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Note

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Chemoselective Carbonyl Allylations with Alkoxyallylsiletanes

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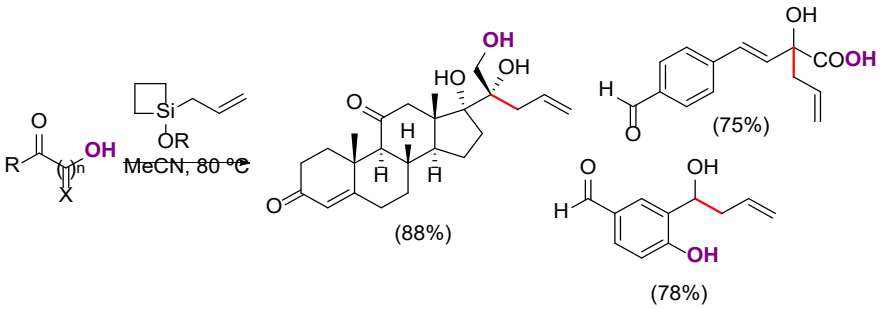


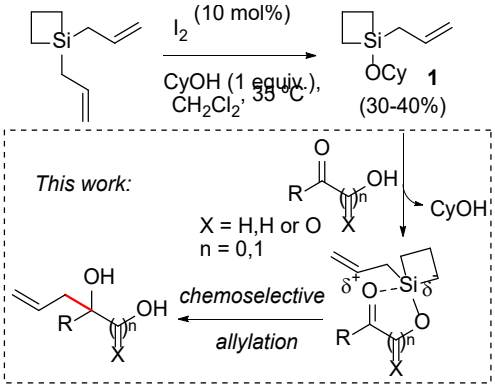
Abstract

Alkoxyallylsiletanes are capable of highly chemo- and diastereoselective carbonyl allylsilylations. Reactive substrates include salicylaldehydes and glyoxylic acids. Chemoselectivity in these reactions is thought to arise from a mechanism involving first exchange of the alkyoxy group on silicon with a substrate hydroxyl followed by activation of a nearby carbonyl by the Lewis acidic siletane and intramolecular allylation. In this way, substrates containing multiple reactive carbonyl groups (e.g. dialdehyde or triketone) can be selectively monoallylated, even overcoming inherent electrophilicity bias.

As part of a program investigating activatable silanes for nucleophilic additions,[1,2] we became interested in allylsilacyclobutanes of type **1**, inspired by Matsumoto's report on the use of siletane **1** for non-catalyzed additions to α-hydroxyketones.[3] Our group recently described a novel

synthesis of this compound by iodine-catalyzed monoetherification of diallylsilacyclobutane (Scheme 1).[4] With reliable access to useful quantities of **1**, we now wish to report on its use in a series of carbonyl allylsilylations. In particular, we have found that reagents of type **1** are capable of remarkably chemoselective nucleophilic additions to various hydroxyl-substituted carbonyls. This chemoselectivity is thought to arise from a mechanism involving first exchange of the alkoxy substituent on silicon with a substrate hydroxyl, followed by intramolecular allylsilylation of a nearby carbonyl activated by the Lewis acidic silacyclobutane.[5-7]

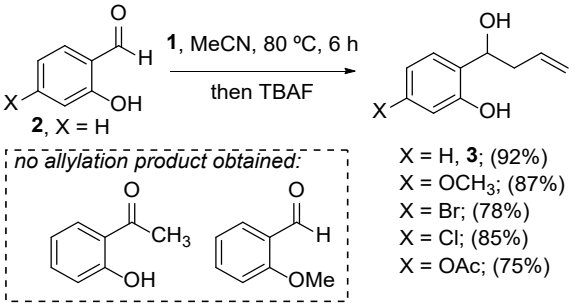
Scheme 1. Synthesis of allylsilacyclobutane **1** by iodine-catalyzed monoetherification and subsequent intramolecular allylation.



To explore the reactivity of allylsiletane **1,** potential substrates were considered that could exploit this exchangeable siloxane to achieve selective allylation reactions. Previous experiments in our lab had shown that benzaldehyde was recalcitrant to react with **1**. We questioned, however, if having a nearby hydroxyl group, such as that in salicylaldehyde (**2**) might promote nucleophilic addition by allowing for an intramolecular allylation following exchange with the alkoxy substituent on **1**. To test this, the reaction of **2** with **1** was examined in several different solvents and temperatures.[8] Low conversions were generally observed when using less polar solvents like tetrahydrofuran, dichloromethane, and toluene. However, polar aprotic solvents

dimethylformamide and acetonitrile gave high conversion to the allylated product **3**, perhaps due to stabilization of a charged transition state such as that depicted in Scheme 1 with coordination of the aldehyde oxygen to silicon and intramolecular allylation. While DMF gave slightly higher yield after 6 h at 100 ºC than MeCN at 80 ºC (99% vs 92% respectively), MeCN is generally preferred in line with recent green chemistry recommendations[9] and its easier removal than higher boiling DMF.

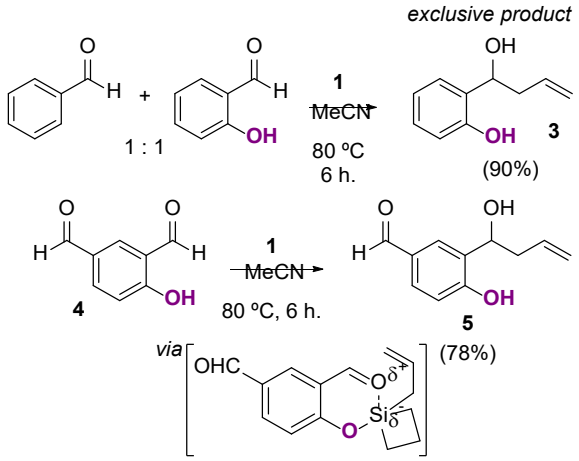
Scheme 2. Scope of salicylaldehyde allylations with siletane **1**.



