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Divergent Diastereoselectivity in the Addition of Nucleophiles to Tetrahydrofuran–derived Oxonium Ions

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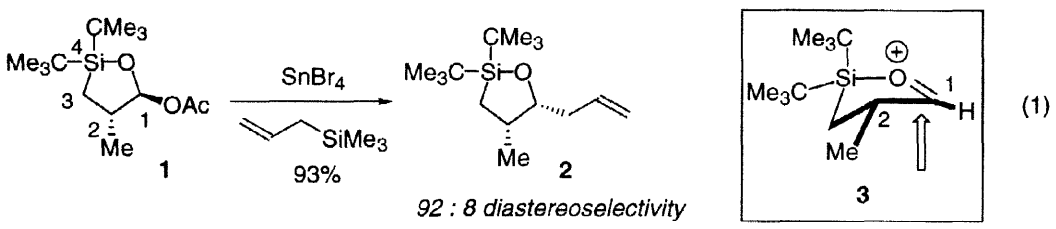
Abstract: Alkyl substituted lactol acetates have been found to undergo highly stereoselective substitution reactions mediated by tin (IV) bromide. The highest selectivity is observed in the case of 4,4–di-isopropyl, 2–methyl substitution in which the selectivity depends on the nucleophile. Allyltrimethylsilane adds with high (95:5) 1,2–*syn* selectivity while 2–methyl–trimethylsiloxy propene adds with high (>98:2) *anti* selectivity. These results can be rationalized through conformational analysis of the oxonium ion intermediate.

Keywords: carbenium ions, furans

The stereoselective synthesis of tetrahydrofurans through nucleophilic addition to five–membered ring oxonium ions[1] represents an important route to a variety of biologically important molecules. While *C*–nucleoside analogs,[2,3] aryl *C*–glycoside antibiotics,[4] acetogenins[5-7] and other tetrahydrofuran structures[7-9] have been constructed by employing oxonium–ion precursors, few studies examining the origin of the diastereoselectivities of these reactions have been published. We have investigated in detail the diastereoselectivity of nucleophilic addition to five–membered ring oxonium ions derived from oxasilacyclopentane acetals.[10,11] Based on insight gained in those studies, we elected to explore the analogous tetrahydrofuran oxonium ions to test our stereochemical model. This report describes our findings concerning substituted oxonium ions that show how conformational effects lead to surprising facial selectivities that are in complete agreement with our previous investigations.

We have previously shown that the oxonium ion derived from the methyl–substituted oxasilacyclopentane acetal in equation 1 shows what appears to be "contrasteric" facial selectivity. This result was explained by examining the conformation of the oxonium ion. In the pseudo–chair conformation, the methyl group is held equatorial and the nucleophile is forced by the axial *tert*–butyl group to approach from the bottom face. This mode of diastereocontrol was unexpected, as the substrate is reminiscent of a Cram–chelate structure and should therefore show 1,2–anti selectivity, not syn selectivity.[12]



(1)

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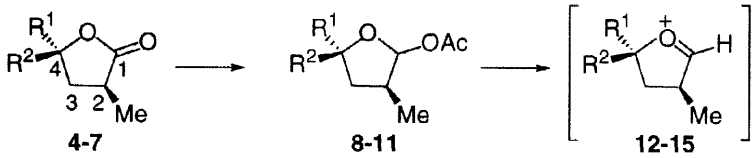
In order to explore this unusual diastereoselectivity more fully, we investigated five-membered ring oxonium ions derived from tetrahydrofuran acetals. The oxasilacyclopentane acetals were limited in their structural variability, because the 4-position possessed *tert*-butyl groups as an artifact of their synthesis from silacyclopropanes. Tetrahydrofuran oxonium ions, on the other hand, suffer from no such structural limitations. The ability to synthesize a variety of oxonium-ion precursors allowed for a thorough examination of the roles of substituents at the 4-position.

Results and Discussion

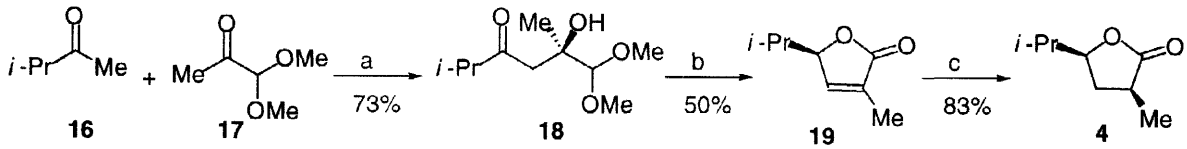
Substrate Synthesis

We have found that the one-pot reduction/acylation of lactones developed by Rychnovsky provides a general synthesis of the lactol acetates used in this study (eq 2).[13] Yields for this reaction process typically exceed 80% and the alkyl-substituted substrates reported here could be purified by bulb-to-bulb distillation. There are few general routes to the requisite lactones, so they were synthesized by several methods.



