Structure and Total Synthesis of Sporol and Neosporol

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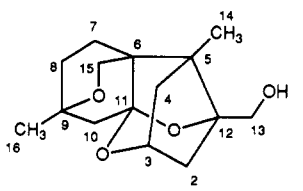
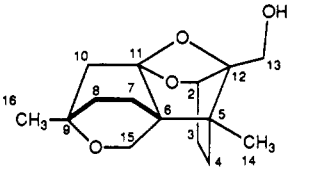
Abstract: The complete details of the synthesis of sporol (**1**) and its formerly assigned structure, neosporol (**2**), are provided. A highly stereoselective Claisen rearrangement sets the C_5–C_6 stereochemistry of the trichothecene skeleton. Subsequent functional group manipulation and ring closures led to the pentacyclic structures. The ^{1}H NMR studies that led to the structure reassignment are also discussed.

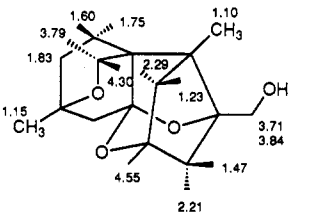
Owing to their diverse biological activity[3] and unique variety of structures, the trichothecene mycotoxins have proved to be a challenge in organic synthesis.[4] As part of a program[5a] to explore stereoselective methods for the synthesis of the trichothecene mycotoxins, we described in 1987 a new Claisen rearrangement approach to the stereoselective formation of the central C_5–C_6 bond of the trichothecene mycotoxins.[5b,6] Prior to this time, solutions to this problem based upon the Claisen rearrangement had, at best, produced only moderate stereoselectivity.

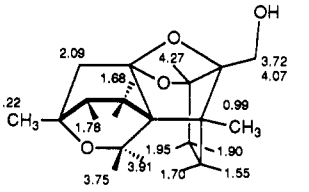
With a view toward applying this method toward the total synthesis of a recently reported, structurally compact trichothecene, sporol,[7] isolated from *Fusarium sporotrichioides*, we prepared a partially functionalized model of this substance. The compound obtained upon completion of the total synthesis was in full accord with the proposed structure of the natural product;[8] however, a reinterpretation and repetition of ^{1}H NMR studies on the natural product, and the synthetic material, resulted in a reassignment of the structure of sporol.[9] The reassigned structure for sporol was confirmed by total synthesis.[10] 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.

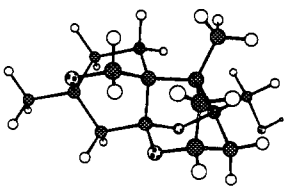
Sporol, a 1,3-dioxane, and neosporol, a 1,3-dioxolane, differ only in the size of these heterocyclic rings. Each of these intramolecular acetals bears an oxygen atom attached to a carbon bearing a methine hydrogen. In the case of sporol, the oxygen is attached to C_3; in neosporol, the oxygen attachment is to C_2. This difference in substitution pattern revealed itself in the NOES observed in the ^{1}H NMR spectrum of each compound.

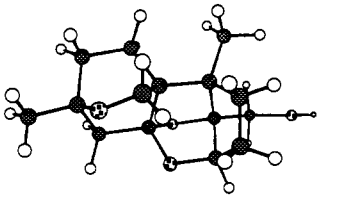












NMR Analysis

In the case of neosporol, irradiation of the C_2–H (δ 4.27, d, J = 3.7 Hz) caused NOE enhancement of the C_{13}–H (δ 3.72) of the methylene group and the C_3–exo-H (δ 1.90); the geminate C_{13}–H (δ 4.07) was too close to the irradiated signal for enhancement to be observed. Conversely, irradiation of the C_3–exo-H (δ 1.90) caused collapse of the C_2–H doublet to a singlet. However, irradiation of the C_{14} methyl group (δ 0.90) caused enhancement of both of the C_{13} protons, the C_4–exo-H (δ 1.55), and the $C_{7\alpha}$–H (δ 1.68, 2.11 Å). Irradiation of the C_{16} methyl group caused enhancement of both C_{10} protons (δ 2.09, 2 H, singlet) and the $C_{8\beta}$–H (δ 1.78). Long-range coupling between the $C_{8\beta}$–H (δ 1.78) and the signal at δ 2.09 (ostensibly only the $C_{10\alpha}$–H through W-coupling) was confirmed through a 2D-COSY experiment. The presence of W-coupling (J = 1.4 Hz) between the $C_{7\alpha}$–H (δ 1.68) and the $C_{15\alpha}$–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 $C_{15\alpha}$–H (δ 3.91) was nearly equidistant to the C_3–endo-H (δ 1.95, 2.36 Å) and the C_4–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 $C_{15\alpha}$–H (δ 3.91).

Unlike neosporol, the methine proton of sporol is not proximate to the C_{14} methyl and C_{13} hydroxymethyl groups. Thus, irradiation of the C_{14} methyl group produced NOE enhancement

(1) Taken in part from the Ph.D. Theses of A.N. (1988) and C.A.M. (1992), Yale University.

(2) X-ray crystallographer, Chemical Instrumentation Center, Yale University.

(3) (a) *Fusarium: Mycotoxins, Taxonomy, and Pathogenicity*; Chelkowski, J., Ed.; Elsevier: New York, 1989. (b) Joffe, A. Z. *Fusarium Species: Their Biology and Toxicology*; Wiley-Interscience: New York, 1986. (c) *Trichothecenes-Chemical Biological and Toxicological Aspects*; Ueno, Y., Ed.; Elsevier: New York, 1983.

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(5) (a) Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* **1990**, *112*, 2749. (b) Ziegler, F. E.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987.

(6) For a highly stereoselective Claisen rearrangement approach to this nucleus, see: Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *30*, 4193. For earlier Claisen routes, see ref 2 of this paper.

(7) Corley, D. G.; Rottinghaus, G. E.; Tempesta, M. S. *Tetrahedron Lett.* **1986**, *27*, 427.

(8) Ziegler, F. E.; Nangia, A.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 1669.

(9) Ziegler, F. E.; Nangia, A.; Tempesta, M. S. *Tetrahedron Lett.* **1988**, *29*, 1665.

(10) Ziegler, F. E.; Metcalf, C. A., III; Schulte, G. *Tetrahedron Lett.* **1992**, *33*, 3117.

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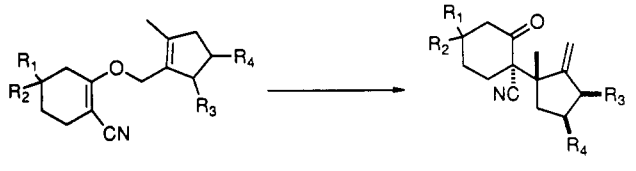
of the C_{13} methylene protons (δ 3.71, 3.84), the $C_{15\alpha}$–H (δ 3.79, 2.84 Å), and the $C_{7\beta}$–H (δ 1.60, 2.43 Å) but not the C_3–H methine signal (δ 4.55, 1 H, m).[11] The signal at $C_{7\beta}$–H (δ 1.60) was correlated with the $C7_\alpha$–H (δ 1.75) in the 2D-COSY spectrum. Indeed, irradiation at δ 1.75 in a homonuclear decoupling experiment removed the W-coupling to the C15α–H, thereby confirming the assignment of the $C_{7\alpha}$–H and $C_{7\beta}$–H.

Irradiation of the proton at δ 4.55 effected NOE enhancement of the unobscured, highly coupled $C_{2\alpha}$–H (δ 2.21) and $C_{4\alpha}$–H (δ 2.29) in addition to the partially obscured $C_{2\beta}$–H (δ 1.47) and $C_{4\beta}$–H (δ 1.23), with no enhancement of the C_{13} methylene group. When the C_3–H was irradiated in a homonuclear decoupling experiment, the vicinal coupling of the C_2 and C_4 endo protons was removed, leaving geminal and W-coupling: $C_{2\alpha}$–H (δ 2.21, J_{gem} = 11.7 Hz, $J_{W(4\alpha)}$ = 3.3 Hz), $C_{4\alpha}$–H (δ 2.29, J_{gem} = 12.4 Hz, $J_{W(2\alpha)}$ = 3.6 Hz). Moreover, the partially obscured $C_{2\beta}$–H (δ 1.47) and $C_{4\beta}$–H (δ 1.23) could also be seen to simplify. Independent irradiation of the $C_{2\beta}$–H and $C_{4\beta}$–H removed the coupling to their respective geminal protons. The proximity (2.06 Å, see **1c**) of the $C_{4\alpha}$–H (δ 2.29) and the $C_{15\beta}$–H (δ 4.30; J_{gem} = 8.1 Hz, $J_{W7\alpha}$ = 3.4 Hz) was revealed as an 11% NOE enhancement of the former proton upon irradiation of the latter.[12] 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 neosporol had three basic components. First, a functionalized Claisen rearrangement would create the correct C_5–C_6 stereochemistry present in the trichothecene nucleus. Secondly, the respective dioxane and dioxolane rings would be formed by intramolecular acetalization. Finally, introduction of the C_{16} methyl group and formation of the C_9–O bond would complete the pentacyclic framework.



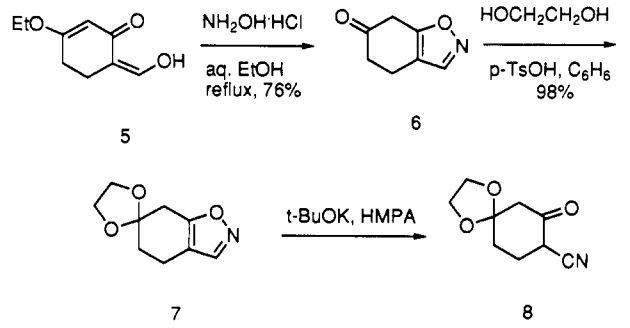
a, R_1=R_2=R_3=R_4=H
b, R_1=R_2=R_4=H, R_3=OTBDMS
c, R_1,R_2=-OCH_2CH_2O-, R_3=OTBDMS, R_4=H
d, R_1,R_2=-OCH_2CH_2O-, R_3=H, R_4=OTBDMS

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.[5b] To achieve the pentacyclic structure of sporol and neosporol, 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.

