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^{13}C NMR Analysis of 3,6-Dihydro-2*H*-pyrans: Assignment of Remote Stereochemistry Using Axial Shielding Effects

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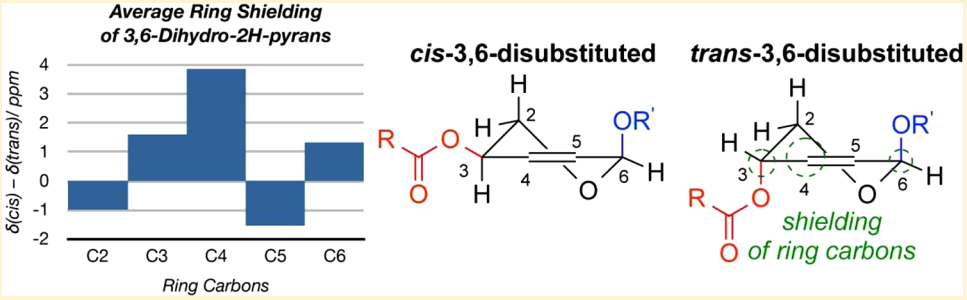
Supporting Information



ABSTRACT: The rational analysis of ^{13}C NMR axial shielding effects has enabled the assignment of remote relative stereochemistry in 3,6-oxygen-substituted 3,6-dihydro-2*H*-pyrans. Comparison of the ^{13}C NMR shifts of equivalent centers in *cis*- and *trans*-substituted 3,6-dihydro-2*H*-pyrans allows the relative configuration at the C3 and C6 positions to be defined in diastereoisomeric mixtures. Density functional calculations were used to validate this method and assess the conformational bias present in the ring system. Ultimately, the coupling of computational chemistry with this ^{13}C NMR-based method provided a reliable and convenient method for stereochemical assignment of a single diastereomer. This approach provides a facile and complementary alternative to the practices previously employed for determining the relative configuration in 3,6-dihydro-2*H*-pyrans.

INTRODUCTION

Relative stereochemical relationships can have a profound effect on the chemical and physical properties of a compound.[1] Complex molecules often exhibit remarkable differences in biological activity, reactivity, and catalysis with the inversion of a single stereocenter. The assignment of atom connectivity and spatial arrangement is, therefore, of fundamental importance, and NMR spectroscopy has emerged as a powerful tool for structure elucidation.[2] However, a number of structural motifs still prove particularly challenging and laborious to assign.[3] The distinctive structural properties of substituted 3,6-dihydro-2*H*-pyrans (i.e., **1**, Figure 1) represent just such a challenge,[4] and new methods for NMR-based analysis[5] are needed to facilitate the use of these valuable "synthons" in chemical research.

The utility of 3,6-dihydro-2*H*-pyrans stems in part from their facile preparation in enantioenriched form and wide range of potential reactivity (Figure 1). Enantioenriched 3,6-dihydro-2*H*-pyrans can be prepared from a variety of sources, including chiral allylic sulfoxides (**2**),[6] furfuryl alcohols (**3**),[7] glycals (**4**)[8] and *gem*-dichlorocyclopropyl-fused furans (**5**),[9] as well as by enzymatic kinetic resolution.[10] This heterocyclic motif is present in a number of natural products, such as aspergillide C (**6**),[11] and also serves as a robust synthetic intermediate.[12] The versatility of 3,6-dihydro-2*H*-pyrans has enabled the synthesis of a number of important synthetic targets such as the hNK-1 receptor antagonist **7**,[13] ethyl deoxymonate B (**8**),[14] and dysiherbaine (**9**).[15] However, the utility of 3,6-dihydro-2*H*-

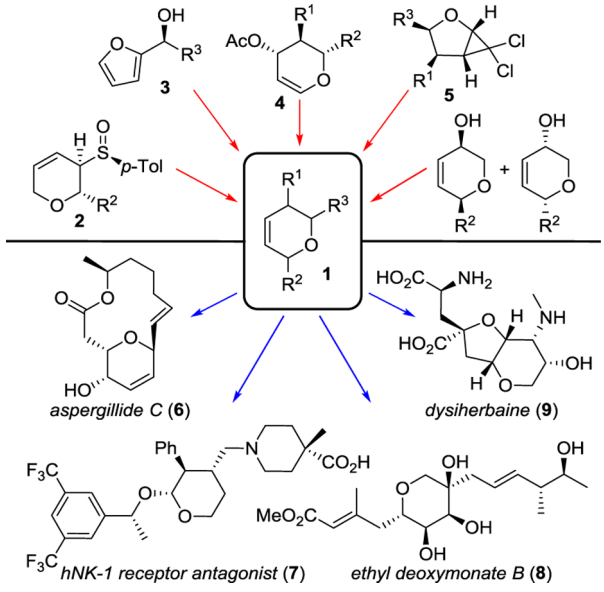


Figure 1. Synthesis and utility of 3,6-dihydro-2*H*-pyrans.

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pyrans is often impeded by the challenging task of assigning the relative orientation of two substituents located on opposite sides of the ring system. Furthermore, they are often isolated as mixtures of diastereoisomers, which may or may not be separable. Previously, methods based on X-ray crystallography, derivatization, or ^{1}H NMR spectroscopy, particularly $^3J_{H,H}$ coupling constants and NOE correlations, have been employed to assign the stereochemistry of 3,6-disubstituted systems.[16] However, these methods require extra steps or are dependent on resolution of the ^{1}H NMR signals for the ring protons and determination of their coupling constants. A complementary spectroscopic tool for assigning the relative configuration of such compounds would be highly beneficial. Herein, we report a facile approach to the assignment of remote relative stereochemistry across the pyran ring system through rational analysis of axial shielding effects on ^{13}C NMR shifts.

RESULTS AND DISCUSSION

Our recent development of a nonsymmetric palladium-catalyzed allylic substitution cascade for the synthesis of, inter alia, furo[3,2-*c*]pyrans led us to prepare both diastereomers of dihydropyran **10a** as synthetic intermediates (Figure 2).[17]

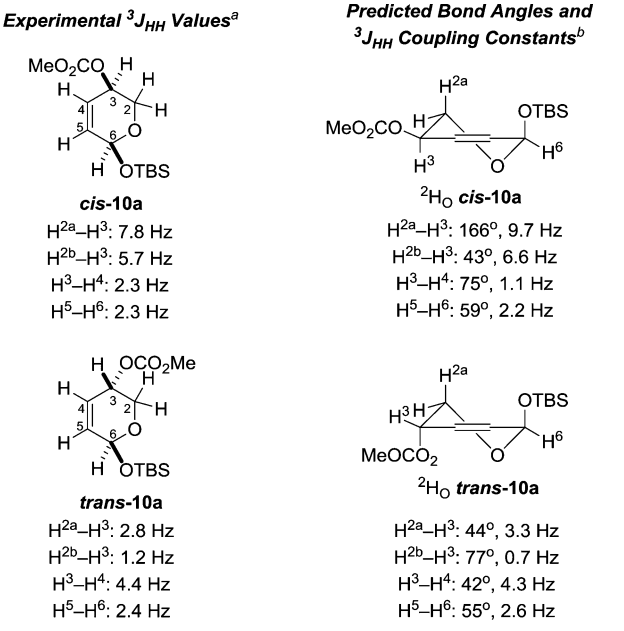

Figure 2. Challenges in the structural assignment of **10a** by ^{1}H NMR spectroscopy.[a]Coupling constants were obtained by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$); all signals were fully assigned by 2D NMR correlations (^{1}H–^{1}H COSY and HSQC). [b]Geometry optimization was performed on the lowest energy half-chair conformer of ***cis***- and ***trans*-10a** using Gaussian '09[21] (mPW1PW91, TZVP) and $^3J_{H,H}$ values were calculated using a modified Karplus equation.[22]

While the synthetic methods used provided reasonable assurance of the stereochemical identity of the two isomers, preliminary NMR analysis did not allow definitive confirmation of the relative configurations at C3 and C6, as the presence of the alkene and ring oxygen cause ambiguity in the through-space interactions across the ring and limit what can be determined from NOE correlation.[18] Previously, $^3J_{HH}$ values have been employed for defining relative configurations in similar systems,[16d,f−i] and our observed coupling constants were consistent with those reported. However, the complexity of the multiplets and the small magnitude of several of the coupling constants lent some uncertainty to the assignments. Additionally, the correlation of these values with the coupling constants calculated for the lowest energy conformations of the 3,6-*cis*- and -*trans*-isomers, the half-chairs ^2H_O, was only modest (Figure 2).[19,20] In particular, the coupling constants observed for H^{2a}-H^3 in ***cis*-10a** and H^{2b}-H^3 in ***trans*-10a** were not completely consistent with those calculated by geometry optimization and subsequent use of the derived dihedral angles in a modified Karplus equation.[22] Together with the lack of pertinent NOE correlations, these discrepancies in observed and calculated coupling constants indicated that the ^{1}H NMR spectroscopic assignment of stereochemistry in substituted 3,6-dihydro-2*H*-pyrans prepared by other methods could be ambiguous. Furthermore, assignment of coupling constants in poorly resolved proton NMR spectra, including those of mixtures containing two inseparable stereoisomers, would be even more challenging. In order to mitigate these problems, we sought to apply ^{13}C NMR shielding by axial substituents to the simple and reliable assignment of relative configuration in 3,6-disubstituted 3,6-dihydro-2*H*-pyrans.