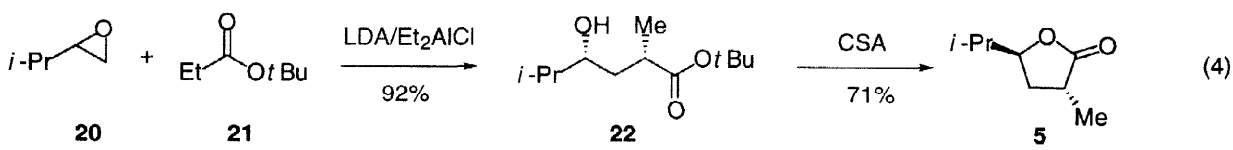
4, 8, 12, R^1 = H, R^2 = *i*-Pr
5, 9, 13, R^1 = *i*-Pr, R^2 = H
6, 10, 14, R^1 = R^2 = *i*-Pr
7, 11, 15, R^1 = R^2 = Me (2)

To draw analogy from our lead result in the oxasilacyclopentane series, we prepared *cis*- and *trans*-2,4-disubstituted substrates **8** and **9** to evaluate the relative importance of each substituent in the 4-position. The *cis*-4-isopropyl-2-methyl δ-lactone **4** could be readily prepared by stereoselective hydrogenation[14] of the butenolide **19**, which was prepared by the method of Tanabe (eq 3).[15,16]



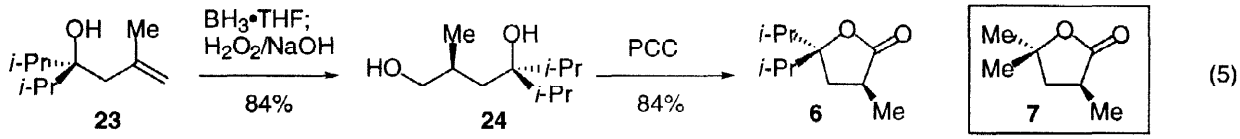
(a) LDA, (b) Cl_3CCO_2H (cat.)/toluene reflux, (c) H_2, Pd/C, >98 : 2 diastereoselectivity

Lactone *trans*-**5** was prepared by the reaction of the lithium enolate of *tert*-butyl propionate with 3-methyl-1,2-epoxy butane (eq 4).[17] Although the diastereoselectivity of this reaction is modest (86:14), isomerically pure material could be obtained by careful chromatographic separation. The pure hydroxy ester **22** was then cyclized to produce lactone **5** with 96:4 isomeric purity.[16]



As a point of direct comparison, we synthesized two "carbon analogs" of oxasilacyclopentane acetate **1** (eq 1), substituting a di-isopropyl methylene for the di-*tert*-butylsilylene unit (eq 5). After exploring several routes to the exceptionally hindered lactone **6**, we found that the most efficient synthesis was based on the allylation of 2,4-dimethyl pentanone with methallyl magnesium chloride to yield tertiary alcohol **23**.[18] After

hydroboration and oxidation to provide diol **25**, the desired lactone was prepared by oxidation with PCC. In addition, **7**, the 4,4–dimethyl analog of **6**, was prepared by known methods.[19]

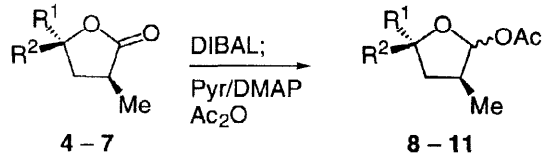


(5)

Finally, the lactones **4–7** were converted to the corresponding lactol acetates by reduction with DIBAL and trapping of the intermediate aluminum lactolate with acetic anhydride. We found that a procedure slightly modified from that reported in the literature[13] was optimal for substrates **4–7**.

Table 1: Yield of Reduction/Acylation

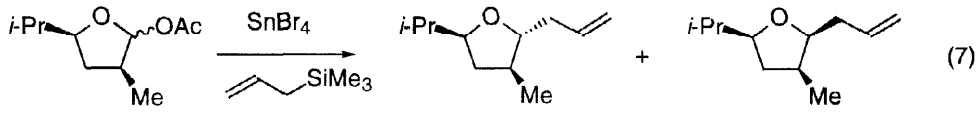
Lactone	R^1	R^2	Acetate	Yield
4	H	*i*-Pr	**8**	82%
5	*i*-Pr	H	**9**	88%
6	*i*-Pr	*i*-Pr	**10**	85%
7	Me	Me	**11**	87%



(6)

Stereoselectivity of Acetal Displacement

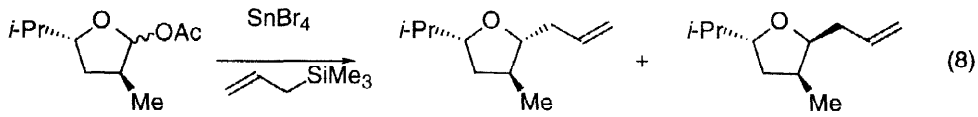
Lactol acetates **8** and **9** were allylated under conditions developed during our investigation of the oxasilacyclopentane acetates (eqs 7 and 8).[10,11] In each case the diastereoselectivity shows a modest preference for formation of the 1,2–*trans* tetrahydrofurans **25** and **27**. The relative configurations of tetrahydrofurans **25–28** were assigned through nOe spectroscopy.



8 **25** **26**

64 : 36 diastereoselectivity

(7)



9 **27** **28**

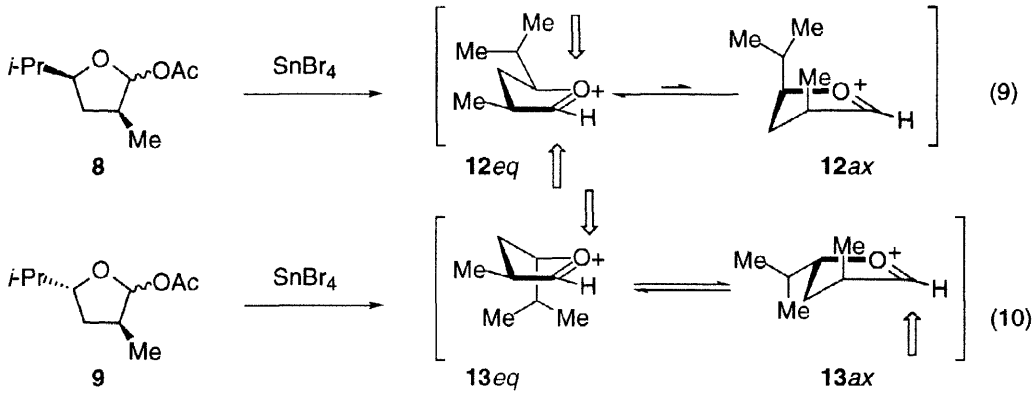
69 : 31 diastereoselectivity

(8)

