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Effect of Conformational Rigidity on the Stereoselectivity of Nucleophilic Additions to Five-membered Ring Bicyclic Oxocarbenium Ion Intermediates

O. Lavinda, Vi Tuong Tran, and K. A. Woerpel*

Nucleophilic substitution reactions of five-membered ring acetals bearing fused rings reveal that subtle changes in structure of the fused ring can exert dramatic influences on selectivity. If the fused ring did not constrain the five-membered ring undergoing substitution, selectivity was comparable to what was observed for an unconstrained system (≥92% diastereoselectivity, favoring the product of inside attack on the oxocarbenium ion). If the ring were more constrained by including at least one oxygen atom in the ring, selectivity dropped considerably (to 60% diastereoselectivity in one case). Transition states of the nucleophilic addition of allyltrimethylsilane to selected oxocarbenium ions were calculated using DFT methods. These computational models reproduced the correlation between additional conformational rigidity and selectivity.

Introduction

Nucleophilic substitution reactions of five-membered ring acetals are important transformations in synthetic chemistry. These reactions are useful in natural product synthesis\(^1,2\) and can be used to control stereochemistry at tetrasubstituted carbon stereocenters.\(^3,6\) These reactions, many of which proceed through oxocarbenium ion intermediates, are also important in carbohydrate\(^7\) and nucleoside chemistry,\(^4,9\) including the synthesis of non-natural nucleosides.\(^10\) Our laboratory\(^11,12\) and others\(^13-16\) have explored the origin of stereoselectivity in reactions of five-membered ring oxocarbenium ions. We have developed a model that accounts for electronic, steric, and torsional effects on these transformations.\(^11,12\) The conclusions of these studies can be used in a number of settings, including reactions of oxocarbenium ions with carbon and hydride nucleophiles\(^17\) and nucleophilic additions to cyclic iminium ions.\(^18,19\) The stereoechemical model can be applied to the chemistry of carbohydrates\(^20\) and nucleosides,\(^21\) which required consideration of the influence of fused rings, which also control the reactions of six-membered-ring acetals.\(^22,23\) For example, we demonstrated that rings fused to the five-membered ring at C-3 and C-4,\(^24\) as long as they are large enough, exert little influence on the selectivity, as evidenced by the similarity of selectivity of substitution reactions that give rise to tetrahydrofurans 1 and 2 (Chart 1).\(^25\) If a fused ring constrains the conformation of the substrate, however, selectivity can be dramatically reduced, as shown for the system 3,\(^12,26\) or reversed.\(^21\)

![Chart 1](image)

In this Article, we demonstrate that the influence of fused rings is subtler than would be anticipated based upon comparison of the reactions forming products 2 and 3. Even in a case where the fused rings are of the same size, replacing specific carbon atoms in the fused ring with heteroatoms can be enough to reduce stereoselectivity dramatically by restricting the conformational freedom of the ring undergoing nucleophilic attack.

Results

Four substrates were chosen to probe the influence of structural perturbations of a fused seven-membered ring on the selectivity of nucleophilic substitution of bicyclic acetals (Chart 2). Acetals 4 and 5 differed only in the introduction of a single heteroatom into the fused ring, which would reveal how slightly
different bond lengths, angles, and torsional preferences of this ring would affect selectivity of the reaction. Although the oxygen atom attached to C-3 of the five-membered ring acetals might inherently favor an axial orientation because of electrostatic effects,\textsuperscript{27,28} such a conformation is unlikely because it would require the fused seven-membered ring to adopt a highly strained pseudo-trans-diaxial orientation, when the diequatorial form should be favored.\textsuperscript{29} Comparison of the selectivities of nucleophilic substitution reactions of acetals 6 and 7 would reveal the relative importance of heteroatoms at different positions of the ring.

