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Oxocarbenium Ion Cyclizations for C-Branched Cyclitols: Synthesis of a Relay Intermediate for Fumagillin Analogues

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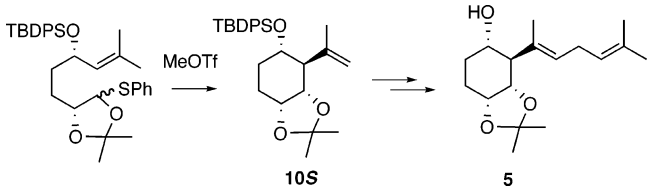

A highly stereoselective oxocarbenium ion-alkene cyclization for synthesis of C-branched cylitols is described. This methodology was applied to **10*S***, a potentially versatile intermediate for side-chain analogues of the antiangiogenic agent fumagillin. Compound **10*S*** was subsequently converted to diene **5**. Because racemic **5** has been converted to racemic fumagillin, this synthesis of **5** constitutes a formal synthesis of the natural product.

Introduction

The natural product fumagillin **1**[1] has attracted renewed interest in light of the discovery that it selectively inhibits angiogenesis in tumor cells[2] (Figure 1). This activity has been related to disruption of endothelial cell proliferation,[3,4] which is believed to result from covalent binding of **1** to, and subsequent inhibition of, methionine aminopeptidase type 2 (MetAP-2).[5] However, the link between MetAP-2 inhibition and disruption of endothelial cell growth has recently been questioned.[6] Structure activity studies have been generally confined to analogues with different ester residues and modified C4 appendages, because of the accessibility of such structures from the natural product, and the finding that these regions contain important contact points to MetAP-2.[2,7−12] The most prominent derivative is TNP-470 **2**, which contains an unnatural ester subunit.[2,7] The development of TNP-470 has, however, been stymied by poor pharmacokinetic behavior and dose-limiting toxicity.[13,14] More recent studies suggest that the side-chain epoxide may

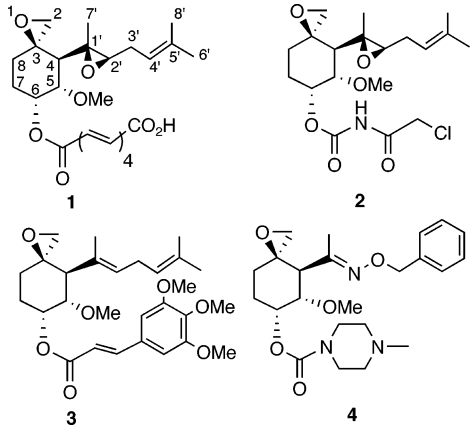

FIGURE 1. Fumagillin and previously reported analogues.

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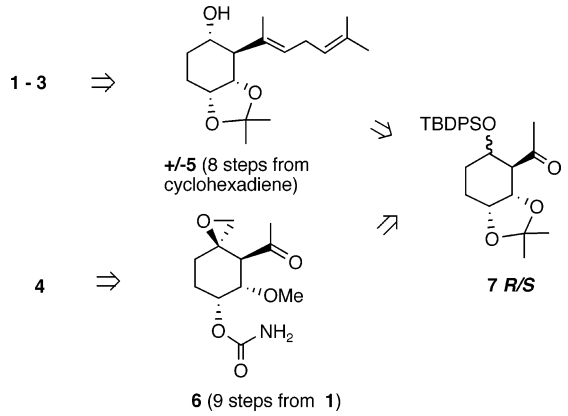
SCHEME 1. Retrosynthesis of Fumagillin Analogues

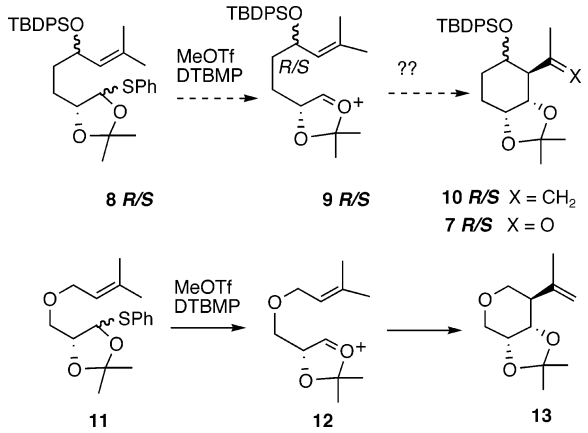


not be critical for activity and that this region could be extensively modified (cf., **3** and **4**[9]), without significant decrease in binding to MetAP-2, as compared to TNP-470.

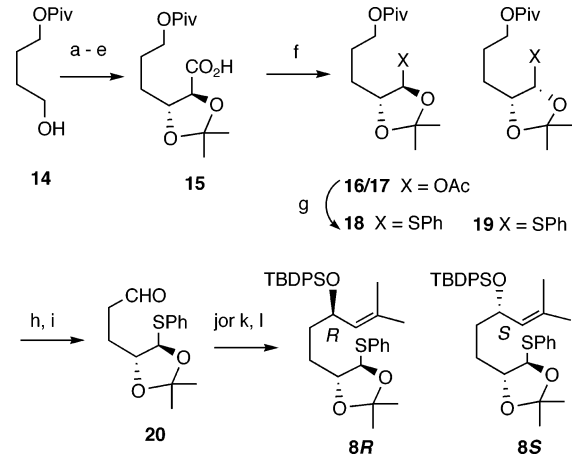
The structural complexity and interesting biological activity of fumagillin has resulted in considerable interest in total synthesis. Such investigations are particularly important because of the limited pool of structures that is available from natural[15] or semisynthetic sources.[7−10,16] Following the first total synthesis by Corey and coworkers,[17] a number of total or formal syntheses of racemic and enantiopure materials have been reported.[18−24] We envisaged that relatively simple C-branched cyclitols **7*R*** or **7*S*** would be useful synthetic intermediates for different side-chain analogues (Scheme 1). Methyl ketones **7*R*** and **7*S*** could be converted to a C1′ epoxide (cf., **1**, **2**) and other analogues (cf., **3**, **4**) via the known intermediates **5**[18] and **6**,[10] previously prepared from cyclohexadiene and the natural product **1**, respectively. Herein, we describe the synthesis of **7*S***, and its conversion to optically active **5**.

