= 8.4 Hz), 6.92 (d, 2 H, J = 8.1 Hz), 6.8 (d, 2 H, J = 8.1 Hz), 6.73 (d, 4 H, J = 8.4 Hz), 6.67 (s, 2 H), 4.61 (d, 2 H, J = 16.8 Hz), 4.23 (s, 2 H), 4.08-4.00 (m, 6 H), 3.81 (s, 2 H), 3.05-2.90 (m, 4 H), 2.81 (t, 4 H, J = 6.0 Hz), 2.59 (t, 4 H, J = 6.7 Hz), 1.97 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.9, 146.3, 135.3, 134.6, 129.6, 127.7, 127.3, 126.7, 125.1, 115.2, 67.0, 66.9, 58.4, 49.4, 47.8, 40.4, 35.3; MS, m/e calcd for $C_{36}H_{40}N_4O_2$ 560.31513, measured 560.31306. A portion of the free amine was converted to the trihydrochloride salt by treatment with excess aqueous HCl and subsequent lyophilization to give the trihydrochloride salt of **2**. Anal. Calcd for $C_{36}H_{43}Cl_3N_4O_2 \cdot 3H_2O$: C, 59.71; H, 6.82; N, 7.74. Found: C, 59.32; H, 6.77; N, 7.40.

Acknowledgment. The bis(sulfonamide) (**4**) used for preparing host **2** was prepared for us by Ly Phan, whose assistance is gratefully acknowledged. This project was supported by a grant from the National Institutes of Health. We are indebted to Professor W. C. Still (Columbia University), who provided the interactive graphics program used for the molecular mechanics calculations.

Structural and Synthetic Studies of the Spore Germination Autoinhibitor Gloeosporone

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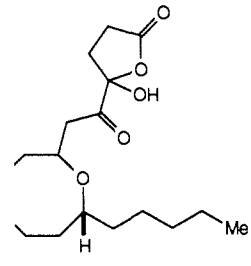
Abstract: Gloeosporone **1** is an autoinhibitor of spore germination that was recently isolated from conidia of *Colletotrichum gloeosporioides*. The structure initially proposed by Meyer et al. contained an unusual oxocane ring system (**1a**). A stereoselective synthesis of one of the two possible stereoisomeric forms of the oxocane structure that cast doubt on the structural proposal is described. Reinvestigation of the natural product resulted in the formulation of a structure that contains a 14-membered macrolide. Two syntheses of this compound are described which confirmed the new proposal and established the relative and absolute configuration of gloeosporone (**1b**). The asymmetric synthesis was achieved with use of an asymmetric reduction catalyst recently reported by Noyori et al. The reassignment of structure suggests that related macrolide natural products such as grahamimycin A_1 (**23**) and colletodiol (**24**) may exhibit similar spore germination inhibitory properties.

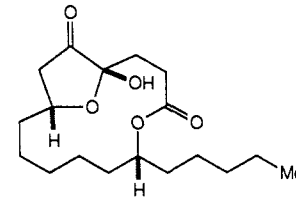
Germination regulatory agents have been identified from conidia of several species of fungi.[1] These compounds are autoinhibitors of spore germination and are believed to promote a favorable spatial distribution of the fungal species. Thus, many fungal spores will germinate efficiently only when their density is low. Self-inhibition to germination occurs under high-density conditions by a structurally specific spore response to the endogeneous autoinhibitors. These observations led to a proposed strategy for the development of fungistatic compounds.[2] The natural autoinhibitors or nonnatural analogues may be expected to mimic the conditions of crowding and result in inefficient spore germination.

In 1982, Lax et al. reported the isolation, biological activity,[3] and structure elucidation[4] of an autoinhibitor of spore germination from conidia of *Colletotrichum gloeosporioides*. The potency of this compound toward several *Colletotrichum* spp., including a pathogenic *Fusarium* species, and the novelty of the proposed structure **1a** are striking. The saturated eight-membered cyclic ether is rare in nature and unique among the known autoinhibitors of spore germination. Gloeosporone serves as a model compound for the development of species-specific fungistats and a biological probe molecule for investigations of the mechanism(s) of germination regulation.

The first report describing the spectroscopic properties of crystalline gloeosporone left a degree of uncertainty concerning the purported structure.[4] Our studies in this area were launched with (inter alia) the intention of clarifying the issue of structure. As will be described shortly, this research prompted a reinvestigation of the structure of gloeosporone, which, through an international effort, resulted in the reassignment of structure **1a** to the macrolide **1b**.[5] In the course of our research several issues that are relevant to the stereocontrolled synthesis of eight-membered ring ethers were probed and several syntheses of **1a** and **1b** were achieved.[6] Herein, we report on these findings.



1a



1b

Gloeosporone: The Oxocane. The original report concerning the oxocane structure of gloeosporone included the finding that a one-hydrogen resonance in the ^{1}H NMR spectrum appeared at δ 5.06.[4] This signal was assigned to the oxocane ring methine of the carbon bearing the pentyl side chain. Although more indicative of a methine bearing an acyloxy than alkoxy group, an anomalous deshielding effect could not be ruled out. Accordingly, a synthetic effort toward the oxocane **1a** was initiated.

The stereochemistry of **1a** was not addressed in the original report, and no data was presented that could distinguish between, for example, ring isomers (i.e., NOEDS). Our initial target was the cis isomer of **1a**, and our plan entailed the utilization of the stereoselective synthesis of cis oxocenes developed earlier in our laboratories in synthetic studies directed toward marine natural

(1) Cochran, V. W. *Physiology of Fungi*; Wiley: New York, 1958.
(2) (a) Allen, P. J. *Phytopathology* **1955**, *45*, 259. (b) Allen, P. J. *Proc. Nat. Acad. Sci. U.S.A.* **1972**, *69*, 3497. (c) Allen, P. J. *Physiological Plant Pathology*; Heitefuss, R., Williams, P. M. H., Eds.; Springer-Verlag: New York, pp 51-85.
(3) Lax, A. R.; Templeton, G. E.; Meyer, W. L. *Phytopathology* **1982**, *74*, 503.
(4) Meyer, W. L.; Lax, A. R.; Templeton, G. E.; Brannon, M. J. *Tetrahedron Lett.* **1983**, *24*, 5059.
(5) Meyer, W. L.; Schweizer, W. B.; Beck, A. K.; Scheifele, W.; Seebach, D.; Schreiber, S. L.; Kelly, S. E. *Helv. Chim. Acta* **1987**, *70*, 281.
(6) Kelly, S. E., Ph.D. Thesis, 1987, Yale University.

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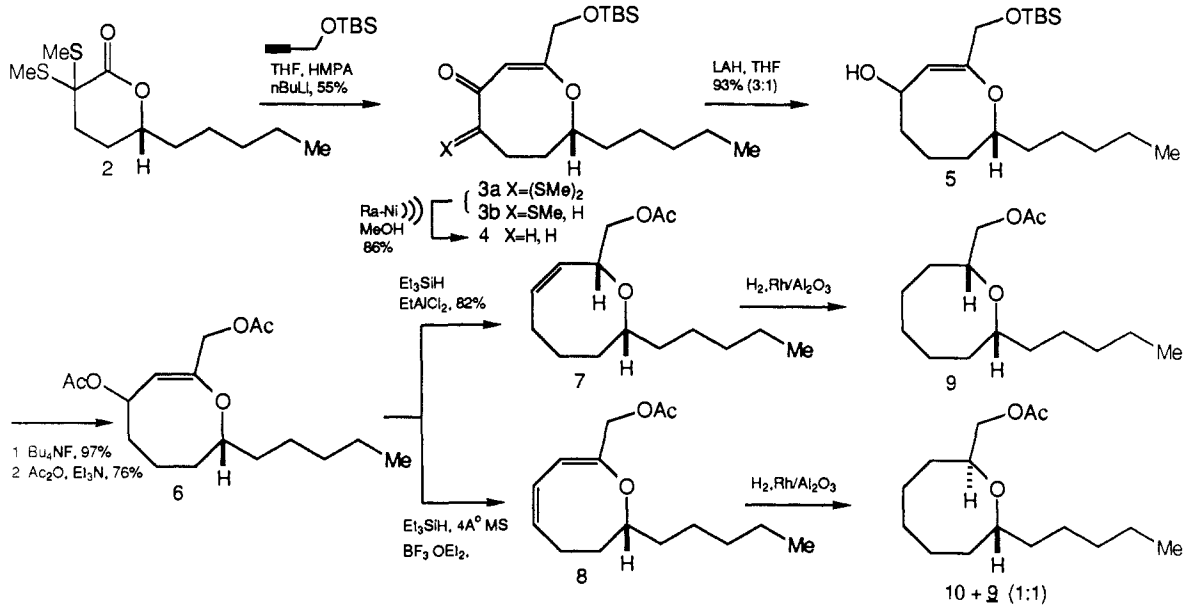
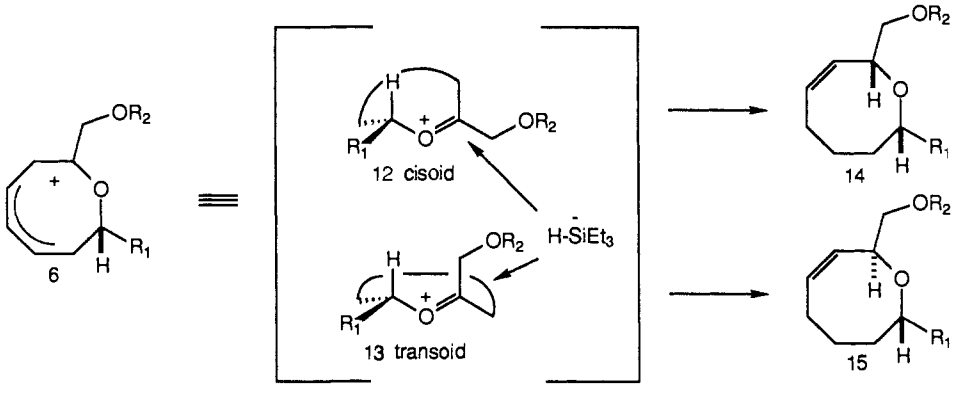
Scheme I



Scheme II



products.[7] The key ring-formation reaction results in the transformation of a δ-valerolactone into an oxocenone after treatment of the lactone with a lithium acetylide. As described in the earlier report, this reaction results in low to moderate yields of the oxocenone and is highly sensitive to the substitution pattern of the lactone and the acetylide. Recently, an interesting variation of this reaction that proceeds with increased efficiency was reported from the laboratory of Tsuchihashi and shows considerable promise for the synthesis of nitrogenous materials.[8]

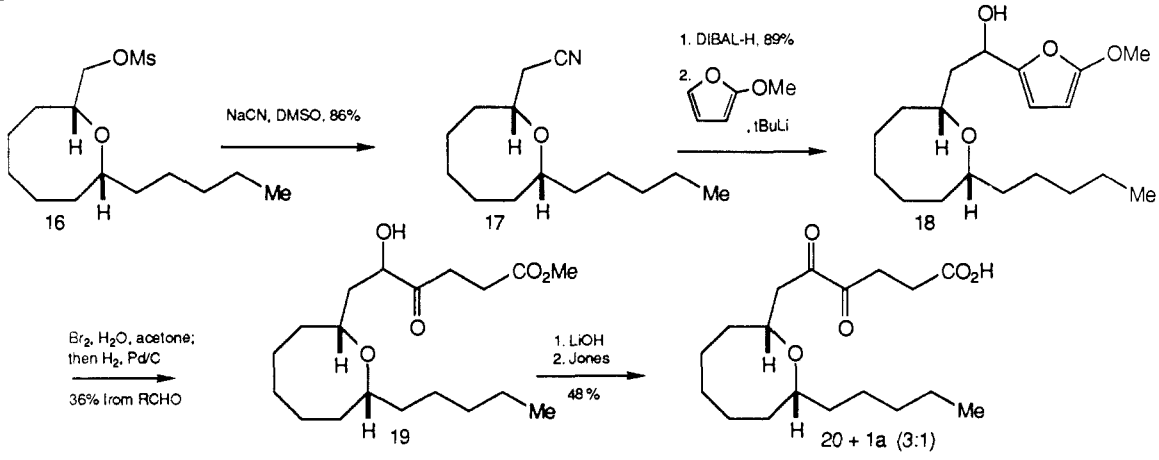
Treatment of the α,α-disubstituted lactone (±)-**2**[9] with 1-lithio-3-(*tert*-butyldimethylsiloxy)propyne in THF/HMPA at −78 °C for 0.5 h and then at room temperature for 5 h afforded the oxocenones **3ab** (2:1) in 55% yield (Scheme I). Although these compounds could be separated by silica gel chromatography, they were routinely used as the mixture in the subsequent desulfurization reaction. The thioacetal was incorporated into the lactone substrate since geminal substitution at this site was previously shown to significantly improve the yield of ring-expansion product.[7] The dithiane was subsequently removed by refluxing in methanol with W-4 Raney nickel *that had been activated by sonication*[10] to afford **4** in 89% yield. The Cioffi method of catalyst activation was essential to the success of this transformation.