Chart 2

Substrates were prepared by several routes, as illustrated in Schemes 1-4. A useful strategy to prepare the trans-fused ring system involved ring-opening reactions of epoxides such as 8 and 15\textsuperscript{30} with allylmagnesium reagents, as illustrated in Schemes 1 and 3.\textsuperscript{31} Functionalization of an allyl group was also used to prepare the oxepane 5 from the known\textsuperscript{32} alcohol 11 (Scheme 2). The known diol 18\textsuperscript{25} was converted to acetal 7 as shown in Scheme 4.

Scheme 1 Synthesis of acetate 4 from cycloheptene oxide (8).

Scheme 2 Synthesis of acetate 5 from oxepane 11.

Scheme 3 Synthesis of acetate 6 from cis-2-butene-1,4-diol (13).

Scheme 4 Synthesis of acetate 7 from lactone diol 18.

Substitution reactions were performed using allylttrimethylsilane as the nucleophile for a number of reasons. These reactions proceed by nucleophilic attack upon an oxocarbenium ion intermediate,\textsuperscript{27} and the nucleophilic addition step is irreversible.\textsuperscript{33} This nucleophile undergoes addition to oxocarbenium ions with minimal development of steric interactions in the transition state, therefore revealing inherent torsional interactions that occur upon nucleophilic attack.\textsuperscript{27} Installation of an allyl group using this nucleophile is also synthetically useful.\textsuperscript{10,34} The substitution reaction using acetal 4 is representative of the reaction conditions employed (eq 1).

Chart 3 indicates the stereoselectivities that were observed and the relative configurations of the products. Diastereomer ratios were established by gas chromatography and confirmed by \textsuperscript{1}H NMR spectroscopy. Stereochemical assignments were made using a number of methods. The tetrahydrofuran with the fused cycloheptane ring, tetrahydrofuran 20, was assigned by examination of NOE difference spectra. The structures of silyl
ether products 22 and 23 were assigned by removing the silyl group to form the diols 24 and 25, respectively (eqs 2 and 3), to provide diols with known configurations. Assigning the structure of alkene 21 with the fused oxepane ring was more difficult, however. NOE difference spectra were not possible because the resonances were poorly resolved in several deuterated solvents. Because the stereoselectivity was low (and because it was similar to the analogous compound 23), additional derivatization experiments were not pursued. Instead, the stereochemical configuration of alkene 21 was tentatively assigned by calculating the $^{13}$C NMR chemical shifts$^{35}$ of both diastereomers and comparing those values to experimentally determined ones. The carbon atom of the fused ring (C-4) gave the most distinct chemical shifts. The observed $^{13}$C chemical shift of C-4 ($2^1$C$_2$D$_2$) for the major product ($\delta$ 83.8 ppm) is in good agreement with the calculated value of the 1,3-trans product ($\delta$ 83.1 ppm); the minor product was more consistent with the 1,3-cis product (observed at $\delta$ 81.7 compared to $\delta$ 82.4 ppm for the calculated structure). Although less diagnostic, the $^{13}$C chemical shifts of C-3 in $2^1$C$_2$D$_2$ are also in better agreement with the major product substituted 1,3-trans (observed at $\delta$ 80.6 ppm compared to the calculated value of $\delta$ 78.9 ppm) and the minor product substituted 1,3-cis (observed at $\delta$ 81.1 ppm compared to the calculated value of $\delta$ 80.3 ppm for the calculated structure). Although the assignment of the major and minor isomers of product 21 should be considered to be tentative, the use of $^{13}$C NMR spectra to assign structures has been validated in many cases.\textsuperscript{36-38}