Our synthetic plan relates **7*R*/*S*** to the alkene precursors **10*R*/*S*** and follows from earlier studies on related oxocarbenium ion-alkene cyclizations (Scheme 2). Thus, treatment of the 1-phenylthio-1,2-*O*-isopropylidene acetal-alkene **11** with methyl triflate led to a single diastereomer **13**, in which the isopropenyl appendage was anti to the syn isopropylidene residue.[25] This reaction presumably proceeds through cyclization of the oxocarbenium ion-alkene intermediate **12**. Extension of this concept to **10*R*/*S*** calls for cyclization precursors **8*R*/*S***. However, it was not clear how the configuration at the allylic alcohol position would affect the stereochemical outcome of the oxocarbenium ion cyclization. The cyclizations of epimeric substrates **8*R*** and **8*S*** were therefore first investigated.

SCHEME 2. C-Branched Cyclitols via Oxocarbenium Ion Cyclizations



SCHEME 3. Synthesis of 8*R* and 8*S*[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2; (b) $Ph_3P{=}CHCO_2Me$, CH_3CN, 65 °C, two steps, 88%; (c) AD-mix-β, *t*-BuOH−H_2O, $MeSONH_2$, 90%; (d) $(MeO)_2CMe_2$, CSA, CH_2Cl_2; (e) THF−aq KOH, two steps, 88%; (f) $PhI(OAc)_2$, I_2, CH_2Cl_2; (g) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, two steps, 80%; (h) DIBALH, CH_2Cl_2, −78 °C, 94%; (i) Swern's Ox., 94%; (j) 2-methy-1-bromopropene, *t*-BuLi, ether, −78 °C; (k) 2-methy-1-bromopropene, *t*-BuLi, ether, −78 °C, $ZnCl_2$, lithium (1*S*,2*R*)-*N*-methylephedrate, 0 °C, 83%; (l) TBDPSCl, imidazole, DMF, 50 °C.

The synthesis of **8*R*** and **8*S*** started from 4-pivaloyloxy-1-butanol **14**[26] (Scheme 3). Alcohol **14** was first converted to the isopropylidene-carboxylic acid **15**. Thus, a straightforward alcohol oxidation-aldehyde olefination sequence on **14** provided methyl (*E*)-1-pivaloyloxy-2-hexenoate,

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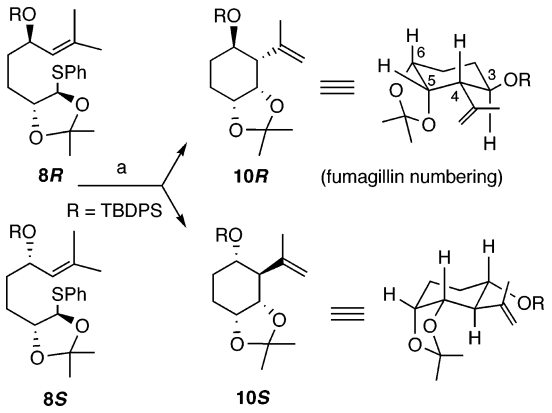
which was treated under standard Sharpless asymmetric dihydroxylation conditions with AD-mix-β. Mosher ester analysis indicated an ee of greater than 95% for the resulting diol, the absolute stereochemistry of which was based on the results for the dihydroxylation of closely related *E*-disubstituted alkenes.[27] Acetonation of the diol, followed by selective hydrolysis of the methyl ester, furnished **15**, in 69% yield, over five steps from **14**. The synthesis of the 1-phenylthio-1,2-*O*-isopropylidene acetal followed a variation of the Suarez radical fragmentation of 1,2-*O*-isopropylidene sugars.[28] Thus, exposure of **15** to iodosobenzene diacetate under anhydrous conditions provided an unseparated mixture of 1-acetoxy-1,2-*O*-isopropylidene acetals **16** and **17**. Boron trifluoride-catalyzed acetal exchange on this mixture with thiophenol at low temperature led to a 9/1 mixture of anti/syn acetal isomers **18** and **19**, in 80% overall yield from **15**. The stereochemistry of **18** and **19** was tentatively assigned by examination of the proton chemical shifts of the two methyl groups of the acetonide. Following ^{1}H NMR trends for anti/syn pairs of 1,2-diol acetonides, the isomer in which the two methyl groups appeared as a 6H singlet (δ 1.46) was assigned as anti (i.e., **18**), and the other which showed resolved 3H singlets (δ 1.38 and 1.63 ppm) was assigned as syn (i.e., **19**)[29] The subsequent reactions were carried out on the major anti isomer, **18**. DIBALH reduction of the pivalate in **18** and oxidation of the resulting alcohol gave aldehyde **20**. Treatment of **20** with 2-propenyllithium provided a 1/1 inseparable mixture of allylic alcohols, which was converted to the corresponding silyl ether derivatives **8*R*** and **8*S***, in 61% yield from **20**. Attempted separation of mixture **8*R*/8*S*** was also not successful. The configuration at the newly formed carbinol carbon was assigned in later derivatives (vide infra). As the results of the subsequent cyclization studies unfolded, it became necessary to develop a stereoselective synthesis of **8*S***. Accordingly, **20** was added to a mixture of 2-propenyllithium, zinc bromide, and lithium (1*S*,1*R*)-*N*-methylephedrate, following the Oppolzer procedure for the addition of chiral alkenyl zinc reagents to aldehydes (Scheme 3).[30] Silylation of the reaction product gave an approximate 1/4 ratio of **8*R*/8*S*** in 83% overall yield from **20**.

