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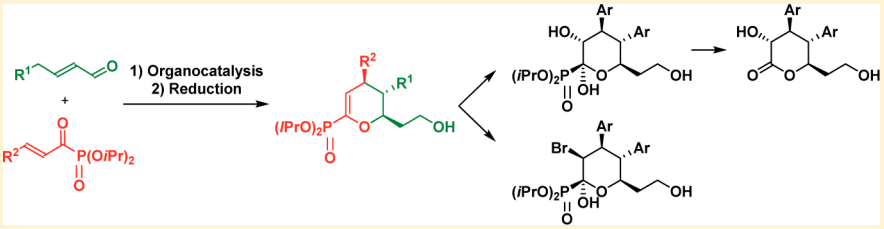
Organocatalytic Access to Enantioenriched Dihydropyran Phosphonates via an Inverse-Electron-Demand Hetero-Diels–Alder Reaction

Christian F. Weise, Vibeke H. Lauridsen, Raoní S. Rambo, Eva H. Iversen, Marie-Luise Olsen, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Supporting Information



ABSTRACT: The enantioselective inverse-electron-demand hetero-Diels–Alder reaction of the remote olefin functionality in dienamines has been developed by the simultaneous activation of α,β-unsaturated aldehydes and acyl phosphonates. The dual activation is based on an organocatalyst that activates both the α,β-unsaturated aldehyde, through dienamine formation, and the acyl phosphonate by hydrogen-bonding. The enantioselective reaction results in the formation of dihydropyran frameworks with three contiguous stereogenic centers. Different substitution patterns are possible for both the heterodiene and the dienophile, and the target products are obtained in good yields and up to 92% ee. The potential of the reaction is demonstrated by transformation of the products into valuable and complex synthons.

INTRODUCTION

The Diels–Alder reaction is a powerful tool for carbon–carbon bond formation and for the generation of complexity in structural motifs.[1] Since its discovery, the reaction has generated much attention and inspired researchers to develop it further.[2] An important variant constitutes the asymmetric inverse-electron-demand hetero-Diels–Alder reaction, which includes the additional incorporation of heteroatoms into the substrates to give access to optically active, heterocyclic structures, which are highly important in medicinal chemistry.[3] A vast number of heterocyclic structures have been generated this way applying Lewis-acid catalysis.[4,5] During the last years, organocatalytic alternatives to these hetero-Diels–Alder reactions have been developed to address the issue of reaction conditions applied, enabling a milder access to these heterocyclic structures.[6] In particular, organophosphorus compounds[7] are of great interest due to their versatile properties.[8] Besides the multitude of oxidation states of phosphorus, changing the property of the molecule, the possibility to manipulate, or even cleave the phosphorus moiety, contributes to its versatility. Organophosphorus compounds show a variety of different bioactiveties, such as antibiotic, antifungal,[9] and HIV-protease inhibiting activity.[10]

Recently, organocatalysts having dual-activation properties have been developed. Such catalysts activate both the aldehyde by enamine/dienamine formation (HOMO raising), as well as the substrate, having nitro-, nitrile-, and oxoesters-functionalities, by hydrogen-bond activation (LUMO lowering).[11] In the following, we would like to present a further development of these activation principles by the organocatalyzed reaction of acyl phosphonates, via a dienamine intermediate, to give access to optically active dihydropyran phosphonates with three contiguous stereocenters (Scheme 1). An attractive feature with the present reaction is that the phosphonate tether influences selectivity and increases reactivity, allowing for a

Scheme 1. Aminocatalytic H-Bond-Directing Strategy for the Inverse-Electron-Demand Hetero-Diels–Alder Reaction

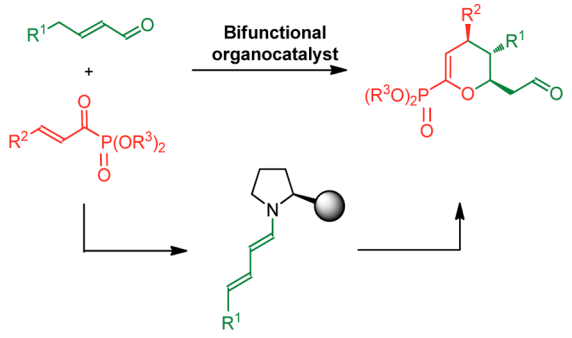


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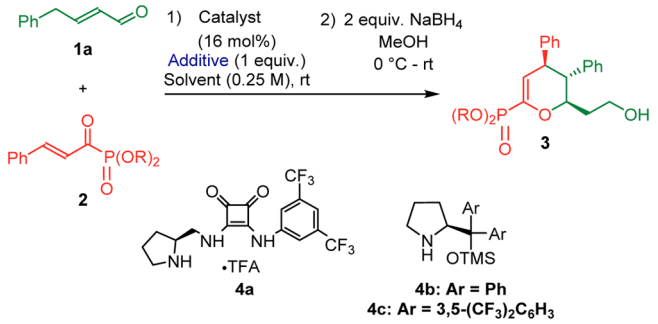
Table 1. Optimization Studies of the Inverse-Electron-Demand Hetero-Diels–Alder Reaction[a]



entry	cat.	R (2)	solvent	add.[b]	conv. [%]	yield [%]	dr[c]	ee [%][d]
1	**4a**	Me (**2a**)	THF	DEA	>95	72	5.5:1	86
2	**4a**	Et (**2b**)	THF	DEA	>95	81	7:1	86
3	**4a**	*i*Pr (**2c**)	THF	DEA	>95	82	8:1	88
4	**4a**	*i*Pr (**2c**)	THF	MEA	>95	86	8.5:1	86
5	**4a**	*i*Pr (**2c**)	PhMe	DEA	>95	68	3.5:1	nd
6	**4a**	*i*Pr (**2c**)	CH_2Cl_2	DEA	95	80	4.5:1	90
7	**4a**	*i*Pr (**2c**)	Et_2O	DEA	>95	75	4:1	nd
8	**4a**	*i*Pr (**2c**)	MeCN	DEA	>95	82	7.5:1	90
9	**4b**	*i*Pr (**2c**)	THF	DEA	0	---	---	---
10	**4c**	*i*Pr (**2c**)	THF	DEA	0	---	---	---

[a]Reactions performed on a 0.1 mmol scale. [b]Additive: DEA = *N*,*N*-diethylacetamide; MEA = *N*-ethylacetamide. [c]Determined by ^{31}P NMR spectroscopy. [d]Determined by UPC[2]; see the Supporting Information).

broader scope of substrates. Furthermore, the functionality also provides the basis for further chemical manipulations.

RESULTS AND DISCUSSION

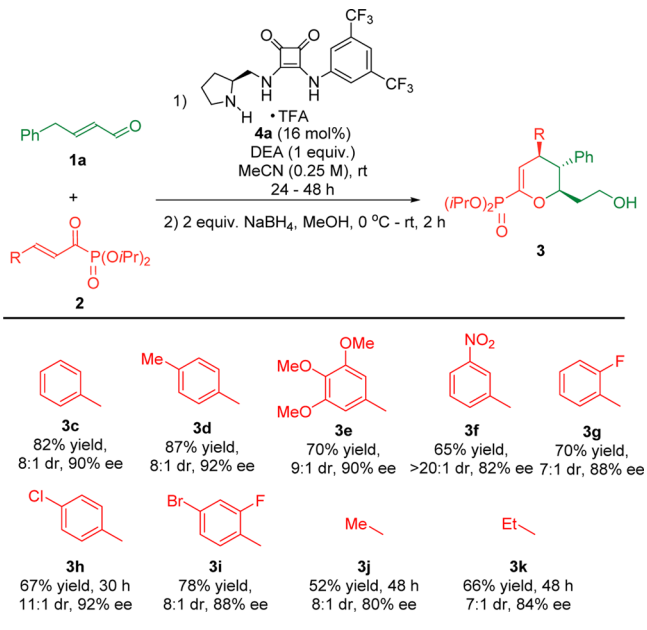
At the outset of the studies, different catalysts and solvents were evaluated. To explore the feasibility of the organocatalyzed inverse-electron-demand hetero-Diels–Alder reaction, the reaction between (*E*)-4-phenylbut-2-enal (**1a**) and dimethyl cinnamoylphosphonate (**2a**) was performed in THF at room temperature in the presence of the squaramide catalyst **4a** (Table 1). In the case of the H-bond-directing aminocatalyst **4a**, *N*,*N*-diethylacetamide (DEA) was used as an additive influencing the catalytic activity of the system.[11,12] Satisfyingly, the desired [4 + 2]-cycloaddition proceeded with more than 95% conversion, affording the target product **3a** in 72% yield and 86% ee (entry 1). In an attempt to improve the enantioselectivity, the reaction was run at 4 °C; however, to reach >95% conversion, the reaction had to stir for 5 d (see the Supporting Information). It was further found that the reaction gave the best results using an excess of aldehyde. In the next stage of the studies, different alkyl groups on the phosphonate moiety in **2** were screened, revealing that increasing the bulk of the phosphonate moiety led to improved diastereocontrol of the reaction (entries 1–3), with diisopropyl phosphonate **2c** giving the best result.

Subsequently, a selection of solvents were screened (Table 1, entries 4–8), with DEA in MeCN or THF proving superior, giving the desired organophosphorous compound **3c** (entries 3 and 8) in 82% yield and with good enantioselectivity as well as diastereoselectivity. However, owing to slightly higher enantiomeric excess, MeCN was used as the solvent of choice. A catalyst survey showed that only the bifunctional squaramide catalyst **4a** promoted the desired asymmetric inverse-electron-demand hetero-Diels–Alder reaction, whereas, using the steric shielding catalyst **4b** or **4c**, no product formation was observed. This highlights the important role of the H-bond activation mode of the bifunctional aminocatalyst **4a**.

With the optimized reaction conditions in hand, the scope of this methodology was investigated. A selection of *α*,*β*-unsaturated acyl phosphonates **2** with various aryl and alkyl groups and different electronic properties were successfully employed, all giving rise to the target dihydropyrans **3** in good yields and stereoselectivities (Scheme 2).