The cis stereochemistry of the 2,8-disubstitution pattern of the target oxocane was secured by the reductive Ferrier-type reaction of the oxocene **6**.[7] The reduction product **5** resulted from the action of lithium aluminum hydride on **4** in THF. Stereoisomeric alcohols were obtained in a 3:1 ratio (stereochemistry not determined) that were not separated at this stage. The silyl ether in **5** proved to be too labile for the subsequent reduction sequence. Accordingly, the silyl ethers were removed, and the resulting diol isomers were separated by silica gel chromatography. Since both isomers could be converted to the same oxocene **7**, the routine processing of this material did not include their chromatographic separation. Considerable experimentation was performed in order to discover a high-yielding process for the conversion of the diacetates **6** into the target oxocanes **9** and **10**. The cis isomer was obtained with excellent stereocontrol by the reaction of **6** with $EtAlCl_2$ and Et_3SiH to provide the single isomer **7**, which was reduced to the oxocane **9**. The trans isomer **10** was acquired via a nonstereoselective reduction of the diene **8**, which resulted in a 1:1 mixture of **9** and **10** that were separated by silica gel chromatography. The stereochemistry was determined by NOEDS experiments. For example, strong enhancements of the ring methine hydrogen signals of **7** were observed upon reciprocal irradiation experiments (irradiation of multiplet at δ 3.40 resulted in 9.5% enhancement of the multiplet at δ 3.68 whereas irradiation of the signal at δ 3.68 resulted in an 11.9% enhancement of the δ 3.40 signal).[7]

The complete stereocontrol in the hydrogen-Ferrier type reaction of oxocenes such as **6** was noted earlier. One possible explanation for this result is depicted in Scheme II. Molecular mechanics calculations were performed on the presumed oxyallyl cation intermediate **11** and cis and trans reaction products, but these results proved inconclusive. However, a local conformational analysis, with assistance from the above method, points to a family

(7) Schreiber, S. L.; Kelly, S. E. *Tetrahedron Lett.* **1986**, *25*, 1757.
(8) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *J. Org. Chem.* **1987**, *52*, 2929.
(9) Prepared from carboethoxycyclopentanone by the sequence (a) $C_5H_{11}I$, K_2CO_3; (b) HCl; (c) MCPBA; (d) LDA, $CH_3SO_2SCH_3$.
(10) For a procedure involving the activation and properties of Raney Ni alloys, see: (a) Cioffi, E. A.; Prestegard, J. H. *Tetrahedron Lett.* **1986**, *27*, 415. (b) Cioffi, E. A.; Willis, W. S.; Suib, S. L. *Langmuir* **1988**, *4*, 697.

Scheme III



of cisoid cations **12** that are expected to result in cis products (observed) **14** and transoid cations **13** that lead to trans products **15**. These conformers minimize the $A^{1,3}$ strain in this region and present only one sterically unencumbered face (peripheral addition).[11] The lower energy of conformer **12** results from the eight-membered ring constraint.

The synthesis of the cis isomer of **1a** was completed by the transformations shown in Scheme III. The mesylate **16** (from **9**: K_2CO_3, MeOH (98%); MsCl, Et_3N (92%)) was homologated to the nitrile **17** and then to **18** by reduction and hydroxyalkylation of 5-lithio-2-methoxyfuran. The furan derivative **18** was converted to the ring-opened product **19** by employment of the conditions developed by Jurczak[12] followed by hydrogenation. Saponification and oxidation provided the target oxocane **1a**, which was found to be the minor isomer in the equilibrium between keto acid **20** and pseudoacid **1a** (**20**/**1a** = 3:1). Similar results have been noted by others.[13] Importantly, it was clear that the target system exhibited spectroscopic properties *that differed from those reported for the natural product.*[14] We concluded that the cis isomer of **1a** did not correspond to the structure of the natural product. Although the possibility existed that gloeosporone had the trans configuration about the oxocane ring, we noted that the trans isomer **10** exhibited ^1H NMR chemical shifts for the ring (ether) methines that were not significantly shifted from those of the cis isomers (e.g. **9**, **20**, **1a**) but which were quite distinct from the natural product ($C_{13}H$ at δ 3.40 in **9**, δ 3.67 in **10** vs δ 5.06 in natural gloeosporone).[15] Confident that the structure had been misassigned, we turned our efforts toward a spectroscopic analysis of gloeosporone.

Gloeosporone: The Macrolide. A small sample (ca. 1 mg) of natural gloeosporone was kindly provided by Professor W. L. Meyer (University of Arkansas).[14] From this material we were able to gather additional ^1H NMR data that proved to be essential to our analysis. A COSY 2D NMR spectrum at 500 MHz allowed numerous assignments of hydrogen resonances. NOEDS experiments provided distance constraints that, in combination with the reported data, allowed us to propose two plausible macrolide structures for gloeosporone, **21** and **22**. A detailed description of these efforts has recently appeared.[5] Although we could not distinguish between these candidate structures, the striking similarity of **21** to the macrodiolides grahamimycin A (**23**)[16] and colletodiol (**24**)[17] (from the fungus *Colletotrichum capsici*) served to bias our opinion in the direction of **21**. *Parenthetically, we note that the potential germination autoinhibitory properties of the natural products* ***23*** *and* ***24*** *have not, to our knowledge, been assayed.*

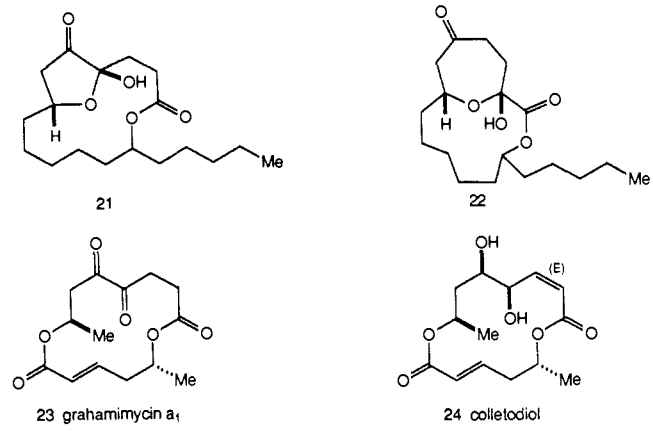
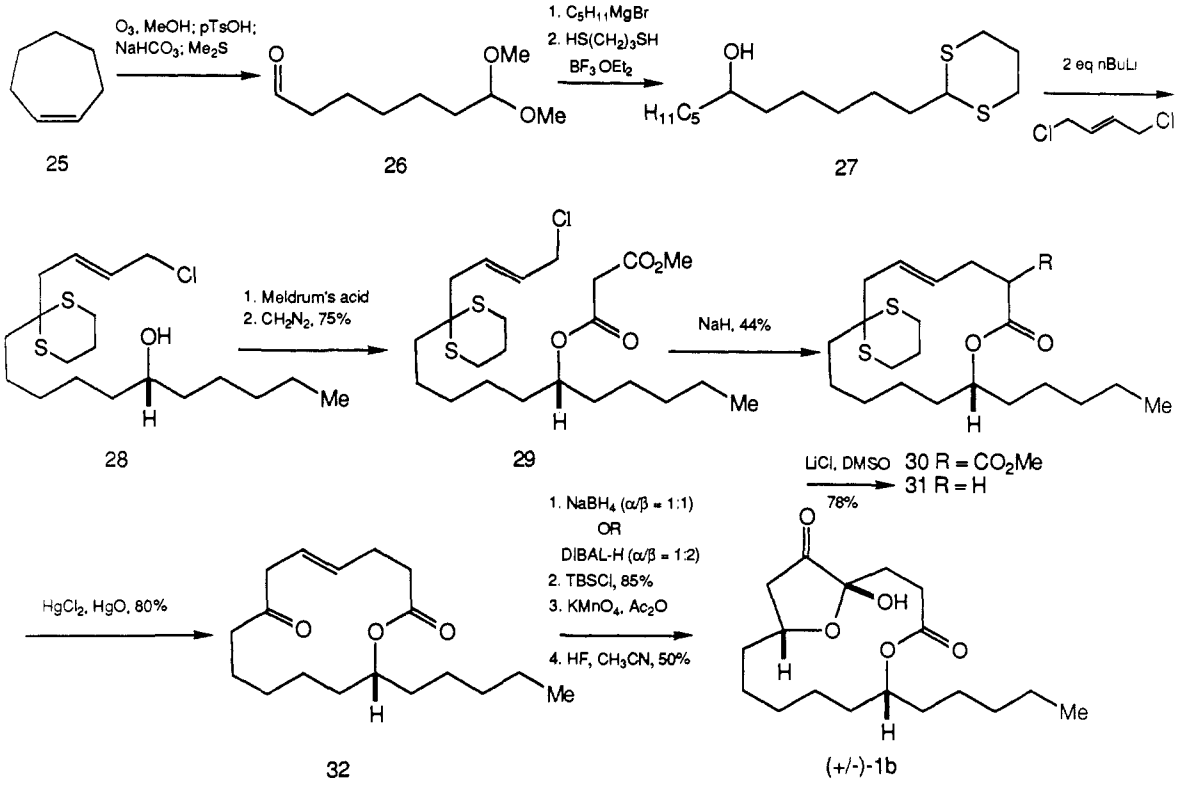


Figure 1.