**Chart 3**

**Discussion**

The diastereoselectivities shown in Charts 1 and 3 roughly correlate with the ring size of the fused ring, but that observation masks subtle differences in selectivity. Although selectivity does generally decrease as the fused ring size decreases, the seven-membered ring substrates exhibit quite different selectivities from each other (Chart 3). The selectivities observed for these compounds depended upon what elements comprised the fused ring (as shown by comparing selectivities for formation of products 20 and 21), and where those atoms were distributed in the ring (as demonstrated by the contrasting selectivities observed for products 22 and 23). It is unlikely that the lower selectivity observed for substrates with an oxygen atom at C-3 (leading to products 21 and 23) was caused by different energies associated with developing eclipsing interactions between the hydrogen atoms of C-2 and the substituent at C-3 (carbon vs. oxygen) upon addition. The barriers to rotation of methyl groups in the anti conformations of H$_2$C–CH$_2$OCH$_3$ and of H$_2$C–CH$_2$OCH$_3$ are quite similar (3.21 kcal/mol and 3.08 kcal/mol, respectively\textsuperscript{22,23}), and the difference in rotational barriers of cyclohexane (10.2 kcal/mol)\textsuperscript{39} and tetrahydropyran (10.3 kcal/mol)\textsuperscript{40} also compare well, so it should make little difference sterically what atom is at C-3.\textsuperscript{22}

The conformational preferences of the fused ring, however, could influence reactivity. The presence of the fused ring increases the conformational rigidity of oxocarbenium ions compared to unconstrained systems,\textsuperscript{12,22,23,41} so the structure of that ring might affect the ability of the ring to adopt an envelope conformation with the fused ring occupying two equatorial positions, as illustrated for the cation 26 (eq 4). Computational studies, however, verified that the oxocarbenium ions formed from all four acetates 4-7 adopted a conformation of the five-membered ring resembling 26, with the seven-membered ring fused diequatorially.\textsuperscript{42} The conformational restriction imposed by the fused ring is evident by the fact that only two or three low-energy minima (within 10 kcal/mol) were located for each oxocarbenium ion.

![Diagram](image-url)

The fused ring likely affects the ability of the oxocarbenium ion to accommodate changes to its conformation upon addition of the nucleophile, thereby affecting the selectivity of its reactions. As illustrated for the cycloheptene-fused oxocarbenium ion 26 (eq 4), addition from both the inside and outside faces would change the conformation of the fused ring as well as the five-membered ring.\textsuperscript{12} Because formation of the outside product A from the oxocarbenium ion 26 appears to cause less
conformational distortion of the seven-membered ring than formation of the inside product B would, the more conformationally rigid the fused ring is, the lower the selectivity for inside attack would be. This trend is illustrated by the fact that reactions of acetals with fused eight-membered rings are selective, whereas reactions of their six-membered ring analogues are not (Chart 1). This explanation would justify the lower selectivity observed in the formation of products 22 and 23, which contain conformationally restrictive disiloxane rings,\(^{25,43}\) compared to the all-carbon system 20 (Chart 3). The lower selectivity for the oxepane system 21 would also be consistent with this explanation, because oxepane adopts deeper conformational minima than cycloheptane does.\(^{44,45}\) The barrier to pseudorotation in cycloheptane is 1.3 kcal/mol, compared to oxepane, which has two predicted barriers to pseudorotation of 2.2 and 4.0 kcal/mol.\(^{46}\) The increased conformational rigidity in oxepane-fused oxocarbenium ion 27 would increase the activation energy for inside attack more than for outside attack, leading to loss of selectivity.

![Scheme 5](image)