Other salicylaldehyde derivatives reacted efficiently with **1** including those containing bromo-, chloro-, and acetyloxy-substituents that might otherwise be incompatible with certain allylorganometallic reagents (Scheme 2). Interestingly, 2'-hydroxyacetophenone failed to undergo allylation,[10] presumably as a result of the lower electrophilicity of the ketone versus an aldehyde. Sato et al. had reported the allylation of 2'-hydroxyacetophenone using trifluoro- or trialkoxysilanes in the presence of triethylamine,[11] with triethylamine suggested to act as a Brønsted base. However the addition of triethylamine failed to promote the allylation of 2'-hydroxyacetophenone with **1**, suggesting some fundamental differences between siletanes and other electrophilic allylsilanes. Additionally 2-methoxybenzaldehyde proved unreactive, consistent with a mechanism involving initial exchange at silicon with a substrate hydroxyl.

To further test the importance of an exchangeable group on the substrate, a competition experiment was performed using a 1:1 mixture of benzaldehyde and salicylaldehyde (Scheme 3). When this mixture was treated with **1** in MeCN at 80 ºC, only product **3** derived from salicylaldehyde was obtained in 90% yield along with unreacted benzaldehyde. Moreover, the reaction of **1** with the dialdehyde 4-hydroxyisophthalaldehyde (**4**) selectively produced compound **5** in 78% yield, addition occurring only at the aldehyde *ortho*- to the hydroxyl group. The chemoselective monoallylation of **4** to produce **5** has previously been described by Ito and coworkers using allyltributyltin.[12] Those authors explained their result by invoking an intramolecular hydrogen bond between the phenol and *ortho*-aldehyde rendering this aldehyde more electrophilic. While hydrogen bonding may be required to explain Ito's results, we contend that exchange of hydroxyl groups onto siletane **1** is rapid, and that it is the intramolecularity of the subsequent allylation that is most responsible for its chemoselectivity.

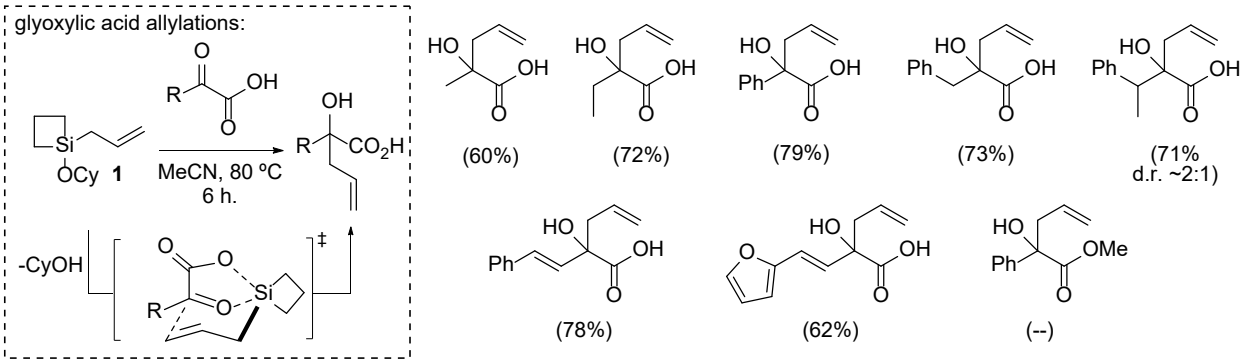
Scheme 3. Chemoselective aldehyde allylations using compound **1**.



To better understand the reactivity and selectivity of siletane **1** and the results obtained with salicylaldehyde, reactions with glyoxylic acids were also investigated (Figure 1). Under the optimized conditions (MeCN, 80 ºC), phenylglyoxylic acid was fully allylated in 6 hours, providing analogous reactivity to salicylaldehyde derivatives. As can be seen in Figure 1, aryl,

heteroaryl, alkyl, and alkenyl glyoxylic acids all react efficiently with **1** to give tertiary α-hydroxy carboxylic acid products in good isolated yields (60-78%) following a simple basic extraction. Tertiary α-hydroxy carboxylic acids appear in a number of biologically relevant natural products, however their synthesis by traditional methods (e.g. organolithium additions to α-oxocarboxylic acids) can be challenging.[13] Wang and coworkers previously reported a similar allylsilylation of glyoxylic acids,[14] however that reaction used moisture-sensitive allyltrichlorosilane (compound **1** can be handled with no special precautions) as well as DMF and HMPA as nucleophilic activators of the silane. Reactions of glyoxylic acids with **1** were all performed in MeCN and without additional additives. Accordingly, the mechanism is proposed to involve first exchange of cyclohexanol on silicon with the carboxylic acid hydroxyl. The bound allylsiletane is then ambiphilic,[15] activating the adjacent ketone due to its Lewis acidity followed by intramolecular allylation.[16] Consistent with this proposal, the methyl ester of phenylglyoxylic acid failed to react with **1** under these conditions.

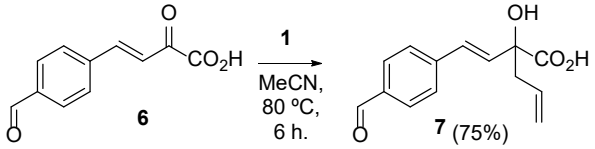
Figure 1. Non-catalyzed glyoxylic acid allylsilylations using allylsilacyclobutane **1**.



In accordance with the proposed glyoxylic acid allylation mechanism, we hypothesized that certain substrates could be made to undergo highly chemoselective reactions with **1**, perhaps even contrary to general carbonyl electrophilicity trends.[17] To that end, aldehyde-containing ketoacid **6**[18] was prepared and treated with **1** in MeCN at 80 °C (Scheme 4). Under these conditions, nucleophilic addition occurred selectively to the ketone giving product **7** in 76% yield.[19] This is