In order to resolve the structural ambiguity, we initiated efforts to prepare **21** and **22** by synthesis. Although a synthesis of **22** was not completed, our efforts in this area were interrupted by a successful completion of the synthesis of **21**. These results are shown in Scheme IV. The differentiated dialdehyde derivative **6** is easily obtained from cycloheptene by the modified ozonolysis procedure.[18] Introduction of the *n*-pentyl side chain via the Grignard reagent and transthioacetalization provided **27**. Alkylation of the dianion with (*E*)-1,4-dichloro-2-butene afforded **28**. The mixed malonate **29** was cyclized to afford the macrolide **30** that was decarbomethoxylated by Krapcho's procedure[19] to afford **31**. Dithiane hydrolysis gave rise to the β,γ-unsaturated ketone **32**. Although the conformational preferences of macrocycles are often manifested in the form of stereoselective ring transformations,[11] attempts to achieve the facially selective reduction of the ketone in **32** were largely unsuccessful. Reduction with Dibal resulted in a 2:1 mixture of isomers that were separated by silica gel chromatography. At this point, we were not able to assign stereochemistry. As we were to discover subsequently (vide infra), the minor isomer in the reduction corresponds to the di-

(11) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
(12) Jurczak, J.; Pikul, S. *Tetrahedron Lett.* **1985**, *26*, 3039.
(13) For other syntheses of oxocane **1a**, see: (a) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (b) Mortimore, M.; Cockerill, G. S.; Kocienski, P.; Treadgold, R. *Tetrahedron Lett.* **1987**, *28*, 3747.
(14) We thank Professor Walter Meyer for providing us with spectroscopic data on gloeosporone and a sample of the natural product.
(15) Recently, this possibility was excluded in a rigorous manner (see ref 13).
(16) Ronald, R. C.; Gurusiddaiah, S. *Tetrahedron Lett.* **1980**, *21*, 681. Seidel, D.; Seebach, D. *Ibid.* **1982**, *23*, 159.
(17) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497. Powell, J. W.; Whalley, W. B. *J. Chem. Soc. C* **1969**, 911. MacMillan, J.; Simpson, T. J. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1487. Amstutz, R.; Hungerbuhler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1796.
(18) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150. Recently we have found that the use of 100% methanol as solvent has certain advantages, i.e. the reaction has been carried out at 2.0 M concentration on an 80-g scale with these conditions (unpublished results of Harold V. Meyers in these laboratories).
(19) Krapcho, A. P.; Weimaster, J. F.; Elridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

Scheme IV



astereomeric configuration found in the natural product. Both C_7 isomers were carried on to the target structures **21** by a two-step procedure. Oxidation of the olefin with conditions developed by Sharpless[20] provided a diketone that was directly treated with HF in acetonitrile to provide, in the case of the C_7-α isomer, (±)-gloeosporone (**1b**) that exhibited spectroscopic properties *that were identical with the natural product.* We then learned from Professor D. Seebach (ETH) that his group had achieved success in the X-ray crystallographic structure determination of gloeosporone.[5] With this information provided to us, we were then able to assign stereochemistry to our ketone reduction products (e.g., the alcohols from **32**). The constitution and relative stereochemistry of gloeosporone was securely defined as **1b**. In analogy to other members of the macrolide class (e.g., **23** and **24**), we felt the likely absolute configuration was as depicted; however, confirmation would await an unambiguous asymmetric synthesis.

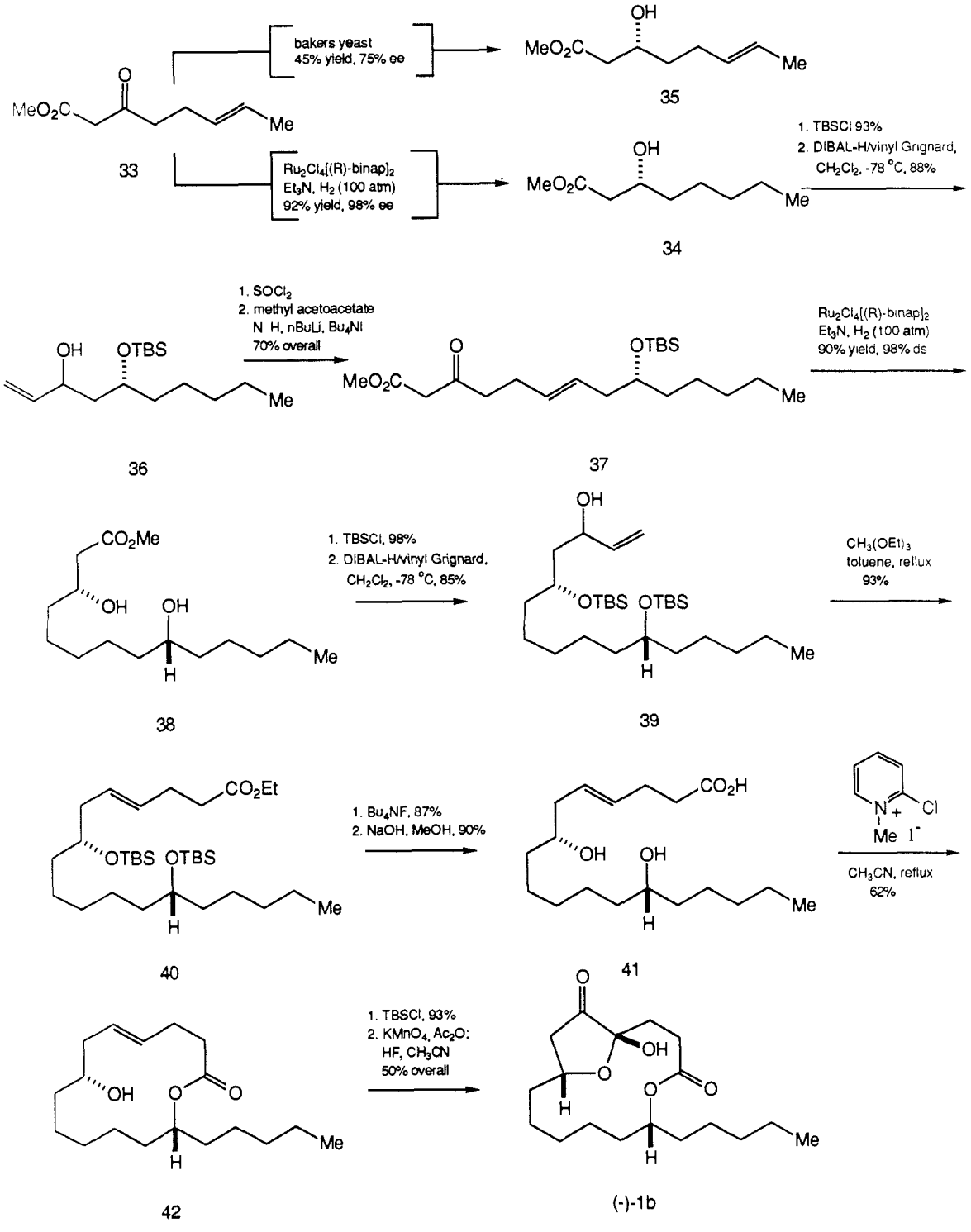
Asymmetric Synthesis of Gloeosporone. The racemic synthesis illustrates that the hemiacetal stereochemistry follows from the geometric constraint of the bridged tetrahydrofuran. The stereochemical issues in the gloeosporone synthesis simplify to a need to control the configuration at the two secondary carbons bearing oxygen substituents. The recently reported asymmetric synthesis of (+)-gloeosporone illustrates the efficient use of readily available materials from the chiral pool.[21] We chose to employ chiral catalysts to achieve the asymmetric hydrogenation of ketonic precursors to the two secondary stereocenters.

In the course of this work, the development of a ruthenium-based catalyst for the asymmetric reduction of β-keto esters was reported by the groups of Akutagawa and Noyori.[22] As we had investigated the use of fermenting bakers' yeast as a more traditional solution to this problem,[23] we carried out a comparison of the two methods. One result is illustrated in Scheme V. The ruthenium(II)–BINAP catalyzed reduction of **33** provided the saturated β-hydroxy ester **34** in excellent yield and enantioselectivity. The reaction is convenient to perform and amenable to substantial material processing. The reduction of **33** with baker's yeast resulted in a 45% yield of the unsaturated β-hydroxy ester **35** in 75% ee. Although these conditions convert the carboxylic acid of **33** into the corresponding β-hydroxy acid with excellent enantioselectivity (ee >98%),[24] the reaction was low yielding (25%), difficult to perform on a multigram scale, and deemed impractical for the present application. Our conclusions concerning the favorable comparison of the ruthenium-based catalyst system to fermenting baker's yeast mirror those of the discoverers of the former system.[22]

The homologation of **34** ($[\alpha]^{27}_D$ −22.2° (*c* 1.44, $CHCl_3$)) into the second reduction substrate **37** ($[\alpha]^{27}_D$ +8.91° (*c* 2.01, $CHCl_3$) proceeded in four steps; notable among these is the one-pot sequential Dibal-H/vinyl Grignard addition to the silyl ether of **34** (see also **38** → **39**).[25] The ruthenium(II)–BINAP catalyst achieved the same levels of stereoinduction with the chiral substrate **37** as had been found with achiral substrates. The stereochemistry of **38** ($[\alpha]^{27}_D$ −10.55° (*c* 1.45, $CHCl_3$), mp 57–59 °C) was assigned on the basis of these previous results with the expectation that the influence of the remote stereocenter in **37** would be negligible. The second homologation resulted in the conversion of **38** into **40** and proceeded via the Johnson–Claisen rearrangement. In this manner the trans stereochemistry of the alkene was secured. Desilylation and saponification of **40** provided the unprotected seco acid **41** (mp 93 °C). Macrolactonization of the diol by the procedure of Mukaiyama[26] proceeded with complete chemoselectivity (14-membered macrolide formed rather than the eight-membered ring alternative) to afford **42** ($[\alpha]^{27}_D$ +28.49° (*c* 0.99, $CHCl_3$), mp 51–52 °C) in 62% yield. Final conversion to (−)-gloeosporone ($[\alpha]^{27}_D$ −63.2° (*c* 0.34, $CHCl_3$), mp 117–118 °C) followed the procedure developed in the racemic synthesis. As reported by Seebach, the (−)-isomer corresponds to the natural

(20) Jensen, H. P.; Sharpless, K. B. *J. Org. Chem.* **1974**, *39*, 2314.
(21) Adam, G.; Zibuck, R.; Seebach, D. *J. Am. Chem. Soc.* **1987**, *109*, 6176.
(22) Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
(23) For a review, see: Sih, C. J.; Chen, C. S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.
(24) Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* 1983, 599.
(25) For related examples, see: (a) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905. (b) Comins, D. L.; Herrick, J. J. *Tetrahedron Lett.* **1984**, *25*, 1321.
(26) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

Scheme V



configuration.[21] The final stereochemical ambiguity was now removed, and the absolute stereostructure of (−)-gloeosporone was confirmed to be 4*S*,7*R*,13*R* as rendered throughout this paper.

Conclusion

Our studies of the germination autoinhibitor (−)-gloeosporone prompted a reinvestigation of the purported oxocane structure **1a** and concluded with the determination of stereostructure **1b**. These findings suggest that the structurally related fungal products grahamimycin A_1 (**23**) and colletodiol (**24**) may also exhibit spore germination inhibitory properties. Our results are entirely consistent with those reported by others that have contributed to the resolution of this problem. In the course of our synthetic work, several findings relevant to the demands of multistage synthesis were uncovered. The synthesis of *cis*-2,8-disubstituted oxocenes, commonly encountered in the area of marine natural products, was achieved. The iterative use of the Ru(II)–BINAP catalyst was found to be a highly effective and practical solution to the stereochemical problems posed by the macrolide structure of gloeosporone. It seems likely that this catalyst will continue to benefit workers in the area of stereocontrolled synthesis.

