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Prins-Pinacol Spiroannulations‡

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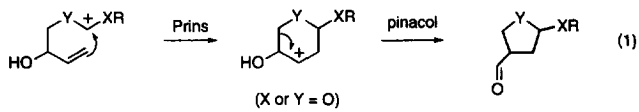
Abstract. Lewis acid-promoted cyclizations of methylenecyclohexane siloxy acetals **14**, **15**, and **21** afford spiro[4.5]decanones **22**, **25**, and **29** in good yield. In all cases, exclusive pinacol rearrangement of C-1 of the original three-carbon acetal side chain is observed suggesting that pinacol rearrangement of the intermediate 9-decalyl cation occurs more rapidly than conformational equilibration. This selectivity should allow Prins-pinacol spiroannulations to be employed in a predictable fashion to construct stereochemically complex spirocycles. © 1997 Elsevier Science Ltd.

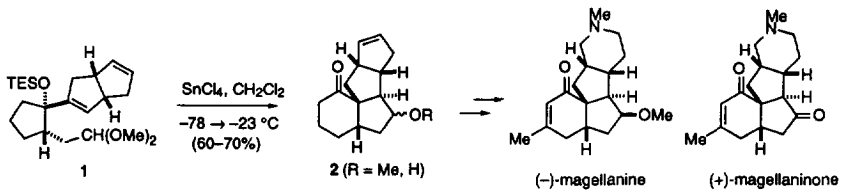
The coupling of a Prins cyclization with a pinacol rearrangement has led to the development of a useful family of reactions for forming five-membered rings (eq 1).[1] The Prins-pinacol synthesis of tetrahydrofurans (X = CH_2, Y = O) has been developed most extensively and shown to be highly effective at



(1)

solving formidable stereochemical problems in the assembly of complex cyclic ethers.[2] The high levels of stereocontrol that are hallmarks of this tetrahydrofuran synthesis are also seen in related Prins-pinacol constructions of cylopentanoids (X = O, Y = CH_2).[3] The conversion of **1** → **2**, which is the central strategic transformation in our recent synthesis of (–)-magellanine and (+)-magellaninone, provides a good illustration (Scheme 1).[4] In this key step a new five-membered ring is formed and the starting cyclopentane ring is expanded by one carbon.

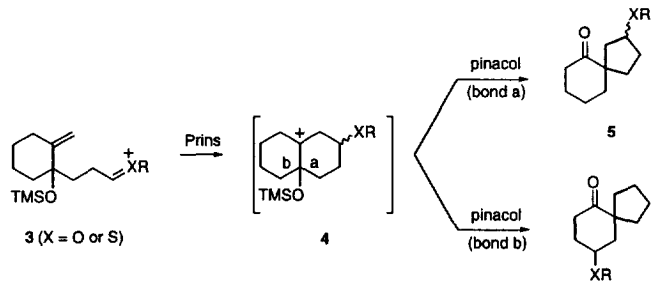
‡Dedicated to Professor Samuel Danishefsky on the occasion of his receipt of the 1996 Tetrahedron Prize.



Scheme 1

The high level of stereo- and regioselectivity observed in the synthesis of carbocycles and oxacycles by Prins-pinacol reactions is believed to derive from conformational preferences in the Prins cyclization step. Slow Prins cyclization (typically proceeding in a chair topography) followed by rapid pinacol rearrangement can account for the stereochemical outcome of most Prins-pinacol reactions. To date, all carbocyclizations have involved alkene and acetal participants that were vicinal substituents on a starting ring; thus, Prins-pinacol reorganization resulted, as in Scheme 1, in ring-enlarging cyclopentane annulation. To further develop the scope of the Prins-pinacol synthesis of carbocycles, we turned to substrates in which the alkene is exocyclic in the starting ring.

As illustrated in Scheme 2, Prins-pinacol reaction of methylenecyclohexane **3** should lead to the formation of spiro[4.5]decan-6-ones. An interesting situation arises since spirocycles of two types, **5** and **6**, could be formed depending on which bond in the presumed decalin carbocation intermediate **4** undergoes pinacol rearrangement. In this paper we report that pinacol rearrangement occurs with complete regioselectivity to form only spiro[4.5]decan-6-one **5**. As a result of this selectivity, Prins-pinacol reactions hold considerable promise for the stereocontrolled assembly of complex spirocyclic structures.

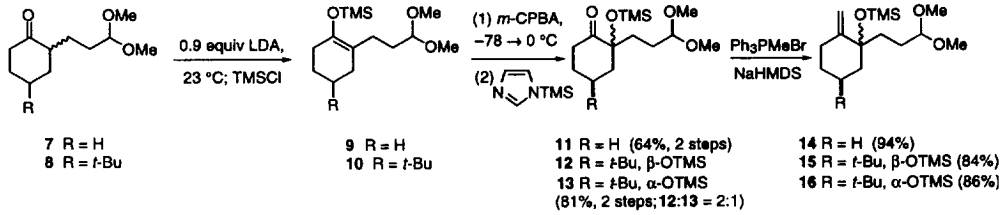


Scheme 2

Results

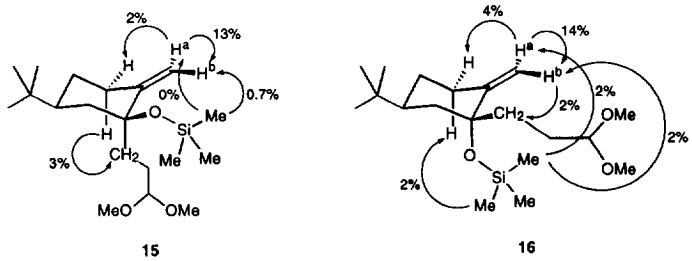
Preparation of Unsaturated Acetals 14-16. Rearrangement substrates **14-16** were assembled by the sequence summarized in Scheme 3. Keto acetals **7** and **8** were deprotonated under thermodynamic conditions and the resulting enolates trapped with TMSCl to afford enoxysilanes **9** and **10**. Only traces of regioisomeric silyl enol ethers were detected by ^1H and ^{13}C NMR analysis of the purified products. Rubottom oxidation of **9**,[5] followed by silylation with *N*-(trimethylsilyl)imidazole yielded siloxy ketone **11**. Wittig methylenation of

11 then delivered rearrangement substrate **14** in good overall yield.[6] Utilizing identical chemistry, *t*-butyl analog **10** was oxidized and the resulting keto alcohol silylated to provide a 2:1 mixture of siloxy ketones **12** and **13**. Separation of these stereoisomers by preparative medium pressure LC (MPLC), followed by Wittig methylenation provided cyclization precursors **15** and **16**.



Scheme 3

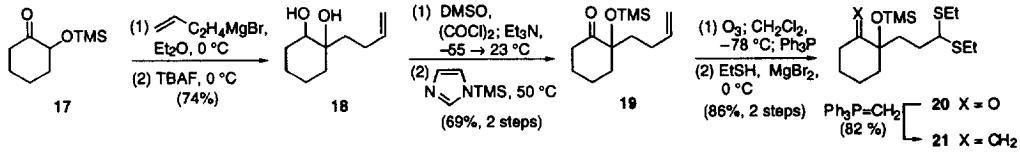
The stereochemical assignments for *t*-butyl substrates **15** and **16** are supported by the ^{1}H NOE's indicated in Figure 1.[7] The chemical shifts of the vinyl hydrogens were also suggestive of the stereostructures. A difference of 0.11 ppm in the chemical shift between H^a and H^b is observed for **16**, while **15** shows a larger difference (0.35 ppm), presumably due to the proximity of H^b to the non-bonded electrons of the siloxy group.