The cyclization of **8*R*** and **8*S*** was next investigated (Scheme 4). Treatment of the 1/1 mixture of **8*R*/*S*** with methyl triflate and 4-methyl-2,6-di-*tert*-butylpyridine in anhydrous dichloromethane led to a 1/1 ratio of two chromatographically separable, cyclization products **10*R*** and **10*S***, in a combined yield of 89%. Under similar conditions, the 1/4 mixture of **8*R*/*S*** afforded **10*R*** and **10*S*** in respective yields of 20% and 74%. The absence of any other diastereomeric cycloadducts suggests that the cyclization process was essentially, completely stereoselective; that is, **8*R*** and **8*S*** produced **10*R*** and **10*S***, respectively. The stereochemistry of **10*R*** and **10*S*** was assigned by analysis of *J* values for vicinal protons on the cyclohexane ring. For **10*R***, $J_{3,4}$, $J_{4,5}$, and $J_{5,6}$ values

SCHEME 4. Cyclization of 8*R* and 8*S*[a]



[a] Reagents and conditions: (a) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, molecular sieves, CH_2Cl_2; **10*R*** (45%) and **10*S*** (44%) from **8*R*/*S*** (1/1); **10*R*** (20%) and **10*S*** (74%) from **8*R*/*S*** (1/4).

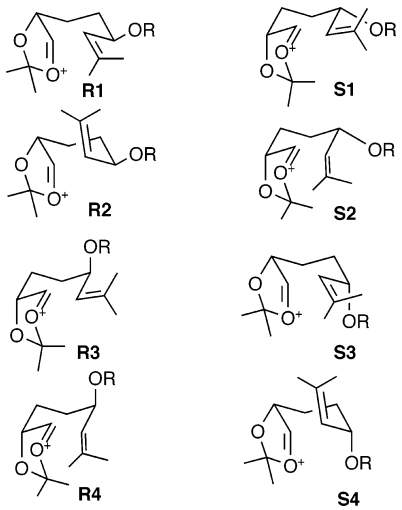


FIGURE 2. Chairlike transition states for oxocarbenium ion cyclizations.

of 9.9, 3.5, and 5.3 are in agreement with a trans diaxial arrangement between H3 and H4, and axial−equatorial relationships between H4 and H5, and H5 and H6. For **10*S***, the corresponding *J* values were 10.0, 10.0, and 4.8, which are consistent with a mutually *trans*-diaxial type arrangement for H3, H4, and H5, and a cis axial−equatorial relationship between H5 and H6.

In the absence of additional data, the stereochemical results appear to be controlled by conformational effects in the cyclization of the intermediate oxocarbenium ions **9*R*/*S*** (Scheme 2). For both **8*R*** and **8*S***, transition states leading to a cis fused isopropylidene are expected to be favored over ones leading to the more strained trans fused system. Therefore, four chairlike[31] transition states **R1**−**R4** and **S1**−**S4** may be considered for **8*R*** or **8*S***, respectively, corresponding to "flip-chair" conformations and an α- or β-orientation of the C4 substituent (Figure 2). In the case of **8*S***, **S1** in which the eventual C3, C4, and C5 substituents on the cyclohexane are mutually trans and all pseudoequatorial appears to be a reasonable pathway to **10*S***. For **8*R***, the inverted chairlike confor-

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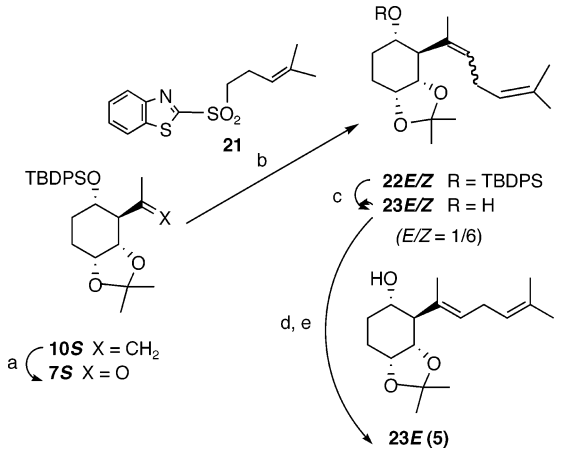
(31) More distorted chair and boat geometries are conceivable. For simplicity, chairlike structures are illustrated.

SCHEME 5. Transformation of 10*S* to Fumagillin Relay Compound 5[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2−MeOH, −78 °C, then Ph_3P, 85%; (b) **21**, LiHMDS, THF, −78 °C, 87%; (c) *n*-Bu_4NF, THF, quant.; (d) $VO(acac)_2$, TBHP, $CHCl_2$; (e) Ph_2PLi, THF, then MeI, two steps, 67%.

mation **R1** in which the C3, C4, and C5 substituents adopt pseudoequatorial, pseudoequatorial, and pseudoaxial orientations, respectively, are in agreement with the observed result. Thus, the configurations at C3 and C6 in the precursor apparently dictate the stereochemistry at the newly formed centers at C4 (trans to C3) and C5 (cis to C6), respectively.