^{13}C NMR spectroscopy has been used previously to deduce the stereochemistry of highly substituted ring systems, such as carbohydrates and inositols.[23] For example, comparing the spectra of two inositol diastereomers, *scyllo*- (**11**) and *myo*-inositol (**12**), illustrates the shielding effects of an axial hydroxyl group on the carbons within the ring system (Figure 3a). Thus,

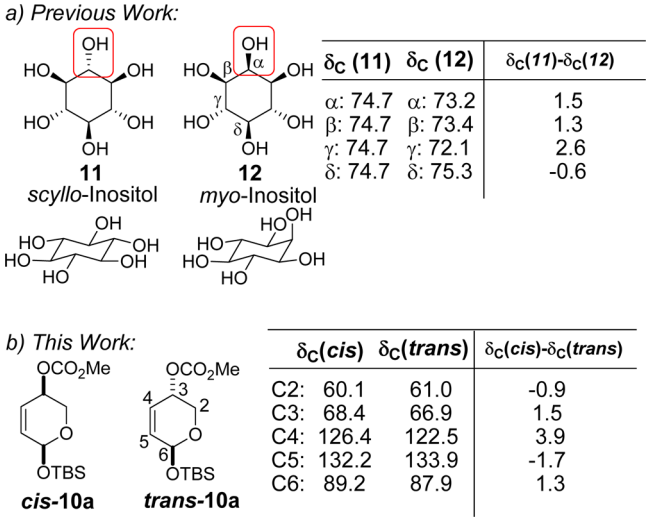

Figure 3. Axial shielding effects on inositol[23] and 3,6-dihydro-2*H*-pyran diastereomers.

the *α*-, *β*-, and *γ*-carbons of *myo*-inositol are relatively shielded by the presence of its axial OH group, while the *δ*-position is slightly deshielded. These observations have been referred to as the *γ*-substituent effect, as a result of the particularly large difference in the chemical shift of the *γ*-carbon relative to the other positions.[24] ^{13}C NMR resonances are influenced by the complex interplay of steric effects, hyperconjugation, and electronic motion present in a given molecule,[25] and therefore, the distorted geometry and polarization of a 3,6-dihydro-2*H*-pyran ring result in a significantly different ring-shielding pattern relative to that observed with the inositol diastereomers (Figure 3b). Thus, the C3, C4, and C6 positions of ***trans*-10a** are shielded relative to ***cis*-10a**, while C2 and C5 are deshielded. In order to interpret the ^{13}C shielding effects of pseudoaxial

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substituents on a 3,6-dihydro-2*H*-pyran ring, the conformational bias of the ring system must be ascertained.[26]

In compounds of type ***cis***- and ***trans*-10**, the planar alkene and divalent oxygen remove several potential 1,3-diaxial interactions between substituents, leaving only the C2 and C6 substituents with the possibility of such a steric interaction (Figure 4). Electronegative substituents at the allylic position of

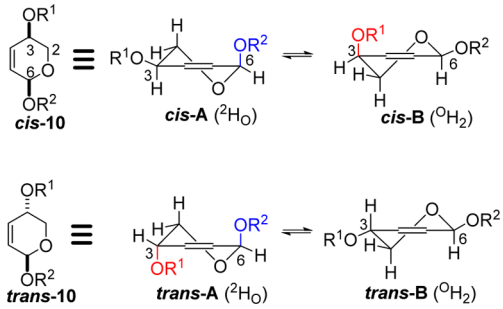

Figure 4. Anomeric (blue) and allylic (red and blue) effects in the conformational preference of 3,6-disubstituted 3,6-dihydro-2*H*-pyrans **10**.

an unsaturated ring have been shown to have a preference for axial orientation, a phenomenon referred to as the allylic effect.[27] This effect is analogous to the anomeric effect, also present here, and is a result of stereoelectronic stabilization via delocalization of electron density from the π-bond into the σ^* orbital of the exocyclic C−X bond. Therefore, for the 3,6-*trans*-diastereomer ***trans*-10**, the combination of favorable anomeric and allylic effects, along with the absence of 1,3-diaxial interactions led us to postulate that the diaxial conformer ***trans*-A** ($^{O}H_2$) should be preferred. Hence, ***trans*-10a** would exhibit a high degree of conformational homogeneity (Figure 4). Alternatively, competition between allylic and anomeric effects in the 3,6-*cis*-diastereomer ***cis*-10** is likely to result in a greater amount of conformational heterogeneity.[28] This conformational hypothesis is supported by the ^{1}H NMR spectra of the diastereomeric pyrans, ***cis***- and ***trans*-10a** (Figure 5). The 3,6-*trans* diastereomer contains diastereotopic protons at C2 that are significantly differentiated. This suggests that one proton resides primarily in the sterically more congested pseudoaxial position in ***trans*-10a**. Based on the chemical shift and coupling values relative to the calculated coupling constants (viz. Figure 2), and the apparent presence of W-coupling in the upfield signal at δ 3.91, it is postulated that the signal at δ 4.21 is the proton in the pseudoaxial position. The ^{1}H NMR spectrum of the 3,6-*cis* diastereomer shows that the oxymethylene peaks have much greater chemical shift similarity. Their appearance as an overlapping multiplet suggests a higher degree of conformational heterogeneity, although additional factors may also contribute.[29]

Observed ^{13}C chemical shifts represent a weighted average of conformers, and therefore, the magnitude of any axial shielding is dependent on the conformational distribution of a compound. For ***trans*-10a**, which is proposed to have a strong preference for the diaxial conformation (***trans*-A**), ^{13}C NMR shielding effects from both substituents are expected. Alternatively, ***cis*-10a**, with a greater amount of conformational heterogeneity and a single axial substituent in each conformer, should experience less shielding of the ring carbons. Subtracting the chemical shifts of ***trans*-10a** from those of ***cis*-10a** (Figure 3b) provided a means of evaluating the magnitude of additional shielding on each ring carbon in the *trans*-isomer. As seen earlier (Figure 3b), the substituted centers, C3 and C6, were shielded in the *trans*-isomer, as was C4. In contrast, C2 and C5 were relatively shielded in the *cis*-isomer. Doboszewski et al. also noted shielding of C2 in *cis*-isomers of purine- and pyrimidine-linked dihydropyrans and put this down to increased steric congestion in the region.[16k] The shielding of C4 in the *trans*-isomer is substantial (ca. 4 ppm), which may be rationalized by considering the stereoelectronic impact of the axial C3 substituent in ***trans*-A** on the neighboring π-system, which is not present for ***cis*-10a** in its presumably preferred conformer ***cis*-A** (due to the combination of anomeric and axial stabilization from the C6 substituent).

The shielding pattern seen for *cis*- and *trans*-**10a** provides the basis of a template for the assignment of relative configuration in similar 3,6-dihydro-2*H*-pyrans with electronegative substituents at C3 and C6. To extend the predictive ability of the template, a range of diastereomeric pairs were investigated

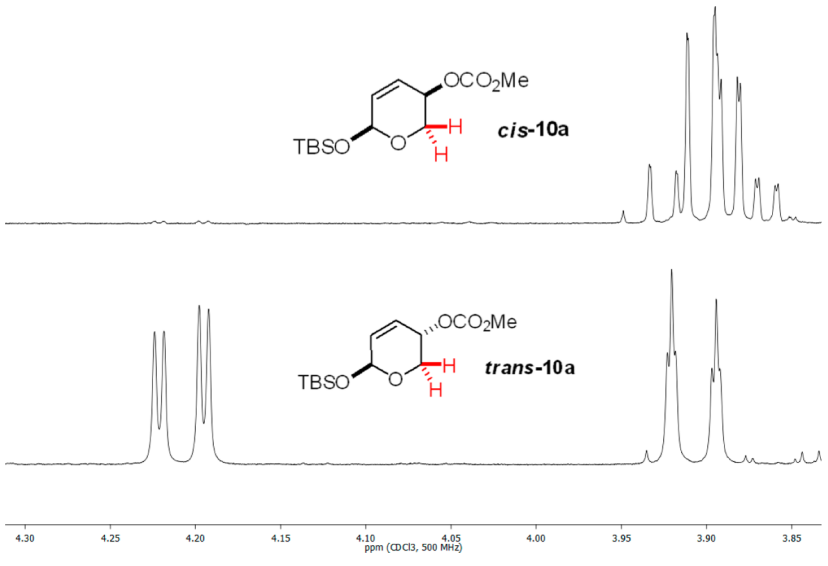

Figure 5. Relative differentiation of C2 proton signals in ***trans*-10a** compared to ***cis*-10a** provides conformational insights.

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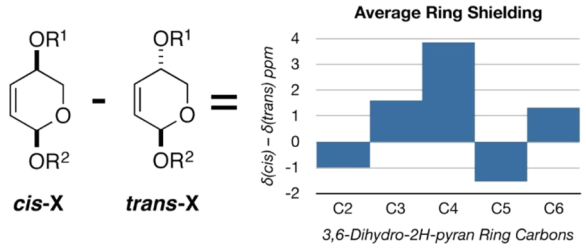
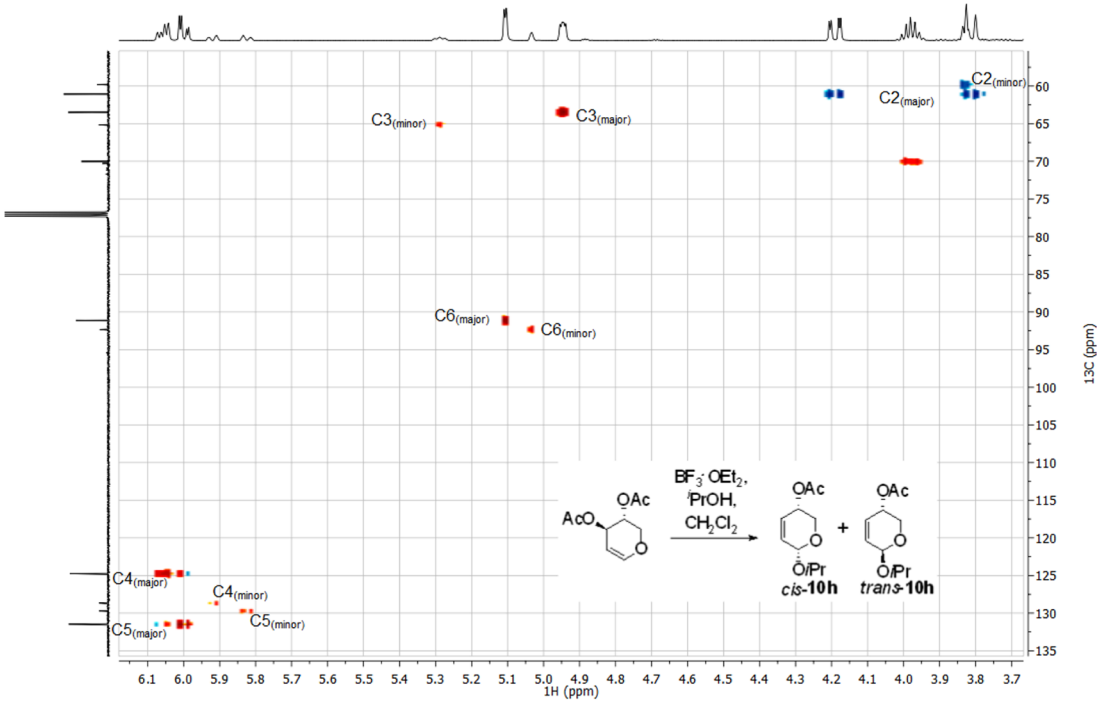
Table 1. Development of a ^{13}C Shielding Template for Compounds of Type *cis*- and *trans*-10



	substituents		$\delta(cis\text{-X}) - \delta(trans\text{-X})^a$ (ppm)				
X	R^1	R^2	C2	C3	C4	C5	C6
10a	CO_2Me	TBS	−0.9	1.5	3.9	−1.7	1.3
10b	Ac	TBS	−0.6	1.5	3.7	−1.2	1.5
10c	Ac	*n*Pr	−1.1	1.6	3.8	−1.6	1.4
10d	Ac	allyl	−1.2	1.7	3.9	−1.7	1.3
10e	Ac	CH_2CCH	−1.5	1.8	4.2	−1.9	1.0
10f[b]	Ac	CH_2Ph	−1.3	1.7	4.2	−1.6	1.3
10g[b]	CO_2Me	H	−0.1	1.5	3.4	−1.0	1.6
	avg $\Delta\delta_C$		−1.0	1.6	3.9	−1.5	1.3
	standard deviation		0.48	0.12	0.28	0.31	0.19

[a]Standard conditions: ^{13}C NMR (125 MHz, $CDCl_3$) chemical shifts were measured relative to chloroform. All carbon assignments are based on COSY and HSQC spectra. A full table of ^1H and ^{13}C NMR assignments can be found in the Supporting Information. [b]Diastereomers were not separated prior to NMR analysis.