15 **16**

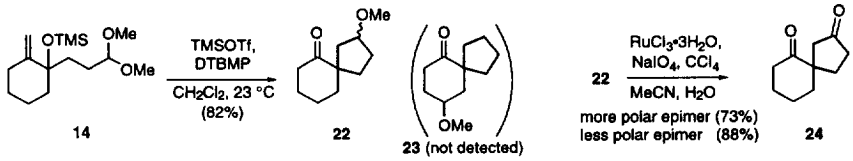
Figure 1

Preparation of Dithioacetal 21. Substrate **21** containing the dithioacetal side chain was prepared by the sequence shown in Scheme 4. Condensation of 2-siloxycyclohexanone **17** with 3-butenylmagnesium bromide, followed by desilylation provided diol **18** as a mixture of stereoisomers. These diols were oxidized under Swern conditions and the resulting hydroxy ketone was silylated to afford **19**.[8] Utilizing a convenient one pot procedure, alkenyl siloxy ketone **19** was cleaved with O_3 and the resulting keto aldehyde selectively protected with EtSH to give dithioacetal **20**.[9] Treatment of **20** with methylenetriphenylphosphorane then provided dithioacetal cyclization precursor **21** in 42% overall yield from siloxy ketone **17**.



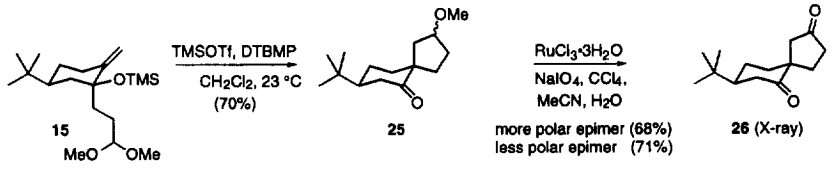
Scheme 4

Prins-Pinacol Spiroannulations. Exposure of alkenyl acetal **14** to an excess of a 1:1 mixture of TMSOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at room temperature promoted clean cyclization to give spirocycle **22**, a 1.5:1 mixture of methoxy epimers, in 82% yield (Scheme 5).[10,11] The conversion of acetal **14** to **22** with excess TBDMSOTf and DTBMP proceeded in slightly higher yield (95%). The ^{13}C NMR spectrum of the crude product mixture revealed only two carbonyl signals (δ 211.5 and 210.0), while the ^{1}H NMR spectrum showed diagnostic signals for only two methoxy groups. Capillary GCMS analysis detected only two compounds with m/z = 182. These products were separated by preparative MPLC and independently oxidized with RuO_4 to give diketone **24**,[12] establishing that the two products are epimeric at the methoxy stereocenter. This result alone signals that spiro[4.5]decan-6-ones **22** are the observed products, since the alternate product **23** of Prins-pinacol cyclization has only one stereocenter. Consistent with this conclusion, **24** shows diagnostic signals for cyclopentanone and cyclohexanone carbonyl groups in the IR spectra at 1744 and 1705 cm^{-1}.[13]



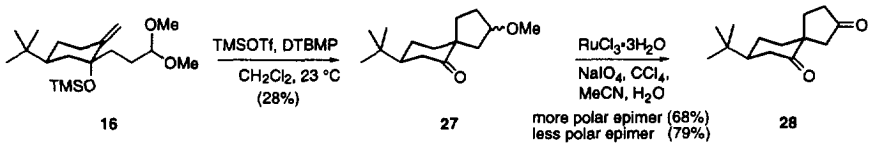
Scheme 5

Cyclization of *t*-butyl analog **15** at room temperature with excess TMSOTf/DTBMP gave two products **25** in a 1.4:1 ratio and 70% yield (Scheme 6). As in the case of the rearrangement of **14**, no other carbonyl signals were seen in the ^{13}C NMR spectra of the crude reaction product nor were other isomers detected by capillary GCMS analysis. Separation of these products and independent oxidation with RuO_4 yielded a single diketone **26**. This material provided single-crystals that allowed the stereochemistry of the spiro center to be established by X-ray crystallography.[14]



Scheme 6

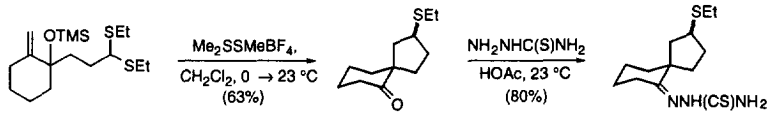
Cyclization of isomeric acetal **16** under identical conditions proceeded inefficiently to give **27**, a 1.5:1 mixture of stereoisomers, in 28% yield (Scheme 7). The two products were again shown to be methoxy epimers by RuO_4 oxidation to diketone **28**. ^{1}H and ^{13}C NMR spectra indicated that **28** and **26** were closely related. Signals for an isolated methylene adjacent to a carbonyl group (δ 1.49 and 3.00, doublets, J = 18 Hz) were readily apparent in the ^{1}H spectra of **28**, while the IR spectra showed both cyclopentanone and cyclohexanone carbonyl signals (1749 and 1706 cm^{-1}).



16 27 28

Scheme 7

Dithioacetal **21** rearranged at 0 → 23 °C in the presence of 2 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to provide a single spirocyclic product **29** in 63% yield (Scheme 8).[15] No trace of a second ketone was seen in the ^1H NMR or ^{13}C NMR spectrum of the crude cyclization product. Conversion of **29** to the crystalline thiosemicarbazone derivative **30** allowed the relative stereochemistry of this derivative to be established by single-crystal X-ray analysis.[14]

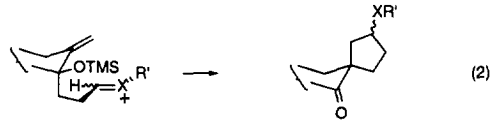


21 29 30 (X-ray)

Scheme 8

Discussion

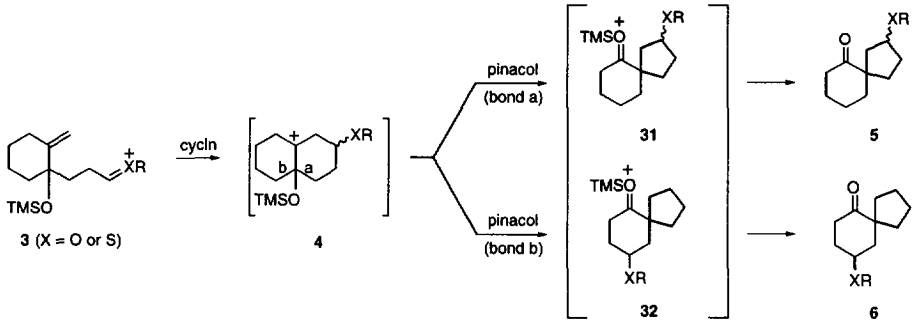
The chemistry reported here allows spiro[4.5]decan-6-ones to be prepared in 6–9 steps and useful overall yields from cyclohexanone precursors. Although demonstrated in the cyclohexanone series only, we anticipate that five-membered rings can be appended to a variety of ketones using Prins-pinacol spiroannulations. One limitation revealed in this initial survey is that the cyclization initiator must not be tethered in the plane of the exocyclic methylene group. Thus, while the conformationally flexible substrates **14** and **21,** and substrate **15** having the tethered cyclization initiator oriented axially, cyclized in high yield, the cyclization of **16** was inefficient. As a result, spiroannulations of the type schematically illustrated in eq 2 should be possible with this chemistry.