The extension of the side chain in **10*S***, the cycloadduct required for fumagillin, was next investigated (Scheme 5). An olefin metathesis approach was initially explored. However, neither a cross metathesis on **10*S*** nor a ring-closing strategy on unsaturated ester derivatives of the alcohol derived from desilylation of **10*S*** was successful. Alkene **10*S*** was therefore transformed to the methyl ketone **7*S***, and elaboration of **7*S*** was pursued. Unstabilized or stabilized Wittig, or conventional Julia reagents, resulted in no reaction. The Kocienski modification[32] of the Julia reaction using benzothiazole sulfone **21** was more successful but unfortunately led to a mixture of **22*E*/*Z*** (*E*/*Z*: ca. 1/6), with the undesired *Z* isomer as the predominant product. All attempts to improve this result by varying the base, solvent, and reaction temperature led to no significant change in stereoselectivity. The isomerization of **22*E*/*Z*** was therefore investigated. Direct, thiol-mediated procedures under photochemical or thermal conditions were unsuccessful, leading to intractable product mixtures. An eventual solution was found in the Vedejs' two-step isomerization protocol.[33] Thus, $VO(acac)_2$ promoted, regiospecific epoxidation of the mixture of homoallylic alcohols **23*E*/*Z*** led to a mixture of epoxides, which was chromatographically separated. Reaction of the major product with Ph_2PLi, followed by treatment of the product with methyl iodide, led to **23*E*** as a single *E*-isomer, in 67% overall yield from the original mixture of homoallylic alcohols **23*E*/*Z*** (*E*/*Z*: 1/6). None of the *Z* isomer that would have resulted from stereospecific inversion of the minor *E* isomer in the starting mixture of **23*E*/*Z*** was observed. This result is presumably due to chromatographic removal of the epoxide derivative from **23*E*** prior to the reaction with Ph_2PLi. The ^1H and ^{13}C NMR data for **23*E*** were essentially identical to that for previously prepared **5**[18] (Supporting Information). Because racemic **5** has been converted to racemic fumagillin, the synthesis described here constitutes a formal synthesis of the natural product.

Conclusion

In summary, the synthesis of **10*S***, a potentially versatile precursor for side-chain analogues of fumagillin, has been developed. The utility of **10*S*** was illustrated by its conversion to the known fumagillin relay compound **5**. On a more general note, the oxocarbenium ion cyclization strategy appears suitable for the preparation of unusual, C-branched cyclitols, such as required as probes in inositol-related biochemical mechanisms.[34] Investigations along these lines are underway.

Experimental Section

(1*R*,2*R*)- and (1*S*,2*R*)-1-*O*-Acetyl-1,2-*O*-isopropylidene-5-pivaloyloxy-pentane-hemiacetal (16 and 17). To a solution of carboxylic acid **15** (10.3 g, 35.8 mmol) in dry dichloromethane (150 mL) were added diacetoxyiodobenzene (13.8 g, 42.9 mmol) and iodine (9.0 g, 35.8 mmol). The reaction mixture was stirred under argon for 4 h and then poured into 10% aqueous Na_2SO_3. The mixture was extracted with ether, and the organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. FCC of the residue provided an unsepararated mixture of **16** and **17** as a colorless oil (9.5 g, 88%): R_f = 0.60 (20% EtOAc/petroleum ether). For major isomer: ^1H NMR (500 MHz) δ 1.21 (s, 9H), 1.49 (s, 6H), 1.62−1.82 (m, 4H), 2.11 (s, 3H), 4.07−4.11 (m, 2H), 4.18−4.22 (m, 1H), 5.99 (d, 1H, J = 2.4 Hz); ^{13}C NMR (125 MHz) δ 21.5, 24.7, 26.9, 27.4, 27.9, 29.6, 38.9, 63.9, 81.8, 99.2, 112.6, 170.7, 178.7. For minor isomer: ^1H NMR (500 MHz) δ 1.21 (s, 9H), 1.40 (s, 3H), 1.52 (s, 3H), 1.62−1.82 (m, 4H), 2.11 (s, 3H), 4.07−4.11 (m, 2H), 4.12−4.17 (m, 1H), 6.23 (d, 1H, J = 3.3 Hz); ^{13}C NMR (125 MHz) δ 21.4, 25.2, 25.5, 25.9, 28.4, 38.8, 64.1, 80.0, 94.5, 111.4, 170.7, 178.7. For mixture: MS(ESI) *m*/*z* 320.2 [M + NH_4].

(1*S*,2*R*)- and (1*R*,2*R*)-1-(*S*)-phenylthio-1,2-*O*-isopropylidene-5-pivaloyloxy-pentane-(*S*)-phenyl-monothiohemiacetal (18 and 19). $BF_3{\cdot}OEt_2$ (3.69 mL, 29.1 mmol) was slowly added at −78 °C, under argon, to a solution of mixture **16/17** (8.8 g, 29.1 mmol) and thiophenol (5.98 mL, 58.3 mmol), in anhydrous CH_2Cl_2 (100 mL). The temperature was warmed to −40 °C, and stirring was continued at this temperature for 1 h (or until the TLC indicated complete disappearance of the starting material). The reaction mixture was quenched by addition of triethylamine (5 mL), then poured into saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether. The organic extract was washed with brine (150 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue gave **18** (8.45 g, 82%) and **19** (0.95 g, 9%). For **18**: R_f = 0.54 (10% EtOAc/petroleum ether); $[\alpha]_D$ +113 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz) δ 1.19 (s, 9H), 1.46 (s, 6H), 1.62−1.85 (m, 4H), 4.05 (m, 1H), 4.10 (t, 2H, J = 5.9 Hz), 5.06 (d, 1H, J = 7.3 Hz), 7.26−7.52 (m, 5H); ^{13}C NMR (125 MHz) δ 25.3, 26.0, 27.4, 27.8, 29.5, 39.0, 64.1, 80.3, 88.6, 111.1, 127.6, 129.2, 131.7, 134.2, 178.2. HRMS(ESI) calcd for $C_{19}H_{29}O_4S$ (M + H) 353.1787, found 353.1788. For **19**: R_f = 0.43 (10% EtOAc/petroleum

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ether); ^{1}H NMR (300 MHz) δ 1.21 (s, 9H), 1.38 (s, 3H), 1.63 (s, 3H), 1.75−1.95 (m, 4H), 4.05−4.20 (m, 2H), 4.30 (m, 1H), 5.58 (d, 1H, J = 4.8 Hz), 7.24−7.53 (m, 5H); ^{13}C NMR (75 MHz) δ 25.8, 26.5, 27.4, 28.3, 39.0, 64.1, 79.1, 88.8, 110.5, 127.3, 129.2, 132.9, 135.0, 178.4. MS(ESI) *m/z* 370.2 [M + NH_4].

