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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b00469 • Publication Date (Web): 11 May 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

A Catalytic Environment-friendly Protocol for Achmatowicz Rearrangement

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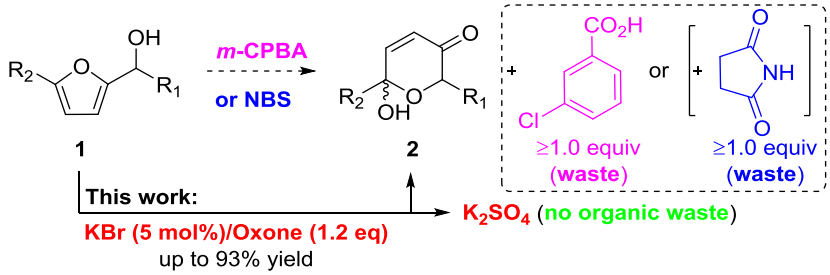


ABSTRACT: The increasing interest in Achmatowicz rearrangement (AchR) in organic synthesis calls for a more environmental friendly protocol since the most popular oxidants *m*-CPBA and NBS produced stoichiometric organic side product (*m*-chlorobenzoic acid or succinimide). Mechanism-guided analysis enables us to develop a new catalytic method (oxone/KBr) for AchR in excellent yield with K_2SO_4 as the only side product, which greatly facilitate the purification. This protocol was integrated with other transformations, leading to a rapid access to the highly functionalized dihydropyranones.

Achmatowicz Rearrangement (AchR),[1] an oxidative ring expansion rearrangement of functionalized furfuryl alcohols to densely functionalized dihydropyranone acetals, has received increasing interest in organic synthesis.[2] As a powerful and versatile synthetic tool for the preparation of tetrahydropyrans, dihydropyranones, oxidopyrylium, δ-lactones, and pyranoses, etc., AchR could be performed with various oxidation methods,[3] including Br_2/MeOH,[1] *N*-bromosuccinimide (NBS),[4] *in situ* generated dimethyl dioxirane (DMDO),[5] *m*-chloroperoxybenzoic acid (*m*-CPBA),[6] magnesium monoperoxypthalate[7], metal-base oxidant (PCC,[8] $VO(acac)_2$/TBHP,[9] titanium(IV) silicalite/H_2O_2[10]), phenyliodine(III) diacetate (PIDA),[11] photolytic oxidation (O_2/*hv*),[12] electrochemical oxidation,[13] and enzymatic transformations.[14]

Among these methods, NBS and *m*-CPBA are the most widely used oxidants for their simple operation in practice, tolerance of many functional groups, and reliably high yield in most cases.[3] However, the major drawback of these two protocols is the generation of stoichiometric organic side product (*m*-chlorobenzoic acid or succinimide), which usually requires immediate purification by column chromatography. Catalytic variants of these two primary methods are not available, which fact prompted us to develop a green, catalytic protocol for AchR with an ultimate goal of no generation of the direct organic side products derived from both the oxidant and the catalyst employed.

Mechanistic consideration of NBS-mediated AchR guided us to explore low-cost, non-toxic, environment-friendly oxone[15] ($2KHSO_5$-$KHSO_4$-K_2SO_4) as the oxidant coupled with an inorganic halide salt as the catalyst (Figure 1). We conceived that the oxidation of an alkali bromide with oxone might generate an active transient brominating agent ([Br^+] such as HOBr or Br_2),[16] which would promote AchR of furfuryl alcohols in the similar way as NBS or Br_2.[4] The ring expansion (ring opening and subsequent ring closure) would produce the dihydropyranone acetal with generation of K_2SO_4 (potassium used as the alkali counter ion) as the only side product and release of the catalytic bromide, which would be oxidized again by oxone for the subsequent catalytic cycles. If this hypothetic mechanism works, a truly green, catalytic, and practical protocol for AchR could be developed. However, at the beginning stage of our investigations we were very concerned on the potentially competing 1) halogenation of the electron-rich furan of type **1**, 2) alcohol oxidation of the furfuryl alcohol, and 3) dihalogenation of the resulting enone functionality of AchR products because the combination of oxone and halide (oxone/MX)[16] has been widely used in oxidation reactions such as halogenation[17] of arenes, dihalogenation[18] of alkenes, α-halogenation[19] of ketones, alcohol oxidation,[20] benzylic oxidation,[21] and halolactonization[22] of alkenoic acids/amides. Nevertheless, the chance of successful AchR with oxone and halide exists if AchR via our hypothetic mechanism precedes oxidation or halogenation reactions.

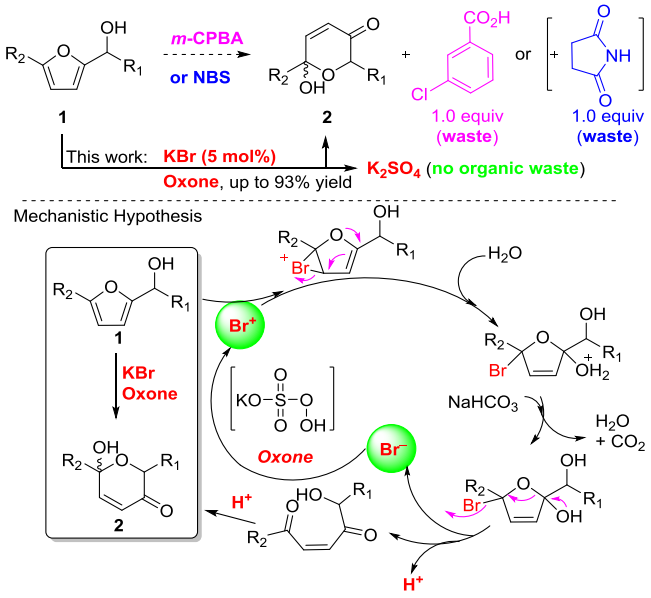
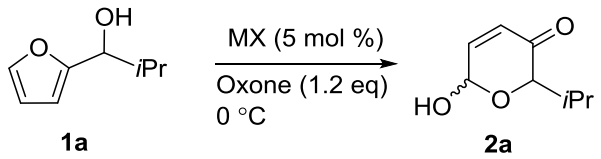


Figure 1. Achmatowicz rearrangement under classical conditions and our catalytic protocol with possible mechanism

To verify our mechanism-guided hypothesis, we carried out AchR of **1a** with oxone and different halides under various conditions (Table 1). To our delight, a combination of catalytic amount of bromide (5 mol %) and stoichiometric oxone (1.2 equiv.)[23] was found to be remarkably efficient (49-93% yield) for AchR of **1a** when a 4/1 mixture of THF and H_2O was used as the solvents (entries 1-5 and 9-14). It was noteworthy that no furan bromination or alcohol oxidation was observed in the NMR spectra of the crude reaction mixture. As shown in Table 1, the change in counter ion (NH_4^+, Li^+, Na^+, K^+, Ca^{2+}, etc) has little effect on the yield and reaction rate (entries 1-5). However, the reaction medium played a crucial role: MeOH/H_2O (entry 6) and CH_2Cl_2/H_2O (entry 7) were not suitable for AchR with oxone/bromide, while MeCN/H_2O (20/1) (entry 8) was a comparable solvent system (79%). On the other hand, the acidity of the reaction medium was found to be a minor factor on the yield (entries 9-14): addition of 0.25-0.5 equivalent of $NaHCO_3$ gave the best yield (92-93%) of **2a** within 30 minutes (entries 12-13). It should be noted that this optimized protocol was developed along with the following control experiments: i) substitution of the bromide with chloride or iodide led to lower or no conversion (entries 15-16); ii) substitution of the bromide with catalytic amount of NBS (entry 17) or *m*-CPBA (entry 18) reduced the efficiency of AchR, providing **2a** with substantially lower yields (71% and 35%, respectively); iii) no reaction was observed in the absence of the catalytic bromide (entry 19); and iv) replacement

of oxone with H_2O_2 (or *t*BuOOH, $PhI(OAc)_2$, *etc*) using catalytic bromide (entry 20) or NBS (entry 21) terminated the AchR.