(2)

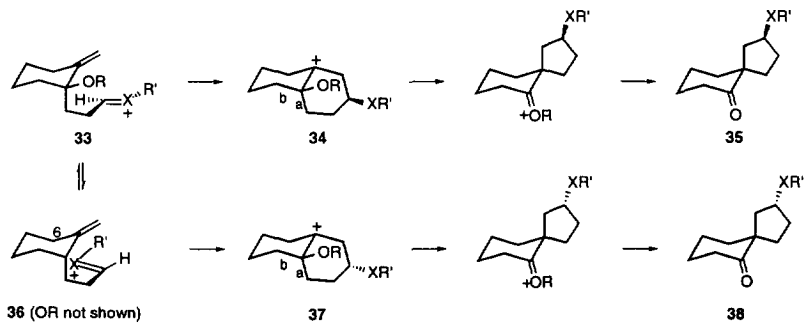
In all cases, including the inefficient cyclization of **16**, exclusive migration of C-1 of the original three-carbon acetal side chain was observed. As illustrated in Scheme 9, this selectivity requires that bond a in the 9-decalyl cation **4** migrates in preference to bond b. When XR is OMe, one possible explanation for this selectivity would be that it arises in the pinacol step from destabilization of **32** by the long-range inductive effect of the oxygen substituent. Specifically, the XR group is separated from the electron-deficient sp^2 carbon of pinacol product **32** by two sequences of four σ-bonds, while the electron-deficient carbon of **31** is

separated from the XR substituent by sequences of four and five σ-bonds. However, the observation of identical migration selectivity when the cyclization initiator is an α-thiocarbenium ion renders this explanation unlikely.[16]



Scheme 9

We favor an alternate stereoelectronic explanation. As noted earlier, Prins-pinacol spiroannulations are efficient only with substrates that tether the initiating electrophile axially. As illustrated in Scheme 10, this axial orientation of the three-carbon side chain allows for excellent overlap of the reacting π-systems in either anti or synclinal approach trajectories, **33** or **36**. Cyclization in either orientation would lead initially to a 9-decalin cation conformer (**34** or **37**) in which only bond a would have good overlap with the vacant p-orbital.[17,18] Thus, if pinacol rearrangement occurred more rapidly than conformational interconversion, only spirocycles **35** and **38** would be formed.[19,20,21] The exclusive formation of **35** with the thionium initiator is presumably a reflection of the longer C–S σ bond which leads to destabilizing steric interactions between the SEt group and the axial C-6 hydrogen in **36**.



Scheme 10 (R = TMS, XR' = OMe or SEt)

Conclusion

Spiro[4.5]decan-6-ones can be prepared from cyclohexanone precursors in 6–9 steps and good overall yield by Prins-pinacol spiroannulations. The selectivity observed in the rearrangement step should allow stereochemically complex spirocycles to be assembled in this way.

Experimental[22]

General Procedure for Preparing of 2-(3,3-Dimethoxypropyl)cycloalkanones 7 and 8.[23] A solution of cyclohexanone cyclohexylimine and THF was deprotonated with $LiNEt_2$ (1.05 equiv) at –78 °C.[24] The reaction was allowed to warm to 0 °C and after 2 h, 1-bromo-3,3-dimethoxypropane (1.1 equiv) was added dropwise at –78 °C.[25] After allowing the solution to warm to rt overnight, a mixture of saturated aqueous NH_4Cl was added and the resulting mixture was heated at reflux (65–70 °C) for 5 h. After cooling to rt, the mixture was extracted with Et_2O (3 x 20 mL) and the ether extract was washed with H_2O (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the residue was purified by vacuum distillation.

2-(3,3-Dimethoxypropyl)cyclohexanone (7). 83% as a colorless liquid: bp 110–112 °C (1.5 mm); ^1H NMR (300 MHz, C_6D_6) δ 4.37 (t, J = 6.8 Hz, 1H), 3.24 (s, 3H), 3.22 (s, 3H), 2.25 (m, 1H), 2.04–1.04 (m, 12H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.6, 104.7, 52.3, 52.0, 50.3, 42.0, 34.2, 30.4, 28.1, 25.2, 25.1; IR (film) 2936, 1710, 1450, 1128, 1060 cm^{-1}. Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 65.71; H, 9.97.

4-*tert*-Butyl-2-(3,3-dimethoxypropyl)cyclohexanone (8). 68% as a colorless liquid that was a 3.5:1 mixture of diastereomers. These isomers were separated by preparative MPLC (10:1 hexanes–EtOAc) and purified by vacuum distillation (bp 115–116 °C, 0.4 mm) for characterization: Major, more polar diastereomer: ^1H NMR (300 MHz, C_6D_6) δ 4.32 (t, J = 5.4 Hz, 1H), 3.18 (s, 3H,), 3.17 (s, 3H), 2.21 (tt, J = 4.5, 13.2 Hz, 1H), 2.04–1.78 (m, 5H), 1.71–1.57 (m, 2H), 1.34–1.26 (m, 1H), 1.15–0.89 (m, 3H), 0.69 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.6, 105.0, 52.5, 52.1, 49.4, 47.1, 41.6, 35.4, 32.2, 30.7, 28.7, 27.6, 25.3; IR (film) 2954, 2869, 1714, 1448, 1366, 1129, 1061, 966 cm^{-1}; HRMS (CI, isobutane) *m/z* 256.1994 (M, 256.2038 calcd for $C_{15}H_{28}O_3$). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.26; H, 11.01. Found: C, 70.15; H, 11.09. Minor, less polar diastereomer: ^1H NMR (300 MHz, C_6D_6) δ 4.29 (t, J = 5.4 Hz, 1H), 3.14 (s, 3H), 3.13 (s, 3H,), 2.29–2.23 (m 1H), 2.18–2.01 (m, 2H), 1.83–1.57 (m, 3H), 1.54–1.37 (m, 3H), 1.33–1.18 (m, 2H), 1.06 (dt, J = 5.4, 12.0 Hz, 1H), 0.68 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.6, 104.3, 52.4, 48.9, 41.3, 38.3, 32.1, 31.8, 30.7, 27.6, 27.4, 26.8, 26.6; IR (film) 2953, 1711, 1458, 1366, 1191, 1127, 1069, 955 cm^{-1}; HRMS (CI, isobutane) *m/z* 256.1928 (M, 256.2038 calcd for $C_{15}H_{28}O_3$). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.26; H, 11.01. Found: C, 70.12; H, 11.03.