Computational studies of nucleophilic additions to the cycloheptane- and oxepane-fused oxocarbenium ions 26 and 27, respectively, were conducted to identify transition state structures for nucleophilic additions by allyltrimethylsilane. Although additions of crotyl silanes to acyclic oxocarbenium ions have been studied computationally,\(^{47}\) additions of allyltrimethylsilane to Z-oxocarbenium ions, such as cyclic oxocarbenium ions, have not been studied (computational studies of five-membered ring iminium ions, however, have appeared).\(^{18,48}\) Transition state structures were identified for inside attack and outside attack on both oxocarbenium ions 26 and 27 at 298 K and 195 K. Transition states were modeled using the M06-2X density functional method\(^ {49}\) with the 6-31+G* basis set.\(^ {50,51} \) Optimizations and frequency calculations were performed both in the gas phase and in dichloromethane solution using a polarized continuum model.\(^ {52} \) All transition states were characterized by the presence of a single imaginary frequency corresponding to the newly formed carbon-carbon bond. Two different types of transition structures were identified, corresponding to synclinal and anti additions of the π-nucleophile to the cation.\(^ {47} \) The synclinal transition states had lower free energies than the anti ones by 0.5 to 1.3 kcal/mol at 195 K, likely because they minimize gauche interactions with the ring. Representations of the transition structures for inside and outside attack are shown in Scheme 5; three-dimensional representations of these structures are provided as supporting information. Critical parameters, such as the length of the developing carbon–carbon bond (ranging between 2.4 and 2.5 Å), agree with values obtained from transition structures identified for allylation of propargylic cations.\(^ {53} \) The carbon–silicon bond is anti-planar to the developing carbon–carbon bond, which would be expected because of stabilization of the incipient carbenionic center by the carbon–silicon σ-bond.\(^ {54,55} \)

Conclusions

Nucleophilic substitution reactions of acetals with fused rings can exhibit selectivities that are distinctly different from unconstrained systems. This phenomenon has been used strategically in reactions of six-membered ring acetals, so the origin of this selectivity difference has been examined extensively in that series.\(^ {56} \) The studies reported here show that nucleophilic addition reactions to fused oxocarbenium ions not only involve conformational changes to the ring undergoing nucleophilic addition, but also on the fused ring. Conformational flexibility or inflexibility of the fused ring can affect the transition state energies and therefore diastereoselectivity ratios in reactions. Calculations of transition structures reproduce these trends.

Experimental Section

General

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on silica gel (SiO\(_2\)) 60 (230–400 mesh). \(^ {1} \)H NMR and \(^ {13} \)C NMR spectra were recorded at ambient temperature using DRX 400 (400 and 100 MHz, respectively), DRX 500 (500 and 125 MHz, respectively) or DRX 600 (600 and 150 MHz, respectively) spectrometers, as indicated. The data are reported as follows: chemical shift in
ppm from internal tetramethylsilane on the δ scale, multiplicity (app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet), coupling constants (Hz), and integration. Due to difficulties with purification of certain products, only distinctive peaks are listed in tabulated 1H NMR spectral data as indicated, and the structures were assigned using a combination of COSY, HMBC, and NOE experiments. Proton count at each carbon was confirmed by HSQC. Gas chromatography–mass spectrometry (GC–MS) was performed with a quadrupole system with a fused silica capillary column (30 m x 0.32 mm x 0.25 μm) wall-coated with DB-5 using electron ionization (70 eV). High resolution mass spectra (HRMS) were acquired on a quadrupole time-of-flight spectrometer or an orthogonal acceleration time-of-flight spectrometer and were obtained by peak matching. Optical rotations were obtained using a digital polarimeter. Analytical thin-layer chromatography was performed on silica gel 60 F254 plates. THF, DMF, and CH2Cl2 were dried by filtration through alumina according to the method of Grubbs. All reactions using Et2O, THF, DMF, and CH2Cl2 as solvents were run under an atmosphere of nitrogen in glassware that was flame-dried under a stream of nitrogen. All starting materials and reagents were commercially available unless otherwise indicated.