	δ_c /ppm minor	major	$\Delta\delta_C$
C2	59.8	61.1	-1.3
C3	65.1	63.5	1.6
C4	128.7	124.8	3.9
C5	129.7	131.5	-1.8
C6	92.3	91.1	1.2

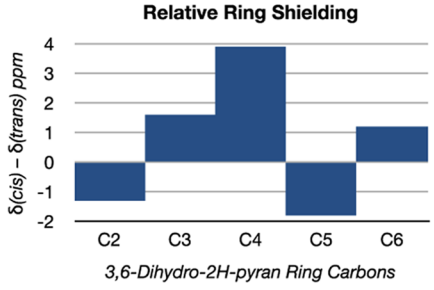


Figure 6. Worked example showing assignment of relative configuration using the axial shielding template: Ferrier reaction of 3,4-di-*O*-acetyl-D-xylal to form *cis*- and *trans*-**10h**.

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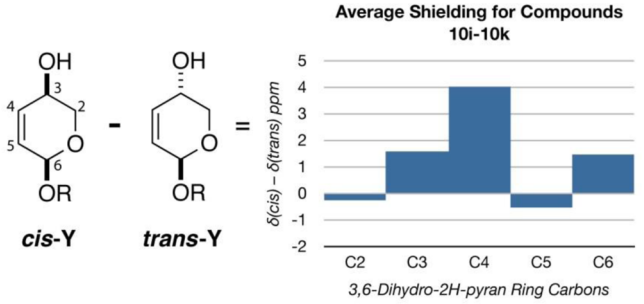
(Table 1). These compounds, bearing ester or carbonate functions at C3, are relevant as structural motifs obtained by Ferrier-type reactions. In general, substrates with oxygen-tethered substituents at C3 and C6 fit all five positions of the template very well. Particular consistency in the $\Delta\delta_C$ at the C3 and C6 positions was observed, with standard deviations from the mean of 0.12 and 0.19, respectively. The largest variation in shielding value was seen at C2, which had a standard deviation of 0.48 from the mean. The remaining positions were fairly consistent, with standard deviations around 0.3. As a note of caution, the varying inductive and steric effects of the different substituents, R^1 and R^2, caused significant changes in the magnitude of the ^{13}C chemical shifts for the respective ring carbons and, in some cases, even changed the relative order of the chemical shifts for C4 and C5. This meant that no reliable conclusions should be drawn from an isolated ^{13}C resonance. Despite this variance in net chemical shift, the relative difference between *cis*- and *trans*-isomers remains relatively constant and may be used to evaluate axial shielding. The resulting ^{13}C shielding template, shown in Table 1, provides a facile method by which the relative configuration of disubstituted 3,6-dihydro-2*H*-pyrans can be assigned. This approach is particularly useful in determining the direction of stereoselectivity in transformations such as the Ferrier reaction,[8] demonstrated in Figure 6 for the reaction of 3,4-di-*O*-acetyl-D-xylal with 2-propanol. In this case, a 3:1 mixture of diastereomers was obtained, and the ^{13}C NMR resonances for the ring carbons of each diastereomer were readily assigned from the HSQC spectrum. Subtracting the ^{13}C NMR resonances of each ring carbon in the major product from those of their diastereomeric counterpart revealed a magnitude pattern of axial shielding. These five values were then compared to, and found to closely match, the shielding template from Table 1, thus confirming that the major product from this reaction is ***trans*-10h**.

Given the propensity of certain carbons in the dihydropyran ring to vary more than others, the standard deviation for each ring carbon obtained from the template development can be used to establish confidence levels and evaluate how well two diastereomers match the shielding template. Any relative difference in chemical shift that falls within the standard deviation of a given ring carbon (i.e., C2: −1.0 ± 0.48, C3: 1.6 ± 0.12, C4: 3.9 ± 0.28, C5: −1.5 ± 0.31, C6: 1.3 ± 0.19) has an excellent match to the shielding template, while a chemical shift difference within twice the standard deviation represents a very good match. (A table outlining the three confidence levels can be found in the Supporting Information, SI Table 2, along with examples of compounds that do not fit the shielding template.) These scenarios provide strong evidence for a given relative stereochemical configuration. Additionally, the analysis of five discrete shielding values serves to both reinforce any stereochemical conclusions and enable the rapid detection of anomalies and inconsistencies. To a certain extent, this provides a safeguard against the mis-assignment of relative configuration. One such anomaly was observed in compounds containing a C3 hydroxyl group (Table 2). There was greater variability in the chemical shift differences than seen in the earlier set of compounds with electron-withdrawing groups at C3. The average chemical shift difference for ring carbons C2, C3, C4, and C6 of compounds **10i−k** displayed excellent or very good fit with the shielding template, whereas C5 did not provide a good match.

Table 2. ^{13}C Shielding Effects in C3-Hydroxy Compounds 10i−k



		δ(*cis*-Y) − δ(*trans*-Y)[a] (ppm)				
Y	R	C2	C3	C4	C5	C6
template value[b]		−1.0	1.6	3.9	−1.5	1.3
10i	TBS	0.3	1.5	3.3	−0.1	1.7
10j[c]	*i*Pr	−0.5	1.6	5.0	−0.7	1.4
10k	allyl	−0.5	1.6	3.8	−0.7	1.3
	avg	−0.2	1.6	4.0	−0.5	1.5

[a]Standard conditions from Table 1 apply. [b]Average values of **10a−g** from Table 1. [c]Diastereomers were not separated prior to NMR analysis.

To extend the utility of this methodology, the use of complementary computational methods was investigated with the aim of ultimately enabling stereochemical assignment using ^{13}C NMR data from a single diastereomer.[30] Given the relatively simple nature of the 3,6-dihydro-2*H*-pyran ring system, we envisaged that density functional methods could be used to accurately calculate ^{13}C NMR resonances of the ring carbons and distinguish the shielding effects that characterize each diastereomer. A preliminary evaluation of this method was performed by attempting to accurately calculate the ^{13}C NMR resonances of the unsubstituted ring system, 3,6-dihydro-2*H*-pyran.[31] GIAO NMR calculations were performed with a range of basis sets and functionals, and it was ultimately discovered that the *m*PW1PW91 functional[32] and decontracted TZVP (decTZVP) basis set,[33] in conjunction with a multistandard (MSTD) referencing method,[34] yielded the most accurate results when compared with the experimentally obtained values (Table 3). Adding carbonate and silyl ether substituents to the ring system (i.e., ***cis*-** and ***trans*-10a**) required consideration and analysis of both ^2H_O and $^OH_2$ half-chair ring conformers and various combinations of substituent orientations. Each of the two substituents can exist in three different staggered conformations about each exocyclic C−O bond (e.g., conformers A, B and C, Figure 7), providing a total of 18 different possible conformers.[35] For ***cis*-10a**, four of these conformers were found to lie within 1.5 kcal/mol (6.3 kJ/mol) of the global minimum and this energy threshold provides an accurate representation of >95% of the total conformer population. GIAO NMR calculations for each of these four conformers and subsequent Boltzmann-weighted averaging provided calculated ^{13}C NMR chemical shifts for the five carbons of the dihydropyran ring system.[36] For ***trans*-10a**, only two conformers were within 1.5 kcal/mol (6.3 kJ/mol) of the global minimum.

The calculated spectra for each diastereomer, ***cis*-** and ***trans*-10a**, were in good agreement with the experimental data, providing both CP3 and DP4 assignment probabilities in excess of 95%.[37] A root-mean-squared error of less than 2.5 ppm was

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Table 3. Calculated ^{13}C Chemical Shifts for Dihydropyrans[a]

	C2	C3	C4	C5	C6	RMS error[b]
			δ_{calc} (δ_{exp}) /ppm			
	63.6 (64.4)	25.2 (25.8)	127.1 (124.6)	130.6 (127.1)	65.6 (65.5)	1.97[c]
***cis*-10a**	59.0 (60.1)	68.8 (68.4)	130.4 (126.4)	134.3 (132.2)	91.5 (89.2)	2.34[d]
***trans*-10a**	60.9 (61.0)	66.5 (66.9)	124.7 (122.5)	137.6 (133.9)	90.3 (87.9)	2.21
			Average Difference Between Calculated and Experimental Data for 10a–10g, δ_{calc}-δ_{exp} [SD] /ppm[e]			
***cis*-10a–g**	-1.5 [0.55]	+0.6 [0.12]	+4.2 [0.46]	+1.9 [0.64]	+2.6 [0.69]	
***trans*-10a–g**	-0.1 [0.13]	-0.1 [0.16]	+2.3 [0.29]	+3.8 [0.24]	+2.9 [0.62]	
			Average calculated δ_{cis}-δ_{trans} for 10a–10g [SD] /ppm[f]			
	-2.4 [0.33]	2.3 [0.10]	5.7 [0.23]	-3.4 [0.45]	1.0 [0.21]	

