3 × CH_3), 20.5 (CH_3), 17.9 (C), −4.6 (CH_3), −4.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{48}NaO_{12}Si$ 627.2813; found 627.2821. $[\alpha]_D^{20}$ = +5.37 (*c* = 0.12, CHCl3).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02167.

> Complete set of reaction conditions described in Table 3; comparison of ^1H NMR data of synthetic euonyminol (**1**); comparison of ^{13}H NMR data of synthetic and calculated euonyminol (**1**); and DFT calculations and copies of ^1H NMR, ^{13}C NMR, and NOESY spectra (PDF)

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Notes

The authors declare no competing financial interest.

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