Table 1. Selected conditions for catalytic Achmatowicz rearragement with oxone/halides.[a]



1a **2a**

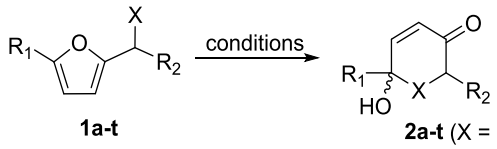
Entry	*Oxidant/ halide*	*Additive (equiv)*	*Solvent*	*Time*	*Yield (%)*
1	oxone/NH_4Br	$NaHCO_3$(2)/NaOAc(1)	THF/H_2O(4/1)	30 min	62
2	oxone/LiBr	$NaHCO_3$(2)/NaOAc(1)	THF/H_2O(4/1)	30 min	80
3	oxone/NaBr	$NaHCO_3$(2)/NaOAc(1)	THF/H_2O(4/1)	30 min	82
4	oxone/$CaBr_2$	$NaHCO_3$(2)/NaOAc(1)	THF/H_2O(4/1)	30 min	77
5	oxone/KBr	$NaHCO_3$(2)/NaOAc(1)	THF/H_2O(4/1)	30 min	82
6	oxone/KBr	$NaHCO_3$(2)/NaOAc(1)	MeOH/H_2O(1/1)	30 min	n.d
7	oxone/KBr	$NaHCO_3$(2)/NaOAc(1)	DCM/H_2O(4/1)	48 h	<5
8	oxone/KBr	$NaHCO_3$(2)/NaOAc(1)	MeCN/H_2O(20/1)	30 min	79
9	oxone/KBr	-	THF/H_2O(4/1)	30 min	49
10	oxone/KBr	$NaHCO_3$(2)	THF/H_2O(4/1)	30 min	73
11	oxone/KBr	$NaHCO_3$(1)	THF/H_2O(4/1)	30 min	83
12	oxone/KBr	$NaHCO_3$ (0. 5)	THF/H_2O(4/1)	30 min	93
13	oxone/KBr	$NaHCO_3$(0.25)	THF/H_2O(4/1)	30 min	92
14	oxone/KBr	$NaHCO_3$(0.1)	THF/H_2O(4/1)	30 min	86
15	oxone/NaCl	$NaHCO_3$(0.5)	THF/H_2O(4/1)	30 h	17
16	oxone/NaI	$NaHCO_3$(0.5)	THF/H_2O(4/1)	30 h	<5
17	oxone/NBS	$NaHCO_3$(0.5)	THF/H_2O(4/1)	30 mim	71
18	oxone/*m*-CPBA	$NaHCO_3$(0.5)	THF/H_2O(4/1)	48 h	35

19	oxone	$NaHCO_3$(0.5)	THF/H_2O(4/1)	24	<20
20	H_2O_2/KBr	$NaHCO_3$(0.5)	THF/H_2O(4/1)	48 h	<5
21	H_2O_2/NBS	$NaHCO_3$(0.5)	THF/H_2O(4/1)	48 h	<5

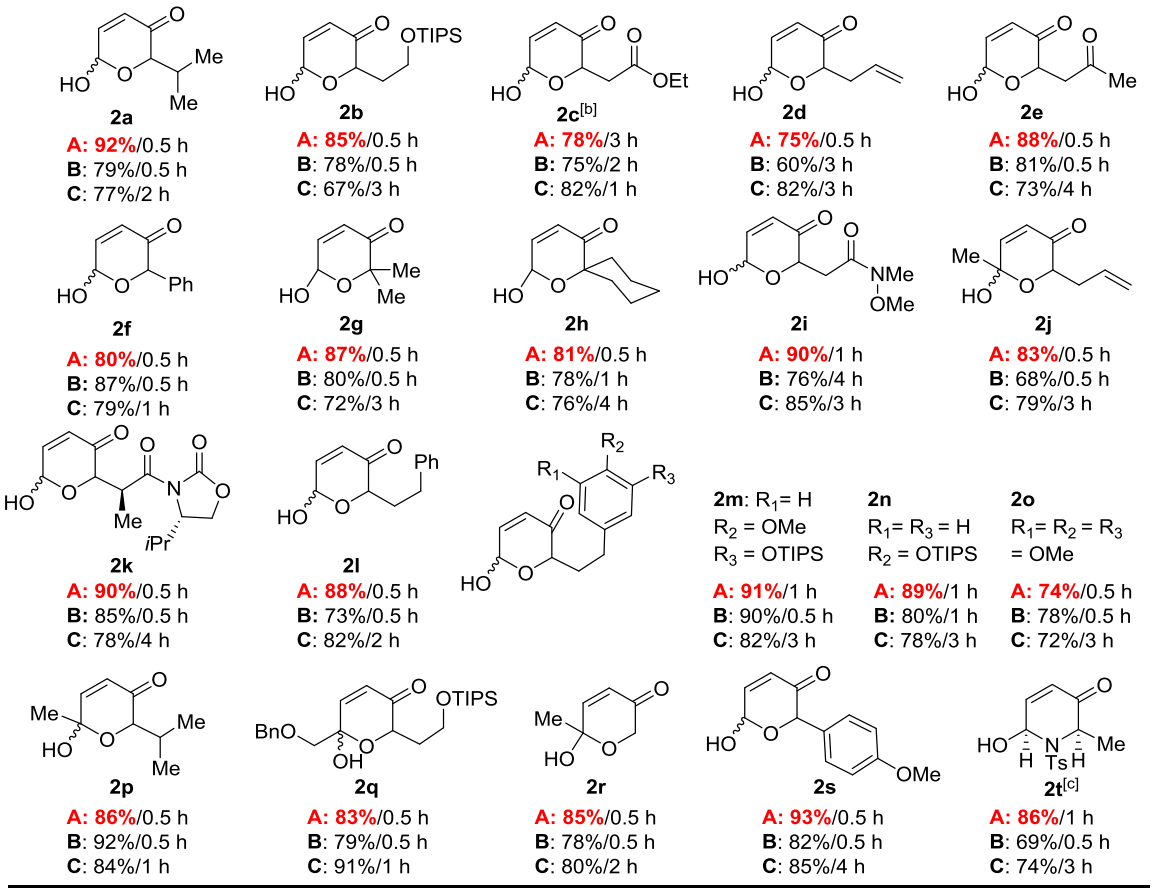
[a] Reaction was performed with 20 mg of **1a** and the yield refers to the isolated yield of **2a**.

To evaluate the advantages and disadvantages of our new catalytic protocol under the optimized condition, we examined the substrate scope using both our new protocol and the conventional NBS- and *m*-CPBA-promoted methods (Table 2). In most cases, our catalytic oxone/KBr could promote the clean AchR in better or competitive yield (74–93% yield, method A) without need of purification by flash column chromatography when comparing to NBS (method B) or *m*-CPBA (method C). Importantly, the oxone/KBr system tolerated various functional groups including silyl ether (**2b** and **2q**, 83–85% yield), ester (**2c**, 78% yield), alkene (**2d** and **2j**, 75–83% yield, respectively), ketone (**2e**, 88% yield), Weinreb amide (**2i**, 90% yield), Evans chiral oxazolidinone (**2k**, 90% yield), and electron-rich arenes (**2m-o** and **2s**, 74–91% yield). There were no potentially competing side reactions including arene bromination, ketone α-bromination, alkene dibromination, and alcohol oxidation, all of which have been reported in the reactions using a combination of oxone and stoichiometric bromide. In particular, the benzyl alcohols, substrates that readily undergo oxidation with oxone/bromide to aldehydes, could be used in the AchR using our catalytic oxone/KBr combination reagent (**2f** and **2s**, 80% and 93% yield, respectively). Primary and tertiary furyl alcohols were also excellent substrates for our catalytic AchR to afford the desired products (**2g, 2h,** and **2r**) in excellent yields (85–87%). Remarkably, the aza-AchR[24] of furyl sulfonamide using oxone/KBr proceeded more efficiently (86% yield) than the use of NBS (69% yield) and *m*-CPBA (74% yield). Notably, compounds (**2l** – **2o** and **2q**) were the key intermediates for total synthesis of musellarins[25] and uprolides.[26]

Table 2. Substrate scope and comparison with NBS and *m*-CPBA.[a]



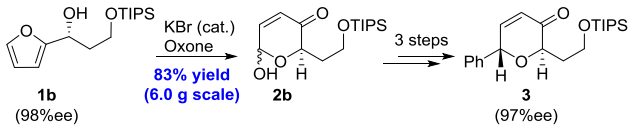
Method A: KBr (5 mol%), Oxone (1.2 eq), $NaHCO_3$ (0.5 eq) in THF/H_2O (4/1) at 0°C
Method B: NBS (1.2 eq), $NaHCO_3$ (2 eq), NaOAc (1 eq) in THF/H_2O (4/1) at 0°C
Method C: *m*-CPBA (1.2 eq) in DCM at 0°C



[a] Isolated yield. [b] Reaction was carried out with KBr (20 mol%), oxone (1.2 equiv) and $NaHCO_3$ (0.5 equiv) in a mixture of THF and H_2O (4/1) at 0 °C. [c] Reaction was carried out with KBr (5 mol%), oxone (1.2 equiv) and $NaHCO_3$ (2 equiv) in a mixture of THF and H_2O (4/1) at 0 °C.

