Structure and Total Synthesis of Sporol and Neosporol

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Abstract: The complete details of the synthesis of sporol (1) and its formerly assigned structure, neosporol (2), are provided. A highly stereoselective Claisen rearrangement sets the C7-C6 stereochemistry of the trichothecene skeleton. Subsequent functional group manipulation and ring closures led to the pentacyclic structures. The 1H NMR studies that led to the structure reassignment are also discussed.

Owing to their diverse biological activity and unique variety of structures, the trichothecene mycotoxins have proved to be a challenge in organic synthesis. As part of a program to explore stereoselective methods for the synthesis of the trichothecene mycotoxins, we described in 1987 a new Claisen rearrangement approach to the stereoselective formation of the central C7-C6 bond of the trichothecene mycotoxins. Prior to this time, solutions to this problem based upon the Claisen rearrangement had, at best, produced only moderate stereoselectivity.

With a view toward applying this method toward the total synthesis of a recently reported, structurally compact trichothecene, sporol, isolated from Fusarium sporotrichioides, we prepared a partially functionalized model of this substance. The compound obtained upon completion of the total synthesis was in full accord with the proposed structure of the natural product; however, a reinterpretation and repetition of 1H NMR studies on the natural product, and the synthetic material, resulted in a reassignment of the structure of sporol. The reassigned structure for sporol was confirmed by total synthesis. In this paper, we present in more detail our studies, both spectroscopic and synthetic, on sporol (1) and neosporol (2), the original structure assigned to sporol.

Sporol, a 1,3-dioxane, and neosporol, a 1,3-dioxolane, differ only in the size of these heterocyclic rings. Each of these intramolecular acetals bears an oxygen atom attached to a carbon bearing a methine hydrogen. In the case of sporol, the oxygen is attached to C1; in neosporol, the oxygen attachment is to C2. This difference in substitution pattern revealed itself in the NOES observed in the 1H NMR spectrum of each compound.

NMR Analysis

In the case of neosporol, irradiation of the C2-H (δ 4.27, d, J = 3.7 Hz) caused NOE enhancement of the C17-H (δ 3.72) of the methylene group and the C3-exo-H (δ 1.90); the geminate C11-H (δ 4.07) was too close to the irradiated signal for enhancement to be observed. Conversely, irradiation of the C2-exo-H (δ 1.90) caused collapse of the C7-H doublet to a singlet. However, irradiation of the C13 methyl group (δ 0.90) caused enhancement of both of the C10 protons (δ 2.09, 2 H, singlet) and the C18-H (δ 1.78). Irradiation of the C16 methyl group caused enhancement of both C10 protons (δ 2.09, 2 H, singlet) and the C18-H (δ 1.78). Long-range coupling between the C16-H (δ 1.78) and the signal at δ 2.09 (ostensibly only the C10-endo-H through W-coupling) was confirmed through a 2D-COSY experiment. The presence of W-coupling (J = 1.4 Hz) between the C10-endo-H (δ 1.68) and the C18-endo-H (δ 3.91) was confirmed upon irradiation of the former signal.

Finally, either molecular models or, more quantitatively, MM2 calculations (see 2c) revealed that the C15a-H (δ 3.91) is nearly equidistant to the C7-endo-H (δ 1.95, 2.36 Å) and the C7-endo-H (δ 1.70, 2.27 Å). This proximity was revealed by NOE enhancement, 3% and 6%, respectively, of both endo signals upon irradiation of the C15a-H (δ 3.91).

Unlike neosporol, the methine proton of sporol is not proximate to the C14 methyl and C13 hydroxymethyl groups. Thus, irradiation of the C14 methyl group produced NOE enhancement.
of the C13 methylene protons (δ 3.71, 3.84), the C15c-H (δ 3.79, 2.84 Å), and the C7a-H (δ 1.60, 2.43 Å) but not the C1-H methine signal (δ 4.55, 1 H, m). The signal at C5-H (δ 1.60) was correlated with the C7a-H (δ 1.75) in the 2D-COSY spectrum. Indeed, irradiation at δ 1.75 in a homonuclear decoupling experiment removed the W-coupling to the C15a-H, thereby confirming the assignment of the C3a-H and C5a-H.

Irradiation of the proton at δ 4.55 effected NOE enhancement of the unobscured, highly coupled C3a-H (δ 2.21) and C4a-H (δ 2.29) in addition to the partially obscured C3-H (δ 1.47) and C5a-H (δ 1.23), with no enhancement of the C11 methylene group. When the C3-H was irradiated in a homonuclear decoupling experiment, the vicinal coupling of the C2 and C3 endo protons was removed, leaving geminal and W-coupling: C3,-H (δ 2.29, Jgem = 12.4 Hz, JW/4 = 3.6 Hz). Moreover, the partially obscured C3a-H (δ 1.47) and C5a-H (δ 1.23) could also be seen to simplify. Independent irradiation of the C3a-H and C5a-H removed the coupling to their respective geminal protons. The proximity (2.06 Å, see 1c) of the C4a-H (δ 2.29) and the C15c-H (δ 4.30; Jgem = 8.1 Hz, JW/4 = 3.4 Hz) was revealed as an 11% NOE enhancement of the former proton. These coupling patterns were corroborated by a 2D-COSY experiment. These studies demonstrated that the methine proton was flanked by methylene groups that were not coupled to protons attached to contiguous carbons.

Synthesis

The strategy that was employed in the synthesis of sporol and neosporal had three basic components. First, a functionalized Claisen rearrangement would create the correct C3-C6 stereochemistry present in the trichothecene nucleus. Secondly, the respective dioxane and dioxolane rings would be formed by intramolecular acetalization. Finally, introduction of the C16 methyl group and formation of the C6-O bond would complete the pentacyclic framework.

