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Synthetic approach to potential precursors of sclerophytin A

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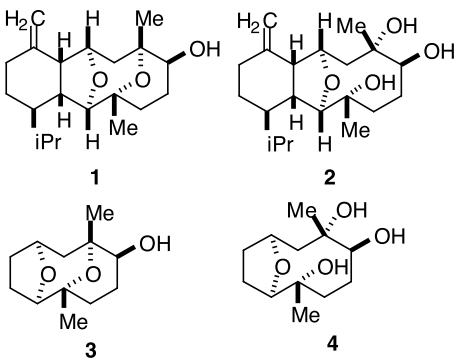
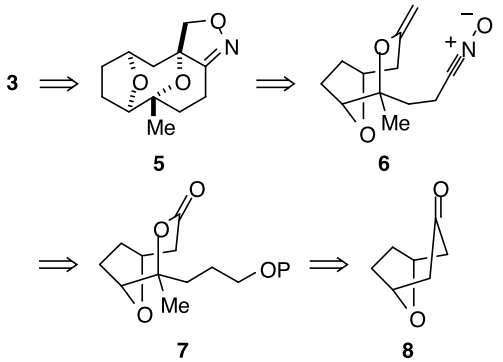
Abstract—A direct approach to simple bicyclic analogues of the antitumor natural diterpene, sclerophytin A, is described. The readily available bicyclic ketone **8** (prepared from furan and trichloroacetone) was enantioselectively methylated to give the optically active ketone **11**. Regioselective allylation using Negishi's method afforded the α,α-dialkyl ketone **12**, which was converted to the chloroacetate **15** by hydroboration–oxidation and protection. Regioselective Baeyer–Villiger oxidation afforded the lactone **7a** which could be transformed into the silyl ether **7b**. Tebbe olefination furnished a mixture of two enol ethers in which the desired product **17** was the minor isomer. Several attempts to use the major endocyclic enol ether **18** to give the tricyclic analogues of sclerophytin proved unsuccessful. Opening of the lactone of **18** and selective protection of the diol afforded the primary alcohol **24** which was oxidized to the keto aldehyde **25**. Unfortunately pinacol coupling of **25** did not give any cyclic product. The diene **27** was also prepared from **25** but all attempts at ring-closing metathesis of **27** met with the same fate. The failure of these various cyclization methods underscores the difficulty in forming medium-sized ring systems, especially those *cis*-fused at the 2- and 5-positions of a tetrahydrofuran ring.

1. Introduction

The isolation of the potently cytotoxic marine metabolite sclerophytin A **1** was reported by Sharma and co-workers in 1988.[1] The compound's strong biological activity and unprecedented tetracyclic structure containing two bridging ether linkages generated considerable synthetic interest.[2] The total synthesis of the presumed structure **1** was reported by the Paquette[2a] and Overman[2b] groups; however, both groups later found that their spectral data of **1** was inconsistent with that reported in the original paper.[1] Re-examination of spectral data and subsequent total syntheses resulted in the reassignment to the structure **2**.[3] In the previous paper[4] we described an attempted synthetic route to the simple tricyclic derivative **3** that met with limited success. Following those studies, we became interested in a new and concise approach to **3** as well as simple bicyclic analogues such as **4** (Scheme 1). For example, the tricyclic analogue **3** might be available via reductions of the tetracyclic isoxazoline **5**, which in turn would result from a key internal [3+2] cycloaddition of the nitrile oxide **6**. The nitrile oxide could be derived from the appropriately functionalized lactone **7**, which would be obtained in optically enriched form from the readily available bicyclic ketone **8** (Scheme 2). We report herein the full details of this approach, namely the facile synthesis of the bicyclic lactone **7** and our attempts to convert it into the sclerophytin analogues **3** and **4**.



Scheme 1.



Scheme 2.

Keywords: sclerophytin A; olefination; potential precursors.

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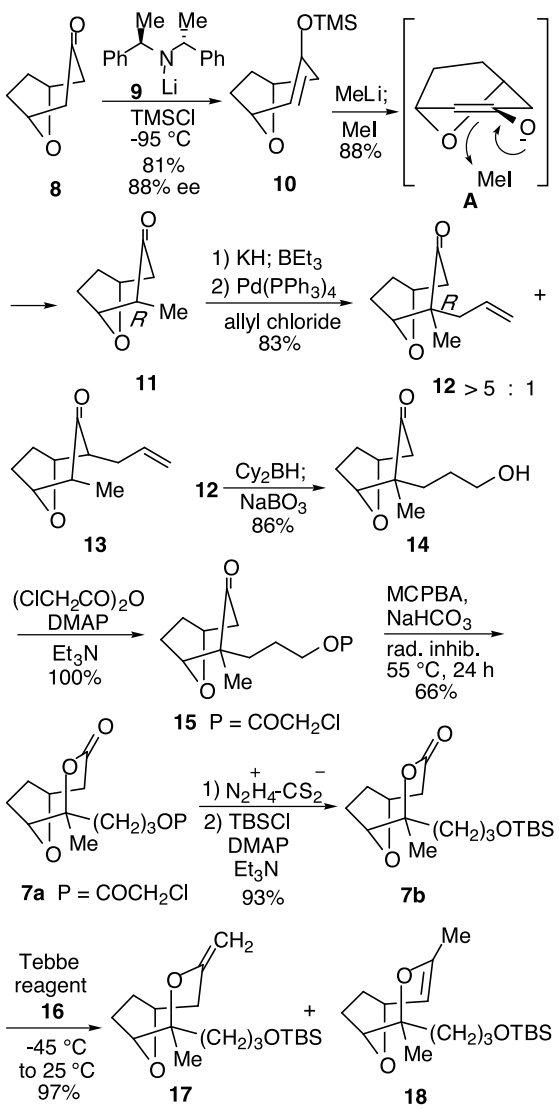
2. Results and discussion