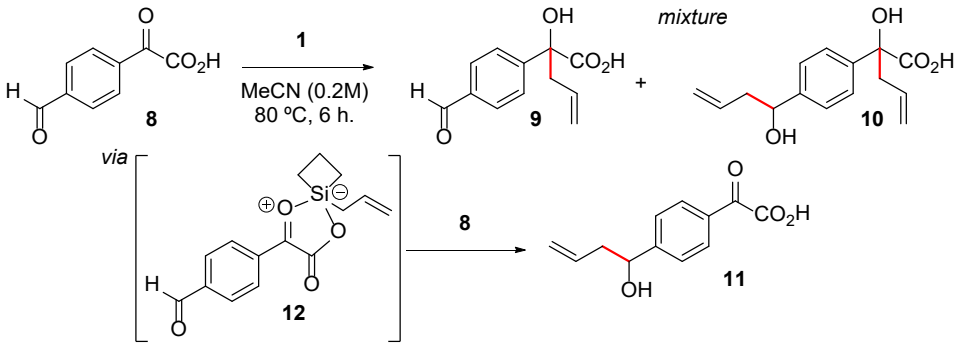
quite remarkable given that compound **6** contains no less than five different electrophilic sites (3 carbonyl groups plus Michael addition and an acidic proton). Moreover, this is one of only a few examples of direct carbon nucleophile addition to a ketone in the presence of an aldehyde. Otera's group reported that ketene silyl acetals will react preferentially with ketones over aldehydes in the presence of $(C_6F_5)_2SnBr_2$,[20] rationalized as due to selective activation of the more electron rich ketone by the Lewis acid. Other examples generally involve protection and deprotection of the more electrophilic aldehyde *in situ*.[21-23]

Scheme 4. Chemoselective monoallylation of substrate **6** containing multiple electrophilic sites.



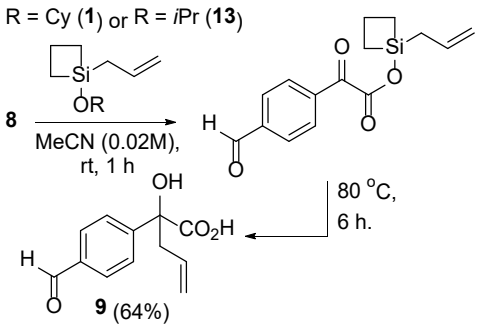
To further probe the chemoselectivity, aldehyde-containing ketoacid **8**[24] was also investigated (Scheme 5). Surprisingly, the reaction of this simpler substrate (i.e. only 4 electrophilic sites) was less chemoselective, giving the desired product **9** along with significant amounts of aldehyde addition products **10** and **11**. It was supposed that aldehyde allylation was the result of an intermolecular reaction of **8** with allylsilanide **12**. Indeed, upon treatment of **8** with **1** the reaction mixture becomes bright orange-colored, which we have ascribed to this charged complex. Additionally, monitoring the reaction by ^{1}H NMR spectroscopy (in MeCN-d_3) shows rapid (<15 min) release of free cyclohexanol indicating exchange with the substrate hydroxyl prior to any allylation product formation.

Scheme 5. First attempts at the chemoselective allylation of aldehyde ketoacid **8**.



The ketone in compound **8** is arguably more sterically hindered than in **6** (*ref.* Scheme 4) which may slow down the intramolecular process and allow for the intermolecular aldehyde allylation to compete. To favor intramolecular allylation, the reaction was performed under dilute conditions (0.02M, Scheme 6). Additionally, compounds **8** and **1** were first reacted at room temperature to allow for exchange of the alkoxy substituents, followed then by heating to 80 ºC in order to promote the allylation. Under these conditions, the chemoselectively allylated product **9** was isolated in 65% yield. The use of isopropoxysiletane **13** gave **9** in identical yield as the cyclohexyloxysilane **1**, consistent with a mechanism involving initial loss of this group.

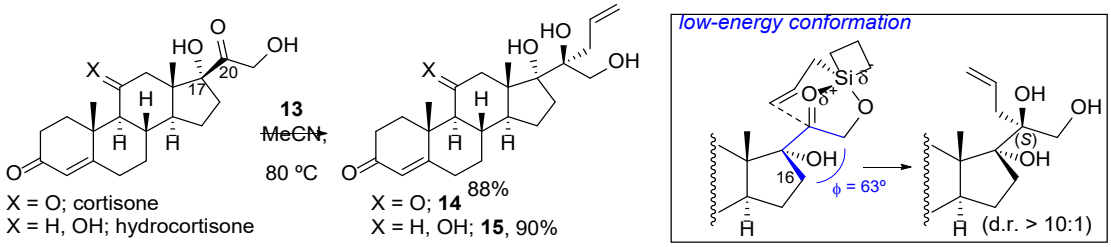
Scheme 6. Successful chemoselective ketone allylation of compound **8** by first alkoxy exchange followed by heating.



As a further demonstration of the utility of this method, treatment of cortisone and hydrocortisone under our standard conditions gave monoallylated products **14** and **15** in 88% and

90% isolated yields respectively, with no evidence for 1,2- or 1,4-addition at the other ketone(s) (Scheme 7). The chemoselectivity in this reaction is assumed to arise from first exchange of the 1º hydroxyl (as opposed to the 3º) followed by intramolecular allylation of the neighboring ketone. By ^{1}H NMR spectroscopy, only a single diastereomer was formed. Attempts to form X-ray quality crystals of compounds **14** and **15** or their derivatives (e.g. benzoate esters) for stereochemical determination were unsuccessful. Adopting Hoye's protocol for structure assignment through computation of NMR chemical shifts (Figure S1),[25] we have assigned the configuration of the newly formed stereocenter as (*S*). Considering the structure of the calculated low-energy conformer (Figure S2 and Scheme 7 inset), the result suggests preferential allylation past the C_{17}-hydroxyl. It could be that the pro-(*R*) face is more sterically hindered by the C_{16}-methylene. Alternatively the C_{17}-hydroxyl group may direct the addition, for instance by interaction with the reactive silicon center, akin to other hydroxyl-directed nucleophilic additions.[26] Further experiments are planned to better elucidate the factors controlling the stereochemical course of this reaction and to demonstrate this process as a new method for chemoselective modification of steroids and other biomolecules containing multiple carbonyl functional groups.

Scheme 7. Selective cortisone and hydrocortisone monoallylation using siletane **13**.



Conclusion

In summary, our investigations have revealed that alkoxyallylsiletanes react efficiently with both salicylaldehydes and glyoxylic acids based on a mechanism involving initial ligand exchange at silicon followed by intramolecular allylation of a proximal carbonyl that has been activated by the Lewis acidic siletane. Consistent with this mechanism, highly chemoselective allylations were achieved. For instance, the reaction of dialdehyde 4-hydroxyisophthalaldehyde with **1** resulted in selective nucleophilic addition to the aldehyde *ortho*- (as opposed to *para*) to the hydroxyl group. We also demonstrated one of only a few examples involving the selective addition of a carbon nucleophile to a ketone in the presence of an aldehyde. Overall, the results suggest that allylsiletanes may be of great utility to target-oriented synthesis campaigns, perhaps as a means of avoiding protecting groups for sequential carbonyl additions. Additionally, biomolecules such as steroids containing multiple carbonyl groups can be selectively modified which may aid in our understanding of their function.