Aldehyde (20). A 1 M solution of DIBALH in heptane (45.9 mL, 45.9 mmol) was added dropwise over 10 min to a solution of **18** (7.70 g, 21.9 mmol) in dry dichloromethane (80 mL), at −78 °C, under an atmosphere of nitrogen. The reaction was allowed to warm to room temperature, stirred at this temperature for 1 h, and then poured into saturated aqueous NH_4Cl and extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by FCC to afford the derived primary alcohol (5.53 g, 94%) as a colorless oil: R_f = 0.24 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz) δ 1.46 (s, 6H), 1.65−1.95 (m, 4H), 3.68 (t, 2H, J = 5.9 Hz), 4.00 (m, 1H), 5.07 (d, 1H, J = 7.3 Hz), 7.26−7.52 (m, 5H); ^{13}C NMR (75 MHz) δ 26.7, 28.3, 29.8, 30.2, 63.2, 81.3, 89.2, 111.4, 128.0, 129.5, 132.4, 135.0. HRMS(ESI) calcd for $C_{14}H_{21}O_3S$ (M + H) 269.1211, found 269.1210.

DMSO (6.80 mL, 97.0 mmol) was added dropwise to a solution of oxalyl chloride (4.20 mL, 48.8 mmol) in CH_2Cl_2 (60 mL), at −78 °C under an argon atmosphere. After the mixture was stirred at this temperature for 20 min, a solution of the alcohol from the previous step (5.20 g, 19.5 mmol) in CH_2Cl_2 was slowly introduced. The reaction was stirred for 25 min at −78 °C, at which time Et_3N (20.8 mL) was added. The solution was warmed to room temperature, stirred for an additional 10 min at this temperature, and then diluted with ether. The mixture was washed with saturated aqueous $NaHCO_3$, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo. FCC of the residue afforded aldehyde **20** (4.90 g, 94% from alcohol) as a yellow oil: R_f = 0.60 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz) δ 1.44 (s, 6H), 1.94 (m, 1H), 2.15 (m, 1H), 2.64 (t, 2H, J = 7.0 Hz), 4.02 (m, 1H), 5.06 (d, 1H, J = 7.3 Hz), 7.26−7.52 (m, 5H), 9.80 (s, 1H); ^{13}C NMR (125 MHz) δ 25.2, 26.0, 27.6, 40.1, 79.6, 88.4, 111.2, 127.7, 129.2, 131.9, 134.1, 201.4. HRMS(ESI) calcd for $C_{14}H_{19}O_3S$ (M + H) 267.1055, found 267.1067.

Thioacetal Alkenes (8*R*/*S*). *tert*-Butyllithium (1.7 M in hexane, 15.5 mL, 26.3 mmol) was added dropwise to a solution of 2-methyl-1-bromopropene (1.60 mL, 15.8 mmol) in dry ether, at −78 °C, under an argon atmosphere. The mixture was warmed to −35 °C and stirred at this temperature for 2 h. A solution of $ZnBr_2$ (0.6 M in ether, 15.8 mmol) was then added, and the mixture was warmed to 0 °C and maintained at this temperature for an additional 1 h. A solution of lithium (1*S*,2*R*)-*N*-methylephedrate was prepared by addition of *n*-BuLi (1.6 M in hexanes, 6.50 mL, 15.8 mmol) to (−)-*N*-methylephedrine (2.80 g, 15.8 mmol) in toluene (60 mL) at 0 °C, in a separate reaction vessel, and then slowly added to the reaction mixture. The resulting solution was stirred for 1 h at 0 °C, at which time a solution of aldehyde **20** (700 mg, 2.60 mmol) in dry ether (10 mL) was added dropwise. After an additional 1 h at 0 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl, the organic phase was separated, and the aqueous layer was extracted with ether. The organic extract was washed with a second portion of aqueous NH_4Cl, dried (Na_2SO_4), and concentrated under reduced pressure. FCC of the residue gave a mixture of allylic alcohol products (700 mg, 83%) as an inseparable mixture. For mixture: R_f = 0.27 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.40 (s, 3H), 1.44 (s, 6H), 1.48 (1.48, 3H), 1.70−2.0 (m, 4H), 4.15−4.22 (m, 1H), 4.23−4.32 (m, 1H), 5.16 (d, 1H, J = 8.4 Hz), 5.23 (d, 1H, J = 7.0 Hz), 5.24 (d, 1H, J = 7.0 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 19.0, 26.4, 26.7, 28.3, 29.5, 34.5, 69.0, 81.5 (major), 81.6 (minor), 89.3 (major), 89.2 (minor), 111.3, 129.5, 135.0. MS(ESI) *m/z* 345.1 [M + Na].