[a]GIAO ^{13}C NMR calculations were performed using Gaussian '09 at the *m*PW1PW91/TZVP//*m*PW1PW91/decTZVP level on conformers within 1.5 kcal/mol (6.3 kJ/mol) of the global minima [four conformers for each *cis*-diastereomer (Figure 7), two conformers for each *trans*-diastereomer]. These data were subjected to Boltzmann averaging, where appropriate, to provide the results shown. See the Supporting Information for full details of computational methodology used. [b]Average RMS error between experimental and calculated ^{13}C NMR chemical shifts. [c]^{13}C NMR data for 3,6-dihydro-2*H*-pyran were taken from the literature.[31] [d]A calculation based on conformers within 4.2 kcal/mol (17.6 kJ/mol) of the global minima (10 conformers) gave very similar results: 2.49 ppm RMS error. [e]SD = standard deviation for the $\delta_{calc} - \delta_{exp}$ results from the seven compounds. [f]SD = standard deviation for the calculated $\delta_{cis} - \delta_{trans}$ values for the seven compounds.

obtained for both ***cis***- and ***trans*-10a**. Interestingly, a large proportion of this error stems from the sp^2 carbons. Based on the results with ***cis***- and ***trans*-10a**, ^{13}C NMR shifts were also predicted for a range of dihydropyrans (**10b–g**) by calculating chemical shifts for the four most dominant conformers of the *cis*-compounds and the two most dominant conformers for the *trans*-isomers, and performing Boltzmann-weighted averaging. Great consistency in the calculated chemical shift values and in the difference between calculated and experimental values was observed across the range of compounds **10a–10g** (Table 3 and Supporting Information Table 3). While the calculated $\delta_{cis} - \delta_{trans}$ values differed somewhat from those of the template determined experimentally, the pattern of relative shielding exactly corresponded, indicating the utility of the additional information provided by the calculations.

The substituted 3,6-dihydro-2*H*-pyrans ***trans*-10l**, ***cis*-10m**, and ***cis*-10n** (Table 4) were obtained as single diastereomers, and therefore, shielding effects could not be evaluated by comparison of ^{13}C NMR resonances from the two possible diastereomers, as demonstrated earlier. To overcome this problem, the aforementioned computational methodology was used to predict the chemical shifts of both the *cis*- and *trans*-diastereomers for each compound. The differential nature of axial shielding on the ring carbons provides the opportunity to match experimental and calculated ^{13}C resonances with a high degree of confidence. The calculated ^{13}C NMR chemical shifts for the dihydropyran ring of the correct diastereomer were found to be in good agreement with experimental data and provided DP4 probabilities in excess of 95% for all three compounds. This statistical analysis places greater weighting on calculated values that differ significantly from experimental values in determining the incorrect isomer.[37a] Thus, for compounds **10l–n**, data pertaining to C4 or C5, which have the largest difference between the experimental value and one of the calculated values (that for the incorrect stereoisomer), contribute most to the probability determination. Overall, by combining ^{13}C NMR calculations with an awareness of how axial shielding differentiates the ring carbons of the *cis*- and *trans*-3,6-dihydro-2*H*-pyran diastereomers, robust evidence to support the assignment of relative stereochemistry was obtained with experimental data from just one diastereomer.

CONCLUSION

In summary, the use of axial shielding magnitudes in the assignment of remote relative stereochemistry for 3,6-disubstituted 3,6-dihydro-2*H*-pyran ring systems has been demonstrated as a complementary method to the currently established use of proton couplings. This approach enables the expeditious characterization of products from reactions that provide both diastereomers, such as the Ferrier reaction or reduction of the corresponding enone. Computational analysis has provided a rigorous understanding of the conformational distribution of these compounds and enabled the accurate

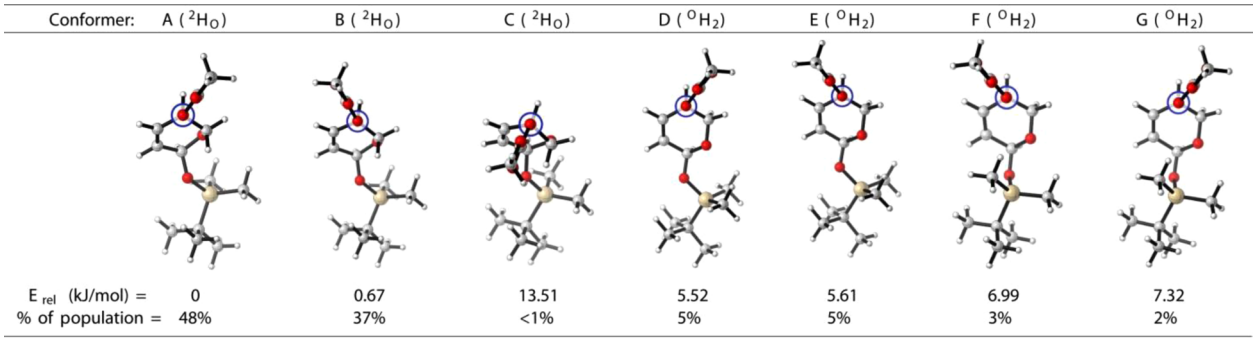

Figure 7. Newman projections for the geometry optimized conformers of ***cis*-10a**, viewed along the O–C3 bond.

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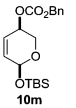
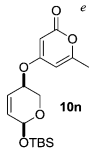
Table 4. Assignment of Relative Configuration from a Single Diastereomer*

Substrate		Exp.[a]	Calc.[b]		$\lvert\delta_{calc}-\delta_{exp}\rvert$[c]		DP4[d]
			cis	*trans*	*cis*	*trans*	
 10l	*C2*	61.4	59.6	**61.3**	1.8	0.1	
	C3	64.0	65.8	**63.6**	1.8	0.4	
	C4	123.3	130.7	**125.6**	7.4	2.3	98.9%
	C5	133.4	134.7	**137.2**	1.3	3.8	
	C6	88.0	91.9	**90.4**	3.9	2.4	
 10m	*C2*	60.0	**59.2**	60.9	0.8	0.9	
	C3	68.5	**68.5**	66.3	0.0	2.2	
	C4	126.4	**130.4**	124.8	4.0	1.6	97.4%
	C5	132.2	**134.5**	137.6	2.3	5.4	
	C6	89.2	**91.7**	90.3	2.5	1.1	
 10n	*C2*	59.8	**58.9**	59.7	0.9	0.1	
	C3	68.6	**68.5**	66.0	0.1	2.6	
	C4	125.2	**127.8**	123.0	2.6	2.2	98.9%
	C5	132.7	**134.8**	138.6	2.1	5.9	
	C6	89.3	**91.4**	90.1	2.1	0.8	

*Key: Exp. = experimental ^{13}C NMR resonances, in ppm; Calc. = calculated ^{13}C NMR resonances, in ppm, for the *cis*- or *trans*-diastereomers of the structure shown; *DP4* = DP4 probability that the calculated ^{13}C NMR resonances for the expected diastereomer (in **bold**) match the experimental data. [a]All carbon assignments are based on COSY and HSQC spectra. Full tables of ^{1}H and ^{13}C NMR assignments can be found in the Supporting Information. [b]GIAO ^{13}C NMR calculations were performed using Gaussian '09 at the *m*PW1PW91/TZVP//*m*PW1PW91/decTZVP level on conformers within 1.5 kcal/mol (6.3 kJ/mol) of the global minima. These data were subjected to Boltzmann averaging, where appropriate, to provide the results shown. See the Supporting Information for full details of the computational methodology used. [c]The absolute value of the difference between calculated and experimental chemical shift values allows calculation of DP4 probability. [d]The DP4 probability was calculated using the web-based applet found at http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/ (last updated March 9, 2010). [e]This pyrone-linked 3,6- dihydro-2*H*-pyran (**10n**) required consideration of only one *cis*-conformer as the others were outside of the 1.5 kcal/mol (6.3 kJ/mol) energy threshold.

prediction of ^{13}C chemical shifts within the pyran ring. Consequently, reliable stereochemical assignments can also be made with experimental data from a single diastereomer. With the accumulation of HSQC data on a wider range of cyclic compounds, we ultimately hope to be able to extend the principles of this methodology to the stereochemical assignment of dihydropyran rings with a greater variety of substitution patterns.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR spectra were recorded at 500 MHz; data are listed as follows: chemical shift in ppm using residual $CHCl_3$ as internal standard (7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, br = broad, app = apparent), integration, peak assignment. ^{13}C NMR spectra were recorded at 125 MHz, and the data are listed as chemical shift in ppm using $CDCl_3$ as internal standard (77 ppm). All ^{13}C NMR experiments were ^{1}H decoupled. The assignment of atom connectivity and spatial relationships are exclusively based on 2D NMR correlations ($^{1}H/^{1}H$ COSY and $^{1}H/^{13}C$ HSQC). See the Supporting Information for full details of general experimental methods.

General Procedure for the Ferrier Reactions of 3,4-Di-*O*-acetyl-D-xylal. *Preparation of (3S,6S)-6-Propoxy-3,6-dihydro-2H-pyran-3-yl Acetate and (3S,6R)-6-Propoxy-3,6-dihydro-2H-pyran-3-yl Acetate, **cis**- and **trans**-10c.* To a solution of 3,4-di-*O*-acetyl-D-xylal (0.100 g, 0.5 mmol, 1 equiv) and *n*-propanol (0.045 mL, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.012 mL, 0.014 g, 0.6 mmol, 1.2 equiv) at 0 °C. The reaction was slowly warmed to room temperature and stirred for 1 h before being diluted with CH_2Cl_2 and quenched with water. The reaction mixture was subsequently extracted with CH_2Cl_2 ,and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (10% EtOAc/petroleum ether). The title compounds were isolated separately as clear, colorless oils ***trans*-10c** (0.0216 g, 22% yield) and ***cis*-10c** (0.0094 g, 9% yield). Characterization data for ***trans*-10c**: R_f = 0.29 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.08−6.03 (complex m, 2H, 2 × HC═), 5.00 (d, J = 2.3 Hz, 1H, CHO*n*Pr), 4.95 (dt, J = 2.9, 1.6 Hz, 1H, CHOAc), 4.17 (dd, J = 13.0, 2.9 Hz, 1H, one of CH_2OR), 3.83 (dd, J = 13.0, 1.2 Hz, 1H, one of CH_2OR), 3.73 (dt, J = 9.5, 6.8 Hz, 1H, one of OCH_2Et), 3.45 (dt, J = 9.5, 6.7 Hz, 1H, one of OCH_2Et), 2.10 (s, 3H, OAc), 1.63 (m, 1H, CH_2Me), 0.94 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 131.0 (C5), 124.9 (C4), 92.9 (C6), 70.2, 63.4 (C3), 61.2 (C2), 22.9, 21.1, 10.6; IR (film) 2964, 2878, 1731, 1371, 1233, 1189, 1104, 1016, 956, 897, 845 cm^{-1}; $[\alpha]_D^{25}$ = +120.7 (c = 1.08, $CHCl_3$). Characterization data for ***cis*-10c**: R_f = 0.35 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.95 (m, 1H, HC═), 5.88 (dt, J = 10.3, 2.0 Hz, 1H, HC═), 5.29 (m, 1H, CHOAc), 4.95 (m, 1H, CHO*n*Pr), 3.86 (dd, J = 11.1, 5.7 Hz, 1H, one of CH_2OR), 3.82 (dd, J = 11.1, 7.9 Hz, 1H, one of CH_2OR), 3.75 (dt, J = 9.4, 6.8 Hz, 1H, one of OCH_2Et), 3.46 (dt, J = 9.4, 6.7 Hz, 1H, one of OCH_2Et), 2.08 (s, 3H, OAc), 1.64 (app sextet, J = 7.2 Hz, 2H, CH_2Me), 0.95 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 129.4 (C5), 128.7 (C4), 94.3 (C6), 70.5, 65.0 (C3), 60.1 (C2), 23.0, 21.0, 10.6; IR (film) 2964, 2880, 1736, 1371, 1231, 1099, 1030, 960, 895 cm^{-1}; $[\alpha]_D^{25}$ = +107.7 (c = 0.47, $CHCl_3$); HRMS-ESI (m/z) calcd for $C_{10}H_{16}O_4Na$ $[M + Na]^+$ 223.0946, found 223.0951, Δ = 2.2 ppm.