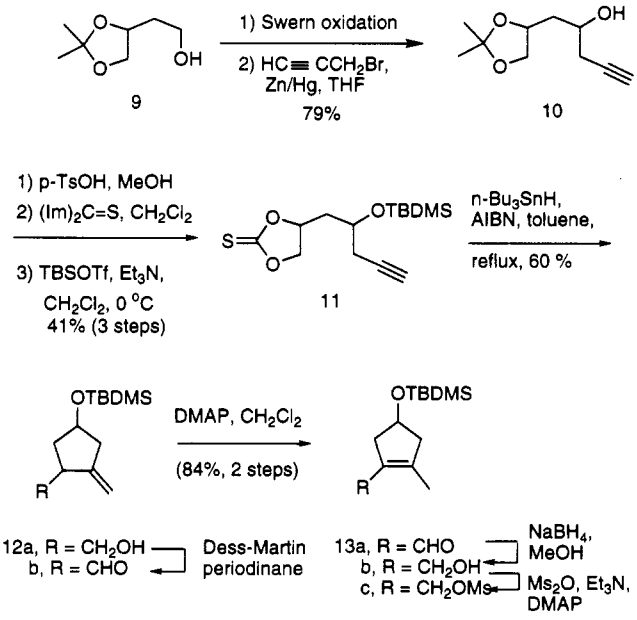
(11) This signal appeared to be a triplet (scale expansion, 500 MHz, ref 7) in the NMR studies conducted on natural sporol. The dihedral angle between the methine proton and each of its four vicinal protons is ~60°, which suggests that the signal may actually be a pentuplet with the outer peaks being of insufficient intensity to detect. The chemical shifts recorded for synthetic sporol (Experimental Section) are 0.01 δ 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.[7]

Scheme I



Scheme II



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 methylene ketone **5** by a modification of Wenkert's formylation of 3-ethoxycyclohex-2-en-1-one[13] 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 fragmentation[14] 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 oxidation[15] of alcohol **9**[16] provided crude homoglyceraldehyde acetonide, 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[18] cyclic thionocarbonates having the

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(14) (a) von Auwers, K.; Bahr, T.; Frese, E. *Justus Liebigs Ann. Chem.* **1925**, *441*, 54. (b) Johnson, W. S.; Shelberg, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 1745.

(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(16) (a) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933. (b) Meyers, A. I.; Lawson, J. R. *Tetrahedron Lett.* **1982**, *23*, 4883. (c) Meyers, A. I.; Lawson, J. R.; Walker, D. G.; Linderman, J. R. *J. Org. Chem.* **1986**, *51*, 5111.

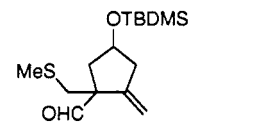
(17) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579.

(18) Ziegler, F. E.; Zheng, Z.-L. *J. Org. Chem.* **1990**, *55*, 1416.

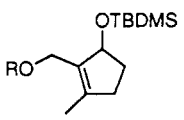
substitution pattern of **11** to undergo preferable homolytic cleavage of the secondary C–O bond in the presence of tri-*n*-butylstannyl radical.[19] However, unlike the former studies,[18] no products derived from primary C–O bond fragmentation could be detected in the cyclization of thiocarbonate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

The use of Swern conditions [$(COCl)_2$, Et_3N, DMSO] for the oxidation of homoallylic 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.[20] The isomeric allylic mesylates **13c** and **15b**, the synthesis of which had been described previously,[5b] 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.

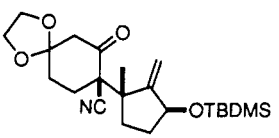
To maximize O-alkylation of the anion of β-keto nitrile **8**, the fragmentation of isoxazole was effected with *t*-BuOK in HMPA; the potassium cation was ligated with 18-crown-6 and added to the solution of the mesylate. Because the mesylates were prepared and employed in situ, excess *t*-BuOK was utilized to neutralize Et_3N^+ OTf^- that was formed during the preparation of the mesylates. Products of C-alkylation were not detected.



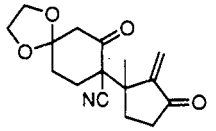
14



15a, R=H
b, R=Ms



16

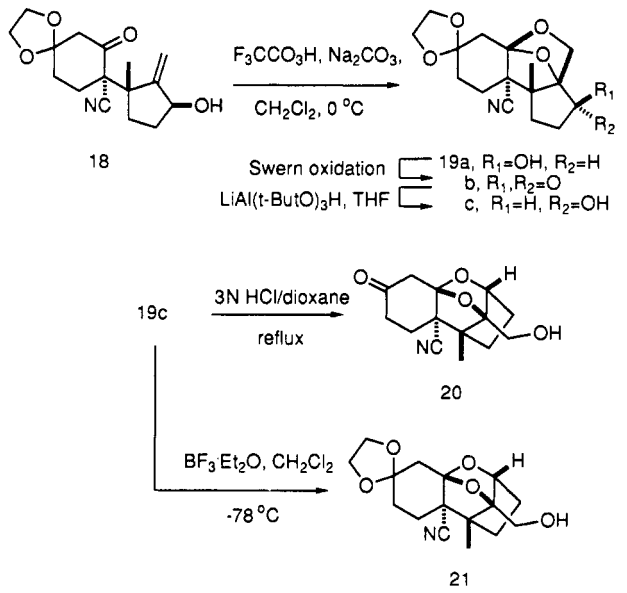


17

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 ^1H NMR spectrum.[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_3CN, 0 °C)[22] and oxidized under Swern conditions to give different enones **17**. This result demonstrated that the stereoisomers differed at the C_5–C_6 juncture and not at the silyloxy center. Accordingly, the minor isomer **16** arises through a boatlike transition state with C–C bond formation most likely occurring trans to the silyloxy group.

Claisen rearrangement of allyl vinyl ether **3d**, which was not plagued by elimination of **4d** presumably because of the nonallylic nature of the silyloxy substituent, did not require silylated glassware. However, a 490-MHz ^1H NMR spectrum of the crude

Scheme III



rearrangement products suggested that as many as four diastereomers (13:2:1:1) had been formed. The major isomer was obtained in 68% yield after chromatography, and its structure was confirmed by single-crystal X-ray analysis. Two of the minor isomers, which had the same molecular ion in their high-resolution mass spectra and similar ^1H NMR spectra, were isolated by chromatography from combined reaction mixtures. Their respective stereochemistries were not assigned.

The next steps in the synthetic plans required the construction of the dioxolane (neosporol) and dioxane (sporol) ring systems. First, the neosporol case is considered. Allylic alcohol **18**, which was readily prepared from **4c** by desilylation with aqueous HF/CH_3CN, was reluctant to undergo a carbonyl epoxide rearrangement[23] under the Kishi–Goto conditions[24] (*m*-CPBA, $ClCH_2CH_2Cl$, reflux) that had proved successful with the alcohol derived from silyl ether **4b**.[5b] Epoxidation with trifluoroperoxyacetic acid, which was prepared from 90% peroxide in the presence of solid Na_2CO_3 as a buffer, led directly to the dioxolane **19a**. The omission of buffer, or the use of Na_2HPO_4 as a buffer, led to unidentifiable products. The methylene protons of the newly formed dioxolane ring appeared as doublets (δ 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.[5b,25] 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 $LiAl(t\text{-}BuO)_3H$ from the convex face with stereoselectivity (12:1) to produce endo alcohol **19c** (Scheme III).

Internal dioxolane exchange was readily effected with $BF_3{\cdot}Et_2O$ at −78 °C (**19c** → **21**). When the same experiment was performed at 0 °C, a mixture of ketal **21** and ketone **20** was obtained. The acyclic hydroxymethylene protons of ketal **21** (δ 4.12 and 3.71) now displayed 12.5-Hz geminal coupling. Hydrolysis and rearrangement of ketal **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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(20) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(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.

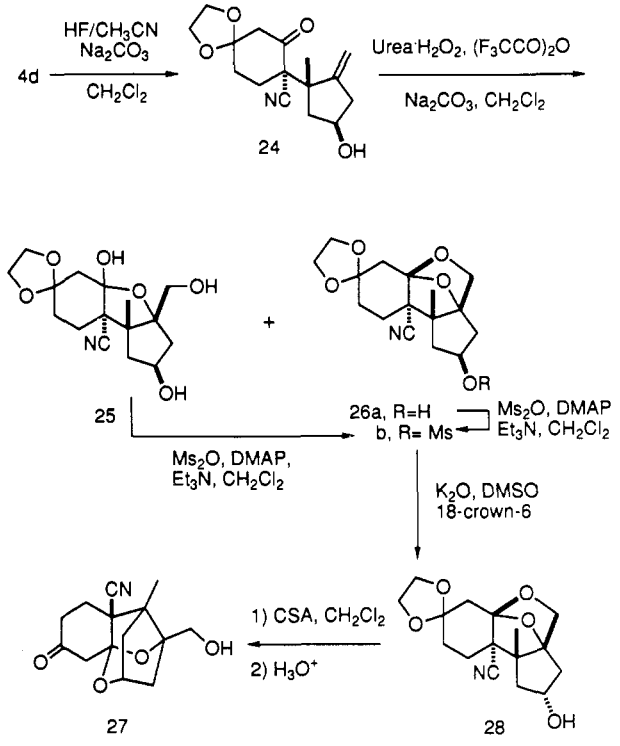
(22) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(23) (a) Demole, E.; Wuest, H. *Helv. Chim. Acta* **1967**, *50*, 1314. (b) Wasserman, H. H.; Barber, E. H. *J. Am. Chem. Soc.* **1969**, *91*, 3674. (c) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267.