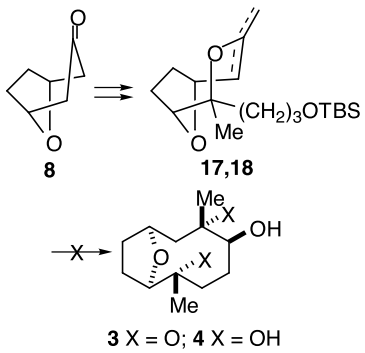
The synthesis begins with the symmetrical bicyclic ketone **8**, which was readily prepared on multi-gram scale in >98% purity and 60% yield[5] from commercially available 1,1,3-trichloroacetone by cycloaddition with furan followed by reduction (Scheme 3). In order to prepare the analogues **3** and **4** in their proper enantiomeric forms, we needed to desymmetrize the ketone. This conversion was easily accomplished by treatment of the ketone **8** with chlorotrimethylsilane and the readily available optically active base **9** to give the optically active silyl enol ether **10** in 81% yield and 88% ee.[6] Subsequent reaction with methyllithium resulted in formation of the enolate **A**; addition of methyl iodide presumably resulted in anti-parallel alkylation via a chair-like transition state, according to the model proposed by Valls and Toromanoff[7] to provide the ketone **11** as a single diastereomer in 88% yield. We then looked at possible methods of carrying out a second alkylation regioselectively at the substituted α-carbon to give the disubstituted bicyclic ketone **12**, e.g. by preparing the thermodynamic trimethylsilyl enol ether, cleaving, and alkylating as before. However, surprisingly, all attempts to generate the more substituted silyl enol ether using standard conditions[8] resulted in extensive decomposition, possibly due to Lewis-acid promoted opening of the tetrahydrofuran ring. Fortunately, treatment of **11** with potassium hydride and triethylborane as described by Negishi[9] furnished the desired thermodynamic boron enolate cleanly. However, this enolate proved to be exceedingly unreactive, probably due to its high stability and steric hindrance. Therefore we subjected it to π-allyl substitution conditions[9] using palladium (0) and allyl chloride to give the desired α,α-disubstituted ketone **12** along with a small amount of the kinetic product **13** (overall yield 62%, 83% based on recovered starting material). This ketone **12** now has the required substitution for the tertiary alcohol stereocenter of **3** and **4** but is lacking the oxygen atom. In order to eventually carry out the desired cyclization, we needed to introduce oxygen functionality on the side chain. Usual hydroboration–oxidation with simple boranes also caused reduction of the ketone so we carried out a chemoselective hydroboration with the hindered dicyclohexylborane, followed by oxidation with sodium perborate[10] to provide the hydroxy ketone **14** in 86% yield. The primary alcohol moiety was then protected as various esters, e.g. acetate and benzoate, etc. and we attempted to carry out the required Baeyer–Villager oxidation[11] of the ketone to the lactone. However, this reaction turned out to be quite difficult, presumably due to the steric hindrance of the ketone, and many oxidants—monoperoxyphthalic acid (MMPP), *p*-nitroperbenzoic acid, and anhydrous trifluoroperacetic acid[11b]—were unsuccessful. Only one set of reaction conditions gave reasonable yields of the desired lactone. Treatment of the ketone **15** (having a chloroacetate protecting group for ease of removal later) with 8 equiv. of pure MCPBA,[12] sodium bicarbonate buffer (12 equiv.), and the radical inhibitor (5-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, 0.01 equiv.) in small batches over a 24-h period at elevated temperatures (55°C, 1,2-dichloroethane, 0.2 M) gave the bicyclic lactone **7a** (55%, 66% based on recovered starting material). Curiously, the yields were extremely poor for ketones having protecting groups other than acetate or chloroacetate,[13] with either no reaction being observed or decomposition occurring.



Scheme 3.

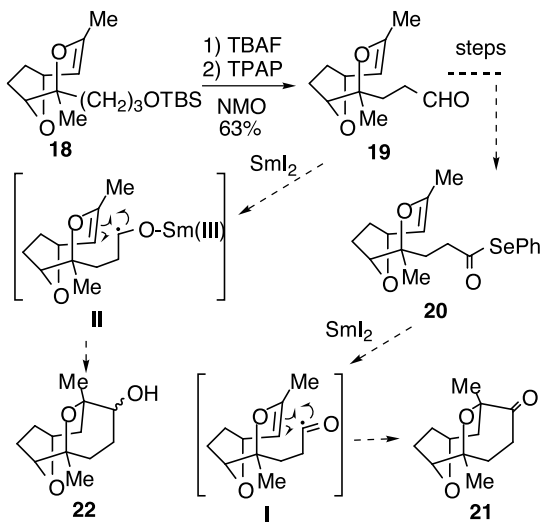
The next key step of the synthesis, a Tebbe olefination,[14] required a protecting group exchange to the more robust *tert*-butyldimethylsilyl group. The chloroacetate group of **7a** was easily removed with hydrazine thiocarbonate solution[15] without concomitant lactone ring opening.[16] Protection of the primary alcohol with *tert*-butyldimethylsilyl chloride then yielded the lactone silyl ether **7b** (93%, two steps). When we tried to carry out the olefination with the Tebbe reagent **16** generated in situ[14e] from $TiCl_2$ and $AlMe_3$ or with the more air-stable Petasis reagent,[17] dimethyl titanocene, only poor yields of the enol ether could be obtained. Fortunately, reaction of **7b** with the purified Tebbe reagent[14f] resulted in smooth methylenation. However, significant isomerization (>50%) of the exocyclic enol ether **17** to the more stable endocyclic enol ether **18** could not be avoided despite taking elaborate precautions, which mostly involved minimizing any acidic impurities or adventitious acid and shortening the reaction time.[18] Complete isomerization could be effected to give **18** in 97% yield if stirring was continued for 1 h after the

completion of the methylenation. The best result was a 1:1 mixture of the two enol ethers **17** and **18**. This failure to be able to cleanly isolate the exocyclic alkene from the Tebbe olefination forced us to abandon the original route using the key [3+2] cycloaddition reaction.