To our delight, phosphonates carrying both electron-withdrawing and electron-donating substituents on the

Scheme 2. Enantioselective Dienamine-Mediated Inverse-Electron-Demand Hetero-Diels–Alder Reaction: *α*,*β*-Unsaturated Acyl Phosphonate Scope



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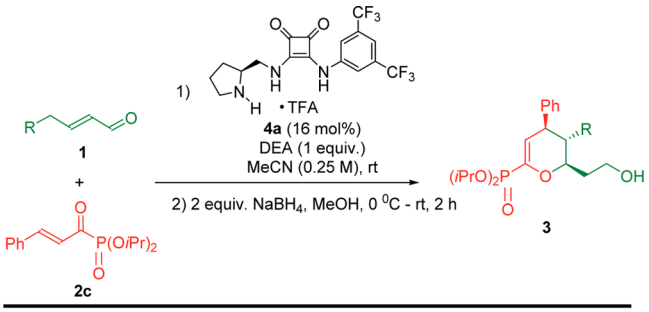
aromatic ring were well tolerated under the optimized reaction conditions (Scheme 2, **3c**−**3i**). In all cases, good yields, high diastereoselectivities, and good enantioselectivities were observed, proving the generality of the reaction. Importantly, good enantiomeric excesses, ranging from 82% to 92% ee, and >65% yields, were obtained independent of the substitution pattern of the aromatic ring. Furthermore, the introduction of two or three substituents on the aromatic ring did not affect the yield or the stereoselectivities as demonstrated for **3e** and **3i**. Surprisingly, introduction of a *meta*-nitro substituent on the aromatic ring of **2** resulted in a slightly lower yield as shown by the synthesis of **3f**. This result suggests that the nitro-group might coordinate to the catalyst, making the reaction less efficient. Previous work has demonstrated that β,γ-unsaturated α-ketoesters having electron-donating substituents on the aromatic ring were less reactive;[11c] however, by utilizing the phosphonate tether, the substrates become much more reactive, showing a notable decrease in reaction time. All reactions were completed within 24 h unless otherwise stated.

To further broaden the generality of the developed [4 + 2]-cycloaddition, aliphatic α,β-unsaturated acyl phosphonates **2** were also applied in the reaction sequence, leading to the formation of the desired alkyl substituted products **3j** and **3k**, albeit in moderate yields and slightly reduced enantiomeric excesses (Scheme 2). A possible explanation being that π-stacking interactions between the aromatic moieties of the formed dienamine intermediate and the phosphonate **2** might be an important factor influencing the outcome of the reaction.

In the interest of achieving higher substituent diversity, the α,β-unsaturated aldehyde **1** scope was investigated. The results are summarized in Scheme 3. Various electron-poor and electron-rich α,β-unsaturated aldehydes **1** were shown to be compatible with the developed reaction protocol. Most of the reactions proceeded in a highly enantio- and diastereoselective manner, providing **3l**−**3s** in good yields, ranging from 64% to 84% (Scheme 3). However, the introduction of a thiophene moiety in the 4-position of the starting α,β-unsaturated aldehyde led to a decrease in yield as well as in selectivity as indicated by the synthesis of **3s**, which might indicate the importance of π-stacking interactions. It is worth noting that the obtained stereoselectivities are slightly higher than those for the α,β-unsaturated phosphonate scope and that the reactions are completed within 24 h. With respect to the substitution pattern, introduction of an *ortho*-methyl or *ortho*-phenyl substituent on the aromatic ring led to increased diastereoselectivity. In an attempt to expand the α,β-unsaturated aldehyde scope, aldehydes bearing different alkyl groups were tested. However, the results indicated that the presence of an aromatic substituent in the γ-position of the starting enals was crucial for obtaining reactivity.

Scheme 3. Enantioselective Dienamine-Mediated Inverse-Electron-Demand Hetero-Diels−Alder Reaction: α,β-Unsaturated Aldehyde Scope



3l 82% yield, 10:1 dr, 92% ee
3m 77% yield, 8:1 dr, 88% ee
3n 84% yield, 15:1 dr, 84% ee
3o 74% yield, 10:1 dr, 86% ee
3p 72% yield, 9:1 dr, 92% ee
3q 80% yield, 11:1 dr, 90% ee
3r 70% yield, >20:1 dr, 94% ee
3s 64% yield, 4:1 dr, 64% ee

In the final studies, the chiral dihydropyran framework was used in the construction of more elaborate derivatives. Initial experiments focused on the stereoselective functionalization of the enolic moiety of **3** (Scheme 4). Treatment of the dihydropyran adduct with osmium tetroxide in the presence of 4-methylmorpholine 4-oxide (NMO) and sodium sulfite afforded the diastereoselective dihydroxylation product **5** in 54% yield, giving rise to two additionally stereogenic centers. Subsequently, addition of 4-dimethylaminopyridine (DMAP) gave **6** in 43% yield. It was also possible to obtain the α-hydroxy lactone **6** in a one-pot fashion, via the intermediacy of the α,β-dihydroxy phosphonate **5**, in an overall yield of 61%. The α-hydroxy lactone **6** belongs to a class of compounds, which, upon reduction, will provide uncommon sugar components of bacterial lipopolysaccharides (LPS) isolated from various pathogene microorganisms.[13]

In this way, tetrahydropyrans having up to five contiguous stereogenic centers were formed in a highly diastereoselective manner. A plausible explanation for the high diastereoselectivity observed in this process might be due to the C-4 aryl substituent, which affects the stereochemical outcome of the reaction due to sterical interactions. Assuming that the dihydropyran ring reacts through its half-chair conformation, the olefinic moiety will be approached from the site opposite to the C-4 aryl substituent. This is confirmed by X-ray analysis of the α-hydroxy lactone **6a** (see the Supporting Information).

The synthetic potential of the dihydropyrans **3** was further demonstrated by the electrophilic addition of *N*-bromosuccinimide (NBS) to the olefinic moiety in **3** (Scheme 4). The dihydropyran **3f** was converted into the corresponding bromohydrin **7** in a highly diastereoselective manner (18:1:1) and with no loss in enantioselectivity. A plausible explanation for the high diastereoselectivity observed in this case might be due to the directing effect of the *meta*-nitro substituent on the aromatic ring, guiding the bromonium ion to approach from the top. This might explain the lower diastereoselectivity observed, when having other substituents on the aromatic ring. The absolute stereochemistry of the obtained product **3a** was unambiguously determined by X-ray analysis (see the Supporting Information). This result allowed assignment of the *cis*-relationship between the H2 and H3 hydrogen atoms in **7**, as elucidated on the basis of ^{1}H NMR and 2D NMR analysis. A relatively small value of the $^3J_{H2H3}$ coupling constant was observed, thus indicating an axial−equatorial alignment of the H2 and H3 protons in the diastereoisomer obtained according to the Karplus curve.[14]

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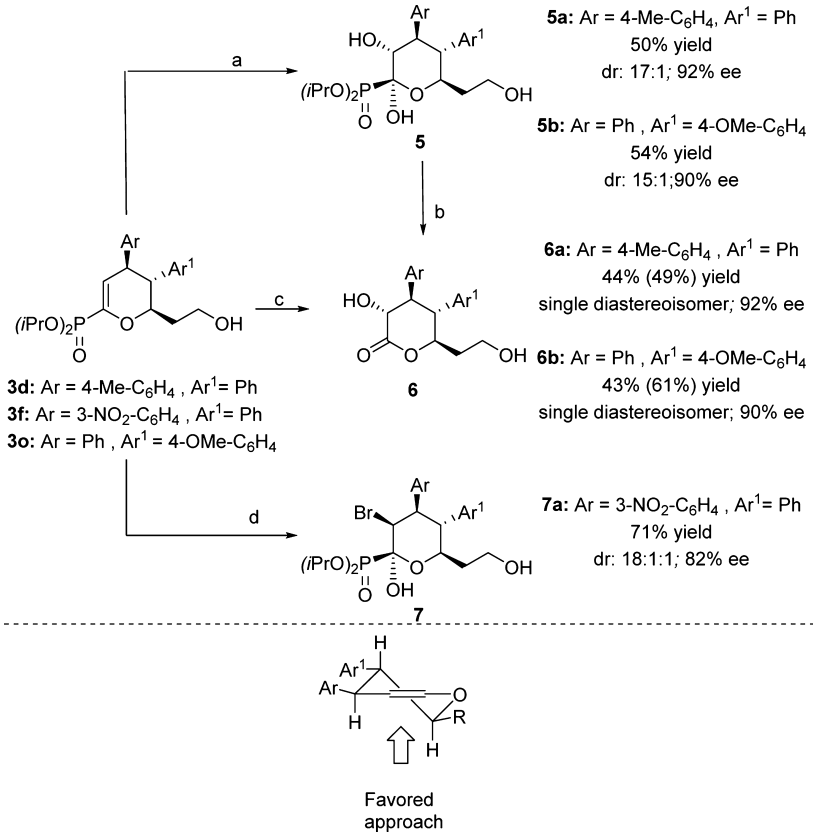
Scheme 4. Product Elaboration[a]



[a]Reagents and conditions: (a) *t*BuOH/H_2O (10:1), 2 equiv NMO, 1 equiv Na_2SO_3, and 10 mol % OsO_4, rt, 3−5 h. (b) 4 equiv DMAP, rt, overnight. (c) (1) *t*BuOH/H_2O (10:1), 2 equiv NMO, 1 equiv Na_2SO_3, and 10 mol % OsO_4, rt, 3−5 h; (2) 4 equiv DMAP, rt, overnight. (d) 2 equiv NBS, *t*BuOH/H_2O (2:1), rt, 2 h. Yields in parentheses refer to the *one-pot* reaction.

CONCLUSION

In conclusion, by employing a bifunctional squaramide-containing aminocatalyst, an efficient and highly regio- and stereoselective methodology for the synthesis of optically active dihydropyran phosphonates bearing three contiguous stereogenic centers has been presented. In general, aliphatic and aromatic α,β-unsaturated acyl phosphonates having electron-withdrawing or electron-donating substituents could be successfully applied in this asymmetric inverse-electron-demand hetero-Diels−Alder reaction, thereby demonstrating its high versatility. Furthermore, a range of α,β-unsaturated aldehydes were shown to be compatible with the presented protocol, providing good yields ranging from 64% to 84%. The derived cycloadducts could be transformed into useful chiral and complex building blocks.

EXPERIMENTAL SECTION

General Methods. NMR spectra were acquired on a spectrometer, running at 400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P, and 376 MHz for ^{19}F, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent signals of $CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR. Chemical shifts (δ) for ^{19}F NMR are reported in ppm relative to $CFCl_3$ as external reference and for ^{31}P NMR relative to H_3PO_4 as external reference. Only the signals from the major diastereoisomer are reported. The following abbreviations are used to indicate the multiplicity in NMR spectra: s - singlet; bs - broad singlet; d - doublet; t - triplet; q - quartet; m - multiplet. Mass spectra were recorded on a MICROTOF-Q spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Optical rotations were measured on a polarimeter and $[\alpha]_D$ values are given in deg·cm·g^{-1}·dm^{-1}; concentration c is listed in g·(100 mL)$^{-1}$. Analytical thin-layer chromatography (TLC) was performed using precoated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ stain. The enantiomeric excess (ee) of the products was determined by chiral stationary phase applying UPC^2 (Ultra Performance Convergence Chromatography) (Daicel Chiralpack IA-3, IB-3, IC-3, and ID-3 columns). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC), silica gel (Silica gel 60, 230−400 mesh) or Iatrobeads (Iatrobeads 6RS-8060) was used.