A sample of the alcohol mixture from the previous step (1.70 g, 5.28 mmol), TBDPSCl (1.78 mL, 6.86 mmol), imidazole (719 mg, 10.6 mmol), in anhydrous DMF (15 mL) was stirred at 50 °C for 4 h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give an inseparable mixture of **8*R*/*S*** (3.00 g, ca. 100% from alcohol mixture) as a yellow oil. The isomer ratio was estimated at 1/4 based on the ratio of the respective signals for isomeric carbinol (81.0 vs 80.9 ppm) and isomeric acetal (88.7 vs 88.9 ppm) carbons, and the stereochemistry was assigned by correlation with the products of the subsequent cyclization reaction (vide infra). R_f = 0.80 (10% EtOAc/petroleum ether); ^{1}H NMR (300 MHz) δ 1.03 (s, 9H), 1.12 (s, 3H), 1.43 (s, 6H), 1.53 (s, 3H), 1.57−1.73 (m, 4H), 3.93 (m, 1H), 4.36 (m, 1H), 4.99 (t, 1H, J = 7.3 Hz), 5.13 (br d, 1H, J = 8.1 Hz), 7.25−7.70 (m, 15H); ^{13}C NMR (75 MHz) δ 18.2, 19.5, 25.8, 26.0, 27.2, 27.8, 28.3, 28.6, 34.5 (minor), 34.6 (major), 70.3 (major), 70.4 (minor), 80.9 (major), 81.0 (minor), 88.7 (minor), 88.9 (major), 110.8, 127.4, 127.6, 128.2, 129.1, 129.5, 129.6, 131.6, 132.7, 132.8, 134.7, 134.9, 136.1, 136.2. HRMS(FAB) calcd for $C_{34}H_{43}O_3Si$ (M − H) 559.2702, found 559.2700.

Cyclitols (10*R* and 10*S*). A portion of the mixture of **8*R*/*S*** from the previous step (720 mg, 1.28 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (2.37 g, 11.6 mmol), and freshly activated, powdered 4A molecular sieves (2.0 g) in anhydrous dichloromethane (15 mL) were stirred for 15 min, at room temperature, under an argon atmosphere, and then cooled to 0 °C. Methyl triflate (1.00 mL, 8.99 mmol) was introduced, and the reaction was warmed to room temperature and stirred for an additional 18 h, at which time Et_3N (1.6 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. FCC afforded **10*R*** (113 mg, 20%) and **10*S*** (433 mg, 74%).

For **10*R***: R_f = 0.68 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz) δ 1.06 (s, 9H), 1.28 (s, 3H), 1.38 (s, 3H), 1.82 (s, 3H), 2.48 (dd 1H, J = 3.5, 9.9 Hz), 4.06−4.14 (m, 2H), 4.21 (dd, 1H, J = 3.5, 5.3 Hz), 4.92 (s, 1H), 4.96 (s, 1H), 7.40−7.85 (m, 10H); ^{13}C NMR δ (125 MHz) δ 19.5, 21.9, 25.7, 26.9, 27.2, 28.1, 30.7, 53.4, 69.4, 74.4, 78.6, 108.2, 113.9, 127.5, 127.6, 129.6, 129.8, 134.1, 135.4, 136.1, 145.3. HRMS(ESI) calcd for $C_{28}H_{39}O_3Si$ (M + H) 451.2668, found 451.2690.

For **10*S***: R_f = 0.60 (10% EtOAc/petroleum ether); $[\alpha]_D$ +14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz,) δ 1.01 (s, 9H), 1.24−1.65 (m, 3H), 1.31 (s, 3H), 1.57 (s, 3H), 1.67 (s, 3H), 1.98 (m, 1H), 2.40 (t, 1H, J = 10.0 Hz), 3.39 (dt, 1H, J = 3.8, 10.0 Hz), 3.82 (dd, J = 4.8, 10.0 Hz, 1H), 4.05 (m, 1H), 4.88 (s, 1H), 4.99 (s, 1H), 7.35−7.80 (m, 10H); ^{13}C NMR (125 MHz) δ 19.5, 20.3, 23.9, 26.5, 27.1, 28.8, 30.0, 57.2, 71.6, 72.8, 77.6, 108.7, 114.9, 127.5, 127.7, 129.6, 129.9, 133.8, 135.2, 136.2, 143.7; HRMS-(FAB) calcd for $C_{28}H_{37}O_3Si$ (M − H) 449.2512, found 449.2511.

Methyl Ketone (7*S*). Alkene **10*S*** (350 mg, 0.77 mmol) was dissolved in a 5/1 mixture of CH_2Cl_2/MeOH (19 mL). The solution was cooled to −78 °C and treated with a stream of O_3 in O_2 until TLC indicated the complete disappearance of the starting material. The reaction was then purged with N_2, and triphenylphosphine (700 mg) was added. The mixture was warmed to room temperature, stirred for 1 h at this temperature, and concentrated under reduced pressure. FCC of the residue afforded **7*S*** (300 mg, 85%) as a colorless oil: R_f = 0.32 (10% EtOAc/petroleum ether); $[\alpha]_D$ = −39.0 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz) δ 0.99 (s, 9H), 1.25−1.40 (m, 2H), 1.31 (s, 3H), 1.60 (m, 1H), 1.62 (s, 3H), 1.95 (m, 1H), 2.36 (s, 3H), 3.02 (t, 1H, J = 9.9 Hz), 3.74 (dt, 1H, J = 3.30, 9.9 Hz), 3.99−4.08 (m, 2H), 7.30−7.80 (m, 10H); ^{13}C NMR (125 MHz) δ 19.5, 23.7, 26.5, 27.0, 28.8, 29.1, 29.9, 34.7, 61.9, 72.5 (two peaks), 77.6, 109.1, 127.6, 127.9, 129.8, 130.1, 132.8, 134.7, 136.0, 136.1, 211.8. HRMS(ESI) calcd for $C_{27}H_{37}O_4Si$ [M + H] 453.2461, found 453.2480.