In an earlier study, we were able to demonstrate that the prototypical rearrangement 3a → 4a provided a 6:1 ratio of diastereomers with the major isomer being formed through a chairlike transition state. Moreover, the rearrangement of the allyl silyl ether 3b → 4b had proved to be more selective (16:1). Not surprisingly, C-C bond formation occurred trans to the silyl ether group. To achieve the pentacyclic structure of sporol and neosporal, a more functionalized cyclohexene ring of 3 was required. Thus, the rearrangements 3c → 4c and 3d → 4d were expected to provide the necessary functionality and appropriate stereochemistry to lead to their respective targets.

The preparation of the allyl vinyl ethers 3c and 3d required O-alkylation of the anion of β-keto nitrile 8 with the appropriate allylic electrophile. Functionalized β-keto nitrile 8 (Scheme I) was prepared from hydroxy methane ketone 5 by a modification of Wenkert's formylation of 3-ethoxycyclohex-2-en-1-one13 that employed refluxing ether/NaH as opposed to benzene/NaOEt at room temperature. Traditional isoxazole formation led to a 5:1 ratio of β-keto isoxazole 6 and its structural isomer. Structure 6 was confirmed by fragmentation14 of the isoxazole 7 to provide the β-keto nitrile 8 and its enol form upon acidification. In practice, the enolate was generated directly from the protected isoxazole 7.

Allylic mesylate 13c, which is required for the synthesis of sporol, was prepared by radical cyclization (Scheme II). Swern oxidation15 of alcohol 9 provided crude homoglyceraldehyde acetone, which, upon addition of propargyl zinc bromide,17 afforded a 12.5:1 ratio of acetylenes 10 to allenes. The diastereomeric acetylenes were formed with only modest selectivity (1.6:1). The radical cyclization was based upon the known preference for unstrained-lg cyclic thionocarbonate having the

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Scheme I

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\[
\text{EtOH} \xrightarrow{\mathrm{H_2O}_2\mathrm{HCl}} \text{OH}_2\text{CH}_2\text{OH} \quad \xrightarrow{\text{TsOH}, \mathrm{MeOH}} \quad \text{HOCH}_2\text{CH}_2\text{OH} \quad \xrightarrow{\text{p-TsOH}, \mathrm{CH}_2\text{H}_5} \quad 99%\]
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Scheme II

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\[
\text{HOCH}_2\text{CH}_2\text{OH} \quad \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{C}} \quad \text{OTBDMS} \quad \xrightarrow{\text{TBSOTf, Et}_3\text{N}, \text{DMAP}} \quad \text{OTBDMS} \quad \xrightarrow{\mathrm{MeOH}} \quad \text{NaBH}_4, \text{MeOH} \quad \xrightarrow{\text{Deas-Martin periodinane}} \quad \text{NaBH}_4, \text{MeOH} \quad \xrightarrow{\text{Des-Martin periodinane}} \quad \text{NaBH}_4, \text{MeOH} \quad \xrightarrow{\text{Des-Martin periodinane}} \quad \text{NaBH}_4, \text{MeOH}
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(11) This signal appeared to be a triplet (scale expansion, 500 MHz, ref 7) in the NMR studies conducted on natural sporol. The dihedral angle between the methine proton and each of its four vicinal protons is ~60°, which suggests that the signal may actually be a pentuplet with the outer peaks being of insufficient intensity to detect. The chemical shifts recorded for synthetic sporol (Experimental Section) are 0.01 8 units higher than those that were obtained for the natural material. The lower values are used for the sake of discussion.

(12) This NOE had been observed previously, but it had been misinterpreted.

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substitution pattern of 11 to undergo preferable homolytic cleavage of the secondary C–O bond in the presence of tri-n-butylstannyl radical.\textsuperscript{19} However, unlike the former studies,\textsuperscript{18} no products derived from primary C–O bond fragmentation could be detected in the cyclization of thio carbonate 11.

The use of Swern conditions ([ClCO]$_2$, Et$_3$N, DMSO) for the oxidation of homoallyl alcohol 12a proved troublesome. Although the desired conjugated aldehyde 13a was observed, the presence of methyl (methylthio) aldehydes 14 derived from α-alkylation of aldehyde 12b with the Pummerer intermediate formed from DMSO under the Swern conditions precluded this method of oxidation. The Dess–Martin periodinane proved to be the reagent of choice for this oxidation.\textsuperscript{20} The isomeric allylic mesylates 13c and 15b, the synthesis of which had been described previously,\textsuperscript{21} had to be prepared in situ because of their instability. Methanesulfonyl anhydride was employed rather than methanesulfonyl chloride because the derived mesylates were susceptible to displacement with chloride ion; the allylic chlorides did not function well as electrophiles.

To maximize O-alkylation of the anion of β-keto nitrile 8, the fragmentation of isoxazole was effected with t-BuOK in HMPA; the potassium cation was ligated with 18-crown-6 and added to the solution of the mesylate. Because the mesylates were prepared and employed in situ, excess t-BuOK was utilized to neutralize Et$_3$N$^+$ OTf$^-$ that was formed during the preparation of the mesylates. Products of C-alkylation were not detected.