*Preparation of (3S,6S)-6-(Allyloxy)-3,6-dihydro-2H-pyran-3-yl Acetate and (3S,6R)-6-(Allyloxy)-3,6-dihydro-2H-pyran-3-yl Acetate, **cis**- and **trans**-10d.* Using the general procedure for the Ferrier reaction, 3,4-di-*O*-acetyl-D-xylal (0.100 g, 0.5 mmol, 1 equiv), allyl alcohol (0.041 mL, 0.035 g, 0.6 mmol, 1.2 equiv), and $BF_3{\cdot}OEt_2$ (0.012 mL, 0.014 g, 0.6 mmol, 1.2 equiv) were added to the reaction. The crude product was purified by silica gel chromatography (10% EtOAc/petroleum ether), and the title compounds were isolated separately as clear, colorless oils ***trans*-10d** (0.036 g, 37% yield) and ***cis*-10d** (0.016 g, 16% yield). Characterization data for ***trans*-10d**: R_f = 0.16 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.08 (dd, J = 10.0, 5.0 Hz, 1H, HC═), 6.03 (dd, J = 10.1, 2.8 Hz, 1H, HC═), 5.92 (dddd, J = 17.1, 10.5, 6.4, 5.3 Hz, 1H, HC═), 5.30 (dd, J = 17.2, 1.6 Hz, 1H, one of $=CH_2$), 5.20 (dd, J = 10.3, 1.3 Hz, 1H, one of $=CH_2$), 5.05 (d, J = 2.4 Hz, 1H, CHOAllyl), 4.95 (m, 1H, CHOAc), 4.25 (ddt, J = 12.7, 5.2, 1.4 Hz, 1H, one of OCH_2C═), 4.17 (dd, J = 13.0, 3.7 Hz, 1H, one of CH_2OR), 4.06 (ddt, J = 12.7, 6.4, 1.1 Hz, 1H, one of OCH_2C═), 3.83 (app d, J = 13.0 Hz, 1H, one of CH_2OR), 2.08 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 134.1, 130.8 (C5), 125.1 (C4), 117.7, 92.1 (C6), 68.9, 63.3 (C3), 61.3 (C2), 21.1; IR (film) 2984, 2920, 1730, 1371, 1232, 1036, 1014, 956 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{10}H_{14}O_4Na$ $[M + Na]^+$ 221.0790, found 221.0790, Δ 0.0 ppm; $[\alpha]_D^{25}$ = +86.1 (c = 1.05, $CHCl_3$).

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Characterization data for ***cis*-10d**: R_f = 0.24 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.97−5.89 (complex m, 2H, 2 × HC═), 5.87 (dt, J = 10.3, 2.1 Hz, 1H, HC═), 5.32−5.27 (complex m, 2H, CHOAc and one of ═CH_2), 5.20 (dd, J = 10.4, 1.3 Hz, 1H, one of ═CH_2), 4.99 (app s, 1H, CHOAllyl), 4.27 (ddt, J = 12.8, 5.2, 1.4 Hz, 1H, one of OCH_2C═), 4.06 (ddt, J = 12.8, 6.3, 1.2 Hz, 1H, one of OCH_2C═), 3.85 (dd, J = 11.0, 5.7 Hz, 1H, one of CH_2OR), 3.81 (dd, J = 11.0, 8.0 Hz, 1H, one of CH_2OR), 2.06 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 134.2, 129.1 (C5), 129.0 (C4), 117.5, 93.4 (C6), 69.1, 65.0 (C3), 60.1 (C2), 21.0; IR (film) 2886, 1736, 1371, 1230, 1094, 1033, 959 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{10}H_{14}O_4Na$ $[M + Na]^+$ 221.0790, found 221.0792, Δ = 0.9 ppm; $[\alpha]_D^{25}$ = +56.66 ($CHCl_3$, c = 0.8).

Preparation of (3S,6S)-6-(Prop-2-yn-1-yloxy)-3,6-dihydro-2H-pyran-3-yl Acetate and (3S,6R)-6-(Prop-2-yn-1-yloxy)-3,6-dihydro-2H-pyran-3-yl Acetate, ***cis-* and *trans*-10e**. Using the general procedure for the Ferrier reaction, 3,4-di-*O*-acetyl-D-xylal (0.100 g, 0.5 mmol, 1 equiv), propargyl alcohol (0.034 g, 0.6 mmol, 1.2 equiv), and $BF_3{\cdot}OEt_2$ (0.012 mL, 0.014 g, 0.6 mmol, 1.2 equiv) were added to the reaction. The crude product was purified by silica gel chromatography (10% EtOAc/petroleum ether). The title compounds were isolated separately as clear, colorless oils ***trans*-10e** (0.021 g, 22% yield) and ***cis*-10e** (0.019 g, 20% yield). Characterization data for ***trans*-10e**: R_f = 0.24 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10 (dd, J = 10.1, 5.2 Hz, 1H, HC═), 6.03 (dd, J = 10.1, 3.0 Hz, 1H, HC═), 5.21 (d, J = 2.8 Hz, 1H, CHOPropargyl), 4.94 (dd, J = 4.8, 2.7 Hz, 1H, CHOAc), 4.29 (d, J = 2.3 Hz, 2H, OCH_2C≡), 4.12 (dd, J = 13.0, 2.7 Hz, 1H, one of CH_2OR), 3.84 (app d, J = 13.0 Hz, 1H, one of CH_2OR), 2.44 (t, J = 2.2 Hz, 1H, HC≡), 2.08 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 130.3, 125.4, 91.3, 79.1, 74.7, 63.1, 61.5, 54.8, 21.1; HRMS-ESI (m/z) calcd for $C_{10}H_{12}O_4Na$ $[M + Na]^+$ 219.0633, found 219.0630, Δ = 1.4 ppm; $[\alpha]_D^{25}$ = +55.3 (c = 1.05, $CHCl_3$). Characterization data for ***cis*-10e**: R_f = 0.30 (10% EtOAc/PE); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.97 (dd, J = 10.3, 1.0 Hz, 1H, HC═), 5.86 (app d, J = 10.3 Hz, 1H, HC═), 5.32 (m, 1H, CHOAc), 5.16 (app s, 1H, CHOPropargyl), 4.31 (s, 2H, OCH_2C≡), 3.87 (dd, J = 10.9, 5.7 Hz, 1H, CH_2OR), 3.77 (dd, J = 10.9, 8.5 Hz, 1H, one of CH_2OR), 2.44 (s, 1H, HC≡), 2.07 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 129.6 (C4), 128.4 (C5), 92.3 (C6), 79.1, 74.7, 64.9 (C3), 60.0 (C2), 54.9, 21.0; HRMS-ESI (m/z) calcd for $C_{10}H_{12}O_4Na$ $[M + Na]^+$ 219.0633, found 219.0635, Δ = 0.9 ppm; $[\alpha]_D^{25}$ = +23.6 (c = 0.97, $CHCl_3$).

Preparation of (3S,6S)-6-(Benzyloxy)-3,6-dihydro-2H-pyran-3-yl Acetate and (3S,6R)-6-(Benzyloxy)-3,6-dihydro-2H-pyran-3-yl Acetate, ***cis-* and *trans*-10f**. Using the general procedure for the Ferrier reaction, 3,4-di-*O*-acetyl-D-xylal (0.100 g, 0.5 mmol, 1 equiv), benzyl alcohol (0.062 mL, 0.6 mmol, 1.2 equiv), and $BF_3{\cdot}OEt_2$ (0.012 mL, 0.014 g, 0.6 mmol, 1.2 equiv) were added to the reaction. The crude product was purified by silica gel chromatography (10% EtOAc/petroleum ether), and the title compounds were isolated together (R_f = 0.28 and 0.20) as a clear, colorless oil (0.099 g, 80% yield, ca. 3:1 *trans*:*cis* ratio). Characterization data for ***trans*-10f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.27 (complex m, 5H, Ph), 6.09 (m, 1H, HC═), 6.04 (dd, J = 10.1, 2.9 Hz, 1H, HC═), 5.10 (dt, J = 2.9, 0.6 Hz, 1H, CHOBn), 4.96 (m, 1H, CHOAc), 4.79 (d, J = 11.7 Hz, 1H, one of OCH_2Ph), 4.59 (d, J = 11.7 Hz, 1H, one of OCH_2Ph), 4.21 (dd, J = 13.1, 2.8 Hz, 1H, CH_2OR), 3.87 (m, 1H, one of CH_2OR), 2.10 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 137.5, 130.7 (C5), 128.5−127.4 (5 × C), 124.9 (C4), 92.0 (C6), 69.9, 63.3 (C3), 61.4 (C2), 21.1. Characterization data for ***cis*-10f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.28 (complex m, 5H), 5.94 (ddt, J = 10.3, 2.2, 1.0 Hz, 1H, HC═), 5.88 (ddd, J = 10.2, 2.4, 1.8 Hz, 1H, HC═), 5.32 (m, 1H, CHOAc), 5.04 (dd, J = 2.4, 1.3 Hz, 1H, CHOBn), 4.82 (d, J = 11.9 Hz, 1H, one of OCH_2Ph), 4.58 (d, J = 11.9 Hz, 1H, OCH_2Ph), 3.94−3.89 (complex m, 2H, CH_2OR), 2.05 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 138.4, 129.07, and 129.06 (C4 and C5), 128.5−127.4 (5 × C), 93.3 (C6), 69.3, 65.0 (C3), 60.1 (C2), 21.1. Characterization data match those reported previously.[38]