Experimental Procedures

(1R*,2R*)-2-Allylcyloheptanol (9). To a solution of 8 (0.236 g, 2.10 mmol) in Et2O (21 mL) at 0 °C was added allylmagnesium chloride (2.0 M in THF, 1.6 mL, 1.6 mmol). The reaction mixture was allowed to stir overnight at room temperature before adding saturated aqueous NaHCO3 (15 mL) and extracting with Et2O (2 x 20 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered, and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (10:90 EtOAc:hexanes) to give 9 as a colorless oil (0.15 g, 46%). 1H NMR (500 MHz, CDCl3) δ 5.84 (dddd, J = 17.1, 10.1, 7.8, 6.5, 1H), 5.08–5.02 (m, 2H), 3.50 (td, J = 7.3, 3.8, 1H), 2.37 (ddtt, J = 13.9, 6.3, 4.8, 1.5, 1H), 2.04 (dtt, J = 13.9, 7.8, 1.1, 1H), 1.82–1.58 (m, 6H), 1.54–1.36 (m, 5H), 1.25–1.18 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 137.8, 116.4, 76.7, 74.3, 39.5, 36.7, 29.05, 29.03, 27.1, 22.5; IR (thin film) 3346, 3075, 2926, 1639, 1444 cm⁻¹; HRMS (TOF MS ES⁺) m/z calced for C16H26NaO4 (M + Na⁺) 221.1154, found 221.1157. Anal. Calcd for C16H26O5Na: C, 71.38; H, 7.80.