General Procedure for Preparation of α,β-Unsaturated Aldehydes 1a−1h. Aldehydes **1a−1g**, **1s** were prepared according to the literature procedure, and all spectral data were in accordance with those previously reported.[15] Aldehyde **1h** was prepared according to a modified Oshima's procedure.[16]

*(E)-4-([1,1′-Biphenyl]-2-yl)but-2-enal (**1h**).* To a solution of butylmagnesium chloride (7.2 mL, 2.0 M solution in THF, 14.4 mmol) in THF (20 mL) was added BuLi (18 mL, 1.6 M solution in hexane, 28.8 mmol) at 0 °C, and the mixture was stirred for 10 min. A solution of 2-bromo-1,1′-biphenyl (12.0 mmol) in THF (20 mL) was added dropwise. After stirring for 0.5 h at 0 °C, the mixture was cooled to −78 °C and allyl bromide (3.6 mL, 43.2 mmol) and a catalytic amount of CuCN·2LiCl were successively added. The resulting solution was stirred for 0.5 h at −78 °C and was subsequently quenched with sat. aq. NH_4Cl. The mixture was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude was then filtered through a plug of silica using a mixture of pentane/Et_2O (8:1) as an eluent. The solvent

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was evaporated to afford the desired product in quantative yield. The spectroscopic data are in accordance with those previously reported.[16]

2-Allyl-1,1′-biphenyl (5.0 mmol) and crotonaldehyde (15.0 mmol) were dissolved in 25 mL of dry CH_2Cl_2 under an argon atmosphere. Hoveyda−Grubbs-II catalyst (0.05 mmol) was added, and the mixture was degassed with argon and heated to 40 °C. The reaction mixture was monitored by ^{1}H NMR spectroscopy until crude NMR analysis indicated full conversion of 2-allyl-1,1′-biphenyl. The solvent was then removed by rotatory evaporation, and the crude product was purified by FC on silica using pentane/Et_2O from 12:1−4:1 to afford the desired product as a clear oil in 71% yield (0.785 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, J = 7.9 Hz, 1H), 7.35−7.16 (m, 9H), 6.75 (dt, J = 15.5, 6.4 Hz, 1H), 5.84 (ddt, J = 15.6, 7.9, 1.6 Hz, 1H), 3.54 (dd, J = 6.4, 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 156.9, 142.2, 141.0, 134.4, 133.4, 130.4, 129.8, 129.0 (2C), 128.3 (2C), 127.8, 127.3, 127.0, 36.6. HRMS calculated for $[C_{16}H_{14}O + Na]^+$: 245.0937; found: 245.0937.

*(E)-4-(4-Methoxyphenyl)but-2-enal (**1e**).* Following the general procedure, **1e** was isolated in 71% (1.49 g) yield as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (d, J = 7.89 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.95 (dt, J = 15.5, 6.7, 6.7 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.09 (dd, J = 15.5, 7.89 Hz, 1H), 3.80 (s, 3H), 3.60 (d, J = 6.6 Hz, 2H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 158.6, 156.9, 133.2, 129.8 (2C), 128.9, 114.2 (2C), 55.3, 38.1. HRMS calculated for $[C_{11}H_{12}O_2 + Na]^+$: 199.0730; found: 199.0730.

*(E)-4-(3,5-Dimethylphenyl)but-2-enal (**1f**).* Following the general procedure, **1f** was isolated in 52% yield (0.453 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, J = 7.91 Hz, 1H), 6.99−6.91 (m, 2H), 6.81 (s, 2H), 6.13 (dd, J = 15.5, 7.9 Hz, 1H), 3.58 (d, J = 6.7 Hz, 2H), 2.32 (d, J = 9.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 156.8, 138.4, 136.8, 133.3 (2C), 128.5, 126.6 (2C), 38.9, 21.2 (2C). HRMS calculated for $[C_{12}H_{14}O + Na]^+$: 197.0937; found: 197.0937.

General Procedure for Preparation of (*E*)-Cinnamoyl/enoylphosphonates 2a−2k. A 12 mmol (1.2 equiv) portion of acid was suspended in 5 mL of anhydrous CH_2Cl_2 (in the case where the acid was liquid, no solvent was used) and cooled to 0 °C. Oxalylchloride (1.02 mL, 12 mmol, 1.2 equiv) was added dropwise, followed by the addition of ca. 2 drops of DMF. The reaction was cooled another 10 min and then stirred at rt until it became a clear solution and gas evolution ceased (ca. 2−3 h), after which crude NMR analysis indicated full conversion to the acid chloride. The reaction was cooled to 0 °C, and 10 mmol (1.0 equiv) of the respective phosphite was added over 1 h, upon which the reaction became yellow. The reaction was stirred at rt overnight, and the solvent was removed under vacuum. The crude reaction mixture was purified by FC on Iatrobeads using pentane/EtOAc from 9:1 to 2:1. To make sure to collect only clean product, ^{31}P NMR spectra were taken of several individual fractions. In the case where the product contained some acid starting material, indicated by NMR analysis, it could be removed by extraction with sat. aq. $NaHCO_3$. All products were stored in the freezer and did not show decomposition during the development of this project.

*(E)-Dimethyl Cinnamoylphosphonate (**2a**).* Following the general procedure, **2a** was isolated in 14% yield (0.246 g) as a yellow oil (93% clean). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 16.3 Hz, 1H), 7.64−7.62 (m, 2H), 7.49−7.40 (m, 3H), 7.08 (dd, J = 16.3, 12.9 Hz, 1H), 3.91 (d, J = 10.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2 (d, J = 175.2 Hz), 149.5 (d, J = 1.8 Hz), 134.3 (d, J = 1.6 Hz), 132.2 (2C), 129.5 (3C), 125.5 (d, J = 66.3 Hz), 54.4 (d, J = 7.2 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.38. HRMS calculated for $[C_{11}H_{13}O_4P + Na]^+$: 263.0444; found: 263.0444.

*(E)-Diethyl Cinnamoylphosphonate (**2b**).* Following the general procedure, **2b** was isolated in 27% yield (0.607 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 16.3 Hz, 1H), 7.64−7.61 (m, 2H), 7.47−7.39 (m, 3H), 7.09 (dd, J = 16.3, 11.9 Hz, 1H), 4.25 (dq, J = 14.2, 7.1 Hz, 4H), 1.33 (t, J = 7.1 Hz, 6H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.0 (d, J = 175.7 Hz), 148.9 (d, J = 1.9 Hz), 134.4 (d, J = 1.6 Hz), 132.0, 129.4 (2C), 129.4 (2C), 125.4 (d, J = 66.0 Hz), 64.2 (d, J = 7.1 Hz, 2C), 16.8 (d, J = 5.7 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −1.61. HRMS calculated for $[C_{13}H_{17}O_4P + Na]^+$: 291.0757; found: 291.0759.

*(E)-Diisopropyl Cinnamoylphosphonate (**2c**).* Following the general procedure, **2c** was isolated in 30% yield (0.145 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 16.3 Hz, 1H), 7.65−7.60 (m, 2H), 7.46−7.40 (m, 3H), 7.12 (dd, J = 16.3, 10.7 Hz, 1H), 4.82 (dq, J = 13.0, 6.3 Hz, 2H), 1.39 (d, J = 6.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6 (d, J = 177.8 Hz), 148.3 (d, J = 2.2 Hz), 134.5 (d, J = 1.7 Hz), 131.9, 129.4 (2C), 129.3 (2C), 125.3 (d, J = 65.7 Hz), 73.3 (d, J = 7.2 Hz, 2C), 24.4 (d, J = 3.8 Hz, 2C), 24.2 (d, J = 4.7 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.17. HRMS calculated for $[C_{15}H_{21}O_4P + Na]^+$: 319.1070; found: 319.1074.

*(E)-Diisopropyl (3-(p-Tolyl)acryloyl)phosphonate (**2d**).* Following the general procedure, **2d** was isolated in 40% yield (1.24 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 16.2 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 16.2, 10.9 Hz, 1H), 4.86−4.75 (m, 2H), 2.39 (s, 3H), 1.39 (d, J = 2.2 Hz, 6H), 1.37 (d, J = 2.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5 (d, J = 177.0 Hz), 148.5 (d, J = 2.2 Hz), 142.7, 131.8 (d, J = 1.6 Hz), 130.2 (2C), 129.4 (2C), 124.4 (d, J = 65.8 Hz), 73.2 (d, J = 7.1 Hz, 2C), 24.4 (d, J = 3.8 Hz, 2C), 24.2 (d, J = 4.7 Hz, 2C), 22.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ = −2.94. HRMS calculated for $[C_{16}H_{23}O_4P + Na]^+$: 333.1226; found: 333.1229.

*(E)-Diisopropyl (3-(3,4,5-Trimethoxyphenyl)acryloyl)phosphonate (**2e**).* Following the general procedure, **2d** was isolated in 10% yield (0.386 g) as a yellow thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 16.2 Hz, 1H), 7.03 (dd, J = 16.1, 11.5 Hz, 1H), 6.85 (s, 2H), 4.84−4.76 (m, 2H), 3.90 (s, 9H), 1.38 (dd, J = 6.2, 2.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9 (d, J = 176.3 Hz), 153.5 (2C), 148.4 (d, J = 1.9 Hz), 141.3, 129.5 (d, J = 1.7 Hz), 124.3 (d, J = 69.1 Hz), 106.2 (2C), 73.1 (d, J = 7.2 Hz, 2C), 61.0, 56.2 (2C), 24.0 (d, J = 4.1 Hz, 2C), 23.9 (d, J = 4.4 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.23. HRMS calculated for $[C_{18}H_{27}O_7P + Na]^+$: 409.1392; found: 409.1390.

*(E)-Diisopropyl (3-(3-Nitrophenyl)acryloyl)phosphonate (**2f**).* Following the general procedure, **2f** was isolated in 28% yield (0.962 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 8.28 (dd, J = 8.2, 1.1 Hz, 1H), 8.10 (d, J = 16.3 Hz, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.18 (dd, J = 16.3, 10.0 Hz, 1H), 4.82 (dq, J = 12.6, 6.3 Hz, 2H), 1.38 (d, J = 7.0 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6 (d, J = 180.7 Hz), 149.1, 144.9 (d, J = 1.9 Hz), 136.2 (d, J = 1.8 Hz), 134.6, 130.5, 127.5 (d, J = 65.7 Hz), 125.8, 123.5, 73.7 (d, J = 7.3 Hz, 2C), 24.4 (d, J = 3.8 Hz, 2C), 24.2 (d, J = 4.7 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.89. HRMS calculated for $[C_{15}H_{20}NO_6P + Na]^+$: 364.0920; found: 364.0923.