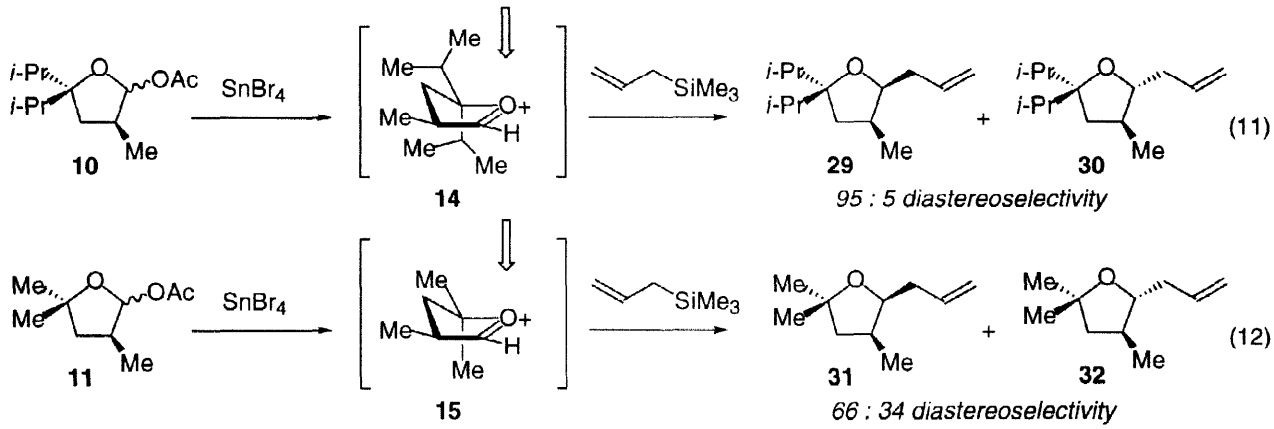
These results are surprising when compared to those obtained by Reissig in his thorough study of monomethyl–substituted tetrahydrofuran oxonium ions.[20] In that investigation, Reissig showed that allylation of the 2– and 4–methyl tetrahydrofuran oxonium ions showed modest selectivity, giving the 1,2–trans and 1,4–trans products in 68:32 and 60:40 diastereoselection, respectively. Based on these selectivities, one might have expected **8** to show high selectivity, due to the synergistic effect of the isopropyl and methyl substituents shielding the same face of the oxonium ion intermediate. In a similar manner, **9** should have shown reduced selectivity due to competing direction between the 2,4–trans substituents.

An interplay between the two substituents in **8** and **9** must account for the observed selectivity. We believe that **12** and **13**, the oxonium ion intermediates formed from **8** and **9**, sit in pseudo–chair conformations (eqs 9

and 10). It is likely that **12** resides predominantly in conformer **12*eq***, in which both substituents are in pseudo–equatorial positions to avoid a deleterious 1,3–diaxial interaction. In this conformer, the absence of an axial group to direct nucleophilic approach leads to low diastereoselection. On the other hand, **13** resides in two competing conformers, each of which possesses one axial and one equatorial substituent. Since **13*eq*** and **13*ax*** would be expected to be relatively close in energy, low diastereoselection reflects poor discrimination between the two conformers.

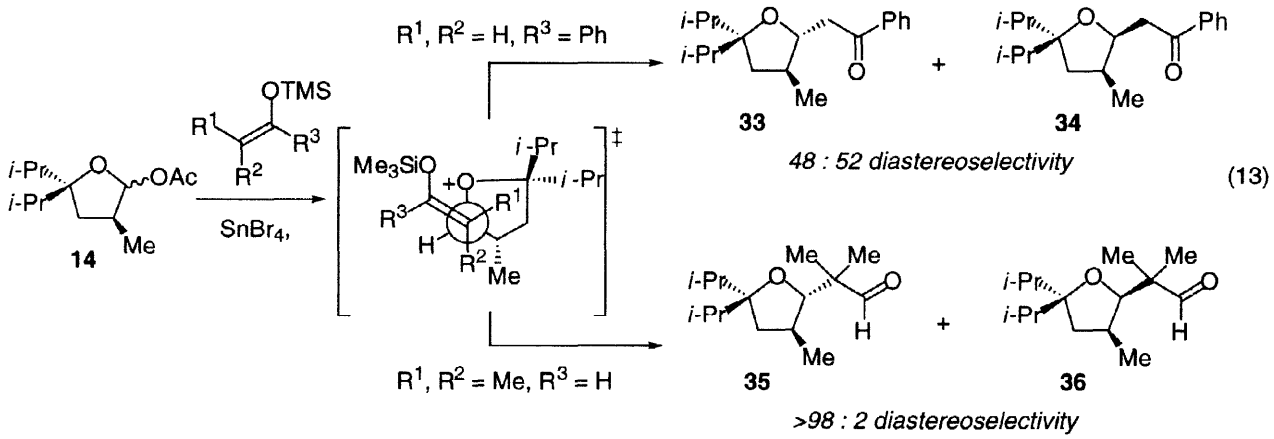


When the trisubstituted lactol acetate **10** was allylated in the presence of $SnBr_4$, high (95:5) 1,2–syn selectivity was observed (eq 11). This result is consistent with our previous findings (eq 1) that demonstrated the profound directing effect that axial substituents have on the approach of unsubstituted nucleophiles such as allyltrimethylsilane.[10,11] Oxonium ion **14** probably resides in a conformation much like **12*eq***, which avoids a strong 1,3–diaxial interaction. Thus, the axial isopropyl group directs nucleophilic approach syn to the equatorial methyl group. An analogous situation arises with **15**, but the methyl groups at the 4–position confer far less facial bias to the oxonium ion intermediate than do the isopropyl groups in **14** (eq 12).

