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Stereospecific Hydrogenolysis of Benzylic Alcohols over Pd/C

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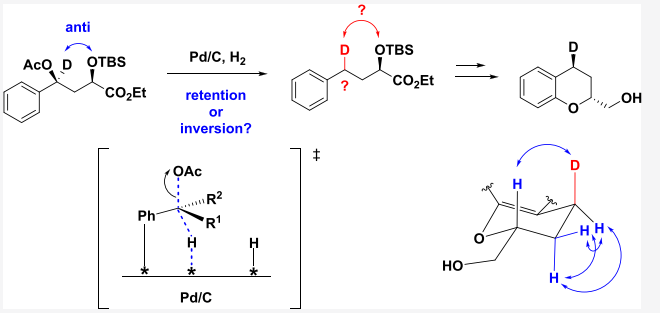
ABSTRACT: Hydrogenolysis of tertiary benzylic alcohols on palladium on carbon (Pd/C) generally proceeds with inversion of configuration. However, little is known about the hydrogenolysis mechanism of primary and secondary benzylic alcohols. Literature precedents suggest that these substrates may interact differently with the catalyst. To study the mechanism, we synthesized a pair of deuterated diastereoisomers with a chiral center at the benzylic position. Chemical derivatization of the hydrogenolysis products showed that the reaction proceeds with inversion of configuration for these substrates.



Benzylic bonds have an unusually low dissociation energy,[1] giving the benzylic position its unique reactivity toward homolytic cleavage of carbon−heteroatom (and recently, carbon−carbon)[2] bonds under mild conditions. A familiar example of such reactivity is the benzyl protecting group, which can be removed from an alcohol by the hydrogenolysis of the benzylic carbon−oxygen bond with transition metal catalysts such as Raney nickel or palladium on carbon (Pd/C).[3]

It is widely accepted that hydrogenolysis reactions on Raney nickel and Pd/C are stereospecific: hydrogenolysis on Raney nickel proceeds with retention of configuration at the benzylic center, and hydrogenolysis on Pd/C proceeds with inversion of configuration. While both metals strongly adsorb the aromatic ring, their reactivity differs in their affinity for oxygen: Raney nickel has a high affinity for oxygen (Figure 1a) and interacts with it preferentially, whereas Pd/C has a low affinity for oxygen (Figure 1b) and interacts with the other substituents.

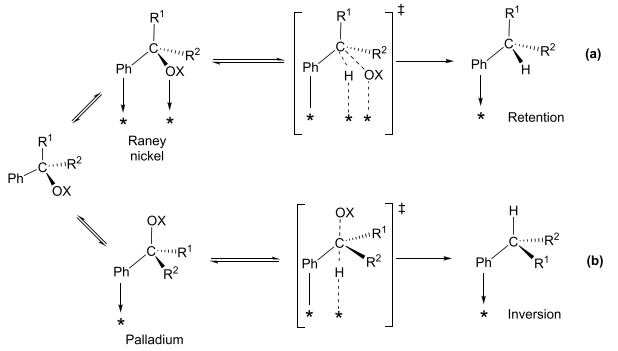


Figure 1. Hydrogenolysis mechanisms on Raney nickel and palladium. Image reproduced from ref 5e.

This explanation has been used to rationalize the opposing stereochemical outcomes of the reactions.[4]

The stereochemistries of Pd/C and Raney nickel hydrogenolysis reactions are supported by a wealth of experimental data. However, for hydrogenolysis reactions on Pd/C, there are many examples in the literature of reactions that proceed with retention of configuration rather than inversion, depending on the size of the benzylic substituents and the identity of the leaving group.[5] For example, the hydrogenolysis of aryl ether leaving groups tends to proceed with retention of configuration (presumably because of adsorption of the aryl on the catalyst), and bulky substituents at the benzylic position can lead to nonselective hydrogenolysis or retention of configuration. Notably, Kieboom[6] observed that benzyl alcohol is more strongly adsorbed on Pd/C than its toluene product, indicating that the oxygen atom may contribute to the adsorption on the catalyst in the case of nontertiary benzylic alcohols. This suggests that the hydrogenolysis mechanism on Pd/C may be fundamentally similar to that on Raney nickel but is more sensitive to the steric crowding of a quaternary benzylic carbon.

To investigate the reaction mechanism on Pd/C, we looked at the hydrogenolysis of deuterated secondary alcohols **3** and **4**, leading to diastereoisomers **1** and **2** (Scheme 1).

These nontertiary alcohols will allow us to probe the fundamental hydrogenolysis mechanism on Pd/C without the added parameter of steric hindrance, while still possessing a

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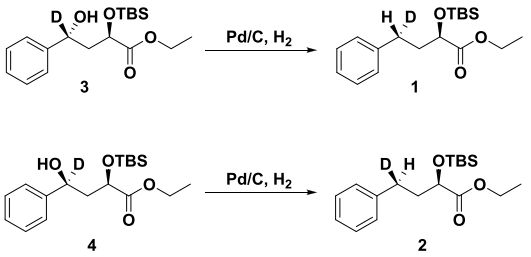
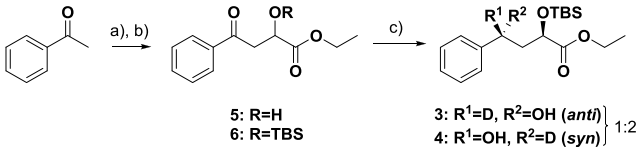
Scheme 1. Hydrogenolysis of Diastereoisomers 3 and 4



chiral center at the benzylic position. Analysis of **1** and **2** will give information about whether the reaction proceeds with inversion or retention of configuration.

Deuterated alcohols **3** and **4** were accessible in three steps from acetophenone (Scheme 2). They are spectroscopically distinct and chromatographically separable.

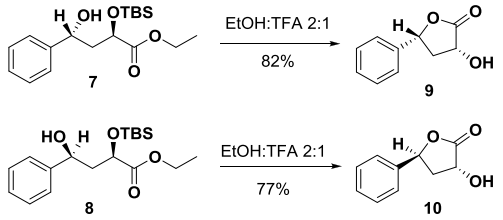
Scheme 2. Synthesis of Deuterated Alcohols 3 and 4[a]



[a]Reagents and conditions: (a) ethyl glyoxylate, 100 °C, 3 days, 75%; (b) TBSCl, imidazole, CH_2Cl_2, rt, 98%; (c) $NaBD_4$, MeOD, 0 °C, 45 min, 92%.

To assign their stereochemistry as *syn* or *anti*, we decided to chemically derivatize their nondeuterated counterparts, **7** and **8** (Scheme 3). Hydroxy esters **7** and **8** readily cyclize to lactones

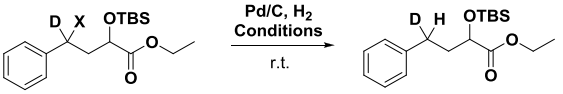
Scheme 3. Cyclization to Lactones 9 and 10



9 and **10**. These lactones, and their relative configurations, are known in the literature and have been verified by ^{1}H NMR and NOE experiments.[7] Lactone **9** (originating from **7**) is *cis* according to literature precedents, allowing us to assign its starting ester **7** (and its deuterated counterpart **3**) as *anti*. Likewise, lactone **10** is *trans* according to the literature, meaning that its starting ester **8** (and its deuterated counterpart **4**) is *syn*.

Our first attempt at the hydrogenolysis of **3**−**1** on Pd/C did prove to be stereospecific (Table 1, entry 1) but suffered from dilution of the isotopic purity (IP): the Pd/C catalyst also hydrogenolyses the deuterium atom off the benzylic center. This (over-) reactivity is known and has been exploited to fully deuterate the benzylic position.[8] To minimize the hydrogenolysis of the deuterium atom, we screened various additives, solvents, and benzylic leaving groups (alcohols **3** and **4**, acetates **11** and **12**, and trifluoroacetates (TFAc) **13** and **14**).