Experimental Section

General Information. All reactions were carried out under N_2 in flame-dried glassware. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All reagents were purchased and used as received unless otherwise mentioned. Heating of reaction mixtures was accomplished using hot plate stirrers equipped with a thermocouple (accuracy ± 2 °C) and aluminum heating block. TLC analysis used 0.25 mm silica layer fluorescence UV_{254} plates. Flash chromatography: silica gel (230-400 mesh). NMR: Spectra were recorded on a 300 or 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. The solvent signals were used

as references ($CDCl_3$: $\delta_c \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm; C_6D_6: $\delta_c \equiv 128.0$ ppm; residual C_6H_6 in C_6D_6: $\delta_H \equiv 7.16$ ppm; residual CHD_2CN in CD_3CN: $\delta_H \equiv 1.94$ ppm).

1-Allyl-1-cyclohexyloxysiletane (1). To a Schlenk flask containing diallylsiletane (1.1 g, 6.9 mmol, 1.0 eq.) in DCM (35 mL) was added I_2 (180 mg, 10 mol %) at room temperature, and the resulting red solution was stirred for 10 min. Cyclohexanol (0.72 mL, 6.9 mmol, 1.0 eq.) was then added and the solution was heated to 35 °C for 30 min. After 30 min. a drop of pyridine was added, and the solution was concentrated *in vacuo*. Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave **1** as a pale yellow oil (0.44 g, 30%, R_f = .98 in 10:1 Hex:EtOAc). *Spectral data for **1** matched that previously reported by Matsumoto*:[3] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.1, 10.2, 8.0 Hz, 1H), 4.94 (ddt, *J* = 17.1, 2.0, 2.0 Hz, 1H), 4.90 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 3.87 (tt, *J* = 9.6, 4.0 Hz, 1H), 2.04 (m, 2H), 2.1 – 1.65 (m, 8H), 1.63 – 1.42 (m, 2H), 1.42 – 1.10 (m, 8H).

1-Allyl-1-isopropoxysiletane (13). To a Schlenk flask containing 1,1-dichlorosilacyclobutane (1.0 mL, 8.4 mmol, 1.0 eq.) at 0 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 8.4 mL, 8.4 mmol, 1.0 eq.) dropwise over 15 min. The solution was stirred for 1 h at 0 °C and then filtered under N_2 using Et_2O (20 mL) to rinse. The solution was cooled back to 0 °C, and diisopropylethylamine (Hünig's base, 2.2 mL, 13 mmol, 1.5 eq.) was added, followed by isopropanol (0.68 mL, 8.9 mmol, 1.1 eq.). The solution was stirred and warmed to room temperature over 3 h and then filtered through cotton using Et_2O and concentrated *in vacuo*. The resulting mixture was triturated with Et_2O followed by purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) giving **13** (0.8 g, 56%) as an oil. IR (ATR) 2970, 2920, 1630, 1388, 1154, 1120, 894, 766 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.3, 10.0, 7.9 Hz, 1H), 4.97 (dq, *J* = 16.9, 1.5 Hz, 1H), 4.91 (ddt, *J* = 8.8, 2.1, 1.1 Hz, 1H), 4.18 (sept, *J* = 6.1 Hz, 1H),

1.96 (m, 1H), 1.75 (dt, J = 8.1, 1.1 Hz, 2H), 1.54 (m, 1H), 1.34-1.22 (m, 4H), 1.21 (d, J = 6.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 133.0, 113.9, 65.9, 25.7, 23.3, 17.8, 13.4. HRMS-TOF (ESI+) Calcd for $C_9H_{18}NaOSi$ (M + Na): 193.1025. Found 193.1020.

General Procedure for Allylations of Salicylaldehydes (2-hydroxybenzaldehydes, Scheme 2). To a Schlenk flask containing a 2-hydroxybenzaldehyde (1.0 eq.) in MeCN was added **1** (1.5 eq.) and the solution was heated to 80 °C for 6 h. The mixture was then cooled to 0 °C before adding TBAF (4.5 eq) and stirring for 15 min. The reaction was quenched with aq. NH_4Cl and the product was extracted twice with EtOAc. The combined organic layers were dried of $MgSO_4$, filtered, and concentrated *in vacuo* and the residue purified by chromatography on silica.

2-(1-hydroxybut-3-en-1-yl)phenol (3). The general procedure was followed with salicylaldehyde (**2**) (50 mg, 0.41 mmol). Purification by chromatography on silica (4:1 to 1:1 Hex:MTBE) gave **3** as a clear oil (60 mg, 89%). (R_f = 0.26 in 4:1 Hex:MTBE). *Spectral data matched that previously reported by Franco*:[27] IR (ATR) 3315, 2927, 1587, 1490, 1456, 1237, 1043, 751 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.18 (m, 1H), 6.98 (dd, J = 7.6, 1.6 Hz, 1H), 6.88 (dd, J = 8.2, 1.0 Hz, 1H), 6.84 (td, J = 7.6, 1.2 Hz, 1H), 5.85 (ddt, J = 21.0, 7.9, 6.4 Hz, 1H), 5.25-5.20 (m, 2H), 4.88 (dd, J = 8.6, 5.2 Hz, 1H), 2.68-2.55 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 155.5, 133.9, 129.0, 127.1, 126.3, 119.8, 119.5, 117.3, 74.7, 42. HRMS-TOF (ESI+) Calcd for $C_{10}H_{12}NaO_2$ (M + Na): 187.0729. Found 187.0722.