Experimental Section

General Methods. NOE experiments were performed on a Bruker WM-500 instrument equipped with an Aspect 2000 computer. The Bruker program 12.5 (NOE difference, direct A-B FID accumulation) was used with relaxation delay of 10 s, NOE generation for 3 s (ca. 2-3 X T1), repetitive cycling with accumulation of eight scans on and off resonance and two dummy scans to assure saturation. Homogated irradiation was used to eliminate spurious noise with irradiation power of less than 0.5 W. Exponential multiplication of 2 Hz was used for data

processing. Enhancements are reported in percent relative to the irradiation signal.

Reactions were monitored by analytical thin-layer chromatographic methods (TLC) with use of E. Merck silica gel 60F glass plates (0.25 mm). Flash chromatography was carried out with the use of E. Merck silica gel 60 (230–400 mesh) as described by Still.[27] High-performance liquid chromatography (HPLC) was performed with a μ-porasil column. Analytical gas chromatographic analyses were performed with a Quadrex 007 series bonded phase fused silica capillary column (50 M 007 methyl phenyl (5%) silicone). High-resolution mass spectra were recorded by Dan Pentek of the Yale University Chemical Instrumentation Center. Chemical-ionization high-resolution mass spectrum were obtained with isobutane as reagent gas.

Acetonitrile (CH_3CN) and dimethylformamide (DMF) were purified to "super-dryness" according to the procedure of Burfield and Smithers.[28]

5,6,7,8-Tetrahydro-2-[[[(dimethylethyl)dimethylsilyl]oxy]methyl]-5,5-bis(methylthio)-8-pentyl-4*H*-oxocen-4-one (3a). To a solution of the TBS propargyl ether (0.990 g, 5.8 mmol, 1.4 equiv) in 50 mL of THF at −78 °C was added *n*-BuLi (2.70 mL, 1.3 equiv) dropwise. The anion was stirred for 0.5 h. The reaction mixture was then transferred, via a stainless steel cannula, to a stirring solution of the lactone (1.095 g, 4.2 mmol, 1 equiv) in 50 mL of THF. The reaction mixture was allowed to warm to room temperature, diluted with 100 mL of THF and HMPA (5.81 mL, 33 mmol, 8 equiv), and stirred for 5 h. It was subsequently poured into a separatory funnel, diluted with 100 mL of ether, and washed sequentially with saturated aqueous solutions of NH_4Cl, $NaHCO_3$, and NaCl. The organic layer was dried over $MgSO_4$, solvents were removed by evaporation, and the residue was purified by flash chromatography to yield the bis(methylthio)oxocenone (0.642 g, 35%), the mono(methylthio) compound (0.329 g, 20%), and the 1,2 addition adduct (0.524 g, 29%): IR (FT, CCl_4) 1659.34 (s), 1471.56 (m), 1463.04 (m), 1455.45 (m), 1120.33 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.25 (s, 1 H), 4.05 (s, 2 H), 3.72 (m, 1 H), 2.3–2.0 (m, 2 H), 1.92 (s, 3 H), 1.90 (s, 3 H), 1.85–1.15 (m, 10 H), 0.88 (s, 9 H), 0.84 (t, 3 H, J = 6.79 Hz), 0.07 (s, 6 H); ^{13}C NMR (62.89, $CDCl_3$) δ 194.66, 163.01, 95.23, 79.85, 79.79, 72.09, 62.70, 36.70, 36.19, 32.00, 31.45, 28.29, 25.79, 25.18, 22.36, 18.25, 13.86, 12.90, 9.84, −5.37, −6.48; MS, m/e (percent) 432 (M^+, 1.1), 417 (2.5), 375 (0.7), 205 (9.3), 203 (100), 157 (69), 120 (41). Anal. Calcd for $C_{21}H_{40}O_3S_2Si_2$: C, 58.28; H, 9.32. Found: C, 58.34; H, 9.36.

5,6,7,8-Tetrahydro-2-[[[(dimethylethyl)dimethylsilyl]oxy]methyl]-8-pentyl-4*H*-oxocen-4-one (4). A solution of W-4 grade Raney nickel in ethanol was deactivated by decanting off the ethanol and adding UV-grade acetone (three 100-mL portions). The acetone solution was refluxed for 3 h in order to remove excess hydrogen. After cooling, the Raney catalyst was washed with 2 × 100-mL portions of water, 2 × 100-mL portions of 95% ethanol, and finally with UV grade methanol. After each of these washings the catalyst was sonicated for approximately 1 min. The reagents were then added to the Raney nickel in UV-grade methanol, and the reaction mixture was refluxed for 2 h. Reaction progress was monitored by thin-layer chromatography, and upon completion of the reaction the flask was cooled, and the mixture was filtered over Celite and washed with methylene chloride and water. The reaction flask was rinsed and sonicated several times to insure complete removal of product. *Caution*: sonicated Raney nickel catalyst is extremely flammable and readily ignites when allowed to dry in air. Always filter with a nonflammable solvent and water. The catalyst should be collected and disposed of in an aqueous solution. When the mono(methylthio) (0.735 g, 1.9 mmol) and bis(methylthio) (0.946 g, 2.2 mmol) oxocenones were subjected to these conditions, approximately 2 g equiv of Raney nickel were used. After filtration, the methylene chloride/water mixture was poured into a separatory funnel, and the organic layer was drained. The aqueous layer was washed with 50 mL of methylene chloride, the combined organic layers were dried over $MgSO_4$, solvent was removed by evaporation, and the residue was purified by flash chromatography (10:1 hexanes/ether) to yield the product (1.20 g, 86%) as a clear liquid: IR (FT, CCl_4) 1653.25 (s), 1640.16 (s), 1471.80 (m), 1463.35 (m), 1456.85 (m), 1258.26 (s), 1157.70 (s), 1126.83 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (s, 1 H), 4.05 (s, 2 H), 3.90 (m, 1 H), 2.66 (ddd, 1 H, J = 17.80, 6.80, 2.17 Hz), 2.46 (ddd, 1 H, J = 17.90, 12.25, 2.2 Hz), 2.05 (m, 1 H), 1.9–1.36 (m, 4 H), 1.25 (br m, 6 H), 0.88 (t, 3 H, J = 7.02 Hz), 0.87 (s, 9 H), 0.048 (s, 6 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 203.86, 167.21, 101.65, 81.76, 62.76, 42.77, 36.09, 35.44, 31.39, 25.71, 25.27, 22.33, 19.33, 18.15, 13.74, −5.59; MS, m/e (percent) 340.1 (0.1, M^+), 325.2 (1.6), 283.2 (71.5), 157.0 (100); HRMS (DIP, EI) calcd for $C_{19}H_{36}O_3Si$ 340.2435, found 340.2414.

5,6,7,8-Tetrahydro-2-(hydroxymethyl)-8-pentyl-2*H*-oxocene Acetate (7). The bis(acetate) **6** (0.097 g, 0.087 mmol, 1 equiv) was dissolved in 2 mL of methylene chloride and cooled to −40 °C. To this stirring solution was added triethylsilane (0.138 mL, 0.864 mmol, 10 equiv) followed by dropwise addition of ethyl aluminum dichloride (0.104 mL, 0.104 mmol, 1.2 equiv). The reaction was allowed to slowly warm to room temperature over 90 min. It was then poured into a separatory funnel containing saturated sodium bicarbonate solution and extracted with 3 × 20-mL portions of ether. The organic phase was washed with brine and dried over $MgSO_4$. Following solvent removal, the crude material was purified by flash chromatography (10:1 hexanes/ether) to yield 0.018 g (82%) of the monoacetate **7**: IR (FT, CCl_4) 1744.52 (s), 1467.24 (m), 1450.91 (m), 1434.96 (m), 1379.37 (m), 1364.67 (m), 1233.33 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.75 (dddd, 1 H, J = 1.29, 8.44, 8.44, 11.51 Hz), 5.31 (ddd, 1 H, J = 1.53, 3.29, 11.51 Hz), 4.21 (m, 1 H), 4.09 (m, 2 H), 3.51 (m, 1 H), 2.76 (m, 2 H), 2.04 (s, 3 H), 1.95–1.23 (m, 12 H), 0.86 (t, 3 H, J = 6.02 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 170.61, 131.91, 127.92, 79.82, 77.65, 66.18, 36.29, 31.95, 31.81, 25.43, 25.19, 24.13, 22.50, 20.66, 13.82; MS, m/e (percent) 207.2 (0.1), 194.2 (14.3), 181.2 (18.0), 176.1 (12.0), 163.2 (15.0), 151.2 (15.3), 137.1 (28.9), 123.2 (29.7), 109.2 (26.5), 97.1 (47.0), 95.2 (100), 79.1 (77.1), 71.2 (23.4). HRMS (GC, EI) calcd for $C_{15}H_{26}O_3$ 255.1961, found 255.1979.

2-(Hydroxymethyl)-8-pentyloxocane Acetate (9). The Ferrier product (0.152 g, 0.59 mmol, 1 equiv) was diluted with 5 mL of distilled ethyl acetate. To this solution was added rhodium on alumina (0.022 g, 14% by weight), and a septa was placed on top of the flask and secured with teflon tape. A balloon of hydrogen gas was placed over the flask, allowing the gas to bubble through the solution by a steel needle. The system was purged by degassing three times with aspirator pressure and flushed with hydrogen gas. After 3 h, the hydrogen balloon was removed, the needle was rinsed with ethyl acetate, and the solution was purged with nitrogen. The reaction was subsequently filtered over Celite, and the flask was washed thoroughly with ethyl acetate. The solvent was removed by evaporation, and the residue was purified by flash chromatography to yield the product (0.142 g, 0.55 mmol, 93%) (10:1 hexanes/ether): IR (FT, CCl_4) 1744.31 (s), 1459.79 (m), 1454.48 (m), 1237.83 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.96 (m, 2 H), 3.68 (m, 1 H), 3.40 (m, 1 H), 2.03 (s, 3 H), 1.77–1.55 (m, 6 H), 1.49–1.25 (m, 12 H), 0.85 (t, 3 H, J = 6.68 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 170.31, 80.67, 77.02, 67.62, 36.48, 33.45, 31.68, 30.50, 26.95, 25.59, 24.08, 23.86, 22.36, 20.47, 13.69; MS, m/e (percent) 257.1 (1.6), 196.2 (11.3), 183.2 (26.1), 165.2 (40.2), 125.2 (22.7), 114.2 (53.9), 109.2 (57.7), 82.1 (100); NOE (500 MHz) irradiation (3.68 ppm) 11.85% enhancement at 3.40 ppm, 7.17% enhancement at 3.96 ppm; (3.40 ppm) 9.5% enhancement at 3.68 ppm, 6.3% enhancement at 3.96 ppm. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.00. Found: C, 70.03; H, 11.16.

2-(2-Nitriloethyl)-8-pentyloxocane (17). The mesylate (0.88 g, 0.30 mmol) was dissolved in 3 mL of freshly distilled DMSO. To this solution was added a catalytic amount of sodium bicarbonate, sodium cyanide (0.073 g, 5 equiv), and sodium iodide (0.224 g, 5 equiv). The reaction was heated in an oil bath at 60 °C overnight. When judged complete by TLC, the reaction was poured into a separatory funnel containing a saturated solution of sodium bicarbonate and extracted with three 50-mL portions of ether. The combined ether extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (10:1 hexanes/ether) to yield the pure nitrile **17** (0.058 g, 0.26 mmol, 86%): R_f 0.49 (1:1 hexanes/ether); IR (FT, CCl_4) 2249.29 (w), 1466.87 (m), 1460.65 (m), 1454.98 (m), 1444.28 (m), 1100.89 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (m, 1 H), 3.52 (m, 1 H), 2.47 (dd, 1 H, J = 16.51, 7.08 Hz), 2.405 (dd, 1 H, J = 16.51, 5.88 Hz), 1.79–1.21 (m, 18 H), 0.867 (t, J = 6.51 Hz, 3 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 117.98, 80.99, 75.23, 36.34, 33.90, 33.01, 31.85, 26.75, 25.73, 25.18, 24.04, 23.92, 22.51, 13.91; MS, m/e (percent) 223.2 (10.1, M^+), 194.2 (8.7), 180.1 (14.6), 166.2 (11.1), 152.1 (100), 134.1 (27.8), 124.1 (41.0); HRMS (DIP) calcd for $C_{14}H_{25}NO$ 223.1938, found 223.1940.