Rigorous purification of the allyl vinyl ether 3c, silylation of the reaction vessel, and rearrangement in 0.02 M nonane led to a 16:1 ratio of crystalline 4c and a stereoisomer, as determined by integration of the vinyl signals in the $^1$H NMR spectrum.\textsuperscript{21} While the successful synthesis of neosporol ultimately confirmed the stereochemistry of 4c, the chairlike transition state and facial selectivity observed in the rearrangement of the prototype 3b was assumed to apply in this instance. The minor, crystalline stereoisomer was isolated from combined chromatographic fractions of several reactions. Both compounds were independently desilylated (aqueous HF/CH$_3$CN, 0 °C)\textsuperscript{22} and oxidized under Swern conditions to give different enones 18\textsuperscript{23} under the Kishi–Goto conditions\textsuperscript{24} (m-CPBA, CHCl$_3$/CH$_2$Cl$_2$, reflux) that had proved successful with the alcohol derived from silyl ether 4b.\textsuperscript{25} Epoxidation with trifluoroacetic acid, which was prepared from 90% peroxide in the presence of solid Na$_2$CO$_3$ as a buffer, led directly to the dioxolane 19a.

The omission of buffer, or the use of Na$_2$HPO$_4$ as a buffer, led to unidentified products. The methylene protons of the newly formed dioxolane ring appeared as doublets (6 4.13 and 3.65) with $J = 7.6$ Hz, a value characteristic of a methylene group adjacent to oxygen in a five-membered ring.\textsuperscript{26,27} The internal dioxolane ring of 19a served to protect the cyclohexanone carbonyl while the stereochemistry of the hydroxyl group of 19a was inverted to allow formation of the dioxolane ring system of neosporol. The Swern oxidation of 19a afforded cyclopentanone 19b (39% from 18), which was reduced with LiAl(t-BuO)$_3$H from the convex face with stereoselectivity (12:1) to produce endo alcohol 19c (Scheme III).

Internal dioxolane exchange was readily effected with BF$_3$-Et$_2$O at ~78 °C (19c → 21). When the same experiment was performed at 0 °C, a mixture of ketol 21 and ketone 20 was obtained. The acyclic hydroxymethylene protons of ketol 21 (δ 4.12 and 3.71) now displayed 12.5-Hz geminal coupling. Hydrolysis and rearrangement of ketol 19c in 3 N HCl/dioxane at reflux led to the crystalline keto nitrile 20, whose structure was corroborated by single-crystal X-ray analysis. These reaction conditions reflect the robustness of the internal dioxolane. In comparison, when

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(21) Integration of the carbonitrile signals at 157.8 (4c) and 158.9 (16) ppm (pulse width 4 μs and repetition delay of 20 s) showed a 13:1 ratio.
Although an experimental protocol had been established to construct the tetracyclic structure of keto nitrile 20, the transformation of silyl ether 4d to the analogous tetracyclic dioxane was not straightforward (Scheme IV). The desilylation of 4d to give alcohol 24 once again employed aqueous HF/CH3CN albeit buffered with Na2CO3. However, efforts to form the dioxolane 26a using the epoxidation conditions that were successful in the neosporol series led to unfavorable mixtures of triol 25 and dioxolane 26a. The presence of water was deemed to be detrimental in this reaction.

After numerous attempts to optimize the formation of 26a, two satisfactory solutions to the problem were uncovered. Commercially available (Aldrich) urea/hydrogen peroxide complex26 served as a source of anhydrous hydrogen peroxide. When buffered trifluoroper oxyacetic acid was prepared from this reagent and was used as the oxidant, the dioxolane 26a and triol 25 were formed in a 7:2 ratio, from which mixture the dioxalane could be isolated in 45% yield upon chromatography. The methylene protons of the dioxolane ring of 26a displayed 7.1-Hz geminal coupling as opposed to 12.6-Hz coupling in the hydroxymethylene group of uncyclized triol 25. Alternatively, the portionwise addition of excess Ms2O/Et3N to triol 25 led to its transformation into mesylate 26b, which was identical with the mesylate derived from alcohol 26a. The derivatization of the secondary hydroxyl group during the ring closure would prove to be a benefit to future transformations.

The oxidation reduction procedure that proved successful in the neosporol series was unsuitable in the sporol series. All efforts to oxidize alcohol 26a to the cyclopentanone led to further reduction; ostensibly, the strained dioxolane ring suffered β-elimination, which was supported by the appearance of a vinyl signal at δ 6.07, and subsequent oxidation. Treatment of mesylate 26b with potassium superoxide effected inversion of the hydroxyl function.27 The crude alcohol 28 was exposed to catalytic camphorsulfonic acid/CH3Cl2, which accomplished intramolecular conversion of the internal dioxolane ring to the dioxane. Finally, hydrolysis removed the ethylene glycol without affecting the dioxane ring to provide keto nitrile 27. The conversion 26a → 27 was achieved in 32% overall yield. Like its neosporol counterpart 20, the structure of 27 was confirmed by single-crystal X-ray analysis.

The final step in the synthesis of neosporol and sporol was viewed as the formation of the oxabicyclo[2.2.2]octane ring system by acid-catalyzed cyclization of a primary alcohol and a tertiary carbocation. Both keto nitriles 20 and 27 required the conversion of the nitrile into a primary alcohol and the ketone into a tertiary alcohol or methylene olefin. Two pathways presented themselves. First, the progenitor ketals of 20 and 27 would permit initial manipulation of the nitrile with subsequent hydrolysis of the ketal and conversion to the tertiary alcohol. When this route was applied in the neosporol series, the keto diol 23 proved to be inert to the addition of MeLi, MeMgBr, and MeCeC12,28 owing to the presumed enolization of the keto nitrile to the carbonyl group.29 Traditional Wittig olefination as well as the Corey DMSO procedure30 were also unsuccessful. Consequently, initial functionalization of the carbonyl group was chosen as the preferred route.