(3aR*,8aS*)-Octahydropyrro[3,2-b]oxepin-2-ol (12). To a solution of 11 (0.068 g, 0.44 mmol) in CH2Cl2 (5 mL) at –78 °C was added a stream of ozone gas until a blue color persisted. After purging with oxygen for 10 min, triphenylphosphate (0.229 g, 0.873 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, and the product was purified by flash column chromatography on silica gel (25:75 EtOAc:hexanes) to give 12 as a colorless oil (0.065 g, 94%). Characterization was performed on a 50:50 mixture of diastereomers: 1H NMR (600 MHz, CDCl3) δ 5.48–5.45 (m, 1H), 4.16 (dt, J = 10.0, 7.9, 0.5H), 4.01 (ddd, J = 10.7, 8.4, 5.2, 0.5H), 3.89–3.84 (m, 1H), 3.82–3.71 (m, 2H), 3.03 (br s, 1H), 2.62 (ddd, J = 14.1, 8.8, 5.8, 0.5H), 2.23–2.14 (m, 1H), 2.06 (ddd, J = 12.4, 10.3, 5.5, 0.5H), 1.87–1.74 (m, 3.5H), 1.71–1.62 (m, 1H), 1.51 (ddd, J = 12.9, 11.0, 8.5, 6.1, 0.5H), 1.40 (ddd, J = 13.1, 10.7, 8.8, 5.7, 0.5H); 13C NMR (150 MHz, CDCl3) δ 97.7, 97.4, 83.9, 80.8, 80.5, 78.6, 71.1, 70.9, 41.0, 40.4 32.5, 30.9, 29.0, 22.7, 23.1, 22.8; IR (ATR) 3397, 2932, 1261 cm⁻¹; HRMS (TOF MS ES⁺) m/z calced for C19H17NaO3 (M + Na⁺) 181.0838, found 181.0838.
(3\(R\),8\(A\)S\*)-Octahydrofuro[3,2-b]oxepin-2-yl acetate (5). To a solution of 12 (0.020 g, 0.13 mmol) in CH\(_2\)Cl\(_2\) (1 mL) at 0 °C was added triethylamine (0.106 mL, 0.759 mmol) and acetic anhydride (0.024 mL, 0.25 mmol). After stirring at room temperature overnight, the reaction mixture was washed with saturated aqueous sodium bicarbonate (20 mL) and extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL). The combined organic layers were filtered through a cotton plug and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (1:59 Et\(_3\)N:EtOAc:hexanes – 1:20:79 Et\(_3\)N:EtOAc:hexanes) to give 5 as a colorless oil (0.017 g, 68%). Characterization was performed on a 50:50 mixture of diastereomers: \(^{1}H\) NMR (600 MHz, CDCl\(_3\)) \(\delta\) 6.21 (dd, \(J = 5.2, 0.5\) Hz), 6.19 (dd, \(J = 6.3, 3.6, 0.5\) Hz), 4.13 (ddd, \(J = 10.5, 8.2, 7.1, 0.5\) Hz), 3.98 (ddd, \(J = 10.7, 8.5, 5.3, 0.5\) Hz), 3.90–3.77 (m, 2.5 Hz), 2.73 (ddd, \(J = 11.7, 5.9, 3.8, 0.5\) Hz), 2.71 (ddt, \(J = 14.2, 9.1, 6.3, 0.5\) Hz), 2.27–2.17 (m, 2H), 2.07 (s, 1.5H), 2.05 (s, 1.5H), 1.97 (ddd, \(J = 14.1, 8.0, 3.6, 0.5\) Hz), 1.88–1.75 (m, 3H), 1.71–1.62 (m, 1H), 1.51–1.42 (m, 1H). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.7, 170.3, 97.43, 97.38, 84.6, 82.5, 79.9, 78.2, 71.3, 71.1, 39.1, 38.9, 32.0, 30.3, 28.9, 28.6, 23.0, 22.8, 21.54. 18. IR (ATR) 2937, 1743, 1231 cm\(^{-1}\); HRMS (TOF MS ES+) \(m/z\) calecd for C\(_{29}\)H\(_{25}\)O\(_4\)Si (M + H\(^{+}\)) 229.1624, found 229.1622. 2,2-Di-tert-butyl-4,7-dihydroxy-1,3,2-dioxasilepine (14). To a solution of cis-2-butene-1,4-diol (107 g, 1.22 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at 0 °C was added 2,6-lutidine (0.283 mL, 2.43 mmol) and di-tert-butylisilys bis(trifluoromethanesulfonate), (0.394 mL, 1.22 mmol). After stirring overnight at room temperature, the reaction mixture was washed with saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were filtered, and concentrated in vacuo. To a solution of crude 14 (0.123 g, 0.538 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at 0 °C was added \(N\)-chloroperoxybenzoic acid (77%, 0.241 g, 1.08 mmol). The reaction mixture was stirred at room temperature overnight before washing sequentially with saturated sodium bisulfite (20 mL) and saturated aqueous sodium bicarbonate (40 mL) and extracting with CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic layers were filtered through a cotton plug and concentrated in vacuo. 11NMR, \(^{13}C\) NMR, IR, and HRMS data were collected for the unpurified reaction mixture: \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) diagnostic peaks \(\delta\) 4.47–4.44 (m, 1H), 4.10–3.69 (m, 3H), 3.30–3.25 (m, 2H), 1.06–1.01 (m, 18H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) diagnostic peaks \(\delta\) 64.1, 56.1, 27.7; IR (ATR) 2965, 1086 cm\(^{-1}\); HRMS (TOF MS ES+) \(m/z\) calecd for C\(_{21}\)H\(_{22}\)NaO\(_3\)Si (M + H\(^{+}\)) 267.1392, found 267.1401.
(0.145 mL, 1.53 mmol). After stirring overnight at room temperature, the reaction mixture was washed with saturated sodium bicarbonate (10 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were filtered through a cotton plug and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (1:10:95 Et₂O:EtOAc:hexanes) to give white solid. The product was purified by column chromatography on silica gel (1:5:49 Et₂O:EtOAc:hexanes) to give 7 as a colorless oil (0.020 g, 82%). Characterization was performed on a 65:35 mixture of diastereomers: 1H NMR (600 MHz, CDCl₃) δ 6.35 (d, J = 5.5, 0.35H), 6.32 (dd, J = 6.4, 4.4, 0.65H), 4.58 (ddd, J = 10.7, 8.0, 6.8, 0.35H), 4.05 (q, J = 8.6, 0.35H), 3.82 (ddd, J = 11.0, 8.3, 2.7, 0.65H), 3.76–3.73 (m, 1.65H), 3.69 (dd, J = 11.8, 1.9, 0.35H), 3.50 (ddd, J = 11.0, 8.1, 2.8, 0.35H), 2.39 (ddd, J = 13.7, 8.5, 6.4, 0.65H), 2.15 (dd, J = 12.9, 6.7, 0.35H), 2.06 (ddd, J = 13.4, 8.9, 4.4, 0.65H), 1.98 (ddd, J = 12.9, 10.7, 5.5, 0.35H), 1.93–1.80 (m, 1.35H), 1.68 (ddd, J = 13.9, 11.0, 8.1, 0.65H), 1.64 (s, 1.95H), 1.59 (s, 1.05H), 1.10 (s, 3.15H), 1.09 (s, 5.85H), 1.05 (s, 3.15H and s, 5.85H). 13C NMR (150 MHz, CDCl₃) δ 169.5, 169.1, 96.9, 96.7, 85.6, 83.3, 78.4, 77.0, 62.3, 62.2, 40.8, 40.6, 37.9, 36.5, 28.4, 28.3, 28.12, 28.05, 21.6, 21.52, 21.46, 20.85, 20.83; IR (ATR) 2934, 1750, 1110 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₄H₂₀Na₂O₃Si (M + Na⁺) 353.1760, found 353.1761. Anal. Calcd for C₁₄H₁₉O₂Si: C, 58.45; H, 9.15. Found: C, 58.45; H, 9.23.