2-(1-hydroxybut-3-en-1-yl)-5-methoxyphenol. The general procedure was followed with 4- 2-hydroxy-4-methoxybenzaldehyde (50 mg, 0.33 mmol). Purification by chromatography on silica (4:1 to 1:1 Hex:EtOAc) gave the allylated product as an oil (56 mg, 87%). IR (ATR) 3370, 2983, 1736, 1709, 1373, 1239, 1041, 734 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.39 (dd, J = 8.4, 2.6 Hz, 1H), 5.83 (dddd, J = 17.7, 9.7, 8.0,

6.3 Hz, 1H), 5.23 – 5.19 (m, 2H), 4.83 (dd, *J* = 8.4, 5.1 Hz, 1H), 3.76 (s, 3H), 2.74 (bs, 1H), 2.64 – 2.54 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 160.4, 156.8, 133.9, 127.7, 119.3, 118.7, 105.8, 102.6, 74.3, 55.2, 42.2. HRMS-TOF (ESI+) Calcd for $C_{11}H_{14}NaO_3$ (M + Na): 217.0835. Found 217.0835.

5-bromo-2-(1-hydroxybut-3-en-1-yl)phenol. The general procedure was followed with 4-bromo-2-hydroxybenzaldehyde (50 mg, 0.25 mmol). Purification by chromatography on silica (4:1 to 1:1 Hex:EtOAc) gave the allylated product as a yellow oil (47 mg, 78%). IR (ATR) 3275, 1705, 1591, 1578, 1484, 1374, 1244, 1224, 1042, 880 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 6.96 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.82 (dddd, *J* = 16.9m 10.4, 7.9, 6.5 Hz, 1H), 5.25 (m, 1H), 5.23 (ddd, *J* = 10.0, 2.6, 0.9 Hz, 1H), 4.85 (ddd, *J* = 7.9, 5.3, 2.3 Hz, 1H), 2.66 (d, *J* = 2.6 Hz, 1H), 2.63 – 2.54 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 156.5, 133.3, 128.2, 125.1, 122.8, 122.0, 120.5, 120.0, 74.3, 42.1. HRMS-TOF (ESI+): Calcd for $C_{10}H_{10}BrO$ (M – H_2O + H): 224.9910. Found 224.9911.

5-chloro-2-(1-hydroxybut-3-en-1-yl)phenol. The general procedure was followed with 4-formyl-3-hydroxyphenyl acetate (50 mg, 0.28 mmol). Purification by chromatography on silica (4:1 to 1:1 Hex:EtOAc) gave the allylated product as a yellow oil (47 mg, 85%). IR (ATR) 3258, 2977, 1581, 1488, 1046, 988, 901, 735 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.89 (s, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.83 (dddd, *J* = 10.7, 3.0, 1.5 Hz, 1H), 4.87 (ddd, *J* = 7.7, 5.2, 1.8 Hz, 1H), 2.63 (d, *J* = 2.3 Hz), 2.61 – 2.56 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 156.4, 134.2, 133.4, 127.9, 124.7, 119.92, 119.89, 117.6, 74.3, 42.1. HRMS-TOF (ESI+): Calcd for $C_{10}H_{10}ClO$ (M – H_2O + H): 181.0415. Found 181.0415.

3-hydroxy-4-(1-hydroxybut-3-en-1-yl)phenyl acetate. The general procedure was followed with 4-chloro-2-hydroxybenzaldehyde (50 mg, 0.32 mmol). Purification by chromatography on silica

(4:1 to 1:1 Hex:EtOAc) gave the allylated product as a yellow oil (53 mg, 75%). IR (ATR) 3332, 2916, 2848, 1736, 1604, 1431, 1370, 1207, 1147, 975, 908 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 6.58 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.84 (dddd, *J* = 17.6, 9.6, 7.9, 6.4 Hz, 1H), 5.26 – 5.20 (m, 2H), 4.87 (dd, *J* = 8.4, 5.1 Hz, 1H), 2.72 (bs, 1H), 2.65 – 2.55 (m, 2H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.4, 156.6, 151.1, 133.7, 127.6, 123.9, 119.7, 112.8, 110.8, 74.3, 42.1, 21.1. HRMS-TOF (ESI+) Calcd for $C_{12}H_{14}NaO_4$ (M + Na): 245.0784. Found 245.0787.

4-Hydroxy-3-(1-hydroxybut-3-en-1-yl)benzaldehyde (5). The general procedure was followed with 4-hydroxyisophthalaldehyde (**4**) (0.10 g, 0.67 mmol). Purification by chromatography on silica (10:1 Hex:MTBE to 0:1 Hex:MTBE; R_f = 0.33 in 1:1 Hex:MTBE) giving **5** as a yellow solid (0.1 g, 78%). IR (ATR) 3177, 2925, 2848, 2753, 1659, 1583, 1433, 1385, 1282, 1201, 1042, 911, 867 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.70 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.84 (ddt, *J* = 17.0, 10.3, 7.2 Hz, 1H), 5.26-5.20 (m, 2H), 4.99 (t, *J* = 7.1 Hz, 1H), 2.64-2.60 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.9, 161.7, 133.1, 132.0, 129.0, 128.9, 126.8, 120.1, 17.9, 74.3, 42.3. HRMS-TOF (ESI+) Calcd for $C_{11}H_{12}NaO_3$ (M + Na): 215.0678. Found 215.0678.

General Procedure for Allylations of Glyoxylic Acids (α-oxocarboxylic acids, Figure 1). To a Schlenk flask containing a glyoxylic acid (1.0 eq.) in MeCN was added **1** (1.5 eq.) and the solution was heated to 80 °C for 6 h. MeCN was removed *in vacuo* and the products were redissolved in Et_2O. The solution was extracted with 1 M NaOH (15 mL x 2). The combined aqueous layers were then acidified to pH 1 with 1 M HCl, and extracted with EtOAc (20 mL x 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*.

2-Hydroxy-2-methyl-4-pentenoic acid. The general procedure was followed with pyruvic acid (100 mg, 1.1 mmol) as starting material giving the allylated product as an oil (89 mg, 60%). *Spectral data matched that previously reported by Kaur:*[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 18.1, 9.3, 7.3 Hz, 1H), 5.20-5.13 (m, 1H), 4.97-4.86 (m, 1H), 2.57 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.43 (dd, 13.9, 7.3 Hz, 1H), 1.47 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 180.9, 131.6, 119.9, 74.5, 44.3, 25.0.