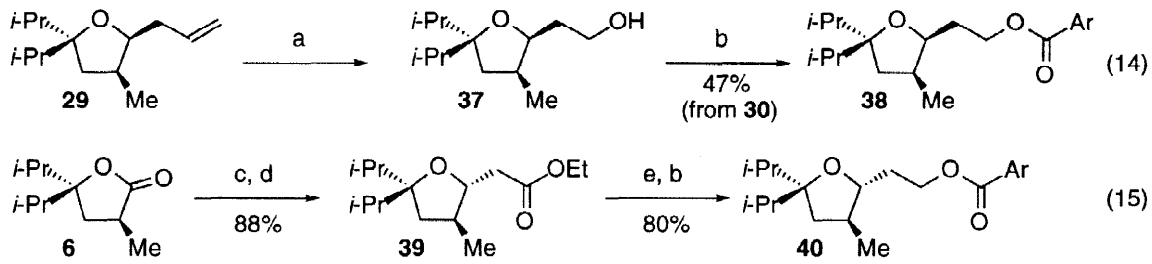


In our previous study, we found that the diastereoselectivity of nucleophilic addition to oxonium ions similar to those derived from **1** diverged when the size of the nucleophile was increased.[10,11] In order to evaluate whether or not the same trend could be observed for acetate **9**, we employed more hindered nucleophiles in the substitution reaction (eq 13). In this case, 1–phenyl–1–(trimethylsiloxy)ethylene produced the ketone products **33** and **34** with almost no diastereoselection. Use of 2–methyl–1–(trimethylsiloxy)–1–

propene, on the other hand, produced the 1,2–*trans* aldehyde **35** with >98:2 selectivity. In both cases, it is apparent that an increase in steric bulk near the reacting center of the nucleophile brings about an overriding interaction with the methyl group at the 2–position of the oxonium ion. These results are also consistent with Reissig's report,[20] in which a large increase in 1,2–anti selectivity was observed when a terminally disubstituted nucleophile was used.



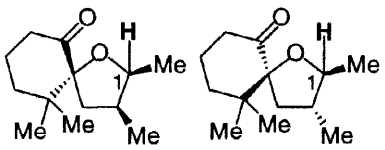
The configurations of addition products **29** and **35** were proven through nOe spectroscopy. For **29**, only limited nOe data was available due to overlapping signals in the ^{1}H NMR spectrum. For this reason, **29** was converted to the 3,5–dinitrobenzoate **38** by ozonolysis, reduction,[21] and acylation (eq 14). In order to assign unambiguously the relative configuration of **38**, the minor diastereomer was synthesized through an independent route. Reduction of **6** followed by olefination gave ester **39** in high yield (eq 15).[22,23] The expected anti selectivity was confirmed by nOe spectroscopy. Reduction and acylation provided **40**, a diastereomer of **38** which was used for further nOe experiments.[24] Aldehyde **35** was used directly for nOe spectroscopy.



(a) O_3/BH_3-DMS, (b) 3,5-$(NO_2)_2C_6H_3COCl/Et_3N$, (c) DIBAL, (d) $(EtO)_2POCH_2CO_2Et/NaH$, (e) $LiAlH_4$

The configurations of **31** and **32** were assigned by chemical shift correlation. Compounds **29**, **30**, **33**, **34**, **36**, and **38–40** conformed to an interesting trend with respect to the chemical shift of H(1) in the ^{1}H NMR spectrum. The chemical shift of the cis diastereomer was uniformly 0.6 to 0.8 ppm further upfield relative to the trans isomer. This chemical shift difference can also be seen in the chemical shifts of H(1) in the heavily substituted tetrahydrofurans **41** and **42** reported by Paquette.[25] Empirical trends, including chemical shift correlation, are often used to assign the relative stereochemistries of tetrahydrofurans and other substituted

five–membered rings.[26-29] While the stereochemistries of **31** and **32** have not been unambiguously proven, chemical shift correlation suggests that the major product is cis (eq 12).



41 **42**

Table 2: ^{1}H NMR Chemical shifts for 1, 3, 4, 4- tetrasubstituted tetrahydrofurans

Compound:	**29/30**	**33/34**[a]	**35/36**	**38/40**	**39**	**31/32**	**41**	**42**
δ (syn)	4.11	4.76	[b]	4.22	[b]	3.97	3.93	[b]
δ (anti)	3.45	3.98	3.49	3.51	3.81	3.52	[b]	3.14

[a] Product epimerized during flash chromatography; thermodynamic product assumed to be 1,2-trans. [b] Chemical shift of minor stereoisomer not available.