General Procedure for Preparing Siloxy Ketones 11-13. A solution of the keto acetal and THF was deprotonated with LDA [prepared from *i*-Pr_2NH (1.0 equiv), *n*-BuLi (0.9 equiv, 2.3 M) and THF at 0 °C]. Enolate equilibration was allowed to take place at rt for 36 h and TMSCl (1.0 equiv) was then added. After 1 h, the reaction was concentrated, pentane (20 mL) was added and the resulting precipitate was removed by filtering under a N_2 atmosphere through a plug of neutral alumina (activity I). The eluent was concentrated and the crude enoxysilanes were used without further purification: Enoxysilane **9**: ^1H NMR (300 MHz, C_6D_6) δ 4.33 (t, J = 5.7 Hz, 1H), 3.16 (s, 6 H), 2.16 (t, J = 7.5 Hz, 2H), 1.94–1.90 (m, 4H), 1.76–1.69 (m, 2H), 1.54–1.40 (m, 4H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 143.7, 114.9, 104.6, 52.0, 31.0, 30.7, 28.2, 26.0, 24.0, 23.5, 0.9; IR (film) 2930, 1680, 1381, 1252, 1061, 857 cm^{-1}; HRMS (CI, isobutane) *m/z* 272.1808 (M, 272.1808 calcd for $C_{14}H_{28}O_3Si$). Enoxysilane **10**: ^1H NMR (300 MHz, C_6D_6) δ 4.37 (t, J = 5.7 Hz, 1H), 3.18 (s, 3H), 3.17 (s, 3H), 2.32–2.23 (m, 1H), 2.17–2.01 (m, 2H), 1.95–1.89 (m, 1H), 1.83–1.74 (m, 4H), 1.66–1.61 (m, 1H), 1.18–1.13 (m, 2H), 0.80 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.7, 114.6,

104.7, 52.1, 52.0, 44.9, 32.2, 31.7, 31.1, 29.6, 27.5, 26.2, 25.1, 0.93; IR (film) 2956, 1686, 1365, 1252, 1059, 844 cm^{-1}; HRMS (CI, isobutane) *m/z* 328.2432 (M, 328.2433 calcd for $C_{18}H_{36}O_3Si$).

A solution of purified[26] *m*-CPBA (1.0 equiv) and CH_2Cl_2 was added dropwise to a CH_2Cl_2 solution of enoxysilane **9** or **10** at –78 °C. The reaction was allowed to warm to 0 °C over 30 min and aqueous NaOH (0.2 M, 40 mL) was added. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4), concentrated, and the crude product was dissolved in *N*-(trimethylsilyl)imidazole (3–5 equiv) and heated at 60 °C overnight. The reaction was then cooled to 0 °C and MeOH (15 mL) was carefully added to quench excess silylating agent. The resulting mixture was partitioned between Et_2O (10 mL) and H_2O (10 mL) and the aqueous layer was extracted (3 x 15 mL) with Et_2O. The combined organic layers were washed with H_2O (3 x 15 mL), dried (Na_2SO_4) and concentrated, and the crude product was purified by column or radial chromatography.

2-(3,3-Dimethoxypropyl)-2-(trimethylsiloxy)cyclohexanone (11). Following the general procedure, a solution of enoxysilane **9** (2.7 g, 88% pure) and CH_2Cl_2 (30 mL) was treated with a solution of *m*-CPBA (1.70 g, 9.98 mmol) and CH_2Cl_2 (15 mL) and the resulting crude hydroxy ketone was silylated with *N*-(trimethylsilyl)imidazole (5.0 mL, 34 mmol) to give **11** (1.67 g, 64%) as a colorless oil after purification by radial chromatography (4 mm thickness, SiO_2, 15:1 hexanes–EtOAc, 1% Et_3N): ^1H NMR (300 MHz, C_6D_6) δ 4.23 (t, *J* = 5.4 Hz, 1H), 3.12 (s, 3 H), 3.11 (s, 3H), 2.22 (td, *J* = 3.0, 12.5 Hz, 1H), 2.07–1.97 (dt, *J* = 6.0, 12.5 Hz, 1H), 1.81–1.73 (m, 3H), 1.67–1.50 (m, 3H), 1.41–1.36 (m, 2H), 1.25–1.19 (m, 2H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.6, 104.6, 82.5, 52.7, 52.2, 41.4, 39.2, 32.7, 27.5, 26.6, 22.7, 2.9; IR (film) 2945, 1723, 1451, 1248, 1126, 1074, 841 cm^{-1}; HRMS (CI, isobutane) *m/z* 288.1763 (M, 288.1757 calcd for $C_{14}H_{28}O_4Si$). Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.30; H, 9.79. Found: C, 58.14; H, 9.79.

(2*R,4*S**)- and (2*R**,4*R**)-4-*tert*-Butyl-2-(3,3-dimethoxypropyl)-2-(trimethylsiloxy)cyclohexanone (12 and 13).** Following the general procedure, a solution of enoxysilane **10** (2.0 g, 85% pure) and CH_2Cl_2 (30 mL) was treated with a solution of *m*-CPBA (1.10 g, 6.39 mmol) and CH_2Cl_2 (15 mL), and the resulting crude hydroxy ketone was silylated with *N*-(trimethylsilyl)imidazole (5.4 mL, 37 mmol) to give a mixture of **12** and **13** (2:1, 1.76 g, 81%) after column chromatography (SiO_2, 5:1 hexanes–EtOAc, 1% Et_3N). Ketoacetals **12** and **13** were separated by preparative MPLC (10:1 hexanes–EtOAc). **12**, major, more polar diastereomer: ^1H NMR (300 MHz, C_6D_6) δ 4.28–4.24 (m, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 2.20–2.00 (m, 3H), 1.93–1.79 (m, 2H), 1.75–1.60 (m, 2H), 1.55–1.47 (m, 1H), 1.45 (app t, *J* = 12.9 Hz, 1H), 1.31 (tt, *J* = 2.7, 12.0 Hz, 1H), 1.07–0.93 (m, 1H), 0.73 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.1, 104.5, 82.5, 52.8, 52.3, 44.4, 42.8, 38.2, 33.3, 32.0, 28.1, 27.4, 26.4, 3.1; IR (film) 2955, 1725, 1447, 1367, 1247, 1124, 1078, 843 cm^{-1}; HRMS (CI, isobutane) *m/z* 344.2390 (M, 344.2383 calcd for $C_{18}H_{36}O_4Si$). **13**, minor, less polar diastereomer: ^1H NMR (300 MHz, C_6D_6) δ 4.38 (t, *J* = 5.1 Hz, 1H), 3.20 (s, 3H), 3.19 (s, 3H), 2.75 (dt *J* = 6.0, 7.5 Hz, 1H), 2.17 (ddd, *J* = 3, 3.9, 12.9 Hz, 1H), 2.03 (td, *J* = 3.3, 13.2 Hz, 1H), 2.00 (m, 1H), 1.95–1.84 (m, 3H), 1.80 (td, *J* = 3.3, 12.3 Hz, 1H), 1.72–1.64 (m, 1H), 1.68 (dd, *J* = 12.6, 13.2 Hz, 1H), 1.07 (ddd, *J* = 4.5, 8.4, 17.0 Hz, 1H), 0.73 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.2, 105.2, 80.0, 52.9, 52.2, 41.7, 40.8, 37.9, 32.8, 31.9, 28.5, 27.7, 27.6, 2.2; IR (film) 2956, 1721, 1367, 1252, 1120, 1063, 823 cm^{-1}; HRMS (CI, isobutane) *m/z* 344.2374 (M, 344.2383 calcd for $C_{18}H_{36}O_4Si$). Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.75; H, 10.54. Found: C, 62.64; H, 10.49.