Table 1. Hydrogenolysis of Benzylic Alcohols, Acetates, and Trifluoroacetates[a]



no.	solvent	X	cat., additive (equiv)	T (min)	%[b]	IP
1	EtOH	OH	Pd/C	80	88	88
2	EtOH	OH	$Pd(OH)_2$	80	19	32
3	EtOH	OH	Pd/Al_2O_3	80	0[d]	
4	EtOH	OH	$Pd/BaSO_4$	80	0[d]	
5	EtOH	OAc	Pd/C	50	67	93
6	EtOH	OAc	Pd/C, AcOH	50	49	86
7	EtOH	OAc	Pd/C, Na_2CO_3	50	94	95
8	EtOH	TFAc	Pd/C	15	87	93[e]
9	EtOAc	TFAc	Pd/C	15	91	92[e]
10	MeOH	TFAc	Pd/C	12	89	94[e]
11	MeOH	TFAc	Pd/C, Na_2CO_3	12	40[f,g]	98[e]
12	EtOAc	TFAc	Pd/C, Na_2CO_3	12	63[g]	94[e]
13	MeOH	TFAc	Pd/C, NaOAc	12	88	97[e]
14	EtOAc	TFAc	Pd/C, NaOAc	12	77	98[e]
15	EtOH	OH	Pd/C, Na_2CO_3	80	0[d]	
16	EtOH	OH	Pd/C, NaOAc	80	0[d]	
17	MeOH	TFAc	Pd/C, EtPh (3)	12	92	97[e]
18	MeOH	TFAc	Pd/C, EtPh (10)	12	95	99[e]
19	EtPh	TFAc	Pd/C	12	0[e,f]	

[a]Reaction conditions: 5 mol % of Pd/C was suspended in the specified solvent under a H_2 atmosphere. The substrate (and additive) were added. After the specified time at rt, the reaction was filtered on Celite. [b]Yield after column chromatography. [c]Isotopic purity (IP) was determined by the integration of the benzylic ^{1}HNMR spectral signal. [d]No reaction. [e]Preactivation of the catalyst (10−20 min). [f]Lactone observed. [g]Alcohol observed (saponified acetate).

In all cases, whether alcohol **3** or **4** was used, the same corresponding diastereoisomer **1** or **2** was consistently obtained. The reaction was highly stereospecific: we did not observe scrambling of the benzylic center at any point during the reaction optimization process. Dilution of the isotopic purity occurred by an overreaction of the product on the catalyst, after hydrogenolysis of the benzylic C−O bond had taken place.

Other palladium catalysts either showed the same dilution of the isotopic purity (entry 2, palladium hydroxide) or were unreactive under the chosen conditions (entries 3 and 4). Acetylating the alcohol shortened the reaction time, which allowed for improved isotopic purity, but was still not optimal (entry 5). Acidic conditions with acetic acid lowered the yield and isotopic purity (entry 6). Basic conditions with sodium carbonate improved the yield and isotopic purity (entry 7). To reach even higher isotopic purity, we installed a trifluoroacetate leaving group and preactivated the catalyst by stirring under the H_2 atmosphere for a given time before adding the substrate. This shortened the reaction time and, even without added sodium carbonate, afforded the deuterated esters in good yield and isotopic purity in various solvents (entries 8, 9, and 10). However, in the presence of sodium carbonate, the yield was lowered (entry 11). This is due to the saponification of the trifluoroacetate group to the alcohol in basic medium, even in a non-nucleophilic solvent (entry 12). With sodium acetate, the yield and isotopic purity improved (entry 13). To verify whether the acetate leaving group itself affected the reaction once saponified, we tested the hydrogenolysis reaction

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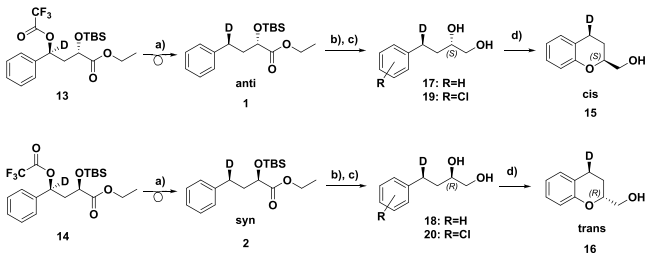
with sodium acetate and sodium carbonate on the free alcohol (entries 15 and 16). There was no reaction after the allotted reaction time. We also tested ethylbenzene (EtPh) as an additive (entries 17 and 18). This afforded the highest yields and almost no dilution of the isotopic purity. We proposed that an excess of EtPh as an additive occupied the free active sites on the catalyst and protected the product from overreaction, acting as a mild catalyst poison. Conducting the reaction in EtPh as the solvent completely inhibited the hydrogenolysis reaction (entry 19).

Next, we sought to prove the stereochemistry of the reaction. X-ray crystallography techniques cannot reliably distinguish between hydrogen and deuterium atoms, and linear esters **1** and **2** were not amenable to NMR techniques like NOESY, which require rigidity of the structure. Thus, we decided to chemically derivatize the linear esters to chromanes **15** and **16**, whose cyclic structures could be analyzed by NMR techniques (Scheme 4).

Scheme 4. Synthesis of Chromane Derivatives[a]



[a]Reagents and conditions: (a) Pd/C, H_2, ethylbenzene, MeOH, rt, 95%; (b) $LiAlH_4$, THF, 0 °C, 92−93%; (c) Oxone, KCl, TFA (cat.), $MeCN/H_2O$ 10:1, 39−55%; (d) $Pd(OAc)_2$, Trixiephos, Cs_2CO_3, toluene, 80 °C, 16%.

The reaction conditions were carefully chosen to avoid scrambling of the chiral centers; no epimerization was observed at any stage of the synthesis. First, esters **1** and **2** could be reduced to diols with concomitant removal of the TBS group by $LiAlH_4$. The diols could then undergo chlorination on the aromatic ring to afford an inseparable mixture of *ortho*- and *para*-chlorinated products, **19** and **20**. These were subjected to Buchwald cyclization conditions[9] to give the desired chromane products **15** and **16**.

Analysis of the methylene coupling constants (Ha, Hb, and Hc) by ^{1}H NMR spectroscopy allowed us to assign chromane **15** as *cis*, meaning that the configuration of ester **1** is *anti* (Figure 2; see Supporting Information for details). Chromane **16** was assigned as having a *trans* configuration, starting from *syn* ester **2**. ROESY experiments showed an interaction between protons Hd and Hc for *cis* chromane **15**, which was not observed in *trans* chromane **16**. As a result, we can conclude that the hydrogenolysis reaction mechanism on Pd/C does fundamentally proceed with inversion of configuration, and the oxygen atom in the leaving group does not interact with the catalyst.

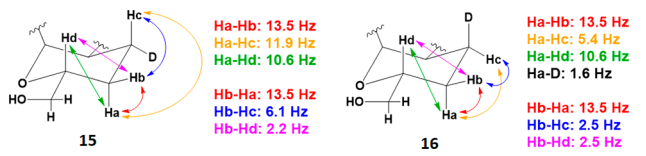
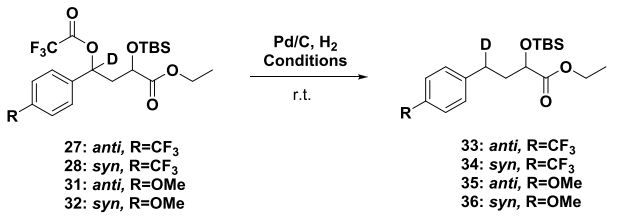


Figure 2. Coupling constants for chromanes **15** and **16**. Note that a chair representation was used for clarity, but the molecule is likely not in a perfect chair conformation.

Given the unique reactivity of the benzylic position and, in drug substances, its ready oxidation by P450 enzymes,[10] labeling this position stereospecifically could be of great interest for the elucidation of reaction mechanisms and drug metabolism pathways. To our knowledge, methods to stereospecifically deuterate the benzylic position are currently limited to S_N2 reactions, where a deuteride displaces a leaving group at the benzylic position.[11] These harsh conditions can often cause the elimination of the leaving group to give a styrene derivative instead of the desired S_N2 product. Thus, we decided to widen the scope of our reaction and optimize the conditions for substrates with electron-withdrawing and electron-donating substituents on the aromatic ring (Table 2). The starting trifluoroacetates were synthesized using the same reaction sequence as for the previous trifluoroacetates (Scheme 5).