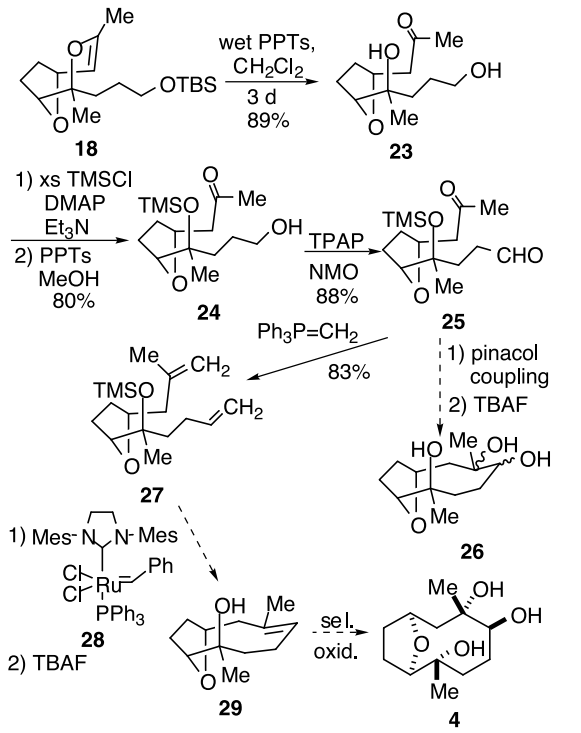


The route was thus modified to permit the use of the endocyclic enol ether **18** which could be prepared in excellent yield as mentioned above. We decided to investigate other key ring-forming reactions (Scheme 4). Silyl deprotection of the primary alcohol with TBAF, followed by TPAP/NMO oxidation[19] provided the unstable aldehyde **19** in 63% yield. We thought that perhaps the aldehyde **19** could be converted via the carboxylic acid into the phenylseleno ester **20** which could be used to generate the acyl radical[20] **I** which should cyclize to give the bridged six-membered ring of the tricylic ketone **21**. Unfortunately, this route could not be carried out because of the failure of the oxidation step, due to the instability of the enol ether to various oxidants. Similarly, direct treatment of the olefinic aldehyde **19** with SmI_2 might cause cyclization via the ketyl radical **II**[21] to give the tricyclic alcohol **22**. However, when this cyclization was attempted, a complex mixture of products was formed, and the routes of Scheme 4 were abandoned. We have no good rationale to explain why these radical based cyclizations to give six-membered cyclization products do not work in this system.

We decided to use the intermediates from this first route to



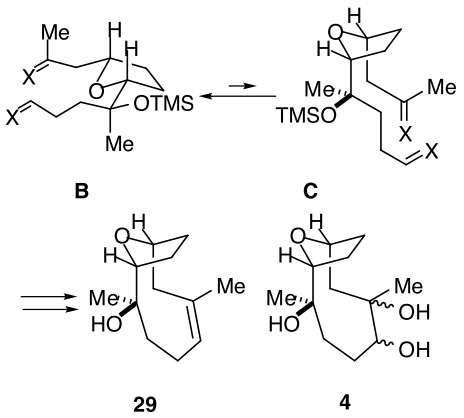
Scheme 4.



Scheme 5.

prepare bicyclic analogues of sclerophytin such as the triol **4** (Scheme 5). The route to such compounds began with a one-pot enol ether hydrolysis and silyl deprotection of **18** with wet pyridinium *p*-toluenesulfonate (PPTs). The diol **23** thus obtained in 89% yield was then protected at the tertiary alcohol by first double protection with excess TMSCl to give the bis-silyl ether and subsequent mono-deprotection of the primary TMS group by reaction with PPTs to provide the keto alcohol **24** in 80% yield for the two steps. Oxidation of the primary alcohol with TPAP/NMO gave the unstable keto aldehyde **25** in 88% yield. We then attempted to use a pinacol reaction as the key ring-closing step to give, after silyl deprotection, the bicyclic diols **26**. Because two new stereocenters would be formed, a mixture of up to four diastereomers could be obtained. It was hoped that the mixture would be separable by HPLC and the isomers would then be characterized and tested for biological activity. Although we were well aware that the synthesis of nine-membered rings was non-trivial and often quite difficult,[22] we were encouraged by the excellent pinacol coupling conditions reported by McMurry, which often gave good yields of medium- to large-sized rings.[23] Unfortunately, attempted coupling with $TiCl_3$-DME and Zn–Cu under high-dilution conditions only led to dimeric products resulting from the intermolecular coupling of the aldehyde moieties. The reaction was also attempted with SmI_2, which has also been shown to be an efficient pinacol coupling reagent.[21] However, again the reaction produced an intractable mixture of products.

A revised strategy was attempted which involved a key ring-closing metathesis (RCM)[24] reaction with Grubb's highly efficient ruthenium–carbene catalyst **28**.[25] Selective oxidations of the RCM product **29** could give bicyclic triols such as **4**. The keto aldehyde **25** was first converted to the diene **27** in 83% yield by a double Wittig olefination. The



Scheme 6.

metathesis reaction was then attempted using high-dilution conditions in various solvents at varying temperatures. No reaction occurred at room temperature and the use of higher temperatures resulted in only dimerization and isomerization of the monosubstituted olefin of **27**. Examination of the existing literature confirmed that successful examples of nine-membered ring formation using ring-closing metathesis are rare.[24h] The inability to form the strained medium-sized ring system is likely a result of increasing strain in the transition state (enthalpic factors), and the low probability of the chain ends meeting (entropic factors).[24] In particular it would appear that any approach which attempts to close the nine-membered ring via a *cis* 2,5-disubstituted tetrahydrofuran is likely to be unsuccessful because of conformational effects (Scheme 6).