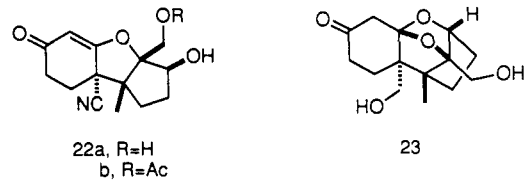
(24) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

(25) Cf. compound **32** in: Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

Scheme IV



the alcohol **19a** was heated in 3 N HCl/HOAc, rupture of the internal dioxolane occurred by β-elimination to give a 2:1 mixture of diol **22a** and its monoacetate **22b**.

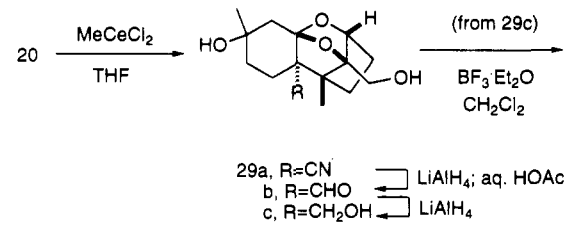


Although an experimental protocol had been established to construct the tetracyclic structure of keto nitrile **20**, the transformation of silyl ether **4d** to the analogous tetracyclic dioxane was not straightforward (Scheme IV). The desilylation of **4d** to give alcohol **24** once again employed aqueous HF/CH_3CN albeit buffered with Na_2CO_3. 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 numerable attempts to optimize the formation of **26a**, two satisfactory solutions to the problem were uncovered. Commercially available (Aldrich) urea/hydrogen peroxide complex[26] served as a source of anhydrous hydrogen peroxide. When buffered trifluoroperoxyacetic 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 dioxolane 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 Ms_2O/Et_3N 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.

(26) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

Scheme V



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 reaction; 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/CH_2Cl_2, 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 $MeCeCl_2$,[28] owing to the presumed enolization or alkoxide addition to the carbonyl group.[29] Traditional Wittig olefination as well as the Corey DMSO procedure[30] 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, $MeCeCl_2$ 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 $LiAlH_4$ in refluxing THF to the imine stage; hydrolysis provided aldehyde **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 $BF_3{\cdot}Et_2O$ in CH_2Cl_2 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 protocol[32] (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 over reduction of the nitrile

(27) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183.

(28) (a) Imamoto, T.; Sugiura, Y.; Yakayama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

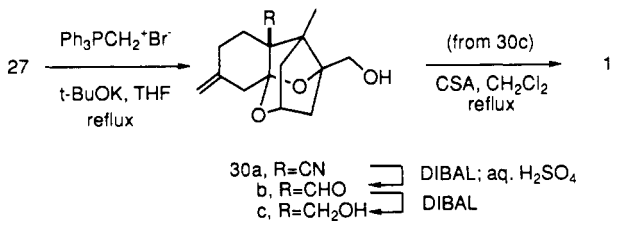
(29) Evidence for the existence of the hemiacetal form of keto diol **23** was evident in the ^1H NMR spectrum. The C_{15} protons of the keto alcohol appeared at δ 3.95 (br s) while the same protons in the hemiacetal resonated at δ 4.32 and 4.22 (d, J_{AB} = 12.5 Hz). Moreover, the C_{10} protons [δ 2.85 (dd, J = 16.6, 1.5 Hz); δ 2.72 (d, J = 16.6 Hz)] integrated for fewer than the full complement of protons.

(30) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(31) Stork, G.; Wakamatsu, S. U. T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945.

(32) Conia, J. M.; Limasset, J. C. *Bull. Soc. Chim. Fr.* **1967**, 1936.

Scheme VI



function was observed when DIBAL was employed rather than $LiAlH_4$. Camphorsulfonic acid effected ring closure of diol **30c** to (±)-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 N_2 unless otherwise noted. Et_2O and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under N_2. Hexanes, CH_2Cl_2, Et_3N, diisopropylamine, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled from CaH_2. Alkyllithiums were titrated by the method of Kofron.[33] Workup means drying organic extracts over anhydrous $MgSO_4$, filtering, and concentrating under reduced pressure. Melting points are uncorrected. Spectra were recorded under the following conditions unless stated otherwise. FTIR spectra were obtained in $CHCl_3$ solution. ^1H NMR spectra were recorded at 250 MHz unless specified otherwise; ^{13}C NMR spectra were recorded at 62.9 MHz. All NMR samples employed $CDCl_3$ (δ 7.27 for ^1H NMR and δ 77.0 for ^{13}C NMR) as an internal standard. GC analysis was performed on a Hewlett-Packard 5890 series II capillary unit with an SPB-5 (Supelco) 30 m × 0.25 mm column.

4,7-Dihydro-1,2-benzisoxazole-6(5*H*)-one (6). To a hexane-washed mechanically stirred suspension of NaH (16.0 g, 0.4 mol, 60%) in Et_2O (750 mL) was added absolute EtOH (2.5 mL). The suspension was heated at a gentle reflux, and a solution of 3-ethoxy-2-cyclohexenone[34] (35.0 g, 0.25 mol) and HCO_2Et (40.0 mL, 0.5 mol, 37.0 g; distilled from CaH_2) in Et_2O (250 mL) was added over 1 h. The initial reaction was somewhat exothermic; heating was carefully monitored to maintain a gentle reflux. After the addition was complete, the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to 25 °C and diluted with cold water (500 mL). After the phases had been stirred for 15 min, the layers were separated and the Et_2O layer was washed with 5% NaOH. The combined alkaline layers were washed with Et_2O and acidified to pH 4 with 15% HCl at 0 °C. The acidified aqueous layer was diluted with H_2O (500 mL) and extracted thoroughly with $CHCl_3$. The organic layer was washed with brine and worked up to provide 40.0 g (95%) of crude material which was a tautomeric mixture of hydroxymethylene ketone **5** (δ 7.20, d, J = 9.0 Hz, hydroxyl vinyl H) and hydroxy enal (<5%) (δ 9.90, s, CHO). The mixture was used in the subsequent reaction without further purification. A small sample was recrystallized from Et_2O/pentane: mp 93–94 °C (lit.[13a] mp 93–93.5 °C, aqueous EtOH).

A solution of crude **5** (39.9 g, 0.238 mol) in 95% EtOH/H_2O (600 mL, 1:1) at 25 °C containing 18.2 g (0.26 mol) of NH_2OH·HCl was heated at reflux for 12 h. The reaction mixture was cooled to 25 °C, diluted with 1 L of cold water, and extracted thoroughly with $CHCl_3$. The organic layer was washed with brine and worked up to provide 35.5 g of crude material. ^1H NMR integration of the aromatic protons of the isoxazoles (δ 8.17 and 8.11) revealed a 5:1 ratio, respectively. Fractional distillation of the crude material (bp 95–100 °C, 0.2 Torr) afforded pure keto isoxazole **6** (24.9 g, 76%): ^1H NMR δ 8.17 (s, 1 H, aromatic), 3.62 (s, 2 H), 2.83 (t, 2 H, J = 6.7 Hz), 2.70 (t, 2 H, J = 6.7 Hz); ^{13}C NMR δ 204.3, 163.5, 148.6, 111.1, 38.0, 37.4, 16.6; IR 1725 cm^{-1}.

Ethylene Glycol Ketal 7. A solution of ketone **6** (24.8 g, 0.18 mol), ethylene glycol (13.6 g, 0.22 mol), and *p*-TsOH·H_2O (3.4 g, 0.018 mol) in benzene (450 mL) was heated at reflux with azeotropic removal of H_2O using a Dean–Stark trap. After 5 h, the mixture was cooled to 25 °C, diluted with Et_2O, and washed with saturated $NaHCO_3$. The aqueous layer was washed with Et_2O, and the combined extracts were washed with brine and worked up to afford 34.0 g of crude ketal. Purification on silica gel (50% EtOAc/hexanes) afforded 32.0 g (98%) of ketal isoxazole **7**: ^1H NMR δ 8.08 (s, 1 H, aromatic), 4.04 (s, 4 H, ketal), 2.95 (s, 2 H), 2.60 (t, 2 H, J = 6.4 Hz), 1.93 (t, 2 H, J = 6.4 Hz); ^{13}C NMR δ 165.3, 148.8, 110.9, 108.3, 64.6 (2×), 33.7, 31.7, 16.5. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 59.52; H, 6.16.

Allyl Vinyl Ether 3c. To a solution of ketal isoxazole **7** (2.17 g, 12.0 mmol) in HMPA (24 mL) at 10 °C was added *t*-BuOK (2.70 g, 24.0 mmol) in small portions. After 1 h, 18-crown-6 (4.23 g, 16.0 mmol) was added and the reaction mixture was stirred for another 1 h. Meanwhile, a solution of allylic alcohol **15a** (1.93 g, 8.0 mmol), Et_3N (1.67 mL, 12.0 mmol, 1.21 g), and 4-(dimethylamino)pyridine (98 mg, 0.8 mmol) in THF (24 mL) was cooled to −25 °C. Methanesulfonic anhydride (1.81 g, 10.4 mmol; sublimed at 95–100 °C, 0.5 Torr) was added over 10 min. After the solution had been stirred for another 15 min at −20 °C, the potassium enolate of **8** was added over 10 min via a pipet. The mixture was stirred at 0 °C for 3 h and then acidified to pH 4 with 5% HCl. Dilution with brine, extraction with Et_2O, and workup gave 9.8 g of crude material. Purification on silica gel (15% EtOAc/hexanes) provided 1.52 g (47%) of vinyl ether **3c**. The vinyl ether was preceded by a higher R_f unidentifiable impurity which, when present, was associated with the formation of dienic byproducts in the subsequent Claisen rearrangement: R_f 0.21 (20% EtOAc/hexanes); mp 58–59 °C (Et_2O/pentane); ^1H NMR δ 4.98 (br d, J = 6.5 Hz, 1 H, CH–OTBDMS), 4.66 (d, 1 H, J = 10.7 Hz, O–CH_2), 4.56 (d, 1 H, J = 10.7 Hz, O–CH_2), 3.99 (s, 4 H, ketal), 2.53 (s, 2 H), 2.47–2.36 (m, 3 H), 2.33–2.18 (m, 2 H), 1.78 (s, 3 H, vinyl CH_3), 1.78–1.60 (m, 3 H), 0.91 (s, 9 H, Si–*t*-Bu), 0.12 (s, 3 H, Si–CH_3), 0.11 (s, 3 H, Si–CH_3); ^{13}C NMR δ 164.2, 142.1, 132.6, 118.2, 106.8, 84.9, 77.8, 64.6 (2×), 62.5, 37.6, 35.9, 32.8, 30.5, 25.8 (3×), 23.6, 18.0, 14.5, −4.5, −5.0; IR 2211, 1641 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_4Si$: C, 65.14; H, 8.70. Found: C, 65.02; H, 8.75.