2-Ethyl-2-hydroxy-4-pentenoic acid. The general procedure was followed with 2-oxobutyric acid (50 mg, 0.49 mmol). For easier purification and characterization purposes, the product was converted to its corresponding methyl ester: To a round bottom containing MeOH (2 mL) was added the crude allylated product and pTSA (7 mg, 0.03 mmol, 0.1 eq.). The solution was refluxed for 4 h, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by chromatography on silica (10:1 to 0:1 Hex:EtOAc; R_f = 0.24 in 10:1 Hex:EtOAc) afforded the methyl ester as an oil (56 mg, 72%). *Spectral data for the methyl ester matched that previously reported by Seto:*[29] ^{1}H NMR (500 MHz, C_6D_6) δ 5.88 (m, 1H), 5.05 – 4.98 (m, 2H), 3.24 (s, 3H), 2.36 (d, *J* = 7.2 Hz, 2H), 1.78 – 1.50 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 176.5, 132.3, 118.4, 77.9, 51.9, 44.0, 32.1, 8.0.

2-hydroxy-2-phenylpent-4-enoic acid. The general procedure was followed with phenyl glyoxylic acid (50 mg, 0.33 mmol) as starting material giving the allylated product as an oil (51 mg, 78%). *Spectral Data matched that previously reported by Howard:*[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.23 (d, *J* = 17 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 3.02 (dd, *J* = 13.8 Hz,

7.1 Hz, 1H), 2.81 (dd, J = 14.3, 6.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 178.9, 140.3, 131.8, 128.4, 128.0, 125.6, 120.1, 44.0.

2-benzyl-2-hydroxypent-4-enoic acid. The general procedure was followed with phenyl pyruvic acid (50 mg, 0.30 mmol) as starting material giving the allylated product as an oil (46 mg, 73%). For characterization purposes, the product was converted to its corresponding methyl ester: To a round bottom containing MeOH (1 mL) was added the allylated product (46 mg, 0.22 mmol, 1.0 eq.) and pTSA (4 mg, 0.02 mmol, 0.1 eq.). The solution was refluxed for 4 hr, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave the methyl ester as a pale yellow oil (R_f = 0.31 in 10:1 Hex:EtOAc). *Spectral data for the methyl ester:* IR (ATR) 2954, 1731, 1602, 1436, 1213, 1053, 974, 812, 701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3H), 7.18 (m, 2H), 5.82 (dddd, J = 17.1, 10.3, 7.7, 6.8 Hz, 1H), 5.16-5.11 (m, 2H), 3.72 (s, 3H), 3.06 (d, J = 13.2 Hz, 1H), 2.95 (d, J = 13.6 Hz, 1H), 2.62 (ddt, J = 13.9, 7.6, 1.0 Hz, 1H), 2.50 (ddt, J = 13.8, 7.1, 1.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 175.5, 135.6, 132.3, 129.9, 128.2. 126.9, 118.9, 78.2, 52.5, 45.1, 43.5. HRMS-TOF (ESI+) Calcd for $C_{12}H_{14}NaO_3$ (M + Na): 229.0835. Found 229.0835.

2-hydroxy-2-(1-phenylethyl)pent-4-enoic acid. The general procedure was followed with 2-oxo-3-phenylbutanoic acid as starting material (50 mg, 0.28 mmol) and gave the allylated product as an oil (45 mg, 71%; d.r. 2.1). For characterization purposes, the product was converted to its corresponding methyl ester: To a round bottom containing MeOH (1 mL) was added the allylated product (32 mg, 0.14 mmol, 1.0 eq.) and pTSA (3 mg, 0.02 mmol, 0.1 eq.). The solution was refluxed for 4 h, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organic phase was dried with $MgSO_4$, filtered, and concentrated *in*

vacuo. Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave the methyl ester as a pale yellow oil (R_f = 0.35 in 10:1 Hex:EtOAc). *Spectral data for the mixture of diastereomeric methyl esters:* IR (ATR) 2955, 1732, 1606, 1436, 1265, 1170, 830, 734 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 10H), 5.76 (ddt, *J* = 21.3, 8.4, 6.4 Hz, 1H), 5.66 (ddt, *J* = 20.6, 8.3, 6.5 Hz, 1H), 5.15-5.07 (m, 2H), 5.04-4.96 (m, 2H), 3.81 (s, 3H), 3.57 (s, 3H), 3.16-3.10 (m, 2H), 2.69 (ddt, *J* = 13.8, 6.3, 1.5 Hz, 1H), 2.49 (ddq, *J* = 13.9, 8.3, 1.1 Hz, 1H), 2.35 (ddd, *J* = 13.9, 8.3, 0.81 Hz, 1H), 2.03 (ddt, *J* = 13.9, 6.3, 1.4 Hz, 1H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 176.5, 175.7, 142.1, 141.5, 132.9, 132.8, 130.1, 129.2, 128.6, 128.3, 128.1, 127.6, 127.5, 127.0, 126.9, 118.7, 118.6, 80.3, 80.2, 52.9, 52.3, 46.7, 46.6, 42.8, 41.7, 16.5, 14.6. HRMS-TOF (ESI+) Calcd for $C_{14}H_{18}NaO_3$ (M + Na): 257.1154. Found 257.1158.

2-Allyl-2-hydroxy-4-phenyl-3-butenoic acid. The general procedure was followed with (E)-2-oxo-4-phenylbut-3-enoic acid (50 mg, 0.28 mmol) as starting material. For easier purification, the crude product was converted to the corresponding methyl ester: To a solution of the crude product in MeOH/DCM (3 mL, 1:1) at room temperature was added $TMSCHN_2$ (0.6 M, 0.56 mL, 0.34 mmol, 1.2 eq.) dropwise over 10 min. After stirring for 20 min, additional $TMSCHN_2$ (0.6 M, 0.28 mL, 0.17 mmol, 0.6 eq.) was added.After stirring for an additional 10 min the reaction was quenched with AcOH (0.10 mL) and diluted with toluene (0.5 mL) and the solvent was removed *in vacuo.* Purification by chromatography on silica (10:1 to 4:1 Hex:EtOAc) gave the methyl ester as an oil (51 mg, 78%). *Spectral data for the methyl ester:* IR (ATR) . ^1H NMR (500 MHz, $CDCl_3$) δ. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ. HRMS-TOF (ESI+) Calcd for $C_{14}H_{16}NaO_3$ (M + Na): 255.0992. Found 255.0994.