2-(5-Carbomethoxy-2-hydroxy-3-oxopentyl)-8-pentyloxocane (19). The aldehyde (0.031 g, 0.137 mmol, 1 equiv) was dissolved in 2 mL of dry diethyl ether. Methoxyfuran (distilled) (0.206 mL, 2.2 mmol, 16 equiv) was dissolved in 2.5 mL of ether and cooled to −40 °C. *tert*-Butyllithium (1.28 mL, 2.0 mmol, 15 equiv) was added, and the anion was stirred for 2 h. The bright yellow solution was cooled to −78 °C, and the aldehyde was added. The reaction was slowly warmed to room temperature over 1 h. The reaction was diluted with ether and poured into a separatory funnel containing brine. The aqueous phase was extracted with 3 × 10-mL portions of ether, the combined organic layers were dried over potassium carbonate and filtered, solvent was removed, and the product was taken immediately to the next step. The furan was subsequently dissolved in 1 mL of UV-grade acetone and 0.2 mL of water. To this solution was added pyridine (0.044 mL, 0.54 mmol, 4 equiv) followed by bromine (0.007 mL, 0.136 mmol, 1 equiv), and the reaction was

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.

stirred for 4 h. It was then poured into a separatory funnel containing brine and extracted with 10 mL of ether. The ether was washed with copper sulfate and then dried over $MgSO_4$. After solvent removal the crude mixture was flushed through a plug of silica with diethyl ether. Solvent was removed, and the product was hydrogenated for approximately 1 h in 2 mL of ethyl acetate with palladium on carbon as catalyst. The reaction was filtered over Celite, and the flask was rinsed thoroughly with ethyl acetate. The crude material was purified by flash chromatography to yield the desired product (16.8 mg, 0.493 mmol, 36%): IR (FT, CCl_4) 3459.99 (m), 1735.20 (s), 1713.10 (s), 1438.84 (s), 1089.30 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.39 (ddd, 1 H, J = 2.42, 4.96, 10.07 Hz), 3.84 (m, 1 H), 3.70 (d, 1 H, J = 4.96 Hz), 3.65 (s, 3 H), 3.59 (m, 1 H), 2.85 (m, 2 H), 2.62 (m, 2 H), 1.90 (ddd, 1 H, J = 2.42, 9.73, 13.85 Hz), 1.78–1.21 (m, 19 H), 0.86 (t, 3 H, J = 6.56 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 211.82, 210.53, 173.26, 79.83, 78.14, 77.20, 76.17, 75.94, 75.56, 51.73, 51.67, 40.55, 38.60, 36.54, 34.36, 33.39, 32.74, 32.45, 31.92, 31.74, 27.62, 27.56, 26.79, 26.44, 25.83, 25.70, 23.82, 23.58, 23.32, 23.26, 22.54, 13.93; MS, m/e (percent) 310.3 (0.9), 239.2 (4.2), 227.3 (5.2), 197.1 (5.5), 183.2 (13.5), 165.2 (10.7), 157.1 (21.2), 146.1 (6.5), 139.1 (53.2), 125.2 (39.3), 117.1 (46.8), 109.2 (24.8), 97.2 (67.4), 85.1 (100.0).

Dihydro-5-hydroxy-5-[(8-pentyl-2-oxocanyl)acetyl]-2(3*H*)-furanone (20, 1a). The hydroxy ester **19** (0.013 g, 0.038 mmol, 1 equiv) was dissolved in 0.7 mL of UV-grade methanol and 0.2 mL of distilled water. The reaction was cooled to 0 °C. Lithium hydroxide (8 mg, 0.19 mmol, 5 equiv) was added, and the reaction mixture was stirred for 45 min. It was then acidified to pH 2 with 10% HCl and extracted with 5 mL of ether. The ether layer was dried over $MgSO_4$ and filtered, and following solvent removal the material was taken on to the oxidation step without purification. The acid was dissolved in UV-grade acetone (1 mL) and cooled to 0 °C. Jones reagent (0.005 mL, 2 equiv) was added dropwise. The reaction was stirred for 1.5 h, and 0.5 mL of 2-propanol was then added. The reaction was diluted with 2 mL of ether, and the organic layer was washed with brine and dried over $MgSO_4$. Following solvent removal the crude product was purified by flash chromatography to yield solid pseudogloeosporone (6.0 mg, 48%) as a 3:1 mixture of open and closed forms: IR (FT, CCl_4) 1714.56 (br, s), 1261.15 (s), 1094.58 (s), 1018.14 (m), 1013.74 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 [(m, 1 H), 3.97 (m, 0.33 H); ca. 3:1 ratio], 3.56 (m, 1 H), 3.43 (m, 1 H), 3.35 (dd, 0.33 H, J = 10.31, 13.04 Hz), 3.13 (m, 1 H), 3.02 (m, 1 H), 2.82–2.55 (m, 5 H), 2.41 (dd, 1 H, J = 3.02, 13.04 Hz), 1.89–1.21 (m, 52 H), 0.86 (m, 5 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 204.13, 197.96, 197.37, 175.34, 174.96, 125.46, 80.63, 79.76, 79.63, 75.12, 43.67, 43.38, 42.95, 37.02, 36.60, 36.44, 34.69, 33.53, 33.34, 33.19, 32.98, 32.54, 31.93, 31.75, 30.85, 30.78, 30.37, 30.31, 29.79, 29.65, 29.42, 29.32, 29.21, 28.88, 28.61, 28.14, 27.34, 26.87, 26.69, 26.59, 26.21, 25.78, 25.50, 25.43, 23.81, 23.70, 23.60, 23.45, 23.17, 23.08, 22.59, 13.99; MS (EI), m/e (percent) 282.2 (1.3), 225.2 (2.6), 207.2 (3.0), 183.3 (6.5), 165.2 (6.2), 109.1 (17.1), 97.2 (28.4), 95.2 (32.3), 83.2 (42.6), 81.1 (28.6), 69.1 (49.3), 57.1 (100.0); MS (DIP, CI, NH_4) 327.24 (M + 1, 22.1), 326.24 (M^+, 17.5), 277.09 (16.4), 225.22 (36.1), 207.23 (74.8), 189.21 (58.3), 183.21 (100), 165.20 (76.3), 123.15 (43.7), 109.12 (81.0), 95.12 (91.4).

7,7-Dimethoxyheptanal (26). Cycloheptene (7.21 g, 75.1 mmol, 1 equiv) was added to a three-neck flask containing 250 mL of UV-grade methanol. The flask was equipped with a calcium chloride drying tube and a glass tube inlet for ozone. The reaction mixture was cooled to −78 °C, and ozone was bubbled through for approximately 20 min until a blue color persisted. The solution was purged with nitrogen until the color was dissipated in order to prevent over oxidation. *p*-Toluenesulfonic acid (1.42 g, 7.5 mmol, 1 equiv) was added, and the reaction mixture was warmed to room temperature and stirred for 2 h. The acid was neutralized with sodium bicarbonate (25.2 g, 300 mmol, 4 equiv) and after the mixture was stirred for 15 min, dimethyl sulfide (12 mL, 163 mmol, 2.2 equiv) was added. After 16 h, the reaction mixture was concentrated by solvent removal on a rotary evaporator and then poured into a separatory funnel containing 100 mL water. The aqueous layer was extracted with 3 × 500-mL portions of ether. The ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was distilled (78–80 °C, high vacuum) to yield the product (10.88 g, 62.5 mmol, 83.4%): IR (FT, thin film) 2944.95 (br, s), 2854.15 (m), 1740.47 (s), 1127.61 (m), 1054.45 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.72 (t, 1 H, J = 1.78 Hz), 4.31 (t, 1 H, J = 5.66 Hz), 3.26 (s, 6 H), 2.38 (dt, 2 H, J = 1.78, 7.25 Hz), 1.56 (m, 4 H), 1.31 (m, 4 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 201.64, 104.48, 52.44, 43.42, 32.18, 28.73, 24.03, 21.77; MS, m/e (percent) 174 (0.01, M^+), 173.2 (0.1), 143.2 (4.9), 125.2 (3.8), 111.2 (4.5), 93.2 (4.8), 83.2 (3.9), 76.1 (3.5), 75.1 (100.0); HRMS (EI) calcd for $C_9H_{18}O_3$ (M − 1) 173.1177, found 173.1176.

2-[6-(2-Carbomethoxy-1-oxoethoxy)undecyl]-2-(1-chloro-4-but-*trans*-2-enyl)-1,3-dithiane (29). To a solution of the alcohol (1.00 g, 30 mmol) in 1,2-dimethoxyethane (10 mL) was added Meldrum's acid (867 mg, 6.0 mmol, 2 equiv), and the solution was heated to reflux for 1.5 h. The solution was then cooled to room temperature, and diazomethane was added until a yellow color persisted. Excess diazomethane was quenched by the addition of 1 drop of formic acid, and the solution was concentrated. Flash chromatography (hexanes and then 20:1 hexanes/ethyl acetate and then 6:1 hexanes/ethyl acetate) provided the mixed malonate (1.07 g, 2.25 mmol, 75%): ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (m, 2 H), 4.95 (m, 1 H), 4.04 (d, 1 H, J = 8.72 Hz), 3.78 (s, 3 H), 3.38 (s, 2 H), 2.85 (m, 4 H), 2.61 (d, 2 H, J = 8.33 Hz), 2.09–1.19 (m, 20 H), .91 (t, 3 H, J = 6.56 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 166.83, 166.01, 130.00, 129.12, 75.44, 52.14, 52.00, 44.49, 41.37, 40.52, 38.24, 34.98, 33.60, 33.54, 31.27, 30.09, 29.18, 26.56, 26.09, 25.71, 24.94, 24.62, 24.52, 24.47, 23.35, 22.14, 13.60.

2-Oxo-3-carbomethoxy-14-pentyl-*trans*-oxacyclotetradec-5-ene-8-spiro-2′-(1,3-dithiane) (30). To a solution of the malonate (180 mg, 0.375 mmol) in DME (37 mL, 0.01 M) was added NaH (38 mg of a 60% solution in mineral oil, washed two times with hexanes, 0.75 mmol, 2 equiv). The solution was heated to reflux for 5 h and then cooled to room temperature. (Although some starting material is still present by TLC analysis at this time, the formation of impurities deemed that the reaction be quenched.) The solution was diluted with 35 mL of ethyl acetate, and the reaction was quenched by the dropwise addition of 1 M HCl (30 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and then concentrated. Flash chromatography (hexanes, then 40:1 hexanes/ethyl acetate and then 20:1 hexanes/ethyl acetate) provided the desired macrolide (72.6 mg, 0.165 mmol, 44%), as a single isomer as judged by NMR analysis, and starting material (25 mg, 0.053 mmol, 14%): IR (FT, thin film) 1750.86 (s), 1730.25 (s), 1457.95 (m), 1434.21 (m), 1235.99 (s), 1156.10 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.57 (m, 2 H), 5.07 (m, 1 H), 3.69 (s, 3 H), 3.36 (dd, 1 H, J = 3.64, 11.95 Hz), 2.86–2.56 (m, 8 H), 1.96–1.21 (m, 20 H), 0.86 (t, 3 H, J = 6.26 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 169.17, 168.76, 129.65, 128.59, 75.15, 52.63, 52.39, 52.14, 36.75, 33.46, 32.25, 31.66, 31.46, 27.28, 26.02, 25.93, 25.57, 25.08, 22.91, 22.52, 21.57, 13.89; MS, m/e (percent) 442 (63.7, M^+), 2.87.2 (66.7), 271.1 (69.2), 270.1 (79.3), 237.2 (13.2), 195.2 (49.3), 154.1 (23.6), 145.1 (82.2), 132.0 (100.0).