β-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 N_2. Allyl vinyl ether **3c** (1.52 g, 3.75 mmol) and *n*-nonane (187 mL) were added to the flask, and the reaction vessel was purged with N_2. The solution was heated at reflux for 4 h; TLC showed complete consumption of starting material. The flask was cooled to 25 °C, and the solvent was evaporated in vacuo. Flash chromatography (15% EtOAc/hexanes) of the residue afforded 745 mg (49%) of β-keto nitrile **4c**. Further elution afforded 190 mg (12%) of a mixture of β-keto nitriles **4c** and **16** and dienes. **4c**: mp 138–139 °C (Et_2O/pentane); ^1H NMR δ 5.32 (d, 1 H, J = 2.4 Hz, exo-methylene), 5.24 (d, 1 H, J = 2.2 Hz, exo-methylene), 4.30 (m, 1 H, CH–OTBDMS), 4.05–3.91 (m, 4 H, ketal), 3.22 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.58 (dd, 1 H, J = 13.5, 2.7 Hz, C_{10}–H_{eq}), 2.38 (td, 1 H, J = 13.3, 4.3 Hz), 2.22–2.12 (m, 1 H), 2.05–1.89 (m, 4 H), 1.49 (s, 3 H, CH_3), 1.60–1.40 (m, 2 H), 0.93 (s, 9 H, Si–*t*-Bu), 0.12 (s, 3 H, Si–CH_3), 0.10 (s, 3 H, Si–CH_3); ^{13}C NMR δ 196.9, 157.8, 119.0, 109.3, 108.7, 76.4, 65.0, 64.7, 57.7, 50.2, 45.3, 32.4, 32.1, 31.5, 27.7, 26.7, 25.9 (3×), 18.2, −4.6, −4.8; IR 2233, 1735, 1656 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_4Si$: C, 65.14; H, 8.70. Found: C, 64.99; H, 8.75.

A pure sample of β-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 β-keto nitrile **16**: mp 105–107 °C (pentane); ^1H NMR δ 5.20 (m, 2 H, exo-methylenes), 4.86 (m, 1 H, CH–OTBDMS), 4.02–3.90 (m, 4 H, ketal), 3.23 (d, 1 H, J = 13.2 Hz, C_{10}–H_{ax}), 2.57 (dd, 1 H, J = 13.2, 2.8 Hz, C_{10}–H_{eq}), 2.48–2.30 (m, 2 H), 2.10–1.87 (m, 3 H), 1.77–1.66 (m, 1 H), 1.60–1.40 (m, 2 H), 1.30 (s, 3 H, CH_3), 0.94 (s, 9 H, Si–*t*-Bu), 0.15 (s, 3 H, Si–CH_3), 0.13 (s, 3 H, Si–CH_3); IR 2230, 1736 cm^{-1}.

Allylic Alcohol 18. A solution of silyl ether **4c** (455 mg, 1.12 mmol) in CH_3CN (11 mL) at 0 °C and aqueous 48% HF/CH_3CN (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 $NaHCO_3$ and brine and worked up to provide 321 mg (98%) of allylic alcohol **18**: ^1H NMR δ 5.38 (d, 1 H, J = 2.6 Hz, exo-methylene), 5.31 (d, 1 H, J = 2.5 Hz, exo-methylene), 4.38 (m, 1 H, C*H*–OH), 4.02–3.90 (m, 4 H, ketal), 3.21 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.58 (dd, 1 H, J = 13.5, 2.8 Hz, C_{10}–H_{eq}), 2.36 (td, 1 H, J = 14.6, 2.8 Hz), 2.26–2.06 (m, 2 H), 2.03–1.90 (m, 4 H), 1.49 (s, 3 H, CH_3), 1.67–1.36 (m, 2 H); D_2O exchange δ 2.03–1.90 (m, 4 H) → δ 2.03–1.90 (m, 3 H, OH); ^{13}C NMR δ 196.8, 158.5, 118.8, 109.0, 108.6, 75.8, 64.9, 64.6, 57.6, 50.1, 45.8, 32.2, 32.1, 31.5, 27.5, 26.6; IR 3588, 3447, 2233, 1738, 1655 cm^{-1}.

(33) Kofron, W. C.; Blaclawski, M. *J. Org. Chem.* **1976**, *41*, 1879.
(34) Gannon, W. F.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 539.

Cyclopentanone 19b. Preparation of 0.5 M peroxytrifluoroacetic acid: To a solution of 90% H_2O_2 (0.2 mL, 7.2 mmol) in CH_2Cl_2 (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 Na_2CO_3 (1.75 g, 16.5 mmol) and CH_2Cl_2 (11 mL) cooled to 0 °C was added slowly the solution of CF_3CO_3H in CH_2Cl_2 (11 mL, 5.5 mmol, 0.5 M). After 1 min, a solution of allylic alcohol **18** (321 mg, 1.1 mmol) in CH_2Cl_2 (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% Na_2SO_3. The layers were separated, and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc and washed with brine. The combined organic layers were 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 to obtain analytical data: ^{1}H NMR δ 4.60 (br s, 1 H, C*H*–OH), 4.13 (d, 1 H, J = 7.6 Hz, O–CH_2), 4.12–3.90 (m, 4 H, ketal), 3.65 (d, 1 H, J = 7.6 Hz, O–CH_2), 2.65 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.52–2.30 (m, 2 H), 2.24 (dd, 1 H, J = 13.5, 2.0 Hz, C_{10}–H_{eq}), 2.20–2.00 (m, 2 H), 2.00–1.70 (m, 5 H), 1.27 (s, 3 H, CH_3); D_2O exchange δ 2.00–1.70 (m, 5 H) → δ 2.00–1.70 (m, 4 H, OH); ^{13}C NMR δ 120.1, 108.6, 108.2, 101.3, 72.3, 67.3, 65.1, 64.2, 58.9, 50.1, 37.9, 37.0, 35.5, 33.1, 23.8, 20.1; IR 3616, 3447, 2235, 1733 cm^{-1}.

To a solution of oxalyl chloride (144 mL, 1.65 mmol, 210 mg) in CH_2Cl_2 (2 mL) at −78 °C was added DMSO (233 mL, 3.3 mmol, 257 mg) in CH_2Cl_2 (2 mL). After 15 min, a solution of crude hydroxy ketal **19a** (337 mg) in CH_2Cl_2 (7 mL) was added. After the solution had been stirred at −78 °C for 15 min, the mixture was briefly warmed to −30 °C (1 min). The reaction mixture was recooled to −78 °C and treated with Et_3N (920 μL, 6.6 mmol, 668 mg) and then warmed to 25 °C over 30 min. Dilution with brine, extraction with EtOAc, and workup afforded 276 mg of crude material, which was purified by flash chromatography (80% EtOAc/hexanes) to provide 131 mg (39%) of cyclopentanone **19b**: mp 200–202 °C ($CHCl_3$/hexanes); ^{1}H NMR δ 4.14–3.90 (m, 5 H, ketal + O–CH_2), 3.71 (d, 1 H, J = 7.4 Hz, O–CH_2), 2.88–2.56 (m, 4 H), 2.30 (dd, 1 H, J = 13.5, 2.0 Hz, C_{10}–H_{eq}), 2.26–2.10 (m, 2 H), 2.10–1.96 (m, 2 H), 1.93–1.87 (m, 1 H), 1.23 (s, 3 H, CH_3); ^{13}C NMR δ 206.5, 119.6, 111.1, 107.8, 93.0, 65.5, 65.0, 64.1, 58.8, 48.8, 38.6, 37.4, 34.0, 33.1, 24.1, 16.8; IR 2235, 1754 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1260.

Keto Nitrile 20. A solution of alcohol **19c** (92 mg, 0.3 mmol) in dioxane (6 mL) at 25 °C and 3 N HCl (3 mL) was heated at reflux for 2 h. The mixture was cooled to 25 °C, diluted with brine, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, and worked up to provide 75 mg of crude keto nitrile. Flash chromatography (60% EtOAc/hexanes) gave 59 mg (75%) of pure keto nitrile. Recrystallization from EtOAc/hexanes at 25 °C afforded crystals suitable for X-ray analysis. **20**: mp 155–156 °C (EtOAc/hexanes); ^{1}H NMR δ 4.31 (d, 1 H, 4.2 Hz, C_2–H), 4.04 (dd, 1 H, J = 12.5, 3.4 Hz, C_{13}–H_2OH), 3.76 (dd, 1 H, J = 12.5, 7.5 Hz, C_{13}–H_2OH), 3.03 (d, 1 H, J = 16.7 Hz, C_{10}–H_2), 2.94 (d, 1 H, J = 16.7 Hz, C_{10}–H_2), 2.80–2.62 (td, 1 H, J = 14.8, 5.0 Hz), 2.64–2.46 (m, 2 H), 2.30–2.14 (m, 1 H), 2.14–1.75 (m, 5 H), 1.17 (s, 3 H, CH_3); D_2O exchange δ 4.04 (dd, 1 H, J = 12.5, 3.4 Hz) → δ 4.04 (d, 1 H, J = 12.5 Hz, CH_2OH), δ 3.76 (dd, 1 H, J = 12.5, 7.5 Hz) → δ 3.76 (d, 1 H, J = 12.5 Hz, CH_2OH), δ 2.14–1.75 (m, 5 H) → δ 2.14–1.55 (m, 4 H, OH); ^{13}C NMR δ 203.4, 118.9, 107.0, 97.5, 82.1, 58.0, 56.7, 52.6, 42.7, 37.6, 35.6, 28.3, 26.4, 16.5; IR 3605, 3437, 2236, 1729 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1170.