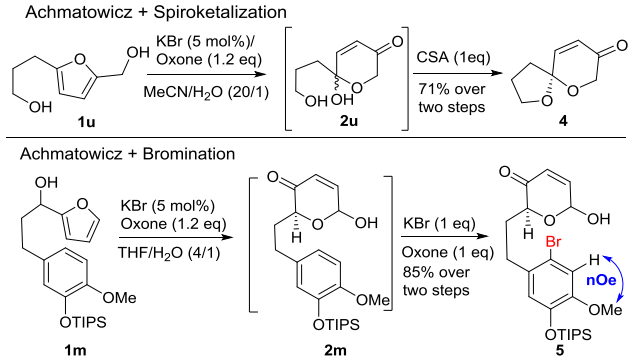
The practicalness of this new catalytic protocol was further examined for scalability and stereochemistry integrity (Scheme 1). To this end, the optically active furfuryl alcohol **1b** (98% ee) was subjected to our standard condition using oxone/KBr for AchR on a 6.0 g scale (20 mmol) and delivered **2b** in 83% yield, which could be used in the subsequent reactions without flash column chromatography. A 3-step functionalization[25] of **2b**: acetylation, γ-deoxygenation and Heck–Matsuda coupling, provided **3**

for determination of the optical purity, which revealed no loss of the ee value (97% ee, the ee value was determined by chiral HPLC). These results clearly suggested the laboratory scalability and stereochemistry integrity of our new catalytic protocol, which will become the first choice among the various methods for AchR. Note: caution should be taken for a large scale reaction since THF can react with bromine via a vigorous gas producing reactions possibly via photocatalysis and light effects should be included in safety reviews before any large scale work.



Scheme 1. Achmatowicz rearrangement of optical active furfuryl alcohol **1b** on a multi-gram scale.

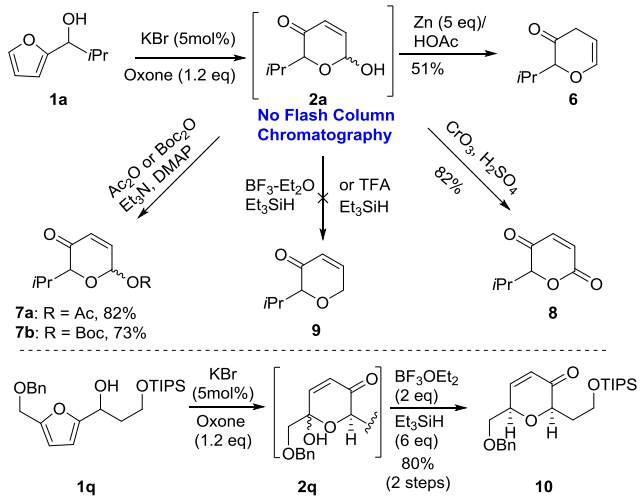
The absence of organic side products when using oxone/KBr offered a great opportunity to us for investigations on AchR-participating one-pot sequential reactions (Scheme 2). Two illustrative examples were shown in the Scheme 2. Treatment of furfuryl diol **1u**[27] with oxone (1.2 equiv) and KBr (5 mol%) in a mixture of MeCN and H_2O (20/1) at 0 ^oC for 30 min gave the AchR product **2u**, which upon treatment of CSA (1 equiv) in the same reaction vessel underwent efficient spiroketalization to provide **4** in 71% overall yield. Similarly, the one-pot AchR/bromination was practically efficient: additions[17] of KBr (1.0 equiv) and oxone (1.0 equiv) to the crude AchR product **2m** gave the mono-brominated product **5** in 85% yield.



Scheme 2. AchR-participating one-pot sequential reactions

Since the column purification is usually required for NBS and *m*-CPBA methods to remove the organic side products (succinimide and *p*-chlorobenzoic acid) that might prevent subsequent transfor-

mations, our catalytic protocol was highly efficient and did not produce any organic side products derived from catalyst (KBr) and oxidant (oxone). In order to demonstrate such an operational advantage, a number of classical transformations were performed using the non-purified **2a** from oxone/KBr-mediated AchR (Scheme 3). The crude AchR product **2a** (obtained by simple extraction, drying over $MgSO_4$, and evaporation of the organic solvents) underwent smoothly γ-deoxygenation (**2a** → **6**),[25] acetylation (**2a** → **7a**),[28] carbonate formation (**2a** → **7b**),[29] and Jones oxidation (**2a** → **8**)[30] in good to excellent yield. It was noted that Kishi[31] reduction (**2a** → **9**) was not successful due to over-reduction and other unknown side reactions. However, the 2,6-disubstituted dihydropyranone acetal **2q** could undergo efficient Kishi reduction to provide *cis*-2,6-disubstituted dihydropyranone **10**, which was a key intermediate in our total synthesis of uprolides.[26] The successful implementation of these transformations greatly expanded the utility of this protocol in organic synthesis.[25, 28-30]



Scheme 3. Use of the crude AchR products for subsequent transformations

In summary, a mechanism-guided analysis enabled us to develop a new, practical, catalytic protocol for Achmatowicz rearrangement, featuring 1) the use of environment-friendly, non-toxic, easy to handle, cheap and stable oxone as the terminal oxidant, 2) employment of KBr as the catalyst, 3) no organic wastes derived from oxidant and catalyst, and 4) no need of column chromatography for purification. The efficiency of this protocol was fully demonstrated in 20 examples and compared with the classical methods using NBS and *m*-CPBA as the oxidant. In addition, the oxone/KBr protocol for

Achmatowicz rearrangement was integrated with other subsequent transformations, leading to a rapid access to highly functionalized dihydropyranones through sequential reactions and/or subsequent functionalization of the crude AchR products.

Experimental Section.

General Experimental Methods. Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane (DCM) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3Å or 4Å molecular sieves. Solvents used in workup, extraction and column chromatography were used as received from commercial suppliers without prior purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC, 0.25 mm) on pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.062 mm). Infrared spectra were measured with neat sample. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C), benzene (7.16 ppm for ^{1}H and 128.06 ppm for ^{13}C), methanol (3.31 ppm for ^{1}H and 49.00 ppm for ^{13}C), acetone (2.09 ppm for ^{1}H and 30.60 ppm for ^{13}C). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were measured using TOF as the analyzer.

Preparation of 1-(Furan-2-yl)-3-(4-((triisopropylsilyl)oxy)phenyl)propan-1-ol (1n). To a stirred solution of 3-(4-hydroxy-phenyl)-propionaldehyde (1.52 g, 10 mmol) in anhydrous DCM (30 mL) were added imidazole (1.71 g, 25.1 mmol) and triisopropoylsilyl chloride (TIPSCl, 2.31 g, 12 mmol) at 0 °C. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched by addition of water (10 mL). The organic fractions were collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude protection product was used for next step without fur-

ther purification. To a stirred solution of furan (2.72 g, 40 mmol) in anhydrous THF (50 mL) was added *n*-BuLi (1.6 M in cyclohexane, 12.5 mL, 20 mmol,) slowly at −78 °C. After completion of the addition, the reaction mixture was allowed to warm up to −20 °C for 1 h. The crude product above was dissolved in THF (10 ml) and then added slowly to the lithiated furan solution at −78 °C. After completion of the addition, the reaction mixture was monitored by TLC. The reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to give the substituted furfuryl alcohol **1n** (3.06 g, 8.12 mmol) can be obtained as a yellowish oil in 81% yield over two steps. IR (neat, cm^{-1}): 3398, 2947, 2862, 1510, 1292, 1231, 1140, 997, 880, 678. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 1.9 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.33 (t, *J* = 2.4 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 4.66 (t, *J* = 6.8 Hz, 1H), 2.76–2.57 (m, 2H), 2.14 (q, *J* = 7.5 Hz, 2H), 1.31–1.21 (m, 3H), 1.13–1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 154.3, 142.0, 133.9, 129.4, 119.9, 110.2, 106.1, 67.1, 37.3, 31.0, 18.1 (6 x C), 12.8 (3 x C). HRMS (TOF, CI^+) *m/z* calc. for $C_{22}H_{34}O_3Si$ $[M]^+$ 374.2277, found 374.2266.