Keto nitrile 20 also underwent enolization with MeLi, and both enolization and addition with MeMgBr. However, MeCeC12 added to the carbonyl group to give a 5:1 mixture of diols 29a (Scheme V). The neopentyl nitrile functionality of the major diol was reduced with LiAIH4 in refluxing THF to the imine 29b.31 Prolonged exposure to the reduction conditions provided the amine. Reduction of the aldehyde to triol 29c was uneventful. Finally, exposure of the triol to BF3-Et2O in CH2Cl2 at 25 °C afforded neosporol 2. These conditions for cyclization were shown earlier (Scheme III) not to affect the dioxolane nucleus.

The Conia Wittig olefination protocol32 (Scheme VI) proved successful in the conversion of keto nitrile 27 to olefin 30a, which was readily characterized by the appearance of exo-methylene vinyl signals at δ 4.82 and 4.78. Less overall reduction of the nitride

(29) Evidence for the existence of the hemiacetal form of keto diol 23 was evident in the 1H NMR spectrum. The C5 protons of the keto alcohol appeared at δ 3.95 (br s) while the same protons in the hemiacetal resonated at δ 4.92 and 4.42 (d, J = 4.32 and 4.42 Hz). Moreover, the C5 protons δ 2.85 (dd, J = 16.6, 1.5 Hz); δ 2.72 (dd, J = 16.6 Hz) integrated for fewer than the full complement of protons.
Scheme VI

![Image](http://example.com/scheme6.png)

function was observed when Dibal-H was employed rather than LiAlH₄. Camphorsulfonic acid affected ring closure of diol 30c to (4)-sporol, which was shown to be identical with natural material by ¹H NMR, mass spectroscopy, and TLC behavior.

Experimental Section

All reactions were performed in flame-dried glassware under N₂ unless otherwise noted. Et₂O and tetrahydrofuran (THF) were distilled from sodium benzenophenone ketyl under N₂. Hexanes, CH₂Cl₂, Et₂N, diisopropylamine, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethyldisilphenamide (HMPSA) were distilled from CaH₂. Alkylithiums were titrated by the method of Kofron. Workup means drying organic extracts over anhydrous MgSO₄, filtering, and concentrating under reduced pressure. Melting points are uncorrected. Spectra were recorded at 250 MHz unless specified otherwise; ¹³C NMR spectra were obtained in CDCl₃ solution. FTIR spectra were obtained in CHCl₃ solution.

**B-S-Keto Nitriles 4c and 16.** A solution containing bis(trimethylsilyl)-acetamide (BSA)/pentane (1:20) was heated at a gentle reflux for 10 h. The solution was cooled to 25 °C, and the BSA/pentane was discarded. The flask was rinsed four or five times with pentane and then dried in a stream of N₂. Alkyllithiums were titrated by the method of Kofron (1.52 g, 3.75 mmol) and NaN₃ (187 mmol) were added to the flask, and the reaction vessel was purged with N₂. The solution was heated at reflux for 4 h; TLC showed complete consumption of starting material. The mixture was cooled to 25 °C, and the volume was evaporated in vacuo. Flash chromatography (15% EtOAc/hexanes) of the residue afforded 745 mg (49%) of B-keto nitrile 4c. Further elution afforded 190 mg (12%) of a mixture of B-keto nitriles 4c and 16 and dienes. 4c: mp 138-139 °C (Et₂O/pentane); ¹H NMR (CDCl₃): δ 5.32 (d, 1 H, J = 16.6 Hz, exo-methylene), 5.24 (d, 1 H, J = 13.5 Hz, C₂-H₂), 2.36 (dd, 1 H, J = 13.5, 4.3 Hz), 2.22-2.12 (m, 1 H), 2.05-1.90 (m, 4 H), 1.87-1.75 (m, 2 H), 1.60-1.40 (m, 1 H, aromatic), 1.49 (s, 3 H, Si-CH₃), 1.04 (s, 9 H, Si-r-Bu), 1.02 (s, 3 H, Si-CH₃); ¹³C NMR (CDCl₃): δ 196.9, 157.8, 119.0, 107.3, 106.8, 84.9, 77.8, 66.4 (2X), 62.5, 37.6, 35.9, 32.8, 30.5 (2X), 23.6, 18.0, 14.5, -4.5, -5.0; IR 2211, 1735 cm⁻¹. Anal. Calcd for C₂₂H₃₅N₃O₄Si: C, 65.14; H, 8.71. Found: C, 64.99; H, 8.75.

A pure sample of B-keto nitrile 16 was obtained in the following manner. The mixture of ketones 4c and 16 and dienes accumulated from several runs was combined and carefully purified by flash chromatography (15% EtOAc/hexanes) to afford fractions in 16, contaminated with a small amount of dienes (TLC, ¹H NMR). Crystallization from pentane at -78 °C gave pure B-keto nitrile 16: mp 105-107 °C (pentane); ¹H NMR δ 5.20 (2 H, exo-methylene), 4.86 (6 H, 1 H, CH=CH(CH₂)], 4.02-3.90 (4 H, CH₄), 3.23 (d, 1 H, J = 13.2 Hz, C₂-H₂), 2.57 (dd, 1 H, J = 13.2, 2.8 Hz, C₂-H₂), 2.48-2.30 (m, 2 H), 2.10-1.87 (m, 3 H), 1.78-1.66 (m, 1 H), 1.60-1.40 (m, 1 H, aromatic), 1.35 (3 H, Si-CH₃), 0.15 (s, 3 H, Si-CH₃), 0.13 (3 H, Si-CH₃); IR 2233, 1735 cm⁻¹.