Dihydroxy Nitrile 29a. A suspension of anhydrous $CeCl_3$ (218 mg, 0.88 mmol; Alfa) in THF (2.9 mL) was stirred at 0 °C for 2 h, cooled to −78 °C, and treated with CH_3Li (572 μL, 0.8 mmol, 1.4 M in Et_2O; Aldrich). After 30 min at −78 °C, a solution of keto nitrile **20** (21 mg, 0.08 mmol) in THF (1 mL) was added and the reaction mixture was allowed to warm to 0 °C over 30 min. The mixture was stirred at 0–10 °C for 3 h and then quenched at 0 °C by the slow addition of excess saturated $NaHCO_3$. Dilution with H_2O, extraction with EtOAc, brine wash, and workup afforded 17 mg of crude material. Flash chromatography (EtOAc) afforded 2 mg (10%) of the minor diol, followed by 10 mg (48%) of the major diol. **29a** (major): R_f 0.25 (EtOAc); ^{1}H NMR δ 4.25 (d, 1 H, J = 4.3 Hz, C_2–H), 4.08 (d, 1 H, J = 12.6 Hz, C_{13}–H_2OH), 3.73 (d, 1 H, J = 12.6 Hz, C_{13}–H_2OH), 2.50 (ddd, 1 H, J = 13.0, 8.3, 4.0 Hz), 2.23–1.70 (m, 11 H), 1.34 (s, 3 H, C_{16}–H_3), 1.16 (s, 3 H, C_{14}–H_3); IR 3594, 3422, 2973, 2949, 2880, 2239, 1785, 1464, 1396, 1030 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{21}NO_4$: 279.1471. Found: 279.1477. **28a** (minor) R_f 0.45 (EtOAc); ^{1}H NMR (partial) δ 4.24 (d, 1 H, J = 4.3 Hz, C_2–H), 4.05 (d, 1 H, J = 12.5 Hz, C_{13}–H_2OH), 3.74 (d, 1 H, J = 12.5 Hz, C_{13}–H_2OH), 1.38 (s, 3 H, C_{16}–H_3), 1.11 (s, 3 H, C_{14}–H_3).

Triol 29c. To a solution of the major dihydroxy nitrile **29a** (7 mg, 0.025 mmol) in THF (5.0 mL) at 25 °C was added $LiAlH_4$ (20 mg, 0.50 mmol), and the mixture was heated at reflux for 6 h. The 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 $NaHCO_3$ and brine and worked up to provide crude aldehyde **29b**: ^{1}H NMR δ 9.84 (d, J = 1.2 Hz, 1 H, CHO), 4.36 (d, 1 H, J = 3.3 Hz, C_2–H), 4.10 (d, 1 H, J = 12.5 Hz, C_{13}–H_2OH), 3.73 (d, 1 H, J = 12.5 Hz, C_{13}–H_2OH), 2.22 (dd, 1 H, J = 15.0, 2.5 Hz, C_{10}–H_{eq}), 2.05–1.50 (m, 11 H), 1.25 (s, 3 H, C_{16}–H_3), 1.10 (s, 3 H, C_{14}–H_3); IR 3567, 3413, 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 $LiAlH_4$ (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 $LiAlH_4$ was decomposed by the slow successive addition of H_2O (1 drop), 15% NaOH (1 drop), and H_2O (3 drops). Dilution with $CHCl_3$ 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**: ^{1}H NMR δ 4.21 (d, 1 H, J = 3.2 Hz, C_2–H), 4.10 (d, 1 H, J = 12.6 Hz, C_{13}–H_2OH), 3.80–3.62 (m, 3 H, C_{13}–H_2OH + C_{15}–H_2OH), 2.40 (m, 1 H), 2.10–1.85 (m, 3 H), 1.83–1.50 (m, 9 H), 1.29 (s, 3 H, C_{16}–H_3), 1.10 (s, 3 H, C_{14}–H_3); IR 3610, 3533, 3442 cm^{-1}.

Neosporol 2. To a solution of triol **29c** (4.2 mg, 0.015 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added BF_3·Et_2O (18 μL, 0.15 mmol, 21 mg); the solution was stirred for 30 min and then for 6 h at 25 °C. The reaction mixture was neutralized with saturated $NaHCO_3$, diluted with brine, and extracted with EtOAc. The organic layer was washed with brine and worked up to provide 2.5 mg of crude material. Flash chromatography (50% EtOAc/hexanes) afforded 2.0 mg of neosporol **2**: ^{1}H NMR δ 4.27 (d, 1 H, J = 3.7 Hz, C_2–H), 4.07 (d, 1 H, J = 12.4 Hz, C_{13}–H_2O), 3.91 (dd, 1 H, J = 8.1, 1.4 Hz, C_{15}–H_2O), 3.75 (d, 1 H, J = 8.1 Hz, C_{15}–H_2O), 3.72 (d, 1 H, J = 12.4 Hz, C_{13}–H_2O), 2.09 (s, 2 H, C_{10}–H_2), 2.00–1.85 (m, 2 H), 1.85–1.45 (m, 7 H), 1.21 (s, 3 H, C_{16}–H_3), 0.99 (s, 3 H, C_{14}–H_3); IR 3602, 3457 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1517.

2,2-Dimethyl-4-(2-hydroxy-4-pentynyl)-1,3-dioxolane (10). To a solution of oxalyl chloride (6.74 mL, 0.077 mol) in CH_2Cl_2 (150 mL) at −78 °C was added cautiously and dropwise (addition funnel, gas evolution) a solution of DMSO (10.96 mL, 0.15 mol) in CH_2Cl_2 (30 mL) over 20 min. The resulting solution was stirred for 3 min. A solution of alcohol **9** (10.26 g, 0.070 mol) in CH_2Cl_2 (60 mL) was added over 35 min. After the solution had been stirred at −78 °C for 50 min, Et_3N (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 Et_3N·HCl gave the crude aldehyde as a clear yellow liquid. The product was redissolved in THF (100 mL) and was 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 ^{1}H NMR of which was in agreement with literature values:[16a] ^{1}H NMR δ 9.81 (m, 1 H, CHO), 4.54 (m, 1 H, CHO), 4.20 (dd, 1 H, J = 8.4, 6.0 Hz, CH_2O), 3.59 (dd, 1 H, J = 8.4, 6.7 Hz, CH_2O), 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 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3).

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 Zn/Hg (11.94 g, 0.18 mol) in dry THF (30 mL) maintained at 0 °C. The resulting dark-green solution was stirred at ambient temperature for 3 h, quenched with saturated aqueous NH_4Cl, and stirred for 5 min. Water, Et_2O, 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 Et_2O, and the combined organic layers were washed successively with 5% HCl, saturated aqueous $NaHCO_3$, H_2O, and brine. Workup followed by chromatography on Florisil (10:1 then 5:1 hexanes/EtOAc) yielded 10.19 g (79%, 2 steps) of an inseparable mixture of alkynes **10** and allenic diastereomers as a clear colorless oil. GC analysis of the

mixture revealed 12.5:1 (1.6:1 (alkynes), 1.6:1 (allenes)) alkyne/allene ratios for the purified products: ^{1}H NMR (major diastereomer) δ 4.36 (m, 1 H, CHO),[35] 4.11 (dd, 1 H, J = 8.1, 6.1 Hz, CH_2O), 4.03 (m, 1 H, CHOH), 3.60 (app t, 1 H, J = 8.1, 6.5 Hz, CH_2O), 2.60 (br d, 1 H, J = 4.9 Hz, OH), 2.44 (m, 2 H, propargyl), 2.06 (t, 1 H, J = 2.6 Hz, alkyne), 1.82 (t, 2 H, J = 6.0 Hz), 1.42 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3); ^{1}H NMR (minor diastereomer) δ 4.30 (m, 1 H, CHO), 4.12 (dd, 1 H, J = 8.1, 5.9 Hz, CH_2O), 4.00 (m, 1 H, CHOH), 3.60 (app t, 1 H, J = 7.6 Hz, CH_2O), 3.28 (d, 1 H, J = 2.0 Hz, OH), 2.47 (ddd, 1 H, J = 16.9, 5.6, 2.7 Hz, propargyl), 2.39 (ddd, 1 H, J = 16.9, 6.8, 2.7 Hz, propargyl), 2.05 (t, 1 H, J = 2.7 Hz, alkyne), 1.94 (dt, 1 H, J = 14.2, 3.2 Hz), 1.73 (dt, 1 H, J = 14.2, 9.4 Hz), 1.44 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3); ^{1}H NMR (allenes, partial) δ 5.29 (m, 1 H), 4.88 (m, 2 H); IR (CCl_4; alkynes + allenes) 3535, 3312, 2121, 1958 cm^{-1}. HRMS (CI, alkynes + allenes) Calcd for $C_{10}H_{17}O_3$ $(M + H)^+$: 185.1178. Found: 185.1184.

4-(2-Hydroxy-4-pentynyl)-1,3-dioxolane-2-thione. A solution of alkynes **10** (9.33 g, 0.051 mol) and *p*-TsOH·H_2O (0.963 g, 5.06 mmol) in absolute MeOH (480 mL) was stirred at 25 °C for 18 h. The solution was treated with H_2O (20 mL), and stirring was continued for 11.5 h. Solid $NaHCO_3$ was added, and the MeOH was evaporated. The residue was diluted with EtOAc and brine, and separated. The brine layer was subjected to continuous extraction with EtOAc for 2.5 days. The combined organic fractions were dried over $MgSO_4$ and concentrated to yield crude, diastereomeric 6-heptyn-1,2,4-triols. This material was suitable for the subsequent reactions: IR (alkynes + allenes) 3587, 3430, 3308, 2124, 1950 cm^{-1}. HRMS (CI) Calcd for $C_7H_{13}O_3$ $(M + H)^+$: 145.0865. Found: 145.0878.