In conclusion, we have demonstrated that the same principles that explain the diastereoselectivity of nucleophilic addition to oxasilacyclopentane acetals can be employed to predict and rationalize the diastereoselectivity of reaction involving tetrahydrofuran oxonium ions. A heavily substituted "all carbon" analog of oxasilacyclopentane acetal **1** shows similarly high and divergent diastereoselectivity. As an outcome of our conformational model, removal of one of the large groups at the 4–position greatly reduces the facial bias of the oxonium ion, as does replacing both large groups with smaller ones.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 500 and 125 MHz, respectively, using a Bruker spectrometer. Coupling constants are reported in Hertz. High resolution mass spectra were acquired on a VG Analytical 7070E or Fisons Autospec spectrometer, and were obtained by peak matching. Microanalyses were performed by Atlantic Microlab, Atlanta, GA or Microlytics, South Deerfield, MA. Melting points are reported uncorrected. Analytical gas-liquid chromatography (GLC) was performed on a Hewlett Packard 5890 Level 4 chromatograph, equipped with split-mode capillary injection system and a flame ionization detector. Fused silica capillary columns (30 x 0.32 mm) wall coated with DB-1 (J & W Scientific) were used with helium gas as the carrier gas. All reagents were used without purification unless noted. Tin (IV) bromide solution (1.0 M in dichloromethane) was prepared by dilution of tin (IV) bromide purchased from Aldrich. THF, CH_2Cl_2, and toluene were dried by the method of Grubbs.[30]

5–Hydroxy–6,6–dimethoxy–2,5–dimethyl–hexan–3–one (18). Diisopropylamine (3.41 mL, 24.3 mmol, freshly distilled from CaH_2) was added to 100 mL of dry THF before cooling to 0 °C and treating with *n*-BuLi (9.3 mL, 22 mmol, 2.4 M hexanes). After 10 min, the solution of LDA was cooled to –78 °C and 3–methyl–2–butanone (2.0 mL, 19 mmol, freshly distilled from CaH_2) was added and the solution was stirred for 20 min. Pyruvic aldehyde dimethyl acetal (2.3 mL, 19 mmol, freshly distilled from CaH_2) was added and the reaction mixture was stirred for 20 minutes at –78 °C, then warmed to 0 °C in an ice bath and stirred for 0.5 h. The reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl, then the majority of the THF was removed *in vacuo*. The resultant material was partitioned between 30 mL each of saturated aqueous NH_4Cl and CH_2Cl_2. The aqueous layer was extracted with 3×15 mL of CH_2Cl_2. The combined organic layers were filtered through a funnel containing a cotton plug and a layer of Na_2SO_4 before reducing *in vacuo*. Flash chromatography (10:90 to 30:70 EtOAc:hexanes) yielded the product as a clear oil (2.783 g, 73%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.25 (s, 1H), 4.08 (s, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 2.85 (d, J = 16.2, 1H), 2.65 (m, 1H), 2.44 (d, J = 16.2, 1H), 1.20 (s, 3H), 1.09 (d, J = 7.0, 3H), 1.08 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.1, 110.3, 75.2, 58.0, 57.9, 44.2, 42.3, 23.4, 17.9, 17.6; IR (thin film) 3482, 2971, 1696, 1104, 1082 cm^{-1}; HRMS (CI/isobutane) m/z calcd for $C_{10}H_{19}O_3$ $(M - OH)^+$ 187.1334, found 187.1340.

5–Isopropyl–3–methyl–2(*5H*)–furanone (19). A solution of **18** (1.03 g, 5.04 mmol) in 50 mL of toluene

was treated with trichloroacetic acid (0.082 g, 0.50 mmol), then the flask was fitted with a Dean/Stark trap and condenser before heating to reflux for 12 h. The reaction was cooled to 25 °C, then quenched by the addition of triethylamine (1 mL). After reducing *in vacuo*, the resultant oil was purified by flash chromatography (0:100 to 3:97 EtOAc:hexanes) to yield the product as a clear oil (0.355 g, 50%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (m, 1H), 4.68 (m, 1H), 1.95 (septet, J = 6.8, 1H), 1.93 (s, 3H), 0.99 (d, J = 6.8, 3H), 0.98 (d, J = 6.8, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 147.2, 130.5, 85.7, 31.7, 17.8, 17.6, 10.6; IR (thin film) 2977, 1752, 1093, 874 cm^{-1}; HRMS (CI/isobutane) m/z calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0839.

2,5–Dimethyl–4–isopropyl–hexane–1,4,–diol (24). 2,5–Dimethyl–4–isopropyl–hexene–4–ol (2.00 g, 11.7 mmol) was dissolved in THF (50 mL) and cooled to 0 °C before treating with BH_3•THF (16.4 mL, 16 mmol, 1.0 M THF). After 2.5 h, the reaction mixture was warmed to 25 °C. Aqueous NaOH (6 mL, 3 M) and 30 % aqueous H_2O_2 (7 mL) were added and the reaction mixture was heated to 50 °C for 1.5 h. The reaction was quenched by the addition of H_2O (50 mL), then extracted with 3×50 mL of CH_2Cl_2. The combined organic layers were filtered through a funnel containing a cotton plug and a layer of Na_2SO_4 before reducing *in vacuo*. Flash chromatography (40:60 EtOAc:hexanes) yielded the product as a white solid (1.84 g, 84%): mp 61 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.04 (s ,br, 1H), 3.57 (dd, J = 3.8, 10.2, 1H), 3.27 (t, J = 9.6, 1H), 3.1 (s, br, 1H), 2.04 (m, 1H), 1.95 (septet, J = 7.0, 1H), 1.86 (septet, J = 6.9, 1H), 1.54 (dd, J = 8.2, 15.1, 1H), 1.45 (dd, J = 2.4, 15.1, 1H), 0.96 (d, J = 6.9, 3H), 0.95 (d, J = 7.0, 3H), 0.93 (d, J = 6.8, 3H), 0.91 (d, J = 7.0, 3H), 0.89 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 70.0, 60.4, 39.1, 35.1, 31.1, 19.5, 17.9 (17.931), 17.9 (17.911), 17.4, 17.3; IR (KBr pellet) 3200 (br, s), 1041 cm^{-1}; HRMS (CI/isobutane) m/z calcd for $C_{11}H_{23}O$ (M – OH)$^+$ 171.1749, found 171.1743. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.00; H, 12.74.