General Procedure For Preparing Alkenyl Acetals 14-16. A solution of siloxy keto acetals **11-13** was added to a bright yellow solution of methylenetripenylphosphorane [prepared from sodium bis(trimethylsilyl)amide (2.0 equiv, 1.0 M in THF), methyltriphenylphosphonium bromide (2.0 equiv), and THF at rt]. After 30 min, the reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted (3 x 10 mL) with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by column or radial chromatography.

2-(3,3-Dimethoxypropyl)-2-(trimethylsiloxy)methylenecyclohexane (14). 94% as a colorless oil after purification by radial chromatography (4 mm thickness, SiO_2, 15:1 hexanes–EtOAc): ^1H NMR (300 MHz, C_6D_6) δ 5.13 (d, *J* = 1.8 Hz, 1H), 4.80 (s, 1H), 4.34 (t, *J* = 5.1 Hz, 1H), 3.16 (s, 6H), 2.21 (td, *J* = 4.4,

14.0 Hz, 1H), 1.97–1.79 (m, 3H), 1.71–1.60 (m, 3H), 1.56–1.48 (m, 3H), 1.39–1.17 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 152.1, 108.1, 105.0, 78.7, 52.2, 41.8, 33.9, 33.2, 28.2, 26.9, 24.1, 2.8; IR (film) 3089, 2938, 1646, 1450, 1261, 1126, 1076, 841 cm^{-1}; HRMS (EI, 70eV) *m/z* 286.1951 (M, 286.1964 calcd for $C_{15}H_{30}O_3Si$). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 63.02; H, 10.55.

(2*R,4*R**)-4-*tert*-Butyl-2-(3,3-dimethoxypropyl)-2-(trimethylsiloxy)methylenecyclohexane (15).** 84% as a colorless oil after purification by column chromatography (Al_2O_3, 10:1 hexanes–EtOAc): ^1H NMR (500 MHz, C_6D_6) δ 5.19–5.18 (m, 1H), 4.84–4.83 (m, 1H), 4.35 (t, *J* = 5.0 Hz, 1H), 3.16 (s, 3H), 3.15 (s, 3H), 2.23 (ddd, *J* = 2.5, 4.0, 14.0 Hz, 1H), 1.97 (dt, *J* = 3.0, 11.5 Hz, 4H), 1.89 (tt, *J* = 5.0, 11.7 Hz, 1H), 1.73–1.66 (m, 1H), 1.62–1.56 (m, 2H), 1.45 (dd, *J* = 12.0, 12.5 Hz, 1H), 0.93 (m, 1H), 0.76 (s, 9H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.9, 107.8, 105.0, 79.4, 52.3, 52.2, 45.6, 43.2, 33.8, 33.3, 32.2, 28.8, 27.6, 26.8, 2.9; IR (film) 3091, 2955, 1649, 1470, 1366, 1116, 1074, 903, 840 cm^{-1}; HRMS (CI, isobutane) *m/z* 342.2585 (M, 342.2590 calcd for $C_{19}H_{38}O_3Si$). Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.62; H, 11.19. Found: C, 66.54; H, 11.19.

(2*R,4*S**)-4-*tert*-Butyl-2-(3,3-dimethoxypropyl)-2-(trimethylsiloxy)methylenecyclohexane (16).** 86% as a colorless oil after purification by column chromatography (Al_2O_3, 10:1 hexanes–EtOAc): ^1H NMR (500 MHz, C_6D_6) δ 4.85 (m, 1H), 4.74 (m, 1H), 4.34 (t, *J* = 5.5 Hz, 1H), 3.17 (s, 3H), 3.16 (s, 3H), 2.50 (dt, *J* = 4.5, 13.5 Hz, 1H), 2.13 (td, *J* = 4.0, 12.5 Hz, 1H), 2.03–1.83 (m, 5H), 1.79–1.68 (m, 2H), 0.99 (dq, *J* = 4.0, 12.5 Hz, 1H), 0.91 (app t, *J* = 12.5 Hz, 1H), 0.81 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.9, 107.5, 105.5, 76.2, 52.9, 52.3, 42.8, 40.6, 35.0, 34.0, 32.1, 29.4, 27.8, 27.7, 2.4; IR (film) 3086, 2955, 2829, 1644, 1365, 1250, 1129, 1052, 840 cm^{-1}; HRMS (CI, isobutane) *m/z* 342.2576 (M, 342.2590 calcd for $C_{19}H_{38}O_3Si$). Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.62; H, 11.19. Found: C, 66.75; H, 11.16.

1-(3-buten-1-yl)-1,2-cyclohexanediol (18). A solution siloxy cyclohexanone **17** (7.43 g, 39.9 mmol)[27] and Et_2O (50 mL) was added at 0 °C to a solution of 3-butenylmagnesium bromide [prepared from 4-bromo-1-butene (6.47 g, 47.9 mmol), Mg (1.5 g, 60 mmol) and Et_2O (100 mL)]. After 2 h at rt, saturated aqueous NH_4Cl (30 mL) was added and the organic layer was separated and concentrated. The residue was dissolved in THF (100 mL), the resulting solution was cooled to 0 °C and TBAF (1.0 M in THF, 44 mL, 44 mmol) was added. After 15 min, Et_2O (20 mL) and H_2O (20 mL) were added, the layers were separated and the aqueous layer was extracted (3 x 10 mL) with Et_2O. The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was vacuum distilled to give **18** as a 5:1 mixture of diastereomers (5.05 g, 74%). The *cis*- and *trans*-diols were separated by preparative MPLC (2:1 hexanes–EtOAc) for characterization. Major diastereomer: bp 89–90 °C (0.3 mm); ^1H NMR (300 MHz, C_6D_6) δ 5.10–5.76 (m, 1H), 5.07 (dd, *J* = 8.5, 17.0 Hz, 1H), 4.98 (d, *J* = 9.9 Hz, 1H), 3.15 (dd, *J* = 4.2, 9.0 Hz, 1H), 2.14–2.03 (m, 2H), 1.78 (s, 1H), 1.71–1.39 (m, 8H), 1.22–1.16 (m, 1H), 1.04–0.95 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.6, 114.3, 73.5, 72.9, 38.2, 33.7, 30.7, 28.0, 23.4, 21.6; IR (film) 3405, 3076, 2937, 2864, 1640, 1456, 1069, 1032, 908 cm^{-1}; HRMS (CI, isobutane) *m/z* 170.1308 (M, 170.1307 calcd for $C_{10}H_{18}O_2$). Minor diastereomer: mp 48–49 °C; ^1H NMR (300 MHz, C_6D_6) δ 6.00–5.85 (m, 1H), 5.13 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.98 (dd, *J* = 0.9, 9.6 Hz, 1H), 3.48 (dd, *J* = 3.9, 9.3 Hz, 1H), 2.80 (s, 1H), 2.43 (s, 1H), 2.36–2.24 (m, 1H), 2.14–2.02 (m, 1H), 1.87–1.74 (m, 3H), 1.62–1.50 (m, 1H), 1.49–1.44 (m, 1H), 1.35–1.28 (m, 2H), 1.23–1.01 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.8, 114.4, 76.6, 74.7, 34.3, 31.6, 30.8, 27.2, 23.5, 22.6; IR (film) 3405, 3076, 2937, 2860, 1640, 1449, 1059, 909 cm^{-1}; HRMS (CI, isobutane) *m/z* 170.1311 (M, 170.1307 calcd for $C_{10}H_{18}O_2$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66. Found: C, 70.55; H, 10.58.