A solution of the crude triols, 1,1′-thiocarbonyldiimidazole (9.35 g, 0.052 mol), and 4-(dimethylamino)pyridine (DMAP, 0.619 g, 5.06 mmol) in CH_2Cl_2 (500 mL) was stirred at 25 °C for 16 h followed by heating at reflux for 6.5 h. The solution was cooled, concentrated, and diluted with Et_2O and H_2O. The separated aqueous layer was extracted with Et_2O; the organic layers were combined and washed successively with dilute HCl, saturated aqueous $NaHCO_3$, and brine. Workup and purification on Florisil (2:1 hexanes/EtOAc) afforded 4.21 g (45%, 2 steps) of the dioxolanethiones as a clear oil: ^{1}H NMR (major diastereomer) δ 5.17 (m, 1 H, CHO), 4.80 (br t, 1 H, J = 8.5 Hz, CH_2O), 4.37 (br t, 1 H, J = 8.5 Hz, CH_2O), 4.05 (m, 1 H, CHOH), 2.50 (ddd, 1 H, J = 16.8, 4.9, 2.6 Hz, propargyl CH_2), 2.40 (ddd, 1 H, J = 16.8, 6.6, 2.6 Hz, propargyl CH_2), 2.21 (br d, 1 H, J = 7.0 Hz, OH), 2.15 (m, 1 H), 2.13 (t, 1 H, J = 2.6 Hz, alkyne), 1.93 (ddd, 1 H, J = 14.2, 10.5, 5.7 Hz); ^{1}H NMR (minor diastereomer) δ 5.18 (m, 1 H, CHO), 4.77 (br t, 1 H, J = 8.3 Hz, CH_2O), 4.50 (br t, 1 H, J = 8.3 Hz, CH_2O), 4.05 (m, 1 H, CHOH), 2.56–1.87 (m, 6 H); ^{1}H NMR (allenes, partial) δ 5.29 (m, 1 H), 4.95 (m, 2 H); IR (alkynes + allenes) 3588, 3447, 3307, 2122, 1957 cm^{-1}. HRMS (EI) Calcd for $C_8H_{10}O_3S$: 186.0351. Found: 186.0341.

4-(2-[(*tert*-Butyldimethylsilyl)oxy]-4-pentynyl)-1,3-dioxolane-2-thione (11). A stirred solution of alkyne **11**/allene mixture (1.09 g, 5.85 mmol) and 2.45 mL (0.018 mol) of Et_3N in CH_2Cl_2 (110 mL) was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, 2.02 mL, 8.80 mmol) was added dropwise, and the resulting solution was stirred at 0 °C for 3 h. The solution was diluted with Et_2O and washed successively with H_2O, 5% HCl, saturated aqueous $NaHCO_3$, and brine. Workup and chromatography (25:1 hexanes/EtOAc) provided 1.63 g (92%) of the alkyne/allene mixture as a clear oil: ^{1}H NMR (major diastereomer) δ 5.08 (m, 1 H, CHOCS), 4.76 (br t, 1 H, J = 8.3 Hz, CH_2OCS), 4.33 (br t, 1 H, J = 8.3 Hz, CH_2OCS), 4.10 (m, 1 H, CHOTBDMS), 2.44 (ddd, 1 H, J = 16.8, 4.2, 2.7 Hz, propargyl), 2.34 (ddd, 1 H, J = 16.8, 7.4, 2.7 Hz, propargyl), 2.24 (ddd, 1 H, J = 14.3, 8.8, 2.6 Hz), 2.05 (t, 1 H, J = 2.7 Hz, alkyne), 1.95 (ddd, 1 H, J = 14.3, 9.9, 4.4 Hz), 0.90 (s, 9 H), 0.14 and 0.13 (s, 2 × 3 H); ^{1}H NMR (minor diastereomer) δ 5.10 (m, 1 H, CHOCS), 4.74 (br t, 1 H, J = 8.4 Hz, CH_2OCS), 4.36 (br t, 1 H, J = 8.4 Hz, CH_2OCS), 4.07 (m, 1 H, CHOTBDMS), 2.50–1.89 (m, 5 H), 0.90 (s, 9 H), 0.11 and 0.08 (s, 2 × 3 H); IR (CCl_4) 3307, 2122, 1959, 1301 cm^{-1}. HRMS (CI, alkynes + allenes) Calcd for $C_{14}H_{25}O_3SSi$ $(M + H)^+$: 301.12945. Found: 301.1299.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-methylene-1-cyclopentanemethanol (12a). Toluene (250 mL, distilled from potassium metal) in a 500-mL three-necked flask (purged with dry N_2 for ~20 min) was heated to reflux with a heating mantle and sun lamp (the flask and sun lamp were wrapped with aluminum foil). A solution of the alkyne **11**/allene thionocarbonates (1.02 g, 3.39 mmol), Bu_3SnH (1.83 mL, 6.79 mmol), and 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.056 g, 0.34 mmol) in dry, degassed toluene (40 mL) was added via addition funnel over 1.5 h. After the addition was complete, the resulting solution was heated at reflux for 3.4 h and then cooled to 25 °C, concentrated, and finally diluted with 170 mL of wet Et_2O. Liquid 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.76 mL, 5.09 mmol) was added followed by titration with an I_2/Et_2O solution until a yellow iodine color persisted.[36] The mixture was eluted with Et_2O through a short silica gel column followed by concentration and flash chromatography (10:1. hexanes/EtOAc) to afford 0.494 g (60%) of alcohol **12a** as a clear colorless oil: ^{1}H NMR (both diastereomers) δ 5.07–4.94 (m, 2 × 2 H, vinyl), 4.31 (m, 2 × 1 H, CHOTBDMS), 3.75–3.62 (m, 2 × 2 H, CH_2OH), 2.87 (m, 1 H, CHC≡C), 2.75 (m, 1 H, CHC≡C), 2.67 (dd, 1 H, J = 6.4, 4.7 Hz, OH), 2.59–1.66 (m, 2 × 4 H), 1.45 (br t, 1 H, J = 6.2 Hz, OH), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 6 H): ^{13}C NMR δ 151.1, 150.6, 107.5, 106.9, 72.5, 71.9, 65.7, 65.1, 44.2, 43.9 (2×), 43.7, 39.3, 39.2, 25.8 (6×), 18.0 (2×), –4.8 (4×); IR (CCl_4) 3624, 1652 cm^{-1}. HRMS (CI) Calcd for $C_{13}H_{27}O_2Si$ $(M + H)^+$: 243.1781. Found: 243.1785.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-cyclopentene-1-carboxaldehyde (13a). To a stirred suspension of the Dess–Martin periodinane[20] (2.41 g, 5.67 mmol) in CH_2Cl_2 (23 mL) was added via syringe a solution of the homoallylic alcohols **12a** (1.25 g, 5.16 mmol) in CH_2Cl_2 (18.5 mL). After the solution had been stirred for 3.5 h at 25 °C, an additional 1.20 g (2.84 mmol) of periodinane was added in one portion. The mixture was stirred an additional 1 h and diluted with EtOAc, and a solution of $Na_2S_2O_3$ (9.50 g, 0.060 mol) in saturated aqueous $NaHCO_3$ (60 mL) was added. After the layers turned clear (20 min), the separated organic layer was washed successively with saturated aqueous $NaHCO_3$, H_2O, and brine. Workup provided the crude deconjugated aldehydes **12b**, which were used immediately without purification in the next step: ^{1}H NMR (both diastereomers, partial) δ 9.53–9.51 (m, 2 × 1 H, CHO), 5.21 (m, 2 H, vinyl), 5.06 (m, 2 H, vinyl), 4.33 (m, 2 × 1 H, CHOTBDMS), 3.52 (m, 1 H, CHC≡C), 3.19 (m, 1 H, CHC≡C), 2.57–2.07 (m, 2 × 4 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 2 × 6 H).

A solution of the crude aldehydes (5.16 mmol) and DMAP (0.315 g, 2.58 mmol) in CH_2Cl_2 (80 mL) was stirred at 25 °C for 12 h. The reaction mixture was diluted with EtOAc and washed successively with 5% HCl, saturated aqueous $NaHCO_3$, and brine. Workup and purification on Florisil (25:1 hexanes/EtOAc) yielded 1.04 g (84%, 2 steps) of aldehyde **13a** as a colorless oil: ^{1}H NMR δ 9.98 (s, 1 H, CHO), 4.48 (m, 1 H, CHOTBDMS), 2.88–2.75 (m, 2 H), 2.57–2.46 (m, 2 H), 2.14 (s, 3 H, vinyl CH_3), 0.87 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 187.8, 159.1, 135.9, 70.0, 50.6, 40.4, 25.8 (3×), 18.1, 14.3, –4.7, –4.9; IR (CCl_4) 1671 cm^{-1}. HRMS (CI) Calcd for $C_{13}H_{25}O_2Si$ $(M + H)^+$: 241.16245. Found: 241.1623.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-cyclopentene-1-methanol (13b). To a solution of aldehyde **13a** (0.094 g, 0.39 mmol) in absolute MeOH (14 mL) was added 0.022 g (0.59 mmol) of $NaBH_4$ in one portion, and the mixture was stirred for 1 h at 25 °C. The excess $NaBH_4$ was quenched with acetone, and the solution was concentrated and diluted with Et_2O and saturated aqueous $NaHCO_3$. The isolated aqueous layer was extracted with Et_2O; the organic layers were combined and washed with brine followed by workup. Chromatography (10:1 hexanes/EtOAc) gave alcohol **13b** as a colorless oil (0.083 g, 87%): ^{1}H NMR δ 4.48 (m, 1 H, CHOTBDMS), 4.17 (s, 2 H, CH_2OH), 2.74 (br dd, 1 H, J = 15.5, 6.1 Hz), 2.60 (br dd, 1 H, J = 16.4, 8.4 Hz), 2.39 (br d, 1 H, J = 15.5 Hz),[37] 2.31 (br d, 1 H, J = 16.4 Hz), 1.68 (s, 3 H, vinyl CH_3), 1.14 (br s, 1 H, OH), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR δ 133.2, 131.9, 70.9, 59.0, 48.7, 44.2, 25.9 (3×), 18.3, 13.7, –4.7 (2×); IR (CCl_4) 3620, 3436, 2956, 2929, 2885, 2857, 1674, 1471, 1361, 1093 cm^{-1}. HRMS (CI) Calcd for $C_{13}H_{27}O_2Si$ $(M + H)^+$: 243.1781. Found: 241.1595 $(M - H)^+$. LRMS (FAB, *m*-nitrobenzyl alcohol/MeOH) 241.15 (24%) $(M - H)^+$, 225.16 (42%) $(M + H - H_2O)^+$.