**Allylic Alcohol 18.** A solution of silyl ether 18 (455 mg, 1.12 mmol) in CH₂Cl₂ (11 mL) at 0 °C and aqueous 48% HF/CH₃CN (11 mL, 1:20) was stirred for 2 h at 0 °C. The reaction mixture was diluted with brine and extracted with EtOAc. The organic layer was washed with saturated NaHCO₃ and brine and worked up to provide 321 mg (98%) of allylic alcohol 18. ¹H NMR δ 5.85 (d, 1 H, J = 2.6 Hz, exo-methylene), 5.31 (d, 1 H, J = 2.5 Hz, exo-methylene), 4.38 (3 H, 1 H, CH=OH), 4.02-3.90 (4 H, CH₄), 3.21 (d, 1 H, J = 13.5 Hz, C₂-H₂), 2.54 (dd, 1 H, J = 13.5, 2.8 Hz, C₂-H₂), 2.48-2.30 (m, 2 H), 2.10-1.87 (m, 3 H), 1.78-1.66 (m, 1 H), 1.60-1.40 (m, 1 H, aromatic), 1.35 (3 H, Si-CH₃), 0.15 (s, 3 H, Si-CH₃), 0.13 (3 H, Si-CH₃); IR 2233, 1735 cm⁻¹.
Cyclopentanone 19b. Preparation of 0.5 M peroxy trifluoroacetic acid: To a solution of 90% H2O2 (0.2 mL, 7.2 mmol) in CH2Cl2 (12 mL) at 0 °C was added trifluoroacetic anhydride (850 μL, 6.0 mmol, 1.26 g over 2 min. The mixture was stirred at 0 °C for 2 h. To a stirred suspension of anhydrous, powdered Na2CO3 (1.7 g, 16.5 mmol) and CH2Cl2 (11 mL) cooled to 0 °C was added slowly the solution of CF3CO2H in CH2Cl2 (11 mL 5.5 mmol, 0.5 M). After 1 min, a solution of allylic alcohol 18 (321 mg, 1.1 mmol) in CH2Cl2 (22 mL) was added to the stirred suspension. After the suspension had been stirred for 45 min at 0 °C, the reaction mixture was diluted with brine and the excess peracid was decomposed with aqueous 10% Na2SO3. The layers were separated, and the organic layer was washed with brine. The aqueous layer was dried with Na2SO4 and concentrated in vacuo, and the crude product was worked up to provide 337 mg of crude hydroxy ketal 19a, which was oxidized without further purification. A small sample from an independent experiment was purified by flash chromatography (60% EtOAc/hexanes) to give 59 mg (75%) of pure keto 19a, suitable for X-ray analysis.

The mixture was cooled to 25 °C, diluted with brine, and extracted with EtOAc (6 mL) at 25 °C and 3 N HCl (3 mL) was heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, treated cautiously with MeOH (1 mL) and acidified with 5% AcOH. After the mixture had been stirred for 10 h at 25 °C, it was diluted with brine (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated NaHCO3 and brine and worked up to provide crude aldehyde 29b: 1H NMR δ 8.47 (d, 1 H, J = 1.2 Hz, H2–C1), 8.43 (d, 1 H, J = 3.3 Hz, H2–C4), 8.41 (d, 1 H, J = 12.5 Hz, C17–H17), 8.37 (d, 1 H, J = 3.3 Hz, C16–H16), 8.01 (s, 1 H, C11–H11), 7.54 (s, 1 H, C2–H2), 7.49 (s, 1 H, C5–H5), 7.20–7.31 (m, 5 H), 2.20–2.00 (m, 5 H), 1.17–1.08 (m, 3 H, CH3), IR 3610, 3533, 1714 cm−1. To a solution of the crude aldehyde (6.5 mg, 0.023 mmol) in THF (2.3 mL) at 25 °C was added LiAlH4 (9.2 mg, 0.23 mmol), and the reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, and excess LiAlH4 was decomposed by the slow successive addition of HOAc (1 drop), 15% NaOH (1 drop), and HOAc (3 drops). Dilution with CHCl3 and workup gave 4.9 mg of crude triol, which was purified by flash chromatography (80% EtOAc/hexanes) to afford 4.2 mg of triol 29c: 1H NMR δ 4.21 (d, 1 H, J = 3.2 Hz, C2–H2), 4.10 (d, 1 H, J = 12.6 Hz, C17–H17), 4.07 (d, 1 H, J = 12.5 Hz, C11–H11), 3.80–3.62 (m, 3 H, C3–H3, C4–H4, C16–H16), 2.40 (m, 1 H), 2.10–1.85 (m, 3 H), 1.83–1.50 (m, 9 H), 1.29 (s, 3 H, C11–H11), 1.10 (s, 3 H, C11–H11), 1.06 (s, 3 H, C2–H2); IR 3602, 3457 cm−1. HRMS (EI) Caled for C17H26O6: 266.1518. Found: 266.1517.