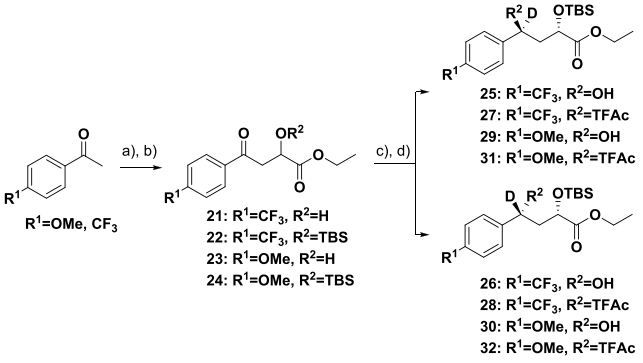
Table 2. Hydrogenolysis of Benzylic Trifluoroacetates with a Varying Electron Density[a]



no.	solvent	R	cat.	*t* (min)	yield (%)[b]	IP (%)[c]
1	EtOH	CF_3	Pd/C	10	47[d]	88
2	EtOH	CF_3	Pd/C, EtPh	5	10[e]	94
3	EtOAc	CF_3	Pd/C	55	92−95	99
4	EtOH	OMe	Pd/C	5	59[e,f]	
5	EtOAc	OMe	Pd/C, EtPh	20	0[f]	
6	EtOAc	OMe	Pd/C	3	41−67	98

[a]Reaction conditions: 5 mol % of Pd/C was suspended in the specified solvent under an H_2 atmosphere and stirred for 20 min. The substrate and additive were added. After the specified time at rt, the reaction was filtered on Celite. [b]Yield after column chromatography. [c]Isotopic purity was determined by the integration of the benzylic ^{1}HNMR spectral signal. [d]Incomplete reaction. [e]Lactone observed. [f]Alcohol observed (saponified trifluoroacetate).

Scheme 5. Synthesis of the Trifluoroacetates[a]



[a]Reagents and conditions: (a) ethyl glyoxylate, 100 °C; (b) TBSCl, imidazole, CH_2Cl_2, rt; (c) $NaBD_4$, ($CeCl_3$), MeOD, 0 °C; (d) TFAA, TEA, 0 °C.

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Even when filtered before reaction completion and with a large excess of EtPh, the isotopic purity of **33** or **34** after hydrogenolysis of **27** or **28** in ethanol did not exceed 94% (entries 1 and 2). However, hydrogenolysis in ethyl acetate allowed for excellent isotopic purity even at long reaction times, and no additives were needed (entry 3).

For electron-rich **35** or **36**, ethyl acetate was again required due to the instability of the trifluoroacetate group to nucleophilic solvents (entry 4). Adding EtPh as a mild catalyst poison caused the trifluoroacetate group to saponify, giving only the free alcohol and lactone (entry 5). The hydrogenolysis of electron-rich substrates **31** and **32** is almost instantaneous, allowing us to reach satisfactory isotopic purities and yields by filtering the reaction after only 3 min (entry 6).

To conclude, we have proven that, for hydrogenolysis reactions on Pd/C of secondary benzylic alcohols, the reaction mechanism fundamentally proceeds with inversion of configuration. Hydrogenolysis on Pd/C is highly stereospecific and takes place rapidly and in high yield in many different solvents at room temperature. The deuterium atom at the benzylic position was prone to hydrogenolysis by the catalyst, lowering the isotopic purity of the product. We were able to modulate the catalyst reactivity with common additives such as sodium carbonate, sodium acetate, or ethylbenzene. Ethylbenzene was especially useful for preventing overreaction on the catalyst and allowed for excellent isotopic purity of the product. Stereospecific benzylic deuteration could also be a useful tool for the elucidation of reaction mechanisms and drug metabolism pathways. Thus, we widened the scope of the hydrogenolysis reaction by optimizing the conditions for substrates bearing electron-rich or electron-poor aromatic rings.

■ EXPERIMENTAL PART

Unless otherwise indicated, all reagents were obtained from commercial suppliers (Fluka, Aldrich, Acros, TCI, Fluorochem, Strem) and were used without further purification. Dry solvents (toluene, CH_2Cl_2, THF, and Et_2O) were obtained from the building's solvent purification system (alumina-packed columns). Deuterated solvents were obtained from Cambridge Isotope Laboratory. Analytical thin-layer chromatography was performed on Kieselgel F-254 precoated aluminum sheet TLC plates from Merck. Visualization was performed with a 254 nm UV lamp and/or a $KMnO_4$ solution. Flash column chromatography was carried out using Brunschwig silica gel (SiO_2, 60 Å, 32−63 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-DRX-300 spectrometers. All NMR spectra were recorded in $CDCl_3$, CD_3CN, and CD_3OD. Data were treated with ACD laboratories software, and all chemical shifts are expressed in parts per million (δ) using residual solvent signals as internal standards. The coupling constants (J) are reported in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), bs (broad singlet), and m (multiplet). IR spectra were recorded with a Fourier transform IR Bruker Tensor 27 spectrometer, neat; absorption bands are in cm^{-1}. ESI mass spectra were carried out with an LTQ Orbitrap XL with a nano ESI spectrometer. Melting point measurements were performed using a Büchi Melting Point B-540 device. Microwave heating was performed on a Biotage Initiator Microwave using Biotage microwave vials.

Ethyl 2-Hydroxy-4-oxo-4-phenylbutanoate (5). Acetophenone (2.9 mL, 25 mmol, 1 equiv) and ethyl 2-oxoacetate 50 wt % in toluene (4.9 mL, 25 mmol, 1 equiv) were heated to 100 °C in an oil bath. After 90 h at this temperature, toluene was removed *in vacuo*, and the resulting yellow oil was purified by column chromatography (eluting with pentane/EtOAc 3:2) to give the title compound (3.55 g, 16.0 mmol, 75%) as a transparent oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−8.09 (m, 2H), 7.38−7.67 (m, 3H), 4.66 (dd, J = 5.9, 4.0 Hz, 1H), 4.26 (qd, J = 7.2, 0.9 Hz, 2H), 3.39−3.61 (m, 2H), 3.32 (bs, 1H), 1.27 ppm (td, J = 7.1, 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 173.7, 136.3, 133.5, 128.6 (2 C), 128.1 (2 C), 67.1, 61.8, 42.1, 14.0; FT-IR (ATR, neat, cm^{-1}) 3486; 2982; 2360; 1732; 1682; 1597; 1682; 1449; 1367; 1268; 1206; 1097; 1040; 758; 691; 624; HR-MS (ESI+) m/z calcd for $C_{12}H_{14}O_4Na$ $[M + Na]^+$ 245.0784, found 245.0784.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-oxo-4-phenylbutanoate (6). Compound **5** (3.55 g, 16.0 mmol, 1 equiv) and imidazole (5.44 g, 79.9 mmol, 5 equiv) were dissolved in dry CH_2Cl_2 (50 mL) under argon, and TBS-Cl (6 g, 40 mmol, 2.5 equiv) was added. The reaction was stirred overnight at rt. $NaHCO_3$ sat. solution (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale yellow oil. It was purified by column chromatography (eluting with pentane/Et_2O 9:1) to give **S2** (5.29 g, 15.7 mmol, 98%) as a transparent oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.91 (m, 2H), 7.62−7.53 (m, 1H), 7.50−7.43 (m, 2H), 4.87 (dd, J = 4.8, 7.6 Hz, 1H), 4.21 (qd, J = 1.5, 7.2 Hz, 2H), 3.47−3.30 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.84 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 173.0, 137.0, 133.2, 128.6 (2C), 128.3 (2C), 69.1, 61.1, 43.5, 25.6, 18.1, 14.1, −5.0, −5.4; FT-IR (ATR, neat, cm^{-1}) 2955; 2930; 2896; 2857; 1752; 1686; 1598; 1581; 1472; 1449; 1363; 1275; 1252; 1179; 1131; 1058; 1029; 952; 831; 778; 689; HR-MS (ESI+) m/z calcd for $C_{18}H_{28}O_4SiNa$ $[M + Na]^+$ 359.1649, found 359.1641.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate (7 and 8). Compound **6** (0.098 g, 0.291 mmol, 1 equiv) was dissolved in 5 mL of MeOH and cooled to 0 °C (ice bath). Then $NaBH_4$ (0.033 g, 0.873 mmol, 3 equiv) was added. After 45 min at 0 °C, NH_4Cl sat. solution (10 mL) was added and stirred at rt for 20 min to neutralize all remaining hydride. MeOH was removed by rotatory evaporation, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The oil was purified by column chromatography (eluting with pentane/EtOAc 92:8) to give the isomer *anti* **7** (0.028 g, 0.082 mmol, 28%) and the isomer *syn* **8** (0.033 g, 0.098 mmol, 34%) as transparent oils, as well as a mixture of both diastereoisomers (0.018 g, 0.053 mmol, 18%). Total yield: 0.079 g, 0.233 mmol, 80%.