4,4–Diisopropyl–2–methyl–butyrolactone (6). A solution of **24** (0.980 g, 5.20 mmol) in CH_2Cl_2 (80 mL) was treated with pyridinium chlorochromate (4.33 g, 20.10 mmol) and the mixture was stirred for 12 h. The reaction mixture was then treated with approx. 50 mL of dry silica gel and the dark brown precipitate was triturated until it had been adsorbed onto the silica gel. The solvent was removed *in vacuo* and the resultant yellow powder was dried on a high vacuum line (approximately 0.1 Torr) for 1 h. The yellow powder was then applied to a short pad of silica that had been packed with 20:80 EtOAc:hexanes, then the product was eluted with 20:80 EtOAc:hexanes. Reduction of the early fractions *in vacuo* yielded the product as a clear oil (0.808 g, 84%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.71 (m, 1H), 2.13 (m, 2H), 2.04 (septet, J = 6.8, 1H), 1.69 (dd, J = 9.0, 13.7, 1H), 1.27 (d, J = 7.3, 3H), 0.95 (d, J = 6.8, 3H), 0.93 (d, J = 6.7, 3H), 0.92 (d, J = 6.8, 3H), 0.88 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.4, 90.7, 35.7, 34.0, 32.8, 32.1, 16.7, 16.5, 16.3; IR (thin film) 2971, 2880, 1762 cm^{-1}; HRMS (CI/isobutane) m/z calcd for $C_{11}H_{21}O_2$ (M + H)$^+$ 185.1541, found 185.1537. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.92; H, 10.73.

General Procedures for Reduction and Acylation of γ–Lactones. A solution of the lactone (0.1 M in CH_2Cl_2) was cooled to –78 °C and treated with DIBAL (1.2 equiv, 1.5 M in toluene) and stirred at –78 °C for 1 h. Pyridine (3.0 equiv) and DMAP (1.2 equiv) were mixed in 1–2 mL of CH_2Cl_2 and added via cannula to the reaction mixture. For multiple reactions run in parallel, a solution of pyridine (3 M) and DMAP (1.2 M) in CH_2Cl_2 was used. Finally, acetic anhydride (3.0 equiv) was added. The reaction mixture was allowed to warm slowly to 25 °C by not replenishing the dry ice bath and then allowed to stir for approximately 10 h. The reaction was quenched by the addition of 2 mL of saturated aqueous NH_4Cl and then reduced *in vacuo* to remove most of the CH_2Cl_2. The resultant material was partitioned between MTBE and saturated aqueous Na_2HPO_4. The organic layer was saved and washed twice with saturated aqueous Na_2HPO_4, three times with saturated aqueous NaH_2PO_4, and once with saturated aqueous $CuSO_4$, then passed through a funnel containing a cotton plug and a layer of Na_2SO_4 before reducing *in vacuo*. The product was purified by bulb to bulb distillation at a pressure of 30 Torr.

(2S*, 4S*)–1–Acetoxy–4–isopropyl–2–methyl–tetrahydrofuran (8). Isolated (boiling range 100–120 °C) as an 81:19 mixture of isomers in 85% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.11 (d, J = 4.5, 0.2H), 5.88 (d, J = 2.3, 0.8H), 3.88 (m, 0.8H), 3.80 (m, 0.2H), 2.34 (m, 1H), 2.19 (m, 0.8H), 2.05 (s, 2.4H), 2.04 (s, 0.6H),

2.00 (m, 0.2H), 1.74 (m, 1H), 1.42 (m, 0.2H), 1.19 (m, 0.8H), 1.11 (d, J = 7.1, 2.4H), 1.03 (d, J = 6.7, 0.6H), 0.98 (d, J = 6.6, 2.4H), 0.95 (d, J = 6.7, 0.6H), 0.88, d, J = 6.8, 2.4H), 0.86 (d, J = 6.8, 0.6H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 170.5, 104.8, 99.2, 86.9, 85.9, 40.0, 38.8, 35.7, 34.1, 33.8, 32.8, 21.4, 21.3, 19.3, 19.1, 18.3, 18.1, 18.1, 12.4; IR (thin film) 2964, 2876, 1746, 1237, 904 cm^{-1}; HRMS (EI) m/z calcd for $C_7H_{11}O_3$ (M – i-Pr)$^+$ 143.0708, found 143.0710.

(2S*, 4R*)-1-Acetoxy-4-isopropyl-2-methyl-tetrahydrofuran (9). Isolated (boiling range 100–120 °C) as a 78:22 mixture of isomers in 88% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (d, J = 4.5, 0.2H), 5.88 (s, 0.8H), 4.03 (m, 0.2H), 3.94 (m, 0.8H), 2.33 (m ,1H), 2.06 (s, 0.6H), 2.02 (s, 2.4H), 1.88 (m, 1H), 1.70 (m, 1.2H), 1.63 (ddd, J = 1.0, 6.2, 12.3, 0.8H), 1.05 (d, J = 7.3, 2.4H), 1.01 (d, J = 6.8, 0.6H), 0.97 (d, J = 6.6, 2.4H), 0.91 (d, J = 6.7, 0.6H), 0.86 (d, J = 6.8, 3.0H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 170.4, 103.7, 99.8, 86.2, 84.7, 39.7, 37.4, 34.0, 33.5, 32.8, 32.6, 21.4, 21.2, 19.3, 18.3, 18.2, 18.0, 16.6, 13.0; IR (thin film) 2966, 1740, 1238, 900 cm^{-1}; HRMS (EI) m/z calcd for $C_7H_{11}O_3$ (M – i-Pr)$^+$ 143.0708, found 143.0705.