Preparation of (3S,6R)-6-Isopropoxy-3,6-dihydro-2H-pyran-3-yl Acetate and (3S,6S)-6-Isopropoxy-3,6-dihydro-2H-pyran-3-yl Acetate, ***cis-* and *trans*-10h**. Using the general procedure for the Ferrier reaction, 3,4-di-*O*-acetyl-D-xylal (0.100 g, 0.5 mmol, 1 equiv), 2-propanol (0.046 mL, 0.036 g, 0.6 mmol, 1.2 equiv), and $BF_3{\cdot}OEt_2$ (0.012 mL, 0.6 mmol, 1.2 equiv) were added to the reaction. The crude product was purified by silica gel chromatography (10% EtOAc/petroleum ether), and the title compounds were isolated together as a clear, colorless oil (0.047 g, 46% yield, 3.4:1 ratio of ***trans*-10h**:***cis*-10h**). ***trans*-10h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.06 (dd, J = 10.1, 5.1 Hz, 1H, HC═), 6.00 (dd, J = 10.1, 2.9 Hz, 1H, HC═), 5.11 (d, J = 3.0 Hz, 1H, CHO*i*Pr), 4.95 (dt, J = 3.6, 1.9 Hz, 1H, CHOAc), 4.19 (dd, J = 13.0, 2.8 Hz, 1H, one of CH_2OR), 3.98 (septet, J = 6.0 Hz, 1H, $OCH(Me)_2$), 3.82 (m, 1H, one of CH_2OR), 2.09 (s, 3H, OAc), 1.23 (d, J = 6.2 Hz, 3H, CH_3), 1.18 (d, J = 6.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 131.5 (C5), 124.8 (C4), 91.1 (C6), 70.0, 63.5 (C3), 61.1 (C2), 23.6, 21.8, 21.1. ***cis*-10h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92 (dd, J = 10.3, 1.1 Hz, 1H, HC═), 5.83 (m, 1H, HC═), 5.29 (app t, J = 7.2 Hz, 1H, CHOAc), 5.03 (app s, 1H, CHO*i*Pr), 3.98 (septet, J = 6.0 Hz, 1H, $OCH(CH_3)_2$), 3.84−3.82 (complex m, 2H, CH_2OR), 2.06 (s, 3H, OAc), 1.24 (m, 3H, CH_3), 1.18 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 129.7 (C5), 128.7 (C4), 92.3 (C6), 70.3, 65.1 (C3), 59.8 (C2), 23.6, 21.8, 21.1. Characterization data match those reported previously.[38]

Synthesis of *cis*-10a and *cis*-10b. *Preparation of (±)-6-Hydroxy-3,6-dihydro-2H-pyran-3-one.* To a solution of furfuryl alcohol (4.0 g, 40.8 mmol, 1.0 equiv) in dichloromethane (98 mL) at 0 °C was added *m*-CPBA (11.0 g, 48.9 mmol, 1.2 equiv) in three portions over 15 min. The reaction mixture was allowed to slowly warm to ambient temperature, and stirring was continued overnight. The reaction was then cooled to −78 °C and stirred for 15 min before removal of insoluble *m*-chlorobenzoic acid (a white precipitate) by filtration. The filtrate was concentrated in vacuo and purified by flash column chromatography (silica gel, 30% EtOAc/petroleum ether). The title compound was isolated as a white crystalline solid (3.6 g, 77% yield): R_f = 0.18 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (dd, J = 10.4, 3.1 Hz, 1H, HC═), 6.17 (d, J = 10.4 Hz, 1H, HC═), 5.65 (dd, J = 4.7, 3.1 Hz, 1H, CHOH), 4.58 (d, J = 16.9 Hz, 1H, one of CH_2OR), 4.14 (d, J = 16.9 Hz, 1H, one of CH_2OR), 3.08 (d, J = 5.2 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 145.5, 128.0, 88.2, 66.6; mp = 51−53 °C (lit.[1] mp =55−57 °C). These data match values previously reported.[39]

Preparation of (±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-one. To a solution of 6-hydroxy-3,6-dihydro-2*H*-pyran-3-one (1.0 g, 8.76 mmol, 1.0 equiv) in THF (60 mL) were added $AgNO_3$ (1.8 g, 10.5 mmol, 1.2 equiv) and pyridine (3.15 mL, 38.9 mmol, 4.44 equiv). The suspension was stirred for 20 min to allow the dissolution of any large lumps of solid. TBSCl (1.72 g, 11.4 mmol, 1.3 equiv) was added at room temperature, and precipitation of a white solid resulted. The reaction was stirred overnight, after which the reaction mixture was filtered and concentrated in vacuo. The resulting crude product was subjected to flash column chromatography (silica gel, 5% EtOAc/petroleum ether) to afford the desired product as a white crystalline solid (1.76 g, 88% yield): R_f = 0.34 (5% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (dd, J = 10.3, 3.1 Hz, 1H, HC═), 6.08 (d, J = 10.3 Hz, 1H, HC═), 5.53 (d, J = 3.1 Hz, 1H, CHOTBS), 4.50 (d, J = 16.8 Hz, 1H, one of CH_2OR), 4.08 (d, J = 16.8 Hz, 1H, one of CH_2OR), 0.92 (s, 9H, $C(CH_3)_3$), 0.17 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.0, 147.2, 126.5, 88.4, 66.5, 25.6, 18.1, −4.5, −5.4; IR (film) 2931, 2858, 1706, 1256, 1105, 1040, 994, 876, 836, 780 cm^{-1}; mp = 28−31 °C (no lit. mp available). These data match values previously reported.[10]

Preparation of cis-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-ol, ***cis*-10i**. To a solution of (±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-one (2.0 g, 8.76 mmol, 1.0 equiv) in 60 mL of methanol was added $CeCl_3{\cdot}7H_2O$ (3.92 g, 10.5 mmol, 1.2 equiv). The reaction mixture was cooled to −20 °C, and sodium borohydride (0.40 g, 10.5 mmol, 1.2 equiv) was added. The reaction was stirred at −20 °C for 30 min before being quenched with 8 mL of acetone. The reaction mixture was warmed to room temperature, concentrated to approximately one-quarter its original volume, diluted with water, extracted with dichloromethane,

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dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc/petroleum ether). The product was isolated as a clear, colorless oil (1.45 g, 72% yield): R_f = 0.33 (20% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.95 (dd, J = 10.2, 2.7 Hz, 1H, HC═), 5.75 (dt, J = 10.2, 1.9 Hz, 1H, HC═), 5.25 (m, 1H, CHOTBS), 4.15 (m, 1H, CHOH), 3.80−3.74 (m, 2H, CH_2OR), 1.65 (br m, 1H, OH), 0.91 (s, 9H, $C(CH_3)_3$), 0.14 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 130.9 (C5), 130.8 (C4), 89.9 (C6), 64.6 (C2), 63.1 (C3), 25.7, 18.1, −3.6, −4.3; IR (film) 3344, 2955, 2930, 2858, 1253, 1028, 989, 866, 835, 778, cm^{-1}. These data match values previously reported in the literature.[10] A small quantity of the minor *trans*-diastereomer was also isolated as a clear colorless oil (0.062 g, 3% yield, see below for full characterization).

Preparation of cis-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-yl Methyl Carbonate, ***cis-10a.*** To a solution of *cis*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-ol (1.34 g, 5.83 mmol, 1.0 equiv) in 70 mL of freshly distilled CH_2Cl_2 was added DMAP (0.89 g, 7.29 mmol, 1.25 equiv), followed by methyl chloroformate (0.563 mL, 0.689 g, 7.29 mmol, 1.25 equiv). The reaction was stirred overnight at room temperature before concentration in vacuo and purification by flash column chromatography (silica gel, 5% EtOAc/petroleum ether). The desired product was isolated as a clear, colorless oil (1.41 g, 84% yield): R_f = 0.31 (5% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92 (ddt, J = 10.3, 2.3, 1.0 Hz, 1H, HC═), 5.85 (ddd, J = 10.3, 2.3, 1.8 Hz, 1H, HC═), 5.28 (m, 1H, CHOTBS), 5.13 (m, 1H, $CHOCO_2Me$), 3.91 (ddd, J = 11.1, 7.9, 0.5 Hz, 1H, one of CH_2OR), 3.87 (ddd, J = 11.1, 5.7, 0.9 Hz, 1H one of CH_2OR) 3.80 (s, 3H, CO_2CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.133 (s, 3H, $SiCH_3$), 0.130 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 132.2 (C5), 126.4 (C4), 89.2 (C6), 68.4 (C3), 60.1 (C2), 54.9, 25.7, 18.0, −4.4, −5.2; IR (film) 2956, 2931, 2856, 1749, 1258, 1034, 837, 779 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{13}H_{24}O_5SiNa^+$ $[M + Na]^+$ 311.1291, found 311.1293; Δ = 0.6. These data match those obtained previously.[17]

Preparation of 6-((tert-Butyldimethylsilyl)oxy)-3,6-dihydro-2H-pyran-3-yl Acetate, ***cis-10b.*** To a solution of *cis*-(±)-6-((*tert*-butyldimethylsilyl)oxy)-3,6-dihydro-2*H*-pyran-3-ol (***cis*-10i**, 0.33 g, 1.43 mmol, 1.0 equiv), 4 Å molecular sieves, and Amano PS-C lipase (0.066 g) in methyl *tert*-butyl ether (15 mL) was added vinyl acetate (0.26 mL, 0.25 g, 2.86 mmol, 2.0 equiv) at room temperature. The reaction was stirred at room temperature for 72 h before being filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc/petroleum ether). The title compound was isolated as a clear oil (0.244 g, 63% yield): R_f = 0.50 (15% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (dd, J = 10.3, 2.1 Hz, 1H, HC═), 5.84 (dt, J = 10.3, 1.7 Hz, 1H, HC═), 5.28 (app s, 1H, CHOTBS), 5.24 (m, 1H, CHOAc), 3.86 (dd, J = 9.5, 5.4 Hz, 1H, one of CH_2OR), 3.83 (dd, J = 9.5, 4.0 Hz, 1H, one of CH_2OR), 2.08 (s, 3H, OAc), 0.92 (s, 9H, $C(CH_3)_3$), 0.141 (s, 3H, $SiCH_3$), 0.139 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 132.1 (C5), 126.9 (C4), 89.5 (C6), 65.0 (C3), 60.6 (C2), 25.7, 21.1, 18.1, −4.4, −5.2. Characterization data match those reported previously.[10]