2-(3-Buten-1-yl)-2-(trimethylsiloxy)cyclohexanone (19). Oxidation of diol **18** was carried out according to the procedure of Swern[8] [**8** (5.0 g, 29mmol), oxalyl chloride (4.1 g, 32 mmol), DMSO (5.5 g, 71 mmol), Et_3N (15 g, 150 mmol) and CH_2Cl_2 (150 mL) at –55 °C]. After the addition of Et_3N, the reaction was allowed to warm to rt over 5 h and then was quenched with saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude hydroxy ketone was dissolved in *N*-(trimethylsilyl)imidazole (6.2 g, 44 mmol) and heated at 50 °C overnight. The resulting mixture was cooled to 0 °C and MeOH (20 mL) was carefully added

to quench excess silylating agent. The resulting mixture was partitioned between Et_2O (20 mL) and H_2O (20 mL) and the organic layer was washed with H_2O (3 x 20 mL). The aqueous washings were back-extracted (3 x 20 mL) with pentane and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (SiO_2, 10:1 hexanes–EtOAc) to give **19** (4.9 g, 69%) as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 5.77–5.69 (m, 1H), 5.00 (dd, J = 10.2, 0.6 Hz, 1H), 4.93 (d, J = 6.3 Hz, 1H), 2.26–2.14 (m, 2H), 1.96–1.88 (m, 2H), 1.74–1.67 (m, 2H), 1.63–1.53 (m, 2H), 1.42–1.34 (m, 2H), 1.28–1.13 (m, 2H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.3, 138.6, 114.7, 82.4, 41.2, 39.3, 37.1, 27.7, 27.5, 22.6, 2.8; IR (film) 3078, 2950, 2865, 1723, 1642, 1452, 1248, 1074, 842 cm^{-1}; HRMS (CI, isobutane) *m/z* 240.1544 (M, 240.1546 calcd for $C_{13}H_{24}O_2Si$). Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.85; H, 10.08.

2-[3,3-Bis(ethylthio)propyl]-2-(trimethylsiloxy)cyclohexanone (20). Following exactly a procedure we had developed earlier,[9] dithioacetal **20** was prepared from siloxy ketone **19** (1.50 g, 6.24 mmol), excess ozone, triphenylphosphine (2.46 g, 9.36 mmol), ethanethiol (0.85 g, 14 mmol), and $MgBr_2{\cdot}Et_2O$ (4.0 g, 16 mmol). The crude product was purified by column chromatography (SiO_2, 10:1 hexanes–EtOAc) to give **20** (1.88 g, 86%) as a slightly yellow oil: ^1H NMR (300 MHz, C_6D_6) δ 3.70 (t, J = 6.3 Hz, 1H), 2.63–2.38 (m, 4H), 2.29–2.22 (m, 1H), 2.14–2.00 (m, 3H), 1.97–1.74 (m, 3H), 1.60–1.51 (m, 1H), 1.43–1.16 (m, 4H), 1.09 (t, J = 7.2 Hz, 6H), 0.30 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 210.5, 82.6, 51.9, 41.5, 39.3, 35.6, 30.0, 27.5, 24.5, 22.7, 14.7, 2.9; IR (film) 2954, 2867, 1722, 1451, 1247, 1122, 1074, 842 cm^{-1}; HRMS (CI, isobutane) *m/z* 240.1544 (M, 240.1546 calcd for $C_{13}H_{24}O_2Si$). Anal. Calcd for $C_{16}H_{32}O_2S_2Si$: C, 55.15; H, 9.26; S, 18.37. Found: C, 55.33; H, 9.39; S, 18.17.

2-[3,3-Bis(ethylthio)propyl]-2-(trimethylsiloxy)methylenecyclohexane (21). Following the general Wittig procedure described earlier, keto acetal **20** (1.88 g, 5.39 mmol) was condensed with methylenetriphenylphosphorane and the resulting crude product was purified by column chromatography (Al_2O_3, 20:1 hexanes–EtOAc) to give **21** (1.78 g, 95%) as a slightly yellow oil: ^1H NMR (500 MHz, C_6D_6) δ 5.18 (dd J = 1.5, 3.0 Hz, 1H), 4.83–4.82 (m, 1H), 3.79 (t, J = 6.5 Hz, 1H), 2.65–2.57 (m, 2H), 2.52–2.45 (m, 2H), 2.25–2.19 (m, 2H), 2.15–2.08 (m, 1H), 2.01 (ddt, J = 1.5, 3.0, 12.5 Hz, 1H), 1.95–1.87 (m, 1H), 1.78–1.70 (m, 2H), 1.62 (dt, J = 4.5, 12.5 Hz, 1H), 1.51–1.48 (m, 2H), 1.42–1.34 (m, 1H), 1.24–1.16 (m, 1H), 1.11 (t, J = 8.0 Hz, 6H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.1, 108.3, 78.9, 52.3, 41.9, 35.9, 33.9, 30.4, 28.1, 24.4, 24.3, 24.2, 14.7, 14.6, 2.8; IR (film) 3091, 2932, 2858, 1646, 1449, 1250, 1119, 840, 753 cm^{-1}; HRMS (CI, isobutane) *m/z* 346.1812 (M, 346.1820 calcd for $C_{17}H_{34}OS_2Si$).

General Procedure for Prins–Pinacol Spiroannulations of Acetal Substrates. A solution of freshly purified TMSOTf (1–2 equiv, approx 0.5 M), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 2–4 equiv) and CH_2Cl_2 was added dropwise to a 0.1 M CH_2Cl_2 solution of the acetal precursor at rt. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the resulting mixture was extracted with Et_2O (3 x 20 mL), and the organic extract was dried (Na_2SO_4) and concentrated. The crude product was purified by radial or column chromatography.