Benzothiazole Sulfone (21).[35] A mixture of mercaptobenzothiazole (500 mg, 2.98 mmol), NaH (299 mg of a 60%

(35) For a similar procedure: Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234.

dispersion in mineral oil, 7.47 mmol), and Bu_4NI (110 mg, 0.29 mmol) in dry DMF (5 mL) was stirred at room temperature for 30 min, under argon. 5-Bromo-2-methyl-2-pentene (0.80 mL, 5.98 mmol) was then added to the reaction mixture, and stirring was continued for 1.5 h. The reaction was quenched with water, and the mixture was extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by FCC to give the derived thioether as a colorless oil (720 mg, 97%): R_f = 0.63 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz) δ 1.63 (s, 3H), 1.69 (s, 3H), 2.49 (q, 2H, J = 7.3 Hz), 3.31 (t, 2H, J = 7.3 Hz), 5.19 (t, 1H, J = 7.3 Hz), 7.20−7.80 (m, 4H); ^{13}C NMR (75 MHz) δ 18.3, 26.0, 28.4, 34.1, 121.1, 121.7, 121.8, 124.3, 126.1, 134.7, 135.4, 153.6, 167.3.

Ammonium molybdate (1.90 g) and hydrogen peroxide (7.72 mL) were combined at 0 °C and stirred for 15 min. The resulting bright yellow solution was added dropwise at 0 °C over 90 min, to a solution of the product from the previous step (200 mg, 0.80 mmol) in EtOH (7.40 mL). The progress of the reaction was carefully monitored via TLC. Upon disappearance of the starting material, the mixture was diluted with water (20 mL) and extracted with ether. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by FCC to provide sulfone **21** (187 mg, 83% from thioether) as a white solid, and another product that was presumed to be the sulfoxide derivative (17 mg, 7% from thioether), as a colorless oil: R_f 0.63 and 0.53 (20% EtOAc/petroleum ether), respectively. For **21**: ^{1}H NMR (300 MHz) δ 1.55 (s, 6H), 2.55 (q, 2H, J = 8.0 Hz), 3.50 (t, 2H, J = 7.7 Hz), 4.99 (t, 1H, J = 8.8 Hz), 7.50−8.20 (m, 4H); ^{13}C NMR (125 MHz) δ 17.9, 21.6, 25.7, 54.7, 119.0, 122.5, 125.6, 127.8, 128.2, 135.9, 136.9, 152.9, 166.2. MS(ESI) *m/z* 282 [M + H]. HRMS(ESI) calcd for $C_{13}H_{16}NO_2S_2$ [M + H] 282.0622, found 282.0627. For sulfoxide: ^{1}H NMR (300 MHz) δ 1.60 (s, 3H), 1.65 (s, 3H), 2.30−2.49 (m, 1H), 2.57 (m, 1H), 3.10−3.30 (m, 2H), 5.10 (t, 1H, J = 7.5 Hz), 7.40−7.59 (m, 2H), 7.90−8.09 (m, 2H); ^{13}C NMR (75 MHz) δ 18.2, 20.9, 25.9, 60.0, 120.0, 122.4, 124.1, 126.2, 127.0, 135.6, 136.2, 154.1, 178.1.

Diene Mixture (22*E*/*Z*). LiHMDS (0.49 mL of a 1.0 M solution in THF, 0.49 mmol) was added dropwise, under argon, to a solution of sulfone **21** (140 mg, 0.49 mmol) and methyl ketone **7*S*** (50 mg, 0.11 mmol) in anhydrous THF (5 mL), at −78 °C. The resulting light yellow solution was stirred for 1.5 h, then warmed to room temperature, and stirred for 10 min at this temperature. The reaction was then quenched by the addition of saturated aqueous NH_4Cl, and the mixture was extracted with ether. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue afforded an inseparable 1/6 mixture of **22*E*/*Z*** (50 mg, 87%) as a colorless oil: R_f = 0.60 (10% EtOAc/petroleum ether). The *E*/*Z* ratio was determined by integration of the ^{1}H NMR signals at δ 5.16 and 5.43 ppm, respectively. For **22*Z***: ^{1}H NMR (500 MHz) δ 1.01 (s, 9H), 1.31 (s, 3H), 1.49−1.74 (m, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.70 (s, 3H), 1.96−2.02 (m, 1H), 2.82−2.90 (m, 2H), 2.96−3.02 (m, 1H), 3.38 (dt, 1H, J = 3.5, 10.0 Hz), 3.88 (dd, 1H, J = 5.5, 9.5 Hz), 4.08 (m, 1H), 5.23 (t, 1H, J = 7.0 Hz), 5.43 (t, 1H, J = 7.0 Hz), 7.28−7.70 (m, 10H); ^{13}C NMR δ (75 MHz) δ 18.1, 19.6, 24.4, 25.9, 26.5, 27.2, 27.5, 28.7, 30.3, 50.9, 71.2, 72.8, 77.5, 108.6, 124.1, 127.5, 127.6, 129.6, 129.7, 129.8, 131.2, 132.3, 134.1, 135.3, 136.1. For **22*E*** (selected signals): ^{1}H NMR (500 MHz) δ 2.31 (t, 1H, J = 10.5 Hz), 2.76−2.81 (m, 1H), 3.82 (dd, 1H, J = 5.0, J = 9.5 Hz), 4.02−4.06 (m, 1H), 5.16 (t, 1H, J = 6.5 Hz), 5.23 (t, 1H, J = 7.0 Hz). HRMS(ESI) mixture calcd for $C_{33}H_{47}O_3Si$ [M + H] 519.3294, found 519.3317.