3-Oxo-14-pentyl-*trans*-oxacyclotetradec-5-ene-2′-(1,3-dithiane) (31). To a solution of the malonate (70 mg, 0.158 mmol) in DMSO (5 mL) was added approximately 500 μL of water and 200 mg of LiCl. The solution was heated to a gentle reflux for 65 min and cooled to room temperature. The solution was then diluted with 50 mL ethyl acetate, washed with brine (2 × 35 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes and then 20:1 hexanes/ethyl acetate) provided the macrolide (47 mg, 0.119 mmol, 78%): IR (FT, neat) 1729.27 (s), 1456.15 (m), 1439.05 (m), 1523.17 (m), 1200.98 (s), 1156.36 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.57 (m, 2 H), 5.02 (m, 1 H, 2.89–2.22 (m, 10 H), 2.01–1.19 (m, 20 H), 0.87 (t, 3 H, J = 6.49 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 172.82, 132.30, 126.73, 73.82, 52.29, 40.43, 36.69, 34.74, 33.71, 32.56, 31.50, 27.46, 27.27, 25.97, 25.88, 25.56, 25.12, 22.32, 21.73, 13.75; MS, m/e (percent) 386.2 (11.7), 385.1 (234.3), 384.1 (99.2), 287.2 (100.0), 270.1 (31.8), 195.2 (16.5), 145.1 (15.8). Anal. Calcd for $C_{21}H_{36}S_2O_2$: C, 65.58; H, 9.43. Found: C, 65.72; H, 9.51.

(*E*)-2,8-Dioxo-14-pentyloxacyclotetradec-5-ene (32). To a solution of the thioketal (40 mg, 0.104 mmol) in 1 mL of 4:1 acetonitrile/water was added HgO (25 mg, 0.115 mmol, 1.1 equiv) followed by $HgCl_2$ (62 mg, 0.23 mmol, 2.2 equiv). The reaction was stirred for 0.5 h and then filtered through Celite and washed with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane and then 20:1 hexane/ethyl acetate) provided the ketone (27 mg, 0.083 mmol, 80%): IR (FT, neat) 1730.16 (s), 1718.42 (s), 1458.28 (m), 1437.03 (m), 1164.53 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.59 (m, 2 H), 4.94 (m, 1 H), 3.01 (d, 2 H, J = 6.28 Hz), 2.44 (m, 6 H), 1.71–1.10 (m, 16 H), .87 (t, 3 H, J = 6.61 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 208.81, 172.52, 133.45, 124.27, 73.50, 48.16, 38.98, 34.93, 33.96, 33.75, 31.60, 27.52, 27.05, 25.08, 23.37, 22.46, 21.69, 13.91. Anal. Calcd for $C_{18}H_{30}O_2$: C, 73.43; H, 10.27. Found: C, 73.65; H, 10.17.

Methyl (*R*)-3-Hydroxyoctanoate (34). The $Ru_2Cl_4[(R)\text{-binap}]_2(C_2H_5)_3N$ was prepared according to Ikariya et al.[29] $RuCl_2(COD)_n$ (27.1 mg, 0.096 mmol) and (*R*)-binap (71.8 mg, 0.115 mmol) were added to a flame-dried Schlenk tube equipped with stir bar under argon. The vessel was charged with 4 mL of dry toluene and 192 μL (1.38 mmol) of triethylamine, and the reaction mixture was refluxed under argon for 8 h. The Schlenk tube was then attached to a high vacuum, and the solvents were removed in vacuo. The β-keto ester (**33**) (5.13 g,

(29) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

30.18 mmol) was dissolved in 60 mL of dry MeOH and degassed by three freeze–pump–thaw cycles. The solution was then transferred to the Schlenk tube and warmed gently to dissolve the catalyst. The resulting orange solution was transferred to a Parr high-pressure autoclave and pressurized to 1400 psi under H_2. The solution was stirred at room temperature for approximately 48 h. The solvent was removed under reduced pressure, and the residue was chromatographed (4:1 hexanes/ethyl acetate) to give (**34**) (4.71 g, 27.4 mmol, 92%) as a clear oil $[\alpha]^{27}_D$ −22.2° (*c* 1.44, $CHCl_3$); IR (film) 3451 (br m), 2931 (s), 2859 (m), 1739 (s), 1437 (m), 1168 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.97 (X of ABX, br m, 1 H), 3.68 (s, 3 H), 2.95 (br, 1 H), 2.49, 2.38 (AB of ABX, 2 H, J_{AB} = 16.26, Hz, J_{AB} = 8.62 Hz (calcd 9.17 Hz), J_{BX} = 3.62 Hz (calcd 3.00 Hz)), 1.48–1.27 (m, 8 H), 0.862 (br t, 3 H, *J* = 6.78 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 173.43, 67.96, 51.53, 41.11, 36.43, 31.57, 25.00, 22.41, 13.81; MS, *m/e* (percent) 43.1 (36.3), 71.1 (37.3), 74.1 (59.1), 83.2 (10.1), 103.1 (100.0); HRMS (DIP, CI) calcd for $C_9H_{18}O_3$ (M + 1) 175.1335, found 175.1322.

(*R*)-MPTA Ester of 34. DMAP (8 mg, 0.066 mmol) was added in one portion to a colorless solution of **34** (39.1 mg, 0.225 mmol, 1 equiv) (*R*)-(+)-MPTA (79.5 mg, 0.337 mmol, 1.5 equiv), and 1,3-diisopropylcarbodiimide (62.4 mg, 0.494 mmol, 2.2 equiv) in 3 mL of dry CH_2Cl_2. The reaction was stirred under argon for 8 h, diluted with ether, and filtered through Celite. Flash chromatography (8:1 hexanes/ethyl acetate) yielded 84 mg (0.213 mmol, 95%) of the (*R*)-MPTA ester (R_f 0.35, 8:1 hexanes/EtOAc): IR (film) 2948.5 (m), 2924.6 (m), 2852.8 (w), 1748.3 (s), 1270.8 (m), 1135.7 (s), 909.9 (s), 734.1 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.37 (m, 3 H), 5.45 (m, 1 H), 3.63 (s, 3 H), 3.52 (s, 3 H), 2.68, 2.58 (AB of ABX, 2 H, J_{AB} = 15.96 Hz, J_{AX} = 7.99 Hz, J_{BX} = 4.94 Hz), 1.63 (m, 2 H), 1.18 (br m, 6 H), 0.817 (br t, 3 H, *J* = 6.24 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 170.58, 166.02, 132.42, 129.56, 128.34, 127.39, 73.32, 55.35, 51.76, 38.52, 33.50, 31.24, 24.18, 22.26, 13.72; MS, *m/e* (percent) 55.1 (76.7), 83.1 (45.9), 97.2 (61.4), 125.1 (100.0), 157.1 (32.8), 189.0 (66.4); HRMS (DIP, CI) calcd for $C_{19}H_{25}O_5F_3$ (M + 1) 391.1733, found 391.1722; Varian 3300 GC analysis (col 190 °C, inj 300 °C, det 200 °C) 41.83 (89.975%), 42.56 (1.101%) (97.6% ee).

Methyl (*R*)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octanoate. The β-hydroxy ester **34** (2.40 g, 13.8 mmol, 1 equiv) was dissolved in 100 mL of dry DMF. The solution was stirred and combined sequentially with imidazole (1.88 g, 27.61 mmol, 2 equiv) and TBSCl (2.26 g, 15 mmol, 1.1 equiv). After 12 h, the solution was diluted with 100 mL of ether and quenched with 30 mL of a saturated sodium bicarbonate solution. The organic layer was extracted five times with distilled water (30 mL) and once with saturated brine (10 mL) and dried over $MgSO_4$. Filtration, concentration, and flash chromatography (10:1 hexanes/ethyl acetate) gave 3.70 g (12.79 mmol, 93%) of the siloxy ester as a clear oil: $[\alpha]^{27}_D$ −20.77° (*c* 1.32, $CHCl_3$); IR (film) 2955 (s), 2930.1 (s), 2857.8 (s), 1743.4 (s), 1255.4 (s), 1169.3 (m), 1094.3 (br m), 836.8 (s), 776.1 (s); ^1H NMR (250 MHz, $CDCl_3$) δ 4.08 (tt, 1 H, *J* = 5.47, 6.2 Hz), 3.62 (s, 3 H), 2.39 (d, 2 H, *J* = 6.14 Hz), 1.45 (m, 2 H), 1.24 (m, 6 H), 0.98 (m, 12 H), −0.006 (s, 3 H), −0.196 (s, 3 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 172.21, 69.60, 51.15, 42.55, 37.63, 31.85, 25.73, 24.56, 22.47, 17.93, 13.77, −4.62, −4.88; MS, *m/e* (percent) 73 (27.2), 89 (100.0), 119 (10.7), 131 (14.2), 189 (17.7), 231 (M − C_4H_9, 72.4). Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.44, H, 11.18. Found: C, 62.40, H, 11.14.

3-Hydroxy-(*R*)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]decene (36). The β-siloxy ester (3.66 g, 12.65 mmol, 1 equiv) was dissolved in 100 mL of dry CH_2Cl_2 and cooled to −78 °C. To the solution was then slowly added dropwise 13.9 mL (1.1 equiv) of a 1.0 M solution of Dibal-H in CH_2Cl_2. After the solution had stirred for 30 min at −78 °C, 31.6 mL (2.5 equiv) of a 1.0 M solution of vinylmagnesium bromide in THF was added in one portion. The reaction was stirred at −78 °C for 30 min and then warmed to room temperature and stirred for 1 h. The light-brown solution was cooled to −78 °C and quenched by the addition of 25 mL of a saturated NH_4Cl solution. The aqueous layer was separated and reextracted twice with 40 mL of CH_2Cl_2. The combined organic layers were washed with saturated brine and dried over $MgSO_4$. Rotary evaporation and flash chromatography (12:1 hexanes/ethyl acetate) yielded the allylic alcohol (**36**) as a 1.4:1 mixture of diastereomers (3.19 g, 11.1 mmol, 88%): R_f 0.33 (10:1 hexanes/ethyl acetate); IR (film) 3409 (br m), 2955.5 (s), 2929.1 (s), 2858.06 (s), 1469 (m), 1255.65 (s), 1061 (br s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.84 (m, 2 H), 5.24 (br d, 2 H, *J* = 17.18 Hz), 5.06 (br d, 2 H, *J* = 10.37 Hz), 4.41 (m, 1 H), 4.26 (m, 1 H), 3.94 (m, 2 H), 3.31 (d, 1 H, *J* = 2.53 Hz), 3.21 (d, 1 H, *J* = 2.19 Hz), 1.66–1.51 (m, 6 H), 1.35–1.17 (m, 9 H), 0.94–0.79 (m, 19 H), 0.096–0.057 (4 overlapping singlets, 10 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 141.74, 141.40, 113.92, 113.66, 72.40, 71.68, 71.05, 69.65, 43.63, 42.48, 37.92, 36.74, 32.00, 31.94, 25.86, 25.08, 24.41, 22.52, 17.96, 13.81, −4.11, −4.47, −4.62, −4.70; MS, *m/e* (percent) 55 (14.7), 7.1 (0.9), 75 (72.2), 83 (43.3), 105 (59.5), 119 (19.2), 159 (17.8), 154 (0.2), 175 (100.0), 215 (7.5). Anal. Calcd for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96. Found: C, 66.98; H, 11.93.