*Ethyl anti-2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate (**7**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.21 (m, 5H), 4.93 (td, J = 2.8, 9.6 Hz, 1H), 4.57 (dd, J = 4.0, 6.8 Hz, 1H), 4.21 (m, 2H), 2.90 (d, J = 2.7 Hz, 1H), 2.23−2.02 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 0.97 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 144.2, 128.4 (2 C), 127.4, 125.6 (2 C), 70.9, 70.6, 61.0, 43.7, 25.7 (3 C), 18.3, 14.2, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 3512; 2954; 2929; 2894; 2857; 1750; 1733; 1471; 1371; 1251; 1184; 1126; 1062; 1028; 979; 090; 835; 778; 700; 666; 624; HR-MS (ESI+) m/z calcd for $C_{18}H_{30}O_4SiNa$ $[M + Na]^+$ 361.1806, found 361.1800.

*Ethyl syn-2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate (**8**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.22 (m, 5H), 5.00 (td, J = 3.1, 8.8 Hz, 1H), 4.46 (dd, J = 5.3, 6.8 Hz, 1H), 4.18 (d, J = 7.1 Hz, 1H), 3.13 (d, J = 2.7 Hz, 1H), 2.26−2.09 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.96 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 143.8, 128.4 (2 C), 127.5, 125.8 (2 C), 71.9, 71.5, 61.1, 43.7, 25.7 (3 C), 18.2, 14.1, −4.8, −5.4; FT-IR (ATR, neat, cm^{-1}) 3492; 2954; 2929; 2887; 2857; 1472; 1373; 1252; 1188; 1126; 1053; 1029; 834; 779; 701; 630; HR-MS (ESI+) m/z calcd for $C_{18}H_{30}O_4SiNa$ $[M + Na]^+$ 361.1806, found 361.1800.

*General Procedure for Cyclization to Lactones **9** and **10**.* Esters **7** or **8** (1 equiv) were dissolved in a 2:1 v/v mixture of EtOH and TFA (0.1 M reaction). After 18 h, the solvents were evaporated, and the resulting oil was purified by column chromatography (eluting with pentane/ethyl acetate 2:3) to give the title lactones. NMR shifts correspond to those in the literature.[7]

***cis*-3-Hydroxy-5-phenyldihydrofuran-2(3*H*)-one (9):** 82% yield, white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.32 (m, 5H), 5.38 (dd, J = 5.2, 11.0 Hz, 1H), 4.72 (dd, J = 8.1, 11.3 Hz, 1H),

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3.04 (dd, J = 4.9, 7.8 Hz, 1H), 2.99 (dd, J = 4.9, 7.8 Hz, 1H), 2.27 (td, J = 11.2, 12.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 137.7, 129.0, 128.9 (2 C), 125.9 (2 C), 77.7, 69.0, 39.5.

***trans*-3-Hydroxy-5-phenyldihydrofuran-2(3*H*)-one (10):** 77% yield, transparent oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.23 (m, 5H), 5.73 (dd, J = 4.4, 7.6 Hz, 1H), 4.58 (t, J = 7.6 Hz, 1H), 2.80−2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 138.7, 128.9 (2 C), 128.5, 125.0 (2 C), 78.7, 67.2, 38.2.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate-4-*d* (3 and 4). Compound **6** (5 g, 14.86 mmol, 1 equiv) was dissolved in 75 mL of MeOD under argon and cooled to 0 °C (ice bath). Then $NaBD_4$ (1.244 g, 29.72 mmol, 2 equiv) was added. After 45 min, NH_4Cl sat. solution (40 mL) was added and stirred at rt for 20 min to neutralize all remaining deuteride. MeOD was removed by rotatory evaporation, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The oil was purified by column chromatography (eluting with pentane/EtOAc 92:8) to give the isomer *anti* **3** (0.912 g, 2.69 mmol, 18%), the isomer *syn* **4** (1.906 g, 5.61 mmol, 38%), and a mixture of both diastereoisomers (1.83 g, 5.4 mmol, 36%) as transparent oils successively. Total yield: 4.65 g, 13.7 mmol, 92%.

*Ethyl anti-2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate-4-d (**3**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.21 (m, 5H), 4.57 (dd, J = 4.1, 6.9 Hz, 1H), 4.21 (ttd, J = 3.8, 7.2, 10.8 Hz, 2H), 2.20−2.01 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 144.2, 128.4 (2 C), 127.4, 125.6 (2 C), 70.6, 70.5 (t, J = 22.6 Hz), 61.0, 43.6, 25.7 (3 C), 18.3, 14.2, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 3512; 2955; 2930; 2895; 2857; 1735; 1472;1371; 1130; 837; 779; 701; 630; HR-MS (ESI+) m/z calcd for $C_{18}H_{29}DO_4SiNa$ $[M + Na]^+$ 362.1868, found 362.1863.

*Ethyl syn-2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutanoate-4-d (**4**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.19 (m, 5H), 4.45 (dd, J = 5.3, 6.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.27−2.07 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 143.9, 128.4, 127.5, 125.8, 71.4 (t, J = 22 Hz), 71.3, 61.0, 43.5, 25.7 (3 C), 18.2, 14.1, −4.9, −5.4; FT-IR (ATR, neat, cm^{-1}) 3497; 2954; 2930; 2896; 2857; 1736; 1472; 1448; 1374; 1252; 1190; 1131; 835; 779; 701; 630; HR-MS (ESI+) m/z calcd for $C_{18}H_{29}DO_4SiNa$ $[M + Na]^+$ 362.1868, found 362.1864.

*General Procedure for Acetylation (**11** and **12**).* Alcohols **3** or **4** (1 equiv) were dissolved in dry CH_2Cl_2 (0.05 M reaction) under argon. Triethylamine (5 equiv) was added, followed by acetic anhydride (2 equiv) and DMAP (0.2 equiv). After 4 h, cold NH_4Cl sat. solution was added to quench the reaction, which was then poured into a separatory funnel. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The acetates were purified by column chromatography (eluting with pentane/Et_2O 9:1).

***anti*-Ethyl 4-Acetoxy-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate-4-*d* (11):** obtained as a transparent oil (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 4.35 (dd, J = 3.3, 9.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.35 (dd, J = 3.3, 14.3 Hz, 1H), 2.07 (s, 3H), 2.02 (dd, J = 9.6, 14.2 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 169.9, 140.6, 128.5 (2 C), 127.9, 126.2 (2 C), 72.1 (t, J = 22.7 Hz), 69.0, 60.9, 42.0, 25.7 (3 C), 21.2, 18.2, 14.1, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 2956; 2930; 2896; 2857; 1744; 1472; 1449; 1368; 1232; 1189; 1125; 1085; 1071; 1022; 975; 938; 837; 779; 700; 667; 647; 629; HR-MS (ESI+) m/z calcd for $C_{20}H_{31}DO_5SiNa$ $[M + Na]^+$ 404.1979, found 404.1963.

***syn*-Ethyl 4-Acetoxy-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate-4-*d* (12):** obtained as a transparent oil (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.24 (m, 5H), 4.30−4.11 (m, 3H), 2.43 (dd, J = 5.0, 14.2 Hz, 1H), 2.21 (dd, J = 6.2, 14.2 Hz, 1H), 2.01 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 0.99−0.89 (m, 9H), 0.08 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 169.7, 140.0, 128.5 (2 C), 128.1, 126.7 (2 C), 71.8 (t, J = 23.5 Hz), 69.0, 60.8, 41.1, 25.7 (3 C), 21.0, 18.2, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2954; 2930; 2887; 2857; 1745; 1472; 1449; 1368; 1248; 1233; 1198; 1139; 1122; 1057; 1019; 936; 894; 836; 779; 701; 668; 631; HR-MS (ESI+) m/z calcd for $C_{20}H_{31}DO_5SiNa$ $[M + Na]^+$ 404.1979, found 404.1966.

*General Procedure for Trifluoroacetylation (**13** and **14**).* Alcohols **3** or **4** (1 equiv) were dissolved in dry CH_2Cl_2 (0.08 M reaction) under argon, and triethylamine (5 equiv) was added. The mixture was cooled to 0 °C (ice bath). Then trifluoroacetic anhydride (2 equiv) was added. After 1.5 h, cold NH_4Cl sat. solution was added to quench the reaction, which was then poured into a separatory funnel. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The trifluoroacetates were purified by column chromatography (eluting with pentane/Et_2O 9:1).