Thus the conformation of the cyclization substrates **C** which is needed for the cyclization to occur to give **29** or **4**, e.g. with the two large groups pseudoaxial in the envelope conformation of the five-membered ring, is much less stable than the alternate conformation **B** in which the two large groups are pseudoequatorial. MM3 calculations on a simpler model (with methyl groups in place of the alkenyl chains and hydroxyl instead of OTMS, i.e. *cis*-α,α,5-trimethyltetrahydrofuranmethanol) indicated an energy difference of ~2.7 kcal/mol in favor of **B**.[26] Thus it is unlikely that the conformation necessary for cyclization **C** is populated very much at all in the substrates for the cyclization, e.g. **25** or **27**. Consequently we decided to abandon all work in this area. It is interesting that in the two published syntheses,[2] the formation of the additional ring (nine-membered in the Overman synthesis, seven-membered in the Paquette synthesis) was carried out on tetrahydrofuran rings *cis*-fused to the required cyclohexane (namely perhydroisobenzofurans) and this presumably helped in achieving the required transition state geometry for the cyclization.

3. Conclusion

In conclusion, we have shown that the bicyclic eight-membered lactones **7ab** having the required tertiary alcohol center of sclerophytin A in the correct enantiomeric form can be easily prepared from the readily available ketone **8** in only seven steps and in good overall yield. Although Tebbe olefination was successful, isomerization of the resulting exocyclic enol ether **17** could not be avoided. Attempts at cyclizing derivatives on the endocyclic enol ether **18**, which could be made in good yield, were unsuccessful for unknown reasons. Finally the dione and diene **25** and **27**, respectively, were easily prepared from **18** in good yield but again attempted cyclizations of these substrates via intramolecular pinacol or Grubbs ring-closing metathesis reactions were unsuccessful. Molecular mechanics calculations indicate that such a cyclization strategy will probably not work due to unfavorable conformational effects.

4. Experimental

4.1. Data for compounds

4.1.1. (1*R*,2*R*,5*S*)-2-Methyl-8-oxabicyclo[3.2.1]octan-3-one (11). To the enol ether **10**[6] (400 mg, 1.88 mmol) in 15 mL THF at 0°C was added dropwise methyllithium (1.40 M in diethyl ether, 1.35 mL, 1.88 mmol). The solution was stirred at 0°C for 3 h, then cooled to −78°C. A solution of methyl iodide (1.17 mL, 2.08 mmol) in 1.3 mL HMPA was then added dropwise via cannula, and the solution was warmed to 21°C over several hours. After stirring for 15 h, the mixture was diluted with diethyl ether (25 mL) and washed with saturated aq. NH_4Cl (40 mL). The aqueous layer was extracted (3×15 mL Et_2O), and the combined extracts were washed with saturated aq. $NaHCO_3$ (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. Subjection of the crude to chromatography on silica gel (60% Et_2O/pentane) gave the ketone **11** as a pale yellow oil (232 mg, 88%). $[\alpha]_D^{20}=-64°$ (c=1.8, CH_2Cl_2); IR (neat) 2967, 2883, 1713, 1472, 1348, 1289, 1196, 1154, 1097, 1059, 945, 924, 868 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.72 (dd, J=6.2, 6.2 Hz, 1H), 4.38 (d, J=7.4 Hz, 1H), 2.86 (dd, J=15.8, 5.3 Hz, 1H), 2.33 (q, J=7.4 Hz, 1H), 2.19 (d, J=15.8 Hz, 1H), 2.22–2.00 (m, 2H), 1.82–1.68 (m, 2H), 1.32 (d, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 211.6, 79.6, 74.8, 53.3, 46.5, 29.2, 28.7, 16.6; HRMS (EI) *m/e* (M^+) calcd for $C_8H_{12}O_2$: 140.0837, found 140.0840.

4.1.2. (1*R*,2*R*,5*S*)-2-Methyl-2-(2-propenyl)-8-oxabicyclo-[3.2.1]octan-3-one (12) and (1*R*,2*R*,4*S*,5*S*)-2-methyl-4-(2-propenyl)-8-oxabicyclo[3.2.1]octan-3-one (13). A solution of the ketone **11** (555 mg, 3.96 mmol) in 3.5 mL degassed THF was added to dry potassium hydride (161 mg, 4.01 mmol). After stirring at 21°C for 0.5 h, triethyl-borane (1.0 M in THF, 4.2 mL, 4.2 mmol) was added dropwise over 5 min. The mixture was stirred for 5 min, then transferred via cannula to a solution of tetrakis(triphenylphosphine)-palladium(0) (229 mg, 0.198 mmol) and allyl chloride (0.80 mL, 9.8 mmol) in 7.5 mL degassed THF. The mixture was stirred in the dark for 16 h, then diluted with 20 mL diethyl ether, and washed with 20 mL 0.5 M aq. HCl. Further extraction of the aqueous layer (2×15 mL Et_2O) was followed by washing of the combined extracts with saturated aq. $NaHCO_3$ (20 mL), and brine (20 mL). Drying over $MgSO_4$, concentration, and chromatography on silica gel (30% Et_2O/pentane) gave an inseparable 5:1 mixture of the ketones **12** and **13** (439 mg, 62%) as a pale yellow oil,