(6*E*)-Methyl 3-Oxo-(*R*)-9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetradec-6-enoate (37). NaH (33.6 mg, 13.9 mmol, 4.8 equiv), obtained from a 60% mineral oil dispersion and subsequent trituration with dry pentane, was suspended in 20 mL dry THF. The solution was cooled to 0 °C, and 1.35 mL (12.6 mmol, 4.3 equiv) of freshly distilled methyl acetoacetate was added via syringe in one portion. After 15 min, 5.30 mL (13.23 mmol, 4.6 equiv) of a 2.49 M BuLi solution in hexanes was added dropwise. The resulting yellow dianion was stirred at 0 °C for a further 10 min before use. The allylic chloride (87.7 mg, 2.87 mmol, 1 equiv) (obtained from **36** quantitatively by treatment with $SOCl_2$/ether) was dissolved in 3 mL of dry THF and added in one portion to the dianion solution. The solution was stirred at 0 °C for 4 h (warming the solution to room temperature caused the formation of undesirable side products). The solution was then transferred into a separatory funnel containing 30 mL of NH_4Cl and diluted with 75 mL of ether. The aqueous layers were extracted with ether, and combined organic layers were wash with a saturated NaCl solution. The combined ether layers were dried ($MgSO_4$) and concentrated. Purification of the residual oil by flash chromatography afforded 772 mg (2.00 mmol, 70%) of the β-keto ester as a clear oil: $[\alpha]^{27}_D$ +8.91° (*c* 2.01, $CHCl_3$); IR (film) 2954.8 (m), 2930.3 (m), 2856.8 (m), 1750.3 (m), 1720.7 (m), 1629.8 (w), 1255.1 (m), 972.8 (w), 836.1 (m), 774.2 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (4.5:1 mixture keto/enol form) δ 5.40 (2 H, m) (AB, J_{AB} = 15.0 Hz from ^1H decoupling), 4.95 (s, enol vinyl H), 3.70 (s, 3 H), 3.69 (s, enol form COMe), 3.59 (m, 1 H), 3.41 (s, 2 H), 2.57 (t, 2 H, *J* = 7.17 Hz), 2.23 (m, 2 H), 2.09 (m, 2 H), 1.34–1.23 (m, 8 H), 0.85 (overlapping t, s, 12 H), 0.005 (s, 6 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 201.85, 167.59, 130.09, 128.49, 72.38, 52.11, 49.02, 42.75, 40.48, 36.83, 31.97, 26.59, 25.87, 24.88, 22.55, 18.08, 13.84, −4.44, −4.57; MS, *m/e* (percent) 73 (100.0), 75 (21.6), 89 (19.5), 115 (19.7), 159 (26.5), 173 (32.4), 215 (92.3), 216 (17.9), 227 (24.0), 253 (2.7, M − OTBS), 309 (7.1), 327 (8.2, M − C_4H_9); HRMS (DIP, CI) calcd for $C_{21}H_{40}O_4Si$ (M + 1) 385.2775, found 385.2775. Anal. Calcd for $C_{21}H_{40}O_4Si$: C, 65.58; H, 10.48. Found: C, 65.67; H, 10.48.

Methyl (*R*,*R*)-3,9-Dihydroxytetradecanoate (38). The same procedure for the preparation of compound **34** was followed. Thus, $RuCl_2(COD)_n$ (24.0 mg, 0.085 mmol, 1 equiv) and 63 mg of (*R*)-binap (0.102 mmol, 12 equiv) were refluxed in toluene for 8 h under argon. The solution was cooled, pumped to dryness, and vigorously mixed with a degassed solution of β-keto ester **37** (1.40 g, 3.64 mmol) in 50 mL of dry MeOH. The solution was transferred via cannula to a degassed autoclave, which was pressurized to 1400 psi under H_2. After being stirred for 48 h at room temperature, the solution was removed from the autoclave and the solvent was evaporated. Chromatography of the solid residue gave 806 mg (3.27 mmol, 90%) of the diol (**38**) as a white solid (mp 57–59 °C): $[\alpha]^{27}_D$ −10.55° (*c* 1.45, $CHCl_3$); IR (film) 3390–3230 (br m), 2921 (s), 2852 (m), 1731.5 (m), 1457 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.97 (X of ABX, m, 1 H), 3.68 (s, 3 H), 3.55 (m, 1 H), 2.88 (d, 1 H, *J* = 3.58 Hz, 1 H), 2.48, 2.39 (AB of ABX, 2 H, J_{AB} = 16.76 Hz, J_{BX} = 8.23 Hz (calcd 9.45 Hz), J_{AX} = 3.48 Hz (calcd 2.67 Hz)), 1.6–1.15 (m, 18 H), 0.865 (br t, 3 H, *J* = 6.3 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 173.26, 71.81, 67.99, 51.44, 41.28, 37.43, 37.30, 36.49, 31.80, 29.44, 25.41, 25.29, 25.17, 22.46, 13.78); MS, *m/e* (percent) 55 (14.6), 71 (12.7, C_5H_{11}), 74 (41.7), 81 (16.2), 83 (33.5), 96 (41.8), 103 (100.0), 124 (62.9), 135 (37.1), 153 (52.9), 156 (40.6), 167 (8.1), 185 (46.2). Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 63.49; H, 10.68.

(*R*,*R*)-3-Hydroxy-5,11-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]hexadecene (39). The bis(siloxy ester) (416 mg, 0.827 mmol, 1 equiv) was dissolved in 10 mL of dry CH_2Cl_2 and cooled to −78 °C under argon. Dibal-H (1.0 M in CH_2Cl_2, 910 μL, 0.91 mmol, 1.1 equiv) was then added dropwise over 0.5 h. After the solution had stirred for a further 10 min, 2.5 mL of a 1.0 M solution of vinylmagnesium bromide (2.5 mmol, 3.02 equiv) was added via syringe in one portion. The reaction mixture was stirred at −78 °C for 30 min and subsequently stirred at room temperature for 1 h. The solution was quenched by the addition of a saturated NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with 20 mL of CH_2Cl_2. The organic layers were combined and washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Concentration of the organics left a pale yellow oil, which was flash chromatographed (10:1 hexanes/ethyl acetate) to give the allylic alcohol (**39**) as a clear oil (355 mg, 0.709 mmol, 85%) (1.2:1 mixture of diastereomers): R_f 0.61 (10:1 hexanes/ethyl acetate); IR (film) 3430 (br w) 2954 (br s), 2930 (s), 2857 (s), 1472.3 (m), 1255.3 (s), 1058.5 (br m), 835.9 (s), 773.6 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.83 (m, 1 H), 5.24 (dm, 2 H, *J* = 17.15 Hz), 5.06 (dm, 2 H, *J* = 10.48 Hz), 4.40, 4.25 (m, 1 H), 3.94 (m, 1 H), 3.58 (m, 1 H), 3.29, 3.19 (d, 1 H, *J* = 2.55, 1.67 Hz), 1.65–1.15 (br m, 18 H), 0.91–0.84 (m, 21 H), 0.0942, 0.0783,

0.06, 0.032, 0.011 (overlapping singlets, 12 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 141.57, 141.21, 113.98, 113.74, 72.57, 72.38, 71.81, 71.10, 69.61, 43.38, 42.16, 37.94, 37.13, 37.04, 36.59, 32.05, 30.06, 29.97, 25.90, 25.82, 25.74, 25.50, 25.23, 24.91, 24.72, 22.58, 18.08, 17.92, 13.89, -4.08, -4.47, -4.66, -4.73; MS, *m/e* (percent) 67 (8.7), 73 (16.9), 81 (25.2), 95 (59.5), 109 (74.2), 123 (24.2), 131 (70.9), 149 (22.5), 165 (100.0), 171 (27.7), 207 (11.8), 215 (50.5), 257 (82.7), 258 (16.5), 297 (38.2), 311 (28.3), 389 (19.9), 443 (3.2, M - C_4H_9); HRMS (DIP, CI) calcd for $C_{28}H_{60}O_3Si_2$ 501.4161 (M + 1), found 501.4119. Anal. Calcd for $C_{28}H_{60}O_3Si_2$: C, 67.13; H, 12.07. Found: C, 67.08; H, 12.01.

(4*E*)-Ethyl 7(*R*),13(*R*)-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]octadec-4-enoate (40). The allylic alcohol (328 mg, 0.655 mmol, 1.0 equiv) was dissolved in 10 mL of freshly distilled toluene. Triethyl orthoacetate (1.06 mL, 5.78 mmol, 8.8 equiv) and 5 μL of propionic acid were added to the reaction flask, and the solution was refluxed for approximately 2 h. The solvents were removed in vacuo, and the residue was chromatographed (10:1 hexanes/ethyl acetate, R_f of product 0.61) to give the Claisen product (**40**) as a clear oil (347 mg, 0.608 mmol, 93%): $[\alpha]^{27}_D$ +5.35° (*c* 1.57, $CHCl_3$); IR (film) 2930.1 (m), 2856.3 (m), 1740.2 (m), 1254.9 (m), 1050 (br m), 835.4 (m) 773.07 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (m, 2 H), 4.11 (q, 2 H, = 7.14 Hz), 3.60 (m, 2 H), 2.33 (m, 4 H), 2.11 (br t, 2 H, *J* = 3.44 Hz), 1.41-1.20 (m, 19 H), 0.92-0.84 (m, 21 H), 0.017 (br s, 12 H); ^{13}C NMR ($CDCl_3$) δ 173.14, 130.41, 128.26, 72.55, 72.47, 60.13, 40.57, 37.17, 36.89, 34.36, 32.09, 30.08, 28.00, 25.93, 25.32, 24.91, 22.59, 18.11, 14.17, 13.84, -4.44; MS, *m/e* (percent) 95 (12.4), 109 (16.0), 149 (9.2), 165 (29.0), 171 (16.4), 189 (3.7), 215 (31.6), 297 (51.4), 355 (10.4), 429 (35.4), 445 (11.2), 499 (3.3, M - C_5H_{11}), 513 (100.1, M - C_4H_9), 514 (38.9), 515 (15.3); HRMS (DIP, CI) calcd for $C_{32}H_{60}O_4Si_2$ (M + 1) 571.4580, found 571.4591.