***anti*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-phenyl-4-(2,2,2-trifluoroacetoxy)butanoate-4-*d* (13):** obtained as a transparent oil (98%); ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 7.45−7.32 (m, 5H), 4.34 (dd, J = 3.9, 8.6 Hz, 1H), 4.05 (d, J = 7.2 Hz, 2H), 2.55 (dd, J = 3.9, 14.5 Hz, 1H), 2.14 (dd, J = 8.6, 14.5 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 173.4, 157.5 (q, J = 41.8 Hz), 138.8, 130.2, 129.9 (2 C), 127.7 (2 C), 115.6 (q, J = 285.4 Hz), 78.5 (t, J = 23.5 Hz), 69.6, 62.0, 41.9, 26.1 (3 C), 18.9, 14.5, −4.5, −5.3; FT-IR (ATR, neat, cm^{-1}) 2956; 2932; 2898; 2859; 1787; 1755; 1735; 1473; 1369; 1253; 1220; 1152; 975; 838; 778; 699; 630; HR-MS (ESI+) m/z calcd for $C_{20}H_{28}DO_5SiF_3Na$ $[M + Na]^+$ 458.1691, found 458.1689.

***syn*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-phenyl-4-(2,2,2-trifluoroacetoxy)butanoate-4-*d* (14):** obtained as a transparent oil (98%); ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 7.42 (m, 5H), 4.28 (dd, J = 4.8, 6.2 Hz, 1H), 4.14 (qd, J = 1.6, 7.1 Hz, 2H), 2.57 (dd, J = 4.7, 14.5 Hz, 1H), 2.31 (dd, J = 6.2, 14.5 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 173.5, 157.3 (q, J = 44.8 Hz), 138.6, 130.3, 130.0 (2 C), 127.9 (2 C), 115.6 (q, J = 285.0 Hz), 77.9 (t, J = 23.7 Hz), 69.3, 61.9, 41.0, 26.1 (3 C), 18.9, 14.5, −4.6, −5.1; FT-IR (ATR, neat, cm^{-1}) 2955; 2932; 2888; 2859; 1786; 1755; 1735; 1473; 1451; 1370; 1253; 1218; 1052; 981; 948; 836; 777; 727; 698; 667; HR-MS (ESI+) m/z calcd for $C_{20}H_{28}DO_5SiF_3Na$ $[M + Na]^+$ 458.1691, found 458.1691.

*General Procedure for Hydrogenolysis (**1** and **2**).* Pd/C 10% weight (0.05 equiv) was weighed in a two-neck round-bottom flask containing a stir bar and suspended in MeOH (0.02 M reaction) under argon. The flask was chosen such that the air volume above the reaction was larger than the reaction volume (for example, for a 60 mL reaction volume, a 250 mL two-neck flask was used). The argon balloon was replaced with a hydrogen balloon. The hydrogen balloon was triple-layered and remade every 2−3 reactions, and it was completely filled with hydrogen for each reaction. The stopper from the second neck was removed briefly to purge the argon out of the flask. The solution was stirred vigorously for 20 min, and the atmosphere was purged with H_2 once more. Then the trifluoroacetate **13** or **14** (1 equiv) in MeOH (5 mL per gram of trifluoroacetate) and ethylbenzene (10 equiv) was injected and vigorous stirring was maintained throughout the reaction. After 12 min, the reaction was filtered on Celite and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography (eluting with pentane/Et_2O 95:5).

Example on gram-scale: 1.143 g (2.62 mmol) **14** gave 0.785 g (2.42 mmol) **2**, 92% yield.

***anti*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-phenylbutanoate-4-*d* (1):** obtained as a transparent oil (58 mg, 0.18 mmol, 98% yield, 99% IP); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.19 (m, 5H), 4.31 (dd, J = 5.3, 6.5 Hz, 1H), 4.29−4.16 (m, 2H), 2.81 (t, J = 8.1 Hz, 1H), 2.15−2.05 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.01 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 141.5, 128.4 (4 C), 125.9, 71.8, 60.7, 36.8, 31.1 (t, J = 19.1 Hz), 25.7 (3 C), 18.3, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2954; 2930; 2895; 2857; 1752; 1732; 1497; 1472; 1370; 1251; 1184;

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1131; 1031; 970; 834; 777; 738; 699; 663; 627; HR-MS (ESI+) *m/z* calcd for $C_{18}H_{29}DO_3SiNa$ $[M + Na]^+$ 346.1919, found 346.1924.

***syn*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-phenylbutanoate-4-*d* (2):** obtained as a transparent oil (43 mg, 0.13 mmol, 98% yield, 99% IP); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.20 (m, 5H), 4.35−4.15 (m, 3H), 3.54 (q, J = 7.0 Hz, 1H), 2.78−2.68 (m, 1H), 2.18−2.00 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.00 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 141.5, 128.4 (4 C), 125.9, 71.8, 60.7, 36.9, 31.1 (t, J = 19.3 Hz), 25.7 (3 C), 18.3, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2954; 2930; 2896; 2857; 1752; 1732; 1472; 1362; 1251; 1181; 1131; 1029; 981; 833; 777; 738; 699; 666; HR-MS (ESI+) *m/z* calcd for $C_{18}H_{29}DO_3SiNa$ $[M + Na]^+$ 346.1919, found 346.1917.

*General Procedure for Reduction to Diols (**17** and **18**).* Deuterated ester **1** or **2** (1 equiv) was dissolved in dry THF (0.03 M reaction) under argon and cooled to 0 °C (ice bath). Then $LiAlH_4$ (3 equiv) was added. After 20 min, the reaction was quenched with NH_4Cl sat. solution and stirred until bubbling ceased. The ice bath was removed, and a saturated solution of Rochelle's salt was added. THF was removed under reduced pressure, and the remaining solution was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (3×). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. It was purified by column chromatography (eluting with EtOAc 100%) to give the desired diol.

*anti-4-Phenylbutane-4-d-1,2-diol (**17**).* transparent oil (93%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32−7.08 (m, 5H), 3.65−3.54 (m, 1H), 3.53−3.40 (m, 2H), 2.83−2.72 (m, 1H), 1.85−1.59 (m, 2H); ^{13}C NMR (101 MHz, methanol-d_4) δ 143.7, 129.6 (2 C), 129.5 (2 C), 126.9, 72.6, 67.5, 36.5, 32.6 (t, J = 19.8 Hz); FT-IR (ATR, neat, cm^{-1}) 3350; 3025; 2926; 2871; 2486; 1603; 1496; 1450; 1367; 1103; 1049; 1031; 979; 849; 746; 701; 632; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{13}DO_2Na$ $[M + Na]^+$ 190.0954, found 190.0946.

*syn-4-Phenylbutane-4-d-1,2-diol (**18**):* transparent oil (92%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.37−7.07 (m, 5H), 3.66−3.54 (m, 1H), 3.52−3.39 (m, 2H), 2.71−2.55 (m, 1H), 1.86−1.58 (m, 2H); ^{13}C NMR (101 MHz, methanol-d_4) δ 143.7, 129.6 (2 C), 129.5 (2 C), 126.9, 72.7, 67.5, 36.5, 32.7 (t, J = 19.1 Hz); FT-IR (ATR, neat, cm^{-1}) 3349; 3025; 2930; 2872; 2482; 1603; 1496; 1451; 1102; 1046; 1031; 975; 929; 915; 855; 746; 700; 655; 622; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{13}DO_2Na$ $[M + Na]^+$ 190.0954, found 190.0944.

*General Procedure for Chlorination (**19** and **20**).* Diol **17** or **18** (1 equiv) was dissolved in MeCN (0.3 M reaction). Water (20 equiv) was added, followed by TFA (0.1 equiv) and KCl (1.3 equiv). Lastly, Oxone (1 equiv) was added, and the reaction was rapidly wrapped in foil. After 5 h of stirring in the dark, the reaction was quenched with $Na_2S_2O_3$ sat. solution and diluted with EtOAc. It was transferred to an extraction funnel, and the aqueous phase was extracted with EtOAc (3×). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a to give a pale yellow oil. It was purified by column chromatography (eluting with EtOAc 100%) to give the desired chlorinated products as an inseparable mixture of *ortho*- and *para*-chlorinated diols in a 1:1 ratio.

*anti-4-(x-Chlorophenyl)butane-4-d-1,2-diol (**19**):* transparent oil (39%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.37−7.07 (m, 4 H), 3.69−3.41 (m, 3H), 2.98−2.70 (m, 1H), 1.89−1.57 (m, 2H); ^{13}C NMR (101 MHz, methanol-d_4) δ 142.5, 141.2, 135.0, 132.7, 131.8, 131.2, 130.6, 129.5, 128.7, 128.2, 72.8, 72.5, 67.5, 36.3, 34.6, 31.9 (t, J = 19.1 Hz) 30.5 (t, J = 19.1 Hz); FT-IR (ATR, neat, cm^{-1}) 3342; 2929; 2874; 2479; 1492; 1473; 1440; 1405; 1092; 1048; 1037; 1015; 986; 9412; 863; 819; 750; 642; 620; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{12}DClO_2Na$ $[M + Na]^+$ 224.0565, found 224.0557.