*(E)-Diisopropyl (3-(2-Fluorophenyl)acryloyl)phosphonate (**2g**).* Following the general procedure, **2g** was isolated in 36% yield (1.127 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 16.4 Hz, 1H), 7.61 (dd, J = 10.8, 4.3 Hz, 1H), 7.45−7.37 (m, 1H), 7.21−7.09 (m, 3H), 4.82 (dq, J = 12.7, 6.3 Hz, 2H), 1.39 (d, J = 6.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8 (d, J = 179.4 Hz), 162.2 (d, J = 255.9 Hz), 140.4, 133.3 (d, J = 8.9 Hz), 129.6 (d, J = 2.5 Hz), 127.4 (d, J = 6.3 Hz), 126.7 (d, J = 6.1 Hz), 124.9 (d, J = 3.7 Hz), 116.7 (d, J = 21.9 Hz), 73.3 (d, J = 7.3 Hz, 2C), 24.4 (d, J = 3.7 Hz, 2C), 24.2 (d, J = 4.8 Hz, 2C). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −112.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.21. HRMS calculated for $[C_{15}H_{20}FO_4P + Na]^+$: 337.0981; found: 337.0974.

*(E)-Diisopropyl (3-(4-Chlorophenyl)acryloyl)phosphonate (**2h**).* Following the general procedure, **2h** was isolated in 10% yield (0.331 g) as a yellow oil that solidified upon cooling. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 16.2 Hz, 1H), 7.56 (d, J = 8.5 Hz), 7.40 (d, J = 8.5 Hz, 2H), 7.07 (dd, J = 16.3, 10.5 Hz, 1H), 4.86−4.76 (m, 2H), 1.38 (d, J = 7.6 Hz, 12H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6 (d, J = 178.5 Hz), 146.7 (d, J = 2.1 Hz), 137.9, 133.0, 130.5 (2C), 129.8 (2C), 125.6 (d, J = 65.8 Hz), 73.4 (d, J = 7.2 Hz, 2C), 24.4 (d, J = 3.8 Hz, 2C), 24.2 (d, J = 4.7 Hz, 2C). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.56. HRMS calculated for $[C_{15}H_{20}ClO_4P + Na]^+$: 353.0680; found: 353.0683.

*(E)-Diisopropyl (3-(4-Bromo-2-fluorophenyl)acryloyl)phosphonate (**2i**).* Following the general procedure, **2i** was isolated in

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30% yield (1.1768 g) as a yellow oil that solidified upon cooling. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 16.5 Hz, 1H), 7.48 (t, J = 8.2 Hz, 1H), 7.35−7.30 (m, 2H), 7.16 (dd, J = 16.4, 9.5 Hz, 1H), 4.87−4.75 (m, 2H), 1.31 (d, J = 6.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7 (d, J = 180.1 Hz), 161.7 (d, J = 260.3 Hz), 139.1 (t, J = 2.7 Hz), 130.4 (d, J = 3.1 Hz), 128.5 (d, J = 3.7 Hz), 127.3 (dd, J = 65.4, 6.2 Hz), 126.3 (d, J = 9.9 Hz), 121.8 (dd, J = 11.6, 1.9 Hz), 120.4 (d, J = 25.0 Hz), 73.4 (d, J = 7.3 Hz, 2C), 24.4 (d, J = 3.7 Hz), 24.2 (d, J = 4.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −110.6. ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.41. HRMS calculated for $[C_{15}H_{19}BrFO_4P + Na]^+$: 415.0081; found: 415.0083.

*(E)-Diisopropyl But-2-enoylphosphonate (**2j**).* Following the general procedure, **2j** was isolated in 31% yield (0.218 g) as a light yellow oil (91% clean). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (tt, J = 13.9, 6.9 Hz, 1H), 6.44 (dd, J = 15.4, 14.4 Hz, 1H), 4.75 (dq, J = 12.5, 6.3 Hz, 2H), 1.99 (dt, J = 7.0 Hz, 1.2 Hz, 3H), 1.35 (d, J = 6.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5 (d, J = 174.7 Hz), 150.5, 131.6 (d, J = 65.0 Hz), 73.1 (d, J = 7.3 Hz, 2C), 24.4 (d, J = 3.8 Hz, 2C), 24.2 (d, J = 4.8 Hz, 2C), 19.4 (d, J = 1.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.20. HRMS calculated for $[C_{10}H_{19}O_4P + Na]^+$: 257.0913; found: 257.0913.

*(E)-Diisopropyl Pent-2-enoylphosphonate (**2k**).* Following the general procedure, **2k** was isolated in 12% yield (0.299 g) as a light yellow oil (90% clean). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dt, J = 16.0, 6.3 Hz, 1H), 6.38 (ddt, J = 15.5, 13.6, 1.7 Hz, 1H), 4.80−4.64 (m, 2H), 2.38−2.18 (m, 2H), 1.31 (dd, J = 6.2, 1.3 Hz, 12H), 1.06 (t, J = 7.4 Hz, 3H).). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6 (d, J = 174.6 Hz), 156.4, 128.8 (d, J = 65.0 Hz), 73.0 (d, J = 7.2 Hz, 2C), 26.6 (d, J = 1.5 Hz), 24.3 (d, J = 3.7 Hz, 2C), 24.1 (d, J = 4.8 Hz, 2C), 12.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ = −3.17. HRMS calculated for $[C_{11}H_{21}O_4P + Na]^+$: 271.1070; found: 271.1069.

General Procedure for Preparation of Dihydropyran Phosphonates 3a−3k. An ordinary screw-cap vial was charged with a magnetic stirring bar and 0.2 mmol (1.0 equiv) of phosphonate **2**. After addition of 0.8 mL of a stock solution of *N*,*N*-diethylacetamide (DEA) in MeCN (1 equiv DEA), 52 μL (0.4 mmol, 2 equiv) of **1a** was added, followed by the addition of 16 mg (0.032 mmol, 0.16 equiv) of catalyst **4a**. The reaction mixture was stirred at rt and monitored by ^{1}H and ^{31}P NMR spectroscopy. After the reaction time given, the reaction was cooled to 0 °C and 15.1 mg (0.4 mmol, 2 equiv) of $NaBH_4$ was added, followed by the addition of ca. 5 drops of MeOH. The reaction was stirred for 2 h at rt, diluted with 30 mL of Et_2O, and extracted 6−8 times with 8 mL of water to remove the additive. The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC on silica (CH_2Cl_2/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford products **3**. The dr after purification was determined by ^{31}P NMR spectroscopy.

*Dimethyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3,4-diphenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3a**).* Following the general procedure (reaction time 24 h), **3a** was isolated by FC on silica in 72% yield (0.0562 g) as a light yellow solid with a mp 137.7−139.1 °C. (dr = 5.5:1). ^{1}H NMR ($CDCl_3$): δ = 7.23−7.17 (m, 3H), 7.13−7.11 (m, 3H), 6.90 (d, J = 6.9 Hz, 2H), 6.85−6.83 (m, 2H), 6.02 (dd, J = 11.0, 2.3 Hz, 1H), 4.43−4.38 (m, 1H), 3.85 (t, J = 10.5 Hz, 6H), 3.72−3.69 (m, 3H), 2.75 (t, J = 10.4 Hz, 1H), 2.25 (bs, 1H), 1.69−1.60 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 144.4 (d, J = 228.9 Hz), 141.0 (d, J = 0.9 Hz), 139.6 (d, J = 1.1 Hz), 128.7 (2C), 128.2 (2C), 128.1 (2C), 127.7 (2C), 127.1, 126.8, 120.4 (d, J = 23.0 Hz), 79.3 (d, J = 8.1 Hz), 59.6, 53.3 (d, J = 2.5 Hz), 53.2 (d, J = 2.3 Hz), 52.6 (d, J = 1.9 Hz), 47.1 (d, J = 12.8 Hz), 35.3. ^{31}P NMR ($CDCl_3$): δ = 11.47. HRMS calculated for $[C_{21}H_{25}O_5P + Na]^+$: 411.1332; found: 411.1336. $[\alpha]_D^{20}$ = −139.5 (c = 1.03, MeCN).

*Diethyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3,4-diphenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3b**).* Following the general procedure (reaction time 24 h), **3b** was isolated by FC on silica in 81% yield (0.0671 g) as a colorless oil (dr = 7:1). ^{1}H NMR ($CDCl_3$): δ = 7.24−7.18 (m, 3H), 7.13−7.12 (m, 3H), 6.91 (d, J = 7.1 Hz, 2H), 6.86−6.83 (m, 2H), 6.03 (dd, J = 11.0, 2.2 Hz, 1H), 4.40 (td, J = 9.4, 3.1 Hz, 1H), 4.25−4.17 (m, 4H), 3.76−3.69 (m, 3H), 2.76 (t, J = 10.4 Hz, 1H), 2.00−1.97 (m, 1H), 1.64−1.56 (m, 2H), 1.43−1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ = 145.4 (d, J = 227.8 Hz), 141.2, 139.7 (d, J = 1.1 Hz), 128.7 (2C), 128.6, 128.5, 128.2, 128.1, 127.7, 127.0, 126.8 (2C), 119.7 (d, J = 23.1 Hz), 79.6 (d, J = 8.2 Hz), 62.8 (t, J = 5.3 Hz, 2C), 60.3, 52.6 (d, J = 2.0 Hz), 47.1 (d, J = 12.9 Hz), 35.3, 16.3 (d, J = 1.4 Hz), 16.4 (d, J = 1.5 Hz). ^{31}P NMR ($CDCl_3$): δ = 8.53. HRMS calculated for $[C_{23}H_{29}O_5P + Na]^+$: 439.1645; found: 439.1651. $[\alpha]_D^{20}$ = −102.1 (c = 0.99, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3,4-diphenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3c**).* Following the general procedure (reaction time 24 h), **3c** was isolated by FC on silica in 82% yield (0.0732 g) as a light yellow oil (dr = 8:1). ^{1}H NMR ($CDCl_3$): δ = 7.23−7.17 (m, 3H), 7.13−7.11 (m, 3H), 6.91−6.90 (m, 2H), 6.84 (dd, J = 6.6, 2.9 Hz, 2H), 6.03 (dd, J = 10.8, 2.3 Hz, 1H), 4.84−4.72 (m, 2H), 4.37 (td, J = 9.7, 3.3 Hz, 1H), 3.73−3.68 (m, 3H), 2.73 (t, J = 10.4 Hz, 1H), 2.18 (bs, 1H), 1.68−1.57 (m, 2H), 1.41−1.36 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.3 (d, J = 227.6 Hz), 140.6 (d, J = 152.2 Hz), 128.7 (2C), 128.5, 128.2 (2C), 128.1, 128.1, 127.8 (2C), 127.1, 126.8, 119.2 (d, J = 23.1 Hz), 79.9 (d, J = 8.0 Hz), 71.6 (d, J = 5.9 Hz), 71.5 (d, J = 5.9 Hz), 60.2, 52.7 (d, J = 1.8 Hz), 47.1 (d, J = 12.8 Hz), 35.3, 24.1 (d, J = 4.1 Hz, 2C), 23.9 (d, J = 4.7 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 6.16. HRMS calculated for $[C_{25}H_{33}O_5P + Na]^+$: 467.1958; found: 467.1960. $[\alpha]_D^{20}$ = −100.8 (c = 1.00, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3-phenyl-4-(p-tolyl)-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3d**).* Following the general procedure (reaction time 48 h), **3d** was isolated in 87% yield (0.0801 g) as a light yellow oil (dr = 8:1). ^{1}H NMR ($CDCl_3$): δ = 7.24−7.17 (m, 3H), 6.93−6.90 (m, 4H), 6.72 (d, J = 8.0 Hz, 2H), 6.01 (dd, J = 10.8, 2.2 Hz, 1H), 4.81−4.73 (m, 2H), 4.34 (td, J = 9.8, 3.0 Hz, 1H), 3.71−3.65 (m, 3H), 2.71 (t, J = 10.4 Hz, 1H), 2.23 (s, 3H), 1.84 (bs, 1H), 1.69−1.53 (m, 2H), 1.42−1.36 (m, 12H).^{13}C NMR ($CDCl_3$): δ = 146.1 (d, J = 227.9 Hz), 139.9 (d, J = 0.9 Hz), 138.2 (d, J = 0.8 Hz), 136.2, 128.9 (2C), 128.7 (2C), 128.1 (2C), 127.6 (2C), 127.0, 119.6 (d, J = 22.9 Hz), 79.9 (d, J = 8.0 Hz), 71.5 (d, J = 5.7 Hz), 71.4 (d, J = 5.7 Hz), 60.2, 52.6 (d, J = 1.7 Hz), 46.6 (d, J = 12.7 Hz), 35.3, 24.1 (d, J = 4.1 Hz, 2C), 23.9 (d, J = 4.4 Hz, 2C), 21.0. ^{31}P NMR ($CDCl_3$): δ = 6.26. HRMS calculated for $[C_{26}H_{35}O_5P + Na]^+$: 481.2114; found: 481.2122. $[\alpha]_D^{29}$ = −125.0 (c = 0.51, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3-phenyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3e**).* Following the general procedure (reaction time 24 h), **3e** was isolated by FC on silica in 70% yield (0.0752 g) as a pale yellow oil (dr = 9:1). ^{1}H NMR ($CDCl_3$): δ = 7.23−7.18 (m, 3H), 6.92 (d, J = 6.9 Hz, 2H), 6.05 (dd, J = 10.7, 2.0 Hz, 1H), 5.97 (s, 2H), 4.83−4.72 (m, 2H), 4.37 (td, J = 9.9, 3.2 Hz, 1H), 3.81 (s, 1H), 3.75 (s, 5H), 3.60 (s, 6H), 2.66 (t, J = 10.5 Hz, 1H), 2.20 (bs, 1H), 1.67−1.60 (m, 2H), 1.42−1.37 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 152.7 (2C), 146.8 (d, J = 227.9 Hz), 140.0 (2C), 136.8 (d, J = 25.6 Hz), 128.7 (2C), 128.2 (2C), 127.0, 118.6 (d, J = 22.9 Hz), 104.6 (2C), 79.7 (d, J = 7.8 Hz), 71.5 (d, J = 2.3 Hz), 71.4 (d, J = 2.2 Hz), 60.5 (d, J = 64.0 Hz, 2C), 55.8 (2C), 52.6 (d, J = 1.5 Hz), 47.2 (d, J = 12.9 Hz), 35.3, 24.1 (d, J = 2.0 Hz), 24.0 (d, J = 2.1 Hz), 23.9 (d, J = 4.7 Hz), 23.8 (d, J = 4.5 Hz). ^{31}P NMR ($CDCl_3$): δ = 6.03. HRMS calculated for $[C_{28}H_{39}O_8P + Na]^+$: 557.2275; found: 557.2279. $[\alpha]_D^{20}$ = −110.4 (c = 1.00, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-4-(3-nitrophenyl)-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3f**).* Following the general procedure (reaction time 24 h), **3f** was isolated in 65% yield (0.064 g) as a yellow oil (dr = >20:1). ^{1}H NMR ($CDCl_3$): δ = 7.99 (dd, J = 8.3, 1.1 Hz, 1H), 7.74 (t, J = 2.0 Hz, 1H), 7.31−7.13 (m, 5H), 6.90 (d, J = 6.4 Hz, 2H), 5.98 (dd, J = 10.7, 2.2 Hz, 1H), 4.86−4.72 (m, 2H), 4.40 (td, J = 9.7, 3.2 Hz, 1H), 3.84 (dt, J = 10.7, 2.8 Hz, 1H), 3.75 (t, J = 5.7 Hz, 2H), 2.71 (t, J = 10.4 Hz, 1H), 2.13 (bs, 1H), 1.70−1.59 (m, 2H), 1.45−1.37 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 148.1, 147.6 (d, J = 226.7 Hz), 143.6, 138.7, 134.1, 129.2, 129.0, 128.0 (2C), 127.6 (2C), 122.6, 122.1, 117.1 (d, J = 23.3 Hz), 79.5 (d, J = 8.0 Hz), 71.9 (d, J = 5.7 Hz), 71.7 (d, J = 5.7 Hz), 59.8, 52.6 (d, J = 1.9 Hz), 46.8 (d, J = 12.9 Hz), 35.3, 24.1 (d, J = 4.2 Hz, 2C), 23.9 (d, J = 4.5 Hz, 2C).^{31}P NMR ($CDCl_3$): δ = 5.51. HRMS calculated for $[C_{25}H_{32}NO_7P + Na]^+$: 512.1809; found: 512.1817. $[\alpha]_D^{26}$ = −96.6 (c = 0.60, MeCN).

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*Diisopropyl ((2R,3R,4S)-4-(2-Fluorophenyl)-2-(2-hydroxyethyl)-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3g**).* Following the general procedure (reaction time 24 h), **3g** was isolated in 70% yield (0.0651 g) as a pale yellow oil (dr = 7:1). ^{1}H NMR ($CDCl_3$): δ = 7.21−7.15 (m, 3H), 7.09−7.01 (m, 2H), 6.98−6.93 (m, 3H), 6.83−6.78 (m, 1H), 5.95 (dd, J = 10.8, 2.2 Hz, 1H), 4.82−4.69 (m, 2H), 4.38 (td, J = 9.7, 3.2 Hz, 1H), 4.05 (d, J = 10.7, Hz, 1H), 3.75−3.72 (m, 2H), 2.89 (t, J = 10.4 Hz, 1H), 2.32 (bs, 1H), 1.68−1.57 (m, 2H), 1.41−1.35 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 160.6 (d, J = 246.6 Hz), 146.0 (d, J = 227.0 Hz), 139.3, 129.4 (d, J = 4.4 Hz), 128.6 (2C), 128.5, 128.4 (d, J = 6.7 Hz), 128.1, 127.9, 127.1, 124.1 (d, J = 3.6 Hz), 118.6 (d, J = 23.1 Hz), 115.3 (d, J = 22.5 Hz), 79.9 (d, J = 8.2 Hz), 71.5 (d, J = 5.5 Hz), 71.4 (d, J = 5.6 Hz), 60.0, 50.7, 40.5 (d, J = 13.2 Hz), 35.3, 24.0 (d, J = 4.2 Hz, 2C), 23.8 (t, J = 4.9 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 6.13. ^{19}F NMR ($CDCl_3$): δ = −115.3. HRMS calculated for $[C_{25}H_{32}FO_5P + Na]^+$: 485.1864; found: 485.1870. $[\alpha]_D^{29}$ = −99.4 (c = 0.827, MeCN).

*Diisopropyl ((2R,3R,4S)-4-(4-Chlorophenyl)-2-(2-hydroxyethyl)-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3h**).* Following the general procedure (reaction time 30 h), **3h** was isolated in 67% yield (0.0641 g) as a pale yellow oil (dr = 11:1). ^{1}H NMR ($CDCl_3$): δ = 7.22−7.18 (m, 3H), 7.08 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 6.6 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.95 (dd, J = 10.8, 2.2 Hz, 1H), 4.81−4.70 (m, 2H), 4.35 (dt, J = 9.3, 3.1 Hz, 1H), 3.74−3.71 (m, 2H), 3.69−3.65 (m, 1 H), 2.65 (t, J = 10.4 Hz, 1H), 2.31 (bs, 1H), 1.64−1.56 (m, 2H), 1.41−1.35 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.7 (d, J = 227.7 Hz), 139.6 (d, J = 47.3 Hz), 132.5 (2C), 129.0 (2C), 128.8 (2C), 128.4 (2C), 128.1 (2C), 127.2, 118.3 (d, J = 22.9 Hz), 79.5 (d, J = 8.1 Hz), 71.6 (d, J = 5.8 Hz), 71.5 (d, J = 5.7 Hz), 59.9, 52.6 (d, J = 1.9 Hz), 46.5 (d, J = 12.8 Hz), 35.3, 24.1 (d, J = 1.5 Hz), 24.0 (d, J = 1.4 Hz), 23.9 (d, J = 1.9 Hz), 23.8 (d, J = 1.9 Hz). ^{31}P NMR ($CDCl_3$): δ = 5.92. HRMS calculated for $[C_{25}H_{32}ClO_5P + Na]^+$: 501.1568; found: 501.1574. $[\alpha]_D^{29}$ = −109.3 (c = 0.58, MeCN).