2.2-Dimethyl-4-(2-hydroxy-4-pentenyl)-1,3-dioxolane (10). To a solution of oxalyl chloride (0.077 mol) in CH2Cl2 (150 mL) at −78 °C was added cautiously and dropwise (addition funnel, gas evolution) a solution of DMSO (0.106 mL, 0.15 mol) in CH2Cl2 (30 mL) over 20 min. The resulting solution was stirred for another 30 min. A solution of 9% HCl in dioxane (0.070 mol) in CH2Cl2 (60 mL) was added over 35 min. After the solution had been stirred at −78 °C for 50 min, Et3N (48.9 mL, 0.35 mol) was added over 15 min. Stirring was continued at −78 °C for 20 min and then at 0–25 °C over 45 min. The resulting yellow slurry was diluted with THF (80 mL), the solution was filtered in vacuo, and the precipitate was washed with THF (80 mL). The combined filtrates were concentrated in vacuo at 25 °C, owing to the sensitive nature of the aldehyde. Repetition of the dilution/filtration/concentration procedure to remove precipitated Et3N·HCl gave the crude aldehyde as a clear yellow liquid. The product was redissolved in THF (100 mL) and used immediately without purification in the next step. A small amount of product from an independent experiment was purified by distillation (Kugelrohr, 100–110 °C, 148 Torr) to obtain analytical data, the 1H NMR spectrum of which was in agreement with literature values. 1H NMR δ 9.81 (s, 1 H, CHO), 4.54 (4H, CH2O), 4.20 (dd, 1 H, J = 8.4, 6.0 Hz, CH2O), 3.59 (dd, 1 H, J = 8.4, 6.7 Hz, CH2O), 2.85 (br dd, 1 H, J = 17.2, 6.6 Hz), 2.66 (br dd, 1 H, J = 17.2, 6.1 Hz), 1.42 (3 H, CH3), 1.37 (3 H, CH3).

To the THF solution of crude aldehyde was added 23.5 mL (80 wt % in toluene; 0.21 mol) of propargyl bromide. The solution was transferred by cannula over 45 min into a stirred suspension of Mg/Hg (11.9 g, 0.18 mol) in THF (30 mL) maintained at 0 °C. The resulting alcoholic solution was stirred at ambient temperature for 3 h, quenched with saturated aqueous NH4Cl, and stirred for 5 min. Water, EtOAc, and sufficient 5% AcOH were added to dissolve the white precipitate, at which time the layers could be separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed successively with 10% NaHCO3 (6 × 10 mL). The combined filtrates were washed with 5% HCl, saturated with brine, and dried over Na2SO4. The solution was followed by chromatography on Florisil (10:1 then 5:1 hexanes/ EtOAc) yielding 10.19 g (79%, 2 steps) of an inseparable mixture of alkenes 10 and allene diastereomers as a colorless oil. GC analysis of the
A solution of the crude triols (9.35 g, 0.05 mol) and p-TsOH·H2O (0.963 g, 5.06 mmol) in absolute MeOH (480 mL) was stirred at 25 °C for 18 h. The solution was treated with dilute HCl, saturated aqueous NaHCO3, and brine. Workup and purification provided the crude deconjugated aldehydes (9.33 g, 64% har). 1H NMR (major diastereomer) δ 4.36 (dt, 1 H, J = 6.4, 6.2 Hz), 2.59 (m, 2 H); 13C NMR (allenes) δ 52.9 (m, 2 H); HRMS (CI) Calcd for C13H27O2Si (M+H)+: 241.1624. Found: 241.1595 (M+H)+.

A solution of the crude aldehydes (5.16 mmol) and DMAP (0.315 g, 2.84 mmol) of periodinane was added in one portion. The mixture was stirred for 60 min, during which a solution of TCI, 4-(2-hydroxy-4-pentynyl)-1,3-dioxolane-2-thione (11b). A solution of alkyl halides (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.

To a solution of alkene 12a (0.394 g, 1.25 mmol) in MeOH (20 mL) was added 12% aq NaOH (20 mL). The solution was stirred at 25 °C for 18 h. The resulting mixture was treated with dioxane (12 mL) and water (12 mL). The organic layer was washed with water, saturated NaCl solution, and brine. Workup and purification provided the crude aldehydes (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.

A solution of the crude aldehyde (5.16 mmol) and DMAP (0.315 g, 2.84 mmol) of MeOH (20 mL) was treated with aq NaOH (20 mL). The solution was stirred at 25 °C for 18 h. The resulting mixture was treated with dioxane (12 mL) and water (12 mL). The organic layer was washed with water, saturated NaCl solution, and brine. Workup and purification provided the crude aldehydes (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.

A solution of the crude aldehyde (5.16 mmol) and DMAP (0.315 g, 2.84 mmol) of MeOH (20 mL) was treated with aq NaOH (20 mL). The solution was stirred at 25 °C for 18 h. The resulting mixture was treated with dioxane (12 mL) and water (12 mL). The organic layer was washed with water, saturated NaCl solution, and brine. Workup and purification provided the crude aldehydes (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.

A solution of the crude aldehyde (5.16 mmol) and DMAP (0.315 g, 2.84 mmol) of MeOH (20 mL) was treated with aq NaOH (20 mL). The solution was stirred at 25 °C for 18 h. The resulting mixture was treated with dioxane (12 mL) and water (12 mL). The organic layer was washed with water, saturated NaCl solution, and brine. Workup and purification provided the crude aldehydes (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.