2-Methoxyspiro[4.5]decan-6-one (22). Following the general procedure, a solution of **14** (466 mg, 1.63 mmol) and CH_2Cl_2 (15.0 mL) was treated with a solution of TMSOTf (723 mg, 3.25 mmol), DTBMP (668 mg, 3.25 mmol) and CH_2Cl_2 (5.0 mL). The crude product was purified by radial chromatography (2 mm thickness, SiO_2, 20:1 hexanes–EtOAc) to give **22** (244 mg, 82%), a 1.5:1 mixture of methoxy epimers, as a colorless oil. The methoxy epimers were separated by preparative MPLC (10:1 hexanes–EtOAc). Minor, more polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.51 (quintet, J = 5.5 Hz, 1H), 3.08 (s, 3H), 2.31 (dd, J = 5.0, 14.0 Hz, 1H), 2.24 (td, J = 8.0, 13.0 Hz, 1H), 2.29–2.09 (m, 2H), 1.75–1.68 (app sextet, 1H), 1.59–1.53 (app sextet, 1H), 1.42–1.33 (m, 3H), 1.31–1.25 (m, 2H), 2.24–1.19 (m, 2H), 1.09 (td, J = 7.5, 12.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.6, 81.9, 56.1, 55.3, 40.7, 40.5, 39.2, 32.3, 31.4, 27.7, 22.8; IR (film) 2930, 1706, 1448, 1101 cm^{-1}; HRMS (CI, isobutane) *m/z* 183.1399 (MH, 183.1385 calcd for $C_{11}H_{19}O_2$). Major, less polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.65–3.62 (m, 1H), 3.01 (s, 3H), 2.36 (dd, J = 6.0, 13.5 Hz, 1H), 2.14–2.11 (m, 2H), 1.93–1.88 (ddd, J = 4.5, 7.5, 12.0 Hz, 1H), 1.69–1.63 (m, 1H), 1.60–

1.50 (m, 3H), 1.48–1.31 (m, 4H), 1.30–1.24 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.5, 82.4, 56.0, 55.9, 40.9, 40.8, 38.9, 33.6, 31.2, 27.3, 22.8; IR (film) 2934, 1703, 1449, 1098 cm^{-1}; HRMS (CI, isobutane) *m/z* 183.1380 (MH, 183.1385 calcd for $C_{11}H_{19}O_2$).

(2*R/*S**,5*S*,*,8*R**)-8-*tert*-Butyl-2-methoxyspiro[4.5]decan-6-one (25).** Following the general procedure, a solution of **15** (60 mg, 0.18 mmol) and CH_2Cl_2 (1.8 mL) was treated with a solution of TMSOTf (78 mg, 0.35 mmol), DTBMP (144 mg, 0.70 mmol) and CH_2Cl_2 (0.7 mL). The crude product was purified by column chromatography (SiO_2, 5:1 hexanes–EtOAc) to give **25** (29 mg, 70%), a 1.4:1 mixture of methoxy epimers, as a colorless oil. The stereoisomers were separated by preparative MPLC (5:1 hexanes–EtOAc). Major, less polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.52 (quintet, *J* = 4.5 Hz, 1H), 3.01 (s, 3H), 2.65 (quintet, *J* = 6.5 Hz, 1H), 2.35 (td, *J* = 2.5, 13.5 Hz, 1H), 1.98 (app t, *J* = 13.0 Hz, 1H), 1.85 (td, *J* = 3.5, 13.5 Hz, 1H), 1.78–1.74 (m, 2H), 1.71 (dd, *J* = 3.5, 13.5 Hz, 1H), 1.57 (dd, *J* = 6.0, 14.0 Hz, 1H), 1.43–1.39 (m, 1H), 1.34–1.27 (m, 2H), 1.29–1.12 (m, 2H), 0.67 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.1, 82.8, 56.1, 54.7, 49.3, 42.1, 40.8, 39.6, 32.4, 31.9, 31.2, 27.1, 24.1; IR (film) 2964, 1703, 1478, 1366, 1238, 1100 cm^{-1}; HRMS (CI, isobutane) *m/z* 238.1929 (M, 238.1933 calcd for $C_{15}H_{26}O_2$). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 11.00. Found: C, 75.30; H, 11.03. Minor, more polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.52 (quintet, *J* = 5.5 Hz, 1H), 3.01 (s, 3H), 2.87–2.82 (m, 1H), 2.35–2.32 (m, 1H), 2.05 (app t, *J* = 13.5 Hz, 1H), 1.84–1.81 (m, 1H), 1.75–1.64 (m, 3H), 1.45–1.37 (m, 2H), 1.25–1.09 (m, 3H), 0.91 (dt, *J* = 8.0, 13.0 Hz, 1H), 0.67 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.3, 82.1, 56.2, 54.4, 49.9, 42.4, 40.7, 39.8, 32.4, 31.5, 31.0, 27.1, 24.0; IR (film) 2956, 1706, 1468, 1366, 1238, 1107, 993 cm^{-1}; HRMS (CI, isobutane) *m/z* 238.1926 (M, 238.1933 calcd for $C_{15}H_{26}O_2$). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 11.00. Found: C, 75.32; H, 11.10.

(2*R/*S**,5*R**,8*R**)-8-*tert*-Butyl-2-methoxyspiro[4.5]decan-6-one (27).** Following the general procedure, a solution of **16** (200 mg, 0.58 mmol) and CH_2Cl_2 (5.8 mL) was treated with a solution of TMSOTf (259 mg, 1.17 mmol), DTBMP (480 mg, 2.34 mmol) and CH_2Cl_2 (2.0 mL). The crude product was purified by column chromatography (SiO_2, 5:1 hexanes–EtOAc) to give **27** (39 mg, 28%), a 1.5:1 mixture of methoxy epimers, as a colorless oil. The stereoisomers were separated by preparative MPLC (5:1 hexanes–EtOAc). Major less polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.60 (quintet, *J* = 5.0 Hz, 1H), 3.20 (s, 3H), 3.06 (dd, *J* = 5.0, 14.0 Hz, 1H), 2.36 (dt, *J* = 3.0, 13.0 Hz, 1H), 1.96 (app t, *J* = 13.0 Hz, 1H), 1.72–1.65 (m, 1H), 1.63–1.58 (m, 1H), 1.56–1.50 (m, 1H), 1.47–1.44 (m, 1H), 1.40–1.31 (m, 2H), 1.20–1.07 (m, 4H), 0.67 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.8, 81.8, 56.0, 54.6, 49.5, 40.7, 39.2, 38.4, 33.0, 32.4, 31.9, 27.0, 23.7; IR (film) 2959, 1707, 1366, 1236, 1104 cm^{-1}; HRMS (CI, isobutane) *m/z* 238.1925 (M, 238.1933 calcd for $C_{15}H_{26}O_2$). Minor, more polar diastereomer: ^1H NMR (500 MHz, C_6D_6) δ 3.80 (quintet, *J* = 3.5 Hz, 1H), 3.08 (s, 3H), 2.97 (dd, *J* = 6.5, 13.5 Hz, 1H), 2.34 (dt, *J* = 3.5, 13.0 Hz, 1H), 2.01 (app t, *J* = 13.5 Hz, 1H), 1.81–1.77 (m, 1H), 1.70–1.65 (m, 1H), 1.62–1.59 (m, 1H), 1.53–1.43 (m, 2H), 1.39–1.31 (m, 2H), 1.28–1.24 (m, 1H), 1.14–1.11 (m, 2H), 0.67 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.0, 82.1, 56.1, 55.3, 49.3, 40.3, 40.0, 39.8, 34.6, 32.3, 31.3, 27.0, 23.8; IR (film) 2960, 1703, 1444, 1366, 1240, 1100 cm^{-1}; HRMS (CI, isobutane) *m/z* 238.1926 (M, 238.1933 calcd for $C_{15}H_{26}O_2$).