followed by recovered **11** (145 mg, 74% conversion). Data for the ketone **12**: $[\alpha]_D^{20}=-110°$ (c=1.3, CH_2Cl_2); IR (neat): 2978, 2963, 2883, 1713, 1640, 1472, 1379, 1350, 1196, 1119, 1057, 1005, 918 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.67–5.55 (m, 1H), 5.11–5.03 (m, 2H), 4.67 (dd, J=2.3, 2.3 Hz, 1H), 4.13 (d, J=3.6 Hz, 1H), 2.81 (ddd, J=15.2, 5.4, 1.6 Hz, 1H), 2.61 (dd, J=13.7, 7.3 Hz, 1H), 2.34 (dd, J=13.7, 7.6 Hz, 1H), 2.10 (d, J=15.0 Hz, 1H), 2.00–1.77 (m, 3H), 1.67–1.58 (m, 1H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 211.5, 132.7, 118.5, 82.1, 75.8, 55.3, 46.6, 41.3, 29.2, 25.0, 16.5; HRMS (EI) m/e (M^+) calcd for $C_{11}H_{16}O_2$: 180.1150, found 180.1148.

4.1.3. (1*R*,2*R*,5*S*)-2-(3-Hydroxypropyl)-2-methyl-8-oxabicyclo[3.2.1]octan-3-one (14). To borane: dimethyl sulfide complex (10 M, 90 μL, 0.90 mmol) in 0.5 mL THF at 0°C was added cyclohexene (182 μL, 1.80 mmol). The thick suspension was stirred at 0°C for 1 h, then the ketone **12** (108 mg, 0.599 mmol) in 0.4 mL THF was added via cannula. Stirring was continued at 0°C for 3 h, then sodium perborate tetrahydrate (415 mg, 2.74 mmol), and 0.9 mL water were added. The mixture was allowed to warm to 21°C and was stirred for an additional 2 h. Ethyl acetate (10 mL) and saturated aq. NH_4Cl (5 mL) were added. Separation and extraction with ethyl acetate (3×7 mL) was followed by drying ($MgSO_4$) and concentration. Chromatography on silica gel (30% CH_2Cl_2/EtOAc) provided the ketoalcohol **14** (102 mg, 86%) as a viscous, colorless oil. $[\alpha]_D^{20}=-95°$ (c=1.6, CH_2Cl_2); IR (neat): 3452, 2957, 2876, 1707, 1474, 1381, 1109, 1057, 1005, 959 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.64 (dd, J=5.9, 5.9 Hz, 1H), 4.09 (m, 1H), 3.56 (t, J=6.3 Hz, 2H), 2.80 (dd, J=15.2, 5.4 Hz, 1H), 2.25–1.70 (m, 5H), 1.65–1.45 (m, 3H), 1.28–1.12 (m, 2H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 212.2, 82.5, 75.8, 62.8, 55.0, 46.5, 33.1, 29.2, 26.9, 25.1, 16.4; HRMS (EI) m/e (M^+) calcd for $C_{11}H_{18}O_3$: 198.1255, found 198.1260.

4.1.4. (1*R*,2*R*,5*S*)-2-[3-(Chloroacetyloxy)propyl]-2-methyl-8-oxabicyclo[3.2.1]octan-3-one (15). A solution of the ketoalcohol **14** (20 mg, 0.10 mmol) and 4-(dimethylamino)pyridine (DMAP, 2 mg, 0.015 mmol) in pyridine (0.5 mL) was cooled to 0°C. Chloroacetic anhydride (52 mg, 0.303 mmol) was added in one portion, and stirring was continued at 0°C for 1.5 h. The reaction mixture was then diluted with diethyl ether (30 mL), washed with water (2×20 mL) and brine (1×20 mL), and dried over $MgSO_4$. Concentration and chromatography on silica gel (10% Et_2O/CH_2Cl_2) gave the chloroacetate **15** as a pale yellow oil (27.6 mg, 100%); $[\alpha]_D^{20}=-80°$ (c=1.8, CH_2Cl_2); IR (neat): 2967, 2940, 1761, 1713, 1472, 1313, 1290, 1175, 1119, 1003, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.68 (dd, J=6.5, 6.5 Hz, 1H), 4.33–4.08 (m, 3H), 4.05 (s, 2H), 2.80 (dd, J=15.3, 5.5 Hz, 1H), 2.18–1.55 (m, 7H), 1.42–1.23 (m, 2H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 211.6, 167.3, 82.5, 75.8, 66.2, 54.9, 46.5, 40.9, 33.0, 29.2, 25.1, 23.0, 16.3; HRMS (EI) m/e (M^+) calcd for $C_{13}H_{19}O_4Cl$: 274.0972, found 274.0976.