A solution of the crude aldehyde (5.16 mmol) and DMAP (0.315 g, 2.84 mmol) of MeOH (20 mL) was treated with aq NaOH (20 mL). The solution was stirred at 25 °C for 18 h. The resulting mixture was treated with dioxane (12 mL) and water (12 mL). The organic layer was washed with water, saturated NaCl solution, and brine. Workup and purification provided the crude aldehydes (12b, which were used immediately without purification in the next step: H'NMR (both diastereomers), 9.35 g, 9.35 g (2 H), 13C NMR (H'), 5.06 (m, 2 H). 1H NMR (major diastereomer) δ 1.42 (s, 9 H), 0.07 (s, 6 H); 13C NMR 6133.2, 131.9, 70.9, 65.7, 65.1, 44.2, 43.9 (2X), 43.7, 39.3, 32.2, 25.8 (6X), 18.0 (2X), 4.48 (4X); IR (CCl4) 3264, 1652 cm⁻¹. HRMS (CI) Calcd for C13H26O Si (M+H)+: 273.1781. Found: 272.1784 (M+H)+.
chromatography (1:1 hexanes/EtOAc) recovered 13b (0.276 g, 53% yield) and allyl vinyl ether 34 (0.666 g, 48%). 1H NMR δ 4.64 (d, 1 H, J = 11.4 Hz, OCH3), 4.57 (d, 1 H, J = 11.4 Hz, OCH3), 4.47 (m, 1 H, CHOTBDMS), 3.99 (s, 4 H, ketal), 3.76-3.66 (br s, 4 H, ketal), 3.57 (d, 9 H, CH3), 2.89 (br d, 1 H, J = 16.2 Hz, C10-Hax), 2.58 (br d, 1 H, J = 16.2 Hz, C10-Hax), 2.49 (s, 4 H, ketal), 2.3-2.24 (m, 4 H), 1.74 (m, 2 H), 1.70 (s, 3 H, CH3), 0.89 (s, 9 H), 0.06 (s, 6 H). 13C NMR δ 164.4, 135.7, 128.0, 118.2, 107.0, 85.6, 70.7, 65.6, 64.7 (2X), 48.7, 44.4, 37.7, 30.6, 25.9 (2X), 23.8, 18.2, 14.0, 4.7 (2X); IR (CCl4) 2216, 1645, 1632 cm⁻¹. HRMS (CI) Calcd for C21H24NO5Si (M + H⁺): 406.2415. Found: 406.2414.

β-Keto Nitriles 4d and Diastereomers. A solution of allyl vinyl ether 34 (0.026 g, 0.069 mmol) in distilled anhydrous tert-butyl methyl ether was added dropwise to a solution of 4d (0.021 g, 0.039 mmol), Et3N (0.016 mmol), and thiourea (0.012 mmol) in CH2Cl2 (0.6 mL) at 0°C was added dropwise to a solution of freshly distilled methanesulfonyl anhydride (0.020 g, 0.12 mmol) in CH2Cl2 (0.2 mL). After the solution had been stirred at 0°C for 1.5 h, brine and EtOAc were added and the mixture was allowed to warm to 25°C. The separated aqueous layer was extracted with EtOAc, and the combined extracts were washed successively with 5% HCl, saturated aqueous NaHCO3, and brine. The following work-up was performed without purification in the next step. 26b: 1H NMR (δ 3.59 (m, 1 H, C1r-H), 4.14-3.91 (m, 5 H, ketal + C13-H), 3.56 (d, 1 H, J = 7.2 Hz, C1r-H), 3.03 (s, 3 H, OMs), 2.89 (dd, 1 H, J = 15.0, 7.1 Hz), 2.80 (dd, 1 H, J = 15.7, 6.9 Hz), 2.64 (dd, 1 H, J = 13.5 Hz, C10-Hax), 2.23 (br d, 1 H, J = 13.5 Hz, C10-Hax), 1.25 (s, 3 H, CH3). LRMS (EI) Calcd for C16H22NO5: 291.1471. Found: 291.1473.