General Procedure for Substitution of Allyltrimethylsilane with Acetals. A solution of acetate (0.10 M) in dry CH₂Cl₂ was cooled to –78 °C. Allyltrimethylsilane (4 equiv) was added to the reaction mixture, followed by dropwise addition of boron trifluoride etherate (1.6 equiv). The reaction mixture was allowed to come slowly to room temperature overnight. A solution of 1:1 dry CH₂Cl₂:MeOH:Et₃N was added to the reaction mixture at –78 °C. The reaction mixture was extracted with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, filtered through a cotton plug, and concentrated in vacuo.

(2R*,3αR*,8αS*)-2,2-Di-tert-butyldihexahydrofuro[3,2-d][1,3,2]dioxasilapin-7(4H)-one (19). To a solution of lactone diol 18(0.044 g, 0.30 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added 2.6-lutidine (0.106 mL, 0.911 mmol), tetrabutylammonium iodide (0.224 g, 0.608 mmol), and di-tert-butylsilyle bis(trifluoromethanesulfonate) (0.098 mL, 0.30 mmol). The reaction mixture was allowed to warm to room temperature overnight before concentrating in vacuo. The product was purified by flash column chromatography on silica gel (10:90 EtOAc/hexanes) to give 19 as a white crystalline solid (0.023 g, 27%). mp 86–89°C; mp 86–89°C; 1H NMR (500 MHz, CDCl₃) δ 6.27 (dd, J = 11.0, 7.6, 1H), 6.25 (d, J = 6.0, 7.6, 1H), 1.76 (ddd, J = 11.0, 7.6, 0.76, 1H), 1.74 (ddd, J = 11.0, 7.6, 0.76, 1H); 13C NMR (125 MHz, CDCl₃) δ 173.5, 85.4, 75.7, 61.7, 38.3, 36.4, 29.3, 27.9, 21.6, 21.5; IR (ATR) 2926, 1749, 1467, 1066 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₆H₂₀Na₂O₃Si (M + Na⁺) 353.1760, found 353.1761. Anal. Calcd for C₁₄H₁₉O₂Si: C, 58.45; H, 9.15. Found: C, 58.53; H, 9.43.