Homoallylic Alcohol Mixture (23*E*/*Z*). A mixture of **22*E*/*Z*** (120 mg, 0.23 mmol) in THF (1.5 mL) and Bu_4NF (2.3 mL of a 1.0 M solution in THF, 0.23 mmol) was stirred at room temperature for 18 h, and then concentrated in vacuo. The residue was purified by FCC to give an inseparable mixture of **23*E*/*Z*** as a colorless oil (65 mg, quant.): R_f = 0.25 (20% EtOAc/petroleum ether). The mixture was determined to be an *E*/*Z* ratio of 1/6 based on integration of ^{1}H NMR signals at δ 5.40 and 5.62 ppm, respectively. For **23*Z***: ^{1}H NMR (300 MHz) δ 1.26 (s, 1H), 1.36 (s, 3H), 1.56 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.74−1.79 (m, 2H), 1.86−1.92 (m, 1H), 2.23−2.27 (m, 1H), 2.71 (t, 1H, J = 10.0 Hz), 2.73−2.92 (m, 2H), 3.42 (t, 1H, J = 9.0 Hz), 4.09 (dd, 1H, J = 5.5, 9.5 Hz), 4.26−4.28 (br s, 1H), 5.13 (t, 1H, J = 7.3 Hz), 5.62 (t, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz) δ 18.0, 19.1, 24.1, 25.8, 26.4, 27.1, 28.3, 28.6, 50.8, 68.3, 73.0, 76.0, 108.8, 123.0, 130.6, 132.3, 132.5. For **23*E***, see below.

E* Homoallylic Alcohol 23*E*.** *tert*-Butyl hydroperoxide in decane (0.08 mL of a 5−6 M solution, ca. 0.5 mmol) was added to a solution of **23 *E*/*Z (80 mg, 0.28 mmol) and vanadyl acetylacetonate (8 mg, 0.03 mmol), in dry CH_2Cl_2 (27 mL), at −10 °C under argon. The mixture was stirred at this temperature for 1 h, then quenched with dimethyl sulfide (0.2 mL), and stirred at 0 °C for an additional 30 min. The volatiles were then evaporated in vacuo, and the residue was purified by FCC to yield a single epoxide derivative (75 mg, 88%) as a colorless oil: R_f = 0.35 (20% EtOAc/petroleum ether). ^{1}H NMR (500 MHz) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 1.55−1.80 (m, 4H), 1.62 (s, 3H), 1.71 (s, 3H), 2.09−2.17 (m, 2H), 2.47−2.52 (m, 1H), 2.74 (dd, 1H, J = 4.03, 8.12 Hz), 3.49 (s, 1H), 3.77−3.81 (m, 1H), 3.98 (dd, 1H, J = 5.64, 9.37 Hz), 4.22−4.24 (m, 1H), 5.24−5.28 (m, 1H); ^{13}C NMR (125 MHz) δ 18.2, 19.5, 23.8, 25.9, 26.1, 28.1, 28.3, 28.4, 49.1, 62.9, 64.4, 69.4, 73.1, 75.6, 109.2, 119.7, 134.6; MS(ESI) *m/z* 297.2 [M + H].

A 0.5 M stock solution of Ph_2PLi was prepared by the addition of a hexane solution of *n*-butyllithium (1.0 mL, 1.6 M) to a solution of Ph_2PH (0.3 mL, 1.68 mmol) in dry THF (2 mL) at room temperature under an argon atmosphere, followed by stirring for an additional 1 h. An aliquot of the red solution of Ph_2PLi (1.95 mL, 1.00 mmol) was added at room temperature to a THF solution (0.8 mL), of a portion of the epoxide derivative (25 mg, 0.08 mmol), from the previous step. The reaction mixture was stirred for 2 h, at which time freshly distilled MeI (0.06 mL, 1.00 mmol) was introduced, and stirring was continued for an additional 1 h. The mixture was then cooled to −78 °C, and *n*-butyllithium (1.0 mL, 1.6 M) was added until the red-yellow color persisted. The mixture was then diluted with ether (10 mL) and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by FCC to afford **23*E*** as a light-yellow oil (18 mg, 76% from epoxide): R_f = 0.47 (20% EtOAc/petroleum ether). $[\alpha]_D$ −107.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.37 (s, 3H), 1.52 (s, 3H), 1.54−1.62 (m, 1H), 1.64 (s, 3H), 1.70 (s, 6H), 1.72−1.78 (m, 1H), 1.79 (br s, 1H), 1.86−1.90 (m, 1H), 2.14 (t, 1H, J = 10.1 Hz), 2.20−2.24 (m, 1H), 2.75−2.88 (m, 2H), 3.41 (dt, 1H, J = 3.7, 10.6 Hz), 4.04 (dd, 1H, J = 4.8, 9.5 Hz), 4.21−4.24 (m, 1H), 5.13 (t, 1H, J = 7.1 Hz), 5.40 (t, 1H, J = 6.6 Hz); ^{13}C NMR (125 MHz) δ 13.2, 18.0, 23.9, 25.9, 26.6, 27.4, 28.0, 28.7, 59.0, 68.1, 73.1, 76.8, 108.8, 122.8, 131.1, 131.3, 132.2; MS(ESI) *m/z* 281.2 [M + H]. HRMS(ESI) calcd for $C_{17}H_{27}O_3$ [M − H] 279.1960, found 279.1966.

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Supporting Information Available: Experimental procedures and physical data for **15**. ^{1}H and ^{13}C NMR charts for **7*S***, **8*R*/*S***, **10*S***, **16/17**, **18**−**21**, **22*Z*/*E***, **23*E*/*Z***, **23*E***, and **23*E***-acetate. This material is available free of charge via the Internet at http://pubs.acs.org.

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