General Procedure A. Achmatowicz rearrangement using oxone and catalytic KBr. To a stirred solution of the furfuryl alcohol (0.5 mmol) in THF (4 mL) and H_2O (1 mL) were added KBr (5.9 mg, 0.025 mmol), $NaHCO_3$ (22 mg, 0.25 mmol) and oxone (0.37 g, 0.6 mmol) at 0 °C. After completion of the addition, the reaction was allowed to stir at 0 °C for 30 min. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (3 x 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure.

General Procedure B. Achmatowicz rearrangement using stoichiometric NBS. To a stirred solution of the furfuryl alcohol (0.5 mmol) in THF (4 mL) and H_2O (1 mL) were added $NaHCO_3$ (85 mg, 1 mmol), NaOAc (40 mg, 0.5 mmol) and *N*-bromosuccinimide (NBS, 90 mg, 0.5 mmol) at 0 °C. After completion of the addition, the reaction was allowed to stir at 0 °C for 30 min. The reaction was then quenched by

addition of saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4 – 1/2) to afford the desired product.

General Procedure C. Achmatowicz rearrangement using stoichiometric *m*-CPBA. To a stirred solution of the furfuryl alcohol (0.5 mmol) in DCM (4 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA, 77%, 0.17 g, 0.75 mmol) at 0 °C. After completion of the addition, the reaction was allowed to stir at 0 °C for 30 min–4 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4 – 1/2) to afford the desired product.

6-Hydroxy-2-isopropyl-2H-pyran-3(6H)-one (2a).[25] Yellowish oil (*dr* 3:2; method A, 72 mg, 92%; method B, 62 mg, 79%; method C, 60 mg, 77%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93–6.87 (m, 1H), 6.13–6.07 (m, 1H), 5.65 (d, J = 4.0 Hz, 1H), 4.39 (dd, J = 3.2, 1.1 Hz, 1H), 2.46–2.38 (m, 1H), 1.04–1.00 (m, 3H), 0.86 (dd, J = 6.9, 1.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 144.7, 128.1, 87.7, 78.5, 28.7, 19.1, 16.4. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93–6.87 (m, 1H), 6.13–6.07 (m, 1H), 5.62 (t, J = 4.0 Hz, 1H), 3.93–3.86 (m, 1H), 2.46–2.38 (m, 1H), 1.04–1.00 (m, 3H), 0.91 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 148.5, 129.5, 91.3, 83.2, 29.0, 19.2, 16.6.

Gram-scale Reaction of 6-Hydroxy-2-(2-((triisopropylsilyl)oxy)ethyl)-2H-pyran-3(6H)-one (1b). To a stirred solution of furfuryl alcohol (+)-**1b** (6.01 g, 20.1 mmol) in THF (40 mL) and water (10 mL) at 0 °C were added $NaHCO_3$ (0.85 g, 10.07 mmol) and KBr (0.12 g, 1.01 mmol). The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed

with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **2b** (5.23 g, 16.7 mmol) was obtained in 83% yield and used for next step without further purification.

6-Hydroxy-2-(2-((triisopropylsilyl)oxy)ethyl)-2H-pyran-3(6H)-one (2b). Yellowish oil (*dr* 2:1; method A, 134 mg, 85%; method B, 123 mg, 78%; method C, 105 mg, 67%). $[\alpha]_D^{20} = +53.2$ (*c* 1.0, MeOH). IR (neat, cm^{-1}): 3385, 2968, 2942, 2889, 2864, 1689, 1464, 1267, 1135, 1010. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93–6.86 (m, 1H), 6.15 – 6.08 (m, 1H), 5.62 (t, *J* = 3.3 Hz, 1H), 4.78 (dd, *J* = 8.4, 3.9 Hz, 1H), 3.98–3.79 (m, 2H), 2.28–2.20 (m, 1H), 1.94–1.78 (m, 1H), 1.14–0.98 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 144.3, 127.7, 87.7, 71.0, 59.0, 33.1, 18.1 (6 x C), 12.1 (3 x C). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93–6.86 (m, 1H), 6.15–6.08 (m, 1H), 5.62 (t, *J* = 3.3 Hz, 1H), 4.35 (dd, *J* = 9.0, 3.7 Hz, 1H), 3.89–3.81 (m, 2H), 2.28–2.20 (m, 1H), 1.96–1.78 (m, 1H), 1.14–0.98 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 147.8, 128.8, 90.9, 75.7, 59.0, 33.9, 18.1 (6 x C), 12.1 (3 x C). HRMS (Cl^+) *m/z* calc. for $C_{16}H_{31}O_4Si$ $[M + H]^+$ 315.1986, found 315.1993.

Ethyl 2-(6-hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate (2c).[32] Yellowish oil (*dr* 5:2; method A, 78 mg, 78%; method B, 75 mg, 75%; method C, 82 mg, 82%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.92 (dd, *J* = 10.3, 3.5 Hz, 1H), 6.14 (d, *J* = 10.2 Hz, 1H), 5.63 (d, *J* = 3.5 Hz, 1H), 5.02 (dd, *J* = 7.7, 3.8 Hz, 1H), 4.16 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.00 (dt, *J* = 16.8, 3.6 Hz, 1H), 2.87–2.67 (m, 1H), 1.26 (td, *J* = 7.1, 2.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 171.1, 144.7, 127.3, 87.9, 70.9, 61.2, 35.4, 14.2. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (dd, *J* = 10.4, 1.5 Hz, 1H), 6.18 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.71 (d, *J* = 1.7 Hz, 1H), 4.57 (ddd, *J* = 7.9, 3.8, 1.2 Hz, 1H), 4.16 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.00 (dt, *J* = 16.8, 3.6 Hz, 1H), 2.87–2.67 (m, 1H), 1.26 (td, *J* = 7.1, 2.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5, 171.1, 148.4, 128.5, 91.0, 75.5, 61.3, 36.2, 14.2.

2-Allyl-6-hydroxy-2H-pyran-3(6H)-one (2d).[33] Yellowish oil (*dr* 5:2; method A, 57.8 mg, 75%; method B, 46.2 mg, 60%; method C, 63.2 mg, 82%). Major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.25 (dd, *J* = 10.3, 3.5 Hz, 1H), 5.95–5.77 (m, 2H), 5.22–5.00 (m, 3H), 4.58 (dd, *J* = 7.7, 3.9 Hz, 1H), 2.80–2.66 (m, 1H), 2.59–2.44 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ: 196.0, 145.2, 134.3, 127.1, 117.8,

87.8, 73.9, 34.5. Minor diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.36 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.95–5.77 (m, 2H), 5.22–5.00 (m, 3H), 4.58 (dd, *J* = 7.7, 3.9 Hz, 1H), 2.80–2.66 (m, 1H), 2.59–2.44 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ: 195.4, 148.7, 134.2, 127.1, 117.9, 91.2, 78.5, 35.2.