2-Allyl-[4-(2-Furanyl)]-2-hydroxy-3-butenoic acid. The general procedure was followed with (E)-4-(furan-2-yl)-2-oxobut-3-enoic acid (50 mg, 0.30 mmol). For easier purification and

characterization purposes, the product was converted to its corresponding *tert*-butyl diphenyl silyl ester: To a Schlenk flask was added DCM (3 mL) and the crude allylated product at 0 °C. Hünig's base (0.13 mL, 0.75 mmol, 2.5 eq.) was added followed by *tert*-butyl(chloro)diphenylsilane (165 mg, 0.19 mmol, 2.0 eq.) and the solution was allowed to warm to room temperature with stirring for 15 h. The reaction was quenched with H_2O (10 mL) and extracted with DCM (10 mL x 3). Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc; R_f = 0.68 in 10:1 Hex:EtOAc) gave the silyl ether/ester as a clear oil (127 mg, 62%). *Spectral data for the bis-silyl derivative:* IR (ATR) 2930, 2857, 1742, 1427, 1259, 1106, 734, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.6 Hz, 2H), 7.63 (d, *J* = 6.6 Hz, 2H), 7.57 (d, *J* = 6.8 Hz, 2H), 7.55 (d, *J* = 6.7 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.35 – 7.26 (m, 6H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 2H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.28 (d, *J* = 16.1 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 6.00 (d, *J* = 3.3 Hz, 1H), 5.95 (m, 1H), 5.11 – 5.04 (m, 2H), 2.73 (dd, *J* = 14.1, 7.5 Hz, 1H), 2.62 (dd, *J* = 14.1, 6.4 Hz, 1H), 1.04 (s, 9H), 1.02 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.7, 152.1, 142.2, 136.3, 136.1, 135.4, 135.32, 135.29, 135.26, 135.1, 132.7, 131.6, 131.5, 129.9, 129.0, 128.7, 127.71, 127.69, 127.66, 127.58, 127.57, 126.99, 126.96, 119.8, 118.8, 111.2, 108.5, 81.0, 44.0, 27.5, 26.9, 19.9, 19.1. HRMS-TOF (ESI+) Calcd for $C_{43}H_{48}NaO_4Si_2$ (M + Na): 707.2989. Found 707.2978.

(3*E*)-2-Allyl-4-(4-formylphenyl)-2-hydroxy-3-butenoic acid (7). The general procedure was followed with **6** (0.10 g, 0.49 mmol). For easier purification, compound **7** was converted to its corresponding methyl ester: To a solution of crude **7** in MeOH/DCM (8.4 mL, 1:1) at room temperature was added $TMSCHN_2$ (0.51 mL, 1.02 mmol, 1.2 eq.) dropwise over 10 min. After stirring for 20 min, additional $TMSCHN_2$ (0.25 mL, 0.51 mmol, 0.6 eq.) was added. After stirring for an additional 10 min, a third addition of $TMSCHN_2$ (0.13 mL, 0.25 mmol, 0.3 eq.) was added, and the solution stirred for 5 min. The reaction was quenched with AcOH (0.10 mL) and diluted

with toluene (0.38 mL) and the solvent was removed *in vacuo.* Purification by chromatography on silica (10:1 to 4:1 Hex:EtOAc; R_f = 0.28 in 4:1 Hex:EtOAc) gave the methyl ester as a pale yellow oil (96 mg, 75%). *Spectral data for the methyl ester:* IR (ATR) 2954, 1731, 1697, 1602, 1436, 1213, 1053, 974, 812, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 15.5 Hz, 1H), 6.49 (d, *J* = 14.6 Hz, 1H), 5.79 (dddd, *J* = 14.5, 9.7, 7.7, 6.8 Hz, 1H), 5.19-5.13 (m, 2H), 3.82 (s, 3H), 2.68 (ddt, *J* = 13.9, 7.9, 1.1 Hz, 1H), 2.54 (ddt, *J* = 13.5, 6.9, 1.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.7, 174.5, 142.3, 135.6, 132.9, 131.6, 130.1, 129.2, 127.2, 119.7, 53.3, 44.0. HRMS-TOF (ESI+) Calcd for $C_{15}H_{17}O_4$ (M + H): 261.1121. Found 261.1120.

2-(4-formylphenyl)-2-hydroxypent-4-enoic acid (9). To a Schlenk flask containing MeCN (14 mL) was added siletane **13** (0.11 g, 0.31 mmol, 1.1 eq.) and **8** (50 mg, 0.28 mmol, 1.0 eq.) and the resulting mixture was allowed to stir for 1 h at room temperature before being heated to 80 °C for 6 h. The reaction was then cooled to room temperature and solvent was removed by rotary evaporator. The resulting product was redissolved in THF (2.8 mL) and TBAF (0.90 mL, 0.90 mmol, 3.0 eq.) was added and the mixture was stirred at room temperature for 30 min. The reaction was quenched with aq. NH_4Cl (20 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* For easier purification and characterization purposes, **9** was converted to its corresponding methyl ester: To a solution of crude **9** in DCM/MeOH (3.0 mL, 1:1) at room temperature was added $TMSCHN_2$ (0.56 mL, 0.34 mmol, 1.2 eq.) dropwise over 10 min. After stirring for 20 min, additional $TMSCHN_2$ (0.28 mL, 0.17 mmol, 0.60 eq.) was added. After stirring for an additional 10 min, a third addition of $TMSCHN_2$ (0.17 mL, 0.085 mmol, 0.30 eq.) was added, and the solution stirred for 5 min. The reaction was quenched with AcOH (0.03 mL), and diluted with toluene (0.01 mL) before

concentrating *in vacuo.* Purification by chromatography on silica (4:1 to 1:1 Hex:EtOAc; R_f = 0.6 in 1:1 Hex:EtOAc) gave the methyl ester as a clear oil (42 mg, 64%). *Spectral data for the methyl ester:* IR (ATR) 3496, 2955, 1732, 1699, 1606, 1436, 1265, 1170, 830, 734 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89-7.86 (m, 2H), 7.81-7.78 (m, 2H), 5.76 (ddt, *J* = 20.5, 7.5, 6.8 Hz, 1H), 5.20-5.13 (m, 2H), 3.8 (s, 3H), 2.98 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.77 (ddt, *J* = 11.7, 6.9, 1.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.8, 174.3, 147.6, 135.8, 131.6, 129.6, 126.4, 119.9, 78.1, 53.6, 44.3. HRMS-TOF (ESI+) Calcd for $C_{13}H_{14}NaO_4$ (M + Na): 257.0784. Found 257.0779.