*Diisopropyl ((2R,3R,4S)-4-(4-Bromo-2-fluorophenyl)-2-(2-hydroxyethyl)-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3i**).* Following the general procedure (reaction time 24 h), **3i** was isolated in 78% yield (0.0842g) as a light yellow oil (dr = 8:1). ^{1}H NMR ($CDCl_3$): δ = 7.24−7.18 (m, 3H), 7.13 (dd, J = 8.3, 1.9 Hz, 1H), 7.00 (dd, J = 9.7, 1.9 Hz, 1H), 6.95−6.90 (m, 3H), 5.90 (dd, J = 10.7, 2.2 Hz, 1H), 4.79−4.70 (m, 2H), 4.38 (td, J = 9.7, 3.1 Hz, 1H), 4.02 (dt, J = 10.8, 3.0 Hz, 1H), 3.75 (t, J = 5.7 Hz, 2H), 2.84 (t, J = 10.4 Hz, 1H), 2.06 (bs, 1H), 1.71−1.57 (m, 2H), 1.41−1.35 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 160.4 (d, J = 251.4 Hz), 146.6 (d, J = 227.1 Hz), 138.9, 130.5 (d, J = 5.1 Hz), 128.8, 128.5, 127.9, 127.5, 127.5, 127.4, 127.3, 120.7 (d, J = 9.7 Hz), 119.0 (d, J = 25.9 Hz), 117.6 (d, J = 23.2 Hz), 79.8 (d, J = 8.2 Hz), 71.6 (d, J = 5.7 Hz), 71.5 (d, J = 5.7 Hz), 59.9, 50.7, 40.2 (d, J = 13.3 Hz), 35.3, 24.0 (d, J = 4.2 Hz, 2C), 23.8 (t, J = 4.2 Hz, 2C). ^{19}F NMR ($CDCl_3$): δ = −114.9. ^{31}P NMR ($CDCl_3$): δ = 5.80. HRMS calculated for $[C_{25}H_{31}BrFO_5P + Na]^+$: 563.0969; found: 563.0977. $[\alpha]_D^{29}$ = −112.7 (c = 0.538, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-4-methyl-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3j**).* Following the general procedure (reaction time 48 h), **3j** was isolated in 52% yield (0.0397 g) as a yellow oil (dr = 8:1). ^{1}H NMR ($CDCl_3$): δ = 7.33−7.30 (m, 2H), 7.24−7.22 (m, 1H), 7.09−7.07 (m, 2H), 5.88 (dd, J = 10.9, 2.1 Hz, 1H), 4.75−4.65 (m, 2H), 4.13 (td, J = 9.8, 3.1 Hz, 1H), 3.69 (t, J = 5.8 Hz, 2H), 2.55 (bs, 1H), 2.30 (t, J = 10.2 Hz, 2H), 1.60−1.50 (m, 2H), 1.36−1.32 (m, 12H), 0.87 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 144.9 (d, J = 227.8 Hz), 140.6, 128.9, 128.5, 128.4, 128.0, 127.1, 121.7 (d, J = 22.1 Hz), 79.9 (d, J = 8.0 Hz), 71.4 (d, J = 5.7 Hz), 71.3 (d, J = 5.5 Hz), 60.2, 52.1 (d, J = 1.8 Hz), 35.3, 34.9 (d, J = 12.8 Hz), 24.0 (dd, J = 4.1, 2.5 Hz, 2C), 23.8 (dd, J = 4.6, 2.9 Hz, 2C), 18.6 (d, J = 1.5 Hz). ^{31}P NMR ($CDCl_3$): δ = 6.90. HRMS calculated for $[C_{20}H_{31}O_5P + Na]^+$: 405.1801; found: 405.1805. $[\alpha]_D^{29}$ = −13.4 (c = 1.07, MeCN).

*Diisopropyl ((2R,3R,4S)-4-Ethyl-2-(2-hydroxyethyl)-3-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3k**).* Following the general procedure (reaction time 48 h), **3k** was isolated in 66% yield (0.0523 g) as a dark yellow oil (dr = 7:1). ^{1}H NMR ($CDCl_3$): δ = 7.34−7.30 (t, J = 7.3 Hz, 2H), 7.25−7.23 (m, 1H),7.09−7.08 (d, J = 7.4 Hz, 2H), 6.00 (d, J = 11.1 Hz, 1H), 4.74−4.66 (m, 2H), 4.11 (t, J = 6.7 Hz, 1H), 3.69 (t, J = 5.8 Hz, 2H), 2.45 (d, J = 5.9 Hz, 2H), 2.26 (bs, 1H), 1.64−1.55 (m, 1H), 1.50−1.45 (m, 1H), 1.37−1.33 (m, 12H), 1.13−1.06 (m, 1H), 1.02−0.94 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 145.2 (d, J = 227.4 Hz), 140.6, 128.9, 128.5, 128.4, 128.1, 127.1, 119.5 (d, J = 22.3 Hz), 80.0 (d, J = 8.0 Hz), 71.4 (d, J = 5.5 Hz), 71.3 (d, J = 5.5 Hz), 60.4, 49.4 (d, J = 1.8 Hz), 41.1 (d, J = 12.3 Hz), 35.4, 24.6, 24.0 (d, J = 2.5 Hz), 24.0 (d, J = 2.6 Hz), 23.8 (d, J = 4.7 Hz), 23.8 (d, J = 5.0 Hz), 10.3. ^{31}P NMR ($CDCl_3$): δ = 6.74. HRMS calculated for $[C_{21}H_{33}O_5P + Na]^+$: 419.1958; found: 419.1961. $[\alpha]_D^{28}$ = −18.3 (c = 0.535, MeCN).

General Procedure for Preparation of Dihydropyran Phosphonates 3l−3s. An ordinary screw-cap vial was charged with a magnetic stirring bar and 59.3 mg (0.2 mmol, 1.0 equiv) of phosphonate **2a**. After addition of 0.8 mL of a stock solution of *N*,*N*-diethylacetamide (DEA) in MeCN (1 equiv DEA), 0.4 mmol (2 equiv) of **1** was added, followed by the addition of 16 mg (0.032 mmol, 0.16 equiv) of catalyst **4a**. The reaction mixture was stirred at rt and monitored by ^{1}H and ^{31}P NMR spectroscopy. After the reaction time given, the reaction was cooled to 0 °C and 15.1 mg (0.4 mmol, 2 equiv) of $NaBH_4$ was added, followed by the addition of ca. 5 drops of MeOH. The reaction was stirred for 2 h at rt, diluted with 30 mL of Et_2O, and extracted 6−8 times with 8 mL of water to remove the additive. The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC (CH_2Cl_2/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford products **3**. The dr after purification was determined by ^{31}P NMR spectroscopy.

*Diisopropyl ((2R,3R,4S)-3-(4-Fluorophenyl)-2-(2-hydroxyethyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3l**).* Following the general procedure (reaction time 24 h), **3l** was isolated in 82% yield (0.0839 g) as a pale yellow oil (dr = 10:1). ^{1}H NMR ($CDCl_3$): δ = 7.47 (d, J = 8.1 Hz, 2H), 7.14−7.13 (m, 3H), 7.03 (d, J = 7.9 Hz, 2H), 6.82 (dd, J = 6.5, 3.0 Hz, 2H), 6.01 (dd, J = 10.8, 2.2 Hz, 1H), 4.83−4.71 (m, 2H), 4.39 (td, J = 9.9, 2.8 Hz, 1H), 3.74 (t, J = 5.5 Hz, 2H), 3.68 (dt, J = 11.1, 2.6 Hz, 1H), 2.82 (t, J = 10.4 Hz, 1H), 2.35 (bs, 1H), 1.66−1.51 (m, 2H), 1.41−1.35 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.5 (d, J = 228.2 Hz), 144.1, 140.7, 129.4 (q, J = 32.6 Hz), 128.5, 128.4 (2C), 127.6 (2C), 127.1, 125.3 (q, J = 3.6 Hz, 2C), 123.9 (q, J = 271.1 Hz), 118.7 (d, J = 22.9 Hz, 2C), 78.9 (d, J = 8.3 Hz), 71.7 (d, J = 5.8 Hz), 71.6 (d, J = 5.8 Hz), 59.6, 52.6 (d, J = 1.9 Hz), 47.2 (d, J = 12.7 Hz), 35.3, 24.1 (d, J = 4.1 Hz, 2C), 23.9 (d, J = 4.6 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 5.92. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.5. HRMS calculated for $[C_{26}H_{32}F_3O_5P + Na]^+$: 535.1832; found: 535.1835. $[\alpha]_D^{25}$ = −87.3 (c = 1.15, MeCN).

*Diisopropyl ((2R,3R,4S)-3-(4-Fluorophenyl)-2-(2-hydroxyethyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3m**).* Following the general procedure (reaction time 24 h), **3m** was isolated in 77% yield (0.0712 g) as a light yellow oil (dr = 8:1). ^{1}H NMR ($CDCl_3$): δ = 7.14−7.12 (m, 3H), 6.93−6.89 (m, 6H), 6.01 (dd, J = 10.8, 2.3 Hz, 1H), 4.83−4.71 (m, 2H), 4.33 (td, J = 9.6, 3.4 Hz, 1H), 3.74 (t, J = 5.2 Hz, 2H), 3.63 (dt, J = 10.7, 3.6 Hz, 1H), 2.72 (t, J = 10.4 Hz, 1H), 2.25 (bs, 1H), 1.64−1.56 (m, 2H), 1.42−1.36 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 161.8 (d, J = 245.8 Hz), 146.4 (d, J = 227.8 Hz), 141.1, 135.6 (d, J = 3.0 Hz), 129.5 (d, J = 7.7 Hz), 128.8, 128.3 (2C), 128.0, 127.7, 126.9, 118.9 (d, J = 22.9 Hz, 2C), 115.6 (d, J = 21.4 Hz), 79.5 (d, J = 8.1 Hz), 71.6 (d, J = 5.8 Hz), 71.5 (d, J = 5.7 Hz), 59.9, 52.0 (d, J = 1.9 Hz), 47.3 (d, J = 12.6 Hz), 35.3, 24.1 (d, J = 4.1 Hz, 2C), 23.9 (d, J = 4.5 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 6.06. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −115.30. HRMS calculated for $[C_{25}H_{32}FO_5P + Na]^+$: 485.1864; found: 485.1872. $[\alpha]_D^{28}$ = −100.3 (c = 0.52, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-4-phenyl-3-(o-tolyl)-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3n**).* Following the general procedure (reaction time 24 h), **3n** was isolated in 84% yield (0.0773 g) as a pale yellow oil (dr = 15:1). ^{1}H NMR ($CDCl_3$): δ = 7.23 (t, J = 7.6 Hz, 1H), 7.14−7.05 (m, 5H), 6.93 (d, J = 7.6 Hz, 1H), 6.82−6.80 (m, 2H), 6.07 (dd, J = 10.8, 2.3 Hz, 1H), 4.86−4.72 (m, 2H), 4.35 (t, J = 9.9 Hz, 1H), 3.73 (bs, 2H), 3.66 (d, J = 10.5 Hz, 1H), 3.05 (t, J = 10.3 Hz, 1H), 2.22 (bs, 1H), 1.65−1.57 (m, 5H), 1.40 (dt, J = 13.9, 6.3 Hz, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.7 (d, J = 228.2 Hz), 141.2,

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137.9 (d, J = 146.4 Hz), 130.1, 128.1, 127.7 (3C), 126.8, 126.7, 126.5 (2C), 125.9, 119.2 (d, J = 23.0 Hz), 80.6 (d, J = 7.9 Hz), 71.5 (dd, J = 9.7, 5.8 Hz, 2C), 60.5, 47.6 (d, J = 12.9 Hz), 47.0, 34.8, 24.1 (d, J = 4.2 Hz, 2C), 23.9 (d, J = 4.6 Hz, 2C), 19.4. ^{31}P NMR ($CDCl_3$): δ = 6.24. HRMS calculated for $[C_{26}H_{35}O_5P + Na]^+$: 481.2114; found: 481.2113. $[\alpha]_D^{28}$ = −95.1 (c = 0.445, MeCN).