6-Hydroxy-2-(2-oxopropyl)-2H-pyran-3(6H)-one (2e). Yellowish oil (*dr* 2:1; method A, 75 mg, 88%; method B, 69 mg, 81%; method C, 62 mg, 73%). IR (neat, cm^{-1}): 3390, 2970, 2938, 2881, 2858, 1686, 1568 1470, 1275, 1145, 1065, 987. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (dd, *J* = 10.3, 3.5 Hz, 1H), 6.10 (d, *J* = 10.3 Hz, 1H), 5.58 (d, *J* = 3.5 Hz, 1H), 5.03 (dd, *J* = 7.5, 3.8 Hz, 1H), 3.11 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.82 (dd, *J* = 17.6z, 7.5 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.1, 195.8, 144.9, 127.0, 87.8, 70.2, 43.8, 30.5. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (dd, *J* = 10.3, 1.4 Hz, 1H), 6.15 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.70 (d, *J* = 1.8 Hz, 1H), 4.59 (ddd, *J* = 7.6, 3.8, 1.4 Hz, 1H), 3.11 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.90 (dd, *J* = 17.8, 7.6 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 195.3, 148.8, 128.5, 91.1, 74.7, 44.2, 30.6. HRMS (Cl^+) *m/z* calc. for $C_8H_{11}O_4$ $[M + H]^+$ 171.0652, found 171.0658.

6-Hydroxy-2-phenyl-2H-pyran-3(6H)-one (2f).[34] Yellowish oil (*dr* 2:1; method A, 76 mg, 80%; method B, 83 mg, 87%; method C, 75 mg, 79%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 5H), 6.92–6.86 (m, 1H), 6.21–6.14 (m, 1H), 5.61 (d, *J* = 2.4 Hz, 1H), 5.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 145.4, 135.3, 130.1, 129.2, 128.7, 127.6, 87.9, 77.0. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 5H), 6.92–6.86 (m, 1H), 6.21–6.14 (m, 1H), 5.65 (s, 1H), 5.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 145.4, 129.5, 129.2, 128.7, 128.5, 128.0, 91.5, 81.1.

6-Hydroxy-2,2-dimethyl-2H-pyran-3(6H)-one (2g).[35] Yellowish oil (method A, 62 mg, 87%; method B, 57 mg, 80%; method C, 51.2 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 (dd, *J* = 10.3, 3.1 Hz, 1H), 6.09 (dd, *J* = 10.5, 3.2 Hz, 1H), 5.78 (d, *J* = 2.9 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.9, 143.3, 126.6, 89.2, 79.5, 27.4, 25.0.

2-Hydroxy-1-oxaspiro[5.5]undec-3-en-5-one (2h).[32] Yellowish oil (method A, 74 mg, 81%; method B, 71 mg, 78%; method C, 69 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82 (dd, *J* = 10.2, 2.0 Hz, 1H), 6.01 (d, *J* = 10.3 Hz, 1H), 5.66 (s, 1H), 4.40 (brs, 1H), 1.92 – 1.45 (m, 9H), 1.31 – 1.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.7, 146.0, 126.7, 87.5, 80.7, 33.4, 31.0, 25.2, 21.0, 20.6.

2-(6-Hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)-N-methoxy-N-methylacetamide (2i). Yellowish oil (*dr* 5:2; method A, 97 mg, 90%; method B, 82 mg, 76%; method C, 91.5 mg, 85%). IR (neat, cm^{-1}): 3395, 2976, 2962, 2920, 2870, 1693, 1665, 1478, 1375, 1277, 1145, 1105, 956. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (dd, *J* = 10.2, 3.5 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 5.58 (d, *J* = 3.5 Hz, 1H), 5.09 (dd, *J* = 8.2, 3.4 Hz, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 3.10–3.00 (m, 1H), 2.99–2.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.1, 171.3, 145.2, 126.9, 87.8, 70.6, 61.4, 33.0. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.15 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.70 (d, *J* = 1.7 Hz, 1H), 4.62 (dd, *J* = 8.0, 3.5 Hz, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 3.10–3.00 (m, 1H), 2.99–2.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 171.3, 149.0, 128.2, 90.9, 75.0, 61.4, 32.3. HRMS (Cl^+) *m/z* calc. for $C_9H_{14}NO_5$ $[M + H]^+$ 216.0866, found 216.0876.

2-Allyl-6-hydroxy-6-methyl-2H-pyran-3(6H)-one (2j).[36] Yellowish oil (*dr* 6:1; method A, 70 mg, 83%; method B, 57.2 mg, 68%; method C, 66.4 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (d, *J* = 10.1 Hz, 1H), 5.98 (d, *J* = 10.1 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.12 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.56 (dd, *J* = 7.6, 3.9 Hz, 1H), 3.45 (s, 1H), 2.66 (ddd, *J* = 15.0, 6.1, 4.4 Hz, 1H), 2.41 (dt, *J* = 14.9, 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 148.5, 133.8, 126.3, 117.6, 92.9, 74.0, 34.0, 28.8.

(4S)-3-((2S)-2-(6-Hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)propanoyl)-4-isopropyloxazolidin-2-one (2k). Yellowish oil (*dr* 5:2; method A, 134 mg, 90%; method B, 126.3 mg, 85%; method C, 116 mg, 78%). $[\alpha]_D^{20}$ = +33.6 (*c* 1.0, CH_2Cl_2). IR (neat, cm^{-1}): 3390, 2970, 2967, 2930, 2875, 1687, 1658, 1475, 1370, 1272, 1140, 1108, 950. Major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.15 (dd, *J* = 10.3, 3.4 Hz, 1H), 5.76 (dt, *J* = 10.3, 1.8 Hz, 1H), 5.20–5.09 (m, 1H), 4.69 (q, *J* = 7.5 Hz, 1H), 4.18 (tt,

J = 7.7, 3.9 Hz, 1H), 3.55–3.36 (m, 2H), 2.16–2.04 (m, 1H), 1.60–1.49 (m, 3H), 0.56 (d, *J* = 7.0 Hz, 3H), 0.44 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ: 196.6, 174.9, 154.2, 148.8, 144.6, 127.0, 87.4, 74.5, 63.3, 58.6, 39.3, 28.9, 17.6, 14.8. HRMS (Cl^+) *m/z* calc. for $C_{14}H_{20}NO_6$ $[M + H]^+$ 298.1285, found 298.1279.

6-Hydroxy-2-phenethyl-2H-pyran-3(6H)-one (2l). Yellowish oil (*dr* 4:3; method A, 96 mg, 88%; method B, 80 mg, 73%; method C, 89.5 mg, 82%). IR (neat, cm^{-1}): 3388, 2963, 2935, 2892, 2860, 1683, 1461, 1262, 1130, 1006. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.21 (m, 5H), 6.97–6.90 (m, 1H), 6.18–6.12 (m, 1H), 5.69–5.66 (m, 1H), 4.61 (dd, *J* = 8.3, 3.7 Hz, 1H), 2.88–2.71 (m, 2H), 2.32–2.25 (m, 1H), 2.15–2.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 148.4, 145.0, 141.4, 128.5, 127.5, 126.2, 87.7, 73.3, 31.5, 31.1. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.21 (m, 5H), 6.97–6.90 (m, 1H), 6.18–6.12 (m, 1H), 5.69–5.66 (m, 1H), 4.07 (dd, *J* = 8.8, 4.0 Hz, 1H), 2.88–2.71 (m, 2H), 2.32–2.25 (m, 1H), 2.15–2.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 145.0, 141.2, 128.7, 128.6, 126.4, 126.2, 91.0, 77.8, 32.2, 31.1. HRMS (Cl^+) *m/z* calc. for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0945.

6-Hydroxy-2-(4-methoxy-3-((triisopropylsilyl)oxy)phenethyl)-2H-pyran-3(6H)-one (2m). Yellowish oil (*dr* 2:1; method A, 191.4 mg, 91%; method B, 189 mg, 90%; method C, 172.5 mg, 82%). IR (neat, cm^{-1}): 3398, 2961, 2935, 2887, 2864, 1687, 1458, 1260, 1134, 1017. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91–6.86 (m, 1H), 6.75–6.70 (m, 2H), 6.13–6.07 (m, 1H), 5.64–5.60 (m, 1H), 4.52 (dd, *J* = 8.3, 3.7 Hz, 1H), 3.76 (s, 3H), 2.78–2.54 (m, 2H), 2.23–2.15 (m, 1H), 2.02–1.90 (m, 1H), 1.33–1.18 (m, 3H), 1.08 (d, *J* = 7.4 Hz, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 149.2, 145.4, 144.6, 134.0, 127.6, 121.3, 121.0, 112.3, 87.8, 73.3, 55.7, 31.6, 30.4, 18.0 (6 x C), 13.0 (3 x C). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.92–6.86 (m, 1H), 6.75–6.70 (m, 3H), 6.13–6.07 (m, 1H), 5.64–5.60 (m, 1H), 4.00 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.76 (s, 3H), 2.78–2.54 (m, 2H), 2.23–2.15 (m, 1H), 2.02–1.90 (m, 1H). 1.33–1.18 (m, 3H), 1.08 (d, *J* = 7.4 Hz, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:

196.4, 149.3, 148.0, 145.5, 133.7, 128.9, 121.3, 121.0, 112.3, 91.1, 77.8, 55.7, 32.3. 30.4, 18.0 (6 x C), 13.0 (3 x C). HRMS (Cl^+) *m/z* calc. for $C_{23}H_{36}O_5Si$ $[M]^+$ 420.2332, found 420.2333.