1-Acetoxy-4,4-diisopropyl-2-methyl-tetrahydrofuran (10). Isolated (boiling range 140–160 °C) as an 61:39 mixture of isomers in 87% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.20 (d, J = 5.4, 0.6H), 5.82 (d, J = 5.9, 0.4H), 2.51 (m, 0.6H), 2.32 (m, 0.4H), 2.07 (s, 1.2H), 2.04 (s, 1.8H), 1.95 (m, 2.6H), 1.82 (dd, J = 8.8, 12.8, 0.4H), 1.54 (t, J = 12.4, 0.6H), 1.46 (dd, J = 10.3, 13.4, 0.4H), 1.09 (d, J = 6.9, 1.2H), 0.98 (d, J = 6.7H, 1.8H), 0.92 (m, 10.2H), 0.85 (d, J = 6.8, 1.8H); ^{13}C NMR ($CDCl_3$, 125 MHz, major isomer) δ 170.7, 104.8, 93.0, 39.9, 35.2, 33.7, 33.6, 21.4, 17.9, 17.8, 17.3, 16.5, 16.2; IR (thin film) 2965, 2879, 1744, 1237 cm^{-1}; HRMS (CI/isobutane) m/z calcd for $C_{10}H_{17}O_3$ (M – i-Pr)$^+$ 185.1178, found 185.1181. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.14; H, 10.64.

1-Acetoxy-2,4,4-trimethyl-tetrahydrofuran (11). Isolated (boiling range 60–90 °C) as a 68:32 mixture of isomers in 87% overall yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.13 (d, J = 4.3, 0.3H), 5.90 (d, J = 2.3, 0.7H), 2.49 (m, 1H), 2.12 (dd, J = 8.2, 12.5, 0.7H), 2.053 (s, 0.9H), 2.046 (s, 2.1H), 1.90 (dd, J = 12.0, 7.6, 0.3H), 1.62 (t, J = 12.3, 0.3H), 1.49 (dd, J = 6.1, 12.5, 0.7H), 1.37 (s, 0.9H), 1.35 (s, 2.1H), 1.34 (s, 2.1H), 1.24 (s, 0.9H), 1.14 (d, J = 7.2, 2.1H), 1.01 (d, J = 6.7, 0.9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.6, 104.9, 99.9, 84.5, 83.7, 44.7, 43.5, 40.5, 38.2, 30.5, 29.8 (29.809), 29.8 (29.755), 28.6, 21.4, 21.3, 18.1, 12.5; IR (thin film) 2973, 2936, 1742, 1240 cm^{-1}; HRMS (EI) m/z calcd for $C_9H_{15}O_3$ (M – H)$^+$ 171.1021 found 171.1025.

General Procedure for Allylation of γ-Lactol Acetates:

A solution of the acetate in CH_2Cl_2 (0.05–0.10 M) was treated with allyltrimethylsilane (4.0 equiv), then cooled to –78 °C. $SnBr_4$ (1.1 equiv, 1.0 M, CH_2Cl_2) was added and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction mixture was then poured into a separatory funnel containing saturated aqueous Na_2HPO_4. The aqueous layer was extracted with two portions of CH_2Cl_2. The crude mixture was analyzed by GC, then purified as indicated.

(2S*, 4S*)-1-Allyl-4-isopropyl-2-methyl-tetrahydrofuran (25 & 26). Purified by filtering the CH_2Cl_2 extracts through a fritted funnel containing a 1 cm pad of Na_2SO_4 on a 1 cm pad of silica gel, then distilling (boiling range 70–90 °C), in 69% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (m, 1H), 5.07 (m, 2H), 3.84 (m, 0.4H), 3.63 (m, 0.6H), 3.47 (m, 1H), 2.34 (m, 1H), 2.25 (m, 1H), 2.17 (m, 0.4H), 2.05 (m, 1H), 1.91 (m, 0.6H), 1.67 (m, 1H), 1.23 (m, 1H), 1.01 (d, J = 6.5, 1.8H), 0.97 (d, J = 6.7, 1.2H), 0.95 (d, J = 7.0, 1.2H), 0.94 (d, J = 6.7, 1.8H), 0.86 (d, J = 6.8, 1.2H), 0.84 (d, J = 6.8, 1.8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.0, 134.4, 116.3, 116.1, 84.3, 84.1, 83.7, 80.7, 39.4, 38.7, 38.5, 37.2, 35.8, 35.7, 33.7, 33.4, 19.6, 19.4, 18.4, 17.9, 16.8, 15.2; IR (thin film) 2958, 1461, 911 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_{19}O$ (M – H)$^+$ 167.1436, found 167.1432. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.67; H, 12.09.

(2S*, 4R*)-1-Allyl-4-isopropyl-2-methyl-tetrahydrofuran (27 & 28). Purified by filtering the CH_2Cl_2 extracts through a fritted funnel containing a 1 cm pad of Na_2SO_4 on a 1 cm pad of silica gel, then distilling (boiling range 70–90 °C), in 39% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86 (m, 1H), 5.06 (m, 2H), 3.88 (m, 0.3H), 3.76 (dd, J = 7.1, 15.5, 0.3H), 3.62 (dd, J = 7.0, 13.8, 0.7H), 3.40 (m, 0.7H), 2.28 (m, 2.3H),

1.18 (m, 1.7H), 1.65 (m, 1.3H), 1.50 (m, 0.7H), 0.98 (d, J = 6.6, 2.1H), 0.94 (d, J = 6.8, 0.9H), 0.934 (d, J = 6.7, 2.1H), 0.929 (d, J = 7.2, 0.9H), 0.84 (d, J = 6.8, 2.1H), 0.83 (d, J = 6.8, 0.9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.5, 135.4, 116.4, 116.2, 85.2, 83.1, 82.2, 80.6, 39.0, 37.7, 37.3, 37.0, 36.0, 35.1, 33.6, 33.2, 19.2, 19.1, 18.3, 17.9, 14.0; IR (thin film) 2958, 1642, 1087, 911 cm^{-1}; HRMS (CI/isobutane) m / z calcd for $C_{11}H_{19}O$ (M – H)$^+$ 167.1436, found 167.1432.