*Diisopropyl ((2R,3R,4S)-2-(2-Hydroxyethyl)-3-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3o**).* Following the general procedure (reaction time 24 h), **3o** was isolated in 74% yield (0.0701 g) as a pale yellow oil (dr = 10:1). ^{1}H NMR ($CDCl_3$): δ = 7.14−7.12 (m, 3H), 6.85−6.80 (m, 4H), 6.75 (d, J = 8.7 Hz, 2H), 6.01 (dd, J = 10.8, 2.3 Hz, 1H), 4.83−4.71 (m, 2H), 4.34−4.28 (m, 1H), 3.74 (s, 5H), 3.65 (ddd, J = 10.5, 3.7, 2.4 Hz, 1H), 2.67 (t, J = 10.4 Hz, 1H), 2.24 (bs, 1H), 1.65−1.57 (m, 2H), 1.42−1.36 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 158.5, 146.2 (d, J = 227.5 Hz), 141.4, 131.7, 129.0 (2C), 128.2 (2C), 127.8 (2C), 126.7, 119.2 (d, J = 22.9 Hz), 114.1 (2C), 80.0 (d, J = 8.0 Hz), 71.5 (d, J = 5.7 Hz), 71.4 (d, J = 5.7 Hz), 60.2, 55.1, 51.8 (d, J = 1.8 Hz), 47.1 (d, J = 12.8 Hz), 35.3, 24.1 (d, J = 4.2 Hz, 2C), 23.9 (d, J = 4.6 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 6.23. HRMS calculated for $[C_{26}H_{35}O_6P + Na]^+$: 497.2063; found: 497.2069. $[\alpha]_D^{28}$ = −122.5 (c = 0.72, MeCN).

*Diisopropyl ((2R,3R,4S)-3-(3,5-Dimethylphenyl)-2-(2-hydroxyethyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3p**).* Following the general procedure (reaction time 24 h), **3p** was isolated in 72% yield (0.0682 g) as a pale yellow oil (dr = 9:1). ^{1}H NMR ($CDCl_3$): δ = 7.16−7.09 (m, 3H), 6.86−6.84 (m, 2H), 6.80 (s, 1H), 6.50 (s, 2H), 6.02 (dd, J = 10.8, 2.3 Hz, 1H), 4.84−4.72 (m, 2H), 4.34−4.28 (m, 1H), 3.75 (t, J = 5.8 Hz, 2H), 3.69 (dt, J = 10.4, 3.0 Hz, 1H), 2.65 (t, J = 10.3 Hz, 1H), 2.28 (s, 1H), 2.20 (s, 6H), 1.66−1.60 (m, 2H), 1.42−1.36 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.2 (d, J = 228.9 Hz), 140.6 (d, J = 193.5 Hz), 138.1 (3C), 128.7 (2C), 128.1 (2C), 127.8, 126.7 (2C), 125.9, 119.5 (d, J = 22.9 Hz), 80.15 (d, J = 8.0 Hz), 71.45 (d, J = 5.8 Hz), 71.35 (d, J = 5.6 Hz), 60.4, 52.4 (d, J = 1.8 Hz), 46.75 (d, J = 12.5 Hz), 35.4, 24.1 (d, J = 4.2 Hz), 23.9 (d, J = 3.5 Hz, 2C), 23.8 (d, J = 3.3 Hz), 21.3 (2C). ^{31}P NMR ($CDCl_3$): δ = 6.24. HRMS calculated for $[C_{27}H_{37}O_5P + Na]^+$: 495.2271; found: 495.2275. $[\alpha]_D^{29}$ = −128.1 (c = 0.54, MeCN).

*Diisopropyl ((2R,3R,4S)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(2-hydroxyethyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3q**).* Following the general procedure (reaction time 24 h), **3q** was isolated in 80% yield (0.0783 g) as a pale yellow oil (dr = 11:1). ^{1}H NMR ($CDCl_3$): δ = 7.17−7.13 (m, 3H), 6.89−6.87 (m, 2H), 6.63 (d, J = 7.9 Hz, 1H), 6.44 (d, J = 1.6 Hz, 1H), 6.33 (dd, J = 7.9, 1.7 Hz, 1H), 6.00 (dd, J = 10.8, 2.3 Hz, 1H), 5.91 (d, J = 6.9 Hz, 2H), 4.77−4.71 (m, 2H), 4.26−4.23 (m, 1H), 3.75 (s, 2H), 3.63 (dt, J = 10.5, 3.0 Hz, 1H), 2.66 (t, J = 10.4 Hz, 1H), 2.24 (bs, 1H), 1.64−1.61 (m, 2H), 1.41−1.34 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 147.4 (d, J = 146.7 Hz), 147.3, 145.2, 141.3, 133.5, 128.7, 128.3, 128.0, 127.8, 126.8, 121.5, 119.1 (d, J = 22.9 Hz), 108.4, 107.9, 101.0, 79.1 (d, J = 8.1 Hz), 71.5 (d, J = 5.7 Hz), 71.4 (d, J = 5.8 Hz), 60.2, 52.3 (d, J = 2.0 Hz), 47.1 (d, J = 12.7 Hz), 35.3, 24.1 (d, J = 4.2 Hz, 2C), 23.9 (d, J = 4.5 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 6.14. HRMS calculated for $[C_{26}H_{33}O_7P + Na]^+$: 511.1856; found: 511.1859. $[\alpha]_D^{25}$ = −114.9 (c = 1.65, MeCN).

*Diisopropyl ((2R,3R,4S)-3-([1,1′-Biphenyl]-2-yl)-2-(2-hydroxyethyl)-4-phenyl-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3r**).* Following the general procedure (reaction time 24 h), **3r** was isolated in 70% yield (0.0732 g) as a pale yellow oil (dr = > 20). ^{1}H NMR ($CDCl_3$): δ = 7.45−7.41 (m, 1H), 7.35−7.31 (m 2H), 7.26−7.12 (m, 7H), 7.02 (d, J = 7.2 Hz, 2H), 6.72 (d, J = 8.1 Hz, 2H), 5.99 (dd, J = 10.8, 2.3 Hz, 1H), 4.87−4.68 (m, 2H), 4.27−4.21 (m, 1H), 3.80−3.76 (m, 1H), 3.67 (bs, 2H), 2.84 (t, J = 10.3 Hz, 1H), 2.17 (bs, 1H), 1.54−1.49 (m, 2H), 1.36−1.29 (m, 12H). ^{13}C NMR ($CDCl_3$): δ = 146.58 (d, J = 228.7 Hz), 143.7, 140.9 (d, J = 63.5 Hz), 137.7, 130.1, 129.2 (2C), 128.3 (2C), 128.2 (2C), 128.1, 127.5 (2C), 126.9, 126.6, 126.3, 126.1 (2C), 119.1 (d, J = 22.9 Hz), 80.9 (d, J = 7.7 Hz), 71.5 (d, J = 4.6 Hz), 71.4 (d, J = 4.4 Hz), 60.6, 47.2 (d, J = 12.7 Hz), 46.9, 34.9, 24.1 (d, J = 4.3 Hz), 24.0 (d, J = 4.4 Hz), 23.9 (d, J = 4.7 Hz), 23.7 (d, J = 4.5 Hz). ^{31}P NMR ($CDCl_3$): δ = 6.17. HRMS calculated for $[C_{31}H_{37}O_5P + Na]^+$: 543.2271; found: 543.2273. $[\alpha]_D^{25}$ = −70.3 (c = 1.6, MeCN).

*Diisopropyl ((2R,3S,4R)-2-(2-Hydroxyethyl)-4-phenyl-3-(thiophen-2-yl)-3,4-dihydro-2H-pyran-6-yl)phosphonate (**3s**).* Following the general procedure (reaction time 24 h), **3s** was isolated in 64% yield (0.0573 g) as a yellow oil (dr = 4:1). ^{1}H NMR ($CDCl_3$): δ = 7.19−7.14 (m, 4H), 6.95−6.92 (m, 2H), 6.83 (dd, J = 5.1, 3.5 Hz, 1H), 6.57 (d, J = 3.5 Hz, 1H), 5.97 (dd, J = 10.7, 2.3 Hz, 1H), 4.85−4.69 (m, 2H), 4.31−4.26 (m, 1H), 3.77−3.68 (m, 3H), 3.11 (t, J = 10.3 Hz, 1H), 2.27 (bs, 1H), 1.76−1.67 (m, 2H), 1.42−1.36 (m, 12H).^{13}C NMR ($CDCl_3$): δ = 146.4 (d, J = 227.6 Hz), 142.5 (d, J = 1.3 Hz), 141.2, 128.7, 128.3, 128.2, 127.7, 127.0, 126.8, 125.7, 124.4, 118.6 (d, J = 22.9 Hz), 80.2 (d, J = 8.1 Hz), 71.6 (d, J = 6.4 Hz), 71.5 (d, J = 5.9 Hz), 60.0, 48.5 (d, J = 12.7 Hz), 48.3 (d, J = 2.0 Hz), 35.3, 24.1 (d, J = 4.2 Hz, 2C), 23.9 (d, J = 4.5 Hz, 2C). ^{31}P NMR ($CDCl_3$): δ = 5.99. HRMS calculated for $[C_{23}H_{31}O_5PS + Na]^+$: 473.1522; found: 473.1523. $[\alpha]_D^{29}$ = −87.3 (c = 0.83, MeCN).

General Procedure for the Formation of Dihydroxy Pyrans. An ordinary screw-cap vial was charged with 0.14 mmol (1 equiv) of compound **3d** or **3o** and 1.4 mL of tBuOH/H_2O solution (10:1). Then, 0.28 mmol (2 equiv) of NMO was added, followed by 0.14 mmol (1 equiv) of Na_2SO_3 and 100 μL of 2.5% (w/w) solution of OsO_4 in tBuOH/H_2O. The reaction mixture was stirred at rt and monitored by ^{1}H and ^{31}P NMR spectroscopy. After the reaction time given (3−5 h), the reaction was diluted with Et_2O (20 mL) and washed with brine (3 × 10 mL) and water (6 × 10 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC on silica (eluent: DCM/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford compounds **5a**,**5b**.