6-Hydroxy-2-(4-((triisopropylsilyl)oxy)phenethyl)-2H-pyran-3(6H)-one (2n). Yellowish oil (*dr* 2:1; method A, 174 mg, 89%; method B, 156 mg, 80%; method C, 152.3 mg, 78%). IR (neat, cm^{-1}): 3387, 2965, 2945, 2880, 2868, 1683, 1466, 1262, 1130, 1013. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, *J* = 8.2 Hz, 2H), 6.89 (td, *J* = 10.5, 2.4 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.7 Hz, 2H), 6.14–6.07 (m, 1H), 5.64–5.60 (m, 1H), 4.54 (dd, *J* = 8.4, 3.7 Hz, 1H), 2.81–2.56 (m, 2H), 2.28–2.20 (m, 1H), 2.01–1.94 (m, 1H), 1.26–1.23 (m, 3H), 1.10–1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 154.3, 148.0, 133.8, 129.5, 127.6, 119.9, 87.7, 73.3, 30.3, 18.0 (6 x C), 12.8 (3 x C). Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, *J* = 8.2 Hz, 2H), 6.89 (td, *J* = 10.5, 2.4 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.7 Hz, 2H), 6.14–6.07 (m, 1H), 4.01 (dd, *J* = 8.9, 3.7 Hz, 1H), 2.81–2.56 (m, 2H), 2.28–2.20 (m, 1H), 2.01–1.94 (m, 1H), 1.26–1.23 (m, 3H), 1.10–1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 154.3, 144.7, 133.5, 129.5, 128.8, 119.9, 91.0, 77.8, 31.6, 18.0 (6 x C), 12.8 (3 x C). HRMS (Cl^+) *m/z* calc. for $C_{22}H_{34}O_4Si$ $[M]^+$ 390.2226, found 390.2225.

6-Hydroxy-2-(3,4,5-trimethoxyphenethyl)-2H-pyran-3(6H)-one (2o). Yellowish oil (*dr* 5:3; method A, 114 mg, 74%; method B, 120.2 mg, 78%; method C, 111 mg, 72%). IR (neat, cm^{-1}): 3381, 2961, 2948, 2885, 2864, 1689, 1460, 1266, 1135, 1010. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 6.95 – 6.89 (m, 1H), 6.43 (s, 2H), 6.08 (d, *J* = 12.0, 1H), 5.67 (s, 1H), 4.57 (dd, *J* = 8.2, 3.6 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 2.77–2.62 (m, 2H), 2.27–2.18 (m, 1H), 2.09–1.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 153.2, 144.6, 137.4, 136.2, 127.7, 105.6, 87.8, 77.4, 73.2, 56.2, 31.6, 31.5. Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 6.95–6.89 (m, 1H), 6.43 (s, 2H), 6.08 (d, *J* = 12.0, 1H), 5.67 (s, 1H), 4.06 (dd, *J* = 8.6, 3.8 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 2.77–2.62 (m, 2H), 2.27–2.18 (m, 1H), 2.09–1.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 153.3, 148.0, 137.2, 136.2, 128.9, 105.6, 91.1, 77.9, 61.0, 56.2, 32.4, 31.6. HRMS (Cl^+) *m/z* calc. for $C_{16}H_{20}O_6$ $[M]^+$ 308.1260, found 308.1260.

6-Hydroxy-2-isopropyl-6-methyl-2H-pyran-3(6H)-one (2p).[33] Yellowish oil (*dr* 6:1; method A, 73.2 mg, 86%; method B, 78.3 mg, 92%; method C, 71.5 mg, 84%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.97 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.32 (s, 1H), 3.36 (brs, 1H), 2.41–2.36 (m, 1H), 1.61 (s, 3H), 1.00 (dd, *J* = 6.9, 2.4 Hz, 3H), 0.82 (dd, *J* = 6.8, 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.5, 148.4, 127.0, 92.6, 78.4, 28.8, 28.7, 19.1, 16.1. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84 (d, *J* = 8.0 Hz, 1H), 5.97 (dd, *J* = 10.2, 2.5 Hz, 1H), 3.94 (t, *J* = 3.1 Hz, 1H), 3.36 (brs, 1H), 2.41–2.36 (m, 1H), 1.56 (s, 3H), 1.00 (dd, *J* = 6.9, 2.4 Hz, 3H), 0.90 (dd, *J* = 6.9, 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 151.2, 126.9, 94.7, 82.1, 29.5, 24.0, 19.0, 16.8.

6-((Benzyloxy)methyl)-6-hydroxy-2-(2-((triisopropylsilyl)oxy)ethyl)-2H-pyran-3(6H)-one (2q).[26b] Yellowish oil (*dr* 7:1; method A, 180.2 mg, 83%; method B, 171.7 mg, 79%; method C, 197.8 mg, 91%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.30 (m, 5H), 6.78 (d, *J* = 10.3 Hz, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 4.79 (dd, *J* = 8.5, 3.7 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 3.85 (dd, *J* = 7.3, 5.3 Hz, 2H), 3.61 (q, *J* = 10.3 Hz, 2H), 2.29 (dtd, *J* = 14.3, 7.3, 3.8 Hz, 1H), 1.86 (ddd, *J* = 14.0, 8.6, 5.2 Hz, 1H), 1.12–1.01 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.0, 144.8, 137.5, 128.6, 128.1, 127.9, 127.5, 93.0, 74.5, 74.2, 71.4, 59.0, 33.1, 18.1 (6 x C), 12.1 (3 x C).

6-Hydroxy-6-methyl-2H-pyran-3(6H)-one (2r).[32] Yellowish oil (method A, 54.5 mg, 85%; method B, 50 mg, 78%; method C, 51.3 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (d, *J* = 10.3 Hz, 1H), 6.06 (d, *J* = 10.3 Hz, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 4.11 (d, *J* = 16.9 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 149.0, 126.6, 93.0, 66.7, 28.1.

6-Hydroxy-2-(4-methoxyphenyl)-2H-pyran-3(6H)-one (2s).[37] Yellowish oil (*dr* 2:1; method A, 102.4 mg, 93%; method B, 90.3 mg, 82%; method C, 93.6 mg, 85%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.22 (m, 3H), 6.98–6.89 (m, 3H), 6.19 (d, *J* = 10.3 Hz, 1H), 5.66 (d, *J* = 3.3 Hz, 1H), 5.52 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.2, 159.9, 145.1, 129.5, 127.9, 114.1, 88.1, 76.8, 55.4. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.22 (m, 3H), 6.98–6.89 (m,

3H), 6.24 (d, *J* = 10.3 Hz, 1H), 5.73 (d, *J* = 1.6 Hz, 1H), 5.02 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 159.9, 148.5, 129.4, 127.6, 114.0, 91.6, 80.9, 55.4.

(2R,6S)-6-Hydroxy-2-methyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (2t).[38] Colorless oil (method A, 121 mg, 86%; method B, 97 mg, 69%; method C, 104.1 mg, 74%). ^{1}H NMR (400 MHz, C_6D_6) δ: 7.56 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 7.9 Hz, 2H), 6.21 (dd, *J* = 10.3, 4.5 Hz, 1H), 5.83 (d, *J* = 4.6 Hz, 1H), 5.56 (d, *J* = 10.3 Hz, 1H), 4.60 (q, *J* = 7.3 Hz, 1H), 1.81 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ: 194.8, 143.8, 143.8, 137.7, 130.1, 127.1, 125.81, 73.8, 57.6, 21.9, 21.1.