*syn-4-(x-Chlorophenyl)butane-4-d-1,2-diol (**20**):* transparent oil (55%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.37−7.07 (m, 4 H), 3.68−3.37 (m, 3H), 2.85−2.54 (m, 1H), 1.90−1.54 (m, 2 H) ^{13}C NMR (101 MHz, methanol-d_4) δ 142.5, 141.2, 135.0, 132.6, 131.8, 131.2, 130.6, 129.5, 128.7, 128.2, 72.8, 72.5, 67.5, 61.7, 36.3, 34.6, 32.0 (t, J = 19.1 Hz) 30.6 (t, J = 19.8 Hz); FT-IR (ATR, neat, cm^{-1}) 3346; 2929; 2872; 2482; 1595; 1492; 1474; 1440; 1092; 1037; 1015; 817; 750; 675; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{12}DClO_2Na$ $[M + Na]^+$ 224.0565, found 224.0558.

*General Procedure for Cyclization (**15** and **16**).* A microwave vial was charged with $Pd(OAc)_2$ (5 mol %), Trixiephos (10 mol %), and Cs_2CO_3 (2.5 equiv). The vial was sealed, evacuated, and backfilled with argon. Aryl chloride **19** or **20** (1 equiv) in dry toluene (0.07 M reaction) was added via syringe. The reaction was heated to 80 °C using microwave irradiation. After 24 h, the reaction was diluted with EtOAc and filtered through a pad of Celite. The organic phase was then extracted with NH_4Cl sat. solution (1×) and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a to give a yellow oil. It was purified by column chromatography (eluting with pentane/EtOAc 3:2) to give the desired chromanes.

(*cis*-Chroman-2-yl-4-*d*)methanol (15): pale yellow oil (16%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.08−6.95 (m, 2H), 6.83−6.51 (m, 2H), 4.17−3.93 (m, 1H), 3.71 (d, J = 5.1 Hz, 2H), 2.84 (m, 1H), 2.01 (ddd, J = 2.3, 6.1, 13.5 Hz, 1H), 1.84−1.67 (m, 1H); ^{13}C NMR (101 MHz, methanol-d_4) δ 156.3, 130.6, 128.3, 123.4, 121.3, 117.8, 78.0, 65.9, 25.3 (t, J = 19.8 Hz) (2 C); FT-IR (ATR, neat, cm^{-1}) 3379; 2925; 2874; 1720; 1609; 1581; 1487; 1455; 1297; 1229; 1088; 1075; 1043; 997; 939; 906; 881; 841; 752; 701; 632; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{11}DO_2Na$ $[M + Na]^+$ 188.0792, found 188.0792.

(*trans*-Chroman-2-yl-4-*d*)methanol (16): pale yellow oil (16%); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.06−6.98 (m, 2H), 6.82−6.69 (m, 2H), 4.06−3.98 (m, 1H), 3.71 (d, J = 5.1 Hz, 2H), 2.74 (dd, J = 2.3, 5.0 Hz, 1H), 2.09−1.95 (m, 1H), 1.83−1.65 (m, 1H); ^{13}C NMR (101 MHz, methanol-d_4) δ 156.3, 130.7, 128.3, 123.3, 121.3, 117.8, 78.0, 65.9, 25.3 (t, J = 19.8 Hz); FT-IR (ATR, neat, cm^{-1}) 3387; 2924; 2876; 1718; 1609; 1580; 1487; 1454; 1396; 1345; 1297; 1275; 1232; 1180; 1079; 1033; 924; 930; 907; 837; 752; 701; 631; HR-MS (ESI+) *m/z* calcd for $C_{10}H_{11}DO_2Na$ $[M + Na]^+$ 188.0792, found 188.0792.

Ethyl 2-Hydroxy-4-oxo-4-(4-(trifluoromethyl)phenyl)-butanoate (21). 1-(4-(Trifluoromethyl)phenyl)-ethan-1-one (5.0 g, 26.6 mmol, 1 equiv) and ethyl 2-oxoacetate (6.3 mL, 32 mmol, 1.2 equiv) (50% in toluene) were stirred at 100 °C in an oil bath for 5 days. Toluene was removed *in vacuo*, and the resulting bright yellow oil was purified by column chromatography (eluting with pentane/EtOAc 7:3) to give **21** (5.4 g, 18.6 mmol, 70%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 4.68 (td, J = 3.9, 5.6 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.62−3.41 (m, 2H), 3.28 (d, J = 5.4 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 173.6, 139.1, 134.9 (q, J = 33.0 Hz), 128.5 (2 C), 125.8 (q, J = 3.7 Hz, 2 C), 123.5 (q, J = 272.2 Hz), 67.0, 62.1, 42.4, 14.1; FT-IR (ATR, neat, cm^{-1}) 3379; 3328; 2996; 2962; 2938; 2914; 1721; 1694; 1514; 1478; 1413; 1389; 1369; 1328; 1278; 1160; 1125; 1068; 1034; 1017; 997; 950; 894; 859; 842; 730; 700; 640; 608; HR-MS (ESI+) *m/z* calcd for $C_{13}H_{13}F_3O_4Na$ $[M + Na]^+$ 313.0664, found 313.0660; mp 65−68 °C.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-oxo-4-(4-(trifluoromethyl)phenyl)butanoate (22). Compound **21** (3.0 g, 10.4 mmol 1 equiv) was dissolved in dry CH_2Cl_2 (60 mL) under argon, and then imidazole (1.5 g, 22.8 mmol, 2.2 equiv) and TBS-Cl (1.7 g, 11.4 mmol, 1.1 equiv) were added. The reaction was stirred overnight and then quenched with NH_4Cl sat. solution (50 mL). The reaction was poured into an extraction funnel, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale yellow oil. It was purified by column chromatography (eluting with pentane/EtOAc 9:1) to give **22** (3.81 g, 9.4 mmol, 91%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 4.86 (dd, J = 4.8, 7.5 Hz, 1H), 4.26−4.18 (m, 2H), 3.48−3.31 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 172.7, 139.7, 134.5 (q, J = 33.0 Hz), 128.6 (2 C), 125.7 (q, J = 4.2 Hz, 2 C), 123.5 (q, J = 272.2 Hz), 69.1, 61.3, 43.7, 25.6 (3 C), 18.1, 14.1, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 2956; 2931; 2899; 2858; 1752; 1693; 1512; 1473; 1410; 1324; 1256; 1170; 1130; 1110; 1066; 1027; 994; 943; 880; 828; 780; 720; 665; 630;

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HR-MS (ESI+) m/z calcd for $C_{19}H_{27}F_3O_4SiNa$ $[M + Na]^+$ 427.1528, found 427.1539.