Preparation of trans-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-yl Benzoate, ***10l.*** To a solution of *cis*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-ol (***cis*-10i**, 0.7243 g, 3.14 mmol, 1.0 equiv), triphenylphosphine (0.907 g, 3.46 mmol, 1.1 equiv), and benzoic acid (0.461 g, 3.77 mmol, 1.2 equiv) in 18.8 mL of THF, at 0 °C, was added 0.67 mL of diisopropyl azodicarboxylate (DIAD, 0.699 g, 3.46 mmol, 1.1 equiv). The reaction was stirred at 0 °C for 30 min before being warmed to room temperature and quenched with water. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc/petroleum ether). The title compound was isolated as a clear yellow oil (1.039 g, 99% yield): R_f = 0.15 (20% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07−8.05 (complex m, 2H, ArH), 7.56 (m, 1H, ArH), 7.44−7.41 (complex m, 2H, ArH), 6.12 (dd, J = 10.0, 5.1 Hz, 1H, HC═), 6.04 (dd, J = 10.0, 3.0 Hz, 1H, HC═), 5.39 (d, J = 3.0 Hz, 1H, CHOTBS), 5.19 (m, 1H, CHOBz), 4.31 (dd, J = 13.0, 2.9 Hz, 1H, one of CH_2OR), 3.97 (dt, J = 13.0, 1.3 Hz, 1H, one of CH_2OR), 0.92 (s, 9H, $C(CH_3)_3$), 0.15 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.3, 133.4 (C5), 133.1, 130.0, 129.8, 128.3, 123.3 (C4), 88.0 (C6), 64.0 (C3), 61.4 (C2), 25.7, 18.1, −4.5, −5.3; IR (film) 2930, 2858, 1776, 1716, 1265, 1108, 1022, 836, 779, 710 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{18}H_{26}O_4SiNa^+$ $[M + Na]^+$ 357.1498, found 357.1493; Δ = 1.4. These data match values previously obtained.[17]

Preparation of trans-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-ol, ***trans-10i.*** To a solution of *trans*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-yl benzoate (**10l**, 1.039 g, 3.106 mmol, 1.0 equiv) in 21 mL of methanol was added potassium carbonate (0.644 g, 4.66 mmol, 1.5 equiv). The yellow solution quickly became colorless and was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo to half the solvent volume, diluted with EtOAc and water, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/petroleum ether). The desired product was isolated as a white crystalline solid (0.483 g, 68% yield): R_f = 0.29 (25% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.06 (dd, J = 10.0, 5.3 Hz, 1H, HC═), 5.85 (dd, J = 10.0, 3.0 Hz, 1H, HC═), 5.29 (d, J = 3.0 Hz, 1H, CHOTBS), 4.16 (dd, J = 12.2, 2.6 Hz, 1H, one of CH_2OR), 3.83 (m, 1H, CHOH), 3.77 (dt, J = 12.2, 1.3 Hz, 1H, one of CH_2OR), 1.85 (d, J = 9.2 Hz, 1H, OH), 0.91 (s, 9H, $C(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 131.0 (C5), 127.5 (C4), 88.2 (C6), 64.3 (C2), 61.6 (C3), 25.7, 18.1, −4.5, −5.3; IR (film) 3379, 2929, 2858, 1251, 1105, 1024, 977, 871, 836, 777 cm^{-1}; mp = 50−52 °C (lit.[10] mp = 39−43 °C). These data are consistent with values previously reported.[10,17]

Preparation of trans-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-yl Methyl Carbonate, ***trans-10a.*** To a solution of *trans*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-ol (0.472 g, 2.05 mmol, 1.0 equiv) in dichloromethane (40 mL) was added DMAP (0.313 g, 2.56 mmol, 1.25 equiv), followed by methyl chloroformate (0.198 mL, 0.242 g, 2.56 mmol, 1.25 equiv). The reaction was stirred overnight at room temperature before concentration in vacuo and purification by flash column chromatography (silica gel, 5% EtOAc/petroleum ether). The desired product was isolated as a clear colorless oil (0.321 g, 54% yield, 70% brsm): R_f = 0.25 (5% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.03 (ddd, J = 10.1, 4.3, 0.8 Hz, 1H, HC═), 6.00 (dd, J = 10.0, 2.6 Hz, 1H, HC═), 5.33 (d, J = 2.4 Hz, 1H, CHOTBS), 4.80 (ddd, J = 4.4, 2.9, 1.4 Hz, 1H, $CHOCO_2Me$), 4.20 (dd, J = 13.1, 2.8 Hz, 1H, one of CH_2OR), 3.90 (dt, J = 13.1, 1.2 Hz, 1H, one of CH_2OR), 3.78 (s, 3H, CO_2CH_3), 0.91 (s, 9H, $C(CH_3)_3$), 0.13 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.4, 133.9 (C5), 122.5 (C4), 87.9 (C6), 66.9 (C3), 61.0 (C2), 54.8, 25.7, 18.1, −4.5, −5.3; IR (film) 2956, 2930, 2858, 1743, 1256, 1025, 944, 869, 837, 779 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{13}H_{24}O_5SiNa^+$ $[M + Na]^+$ 311.1291, found 311.1294, Δ = 1.0 ppm. These data match those previously obtained.[17]

Preparation of trans-(±)-6-((tert-Butyldimethylsilyl)oxy)-3,6-dihydro-2H-pyran-3-yl Acetate, ***trans-10b.*** To a solution of (±)-*trans*-6-((*tert*-butyldimethylsilyl)oxy-3,6-dihydro-2*H*-pyran-3-ol (***trans*-10i**, 0.0064 g, 0.028 mmol, 1.0 equiv) in pyridine (0.5 mL) was added acetic anhydride (0.5 mL). The reaction was stirred overnight at room temperature before quenching with 3 mL of H_2O. The reaction mixture was then cyclic loaded onto HP20 resin by repeatedly passing the eluted solution through the column with addition of increasing amounts of MeOH (in 1 mL increments up to 5 mL of MeOH). The resin was then washed three times with H_2O, and the product was subsequently eluted with acetone. The volatiles were removed in vacuo, and the product was redissolved in EtOAc, washed sequentially with $CuSO_4$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The title compound was isolated as a clear film (0.007 g, 92% yield): R_f = 0.29 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.01 (m, 1H, HC═), 6.00 (m, 1H, HC═), 5.35 (d, J = 1.9 Hz, 1H, CHOTBS), 4.95 (m, 1H, CHOAc), 4.2 (dd, J = 13.0, 2.8

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Hz, 1H, one of CH_2OR), 3.82 (dd, J = 13.0, 1.2 Hz, 1H, one of CH_2OR), 2.09 (s, 3H, OAc), 0.91 (s, 9H, $C(CH_3)_3$), 0.140 (s, 3H, $SiCH_3$), 0.136 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 133.2 (C5), 123.2 (C4), 87.9 (C6), 63.5 (C3), 61.2 (C2), 25.7, 21.1, 18.1, −5.3, −4.5; IR (film) 2955, 2931, 2858, 1739, 1372, 1237, 1109, 1031, 960, 870, 838 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{13}H_{24}O_4SiNa^+$ $[M + Na]^+$ 295.1342, found 295.1345, Δ = 1.0 ppm.

*Preparation of (±)-6-Hydroxy-3,6-dihydro-2H-pyran-3-yl Methyl Carbonate, **cis-** and **trans-10g**.* To a solution of *trans*-**10a** (0.096 g, 0.33 mmol, 1.0 equiv) in acetonitrile (8 mL), at room temperature, was added HF·pyridine (0.240 mL, 0.266 g, 13.3 mmol, 40 equiv). The reaction was stirred overnight before being quenched with saturated aqueous sodium bicarbonate, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (50% EtOAc/petroleum ether). The desired product was isolated as a clear oil composed of a ca. 3:1 mixture of *trans*- and *cis*-diastereomers, respectively. (0.018 g, 31% yield). R_f = 0.23 (40% EtOAc/petroleum ether). Characterization data for *trans*-**10g**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.14 (m, 1H, HC═), 6.10 (dd, J = 10.1, 2.6 Hz, 1H, HC═), 5.42 (dd, J = 4.8, 2.5 Hz, 1H, CHOH), 4.84 (ddd, J = 4.6, 3.0, 1.6 Hz, 1H, $CHCO_2Me$), 4.28 (dd, J = 13.1, 2.9 Hz, 1H, one of CH_2OR), 3.95 (m, 1H, one of CH_2OR), 3.80 (s, 3H, OCO_2CH_3), 2.77 (d, J = 4.2 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 132.0 (C5), 124.5 (C4), 87.7 (C6), 66.5 (C3), 61.1 (C2), 55.0. Characterization data for *cis*-**10g**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.04 (dd, J = 10.3, 2.8 Hz, 1H, HC═), 5.96 (dt, J = 10.3, 1.8 Hz, 1H, HC═), 5.33 (m, 1H, CHOH), 5.10 (dddt, J = 6.6, 5.0, 3.1, 1.7 Hz, 1H, $CHOCO_2Me$), 3.95 (m, 2H, CH_2OR), 3.80 (s, 3H, OCO_2CH_3), 2.90 (d, J = 6.4 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 131.0 (C5), 127.9 (C4), 89.3 (C6), 68.0 (C3), 61.0 (C2), 54.9. Combined data: IR (film) 3413, 2959, 2925, 1740, 1443, 1252, 1061, 975, 937 cm^{-1}; HRMS-ESI (m/z) calcd for $C_7H_{10}O_5Na^+$ $[M + Na]^+$ 197.0426, found 197.0422, Δ = 2.0 ppm. These data match those previously obtained.[17]