Preparation of (2R,6S)-6-Phenyl-2-(2-((triisopropylsilyl)oxy)ethyl)-2H-pyran-3(6H)-one (3): To a stirred solution of the crude product **2b** (5.23 g, 16.7 mmol) in CH_2Cl_2 (40 mL) were added acetic anhydride (Ac_2O, 2.56 g, 25.1 mmol), Et_3N (2.54 g, 25.1 mmol) and 4-dimethylaminopyridine (DMAP, 0.41 g, 3.34 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/8–1/3) to afford the desired acetylated product (5.72 g, 16.0 mmol, 96% yield) as a 5:4 diastereomeric mixture. $[\alpha]_D^{20} = +16.8$ (*c* 1.1, MeOH). IR (neat, cm^{-1}): 2944, 2867, 1757, 1699, 1464, 1370, 1222, 1172, 1103, 998, 932. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.86–6.81 (m, 1H), 6.47 (d, *J* = 3.2 Hz, 1H), 6.22–6.18 (m, 1H), 4.72 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.83–3.78 (m, 2H), 2.27–2.23 (m, 1H), 2.10 (s, 3H), 1.83–1.78 (m, 1H), 1.06–1.01 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.9, 169.6, 143.0, 128.8, 88.0, 76.2, 58.6, 35.9, 21.1, 18.0 (6 x C), 12.0 (3 x C). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.86–6.81 (m, 1H), 6.53 (s, 1H), 6.22–6.18 (m, 1H), 4.47 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.83–3.78 (m, 2H), 2.27–2.23 (m, 1H), 2.07 (s, 3H), 2.00–1.96 (m, 1H), 1.06–1.01 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 169.2, 141.2, 128.7, 87.1, 72.5, 58.3, 33.1, 21.0, 18.0 (6 x C), 12.0 (3 x C). HRMS (TOF, CI$^+$) *m/z* calc. for $C_{18}H_{33}O_5Si$ $[M + H]^+$ 357.2097, found 357.2097. To a stirred solution of the substrate above (3.04 g, 9.67 mmol) in acetic acid (20 mL) was added activated

Zn powder (3.09 g, 48.34 mmol) at room temperature. The reaction mixture was stirred for 1.5 h. The reaction was then quenched by addition of saturated aqueous K_2CO_3 (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used for next step without further purification. To a stirred solution of the crude product obtained above in CH_3CN (10 mL) were added $Pd_2(dba)_3$ (0.70 g, 0.76 mmol), NaOAc (1.88 g, 22.9 mmol) and phenyldiazonium salt (2.92 g, 15.2 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/10–1/4) to afford the desired product (–)-**3** (2.61 g, 6.96 mmol, 72% yield over two steps) as a reddish oil. $[\alpha]_D^{20} = -18.6$ (*c* 1.0, MeOH). IR (neat, cm^{-1}): 3032, 2943, 2866, 1693, 1463, 1384, 1259, 1102, 1055, 998, 883. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.35 (m, 5H), 7.16 (dd, *J* = 10.4, 3.2, 1H), 6.24 (dd, *J* = 10.4, 1.9, 1H), 5.50 (brs, 1H), 4.36 (dd, *J* = 9.2, 3.9, 1H), 3.82 (dd, *J* = 7.4, 5.1, 2H), 2.12 (dtd, *J* = 14.5, 7.4, 4.0, 1H), 1.93 (ddt, *J* = 14.2, 9.7, 5.0, 1H), 0.98 (d, *J* = 4.4, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 149.1, 136.8, 128.8 (2 x C), 128.7, 128.0 (2 x C), 126.5, 73.6, 72.7, 59.1, 33.0, 18.1 (4 x C), 17.8 (2 x C), 12.4 (2 x C), 12.0. HRMS (TOF, Cl^+) *m/z* calc. for $C_{22}H_{35}O_3Si$ $[M + H]^+$ 375.2355, found 375.2360.

Preparation of 1,6-Dioxaspiro[4.5]dec-9-en-8-one (4). To a stirred solution of furfuryl alcohol **1u** (102 mg, 0.74 mmol) in MeCN (4 mL) and H_2O (0.2 mL) were added KBr (4.4 mg, 0.037 mmol), $NaHCO_3$ (31 mg, 0.37 mmol) and oxone (0.55 g, 0.89 mmol) at 0 °C. After completion of the addition, the reaction was allowed to stir at 0 °C for 30 min. After completion of the Achmatowicz reaction as monitored by TLC, 10-camphorsulfonic acid (CSA, 150 mg, 0.74 mmol) was added and the reaction mixture was allowed to warm up to room temperature for 1 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) with EtOAc (3 x 1 mL). The combined organic fractions were

washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/10–1/5) to afford the desired product **4**[27] (81 mg, 0.53 mmol, 71% yield over two steps) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 10.2 Hz, 1H), 6.11 (d, *J* = 10.2 Hz, 1H), 4.49 (d, *J* = 16.8 Hz, 1H), 4.11–3.98 (m, 3H), 2.27–2.16 (m, 2H), 2.11–1.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 147.6, 128.0, 102.3, 68.9, 67.1, 37.8, 24.8.

Preparation of (2S)-2-(2-Bromo-4-methoxy-5-((triisopropylsilyl)oxy)phenethyl)-6-hydroxy-2H-pyran-3(6H)-one (5). To a stirred solution of furfuryl alcohol **1m** (104 mg, 0.27 mmol) in THF (1 mL) were added KBr (0.1 M in H_2O, 0.13 mL, 0.013 mmol), $NaHCO_3$ (1 M in H_2O, 0.13 mL, 0.13 mmol) and oxone (0.20 g, 0.32 mmol) at 0 °C. After completion of the addition, the reaction was allowed to stir at 0 °C for 30 min. After completion of the Achmatowicz reaction as monitored by TLC, KBr (32 mg, 0.27 mmol) and oxone (0.17 g, 0.27 mmol) was added and the reaction mixture was allowed to warm up to room temperature for 1 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and EtOAc (3 x 1 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/10–1/5) to afford the desired product **5** (115 mg, 0.23 mmol, 85% yield) as a yellowish oil (*dr* = 2/1). IR (neat, cm^{-1}): 3395, 2964, 2937, 2883, 2860, 1684, 1452, 1264, 1130, 1014. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 6.94–6.85 (m, 1H), 6.76 (s, 1H), 6.11 (dd, *J* = 15.1, 10.2 Hz, 1H), 5.74–5.59 (m, 1H), 4.55 (dd, *J* = 8.3, 3.7 Hz, 1H), 3.75 (s, 3H), 2.82–2.68 (m, 2H), 2.26–2.10 (m, 1H), 1.94 (tdd, *J* = 17.0, 8.8, 4.6 Hz, 1H), 1.22 (ddd, *J* = 14.7, 9.6, 7.1 Hz, 4H), 1.06 (d, *J* = 7.4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 150.0, 144.6, 132.7, 127.6, 122.0, 116.3, 114.6, 87.8, 73.4, 55.8, 30.9, 30.1, 18.0 (6 x C), 13.0 (3 x C). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 6.94–6.85 (m, 1H), 6.76 (s, 1H), 6.11 (dd, *J* = 15.1, 10.2 Hz, 1H), 5.74–5.59 (m, 1H), 4.03 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.75 (s, 3H), 2.82–2.68 (m, 2H), 2.26–2.10 (m, 1H), 1.94 (tdd, *J* = 17.0, 8.8, 4.6 Hz, 1H), 1.22 (ddd, *J* = 14.7, 9.6, 7.1 Hz, 4H), 1.06

(d, J = 7.4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.1, 149.9, 147.9, 145.0, 132.5, 128.8, 122.1, 116.4, 114.7, 91.0, 77.8, 55.8, 30.9, 18.0 (6 x C), 13.0 (3 x C). HRMS (Cl^+) *m/z* calc. for $C_{23}H_{35}BrO_5Si$ $[M]^+$ 498.1437, found 498.1431.