4.1.5. (1*R*,2*R*,6*S*)-2-[3-(Chloroacetyloxy)propyl]-2-methyl-3,9-dioxabicyclo[4.2.1]nonan-4-one (7a). To a solution of the chloroacetate **15** (103 mg, 0.375 mmol) in 1,2-dichloroethane (2 mL) was added $NaHCO_3$ (96 mg, 1.1 mmol), 5-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (3 mg, 0.0008 mmol), and *m*-CPBA (130 mg, 0.757 mmol). A reflux condenser was attached and the suspension was stirred and heated at 55°C for 7 h. After the mixture was cooled, additional $NaHCO_3$ (96 mg, 1.1 mmol), 5-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (3 mg, 0.0008 mmol), and *m*-CPBA (130 mg, 0.757 mmol) were added. Again the mixture was heated at 55°C for 7 h, and after cooling, additional reagents were added as before. This process was repeated a total of four times, and after 28 h the mixture was cooled and diluted with dichloromethane (5 mL). Careful quenching with saturated aq. sodium bisulfite (2 mL) was followed by dichloromethane extraction (2×5 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (2×5 mL) and brine (2×5 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. Chromatography on silica gel (gradient elution 5% Et_2O/CH_2Cl_2 to 10% Et_2O/CH_2Cl_2) gave the starting material **15** (19 mg, 82% conversion), followed by the lactone **7a** (57 mg, 52%) as a pale yellow oil. $[\alpha]_D^{20}=-53°$ (c=1.6, CH_2Cl_2); IR (neat): 2965, 1754, 1701, 1468, 1414, 1366, 1282, 1236, 1171, 978, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.42–4.33 (m, 1H), 4.22 (t, J=5.0 Hz, 2H), 4.17 (d, J=6.1 Hz, 1H), 4.06 (s, 2H), 3.02 (dd, J=13.3, 2.0 Hz, 1H), 2.88 (dd, J=13.3, 3.0 Hz, 1H), 2.18–2.09 (m, 4H), 1.89–1.70 (m, 4H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.2, 167.1, 87.0, 82.5, 72.7, 65.8, 46.0, 40.7, 33.1, 28.5, 24.2, 23.0, 22.9; HRMS (EI) m/e (($M+H)^+$) calcd for $C_{13}H_{20}O_5Cl$: 291.0999, found 291.0995.

4.1.6. (1*R*,2*R*,6*S*)-2-(3-[(1,1-Dimethyl)ethyldimethylsilyl]-oxy-propyl)-2-methyl-3,9-dioxabicyclo-[4.2.1]nonan-4-one (7b). To the lactone **7a** (159 mg, 0.547 mmol) in lutidine (4.1 mL) and acetic acid (1.4 mL) was added a stock solution of hydrazine thiocarbonate[15] (0.37 M, 4.7 mL, 1.7 mmol). The yellow mixture was stirred at 21°C for 20 min, then diluted with ethyl acetate (150 mL) and brine (40 mL). The mixture was separated and the aqueous layer was extracted with ethyl acetate (4×50 mL). The combined organics were dried over $MgSO_4$, and concentrated to give a solution of the crude hydroxy lactone in lutidine, which was removed at high vacuum over several hours. The resulting crude hydroxy lactone was isolated as a viscous yellow oil (109 mg, 93%). To a sample of the crude hydroxy lactone (90 mg, 0.42 mmol), 4-(dimethylamino)-pyridine (DMAP, 9 mg, 0.07 mmol), and triethylamine (0.12 mL, 0.84 mmol) in dichloromethane (2 mL) was added *tert*-butylchlorodimethylsilane (TBSCl, 95 mg, 0.63 mmol). The mixture was stirred for 3 h at 21°C and then concentrated. Column chromatography on silica gel (gradient elution CH_2Cl_2 to 5% Et_2O/CH_2Cl_2) provided the lactone silyl ether **7b** (131 mg, 100%) as a pale yellow oil. $[\alpha]_D^{20}=-43°$ (c=1.8, CH_2Cl_2); IR (neat): 2959, 2859, 1725, 1472, 1362, 1252, 1173, 1100, 1005, 978, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.38–4.33 (m, 1H), 4.18 (d, J=7.7 Hz, 1H), 3.69–3.59 (m, 2H), 3.02 (dd, J=16.5, 2.6 Hz, 1H), 2.76 (dd, J=16.5, 3.8 Hz, 1H), 2.20–2.04 (m, 4H), 1.88–1.77 (m, 2H), 1.63–1.53 (m, 2H), 1.26 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.6, 87.0, 82.6, 72.8, 62.8, 46.1, 33.0, 28.6, 27.2, 25.9, 24.4, 23.3, 18.3, −5.3; HRMS (EI) m/e (($M+H)^+$) calcd for $C_{17}H_{33}O_4Si$: 329.2147, found 329.2142.

4.1.7. (1*R*,2*R*,6*S*)-2-(3-[(1,1-Dimethyl)ethyldimethylsilyl]-oxypropyl)-2,4-dimethyl-3,9-dioxabicyclo[4.2.1]-non-4-ene (18). A solution of the lactone **7b** (32 mg, 0.097 mmol) and pyridine (2.0 μL, 0.025 mmol) in a 1:1 mixture of toluene/THF (0.40 mL) was cooled to −45°C (acetonitrile–Dry Ice bath). Tebbe reagent, μ-dichloro-μ-methylene-[bis(cyclopentadienyl)titanium]dimethylaluminum,[14f] (0.59 M in toluene, 0.42 mL, 0.25 mmol) was added dropwise over 10 min via a gastight syringe. The flask was shielded from light and stirring was continued at −45°C for 30 min. The red-orange mixture was then allowed to warm to 21°C over 2 h, and stirred at 21°C for an additional 30 min. The mixture was then cooled to −10°C, and 15% aq. NaOH (75 μL) was added. After stirring at −10°C for 5 min, the mixture was stirred at 21°C for 20 min, and filtered through a plug of Celite. Concentration, followed by chromatography on neutral alumina (1 cm×8 cm column, 15% Et_2O/hexane), provided the enol ether **18** as a pale yellow oil (31 mg, 97%). Up to a 1:1 mixture of the exocyclic enol ether **17** and the endocyclic enol ether **18** can be obtained if the stirring time is shortened. Data for the exocyclic enol ether **17**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.29 (s, 1H), 4.46–4.27 (m, 1H), 4.06–3.98 (m, 2H), 3.75–3.54 (m, 2H), 2.86 (dd, *J*=16.0, 1.5 Hz, 1H), 2.44 (dd, *J*=16.0, 2.0 Hz, 1H), 2.30–1.45 (m, 8H), 1.15 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.0, 95.2, 83.5, 83.4, 75.4, 63.6, 42.3, 33.9, 28.5, 27.5, 26.0, 25.2, 23.2, 22.5, −5.3. Data for the endocyclic enol ether **18**: $[\alpha]_D^{20}=-33°$ (*c*=2.3, CH_2Cl_2); IR (neat): 2980, 2951, 2859, 1669, 1464, 1379, 1327, 1266, 1179, 1100, 960, 839, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.88 (d, *J*=6.7 Hz, 1H), 4.39 (dd, *J*=6.8, 6.8 Hz, 1H), 3.64 (dd, *J*=5.3, 5.3 Hz, 1H), 3.71–3.60 (m, 2H), 2.04–1.97 (m, 2H), 1.97–1.87 (m, 2H), 1.87–1.77 (m, 1H), 1.74 (s, 3H), 1.72–1.62 (m, 2H), 1.62–1.52 (m, 1H), 1.18 (s, 3H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.8, 107.8, 82.5, 82.4, 74.2, 63.5, 33.6, 30.6, 27.9, 25.8, 23.9, 22.9, 22.3, 18.2, −5.4; HRMS (EI) *m/e* (M^+) calcd for $C_{18}H_{34}O_3Si$: 326.2277, found 326.2265.