(5αR*,8αS*)-2,2-Di-tert-butyltetrahydrofuro[3,2-d][1,3,2]dioxasilapin-7-yl acetate (7). To a solution of 19 (0.021 g, 0.073 mmol) in CH₂Cl₂ (1 mL) at –78 °C was added di-iso-butylalumina hydride (1.0 M in toluene, 0.15 mL, 0.15 mmol). After 1 h at –78 °C, a solution of dimethylaminopyridine (0.018 g, 0.15 mmol) in CH₂Cl₂ (1 mL), pyridine (0.018 mL, 0.22 mmol), and acetic anhydride (0.042 mL, 0.44 mmol) were added. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to 0 °C before adding saturated aqueous sodium potassium tartrate (1 mL) and saturated aqueous ammonium chloride (1 mL). The reaction mixture was allowed to warm to room temperature and was stirred until the layers were completely separated. The reaction mixture was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phases were filtered through a cotton plug and concentrated in vacuo to give a white solid. The product was purified by column chromatography on silica gel (1:5:2 Et₂O:EtOAc:hexanes) to give 7 as a colorless oil (0.020 g, 82%).
(10:90 EtOAc:hexanes) to give 21 as a colorless oil (0.013 g, 86%). Characterization was performed on a 60:40 mixture of diastereomers: $^1$H NMR (600 MHz, CD$_2$D$_2$) $\delta$ 5.85–5.77 (m, 1H), 5.06–4.99 (m, 2H), 4.27–4.22 (m, 1H), 4.05 (dq, $J$ = 8.6, 5.9, 0.63H), 3.99 (dq, $J$ = 9.4, 6.3, 0.37H), 3.82 (dd, $J$ = 6.9, 2.3, 1.26H), 3.81 (dd, $J$ = 5.2, 2.4, 0.74H), 3.57 (dd, $J$ = 10.8, 8.2, 2.7, 0.37H), 3.42 (dd, $J$ = 10.7, 7.9, 2.6, 0.63H), 2.35 (dtt, $J$ = 14.0, 6.6, 1.3, 0.37H), 2.23 (dtt, $J$ = 14.1, 6.9, 5.9, 1.3, 0.63H), 2.20–2.10 (m, 1.37H), 2.01–1.91 (m, 2.26H), 1.82–1.71 (m, 1.37H), 1.16 (s, 9H), 1.11 (s, 5.67H), 1.10 (s, 3.33H); $^1$C NMR (150 MHz, CD$_2$D$_2$) $\delta$ 135.1, 134.9, 117.11, 117.09, 85.0, 83.4, 79.6, 78.8, 76.8, 76.5, 62.5, 62.4, 41.7, 41.3, 40.7, 39.2, 37.8, 37.2, 28.5, 28.4, 28.23, 28.22, 21.70, 21.67, 21.6; IR (ATR) 3078, 2939, 1643, 1062 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calecd for C$_{17}$H$_{20}$O$_2$Si (M + H)$^+$ 313.2199, found 313.2197. Analyzed Caled for C$_{17}$H$_{20}$O$_2$Si: C, 65.33; H, 10.32. Found: C, 65.21; H, 10.24.

((2R,3S,5R)-5-Allyltetrahydrofuran-2,3-diyldimethanol (24). To a solution of 22 (0.195 g, 0.625 mmol) in THF (6 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 1.9 mL, 1.9 mmol). The reaction mixture was stirred overnight, then concentrated in vacuo. The product was purified by flash column chromatography on silica gel (EtOAc) to provide 24 as a colorless oil (0.050, 46%). The $^1$H NMR spectrum of CDCl$_3$ of the previously reported compound was determined by gas chromatography: 117.4, 117.2, 85.6, 84.5, 84.3, 81.7, 81.0, 76.6, 76.1, 70.2, 70.0, 41.2, 38.4, 37.5, 31.9, 30.8, 28.9, 28.8, 22.9, 22.5; IR (ATR) 3078, 2939, 1643 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calecd for C$_{17}$H$_{20}$Na$_2$O$_2$ (M + Na)$^+$ 195.0997, found 195.0995.

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Notes and references
Department of Chemistry, New York University, New York, New York 10003, United States. Email: kwoerpel@nyu.edu

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Electronic Supplementary Information (ESI) available: Stereochemical proofs and spectroscopic data for all compounds, computational details, and $^1$H and $^{13}$C NMR spectra. See DOI: 10.1039/b000000X/

24. The numbering used in this paper considers the carboxycationic carbon as C-1.
42. Low-energy conformations were identified by conformational searching using semi-empirical methods (PM3). The lowest-energy structures were optimized using PCM-B3LYP/6-31+G**. Details are provided as supporting information.