Preparation of 2-Isopropyl-2H-pyran-3(4H)-one (6). To a stirred solution of furfuryl alcohol **1a** (0.1 g, 0.71 mmol) in THF (4 mL) at 0 °C were added KBr (0.1 M in H_2O, 0.13 mL, 0.013 mmol), $NaHCO_3$ (1 M in H_2O, 0.13 mL, 0.13 mmol) and oxone (0.20 g, 0.32 mmol) at 0 °C. The reaction was left to stir for 30 min. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **2a** was used for next step without further purification. To a stirred solution of the crude product **2a** in acetic acid (2 mL) was added activated Zn powder (0.23 g, 3.55 mmol) at room temperature. The reaction mixture was stirred for 1.5 h. The reaction was then quenched by addition of saturated aqueous K_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/10 – 1/5) to afford the desired product **6**[25] (51 mg, 0.36 mmol, 51% yield over two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.29–6.09 (m, 1H), 4.34 (dt, J = 5.4, 3.6 Hz, 1H), 3.67 (d, J = 4.6 Hz, 1H), 2.54–2.28 (m, 2H), 2.21 (dq, J = 13.4, 6.6 Hz, 1H), 0.89 (dd, J = 15.8, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.0, 143.6, 98.1, 86.0, 35.0, 29.5, 18.8, 17.2.

Preparation of 6-Isopropyl-5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (7a). To a stirred solution of crude product **2a** [obtained from furfuryl alcohol **1a** (0.1 g, 0.71 mmol) without purification] in CH_2Cl_2 (20 mL) were added acetic anhydride (Ac_2O, 0.11 g, 1.07 mmol), Et_3N (0.11 g, 1.07 mmol) and 4-dimethylaminopyridine (DMAP, 6.1 mg, 0.04 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (4 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic fractions were washed with brine, dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product **7a**[25] (115 mg, 0.58 mmol) in 82% yield over two steps as a 1.1:1 diastereomeric mixture. Major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.35 (dd, *J* = 13.6, 2.7 Hz, 1H), 6.19 – 6.06 (m, 1H), 5.91–5.73 (m, 1H), 4.18 (d, *J* = 2.8 Hz, 1H), 2.46 (pd, *J* = 7.0, 2.8 Hz, 1H), 1.60 (dd, *J* = 5.2, 1.1 Hz, 3H), 1.04–0.85 (m, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ: 194.9, 168.8, 141.4, 128.9, 87.3, 80.1, 30.3, 18.9, 16.2. Minor diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.35 (dd, *J* = 13.6, 2.7 Hz, 1H), 6.19–6.06 (m, 1H), 5.91–5.73 (m, 1H), 3.64 (d, *J* = 5.6 Hz, 1H), 2.30 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.60 (dd, *J* = 5.2, 1.1 Hz, 3H), 1.04–0.85 (m, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ: 194.4, 168.6, 143.6, 129.3, 88.5, 84.1, 29.1, 20.4, 17.6.

Preparation of *tert*-Butyl (6-isopropyl-5-oxo-5,6-dihydro-2H-pyran-2-yl) carbonate (7b). Following the similar procedure for synthesis of **7a**, **7b**[25] (133 mg, 0.52 mmol) (dr = 1.2:1) was obtained from **1a** (0.1 g, 0.71 mmol) using $(Boc)_2O$ (0.23 g, 1.07 mmol), Et_3N (0.11 g, 1.07 mmol) and 4-dimethylaminopyridine (DMAP, 6.1 mg, 0.04 mmol) in 73% yield over 2 steps. Major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.23 (dd, *J* = 15.0, 2.8 Hz, 1H), 6.13 (ddd, *J* = 10.2, 3.7, 1.3 Hz, 1H), 5.77 (dd, *J* = 14.2, 10.2 Hz, 1H), 4.21 (d, *J* = 2.9 Hz, 1H), 2.40 (dtt, *J* = 9.8, 7.1, 2.8 Hz, 1H), 1.35–1.26 (m, 9H), 1.00–0.84 (m, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ: 194.7, 152.4, 140.7, 129.1, 90.5, 82.5, 79.8, 28.9, 27.6, 18.8, 16.1. Minor diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ: 6.23 (dd, *J* = 15.0, 2.8 Hz, 1H), 6.13 (ddd, *J* = 10.2, 3.7, 1.3 Hz, 1H), 5.77 (dd, *J* = 14.2, 10.2 Hz, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 2.30 (dq, *J* = 13.5, 6.9 Hz, 1H), 1.35–1.26 (m, 9H), 1.00–0.84 (m, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ: 194.4, 152.4, 142.5, 129.1, 89.7, 84.3, 82.7, 30.7, 27.6, 18.8, 18.0.

Preparation of 6-Isopropyl-2H-pyran-2,5(6H)-dione (8). To a stirred solution of the crude product **2a** [obtained from furfuryl alcohol **1a** (0.2 g, 1.43 mmol) without purification] in acetone (10 mL) at 0 ºC was added Jones reagent (1.5 mL, 2.9 M) dropwise. After stirring at 0 ºC for 30 min, TLC showed the complete consumption of **2a** and the reaction was quenched by slow addition of *i*-PrOH (0.7 mL) at 0 ºC. The mixture was filtered through a pad of celite and washed with diethyl ether. The filtrate was

washed with brine (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product **8** (183 mg, 1.19 mmol) in 83% yield over 2 steps. IR (neat, cm^{-1}): 2945, 2922, 2855, 1725, 1693, 1465, 1363, 1267, 1126, 1087, 967. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.80 (d, *J* = 10.1 Hz, 1H), 6.68 (d, *J* = 10.2 Hz, 1H), 4.69 (d, *J* = 3.4 Hz, 1H), 2.39–2.18 (m, 1H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.3, 160.6, 138.7, 135.3, 88.3, 33.1, 18.5, 15.7. HRMS (Cl^+) *m/z* calc. for $C_8H_{11}O_3$ $[M + H]^+$ 155.0703, found 155.0704.

Preparation of (2R,6R)-6-((Benzyloxy)methyl)-2-(2-((triisopropylsilyl)oxy)ethyl)-2H-pyran-3(6H)-one (10). To a stirred solution of furfuryl alcohol **1q** (0.1 g, 0.24 mmol) in THF (1 mL) at 0 °C were added KBr (0.1 M in H_2O, 0.12 mL, 0.012 mmol), $NaHCO_3$ (1 M in H_2O, 0.12 mL, 0.12 mmol) and oxone (0.18 g, 0.29 mmol) at 0 °C. The reaction was allowed to stir for 30 min. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **2q** was used for next step without further purification. To a stirred solution of the crude pyranone product **2q** in CH_2Cl_2 (2 mL) at −78 °C under nitrogen atmosphere were added triethylsilane (Et_3SiH, 0.23 mL, 1.44 mmol) and boron trifluoride diethyl etherate (BF_3-Et_2O, 0.06 mL, 0.48 mmol) dropwise. The reaction mixture was stirred at −78 °C for 1 h, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate /hexane = 1/20–1/10) to give the dihydropyranone product **10**[26] (80 mg, 0.19 mmol, 80% yield over two steps) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.27 (m, 5H), 7.06 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.16 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.70–4.55 (m, 2H), 4.50 (dq, *J* = 6.4, 2.8 Hz, 1H), 4.25 (dt, *J* = 9.1, 2.6 Hz, 1H), 3.96–3.79 (m,

2H), 3.71 (dd, J = 10.0, 5.5 Hz, 1H), 3.59 (dd, J = 10.0, 5.9 Hz, 1H), 2.34 (dddd, J = 12.9, 9.4, 6.2, 3.4 Hz, 1H), 1.78 (ddt, J = 13.8, 9.0, 4.5 Hz, 1H), 1.05 (d, J = 5.0 Hz, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 148.7, 137.9, 128.6, 128.0, 127.9, 127.8, 77.2, 73.8, 73.7, 71.2, 58.9, 33.1, 18.1 (6 x C), 12.1 (3 x C).

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H- and ^{13}C-NMR spectra of new compounds and the HPLC chromatograms of compounds **1b** and **3**. 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.

ACKNOWLEDGMENT

This research was financially supported by HKUST (R9309), Research Grant Council of Hong Kong (ECS 605912, GRF 605113 and GRF 16305314), and National Natural Science Foundation of China (NSFC 21472160).

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