(8S,9S,10R,13S,14S,17R)-17-(1,2-dihydroxypent-4-en-2-yl)-17-hydroxy-10,13-dimethyl-1,6,7,8,9,10,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthrene-3,11(2H)-dione (14). To a solution of cortisone (100 mg, 0.28 mmol, 1 eq.) in MeCN (2.8 mL) was added siletane **13** (190 mg, 0.55 mmol, 2.0 eq.) and the mixture was heated to 80 ºC for 6 h. The solution was then cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography on silica (5% MeOH/DCM) gave **14** (99 mg, 88%) as a white solid (mp. 88.6 – 89.5 ºC). $[\alpha]_D^{20}$ = 97.25 (*c* 0.8, MeOH). IR (ATR) 3383, 2930, 1697, 1645, 1632, 1231, 987, 972 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 16.0, 10.0, 7.9 Hz, 1H), 5.72 (s, 1H), 4.97 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.92 (ddt, 0.9, 1.7, 10.0 Hz, 1H), 3.96 (dd, *J* = 10.9, 1.1 Hz, 1H), 3.87 (d, *J* = 10.9 Hz, 1H), 2.85 (d, *J* = 12.7 Hz, 1H), 2.78 (ddd, *J* = 13.7, 5.1, 3.2 Hz, 1H), 2.49 (dd, *J* = 14.8, 5.0 Hz, 1H), 2.46 (dd, *J* = 14.3, 4.7 Hz, 1H), 2.44 (*J* = 11.9 Hz, 1H), 2.41 – 2.25 (m, 2H), 2.00 – 1.80 (m, 6H), 1.74 – 1.59 (m, 3H), 1.41 (s, 3H), 1.35 – 1.20 (m, 2H), 0.94 (s, 3H), 0.79 (dtd, *J* = 18.0, 10.2, 4.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 211.0, 199.9, 169.1, 131.4, 124.5, 115.7, 90.4, 75.9, 70.6, 62.5, 53.3, 52.4, 49.5, 45.7, 38.1, 36.3, 34.8, 33.7, 22.8, 21.5, 19.6, 17.2, 16.9, 14.1. HRMS-TOF (ESI+) Calcd for $C_{24}H_{35}O_5$ (M + H): 403.2484. Found 403.2482.

(8S,9S,10R,11S,13S,14S,17R)-17-(1,2-dihydroxypent-4-en-2-yl)-11,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-one (15). To a solution of hydrocortisone (100 mg, 0.28 mmol, 1 eq.) in MeCN (5.5 mL) was added siletane **13** (120 mg, 0.55 mmol, 2.0 eq.) and the mixture was heated to 80 ºC for 8 h. The solution was then cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography on silica (5% MeOH/DCM) gave **15** (100 mg, 90%) as a white solid (mp. 249.5 – 251.0 ºC). $[\alpha]_D^{20}$ = 47.20 (*c* 1.0, MeOH). IR (ATR) 3430, 2927, 1651, 1108, 1040, 948 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 17.1, 10.1, 7.6 Hz, 1H), 5.67 (s, 1H), 4.96 (dq, *J* = 17.0, 1.0 Hz, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.44 (m, 1H), 4.02 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.92 (d, *J* = 10.3 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.41 – 2.30 (m, 2H), 2.30 – 2.16 (m, 2H), 2.12 (dd, *J* = 14.0, 2.5 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.92 – 1.83 (m, 2H), 1.81 – 1.53 (m, 3H), 1.47 (s, 3H), 1.37 – 1.05 (m, 4H), 1.25 (s, 3H), 1.05 – 0.92 (m, 2H), 0.79 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 199.8, 172.7, 131.6, 122.3, 115.4, 91.1, 76.5, 71.0, 68.8, 56.2, 51.5, 48.0, 45.1, 42.7, 39.2, 35.0, 33.8, 31.1, 23.2, 21.7, 20.9, 19.7, 18.9, 14.4. HRMS-TOF (ESI+) Calcd for C24H37O5 (M + H): 405.2636. Found 405.2628.

NMR Calculations. The evaluation of Boltzmann-averaged ^{13}C and ^1H magnetic shielding tensors and isotropic chemical shifts from density functional theory (DFT) followed Hoye's protocol[25] adapted as follows. For the two candidate diastereomers, we applied the ETKDG conformational search algorithm[31] as implemented in RDKit[32] to obtain nine low-energy conformations of each structure which were then optimized at the B3LYP/6-31G* level of theory[33] together with the PCM implicit solvent model[34] with dielectric constant ε = 4.81 as implemented in Q-Chem 5.1.[35] NMR shielding tensors were evaluated using gauge-including atomic orbitals (GIAOs)[36,37] at the same B3LYP/6-31G*/PCM level for each optimized conformer, and shielding

tensors were Boltzmann-averaged to obtain ^{1}H and ^{13}C isotropic chemical shifts relative to those predicted for TMS at the same level of theory. Further discussion of the stereocenter assignment based on these data is provided in the Supporting Information.

Conformational Analysis. To better understand the chemoselectivity highlighted in Scheme 7, a relaxed potential energy scan on a model cortisone compound was performed at the B3LYP/6-31G*/PCM level of theory in Q-Chem 5.1.[34] In the model compound, the C and D rings were preserved to retain the integrity of steric interactions near the new stereocenter while the A and B rings were replaced with simpler cyclohexane units. Along this scan, the C_{16}-C_{17}-C_{20}-C_{21} dihedral angle was constrained in increments of 10° while allowing all other degrees of freedom to relax through geometry optimization.

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Supporting Information Available: Copies of ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra; comparison of experimental and simulated NMR chemical shifts; potential energy scan of model cortisone compound. This material is available free of charge via the internet at http://pubs.acs.org

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