General Procedure for the Saponification of 3,6-Dihydro-2*H*-pyran-3-yl Acetates. *Preparation of (3S,6R)- and (3S,6S)-6-Isopropoxy-3,6-dihydro-2H-pyran-3-ol, **cis-** and **trans-10j**.* To a solution of (3*S*,6*S*)- and (3*S*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-3-yl acetate (**10h**, 0.047 g, 0.232 mmol, 1.0 equiv, 3.4:1 ratio of ***trans*-10h**:***cis*-10h**) in methanol (2.5 mL) was added K_2CO_3 (0.160 g, 1.16 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 3 h before being quenched with H_2O and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The title compounds were isolated together as a clear colorless oil. Characterization data for *trans*-**10j**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.11 (dd, J = 10.0, 5.3 Hz, 1H, HC═), 5.85 (dd, J = 10.0, 3.1 Hz, 1H, HC═), 5.04 (d, J = 3.0 Hz, 1H, CHO*i*Pr), 4.14 (dd, J = 12.3, 2.6 Hz, 1H, one of CH_2OR), 3.98 (m, 1H, $OCH(Me)_2$), 3.81 (app s, 1H, CHOH), 3.77 (app d, J = 12.3 Hz, 1H, one of CH_2OR), 2.11 (br. s, 1H, OH), 1.23 (d, J = 6.4 Hz, 3H, CH_3), 1.17 (d, J = 6.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 129.07 (C5), 128.95 (C4), 91.31 (C6), 69.82, 64.11 (C2), 61.63 (C3), 23.53, 21.82. Characterization data for *cis*-**10j**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.00 (m, 1H, HC═), 5.74 (dt, J = 10.2, 2.1 Hz, 1H, HC═), 5.01 (app s, 1H, CHO*i*Pr), 4.22 (app s, 1H, CHOH), 3.98 (m, 1H, $OCH(Me)_2$), 3.79−3.69 (m, 2H, CH_2OR), 1.84 (br. s, 1H, OH), 1.24 (d, J = 7.0 Hz, 3H, CH_3), 1.17 (d, J = 6.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.8 (C4), 128.4 (C5), 92.7 (C6), 70.3, 63.6 (C2), 63.2 (C3), 23.6, 21.9. Characterization data match those reported previously.[38]

*Preparation of (3S,6R)-6-Allyloxy-3,6-dihydro-2H-pyran-3-ol, trans-**10k**.* Using the general procedure for acetate saponification, (3*S*,6*S*)-6-allyloxy-3,6-dihydro-2*H*-pyran-3-yl acetate (0.036 g, 0.18 mmol, 1.0 equiv), MeOH (2.5 mL) and K_2CO_3 (0.124 g, 0.90 mmol, 5.0 equiv) were added to the reaction. The title compound was obtained as a clear colorless oil (0.010 g, 36% yield): ^1H NMR ($CDCl_3$, 500 MHz) δ 6.14 (ddt, J = 10.0, 5.3, 1.1 Hz, 1H, HC═), 5.95 (m, 1H, HC═), 5.90 (dd, J = 10.0, 3.3 Hz, 1H, HC═), 5.30 (ddd, J = 17.2, 3.6, 2.0 Hz, 1H, one of $═CH_2$), 5.21 (m, 1H, one of $═CH_2$), 4.99 (d, J = 3.1 Hz, 1H, CHOAllyl), 4.26 (ddt, J = 12.7, 5.2, 1.4 Hz, 1H, one of $OCH_2C═$), 4.13 (dd, J = 12.2, 2.5 Hz, 1H, one of CH_2OR), 4.06 (ddt, J = 12.7, 5.2, 1.4 Hz, 1H, one of $OCH_2C═$), 3.93 (app s, 1H, CHOH), 3.79 (dt, J = 12.2, 1.3 Hz, 1H, one of CH_2OR), 2.00 (d, J = 8.9 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.19, 129.22 (C4), 128.47 (C5), 117.56, 92.31 (C6), 68.5, 64.30 (C2), 61.54 (C3); IR (film) 3398, 2922, 1399, 1319, 1260, 1188, 1099, 1077, 1033, 964, 930, 833 cm^{-1}; $[\alpha]_D^{25}$ = +68.3 (c = 0.5, $CHCl_3$); HRMS-ESI (m/z) calcd for $C_8H_{12}O_3Na^+$ $[M + Na]^+$ 179.0684, found 179.0688, Δ = 2.2 ppm.

*Preparation of (3S,6S)-6-allyloxy-3,6-dihydro-2H-pyran-3-ol, cis-**10k**.* Using the general procedure for acetate saponification, (3*S*,6*R*)-6-allyloxy-3,6-dihydro-2*H*-pyran-3-acetate (0.016 g, 0.081 mmol, 1.0 equiv), MeOH (2.5 mL), and K_2CO_3 (0.056 g, 0.40 mmol, 5.0 equiv) were added to the reaction. The title compound was obtained as a clear colorless oil (0.004 g, 32% yield): ^1H NMR ($CDCl_3$, 500 MHz) δ 6.04 (m, 1H, HC═), 5.95 (m, 1H, HC═), 5.80 (dt, J = 10.3, 2.0 Hz, 1H, HC═), 5.31 (m, 1H, one of $═CH_2$), 5.21 (m, 1H, one of $═CH_2$), 4.98 (m, 1H, CHOAllyl), 4.28 (m, 1H, one of $OCH_2C═$), 4.25 (m, 1H, CHOH), 4.07 (dd, J = 12.7, 6.3 Hz, 1H, one of $OCH_2C═$), 3.82 (dd, J = 11.0, 5.3 Hz, 1H, one of CH_2OR), 3.72 (dd, J = 11.0, 8.0 Hz, 1H, one of CH_2OR), 1.56 (br. s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.2, 133.0, 127.8, 117.5, 93.7, 69.2, 63.8, 63.2; IR (film) 3397, 2919, 1395, 1276, 1261, 1186, 1032, 935, 884 cm^{-1}; $[\alpha]_D^{25}$ = +34.7 (c = 0.19, $CHCl_3$); HRMS-ESI (m/z) calcd for $C_8H_{12}O_3Na^+$ $[M + Na]^+$ 179.0684, found 179.0681, Δ = 1.7 ppm.

*Preparation of Benzyl cis-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-yl Carbonate, **10m**.* To a solution of *cis*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-ol (0.753 g, 3.27 mmol, 1.0 equiv) in 32 mL of freshly distilled CH_2Cl_2 was added DMAP (0.499 g, 4.08 mmol, 1.25 equiv), followed by benzyl chloroformate (0.582 mL, 0.696 g, 4.08 mmol, 1.25 equiv). The reaction was stirred overnight at room temperature before concentration in vacuo and purification by flash column chromatography (silica gel, 5% EtOAc/petroleum ether). The desired product was isolated as a clear colorless oil (0.604 g, 51% yield). R_f = 0.26 (5% EtOAc/petroleum ether): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.32 (complex m, 5H, ArH), 5.92 (ddt, J = 10.3, 2.2, 1.0 Hz, 1H, HC═), 5.84 (dt, J = 10.3, 2.0 Hz, 1H, HC═), 5.27 (app s, 1H, CHOTBS), 5.18−5.16 (complex m, 2H, OCH_2Ph), 5.14 (tdd, J = 5.6, 2.8, 1.3 Hz, 1H, $CHOCO_2Bn$), 3.91 (dd, J = 11.1, 7.9 Hz, 1H, one of CH_2OR), 3.87 (ddd, J = 11.2, 5.8, 1.0 Hz, 1H, one of CH_2OR), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6, 135.0, 132.2 (C5), 128.6, 128.6, 128.3, 126.4 (C4), 89.2 (C6), 69.8, 68.5 (C3), 60.0 (C2), 25.7, 18.0, −4.4, −5.2; IR (film) 2954, 2930, 2857, 1742, 1384, 1246, 1099, 1034, 867, 837, 779 cm^{-1}; HRMS-ESI (m/z) calcd for $C_{19}H_{28}O_5SiNa^+$ $[M + Na]^+$ 387.1604, found 387.1602; Δ = 0.5 ppm.

*Preparation of 4-[[cis-(±)-6-[(tert-Butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran-3-yl]oxy]-6-methyl-2H-pyran-2-one, **10n**.* A reaction vessel was charged with 4-hydroxy-6-methyl-α-pyrone (0.040 g, 0.315 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (0.0037 g, 0.0032 mmol, 1 mol %), evacuated, and backfilled with argon. Toluene (6 mL, degassed by sparging with argon for approximately 20 min) was added to the reaction vessel, followed by the substrate, *cis*-(±)-6-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-3-yl methyl carbonate (0.091 g, 0.315 mmol, 1.0 equiv). The reaction was stirred overnight at room temperature before being concentrated *in vacuo* and purified by flash column chromatography (silica gel, 30% EtOAc/petroleum ether). The title compound was isolated as a yellow oil (0.009 g, 9% yield): R_f = 0.20 (30% EtOAc/petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.95 (app dt, J = 10.3, 0.9 Hz, 1H, HC═), 5.89 (app dt, J = 10.3, 1.9 Hz, 1H, HC═), 5.77 (m, 1H, PyH), 5.41 (d, J = 2.1 Hz, 1H, CHOTBS), 5.30 (s, 1H, PyH), 4.79 (m, 1H, PyOCH), 3.95 (dd, J = 11.1, 8.0 Hz, 1H, one of CH_2OR), 3.88 (ddd, J = 11.1, 5.4, 0.9 Hz, 1H, one of CH_2OR), 2.20 (s, 3H, $PyCH_3$), 0.91 (s, 9H, $C(CH_3)_3$), 0.13 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 164.7, 162.6, 132.7 (C5), 125.2 (C4), 100.6, 89.3 (C6), 88.4, 68.6 (C3), 59.8 (C2), 25.7, 19.9, 18.0, −4.4, −5.3; IR (film) 2929, 2857, 1731, 1711, 1650, 1563, 1248, 1035, 838, 781 cm^{-1}; HRMS-ESI (m/z) calcd for

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$C_{17}H_{26}O_5SiNa^+$ $[M + Na]^+$ 361.1447, found 361.1443; Δ = 1.1. These data match those previously obtained.[17]

■ ASSOCIATED CONTENT

Supporting Information

Additional chemical shift analysis of compounds that do not fit the template, use of RMS variance to assess template matching and assign confidence levels, a listing of calculated ^{13}C NMR shifts of compounds **10a** to **10h**, 1 and 2D NMR data tables showing the assignment of all ^{13}C and ^{1}H resonances, ^{1}H and ^{13}C NMR spectra for all novel compounds, a description of computational methods, Cartesian coordinates, and energies derived from density functional calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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