Allyl Vinyl Ether 3d. Using the protocol for the formation of allyl vinyl ether **3c**, alcohol **13b** (0.835 g, 3.44 mmol) gave upon flash

(35) The coupling constants were obtained from homonuclear decoupling experiments of the diastereomeric mixture as follows: Irradiation of the overlapping signals at δ 4.36 and 4.30 revealed the vicinal coupling constant δ 3.60 (t, J = 7.7 Hz, 1 H, $-CH_2O-$) → δ 3.60 (d, J = 6.5 Hz), while irradiation of the overlapping signals at δ 4.12 and 4.11 revealed the geminal coupling constant δ 3.60 (t, J = 7.7 Hz, 1 H, $-CH_2O-$) → δ 3.60 (d, J = 8.1 Hz).

(36) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1986**, *51*, 5111.

(37) The coupling constants and chemical shifts for the partially obscured broad doublets at δ 2.39 and 2.31 were obtained from homonuclear decoupling experiments. Irradiation of the broad doublet of doublets at δ 2.74 collapsed the broad doublet at δ 2.39 to a singlet, which allowed observation of the δ 2.31 (br d, J = 16.4 Hz, 1 H) signal.

chromatography (10:1 hexanes/EtOAc) recovered **13b** (0.276 g) and allyl vinyl ether **3d** (0.666 g, 48%): ^{1}H NMR δ 4.64 (d, 1 H, J = 11.4 Hz, OCH_2), 4.57 (d, 1 H, J = 11.4 Hz, OCH_2), 4.47 (m, 1 H, CHOTBDMS), 3.99 (s, 4 H, ketal), 2.76 (br dd, 1 H, J = 16.2, 6.9 Hz), 2.58 (br dd, 1 H, J = 16.2, 7.1 Hz), 2.49 (s, 2 H), 2.43–2.26 (m, 4 H), 1.74 (m, 2 H), 1.70 (s, 3 H, vinyl CH_3), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 164.4, 135.7, 128.0, 118.2, 107.0, 85.6, 70.7, 65.6, 64.7 (2×), 48.7, 44.4, 37.7, 30.6, 25.9 (3×), 23.8, 18.2, 14.0, –4.7 (2×); IR (CCl_4) 2216, 1645, 1632 cm^{-1}. HRMS (CI) Calcd for $C_{22}H_{36}NO_4Si$ $(M + H)^+$: 406.2415. Found: 406.2414.

β-Keto Nitriles 4d and Diastereomers. A solution of allyl vinyl ether **3d** (0.028 g, 0.069 mmol) in distilled nonane (3.5 mL) was heated at reflux for 6 h. The solvent was removed, and the residue was subjected to flash chromatography in (10:1 hexanes/EtOAc) to yield 0.019 g (68%) of the major diastereomer **4d** along with two isolated minor diastereomers. Recrystallization of the major diastereomer from *n*-hexane provided crystals suitable for X-ray analysis. **4d**: mp 102.8–103.2 °C (hexanes); ^{1}H NMR δ 5.28 (m, 1 H, vinyl), 5.14 (m, 1 H, vinyl), 4.23 (m, 1 H, CHOTBDMS), 3.98 (m, 4 H, ketal), 3.22 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.58 (dd, 1 H, J = 13.5, 2.9 Hz, C_{10}–H_{eq}), 2.41–2.19 (m, 4 H), 2.09–1.81 (m, 4 H), 1.61 (s, 3 H, CH_3), 0.87 (s, 9 H), 0.04 and 0.03 (s, 2 × 3 H); ^{13}C NMR δ 197.2, 155.6, 119.3, 109.8, 109.4, 71.2, 65.0, 64.7, 58.6, 50.2, 47.0, 46.9, 46.8, 32.4, 27.4, 27.3, 25.8 (3×), 18.0, –4.8 (2×); IR (CCl_4) 2228, 1739, 1653 cm^{-1}. HRMS (CI) Calcd for $C_{22}H_{36}NO_4Si$ $(M + H)^+$: 406.2415. Found: 406.2386.

Higher R_f minor diastereomer: R_f (2:1 hexanes/EtOAc); ^{1}H NMR δ 5.30 (br d, 1 H, J = 2.2 Hz, vinyl), 5.10 (br d, 1 H, J = 2.2 Hz, vinyl), 4.13 (m, 1 H, CHOTBDMS), 3.99 (m, 4 H, ketal), 3.24 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.58 (dd, 1 H, J = 13.5, 2.9 Hz, C_{10}–H_{eq}), 2.56 (m, 1 H), 2.44–2.18 (m, 5 H), 1.99 (m, 1 H), 1.62 (dd, 1 H, J = 13.7, 9.0 Hz), 1.45 (s, 3 H, CH_3), 0.88 (s, 9 H), 0.06 (s, 6 H); IR (CCl_4) 2229, 1740, 1648 cm^{-1}. HRMS (CI) Calcd for $C_{22}H_{36}NO_4Si$ $(M + H)^+$: 406.2415. Found: 406.2418.

Lower R_f minor diastereomer: R_f 0.49 (2:1 hexanes/EtOAc); ^{1}H NMR δ 5.15 (m, 1 H, vinyl), 5.08 (m, 1 H, vinyl), 4.30 (m, 1 H, CHOTBDMS), 3.99 (m, 4 H, ketal), 3.23 (d, 1 H, J = 13.2 Hz, C_{10}–H_{ax}), 3.00 (m, 1 H), 2.56 (dd, 1 H, J = 13.2, 2.8 Hz, C_{10}–H_{eq}), 2.45–2.33 (m, 3 H), 2.10–1.83 (m, 4 H), 1.44 (s, 3 H, CH_3), 0.87 (s, 9 H), 0.04 (s, 6 H); IR (CCl_4) 2230, 1740, 1650 cm^{-1}. HRMS (CI) Calcd for $C_{22}H_{36}NO_4Si$ $(M + H)^+$: 406.2415. Found: 406.2412.

Alcohol 24. To a solution of β-keto nitrile (0.024 g, 0.059 mmol) in CH_3CN (0.6 mL) at 0 °C buffered with 6.0 mg (0.059 mmol) of Na_2CO_3 was added dropwise 0.59 mL (0.77 mmol) of an aqueous 48% HF/CH_3-CN (1:20) solution. The resulting solution was stirred at 0 °C for 15.5 h, diluted with brine, extracted with EtOAc, and washed with saturated aqueous $NaHCO_3$ and brine. Workup and flash chromatography (2:1 hexanes/EtOAc) afforded 0.016 g (94%) of alcohol **24**: mp 105–107 °C (*n*-hexane); ^{1}H NMR δ 5.36 (m, 1 H, vinyl), 5.24 (m, 1 H, vinyl), 4.34 (m, 1 H, CHOH), 3.99 (m, 4 H, ketal), 3.23 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.59 (dd, 1 H, J = 13.5, 2.9 Hz, C_{10}–H_{eq}), 2.49 (m, 2 H), 2.44–1.85 (m, 6 H), 1.64 (s, 3 H, CH_3), 1.33 (br s, 1 H, OH, D_2O exchange); ^{13}C NMR δ 197.2, 154.8, 119.1, 110.9, 109.3, 70.9, 65.1, 64.7, 58.7, 50.2, 46.9, 46.6, 46.2, 32.4, 27.8, 27.4; IR (CCl_4) 3620, 2229, 1738, 1653 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{21}NO_4$: 291.1471. Found: 291.1470.

Dioxolane 26a and Triol 25. To a solution of urea·H_2O_2 (0.197 g, 2.09 mmol) and solid Na_2CO_3 (dried at 120 °C; 0.195 g, 1.84 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added dropwise 0.074 mL (0.52 mmol) of $(CF_3CO)_2O$. The resulting solution was stirred for ~2 min at 0 °C and then 5 min at 30 °C followed by the dropwise addition of alcohol **24** (0.061 g, 0.21 mmol) in CH_2Cl_2 (2.2 mL). After the solution had been stirred at 25 °C for 1.5 h, it was heated at reflux for 21 h. The solution was cooled to 25 °C and diluted with brine, and excess oxidant was decomposed with excess 10% Na_2SO_3. The isolated aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine. Workup and Chromatotron purification in 2:1 (EtOAc/hexanes) provided 29 mg (45%) of 1,3-dioxolane **26a**: ^{1}H NMR δ 4.76 (m, 1 H, C_3–H), 4.14–3.90 (m, 4 H, ketal), 4.00 (d, 1 H, J = 7.1 Hz, C_{13}–H), 3.54 (d, 1 H, J = 7.1 Hz, C_{13}–H), 2.74 (dd, 1 H, J = 14.4, 7.0 Hz), 2.64 (d, 1 H, J = 13.6 Hz, C_{10}–H_{ax}), 2.52 (dd, 1 H, J = 14.7, 6.5 Hz), 2.22 (dd, 1 H, J = 13.6, 2.0 Hz, C_{10}–H_{eq}), 2.14 (m, 1 H), 2.09–1.73 (m, 4 H), 1.85 (dd, 1 H, J = 14.7, 6.5 Hz), 1.67 (dd, 1 H, J = 14.4, 5.4 Hz), 1.24 (s, 3 H, CH_3); IR ($CHCl_3$) 3603, 3494, 2237 cm^{-1}. HRMS (CI) Calcd for $C_{16}H_{22}NO_5$ $(M + H)^+$: 308.1499. Found: 308.1496. **25**: ^{1}H NMR (partial) δ 4.52 (m, 1 H, C_3–H), 3.96 (m, 4 H, ketal), 3.72 (d, 1 H, J = 12.6 Hz, C_{13}–H), 3.66 (br s, 1 H), 3.60 (d, 1 H, J = 12.6 Hz, C_{13}–H), 3.21 (dd, 1 H, J = 14.0, 5.0 Hz), 2.70 (br s, 1 H, OH), 2.62 (m, 1 H), 2.50 (dd, 1 H, J = 15.1, 5.2 Hz), 2.26 (dd, 1 H, J = 14.1, 2.2 Hz), 2.10 (d, 1 H, J = 14.1 Hz), 1.48 (s, 3 H, CH_3); IR ($CHCl_3$) 3599, 3479, 2241 cm^{-1}. HRMS (CI) Calcd for $C_{16}H_{24}NO_6$ $(M + H)^+$: 326.1604. Found: 326.1596.