Ethyl 2-Hydroxy-4-(4-methoxyphenyl)-4-oxobutanoate (23). 1-(4-Methoxyphenyl)ethan-1-one (6 g, 40 mmol, 1 equiv) and ethyl 2-oxoacetate (8 mL, 40 mmol, 1 equiv) (50% in toluene) were stirred at 100 °C in an oil bath for 5 days. Toluene was removed *in vacuo*, and the resulting yellow oil was purified by column chromatography (pentane/EtOAc 2:3) to give **23** (7.96 g, 31.6 mmol, 79%) as a pale yellow crystalline solid. NMR shifts correspond to those in the literature:[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.90 (m, 2H), 6.98−6.90 (m, 2H), 4.69−4.61 (m, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.54−3.36 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 173.8, 163.9, 130.5 (2 C), 129.5, 113.8 (2 C), 67.4, 61.8, 55.5, 41.7, 14.1.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-4-oxobutanoate (24). Compound **23** (6.14 g, 24.35 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (60 mL) under argon, and imidazole (3.98 g, 58.44 mmol, 2.4 equiv), followed by TBS-Cl (4.40 g, 29.22 mmol, 1.2 equiv), was added. The reaction was stirred overnight. It was then quenched with $NaHCO_3$ sat. solution (60 mL) and poured into an extraction funnel. The aqueous layer was extracted with CH_2Cl_2(3 × 50 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a brown oil. It was purified by column chromatography (eluting with pentane/EtOAc 9:1) to give **24** (6.89 g, 18.8 mmol, 77%) as a transparent oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.91 (m, 2H), 6.99−6.89 (m, 2H), 4.85 (dd, J = 4.7, 7.6 Hz, 1H), 4.21 (dd, J = 1.3, 7.2 Hz, 2H), 3.43−3.22 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.83 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 173.1, 163.6, 130.6 (2 C), 130.3, 113.7 (2 C), 69.3, 61.1, 55.5, 43.2, 25.6 (3 C), 18.2, 14.1, −5.0, −5.4; FT-IR (ATR, neat, cm^{-1}) 2955; 2930; 2902; 2857; 1750; 1676; 1599; 1576; 1511; 1463; 1420; 1363; 1256; 1213; 1168; 1060; 1009; 990:955; 938; 879; 828; 779; 630; HR-MS (ESI+) m/z calcd for $C_{19}H_{30}O_5SiNa$ $[M + Na]^+$ 389.1755, found 389.1765.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)butanoate-4-*d* (25 and 26). Compound **22** (3.68 g, 9.10 mmol, 1 equiv) was dissolved in MeOD (65 mL) and cooled to 0 °C (ice bath). Then $NaBD_4$ (762 mg, 18.2 mmol, 2 equiv) was added in portions. After 20 min, the reaction was quenched with NH_4Cl sat. solution (30 mL) and stirred at rt for 20 min. Then the reaction was concentrated *in vacuo* to give a paste. The paste was diluted with EtOAc (50 mL) and NH_4Cl sat. solution (20 mL) and poured into an extraction funnel. The aqueous phase was extracted with EtOAc (3 × 50 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. It was purified by column chromatography (eluting with pentane/EtOAc 9:1) to afford successively the *anti* isomer **25** (0.63 g, 1.55 mmol, 17%) as a transparent oil and the *syn* isomer **26** (1.45 g, 3.56 mmol, 39%) as a white solid, followed by a mixture of both diastereoisomers (1.23 g, 3.0 mmol, 33%) as a transparent oil. Total yield: 3.38 g, 8.297 mmol, 91%.

anti-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)butanoate-4-d ***(25):*** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 4.56 (t, J = 5.2 Hz, 1H), 4.22 (dd, J = 4.8, 7.2 Hz, 2H), 3.28 (s, 1H), 2.10 (d, J = 5.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 0.97 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 148.1, 129.6 (q, J = 32.3 Hz), 125.9 (2 C), 125.4 (q, J = 3.7 Hz, 2 C), 124.1 (q, J = 272.2 Hz) 70.7, 70.2 (t, J = 22.0 Hz), 61.2, 43.3, 25.7 (3 C), 18.2, 14.2, −4.9, −5.6; FT-IR (ATR, neat, cm^{-1}) 3489; 2955; 2931; 2888; 2859; 1734; 1621; 1465; 1410; 1326; 1256; 1164; 1127; 1068; 1032; 839; 726; 668; 631; HR-MS (ESI+) m/z calcd for $C_{19}H_{28}DF_3O_4SiNa$ $[M + Na]^+$ 430.1748, found 430.1726.

syn-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)butanoate-4-d ***(26):*** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.51−4.44 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.22−2.07 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 0.96 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 147.9, 129.6 (q, J = 32.3 Hz), 126.0 (2 C), 125.3 (q, J = 3.7 Hz, 2 C), 124.2 (q, J = 271.0 Hz), 71.3, 70.9 (t, J = 22.0 Hz), 61.2, 43.4, 25.7 (3 C), 18.2, 14.1, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 3496; 2953; 2932; 2886; 2860; 1734; 1619; 1464; 1406; 1406; 1375; 1323; 1253; 1221; 1103; 1088; 1066; 1011; 970; 956; 885; 832; 779; 723; 664; 638; HR-MS (ESI+) m/z calcd for $C_{19}H_{28}DF_3O_4SiNa$ $[M + Na]^+$ 430.1748, found 430.1735; mp 53−55 °C.

*General Procedure for Trifluoroacetylation (**27** and **28**).* Alcohols **25** or **26** (1 equiv) were dissolved in dry CH_2Cl_2 (0.06 M reaction) under argon, and triethylamine (5 equiv) was added. The mixture was cooled to 0 °C with an ice bath. Then trifluoroacetic anhydride (2 equiv) was added. After 1.5 h, cold NH_4Cl sat. solution was added to quench the reaction, which was then poured into a separatory funnel. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The trifluoroacetates were purified by column chromatography (eluting with pentane/Et_2O 9:1). The trifluoroacetates degrade rapidly after purification (an exact mass was not obtained). They were used immediately in the next reaction.

anti-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(2,2,2-trifluoroacetoxy)-4-(4-(trifluoromethyl)phenyl)butanoate-4-d ***(27):*** transparent oil (84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.36 (dd, J = 3.4, 9.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.51 (dd, J = 3.3, 14.5 Hz, 1H), 2.16 (dd, J = 9.5, 14.5 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.5 (q, J = 42.9 Hz), 141.7 (d, J = 1.1 Hz), 131.2 (q, J = 33.0 Hz, 2 C), 126.8 (2 C), 125.9 (q, J = 3.9 Hz, 2 C), 123.7 (q, J = 272.3 Hz), 114.4 (q, J = 286.1 Hz), 75.9 (t, J = 22.6 Hz), 68.3, 61.3, 41.2, 25.6 (3 C), 18.1, 14.0, −4.9, −5.8; FT-IR (ATR, neat, cm^{-1}) 2956; 2932; 2898; 2861; 1788; 1755; 1735; 1623; 1473; 1412; 1367; 1325; 1254; 1222; 1127; 1069; 1029; 977; 837; 777; 729; 667; 630; 609.

syn-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(2,2,2-trifluoroacetoxy)-4-(4-(trifluoromethyl)phenyl)butanoate-4-d ***(28):*** transparent oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 4.34−4.13 (m, 3H), 2.62 (dd, J = 4.3, 14.5 Hz, 1H), 2.28 (dd, J = 6.5, 14.5 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.3 (q, J = 42.4 Hz) 141.6, 131.3 (q, J = 32.5 Hz) 127.0 (2 C), 126.0 (q, J = 3.9 Hz, 2 C), 123.8 (q, J = 272.3 Hz), 114.4 (q, J = 286.1 Hz), 75.4 (t, J = 22.6 Hz), 68.3, 61.2, 40.6, 25.6 (3 C), 18.2, 14.0, −4.9, −5.5; FT-IR (ATR, neat, cm^{-1}) 2955; 2933; 2888; 2860; 1788; 1755; 1473; 1412; 1369; 1326; 1254; 1222; 1132; 1068; 1025; 1013; 941; 838; 778; 728; 669; 630; 609.

Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-methoxyphenyl)butanoate-4-*d* (29 and 30). $CeCl_3{\cdot}7H_2O$ (8.1 g, 21.8 mmol, 2 equiv) was placed in a flask and heated to 90 °C under a vacuum with stirring for 4 h. Then it was heated to 145 °C under a vacuum with stirring overnight. The dry $CeCl_3$ was placed under an argon atmosphere, cooled to rt, and then covered with MeOD (50 mL). Compound **24** (4.0 g, 10.9 mmol, 1 equiv) in MeOD (5 mL) was injected, and the mixture was cooled to 0 °C (ice bath). Then $NaBD_4$ (915 mg, 21.8 mmol, 2 equiv) was added in portions. After 10 min, the reaction was quenched with NH_4Cl sat. solution (20 mL) and stirred at rt for 20 min. Then the reaction was concentrated *in vacuo* to give a paste. The paste was diluted with EtOAc (50 mL) and NH_4Cl sat. solution (30 mL) and poured into an extraction funnel. The aqueous phase was extracted with EtOAc (3 × 50 mL). The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. It was purified by column chromatography (pentane/EtOAc 17:3) to afford successively the *anti* isomer **29** (1.12 g, 3.0 mmol, 28%), the *syn* isomer **30** (1.46 g, 3.94 mmol, 36%), and a mixture of both isomers (0.61 g, 1.66 mmol, 15%) as transparent oils. Total yield: 3.19 g, 8.63 mmol, 79%.

anti-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-methoxyphenyl)butanoate-4-d ***(29):*** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.54 (dd, J = 3.8, 7.2 Hz, 1H), 4.26−4.15 (m, 2H), 3.80 (s, 3H), 2.84−2.79 (m, 1H), 2.17−1.99 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.15 (s,

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3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 158.8, 136.4, 126.7 (2 C), 113.7 (2 C), 70.4, 69.8 (t, J = 21.3 Hz), 60.8, 55.2, 43.5, 25.6 (3 C), 18.1, 14.1, −5.1, −5.6; FT-IR (ATR, neat, cm^{-1}) 3499; 2954; 2930; 2899; 2857; 1749; 1733; 1613; 1513; 1471; 1362; 1301; 1248; 1176; 1131; 1101; 1037; 836; 780; 734; 669; 632; HR-MS (ESI+) m/z calcd for $C_{19}H_{31}O_5SiDNa$ [M + Na]$^+$ 392.1974, found 392.1988.