(2*R,5*R**)-2-(Ethylthio)spiro[4.5]decan-6-one (29).** A solution of **21** (210 mg, 0.61 mmol) and CH_2Cl_2 (3 mL) was added at 0 °C with stirring to a suspension of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) (237 mg, 1.21 mmol)[15b] and CH_2Cl_2 (10 mL). The reaction was allowed to warm to rt over 1 h and saturated aqueous $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous layer was extracted (3 x 10 mL) with Et_2O. The combined organic layers were dried (Na_2SO_4), concentrated, and the crude product was purified by column chromatography (SiO_2, 10:1 hexanes–EtOAc) to give **29** (81 mg, 63%) as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 2.89–2.83 (m, 1H), 2.34 (q, *J* = 7.5 Hz, 2H), 2.23 (ddd, *J* = 3.5, 8.5, 12.8 Hz, 1H), 2.14–2.03 (m, 3H), 1.83–1.77 (m, 1H), 1.69 (dd, *J* = 7.5, 13.5 Hz, 1H), 1.59–1.51 (m, 1H), 1.43–1.32 (m, 2H), 1.29–1.19 (m, 4H), 1.10 (t, *J* = 7.5 Hz, 3H), 1.07–1.00 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.5, 56.1, 43.0, 42.2, 40.1, 39.3, 34.7, 33.8, 27.2, 25.4, 22.6, 15.3; IR (film) 2930, 2863,

1707, 1448, 1260, 1127, 948 cm^{-1}; HRMS (CI, isobutane) *m/z* 212.1240 (M, 212.1235 calcd for $C_{12}H_{20}OS$). Anal. Calcd for $C_{12}H_{20}OS$: C, 67.88; H, 9.50; S, 15.07. Found: C, 67.99; H, 9.44; S, 15.14.

(2*R,5*R**)-2-(Ethylthio)spiro[4.5]decan-6-one thiosemicarbazone (30).** Spirocycle **29** (10 mg, 0.05 mmol) and thiosemicarbazide (17 mg, 0.19 mmol) were dissolved in glacial HOAc (0.5 mL) and after 18 h at rt, HOAc was removed azeotropically with toluene (3 x 10 mL). The residue was purified by column chromatography (2:1 hexanes–EtOAc) to afford **30** (11 mg, 80%) as a colorless solid. Single-crystals were obtained by recrystallization from acetonitrile: mp 162–163 °C; ^1H NMR (500 MHz, CD_3CN) δ 8.57 (br s, 1H), 7.28 (br s, 1H), 6.43 (br s, 1H), 3.00–2.94 (m, 1H), 2.28 (dd J = 6, 15.5 Hz, 1H), 2.21–2.17 (m, 1H), 2.02–1.98 (m, 2H), 1.85–1.77 (m, 2H), 1.68–1.63 (m, 3H), 1.40–1.19 (m, 7H), 0.96–0.93 (m, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 180.8, 160.9, 52.0, 44.0, 42.4, 40.5, 36.4, 33.6, 26.7, 26.3, 25.0, 23.2, 15.3; IR (film) 3334, 3212, 3151, 2953, 2927, 2853, 1602, 1500, 1447, 1073, 816 cm^{-1}; HRMS (FAB) *m/z* 286.1411 (MH, 286.1412 calcd for $C_{13}H_{24}N_3S_2$).

General Procedure for Oxidation of Spirocyclic Ethers 22, 25, and 27. Following a procedure by Sharpless,[12] methoxy ketone **22**, **25**, or **27**, $NaIO_4$ (5.0 equiv), and $RuCl_3{\cdot}3H_2O$ (0.03 equiv) were dissolved in CCl_4–CH_3CN–pH 7 buffer (5:5:8 by vol). The reaction was followed by TLC analysis until the starting ether could no longer be detected (reaction time 24–42 h). The reaction was then filtered through Celite and the filtrate was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography.

Spiro[4.5]decane-2,6-dione (24). A colorless oil after purification by column chromatography (SiO_2, 5:1 hexanes–EtOAc), 88% from the major epimer of **22** and 72% from the minor epimer: ^1H NMR (500 MHz, C_6D_6) δ 2.58 (d, *J* = 17.7 Hz, 1H), 2.02–1.94 (m, 2H), 1.90–1.77 (m, 3H), 1.57 (d, *J* = 18.3 Hz, 1H), 1.39–1.28 (m, 1H), 1.26–1.05 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.1, 210.7, 53.3, 47.1, 38.3, 38.2, 36.2, 31.2, 26.9, 21.7; IR (film) 2934, 2864, 1744, 1703, 1449, 1404, 1165, 1128, 908 cm^{-1}; HRMS (CI, NH_3) *m/z* 167.1078 (MH, 167.1072 calcd for $C_{10}H_{15}O_2$).

(5*R*,*8*S)-8-*tert*-Butylspiro[4.5]decane-2,6-dione (26).** A colorless solid after purification by column chromatography (SiO_2, 5:1 hexanes–EtOAc), 68% from the major epimer of **25** and 71% from the minor epimer. Single-crystals were obtained by recrystallization from hexanes: mp 89–91 °C; ^1H NMR (500 MHz, C_6D_6) δ 2.50–2.44 (m, 1H), 2.28 (quintet, *J* = 8.5 Hz, 1H), 2.20 (ddd, *J* = 2.5, 3.5, 13.5 Hz, 1H), 1.94 (d, *J* = 17.5 Hz, 1H), 1.93–1.89 (m, 1H), 1.79 (d, *J* = 18.0 Hz, 1H), 1.69 (app t, *J* = 13.5 Hz, 1H), 1.28–1.23 (m, 2H), 1.10–0.99 (m, 3H), 0.86–0.77 (m, 1H), 0.61 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.0, 211.3, 52.5, 49.3, 47.4, 40.4, 38.1, 37.0, 32.3, 30.4, 26.9, 23.5; IR (CCl_4) 2964, 1746, 1709, 1550, 1479, 1251, 1037 cm^{-1}; HRMS (CI, isobutane) *m/z* 223.1701 (MH, 223.1698 calcd for $C_{14}H_{22}O_2$). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98. Found: C, 75.58; H, 9.98.

(5*R*,*8*R)-8-*tert*-Butylspiro[4.5]decane-2,6-dione (28).** A colorless solid after purification by column chromatography (SiO_2, 5:1 hexanes–EtOAc), 79% from the major epimer of **27** and 68% from the minor epimer: mp 89–90 °C; ^1H NMR (500 MHz, C_6D_6) δ 3.00 (d, *J* = 18 Hz, 1H), 2.25 (dt *J* = 4.0, 13.5 Hz, 1H), 1.87–1.81 (m, 3H), 1.49 (app t, *J* = 18.0 Hz, 1H), 1.44–1.38 (m, 1H), 1.28 (dt, *J* = 3.0, 13.0 Hz, 1H), 1.30–1.16 (m, 2H), 1.07–0.88 (m, 3H), 0.64 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.1, 211.0, 52.4, 48.8, 46.6, 39.7, 36.7, 35.9, 32.3, 31.5, 26.9, 22.5; IR (CCl_4) 2964, 2869, 1749, 1706, 1367, 1239, 1161, 1131 cm^{-1}; HRMS (CI, isobutane) *m/z* 223.1693 (MH, 223.1698 calcd for $C_{14}H_{22}O_2$).

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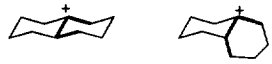
(17) Molecular mechanics calculations (MM2* force field) find the decalin conformation related to **34** and **37** to be within 1.4 kcal/mol of the minimum energy conformation.[18]



E_{rel}MM2* (kcal/mol)	0	1.4
dihedral angle	43°	61°

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