4.1.8. (1*R*,2*R*,6*S*)-2,4-Dimethyl-3,9-dioxabicyclo[4.2.1]-non-4-ene-2-propanal (19). To the enol ether **18** (17.0 mg, 0.0520 mmol) in THF (0.5 mL) at 21°C was added dropwise tetrabutylammonium fluoride (TBAF, 1.0 M, 71 μL, 0.068 mmol), and stirring was continued for 2 h. The mixture was dried (Na_2SO_4) and filtered through basic alumina (pipette column, ethyl acetate) to provide the crude hydroxy enol ether (11 mg, 100%) as an unstable, viscous, colorless oil. A sample of the hydroxy enol ether (4.8 mg, 0.023 mmol) was immediately combined with 4 Å molecular sieve powder (11 mg) and 4-methylmorpholine-*N*-oxide (NMO, 4.0 mg, 0.034 mmol) in dichloromethane (0.5 mL) and stirred for 10 min. Tetrapropylammonium perruthenate (TPAP, 0.5 mg, 0.001 mmol) was then added in one portion, and the mixture was stirred for an additional 15 min. The mixture was quickly filtered through a pipette of neutral alumina (ethyl acetate elution) to give the aldehyde **19** (3.0 mg, 63%) as an unstable, pale yellow oil, which rapidly decomposed at room temperature. $[\alpha]_D^{20}=-71°$ (*c*=1.1, CH_2Cl_2); IR (neat): 2978, 2944, 1725, 1667, 1628, 1464, 1379, 1251, 1186, 1117, 1035, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.78 (t, *J*=1.7 Hz, 1H), 4.83 (d, *J*=6.5 Hz, 1H), 4.36 (dd, *J*=6.6, 6.6 Hz, 1H), 4.09 (m, 1H), 2.66–2.50 (m, 1H), 2.50–2.37 (m, 1H), 2.37–2.25 (m, 1H), 2.10–1.84 (m, 5H), 1.70 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.1, 175.4, 96.0, 83.3, 75.5, 58.5, 42.1, 38.7, 29.9, 28.3, 25.1, 22.9. HRMS (EI) *m/e* (M^+) calcd for $C_{12}H_{18}O_3$: 210.1256, found 210.1254.

4.1.9. (α*R*,2*R*,5*S*)-α-(3-Hydroxypropyl)-α-methyl-5-(2-oxo-propyl)tetrahydrofuran-2-methanol (23). To the enol ether **18** (12.5 mg, 0.0382 mmol) in 0.5 mL dichloromethane was added pyridinium *p*-toluenesulfonate (PPTs, 16 mg, 0.0637 mmol) and water (2.1 μL, 0.12 mmol). The mixture was stirred for 3 days, evaporated to half volume, and subjected to chromatography on silica gel (pipette column, 5% MeOH/EtOAc) to give the ketodiol **23** (7.8 mg, 89%) as a viscous, colorless oil. $[\alpha]_D^{20}=2°$ (*c*=0.90, CH_2Cl_2); IR (neat): 3459, 2950, 2876, 1708, 1361, 1069, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.38–4.30 (m, 1H), 3.77 (dd, *J*=7.2, 7.2 Hz, 1H), 3.65 (t, *J*=5.6 Hz, 2H), 2.68 (dd, *J*=15.0, 7.7 Hz, 1H), 2.60 (dd, *J*=15.0, 5.5 Hz, 1H), 2.20 (s, 3H), 2.14–2.03 (m, 1H), 1.98–1.78 (m, 2H), 1.78–1.62 (m, 4H), 1.62–1.50 (m, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.6, 85.5, 75.1, 72.5, 63.4, 49.7, 37.0, 31.5, 30.4, 27.1, 25.1, 21.5; HRMS (EI) *m/e* ($(M+H)^+$) calcd for $C_{12}H_{23}O_4$: 231.1596, found 231.1601.