Keto Nitrile 27. To a solution of alcohol **24** (0.012 g, 0.039 mmol), DMAP (0.5 mg, 0.0039 mmol), and Et_3N (0.016 mL, 0.12 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C was added dropwise a solution of freshly distilled methanesulfonic anhydride (0.020 g, 0.12 mmol) in CH_2Cl_2 (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 $NaHCO_3$, and brine followed by workup. The resulting crude mesylate **26b** was used without purification in the next step. **26b**: ^{1}H NMR (partial) δ 5.39 (m, 1 H, C_3–H), 4.14–3.91 (m, 5 H, ketal + C_{13}–H), 3.56 (d, 1 H, J = 7.2 Hz, C_{13}–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 (d, 1 H, J = 13.5 Hz, C_{10}–H_{ax}), 2.23 (br d, 1 H, J = 13.5 Hz, C_{10}–H_{eq}), 1.25 (s, 3 H, CH_3). LRMS (EI) Calcd for $C_{17}H_{23}NO_7S$: 385. Found: 385.

In a N_2-purged glovebag was added 0.022 g (0.31 mmol) of KO_2 to a 15-mL flame-dried flask, followed by 18-crown-6 (0.093 g, 0.35 mmol) and 3-Å powdered sieves (0.020 g, 0.5 g/mmol). After dilution with anhydrous DMSO (0.5 mL), the bright-yellow mixture was flushed with dry N_2 and the crude mesylate (0.039 mmol) in anhydrous DMSO (0.5 mL) at 25 °C was added. Evolution of gas was evident during and after the addition of the mesylate. After the solution had been stirred for 50 min, the reaction mixture was diluted with saturated aqueous NH_4Cl followed by the addition of 5 drops of dimethyl sulfide. The mixture was stirred for 10 min followed by dilution with EtOAc and brine. The separated aqueous layer was extracted with EtOAc, and the combined extracts were washed with brine and worked up to give crude alcohol **28**: ^{1}H NMR (partial) δ 4.51 (m, 1 H, C_3–H), 4.12–3.90 (m, 5 H, ketal + C_{13}–H), 3.57 (d, 1 H, J = 7.2 Hz, C_{13}–H), 2.71 (d, 1 H, J = 13.8 Hz, C_{10}–H_{ax}), 2.60 (br d, 1 H, J = 14.5 Hz), 1.26 (s, 3 H, CH_3). Because chromatographic purification indicated partial cyclization, the material was cyclized without purification.

A solution of the crude alcohol **28** and (1*S*)-(+)-10-camphorsulfonic acid (0.005 g, 0.020 mmol) in CH_2Cl_2 (0.8 mL) was stirred at 25 °C for 7.5 h. After dilution of the solution with aqueous $NaHCO_3$ 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 ketal of **27**, which was contaminated (unidentified AB resonance at δ 3.5). This impurity persisted after attempted purification on either silica gel or Florisil. Impure ketal of **28**: ^{1}H NMR (partial) δ 4.64 (m, 1 H, C_3–H), 4.08–3.89 (m, 4 H, ketal), 3.85 (d, 1 H, J = 12.9 Hz, C_{13}–H), 3.70 (d, 1 H, J = 12.9 Hz, C_{13}–H), 2.85 (br d, 1 H, J = 13.1 Hz, C_4–H_{endo}), 2.17 (s, 2 H), 2.14 (br d, 1 H, J = 12.0 Hz, C_2–H_{endo}), 1.60 (br d, 1 H, J = 13.1 Hz, C_4–H_{exo}), 1.51 (br d, 1 H, J = 12.0 Hz, C_2–H_{exo}), 1.35 (s, 3 H, CH_3); IR ($CHCl_3$) 3475, 2237 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{21}NO_5$: 307.1420. Found: 307.1406.

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 $NaHCO_3$ 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); ^{1}H NMR δ 4.69 (m, 1 H, C_3–H), 3.79 (dd, 1 H, J = 2.6, 6.3 Hz, C_{13}–H), 3.71 (dd, 1 H, J = 12.6, 6.5 Hz, C_{13}–H), 2.87 (br d, 1 H, J = 13.3 Hz, C_4–H_{endo}), 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, C_4–H_{exo}), 1.55 (br d, 1 H, J = 12.5 Hz, C_2–H_{exo}), 1.39 (s, 3 H, CH_3); IR ($CHCl_3$) 3599, 2238, 1725 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1171.

Unsaturated Nitrile 30a. A mixture of 0.163 g (0.46 mmol) of methyltriphenylphosphonium bromide and *t*-BuOK/THF (0.55 mL, 0.83 M in THF) was stirred at reflux for 5 min. A solution of keto nitrile **27** (8.6 mg, 0.033 mmol) in THF (0.5 mL) was added dropwise. After the solution had been stirred for 30 min, it was cooled to 25 °C and filtered through silica gel (THF). Chromatography in (2:1 hexanes/EtOAc) yielded olefin **30a** (7.0 mg, 82%): ^{1}H NMR δ 4.82 (m, 1 H, vinyl), 4.78 (m, 1 H, vinyl), 4.66 (m, 1 H, C_3–H), 3.77 (dd, 1 H, J = 12.5, 6.4 Hz, C_{13}–H), 3.72 (dd, 1 H, J = 12.5, 5.9 Hz, C_{13}–H), 2.85 (br d, 1 H, J = 13.5 Hz, C_4–H_{endo}), 2.59 (s, 2 H), 2.43–2.37 (m, 2 H), 2.15 (br d, 1 H, J = 12.0 Hz, C_2–H_{endo}), 1.95–1.79 (m, 3 H), 1.63–1.51 (m, 2 H, C_4– +

C_2–H_{exo}), 1.31 (s, 3 H, CH_3); IR ($CHCl_3$) 3688, 2242, 1655 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{19}NO_3$: 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.[38] 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. **30b**: ^{1}H NMR (partial) δ 10.0 (br s, 1 H, CHO), 4.77 (m, 2 H, vinyl), 4.67 (m, 1 H, C_3–H).

The above procedure was repeated on the crude aldehyde, which after flash chromatography (25:1 to 1:1 hexanes/EtOAc) yielded 0.9 mg (37%) of diol **29c**: ^{1}H NMR δ 4.76 (m, 1 H, vinyl), 4.72 (m, 1 H, vinyl), 4.59 (m, 1 H, C_3–H), 4.08 (br d, 1 H, J = 11.8 Hz, C_{15}–H), 3.95 (br d, 1 H, J = 11.8 Hz, C_{15}–H), 3.79 (dd, 1 H, J = 12.2, 6.0 Hz, C_{13}–H), 3.71 (dd, 1 H, J = 12.2, 6.9 Hz, C_{13}–H), 2.75 (br d, 1 H, J = 13.0 Hz, C_4–H_{endo}), 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–H_{endo}), 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–H_{exo}), 1.35 (br d, 1 H, J = 13.0 Hz, C_4–H_{exo}), 1.19 (s, 3 H, CH_3). LRMS (EI) Calcd for $C_{14}H_{22}O_4$: 266. Found: 266.

Sporol (1). Diol **30c** (0.002 g, 0.0075 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (0.9 mg, 0.0038 mmol) in CH_2Cl_2 (0.3 mL) was heated at reflux for 7.5 h. The solution was cooled, diluted with aqueous $NaHCO_3$, and extracted with EtOAc, and the combined extracts were washed with brine. Workup and flash chromatography (25:1 to 1:1 hexanes/EtOAc) yielded 0.9 mg (45%) of synthetic (±)-sporol: ^{1}H NMR δ 4.56 (m, 1 H, C_3–H), 4.31 (dd, 1 H, J = 8.1, 3.3 Hz, C_{15}–H), 3.86 (d, 1 H, J = 12.1 Hz, C_{13}–H), 3.80 (d, 1 H, J = 8.1 Hz, C_{15}–H), 3.72 (dd, 1 H, J = 12.1, 7.1 Hz, C_{13}–H), 2.30 (br d, 1 H, J = 12.4 Hz, C_4–H_{endo}), 2.22 (br d, 1 H, J = 11.8 Hz, C_2–H_{endo}), 1.84 (s, 2 H, C_{10}–H), 1.81–1.73 (m, 3 H), 1.67–1.55 (m, 2 H), 1.48 (br d, 1 H, J = 11.8 Hz, C_2–H_{exo}), 1.24 (br d, 1 H, J = 12.4 Hz, C_2–H_{endo}), 1.15 (s, 3 H, C_{16}–H), 1.10 (s, 3 H, C_{14}–H). GC/LRMS (EI) Calcd for $C_{14}H_{22}O_4$: 266. Found: 266. HRMS (EI) Calcd for $C_{14}H_{22}O_4$: 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.

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