(4*E*)-Ethyl (*R*,*R*)-7,13-Dihydroxyoctadec-4-enoate. Three milliliters of a 1.0 M solution of Bu_4NF in THF (3 mmol, 5.02 equiv) was added to 340.8 mg of the bis(siloxy ester) **40** (0.597 mmol, 1 equiv), and the solution was stirred at room temperature. After 8 h, TLC analysis indicated the formation of a single lower R_f product (R_f 0.55, EtOAc). The reaction was diluted with 25 mL of ether and quenched at 0 °C with 5 mL of a saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. Filtration and concentration of the organic material afforded a solid, which was purified by flash chromatography (1:1 hexanes/ethyl acetate) to give the diol ester (177 mg, 0.519 mmol, 87%) as a white foamy solid (mp 70-71 °C): $[\alpha]^{27}_D$ -1.91° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3603 (br w), 3474 (br w), 2930 (br m), 2859 (m), 1726 (m), 1374.3 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.47 (m, 2 H), 4.09 (q, 2 H, *J* = 7.07 Hz), 3.55 (br m, 2 H), 2.33 (m, 3 H), 2.25-1.95 (m, 3 H), 1.75 (br, 1 H), 1.5-1.15 (m and overlapping t, 20 H), 0.86 (br t, 3 H, *J* = 6.66 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 172.99, 131.95, 127.51, 71.88, 70.83, 60.24, 40.62, 37.49, 37.39, 36.65, 34.17, 31.89, 29.66, 27.96, 25.59, 25.56, 25.28, 22.58, 14.19, 13.93; MS, *m/e* (percent) 68.1 (32.0), 83.1 (10.1), 88.1 (28.7), 95.2 (21.2), 96.1 (21.5), 109.1 (17.0), 142.1 (100.0), 165.1 (29.5), 183.2 (18.0), 201.2 (6.1, M - $C_8H_{13}O_2$), 253.3 (9.8, M - $C_5H_{13}O$), 279.2 (1.0, M - OC_2H_5 - H_2O); HRMS (DIP, CI) calcd for $C_{20}H_{38}O_4$ (M + 1) 343.2849, found 343.2861.

(8*R*,14*R*)-2-Oxo-14-pentyl-*trans*-oxacyclotetradec-5-en-8-ol (42). The diol acid **41** (mp 93 °C) (90.0 mg, 0.287 mmol, 1.0 equiv) was dissolved in 2 mL of dry THF and added dropwise via syringe pump over 6 h to a refluxing solution of 2-chloro-1-methylpyridinium iodide (277 mg, 1.08 mmol, 4 equiv) and triethylamine (300 μL, 2.15 mmol, 7.5 equiv.) in 50 mL of dry acetonitrile. At the end of the addition, the red solution was refluxed for a further 2 h, and finally cooled to room temperature. Concentration and purification of the residue by flash chromatography (4:1 hexanes/ethyl acetate) gave 52.7 mg of the macrolide (**42**) as a clear oil, which crystallized upon standing (0.178 mmol, 62%): mp 51-52 °C; R_f 0.26 (3:1 hexanes/ethyl acetate); $[\alpha]^{27}_D$ +28.49° (*c* 0.99, $CHCl_3$); IR (film) 3540 (br w), 2928.7 (s), 2858.2 (m), 1730.9 (s), 1439.2 (w), 1223.4 (w), 974.3 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.46 (m, 2 H), 4.93 (m, 1 H), 3.61 (m, 1 H), 2.55-2.0 (m, 6 H), 1.7-1.1 (m, 18 H), 0.85 (br t, 3 H, *J* = 6.67 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 173.11, 131.75, 127.61, 74.29, 70.66, 40.16, 34.39, 34.15, 33.69, 32.34, 31.59, 27.47, 26.32, 25.23, 22.53, 22.42, 21.96, 13.81; MS, *m/e* (percent) 68.1 (34.2), 81.1 (26.4), 83.1 (27.7), 95.2 (60.9), 96.0 (47.9), 109.1 (45.0), 114.1 (100.0), 164.1 (16.4), 165.1 (47.8), 183.2 (23.0), 225.2 (0.6, M - C_5H_{11}), 278.2 (0.6, M - 18), 296.2 (3.4, M^+); HRMS (DIP, EI) calcd for $C_{18}H_{32}O_3$ 296.2352, found 296.2344.

(8*R*,14*R*)-8-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-oxo-14-pentyl-*trans*-oxacyclotetradec-5-ene. The macrolide **42** (58.0 mg, 0.196 mmol, 1 equiv) was dissolved in 1 mL of dry DMF. TBSCl (35.4 mg, 0.235 mmol, 1.2 equiv) and imidazole (19 mg, 0.279 mmol, 1.4 equiv) were then added, and the solution was stirred under a closed system of argon for 5 h at room temperature. The solution was finally diluted with ether (30 mL), and the ether layer was washed (4 × 10 mL) with distilled water. The ether layer was extracted with brine and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation, and the residual oil was chromatographed (10:1 hexanes/EtOAc, R_f 0.73, 3:1 hexanes/EtOAc) to give the desired silyl ether (74 mg, 0.182 mmol, 93%): $[\alpha]^{27}_D$ +13.5° (*c* 1.2, $CHCl_3$); IR (film) 2928 (s), 2857.3 (s), 1733.9 (s), 1254.3 (m), 835.8 (s), 773.6 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.44 (m, 2 H), 4.94 (m, 1 H), 3.53 (m, 1 H), 2.43-1.98 (m, 6 H), 1.67-1.08 (m, 18 H), 0.87 (m, 12 H), 0.029 (s, 3 H), 0.022 (s, 3 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 173.05, 131.12, 128.35, 74.29, 71.23, 40.40, 34.43, 34.33, 33.68, 32.80, 31.62, 27.59, 26.69, 25.83, 25.26, 22.70, 22.44, 21.91, 18.01, 13.81, -4.46, -4.71; MS, *m/e* (percent) 73.0 (12.2), 89.1 (10.0), 95.2 (19.7), 109.1 (21.4), 165.2 (32.4), 171.1 (100.0), 172.1 (16.4), 219.2 (10.0), 243.2 (28.4), 261.2 (26.8), 279.2 (1.9, M - OTBS), 297.3 (45.9), 335.2 (86.2), 336.2 (23.8), 353.3 (84.3, M - C_4H_9), 354.3 (20.9), 410.2 (0.6, M^+), 411.2 (0.3, M + 1); HRMS (DIP, CI) calcd for $C_{24}H_{46}O_3Si$ (M + 1) 411.3296, found 411.3263.

(-)-Gloeosporone. The olefin (65 mg, 0.158 mmol, 1.0 equiv) was combined with 2 mL of freshly distilled acetic anhydride and cooled to 0 °C. Potassium permanganate (150 mg, pulverized, 0.95 mmol, 6 equiv) was then added portionwise over 15 min, and the reaction mixture was warmed to room temperature and stirred for 4 h. The solution was diluted with 10 mL of a 1:1 hexanes/ethyl acetate mixture and quenched with a saturated solution of $NaHSO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed by evaporation, and the acetic anhydride was removed under high vacuum. The resulting yellow oil was dissolved in 2 mL of acetonitrile and stirred vigorously with 1 mL of a 10:1 CH_3CN/49% aqueous HF solution. TLC indicated that the product formed had identical mobility with an authentic sample of natural gloeosporone (R_f 0.44, 3:1 hexanes/ethyl acetate). The reaction was quenched by addition of saturated sodium bicarbonate and diluted with ethyl acetate, and the organic layer was washed with water and brine. The organic layer was finally dried with $MgSO_4$, solvent was removed, and the solid residue was purified by silica gel chromatography (5:1 hexanes/ethyl acetate) to give 25.7 mg (0.079 mmol, 50%) of gloeosporone: mp 117-118 °C (lit.[21] mp 108-110 °C (nat), 117-118 °C synthetic (+)); $[\alpha]^{27}_D$ -63.2° (*c* 0.34, acid free $CHCl_3$) (lit.[21] $[\alpha]^{D}_{27}$ -61° (*c* 0.34, acid free $CHCl_3$)); IR (FT, CCl_4) 1772.1 (s), 1733.6 (m), 1713.7 (s), 1278.07 (m), 1220.02 (m), 1142.8 (m), 1073.4 (s) cm^{-1}; IR (FT, DMSO, $CDCl_3$) 1763.6 (s), 1724.9 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.06 (m, 1 H), 4.43 (m, 1 H), 2.73 (dd, 1 H, *J* = 6.3, 18.7 Hz), 2.44 (ddd, 1 H, *J* = 4.1, 8.5, 15.4 Hz), 2.35 (ddd, 1 H, *J* = 4.1, 9.1, 14.6 Hz), 2.28 (dd, 1 H, *J* = 3.8, 9.1, 15.4 Hz), 2.10 (ddd, 1 H, *J* = 3.8, 8.5, 14.6 Hz), 2.04 (dd, *J* = 8.2, 18.7 Hz, 1 H), 1.7-1.2 (m, 18 H), 0.88 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 208.77, 174.32, 99.02, 74.44, 73.52, 40.28, 34.66, 32.39, 32.30, 31.68, 30.04, 29.44, 26.18, 25.14, 25.03, 22.43, 21.43, 13.80; MS, *m/e* (percent) 54.1 (9.4), 67.1 (11.2), 82.1 (28.7), 96.1 (32.6), 101.1 (68.4), 109.1 (14.3), 110.2 (14.3), 119.1 (100.0), 152.1 (7.9), 180.2 (6.6), 209.1 (2.0), 237.1 (1.7), 308.2 (0.5, M - 18); HRMS (DIP, CI) calcd for $C_{18}H_{30}O_5$ (M + 1) 327.2172, found 327.2150.

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Registry No. 1a, 115512-01-1; (±)-**1b**, 115586-58-8; (-)-**1b**, 88936-02-1; **2**, 115482-13-8; **3a**, 115482-15-0; **3b**, 115482-14-9; **4**, 115482-16-1; (*trans*)-**5**, 115511-76-7; (*cis*)-**5**, 115482-17-2; (*trans*)-**5** (diol), 115482-18-3; (*cis*)-**5** (diol), 115482-19-4; (*trans*)-**6**, 115482-20-7; (*cis*)-**6**, 115482-21-8; **7**, 115482-22-9; **8**, 115482-23-0; **9**, 115482-24-1; **10**, 115482-25-2; **10** (alcohol), 104514-63-8; **16**, 115482-26-3; **17**, 115482-27-4; **17** (aldehyde), 115482-28-5; **18**, 115482-29-6; **19**, 115482-30-9; **20**, 115482-31-0; **25**, 628-92-2; **26**, 60090-77-9; **27**, 115482-32-1; **28**, 115482-33-2; **29**, 115482-34-3; **30**, 115482-35-4; **31**, 115482-36-5; **32**, 115482-37-6; **33**, 62344-14-3; **34**, 78672-90-9; **34** (MPTA ester), 115482-38-7; **34** (TBS ether), 115482-39-8; **36** (isomer 1), 115482-40-1; **36** (isomer 2), 115482-52-5; **36** (allylic chloride, isomer 1), 115482-41-2; **36** (allylic chloride, isomer 2), 115482-53-6; **37**, 115482-42-3; **38**, 115482-43-4; **38** (bis(TBS)ether), 115482-44-5; **39** (isomer 1), 115482-45-6; **39** (isomer 2), 115586-59-9; **40**, 115482-46-7; **40** (diol ester), 115482-47-8; **41**, 115482-48-9; **42**, 115482-49-0; **42** (TBS ether), 115482-50-3; (*R*)-MPTA, 20445-31-2; TBS propargyl ether, 76782-82-6; methoxyfuran, 25414-22-6; 1,4-dichloro-2-butene, 110-57-6; meldrum's acid, 2033-24-1; methyl acetoacetate, 105-45-3; triethyl orthoacetate, 78-39-7; 6-pentyl-2-[(*tert*-butyldimethylsilyl)oxy-1-propynyl]-2-tetrahydropyranol, 115482-51-4.