4.1.10. (δ*R*,2*R*,5*S*)-δ-Methyl-5-(2-oxopropyl)-δ-trimethylsilyl-oxytetrahydrofuran-2-butanol (24). To the ketodiol **23** (17.0 mg, 0.0738 mmol), 4-(dimethylamino)-pyridine (DMAP, 10 mg, 0.081 mmol), and triethylamine (82 μL, 0.591 mmol) in dichloromethane (1 mL) at 0°C was added dropwise chlorotrimethylsilane (TMSCl, 56 μL, 0.44 mmol). The mixture was stirred at 0°C for 30 min, then at 21°C for 20 h. Evaporation, followed by trituration of the residue (5×2 mL diethyl ether), and evaporation of the solvent, gave a yellow oil. The oil was dissolved in dichloromethane (0.5 mL), and methanol (50 μL) and pyridinium *p*-toluenesulfonate (PPTs, 5 mg, 0.02 mmol) were added. Stirring was continued for 1 h. The mixture was then directly subjected to chromatography on silica gel (40% Et_2O/CH_2Cl_2) to give the hydroxy ketone **24** (18.0 mg, 80%) as a viscous, pale yellow oil; further elution (5% MeOH/EtOAc) gave the starting ketodiol **23** (2 mg). $[\alpha]_D^{20}=-3°$ (*c*=1.3, CH_2Cl_2); IR (neat): 3420, 2932, 2876, 1715, 1360, 1165, 1070, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.25–4.20 (m, 1H), 3.74 (dd, *J*=7.3, 7.3 Hz, 1H), 3.62 (t, *J*=5.9 Hz, 2H), 2.76 (dd, *J*=15.7, 7.1 Hz, 1H), 2.51 (dd, *J*=15.7, 5.7 Hz, 1H), 2.18 (s, 3H), 2.11–1.90 (m, 2H), 1.90–1.71 (m, 2H), 1.71–1.55 (m, 3H), 1.55–1.40 (m, 2H), 1.14 (s, 3H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.6, 85.2, 77.1, 75.4, 63.4, 49.7, 35.8, 31.5, 30.8, 27.3, 26.1, 23.4, 2.6; HRMS (EI) *m/e* ($(M+H)^+$) calcd for $C_{15}H_{31}O_4Si$: 303.1991, found 303.1991.

4.1.11. (δ*R*,2*R*,5*S*)-δ-Methyl-5-(2-oxopropyl)-δ-trimethylsilyl-oxytetrahydrofuran-2-butanal (25). A mixture of the hydroxy ketone **24** (16.0 mg, 0.053 mmol), 4 Å molecular sieve powder (35 mg) and 4-methylmorpholine-*N*-oxide (NMO, 14 mg, 0.12 mmol) in dichloromethane (1 mL) was stirred for 10 min. Tetrapropylammonium perruthenate (TPAP, 1 mg, 0.003 mmol) was then added in one portion, and the mixture was stirred for an additional 15 min. The mixture was loaded directly onto a short silica gel

column (1 cm×5 cm) and elution (10% Et_2O/CH_2Cl_2) gave the keto aldehyde **25** (14.0 mg, 88%) as an unstable, pale yellow oil, which was used immediately in subsequent reactions. IR (neat): 2957, 2878, 1721, 1375, 1250, 1129, 1075, 841, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 9.79 (t, J=1.7 Hz, 1H), 4.30–4.24 (m, 1H), 3.75 (dd, J=7.4, 7.4 Hz, 1H), 2.80 (dd, J=15.8, 7.1 Hz, 1H), 2.83–2.77 (m, 3H), 2.23 (s, 3H), 2.13–2.04 (m, 1H), 1.92–1.75 (m, 4H), 1.55–1.45 (m, 1H), 1.19 (s, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.1, 202.8, 85.3, 76.2, 75.3, 49.5, 38.9, 31.6, 31.3, 30.6, 26.1, 23.2, 2.3.

4.1.12. (2*R*,5*R*)-5-[3-(2-Methyl-2-propenyl)]-2-[(1*R*)-1-methyl-1-trimethylsilyloxy-4-pentenyl]-tetrahydrofuran (27). To methyltriphenylphosphonium bromide (140 mg, 0.392 mmol) in THF (1.5 mL) at 0°C was added *n*-butyllithium (1.55 M in hexane, 245 μL, 0.380 mmol). The yellow suspension was warmed to 25°C and stirred for 30 min, then re-cooled to 0°C. A solution of the keto aldehyde **25** (33 mg, 0.11 mmol) in THF (1 mL) was then added dropwise via cannula, and the mixture was stirred at 0°C for 15 min, then at 21°C for 30 min. The mixture was evaporated to half-volume and then chromatographed on silica gel (pipette column, 5% Et_2O/hexane) to provide the diene **27** (27 mg, 83%) as a pale yellow oil. $[\alpha]_D^{20}=-5°$ (c=1.1, CH_2Cl_2); IR (neat): 2957, 2855, 1641, 1453, 1375, 1250, 1070, 839, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.88–5.81 (m, 1H), 5.01 (d, J=17.1 Hz, 1H), 4.92 (d, J=10.1 Hz, 1H), 4.75 (s, 1H), 4.72 (s, 1H), 3.99 (m, 1H), 3.72 (dd, J=6.3, 6.3 Hz, 1H), 2.36 (dd, J=12.3, 6.2 Hz, 1H), 2.20–2.02 (m, 3H), 1.94–1.83 (m, 2H), 1.76 (s, 3H), 1.57–1.42 (m, 4H), 1.16 (s, 3H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.3, 139.5, 113.7, 111.7, 85.2, 78.0, 77.3, 43.9, 38.4, 31.0, 28.2, 26.0, 23.3, 22.9, 2.5; HRMS (CI) *m/e* ($(M-CH_3)^+$) calcd for $C_{16}H_{29}O_2Si$: 281.1936, found 281.1922.

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26. The conformations shown in **B** and **C** are not exact since the five-membered ring tends to rotate slightly to avoid eclipsing interactions in the basic envelope conformation. The energy calculations for **B** were fairly easy since it is the more stable isomer and all calculations converge on its structure. The energy calculations for **C** were done by constraining the structure so that at least one of the two alkyl groups was held in a pseudoaxial position since if no constraints were applied, the molecule rotated so that the two large groups were both in pseudoequatorial positions. Thus the energy difference cited is not exact but rather an estimate.