1–Allyl–4,4–diisopropyl–2–methyl–tetrahydrofuran (29). Isolated by flash chromatography (0:100 to 1:99 to 2:98 EtOAc:hexanes) in 78% yield as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (m, 1H), 5.05 (m, 2H), 4.09 (dt, J = 5.1, 8.7, 1H), 2.51 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.92 (m, 3H), 1.41 (dd, J = 9.0, 13.2, 1H), 0.96 (d, J = 7.1, 3H), 0.919 (d, J = 6.5, 3H), 0.916 (d, J = 6.9, 3H), 0.91 (d, J = 6.4, 3H), 0.90 (d,J = 6.7, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.8, 115.9, 89.2, 81.5, 37.3, 36.7, 36.1, 34.8, 33.8, 18.7 (18.741), 18.7 (18.719), 18.4, 18.3, 15.6; IR (thin film) 2961, 2877, 1471, 1047 cm^{-1}; HRMS (EI) m / z calcd for $C_{11}H_{19}O$ (M – i-Pr)$^+$ 167.1436, found 167.1436. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.70; H, 12.46.

1–Allyl–2,4,4–trimethyl–tetrahydrofuran (31 & 32). Purified by filtering the CH_2Cl_2 extracts through a fritted funnel containing 1 cm pad of Na_2SO_4 on a 1 cm pad of silica gel, then distilling (boiling range 40–50 °C) in 88% yield as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.87 (m, 1H), 5.07 (m, 2H), 3.97 (m, 0.7H), 3.52 (m, 0.3H), 2.38 (m, 1H), 2.21 (m, 1.7H), 2.01 (m, 0.3H), 1.95 (m, 1H), 1.47 (m, 1H), 1.32 (s, 2.1H), 1.28 (s, 0.9H), 1.21 (s, 3H), 0.98 (d, J = 6.2, 2.1H), 0.97 (d, J = 7.1, 0.9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.8, 135.2, 116.5, 116.3, 84.2, 80.1, 79.4, 48.1, 46.5, 38.5, 38.4, 36.3, 35.6, 30.4, 29.6, 29.3, 28.8, 16.4, 14.7; IR (thin film) 2968, 2874, 1455, 909 cm^{-1}; HRMS (EI) m / z calcd for $C_{10}H_{17}O$ (M – H)$^+$ 153.1279, found 153.1280.

General Procedure for Addition of Enol Silanes to Lactol Acetates:

A solution of the acetate (0.5 M, CH_2Cl_2) was treated with the enol silane (1.2 equiv), then cooled to –78 °C and treated with $SnBr_4$ (1.1 equiv, 1.0 M, CH_2Cl_2). After 10 minutes, the cold reaction mixture was poured into a separatory funnel containing saturated aqueous NaH_2PO_4 and further diluted with CH_2Cl_2. The organic layer was saved and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers are passed through a funnel containing a cotton plug and a layer of Na_2SO_4 before reducing *in vacuo*. The product was then purified by flash chromatography.

Ketones 33 & 34. Flash chromatography (2:98 EtOAc:hexanes yielded the product in 100% yield as a clear oil. GC Analysis showed that the product ratio had changed from 48:52 to 79:21 during purification. ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 8.01 (m, 2H), 7.55 (t, J = 7.4, 1H), 7.45 (m, 2H), 4.76 (m, 1H), 3.27 (dd, J = 7.7, 14.9, 1H), 2.94 (dd, J = 3.9, 14.9, 1H), 1.97 (m, 3H), 1.82 (m, 1H), 1.50 (dd, J = 10.9, 13.1, 1H), 0.99 (d, J = 6.4, 3H), 0.89 (d, J = 6.7, 3H), 0.87 (d, J = 6.8, 3H), 0.84 (d,J = 6.9, 3H), 0.83 (d, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 132.9, 132.8, 128.5, 128.4, 88.9, 82.5, 43.5, 40.3, 37.6, 34.4, 33.6, 18.3, 18.1, 17.4, 17.3, 16.2; IR (thin film) 2960, 1686, 1473, 1449, 691 cm^{-1}; HRMS (CI/isobutane) m / z calcd for $C_{19}H_{29}O_2$ (M+H)$^+$ 289.2167, found 289.2177. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.28. Found: C, 79.30; H, 9.60.

Aldehyde 35: Flash chromatography (0:100 to 2:98 EtOAc:hexanes) yielded the product in 80% yield as a clear oil. GC Analysis showed that the product ratio was unchanged during purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.63 (s, 1H), 3.49 (d, J = 10.0, 1H), 2.01 (m, 2H), 1.86 (m, 2H), 1.46 (dd, J = 10.6, 13.1, 1H), 1.11 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 6.3, 3H), 0.91 (d, J = 6.8, 3H), 0.87 (d, J = 6.8, 3H), 0.86 (d,J = 6.8, 3H), 0.83 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.2, 88.8, 87.0, 49.2, 38.6, 35.1, 34.4, 33.8, 19.5, 18.4, 18.2, 17.9, 17.7, 17.6, 17.4; IR (thin film) 2963, 1727, 1473, 1050 cm^{-1}; HRMS (CI/isobutane) m / z calcd for $C_{15}H_{29}O_2$ (M–H)$^+$ 239.2011, found 239.2008.

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Footnotes and References

(1) We have used the term "oxonium ion" instead of "oxocarbenium ion" because the former is used more commonly than the latter.

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