*Diisopropyl ((2R,3R,4R,5R,6R)-2,3-Dihydroxy-6-(2-hydroxyethyl)-5-phenyl-4-(p-tolyl)tetrahydro-2H-pyran-2-yl) (**5a**).* Following the aforementioned procedure, **5a** was isolated in 50% yield (0.0342 g) as a white solid (dr = 17:1). ^{1}H NMR ($CDCl_3$): δ = 7.13−6.92 (m, 9H), 5.88 (bs, 1H), 4.91−4.82 (m, 2H), 4.57−4.51 (m, 1H), 4.16 (dd, J = 10.4, 4.9 Hz, 1H), 3.80−3.76 (m, 1H), 3.61−3.56 (m, 1H), 3.46 (bs, 1H), 3.33 (t, J = 11.1 Hz, 1H), 3.20 (bs, 1H), 2.84 (t, J = 11.2 Hz, 1H), 2.18 (s, 3H), 1.51−1.47 (m, 2H), 1.44 (d, J = 6.2 Hz, 3H), 1.38 (t, J = 6.0 Hz, 9H). ^{13}C NMR ($CDCl_3$): δ = 138.8 (d, J = 1.6 Hz), 136.5 (d, J = 1.5 Hz), 135.9, 128.8 (4C), 128.3 (2C), 128.0 (2C), 126.6, 95.9 (d, J = 207.9 Hz), 73.5 (d, J = 6.9 Hz), 72.9 (d, J = 7.9 Hz), 72.1 (d, J = 9.1 Hz), 71.9 (d, J = 6.4 Hz), 59.6, 53.8 (d, J = 1.7 Hz), 48.9 (d, J = 8.9 Hz), 35.2, 24.4 (d, J = 2.5 Hz), 24.1 (d, J = 3.6 Hz), 23.9 (d, J = 4.8 Hz), 23.6 (d, J = 5.5 Hz), 21.0. ^{31}P NMR ($CDCl_3$): δ = 15.59. HRMS calculated for $[C_{26}H_{37}O_7P + Na]^+$: 515.2169; found: 515.2175. $[\alpha]_D^{25}$ = −29.9 (c = 1.00, MeCN).

*Diisopropyl ((2R,3R,4R,5R,6R)-2,3-Dihydroxy-6-(2-hydroxyethyl)-5-(4-methoxyphenyl)-4-phenyltetrahydro-2H-pyran-2-yl)phosphonate (**5b**).* Following the aforementioned procedure, **5b** was isolated in 54% yield (0.0384 g) as a white solid (dr = 15:1). ^{1}H NMR ($CDCl_3$): δ = 7.16−7.12 (m, 2H), 7.07−7.06 (m, 3H), 6.94−6.88 (m, 2H), 6.64 (d, J = 8.2 Hz, 2H), 4.91−4.81 (m, 2H), 4.52−4.47 (m, 1H), 4.19 (dd, J = 10.4, 4.9 Hz, 1H), 3.81−3.71 (m, 2H), 3.67 (s, 3H), 3.12−3.57 (m, 1H), 3.30 (t, J = 11.1 Hz, 2H), 2.79 (t, J = 11.2 Hz, 1H), 1.51−1.47 (m, 2H), 1.43 (d, J = 6.2 Hz, 3H), 1.39−1.36 (m, 10H). ^{13}C NMR ($CDCl_3$): δ = 158.1, 139.9, 130.7 (d, J = 1.5 Hz), 128.3 (2C), 128.1 (4C), 126.5, 113.7 (2C), 95.9 (d, J = 207.8 Hz), 73.5 (d, J = 6.9 Hz), 72.9 (d, J = 8.0 Hz), 72.4 (d, J = 10.8 Hz), 71.9 (d, J = 8.4 Hz), 59.8, 55.0, 53.0 (d, J = 1.7 Hz), 49.6 (d, J = 8.9 Hz), 35.1, 24.4 (d, J = 2.4 Hz), 24.0 (d, J = 3.8 Hz, 2C), 23.6 (d, J = 5.4 Hz). ^{31}P NMR ($CDCl_3$): δ = 15.50. HRMS calculated for $[C_{26}H_{37}O_8P + Na]^+$: 531.2118; found: 531.2121. $[\alpha]_D^{25}$ = −36.2 (c = 1.41, MeCN).

General Procedure for the Formation of α-Hydroxy Lactones from Dihydroxy Pyrans. An ordinary screw-cap vial was charged with 0.17 mmol (1 equiv) of compound **5a** or **5b**, 0.68 mmol (4 equiv) of DMAP, and CH_2Cl_2 (1.7 mL). The reaction was stirred overnight at rt. Then, the reaction mixture was diluted with Et_2O (10 mL) and washed with 0.5 M HCl (3 × 10 mL) and water (3 × 10 mL). The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC on silica (eluent: CH_2Cl_2/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford compounds **6a**,**6b**.

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General Procedure for One-Pot Formation of α-Hydroxy Lactones. An ordinary screw-cap vial was charged with 0.14 mmol (1 equiv) of compound **3d** or **3o** and 1.4 mL of *t*BuOH/H_2O solution (10:1). Then, 0.28 mmol (2 equiv) of NMO was added, followed by 0.14 mmol (1 equiv) of Na_2SO_3 and 100 μL of 2.5% (w/w) solution of OsO_4 in *t*BuOH/H_2O. The reaction mixture was stirred at rt and monitored by ^1H and ^{31}P NMR spectroscopy. After the reaction time given (3−5 h), 0.56 mmol (4 equiv) of DMAP was added and the reaction was stirred overnight at rt. The reaction was diluted with Et_2O (20 mL) and washed with 0.5 M HCl (3 × 10 mL), brine (3 × 10 mL), and water (6 × 10 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC on silica (eluent: CH_2Cl_2/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford compounds **6a**,**6b**.

*(3R,4R,5R,6R)-3-Hydroxy-6-(2-hydroxyethyl)-5-phenyl-4-(p-tolyl)-tetrahydro-2H-pyran-2-one (**6a**).* Following the aforementioned procedures, **6a** was isolated as a single diastereoisomer in 44% yield (0.0243 g) (method A) and 49% yield (0.0226 g) (method B) as a white solid with a mp 137.4−138.7 °C. ^1H NMR ($CDCl_3$): δ = 7.20−7.10 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.98−6.94 (m, 4H), 4.84 (ddd, *J* = 11.7, 9.0, 3.2 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 3.82−3.71 (m, 2H), 3.41 (t, *J* = 11.5 Hz, 1H), 3.28−3.22 (m, 2H), 2.20 (s, 3H), 1.88−1.72 (m, 2H), 1.66 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ = 173.4, 137.0, 136.7, 134.9, 129.2 (2C), 128.8 (2C), 128.3 (2C), 127.5 (3C), 83.4, 72.0, 58.7, 51.9, 51.2, 36.4, 21.0. HRMS calculated for $[C_{20}H_{22}O_4 + Na]^+$: 349.1410; found: 349.1413. $[\alpha]_D^{25}$ = −30.9 (*c* = 0.493, MeCN).

*(3R,4R,5R,6R)-3-Hydroxy-6-(2-hydroxyethyl)-5-(4-methoxyphenyl)-4-phenyltetrahydro-2H-pyran-2-one (**6b**).* Following the aforementioned procedures, **6b** was isolated as a single diastereoisomer in 43% yield (0.0252 g) (method A) and 61% yield (0.0293 g) (method B) as a white solid. ^1H NMR ($CDCl_3$): δ = 7.18 (t, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.09−7.05 (m, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 4.82−4.77 (m, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 3.81−3.73 (m, 2H), 3.70 (s, 3H), 3.39 (t, *J* = 11.5 Hz, 1H), 3.21 (t, *J* = 11.2 Hz, 1H), 1.79−1.74 (m, 2H), 1.60 (bs, 1H), 1.25 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 173.4, 158.7, 138.1, 129.2 (3C), 128.7 (2C), 128.5, 127.7, 127.2, 114.2 (2C), 83.6, 71.9, 58.8, 55.1, 51.7, 51.0, 36.3. HRMS calculated for $[C_{20}H_{22}O_5 + Na]^+$: 365.1359; found: 365.1364. $[\alpha]_D^{25}$ = −31.1 (*c* = 0.787, MeCN).

General Procedure for Preparation of Bromohydrin 7a. An ordinary screw-cap vial was charged with 0.16 mmol (1 equiv) of compound **3f**, 0.33 mmol (2 equiv) of NBS, 0.6 mL of *t*BuOH, and 0.3 mL of H_2O. The reaction was stirred for 2 h (followed by ^1H and ^{31}P NMR spectroscopy) at rt. The reaction mixture was diluted with Et_2O (10 mL) and washed with brine (3 × 10 mL) and water (6 × 10 mL). The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude product was purified by FC on silica (eluent: CH_2Cl_2/MeOH 100:0 → 200:1 → 200:2 → 200:3 → 200:4) to afford compound **7a**.

*Diisopropyl ((2R,3S,4R,5R,6R)-3-Bromo-2-hydroxy-6-(2-hydroxyethyl)-4-(3-nitrophenyl)-5-phenyltetrahydro-2H-pyran-2-yl)phosphonate (**7a**).* Following the aforementioned procedure, **7a** was isolated in 71% yield (0.0671 g) as a white solid (dr = 18:1:1). ^1H NMR ($CDCl_3$): δ = 8.10 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.15 (d, *J* = 4.4 Hz, 3H), 7.08−7.03 (m, 1H), 4.94−4.79 (m, 2H), 4.62−4.56 (m, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 2.8 Hz, 1H), 3.97−3.82 (m, 2H), 3.51−3.46 (m, 2H), 1.65−1.55 (m, 2H), 1.50 (d, *J* = 6.1 Hz, 3H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.44 (s, 1H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 147.7, 141.4 (d, *J* = 1.4 Hz), 138.0 (d, *J* = 1.4 Hz), 135.7, 128.8 (3C), 128.6 (2C), 127.1, 124.7, 121.8, 96.6 (d, *J* = 221.0 Hz), 74.6 (d, *J* = 6.9 Hz), 72.7 (d, *J* = 8.2 Hz), 71.5 (d, *J* = 10.6 Hz), 57.9, 56.1 (d, *J* = 7.0 Hz), 45.7, 45.1 (d, *J* = 5.4 Hz), 35.3, 24.5 (d, *J* = 2.2 Hz), 24.1 (d, *J* = 3.7 Hz), 23.7 (d, *J* = 5.0 Hz), 23.4 (d, *J* = 5.6 Hz). ^{31}P NMR ($CDCl_3$): δ = 14.61. HRMS calculated for $[C_{25}H_{33}BrNO_8P + Na]^+$: 608.1019; found: 608.1021. $[\alpha]_D^{20}$ = +3.8 (*c* = 1.00, MeCN).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Screening of temperature and equivalents of aldehyde; calculation of the dihedral angle; X-ray structures of compounds **6a** and **3a**; ^1H and ^{13}C NMR spectra of aldehydes **1h**, **1e**, and **1f**; ^1H, ^{31}P, and ^{13}C NMR of α,β-unsaturated acyl phosphonates; ^1H, ^{31}P, and ^{13}C NMR of the dihydropyran phosphonates; and ^1H, ^{31}P, and ^{13}C NMR of the dihydropyran derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kaj@chem.au.dk.

Notes

The authors declare no competing financial interest.

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