In a N2-purged glovebox was added 0.022 g (0.31 mmol) of KO2 to a 15-mL flame-dried flask, followed by 18-crown-6 (0.093 g, 0.35 mmol) and 3-A powdered sieves (0.020 g, 0.5 g/mm). After diastereofacially pure 34 (0.050 g, 0.12 mmol) in CH2Cl2 (0.4 mL) was stirred at 25°C for 7.5 h. After addition of the mesylate. After the solution had been stirred for 50 min, the reaction mixture was diluted with saturated aqueous NaHCO3 followed by the addition of 5 drops of dimethylsulfide. The mixture was stirred for 10 min following addition of EtOAc. The separated aqueous layer was extracted with EtOAc, and the combined extracts were washed with brine and worked up to give crude alcohol 28: 1H NMR (δ 4.51 (m, 1 H, C13-H), 4.12-3.90 (m, 5 H, ketal + C13-H), 3.57 (d, 1 H, J = 7.2 Hz, C1r-H), 2.71 (d, 1 H, J = 13.8 Hz, C10-Hax), 2.60 (br d, 1 H, J = 14.5 Hz), 1.26 (s, 3 H, CH3). Because chromatographic purification indicated partial cyclization, the material was purified without further purification. A solution of the crude alcohol 28 and (1S,2S)-(+)-camphorsulfonic acid (0.005 g, 0.020 mmol) in CH2Cl2 (0.8 mL) was stirred at 25°C in 6.4. After dilution of the solution with 14% aqueous NaHCO3 and EtOAc, the isolated aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine. Workup and flash chromatography (EtOAc) afforded 4.4 mg of the impure keto of 27, which was contaminated with unidentified AB resonance at δ 3.5. This impurity persisted after attempted purification on either silica gel or Florisil. Impure keto of 28: 1H NMR (δ 4.64 (m, 1 H, C13-H), 4.08-3.89 (m, 4 H, ketal), 3.85 (d, 1 H, J = 12.9 Hz, C10-Hax), 3.70 (d, 1 H, J = 12.9 Hz, C10-Hax), 2.85 (br d, 1 H, J = 13.1 Hz, C1r-H), 2.17 (s, 2 H), 2.14 (br d, 1 H, J = 12.0 Hz, C1r-Hax), 1.60 (br d, 1 H, J = 13.1 Hz, C10-Hax), 1.51 (br d, 1 H, J = 12.0 Hz, C10-Hax), 1.35 (s, 3 H, CH3); IR (CHCl3) 3475, 2237 cm⁻¹. HRMS (EI) Calcd for C16H22NO5: 291.1473. Found: 291.1478. The ketal (4.4 mg, 0.014 mmol) in p-dioxane (0.46 mL) and 3 N HCl (0.23 mL) was heated at reflux for 1 h. The solution was cooled to 25°C, diluted with brine, and extracted with EtOAc. The organic extracts were washed with saturated aqueous NaHCO3 and brine. Workup and flash chromatography in (2:1 hexanes/EtOAc) gave 3.4 mg (32% from 26a) of a white solid. Recrystallization from EtOAc/n-hexane afforded crystals suitable for X-ray analysis: 27: mp 137-139°C (hexane/EtOAc); 1H NMR δ 4.69 (m, 1 H, C10-Hax), 3.71 (dd, 1 H, J = 12.6, 5.5 Hz, C10-Hax), 2.87 (br d, 1 H, J = 13.3 Hz, C1r-Hax), 2.81 (m, 2 H), 2.75-2.61 (m, 1 H), 2.49 (br d, 1 H, J = 14.9 Hz), 2.23-2.09 (m, 3 H), 1.82 (br t, 1 H, OH), 1.66 (br d, 1 H, J = 13.3 Hz, C10-Hax), 1.55 (br d, 1 H, J = 12.5 Hz, C10-Hax), 1.39 (s, 3 H, CH3); IR (CHCl3) 3599, 2338, 2175 cm⁻¹. HRMS (EI) Calcd for C16H22NO5: 263.1158. Found: 263.1171. Ketone 27. To a solution of alcohol 26a (0.012 g, 0.039 mmol), DMAP (0.5 mg, 0.0039 mmol), and Et3N (0.016 mmol, 0.12 mmol) in CH2Cl2 (0.6 mL) at 0°C was added dropwise a solution of freshly distilled methanesulfonyl anhydride (0.020 g, 0.12 mmol) in CH2Cl2 (0.2 mL). The reaction mixture was allowed to warm to 25°C. The separated aqueous layer was extracted with EtOAc, and the combined extracts were washed successively with 5% HCl, saturated aqueous NaHCO3, and brine. The following work-up was performed without purification in the next step. 26b: 1H NMR (δ 3.59 (m, 1 H, C1r-H), 4.14-3.91 (m, 5 H, ketal + C13-H), 3.56 (d, 1 H, J = 7.2 Hz, C1r-H), 3.03 (s, 3 H, OMs), 2.89 (dd, 1 H, J = 15.0, 7.1 Hz), 2.80 (dd, 1 H, J = 15.7, 6.9 Hz), 2.64 (dd, 1 H, J = 13.5 Hz, C10-Hax), 2.23 (br d, 1 H, J = 13.5 Hz, C10-Hax), 1.25 (s, 3 H, CH3). LRMS (EI) Calcd for C16H22NO5: 291.1471. Found: 291.1473.
Structure and Total Synthesis of Sporol and Neosporol

\( \text{C}_2\text{-Hc}_{60} \), 1.31 (s, 3 H, CH\_3); 1R (CHCl\_3) 3688, 2242, 1655 cm\(^{-1}\). HRMS (El) Caled for \( \text{C}_{17}\text{H}_{30}\text{NO}_3 \): 261.1366. Found: 261.1383.

Diols 30c. To a solution of olefin 29a (2.4 mg, 0.0092 mmol) in CH\_2Cl\_2 (0.3 mL) at -78 °C was added 0.055 mL (0.055 mmol, 1.0 M) of diisobutylaluminum hydride (DIBALH) in hexane. After the solution was stirred at 25 °C for 40 min, it was diluted with saturated aqueous NH\_4Cl at 0 °C, stirred at 25 °C for 20 min, treated with 5% H\_2SO\_4 (0.5 mL), and diluted with brine. Extraction of the separated aqueous layer with EtOAc followed by washing of the extracts with saturated aqueous NaHCO\_3 and brine and workup afforded crude aldehyde 30b. The product was used immediately without purification in the next step.

\( \text{C}_3\text{-Hc}_{60} \), 1H NMR (partial) \( \delta \) 10.0 (br s, 1 H, CHO), 4.77 (m, 2 H, vinyl), 4.67 (m, 1H, vinyl), 4.59 (m, 1H, C\(_3\)-H), 4.08 (br d, 1 H, J = 11.8 Hz, C\(_1\)-H), 3.79 (dd, 1 H, J = 12.2, 6.0 Hz, C\(_1\)-H), 3.71 (dd, 1 H, J = 12.2, 6.9 Hz, C\(_1\)-H), 2.75 (br d, 1 H, J = 13.0 Hz, C\(_4\)-Hendo), 2.45 (br d, 1 H, J = 14.2 Hz), 2.32-2.22 (m, 3 H), 2.15 (br d, 1 H, J = 11.7 Hz, C\(_2\)-Hendo), 2.05 (br t, 1 H, OH), 1.85 (br t, 1 H, OH), 1.69-1.55 (m, 2 H), 1.49 (br d, 1 H, J = 11.7 Hz, C\(_2\)-Hendo), 1.35 (br d, 1 H, J = 13.0 Hz, C\(_3\)-Hcru), 1.19 (s, 3 H, CH\_3). LRMS (El) Caled for \( \text{C}_{16}\text{H}_{22}\text{O}_4 \): 266. Found: 266. HRMS (El) Caled for \( \text{C}_{16}\text{H}_{22}\text{O}_4 \): 266.1519. Found: 266.1512.

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Supplementary Material Available: Experimental and analytical data for compounds 22a and 23 and X-ray structures and parameters for keto nitriles 4d, 20, and 27 (38 pages). Ordering information is given on any current masthead page.