*syn-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-4-(4-methoxyphenyl)butanoate-4-d (**30**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.41 (dd, J = 5.1, 7.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.80 (bs, 1H), 3.02 (s, 3H), 2.22−2.05 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 159.0, 136.1, 126.8 (2 C), 113.8 (2 C), 71.3, 71.0 (t, J = 22.0 Hz), 61.0, 55.2, 43.5, 25.7 (3 C), 18.2, 14.1, −4.9, −5.4; FT-IR (ATR, neat, cm^{-1}) 3506; 2954; 2930; 2898; 2857; 1749; 1736; 1613; 1513; 1464; 1362; 1300; 1247; 1175; 1130; 1035; 972; 939; 834; 778; 732; 667; 626; HR-MS (ESI+) m/z calcd for $C_{19}H_{31}O_5SiDNa$ [M + Na]$^+$ 392.1974, found 392.1991.

*General Procedure for Trifluoroacetylation (**31** and **32**).* Alcohols **29** or **30** (1 equiv) were dissolved in dry CH_2Cl_2 (0.03 M reaction) under argon, and triethylamine (5 equiv) was added. The mixture was cooled to 0 °C with an ice bath. Then trifluoroacetic anhydride (2 equiv) was added. After 1.5 h, cold NH_4Cl sat. solution was added to quench the reaction, which was then poured into a separatory funnel. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were gathered, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a transparent oil. The trifluoroacetates were purified by column chromatography (eluting with pentane/Et_2O 17:3). The trifluoroacetates are unstable; an exact mass or ^{13}C NMR could not be measured. They were used rapidly in the next reaction.

*anti-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-4-(2,2,2-trifluoroacetoxy) butanoate-4-d (**31**):* transparent oil (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.32 (dd, J = 3.4, 9.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.53 (dd, J = 3.4, 14.4 Hz, 1H), 2.13 (dd, J = 9.4, 14.4 Hz, 1H), 1.28 (t, J = 7.2 Hz, 2H), 0.94 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

*syn-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-4-(2,2,2-trifluoroacetoxy) butanoate-4-d (**32**):* transparent oil (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.27−4.12 (m, 3H), 3.81 (s, 3H), 2.59 (dd, J = 5.5, 14.3 Hz, 1H), 2.31 (dd, J = 6.0, 14.3 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H).

*General Procedure for Hydrogenolysis (**33** and **34**).* Pd/C 10% weight (0.05 equiv) was weighed in a two-neck round-bottom flask containing a stir bar and suspended in EtOAc (0.02 M reaction) under argon. The flask was chosen such that the air volume above the reaction was larger than the reaction volume (for example, for a 60 mL reaction volume, a 250 mL two-neck flask was used). The argon balloon was replaced with a hydrogen balloon. The hydrogen balloon was triple-layered and remade every 2−3 reactions, and it was completely filled with hydrogen for each reaction. The stopper from the second neck was removed briefly to purge the argon out of the flask. The solution was stirred vigorously for 20 min, and the atmosphere was purged with H_2 once more. Then the trifluoroacetate **27** or **28** (1 equiv) in EtOAc (5 mL per gram of trifluoroacetate) was injected and vigorous stirring was maintained throughout the reaction. After 55 min, the reaction was filtered on Celite and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography (eluting with pentane/Et_2O 95:5).

*anti-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(4-(trifluoromethyl)-phenyl)butanoate-4-d (**33**):* transparent oil (712 mg, 1.82 mmol, 95% yield, 99% IP); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.26 (t, J = 5.9 Hz, 1H), 4.22−4.13 (m, 2H), 2.79 (t, J = 8.1 Hz, 1H), 2.11−1.98 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 145.7, 128.7 (2 C), 128.4 (q, J = 32.3 Hz), 125.3 (q, J = 3.7 Hz, 2 C), 124.3 (q, J = 271.4 Hz), 71.6, 60.8, 36.4, 25.7 (3 C), 18.3, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2954; 2930; 2896; 2859; 1751; 1731; 1620; 1473; 1464; 1324; 1252; 1185; 1163; 1122; 1067; 1050; 1019; 971; 832; 813; 777; HR-MS (ESI+) m/z calcd for $C_{19}H_{28}DF_3O_3SiNa$ [M + Na]$^+$ 414.1799, found 414.1814.

*syn-Ethyl 2-((tert-Butyldimethylsilyl)oxy)-4-(4-(trifluoromethyl)-phenyl)butanoate-4-d (**34**):* transparent oil (665 mg, 1.70 mmol, 92% yield, 99% IP); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.31−4.10 (m, 3H), 2.74 (t, J = 8.1 Hz, 1H), 2.10−2.00 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 145.7, 128.7 (2 C), 128.4 (q, J = 32.3 Hz), 125.3 (q, J = 3.7 Hz, 2 C), 124.3 (q, J = 271.4 Hz), 71.6, 60.8, 36.5, 30.9 (t, J = 19.8 Hz), 25.7 (3 C), 18.3, 14.2, −4.9, −5.4; FT-IR (ATR, neat, cm^{-1}) 2955; 2931; 2893; 2859; 1752; 1731; 1620; 1473; 1324; 1251; 1163; 1110; 1067; 1019; 834; 778; 662; 630; HR-MS (ESI+) m/z calcd for $C_{19}H_{28}DF_3O_3SiNa$ [M + Na]$^+$ 414.1799, found 414.1799.

General Procedure for Hydrogenolysis (35 and 36). Pd/C 10% weight (0.05 equiv) was weighed in a two-neck round-bottom flask containing a stir bar and suspended in EtOAc (0.02 M reaction) under argon. The flask was chosen such that the air volume above the reaction was larger than the reaction volume (for example, for a 60 mL reaction volume, a 250 mL two-neck flask was used). The argon balloon was replaced with a hydrogen balloon. The hydrogen balloon was triple-layered and remade every 2−3 reactions, and it was completely filled with hydrogen for each reaction. The stopper from the second neck was removed briefly to purge the argon out of the flask. The solution was stirred vigorously for 20 min, and the atmosphere was purged with H_2 once more. Then the corresponding trifluoroacetate **31** or **32** (1 equiv) in EtOAc (5 mL per gram of trifluoroacetate) was injected and vigorous stirring was maintained throughout the reaction. After 3 min, the reaction was filtered on Celite and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography (eluting with pentane/Et_2O 95:5).

***anti*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)butanoate-4-*d* (35):** obtained as a transparent oil (288 mg, 0.43 mmol, 41% yield, 98% IP); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.28−4.09 (m, 3H), 3.79 (s, 3H), 2.69 (t, J = 8.1 Hz, 1H), 2.07−1.93 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 157.9, 133.6, 129.3 (2 C), 113.8 (2 C), 71.8, 60.7, 55.2, 37.2, 30.2 (t, J = 19.8 Hz), 25.7 (3 C), 18.3, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2953; 2930; 2899; 2857; 1751; 1731; 1613; 1513; 1464; 1370; 1246; 1179; 1132; 1037; 971; 835; 778; 665; 629; HR-MS (ESI+) m/z calcd for $C_{19}H_{31}DO_4SiNa$ [M + Na]$^+$ 376.2030, found 376.2030.

***syn*-Ethyl 2-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)butanoate-4-*d* (36):** obtained as a transparent oil (423 mg, 0.79 mmol, 67% yield, 98% IP); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.29−4.09 (m, 3H), 3.79 (s, 3H), 2.68−2.57 (m, 1H), 2.10−1.91 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 157.8, 133.5, 129.3 (2 C), 113.8 (2 C), 71.8, 60.7, 55.2, 37.1, 30.2 (t, J = 19.3 Hz), 25.7 (3 C), 18.3, 14.2, −4.9, −5.3; FT-IR (ATR, neat, cm^{-1}) 2954; 2930; 2903; 2857; 1751; 1731; 1613; 1513; 1464; 1370; 1247; 1178; 1132; 1037; 835; 779; 665; 632; HR-MS (ESI+) m/z calcd for $C_{19}H_{31}DO_4SiNa$ [M + Na]$^+$ 376.2030, found 376.2029.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00827.

Structural assignment of chromanes and copies of spectral data for all compounds (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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